13.13 Product Class 13: 1,2,3-Triazoles

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General Introduction

Previously published information regarding this product class can be found in Houben–Weyl, Vol. E 8d, pp 305–405 (1,2,3-triazoles)\(^1\) and pp 406–478 (benzotriazoles).\(^2\) Other important reviews on the chemistry of 1,2,3-triazoles and their benzo derivatives are also available.\(^3\)–\(^9\)

1,2,3-Triazoles and benzotriazoles are important types of heterocyclic compounds. They find numerous applications in industry, namely as dyestuffs, fluorescent whiteners, photostabilizers of polymers, optical brightening agents, corrosion inhibitors and as photographic photoreceptors.\(^6\),\(^7\) Also, due to their extensive biological activities, they find successful application in medicine and as agrochemicals.\(^6\),\(^7\) Beyond this, these compounds are intensively studied by many research groups due to their theoretical interest and synthetic usefulness.

The 1,2,3-triazoles can be divided in three main groups: monocyclic 1,2,3-triazoles, benzotriazoles, and 1,2,3-triazolium salts. As indicated in Scheme 1, for monocyclic 1,2,3-triazoles three subclasses can be recognized, depending on the position of the substituents in the ring. While 1\(H\)- and 2\(H\)-1,2,3-triazoles are aromatic compounds their 4\(H\)-isomers are not. This fact is reflected in the abundance of examples of 1\(H\)- and 2\(H\)-1,2,3-triazoles and the rarity of 4\(H\)-1,2,3-triazoles.\(^3\) In the literature, the 1,2,3-triazole system is sometimes named as “\(v\)-triazole” in order to distinguish it from “s-triazole”, the 1,2,4-triazole system.

Scheme 1 Classes of 1,2,3-Triazoles

for references see p 587
N-Unsubstituted 1,2,3-triazoles can be regarded either as 1H- or as 2H-derivatives since these two tautomeric forms are in equilibrium, both in solution and in the gas phase (Scheme 2). In this article, for simplification, this type of compound will be represented as 1H-triazoles, independently of the predominant tautomer.

The two tautomeric forms of 1,2,3-triazole and benzotriazole are in equilibrium, both in solution and in the gas phase (Scheme 2). However there is an extraordinary difference in stability between 1,2,3-triazole and benzotriazole tautomers. In the gas phase, the 2H-tautomer of 1,2,3-triazole represents more than 99.9% of the equilibrium mixture, whereas in benzotriazole the 1H-tautomer is the predominant one (more than 99.99% at equilibrium). In solution, the much higher dipole moment of 1H-tautomers favor these structures and, as a consequence, mixtures of 1H- and 2H-1,2,3-triazole are observed in solution whereas the higher stability of 1H-benzotriazole is reinforced. In the solid state, 1,2,3-triazole exists as a 1:1 mixture of 1H- and 2H-tautomers, while 4-phenyl-1,2,3-triazole and 4-nitro-1,2,3-triazole are, respectively, in the 2H- and 1H- tautomeric forms.

The experimental dipole moment in benzene for the tautomeric mixture of 1H- and 2H-1,2,3-triazole is 1.85 D at 25°C and 2.08 D at 45°C. The experimental dipole moments are as follows: 1H-1,2,3-triazole 4.38 D, 2H-1,2,3-triazole 0.22 D, 1H-benzotriazole 4.15 D, and 2-methyl-2H-benzotriazole 0.49 D.

1H-1,2,3-Triazole is both a weak base (pKₐ 1.17) and a weak acid (pKₐ 9.4) of comparable strength to phenol. 1H-1,2,3-Triazole-4,5-dicarbonitrile (pKₐ 2.53), 4,5-dibromo-1H-1,2,3-triazole (pKₐ 5.37), and 4-nitro-1H-1,2,3-triazole (pKₐ 4.80) are much more acidic compounds. 1-Methyl-1H-1,2,3-triazole (pKₐ 1.25) shows a basicity comparable to 1H-1,2,3-triazole, but 2-methyl-2H-1,2,3-triazole is a much weaker base. The basicity of N-unsubstituted and N-methyl-1,2,3-triazoles in the gas phase, in solution, and in the solid state has been determined. The fused benzene ring in benzotriazole (pKₐ 8.2) is base-weakening and acid-strengthening. Substitution of hydrogen atoms by chlorine in the benzene ring results in increased acidity: 5-chlorobenzotriazole, pKₐ 7.7, 4,5,6,7-tetrachlorobenzotriazole, pKₐ 5.5.

The application of semi-empirical and ab initio methods in theoretical calculations for 1,2,3-triazoles and benzotriazoles and the description of a number of instrumental techniques used in the characterization of these systems have been reviewed.

1,2,3-Triazoles with a strong electron-withdrawing group at N1 (e.g., cyano, nitro, or arylsulfonyl groups) undergo ready and reversible ring opening to α-diazoimine tautomers (Scheme 3). This ring–chain tautomerism, also observed in some benzotriazole derivatives, is markedly temperature dependent.
This type of tautomerism is also involved, for example, in the interconversion of 1-aryl-1,2,3-triazol-5-amines and 5-anilino-1,2,3-triazoles ($R_1 = \text{aryl}$) (Scheme 4). This isomerization is known as the Dimroth rearrangement. It is also observed in the interconversion of triazoles with other substituents at position 5 (or 4) and in the conversion of 1,2,3-triazoles into other ring systems. The equilibrium is established thermally, but its position is influenced by the basicity of the solvent. In pyridine, for example, the equilibrium position is shifted to the more acidic NH triazoles. It is also observed that electron-withdrawing groups and large, rigid groups tend to favor the exocyclic nitrogen while alkyl groups tend to favor the cyclic nitrogen. This subject has been reviewed.\[21\]

In terms of stability, monocyclic 1,2,3-triazoles and benzotriazoles are remarkably stable compounds. The triazole ring is not normally cleaved by hydrolysis or oxidation and reductive cleavage only occurs under forcing conditions. The presence of substituents that have a destabilizing effect on the ring system can facilitate the cleavage. When subjected to pyrolysis or photolysis, 1,2,3-triazoles and benzotriazoles extrude nitrogen and produce very reactive species which react further to form a range of stable compounds: nitriles, ketenimines, azirines, pyrazines, indoles, etc. The thermal or photochemical extrusion of nitrogen from 1-arylbenzotriazoles leads to the formation of carbazoles (Scheme 5).
Both monocyclic 1,2,3-triazoles and benzotriazoles are readily alkylated on nitrogen by alkyl halides, dimethyl sulfate, diazoalkanes, methyl sulfonates, and other alkylating agents; generally mixtures of all possible N-alkyl isomers are obtained. With more reactive reagents, or under forcing reaction conditions, triazolium salts are obtained. N-Arylation is also possible if activated aryl halides are used. 1,2,3-Triazoles and benzotriazoles also react with acyl halides and anhydrides to furnish the corresponding N-acyl derivatives. These compounds also react with sulfonyl chlorides, isocyanates, chlorotrimethylsilane, etc. to give the corresponding N-substituted derivatives. Electrophilic substitution at CH positions is also possible: halogenation and nitration are examples of such transformations. Lithiation of triazoles followed by addition of electrophilic reagents is another versatile approach to functionalization of these compounds at CH positions. Triazoles can also be activated toward electrophiles by introduction of an N-oxide group.

All these types of reactions, and many others that produce new 1,2,3-triazole derivatives, are described in this section. Also, the synthetic methods available for the construction of the 1,2,3-triazole ring are reviewed.

13.13.1  Product Subclass 1:
Monocyclic N-Unsubstituted and 1-Substituted 1,2,3-Triazoles

13.13.1.1  Synthesis by Ring-Closure Reactions

13.13.1.1.1  By Formation of One N–N and One N–C Bond

13.13.1.1.1.1  Fragments C–C–N–N and N

13.13.1.1.1.1.1  Method 1:
From 2-Diazo-1,3-dicarbonyl Compounds and Amine Derivatives

The cyclocondensation reaction of 2-diazo-1,3-dicarbonyl compounds with amine derivatives is an old but versatile, simple, and completely regioselective method for the preparation of 1H-1,2,3-triazoles. This method was developed by Wolff at the beginning of the 20th century; he reported the synthesis of triazoles 3 by the reaction of ethyl 2-diazo-3-oxobutanoate (1) with phenylhydrazine, semicarbazide, hydroxylamine, aniline, or ammonia (Scheme 6).[22,23,246] The mechanism of the reaction involves the in situ formation of α-diazoimines of type 2 followed by ring closure. Several variations of this method appeared since then and a range of 2-diazo-1,3-dicarbonyl compounds can be used: α-diazo-β-oxo esters, α-diazo-β-formyl esters, α-diazo-β-oxoaldehydes, diazomalonaldehyde, and diazomalonates.
The 1H-1,2,3-triazol-1-ol (Z = OH) is obtained in 53% yield by reaction of 1 with an excess of hydroxylamine (EtOH/H₂O 1:1, 80 °C, 5 h). The method described by Wolff can be extended to α-diazo-β-oxo esters with bulky substituents. For example, the 5-(1-adamantyl)-1H-1,2,3-triazoles 5 are prepared by the reaction of the diazo compound 4 with aniline and methylamine, respectively (Scheme 7). In this case titanium(IV) chloride is used as catalyst to promote the formation of the intermediate imine and thus facilitate the formation of the triazole.

**Scheme 7** Reaction of Ethyl 3-(1-Adamantyl)-2-diazo-3-oxopropanoate with Amines

Ethyl 5-(1-Adamantyl)-1-phenyl-1H-1,2,3-triazole-4-carboxylate (5, R¹ = Ph); Typical Procedure

A soln of 4 (28 mg, 0.1 mmol), PhNH₂ (13 mg, 0.14 mmol), and TiCl₄ (19 mg, 0.1 mmol) in dry 1,2-dichloroethane (2 mL) was refluxed for 15 h, and the resulting mixture was basified with 1 M NaOH (1 mL). After adding Et₂O/H₂O (1:1, 10 mL) and shaking, the organic layer was separated, washed with H₂O and dried (Na₂SO₄). Evaporation of the solvent left a residue, which was chromatographed to give 5 (R¹ = Ph) as crystals; yield: 26 mg (74%); mp 134–138 °C.

**Variation 1:** From 2-Diazo-3-oxopropanoates and Amin Derivatives

Ethyl 2-diazo-3-oxopropanoate (6) reacts with a range of amine derivatives to give the corresponding triazoles 7 (R¹ = H, alkyl, aryl, OH, NHPh, NHCONH₂) (Scheme 8). The yields of the reactions are highly dependent on the amine derivative used. The reaction of compound 6 with 2-aminoethanol gives triazole 7 (R¹ = CH₂CH₂OH), which is used as precursor to several 1,2,3-triazole-containing antibiotics.
Scheme 8  Reaction of Ethyl 2-Diazo-3-oxopropanoate with Amine Derivatives[26–28]

<table>
<thead>
<tr>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;NH&lt;sub&gt;2&lt;/sub&gt;</th>
<th>Conditions</th>
<th>Yield (%)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>NH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>AcOH, 100°C, 3–4 h</td>
<td>50</td>
<td>[27]</td>
</tr>
<tr>
<td>H</td>
<td>NH&lt;sub&gt;2&lt;/sub&gt;OH</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;O, rt, 48 h</td>
<td>7</td>
<td>[27]</td>
</tr>
<tr>
<td>NHCONH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;NHCONH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;O, rt, 48 h</td>
<td>35</td>
<td>[27]</td>
</tr>
<tr>
<td>Ph</td>
<td>PhNH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>EtOH, AcOH, rt, 30 min</td>
<td>74</td>
<td>[26]</td>
</tr>
<tr>
<td>Ph</td>
<td>PhNH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>EtOH, AcOH, rt, 16 h</td>
<td>70</td>
<td>[26]</td>
</tr>
<tr>
<td>Bu&lt;sub&gt;i&lt;/sub&gt;</td>
<td>Bu&lt;sub&gt;i&lt;/sub&gt;N</td>
<td>EtOH, AcOH, rt, 16 h</td>
<td>81</td>
<td>[26]</td>
</tr>
</tbody>
</table>

Ethyl 1-Phenyl-1H-1,2,3-triazole-4-carboxylate (7, R<sup>1</sup> = Ph): Typical Procedure:[28]
Ethyl 2-diazo-3-oxopropanoate (6; 0.426 g, 3 mmol) was dissolved in EtOH (3 mL). A soln of PhNH<sub>2</sub> (0.27 g, 2.9 mmol) in EtOH (1.8 mL) and AcOH (0.6 mL) was added and the mixture was stirred at rt for 16 h. On removal of the solvent a solid was obtained, and crystallization (EtOH) gave white needles of the triazole 7 (R<sup>1</sup> = Ph); yield: 0.45 g (70%); mp 86–87°C.

13.13.1.1.1.2 Variation 2: From 2-Diazo-3-oxoaldehydes and Amine Derivatives

2-Diazo-3-oxoaldehydes 8 react with anilines, hydroxylamine, or semicarbazide yielding 4-acyl-1-substituted 1H-1,2,3-triazoles 9 in moderate to good yields (Scheme 9).[26,27] They also react with ammonia to give N-unsubstituted 1,2,3-triazoles in 20–26% yield. In the condensations with hydroxylamine and semicarbazide the reaction goes further and the ketone functions are converted into oximes and semicarbazones, respectively.[27] A newer method for the preparation of a wide range of the required 2-diazo-3-oxoaldehydes has been published.[31] Diazomalonaldehyde (8, R<sup>1</sup> = H) reacts with aniline hydrochloride, in water and at room temperature to yield 1-phenyl-1H-1,2,3-triazole-4-carbaldehyde (9, R<sup>1</sup> = H; R<sup>2</sup> = Ph) in 96% yield.[32]
Condensation of 2-Diazo-3-oxoaldehydes with Aniline; General Procedure\(^{[27]}\)

A soln of the 2-diazo-3-oxoaldehyde \(8\) (10 mmol) in EtOH (6 mL) and a mixture of \(\text{PhNH}_2\) (10.7 mmol) and \(\text{AcOH}\) (1.25 mL) were mixed. The mixture was stirred at rt for 30 min. In most cases during this time the triazoles precipitated and were obtained pure after recrystallization (EtOH). The yields were within the range of 26–87%.

**Variation 3:**

**From Dimethyl Diazomalonate and Amines**

Dimethyl diazomalonate (10) undergoes reaction with primary alkylamines to generate the corresponding primary ammonium salts of methyl 1-alkyl-5-hydroxy-1-\(\text{H}\)-1,2,3-triazole-4-carboxylates 12 in 66–98% yield (Scheme 10).\(^{[33]}\) The probable mechanism of this reaction involves the formation of the intermediate diazoamide 11, which then undergoes base-catalyzed cyclization to the 1,2,3-triazole salt 12. Acidification of an aqueous solution of 12 and extraction with dichloromethane gives the free triazolols. However, since triazol-5-ols undergo facile isomerization to the corresponding diazoamides, care must be taken during their formation and purification. The major limitation of this reaction is the fact that aromatic amines, e.g. aniline, fail to react. This is consistent with the reduced nucleophilicity of the nitrogen in aromatic amines.\(^{[33]}\)

### Scheme 10 Reaction of Dimethyl Diazomalonate with Amines\(^{[33]}\)

<table>
<thead>
<tr>
<th>R(^1)</th>
<th>Amine</th>
<th>Time (d)</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bu</td>
<td>(\text{BuNH}_2)</td>
<td>3</td>
<td>82</td>
<td>111–113</td>
<td>[33]</td>
</tr>
<tr>
<td>((\text{CH}_2)_)(_2)Me</td>
<td>Me((\text{CH}_2))_2\text{NH}_2</td>
<td>5</td>
<td>85</td>
<td>110–113</td>
<td>[33]</td>
</tr>
<tr>
<td>((\text{CH}_2)_)(_2)Me</td>
<td>Me((\text{CH}_2))_2\text{NH}_2</td>
<td>3</td>
<td>70</td>
<td>120–122</td>
<td>[33]</td>
</tr>
<tr>
<td>Cy</td>
<td>(\text{CyNH}_2)</td>
<td>3</td>
<td>66</td>
<td>154–157</td>
<td>[33]</td>
</tr>
<tr>
<td>((\text{CH}_2)_)(_3)OH</td>
<td>HO((\text{CH}_2))_3\text{NH}_2</td>
<td>3</td>
<td>98</td>
<td>119–124</td>
<td>[33]</td>
</tr>
<tr>
<td>Bn</td>
<td>(\text{BnNH}_2)</td>
<td>3</td>
<td>84</td>
<td>153–156</td>
<td>[33]</td>
</tr>
<tr>
<td>2-thienyl</td>
<td>2-thienylamine</td>
<td>3</td>
<td>67</td>
<td>160–161</td>
<td>[33]</td>
</tr>
<tr>
<td>3-thienyl</td>
<td>3-thienylamine</td>
<td>6</td>
<td>72</td>
<td>160–162</td>
<td>[33]</td>
</tr>
</tbody>
</table>

**1,2,3-Triazole Salts 12; General Procedure\(^{[33]}\)**

Dimethyl diazomalonate (10 mmol) was added to a large excess of the amine and the mixture was stirred at rt and monitored by IR spectroscopy until the diazo ester was completely consumed (3–6 d). At this point the resultant salt had crystallized from soln and was isolated by filtration and recrystallized. Alternatively, the reaction could be performed in toluene using 2–5 equiv of amine; yield: 66–98%.

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Method 2: From Vinyldiazonium Salts and Amine Derivatives

Vinyldiazonium salts 13 react with ammonia and amine derivatives (primary amines, hydrazines, hydroxylamine ethers) to give 1-substituted 1,2,3-triazoles 14 (Scheme 11). [34–36]

A probable mechanism for this reaction is represented in Scheme 11. [36] The reaction of vinyldiazonium salts 13 with $\omega,\omega'$-diaminoalkanes leads to $\omega,\omega'$-bis(1H-1,2,3-triazol-1-yl)alkanes. [37]

Scheme 11 Reaction of Vinyldiazonium Salts with Amine Derivatives [36]

<table>
<thead>
<tr>
<th>$R^1$</th>
<th>$R^2$</th>
<th>$R^3$</th>
<th>$X$</th>
<th>$R^4$</th>
<th>$R^5$</th>
<th>Yield (%)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>OEt</td>
<td>OEt</td>
<td>SbCl₆</td>
<td>H</td>
<td>OEt</td>
<td>65</td>
<td>[36]</td>
</tr>
<tr>
<td>H</td>
<td>OEt</td>
<td>OEt</td>
<td>SbCl₆</td>
<td>3-morpholinopropyl</td>
<td>OEt</td>
<td>54</td>
<td>[36]</td>
</tr>
<tr>
<td>H</td>
<td>OEt</td>
<td>OEt</td>
<td>SbCl₆</td>
<td>Cy</td>
<td>OEt</td>
<td>62</td>
<td>[36]</td>
</tr>
<tr>
<td>H</td>
<td>OMe</td>
<td>4-MeOC₆H₄</td>
<td>SbCl₆</td>
<td>furfuryl</td>
<td>4-MeOC₆H₄</td>
<td>63</td>
<td>[36]</td>
</tr>
<tr>
<td>4-O₂NC₆H₄</td>
<td>OEt</td>
<td>piperidino</td>
<td>SbCl₆</td>
<td>H</td>
<td>piperidino</td>
<td>48</td>
<td>[36]</td>
</tr>
<tr>
<td>4-O₂NC₆H₄</td>
<td>OEt</td>
<td>piperidino</td>
<td>SbCl₆</td>
<td>furfuryl</td>
<td>piperidino</td>
<td>80</td>
<td>[36]</td>
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<tr>
<td>4-O₂NC₆H₄</td>
<td>OEt</td>
<td>piperidino</td>
<td>SbCl₆</td>
<td>3-morpholinopropyl</td>
<td>piperidino</td>
<td>65</td>
<td>[36]</td>
</tr>
<tr>
<td>4-O₂NC₆H₄</td>
<td>OEt</td>
<td>piperidino</td>
<td>BF₄⁻</td>
<td>4-MeOC₆H₄</td>
<td>OEt</td>
<td>51</td>
<td>[36]</td>
</tr>
<tr>
<td>4-O₂NC₆H₄</td>
<td>OEt</td>
<td>piperidino</td>
<td>BF₄⁻</td>
<td>NH₂</td>
<td>OEt</td>
<td>24</td>
<td>[36]</td>
</tr>
</tbody>
</table>

2-(Benzoyloxy)alk-1-enediazonium trifluoromethanesulfonates 17 [generated in situ from the reaction of $\alpha$-diazo ketones 15 and benzoyl trifluoromethanesulfonate (16)] react with isopropylamine to give the corresponding 1-isopropyl-1H-1,2,3-triazoles 18 in high yields (Scheme 12). [38]
1-Isopropyl-4,5-dimethyl-1H-1,2,3-triazole (18, R1 = Me); Typical Procedure:[38]

A soln of benzoyl trifluoromethanesulfonate (5.20 g, 20.4 mmol) in CH2Cl2 (50 mL) was cooled to −70°C and a soln of 15 (R1 = Me; 2.00 g, 20.4 mmol) in CH2Cl2 (50 mL) was added dropwise. After the addition, the suspension was stirred at −70°C for 1 h and at −50°C for 3 h. iPrNH2 (6.00 g, 102 mmol) was gradually added after cooling to −70°C. A homogeneous soln was formed and after 2 h at rt it was extracted with H2O (4 × 1). The organic layer was dried (MgSO4) and the solvent was removed at 15 Torr. Distillation (90°C/0.05 Torr, Kugelrohr apparatus) gave triazole 18 (R1 = Me); yield: 2.19 g (77%).

13.13.1.1.3 Method 3: From Dichloro- or Trichloroacetaldehyde Sulfonylhydrazones and Primary Amines

Tosyl and mesyl hydrazones of dichloroacetaldehyde and trichloroacetaldehyde react with ammonia and primary amines to produce 1H-1,2,3-triazoles 20 and 22, respectively, in good yields (Scheme 13).[39,40] This is a much more convenient and secure reaction system, especially for large-scale production of triazoles, than some alternative methods where thermally unstable, or explosive, starting materials are used, namely diazo and azido derivatives. For example, 1H-1,2,3-triazole itself can be prepared in 75% yield from the reaction of dichloroacetaldehyde tosylhydrazone (19, X = Ts) with ammonia.[40] The same hydrazone can be converted into 1-benzyl-1H-1,2,3-triazole, 1-phenyl-1H-1,2,3-triazole, or 1H-1,2,3-triazol-1-amine in similar yields. These triazoles can also be prepared from the mesylhydrazone 19 (X = Ms) in almost the same yields (60–85%). When trichloroacetaldehyde tosylhydrazone (21) is treated with aqueous ammonia only unidentified materials are obtained, but the reaction with methylamine or benzylamine gives the 1,5-disubstituted triazoles 22.[39]

Scheme 12 Reaction of 2-(Benzoyloxy)alk-1-enediazonium Trifluoromethanesulfonates with Isopropylamine[38]

Scheme 13 Reaction of Dichloro- or Trichloroacetaldehyde Sulfonylhydrazones with Ammonia and Primary Amines[39,40]
\( \alpha, \alpha \)-Dichloro ketone tosylhydrazones can also be used as precursors of \( 1^H \)-1,2,3-triazoles. For example, 1,1-dichloroacetone tosylhydrazone (23) is converted into 1-benzyl- and 1-allyl-4-methyl-\( 1^H \)-1,2,3-triazoles 24 in good yields (Scheme 14).[39] Also, an attempted synthesis of tosylhydrazone 26 from 2,2-dichloro-1-phenylethanone 25 gives the triazole directly 27.[39]

**Scheme 14** Reaction of \( \alpha, \alpha \)-Dichloro Ketone Tosylhydrazones with Primary Amines[39]

\( 1^H \)-1,2,3-Triazole (20, \( R_1 = H \)); Typical Procedure[40]

To a soln of \( \text{NH}_3/\text{H}_2\text{O} \) (8.9 g, 523 mmol) in MeOH (40 mL) under ice-cooling was added slowly dichloroacetaldehyde tosylhydrazone (19, \( X = \text{Ts} \); 4.4 g, 15.7 mmol) in MeOH (60 mL). The mixture was stirred at 22°C for 9 h and then it was filtered to remove \( \text{NH}_4\text{Cl} \). The filtrate was concentrated and chromatographed (silica gel, EtOAc/hexane 1:1) to give \( 1^H \)-1,2,3-triazole as a colorless oil; yield: 0.81 g (75%); bp 208–210°C.

**13.13.1.1.2** Fragments \( \text{C—C—N} \) and \( \text{N—N} \)

**13.13.1.1.2.1** Method 1:

From Enaminones and Diazotransfer Reagents

Enaminones react with a range of diazo transfer reagents to give \( 1^H \)-1,2,3-triazoles. 3-Diazo-1,3-dihydro-\( 2^H \)-indol-2-one derivatives and sulfonyl azides are particularly useful in these reactions.

**13.13.1.1.2.1.1** Variation 1:

From Enaminones and 3-Diazo-1,3-dihydro-\( 2^H \)-indol-2-one Derivatives

\( \beta \)-Amino-\( \alpha \)-unsaturated ketones (enamino ketones) 28 (\( R^2 = \text{Me} \)) and \( \beta \)-amino-\( \alpha \)-unsaturated esters (enamino esters) 28 (\( R^2 = \text{OEt} \)) react with 3-diazo-1,3-dihydro-\( 2^H \)-indol-2-one derivatives to give \( 1^H \)-1,2,3-triazoles of type 30 in good to excellent yields (Scheme 15).[41,42] Various 3-diazo-1,3-dihydro-\( 2^H \)-indol-2-ones can be used but the best results are obtained with the nitro derivatives 29 and 31.[41] When cyclic enaminoles 33 or 34 are used, carbocyclic fused 1,2,3-triazoles of types 33 and 35 are obtained in good yields (49–
83\%).\[^{42}\] The 3-diazobenzo[b]thiophen-2-one also reacts with enaminones to give 1,2,3-triazoles.\[^{41}\] In these reactions, compounds 29, 31, and 3-diazobenzo[b]thiophen-2-one act as diazo transfer reagents; a probable mechanism has been described.\[^{41}\]

**Scheme 15** Reaction of Enaminones with 3-Diazo-1,3-dihydro-2H-indol-2-ones\[^{41,42}\]

\[
\begin{align*}
28 & \quad + \quad 29 & \quad \rightarrow \quad 30 \\
28 & \quad + \quad 31 & \quad \rightarrow \quad 30 \\
32 & \quad + \quad 29 & \quad \rightarrow \quad 33 \\
34 & \quad + \quad 29 & \quad \rightarrow \quad 35
\end{align*}
\]

**Reaction of Enaminones with 3-Diazo-1,3-dihydro-2H-indol-2-ones; General Procedure**\[^{41}\]

A mixture of the diazocarbonyl compound (1 mmol) and the enaminone (1 mmol) in dry toluene (30 mL) was refluxed until the disappearance of the $N_2$ absorption band at 2100 cm$^{-1}$ in the IR spectrum. The solvent was evaporated and the residue was submitted to column chromatography (Florisil, hexane/CH$_2$Cl$_2$/MeOH mixtures). The products were further purified by preparative TLC (silica gel, CHCl$_3$/MeOH 100:1).

for references see p 587
13.13.1.2.1.2 Variation 2: From Enaminones and Sulfonyl Azides
Mesyl and tosyl azides can act as diazo transfer reagents to enaminones yielding triazoles 36 in good yields (Scheme 16).[43] For this purpose, mesyl azide is a much better reagent than tosyl azide (yields of 20–97% and 2–50%, respectively). The reaction works better with N-alkyl-substituted enaminones (72–97%) than N-aryl-substituted enaminones (20–37%).

Scheme 16 Reaction of Enaminones with Sulfonyl Azides[43]

Reaction of Enaminones with Sulfonyl Azides; General Procedure:[43]
To a stirred mixture of NaH (6.67 mmol; free of oil) in anhyd MeCN (4 mL), under N₂ at rt, was added a soln of the enaminone (1.85 mmol) in anhyd MeCN (4 mL). The stirring was continued for 30 min, followed by dropwise addition of mesyl azide (5 mmol) in anhyd MeCN (1 mL). Stirring was maintained for 24 h and the reaction was quenched with NaOH soln (10%). The separated organic layer was dried (MgSO₄) and the solvent was removed under reduced pressure to give a residue that was extracted with CH₂Cl₂ (3 × 10 mL). The crude 1,2,3-triazoles were purified by column chromatography (silica gel, hexane/EtOAc 9:1).

13.13.1.2 By Formation of One N—N and One C—C Bond
13.13.1.2.1 Fragments C—N—N and C—N
13.13.1.2.1.1 Method 1: From Diazooalkanes and Nitriles
Diazooalkanes react with activated nitriles such as cyanogen, cyanogen halides, methyl cyanoformate, aryl cyanates, sulfonyl cyanides, and others to give 1,2,3-triazoles (Scheme 17). These reactions can formally be regarded as 1,3-dipolar cycloadditions.[3] If an excess of diazooalkane is used the triazoles may be N-alkylated; generally mixtures of the three possible N-alkyl-1,2,3-triazoles are obtained. For example, cyanogen bromide reacts with excess diazomethane to give a mixture of the 4-bromo-2-methyl-2H-1,2,3-triazole (21%), 5-bromo-1-methyl-1H-1,2,3-triazole (6.4%), and 4-bromo-1-methyl-1H-1,2,3-triazole (5.5%).[44] Tosyl cyanide reacts with 1 equivalent of diazomethane to afford 4-tosyl-1H-1,2,3-triazole (37, R¹ = H; X = Ts) in 68% yield. With excess diazomethane it gives a mixture (95%) of the three isomeric N-monomethylated triazoles 38 (R¹ = H; X = Ts).[45] Similarly, 4-oxo-4H-1-benzopyran-2-carbonitriles react with diazomethane to yield mixtures of three isomeric N-methyl-1,2,3-triazoles.[46]
The importance of the nature of electron-withdrawing groups in nitriles with respect to their reactivity toward diazomethane is demonstrated by the relative yields of \(N\)-methyltriazoles \(39-41\) given in Table 1.\(^{47}\) For example, 1-methyl-1H-imidazole-4,5-dicarbonitrile reacts with diazomethane only at the 5-cyano group.

### Table 1 Examples of \(N\)-Methyltriazoles Obtained by Reaction of Diazomethane with Activated Nitriles\(^{47}\)

<table>
<thead>
<tr>
<th>(R^1)</th>
<th>39</th>
<th>40</th>
<th>41</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCl(_3)</td>
<td>88.6</td>
<td>9.8</td>
<td>1.6</td>
<td>(^{47})</td>
</tr>
<tr>
<td>CO(_2)(<em>2)(</em>\text{Et})</td>
<td>23.6</td>
<td>74.8</td>
<td>1.6</td>
<td>(^{47})</td>
</tr>
<tr>
<td>Bz</td>
<td>62.2</td>
<td>34.5</td>
<td>3.3</td>
<td>(^{47})</td>
</tr>
<tr>
<td></td>
<td>91.5</td>
<td>3.1</td>
<td>5.4</td>
<td>(^{47})</td>
</tr>
<tr>
<td></td>
<td>55.7</td>
<td>42.2</td>
<td>2.1</td>
<td>(^{47})</td>
</tr>
</tbody>
</table>

Diazomethane also undergoes addition to the C=N bond of chloro(fluoroimino)acetonitrile \(42\) to yield triazole \(43\) (Scheme 18). Two equivalents of diazomethane are consumed in this reaction; the insertion of a methylene group is observed in the final product.\(^{48}\)
Reaction of Activated Nitriles with Diazomethane; General Procedure:

**CAUTION:** Diazomethane is explosive by shock, friction, or heat, and is highly toxic by inhalation.

A soln of CH₂N₂ (0.13 mol) in Et₂O (600 mL) was added to the nitrile (0.02 mol). The reaction was monitored by TLC until the nitrile was completely consumed (several days). The solvent was evaporated and the residue was submitted to column chromatography (silica gel). The isomeric N-methyltriazoles were separated using appropriate eluents.

### Variation 1:
**From Diazoalkanes and Aryl Cyanates**

Aryl cyanates 44 react with diazoalkanes in a 2:1 proportion to yield the aryl 4-(aryloxy)-1H-1,2,3-triazole-1-carboximidates 45 (44–83%), which after hydrolysis give the corresponding N-unsubstituted triazoles 46 (Scheme 19). [49]

![Scheme 19](image)

Ar¹ = Ph, 4-Tol, 4-MeOC₆H₄, 4-ClC₆H₄; R¹ = H, CO₂Et

### Variation 2:
**From Diazoalkanes and Unactivated Nitriles**

Unactivated nitriles generally do not react with diazomethane or other diazoalkanes, however, reaction can occur in the presence of a catalyst. Aluminum trichloride, triethylaluminum, and other aluminum complexes can be used as catalysts in the reaction of diazomethane with benzonitrile. [50] Aryldiazomethanes also react with benzonitriles in the presence of potassium tert-butoxide (molar ratio 1:1:1), in toluene, to give 4,5-diaryl-1H-1,2,3-triazoles, mostly in good to satisfactory yields (26–75%). [51] A plausible mechanism for this reaction is shown in Scheme 20. The reaction can be carried out at room temperature or in refluxing toluene.
Scheme 20  Synthesis of 4,5-Diaryl-1H-1,2,3-triazoles by Reaction of Aryldiazomethanes with Benzonitriles in the Presence of Potassium tert-Butoxide\textsuperscript{[51]}

\[
\text{Ar}^1\text{CN} + \text{Ar}^2\text{CHN}_2 \rightarrow H_{\text{BuOK}} \rightarrow H_{\text{BuOK}} + \text{H}_2\text{O}^* \\
\begin{array}{c}
\text{Ar}^1\text{N} \text{N} \text{N} \\
\text{Ar}^2 \text{N} \text{N} \text{H} \\
47
\end{array}
\]

<table>
<thead>
<tr>
<th>Ar\textsuperscript{1}</th>
<th>Ar\textsuperscript{2}</th>
<th>Conditions</th>
<th>Yield (%)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>rt, 24 h</td>
<td>69</td>
<td>[51]</td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>110,°C, 2 h</td>
<td>75</td>
<td>[51]</td>
</tr>
<tr>
<td>4-ClC\textsubscript{6}H\textsubscript{4}</td>
<td>4-ClC\textsubscript{6}H\textsubscript{4}</td>
<td>110,°C, 2 h</td>
<td>70</td>
<td>[51]</td>
</tr>
<tr>
<td>4-ClC\textsubscript{6}H\textsubscript{4}</td>
<td>Ph</td>
<td>110,°C, 2 h</td>
<td>44</td>
<td>[51]</td>
</tr>
<tr>
<td>4-BrC\textsubscript{6}H\textsubscript{4}</td>
<td>Ph</td>
<td>rt, 24 h</td>
<td>66</td>
<td>[51]</td>
</tr>
<tr>
<td>4-Tol</td>
<td>Ph</td>
<td>110,°C, 2 h</td>
<td>26</td>
<td>[51]</td>
</tr>
</tbody>
</table>

13.13.1.2.1.1.3 Variation 3: From [Diazo(trimethylsilyl)methyl]lithium and Nitriles

\text{[Diazo(trimethylsilyl)methyl]lithium (48)} \text{generated in situ from the reaction of diazo(trimethylsilyl)methane and butyllithium} reacts smoothly with nitriles to give 4-substituted 5-(trimethylsilyl)-1,2,3-triazoles 49 in excellent yields (Scheme 21).\textsuperscript{[52,53]} Various nitriles, including aromatic, heteroaromatic, and aliphatic nitriles, react efficiently with 48 to give 4-(trimethylsilyl)triazoles 49. Since treatment of diazo(trimethylsilyl)methane with butyllithium followed by protonation gives 4,5-bis(trimethylsilyl)-1H-1,2,3-triazole,\textsuperscript{[54]} the generation of 48 needs to be carefully controlled.

Scheme 21  Reaction of Nitriles with [Diazo(trimethylsilyl)methyl]lithium\textsuperscript{[52,53]}

\[
\text{R}^1\text{CN} + \text{TMSLi} \rightarrow \text{H}_2\text{O}, 0\,°\text{C}, 3\,h \\
\begin{array}{c}
\text{TMS} \text{N} \text{N} \text{N} \\
\text{R}^1 \text{N} \text{N} \text{H} \\
49
\end{array}
\]

\text{R}^1 = \text{Pr, } 1\text{-Bu, } \text{Br, } 3,7\text{-dimethylocta-2,6-dienyl, Ph, } 1\text{-naphthyl, } 2\text{-pyridyl, } 1\text{-isoquinolyl, SEt, OPh, PO(OEt)}_2, \text{TMS}

Triazoles 49; General Procedure\textsuperscript{[52]}

15% BuLi in hexane (0.76 mL, 1.2 mmol) was added dropwise to a soln of TMSCHN\textsubscript{2} (0.55 mL, 1.2 mmol) in Et\textsubscript{2}O (10 mL) at 0\,°C under argon and the mixture was stirred for 20 min at 0\,°C. To the resulting soln was added dropwise a soln of a nitrile (1 mmol) in Et\textsubscript{2}O (3 mL) at 0\,°C, then the mixture was stirred at 0\,°C for 3 h. The mixture was treated with sat. aq NH\textsubscript{4}Cl and extracted with Et\textsubscript{2}O. The Et\textsubscript{2}O extracts were washed with H\textsubscript{2}O and dried (MgSO\textsubscript{4}). Concentration of the solvent gave a residue, which was purified by preparative layer chromatography to give the triazole.

\textit{for references see p 587}
13.13.1.2.1.2 **Method 2:**
*From Diazoalkanes and Imines, Oximes, or Diarylazines*

The 1,3-dipolar cycloaddition of diazoalkanes to \(\text{C}=\text{N}\) bonds is a general method for the synthesis of 4,5-dihydro-1\(\text{H}\)-1,2,3-triazoles and 1\(\text{H}\)-1,2,3-triazoles (Scheme 22).\[^4\] It is an especially useful method for the regioselective preparation of 1\(\text{H}\)-1,2,3-triazoles with bulky substituents in positions 1 and 5. Imines are the most versatile \(\text{C}=\text{N}\) system to be used in this method, but oximes and diarylazines can also be used.

![Scheme 22](image)

4,5-Dihydro-1\(\text{H}\)-1,2,3-triazoles 51 are the expected products from the cycloaddition reaction of imines 50 with diazoalkanes but in some cases they spontaneously aromatize to the corresponding triazoles. When the 4,5-dihydro-1\(\text{H}\)-1,2,3-triazoles are the isolated products they can be converted into triazoles by a large number of alternative procedures (see Section 13.13.1.3).

The addition of diazoalkanes (especially diazomethane) to imines, to give 4,5-dihydro-1\(\text{H}\)-1,2,3-triazoles 51, is very well studied.\[^6\] In general it is favored by the presence of electron-withdrawing substituents in the imine, especially on an \(\text{N}\)-aryl moiety.\[^55,56\] Though kinetic investigations of this reaction show that it follows essentially a concerted process and is not generally dependent on solvent polarity, a sizable increase in rate is noticed in the presence of protic solvents such as water or alcohols.\[^57\] For example, while reaction of diazomethane with \(\text{N}\)-benzylideneaniline (52, \(\text{Ar}^1 = \text{Ar}^2 = \text{Ph}\)) does not occur in dry ether, it does occur in aqueous dioxane giving the 4,5-dihydro-1\(\text{H}\)-1,2,3-triazole 53 (\(\text{Ar}^1 = \text{Ar}^2 = \text{Ph}\)) in 53\% after eight days (Scheme 23).\[^55\] This solvent system can be successfully used for the preparation of 5-hetaryl-substituted 4,5-dihydro-1\(\text{H}\)-1,2,3-triazoles of type 53 (\(\text{Ar}^1 = 2\text{- or } 3\text{-pyridyl, } 2\text{-quinolyl}\)).\[^58,59\] Triethylaluminum and other aluminum complexes have been used as catalysts in the reaction of diazomethane with imines.\[^50\]

![Scheme 23](image)

Diazomethane undergoes addition to hexafluoroacetone imines 54 to give 4,5-dihydro-1\(\text{H}\)-1,2,3-triazoles 55 as the sole product or to give mixtures of 4,5-dihydro-1\(\text{H}\)-1,2,3-triazoles 55 and 56 (the latter produced as a result of the addition of diazomethane to the \(\text{C}=\text{C}\) bond) (Scheme 24).\[^60\]
Scheme 24  Addition of Diazomethane to Hexafluoroacetone Imines

![Chemical structure](image)

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>Yield (%)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Me</td>
<td>91</td>
<td>[60]</td>
</tr>
<tr>
<td>Ph</td>
<td>H</td>
<td>88</td>
<td>[60]</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>30</td>
<td>32</td>
</tr>
<tr>
<td>iPr</td>
<td>H</td>
<td>42</td>
<td>51</td>
</tr>
</tbody>
</table>

Diazomethanes of the types $\text{57}$, $\text{58}$, and $\text{59}$ react with formimidamides $\text{60}$ to give directly the corresponding triazoles $\text{61}$ in 11–62% yields (Scheme 25).

Scheme 25  Addition of Substituted Diazomethanes to Formimidamides

![Chemical structure](image)

Variation 2:  From Diazoalkanes and Oximes

Diazomethane undergoes addition to oximes to give 4,5-dihydro-1H-1,2,3-triazoles. The O-methyl oxime $\text{62}$ reacts with diazomethane to yield the unstable 4,5-dihydro-1H-1,2,3-triazole $\text{63}$ (87%) that on treatment with piperidine gives the triazole $\text{64}$ in 50% yield (Scheme 26).

for references see p 587
13.13.1.2.1.3 Variation 3: From Diazoalkanes and Diarylazines

Aromatic aldehyde azines 65 react with aryl diazomethanes in the presence of potassium tert-butoxide to give N-unsubstituted 4,5-diaryl-1H-1,2,3-triazoles 66 (Scheme 27).[51] The scope of this method has yet to be demonstrated since only two symmetrical triazoles 66 are prepared by this way. The mechanism of this reaction seems to involve one 1,3-dipolar cycloaddition followed by base elimination of an aromatic imide anion. However it should be noted that even in the absence of the aryl diazomethanes, the aromatic aldehyde azines (DMSO, rt) in the presence of potassium tert-butoxide (1 equiv), give the same 4,5-diaryl-1H-1,2,3-triazoles, although in much lower yields.[51]

13.13.1.2.1.3 Method 3: From Diazoalkanes and Heterocumulenes

The reaction of diazoalkanes (or their organometallic derivatives) with heterocumulenes is a versatile method for the synthesis of 1H-1,2,3-triazoles. The reactions with ketenimines, carbodiimides, isocyanates, and isothiocyanates are performed under very mild conditions and generally they give the desired triazoles in moderate to excellent yields.
Variation 1: From Diazoalkanes and Ketenimines

Diazomethane reacts with ketenimines 67 (rt, 4 d) to give triazoles of type 68 in moderate yields (Scheme 28). Other diazoalkanes fail to react with ketenimines 67 to give the corresponding 1,2,3-triazoles. 

Scheme 28 Reaction of Ketenimines with Diazomethane

\[
\begin{array}{cccc}
 & \text{Ph} & \equiv & \equiv \text{NAr}^1 \quad + \quad \text{CH}_2\text{N}_2 \quad \xrightarrow{\text{Et}_2\text{O, rt, 4 d}} \quad \begin{array}{c}
\text{Ph} \\
\equiv \equiv \text{NAr}^1
\end{array} \\
\text{Ar}^1 \quad = \quad \text{Ph, 4-Tol, 4-ClC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4
\end{array}
\]

Better yields of triazoles are obtained if [diazo(trimethylsilyl)methyl]lithium (48) is used (Scheme 29). For example, alkyl and aryl ketenimines 69, \((R_1 = R_2 = X = \text{alkyl, aryl})\) react smoothly with 48 [prepared from diazo(trimethylsilyl)methane and butyllithium] to give 4-(trimethylsilyl)-1,2,3-triazoles 71 in good yields. Since desilylation of 71 is readily achieved in almost quantitative yields (10% aq KOH/MeOH, reflux, 6 h), reagent 48 can be used, with better results, as a diazomethane equivalent.

The reaction of 48 with ketenimines bearing electron-withdrawing groups (69, \(X = \text{EWG}\)) also gives 1,2,3-triazoles but in some cases only pyrazoles are obtained: it can give either 1\(H\)-1,2,3-triazoles 71 or pyrazoles 72 as the sole product or mixtures of these compounds (Scheme 29). The nature and the yields of the products change with the solvent used in the reaction. The betaines 70 are likely to be intermediates in these reactions: the triazoles are formed by the attack of the nitrogen anion on the diazonium nitrogen.

Scheme 29 Reaction of Ketenimines with [Diazo(trimethylsilyl)methyl]lithium

\[
\begin{array}{cccc}
 & \equiv \equiv \text{NAr}^1 \quad + \quad \equiv \equiv \text{NR}^2 \quad \xrightarrow{\text{Et}_2\text{O, 0\,^\circ\,C, 2 h}} \quad \begin{array}{c}
\equiv \equiv \text{NAr}^1 \\
\equiv \equiv \text{NR}^2
\end{array} \\
\text{Ar}^1 \quad = \quad \text{Ph, 4-Tol, 4-ClC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4
\end{array}
\]

\(Z = X, H\)

for references see p 587
Reaction of Ketenimines with [Diazotrimethylsilylmethyl]lithium;

**General Procedure:**

To 1.87 M TMSCHN₂ in hexane (0.64 mL, 1.2 mmol) in Et₂O (10 mL) was added, dropwise 15% BuLi in hexane (0.76 mL, 1.2 mmol) at 0°C under argon. The mixture was stirred at this temperature for 20 min. A soln of an alkyl or aryl ketenimine (1 mmol) in Et₂O (2 mL) was then added dropwise at 0°C. The mixture was stirred at 0°C for 2 h. After addition of cold H₂O, the mixture was extracted with benzene (CAUTION: carcinogen). The organic layer was washed with H₂O, dried (MgSO₄), and concentrated in vacuo. The residue was purified by column chromatography (silica gel) to give triazoles 71.

### Variation 2:

**From Diazoalkanes and Carbodiimides**

Carbodiimides 73 react with diazoalkanes to give 1H-1,2,3-triazoles 74 (Scheme 30). For example, reaction of diazomethane with di(1- or 2-naphthyl)carbodiimides [67] or with bis(4-X-phenyl)carbodiimides (X = H, NMe₂, OMe, Me, Cl, Br, Ac) gives triazoles 74 (R¹ = H) in low to moderate yields [63,68,69].

**Scheme 30** Reaction of Carbodiimides with Diazoalkanes [63,67–69]

Organometallic diazomethanes also react with carbodiimides to form 1,2,3-triazoles, for example diazotrimethylsilylmethane and diazobis(trimethylstannyl)methane give, respectively, compounds 75 (19%) and 76 (96%) by reaction with 73 (Ar¹ = 4-Tol) (Scheme 31).[68]
Reaction of Carbodiimides with Diazomethane; General Procedure

**CAUTION:** Diazomethane is explosive by shock, friction, or heat, and is highly toxic by inhalation.

A freshly prepared ethereal soln of \( \text{CH}_2\text{N}_2 \) (12 mmol) was added to the carbodiimide (10 mmol) dissolved in a sufficient quantity of Et\(_2\)O. The mixture was allowed to stand at rt for 4 d. The separated crystals were collected by filtration and washed with Et\(_2\)O. The triazoles 74 were then recrystallized (MeOH or aq acetone).

### Variation 3:

**From Diazoalkanes and Isocyanates**

Alkyl and aryl isocyanates react with \([\text{diazo(trimethylsilyl)methyl}]\text{lithium}\) (48) to give 1-substituted 1\(H\)-1,2,3-triazol-5-ols 77 in good yields (Scheme 32). Experimental data indicate that these reactions proceed by a stepwise process, not by a concerted 1,3-dipolar cycloaddition process.

**Scheme 32** Reaction of Isocyanates with \([\text{Diazo(trimethylsilyl)methyl}]\text{lithium}\)

<table>
<thead>
<tr>
<th>( \text{R}^1 )</th>
<th>Conditions</th>
<th>Yield (%)</th>
<th>mp ((^\circ)C)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bu</td>
<td>Et(_2)O, –78(^\circ)C, 1.5 h; rt, 3.5 h</td>
<td>63</td>
<td>132–133</td>
<td>[70]</td>
</tr>
<tr>
<td>t-Bu</td>
<td>Et(_2)O, 0(^\circ)C, 1 h; reflux, 6 h</td>
<td>53</td>
<td>126–131 (dec)</td>
<td>[70]</td>
</tr>
<tr>
<td>Cy</td>
<td>Et(_2)O, 0(^\circ)C, 1 h; rt, 1.7 h</td>
<td>71</td>
<td>148</td>
<td>[70]</td>
</tr>
<tr>
<td>Ph</td>
<td>Et(_2)O, 0(^\circ)C, 2 h</td>
<td>79</td>
<td>113–115 (dec)</td>
<td>[70]</td>
</tr>
<tr>
<td>4-ClC(_6)H(_4)</td>
<td>Et(_2)O, 0(^\circ)C, 2 h</td>
<td>83</td>
<td>111 (dec)</td>
<td>[70]</td>
</tr>
<tr>
<td>1-naphthyl</td>
<td>Et(_2)O, 0(^\circ)C, 1 h</td>
<td>83</td>
<td>125 (dec)</td>
<td>[70]</td>
</tr>
</tbody>
</table>
Benzoyl isocyanate reacts with ethyl diazoacetate, in refluxing xylene, to give ethyl 1-benzenzoyl-5-hydroxy-1\textsubscript{H}-1,2,3-triazole-4-carboxylate in 60\% yield (Scheme 33).

**Scheme 33** Reaction of Benzoyl Isocyanate with Ethyl Diazoacetate

\[
\text{BzNCO} + \text{EtO}_2\text{CHN}_2 \xrightarrow{\text{xylene, reflux}} \text{EtO}_2\text{C} \quad 60\%
\]

1-(4-Chlorophenyl)-1\textsubscript{H}-1,2,3-triazole (77, \(R^1 = 4\text{-ClC}_6\text{H}_4\)); Typical Procedure for the Reaction of Isocyanates with [Diazo(trimethylsilyl)methyl]lithium:

To 2 M TMSCHN\(_2\) in hexane (0.6 mL, 1.2 mmol) in Et\(_2\)O (10 mL) was added dropwise, 15\% BuLi in hexane (0.76 mL, 1.2 mmol) at 0\(^\circ\)C under argon. The mixture was stirred at this temperature for 20 min. A soln of 4-chlorophenyl isocyanate (154 mg, 1 mmol) in Et\(_2\)O (3 mL) was then added dropwise at 0\(^\circ\)C. The mixture was stirred at 0\(^\circ\)C for 2 h and ice water was then added. The aqueous layer was separated and the organic phase was extracted with H\(_2\)O. The combined aqueous layer was acidified with 2 M HCl. The resulting white precipitates were collected by filtration, dried in vacuo, and purified by column chromatography (silica gel) to give 77 (\(R^1 = 4\text{-ClC}_6\text{H}_4\)); yield: 162 mg (83\%).

13.13.1.2.1.3.4 Variation 4: From Diazoalkanes and Isothiocyanates

Treatment of isothiocyanates with [diazo(trimethylsilyl)methyl]lithium (48) in tetrahydrofuran, followed by quenching with alkyl halides, gives 1-substituted 5-(alkylsulfanyl)-4-(trimethylsilyl)-1\textsubscript{H}-1,2,3-triazoles 78 in excellent yields (Scheme 34). A dramatic solvent effect is observed in this reaction: changing tetrahydrofuran for diethyl ether leads to the exclusive formation of 1,3,4-thiadiazol-2-amines in good yields. This is in contrast to the results observed with isocyanates (Scheme 32). Removal of the trimethylsilyl group from 78 is readily carried out with 10\% aqueous potassium hydroxide in boiling methanol to give triazoles 79 in almost quantitative yields.
**Reaction of Isothiocyanates with [Diazotrimethylsilylethyl]lithium;**

**General Procedure:**

To a soln of 2 M TMSCHN₂ in hexane (0.6 mL, 1.2 mmol) in THF (10 mL) was added dropwise 15% BuLi in hexane (0.76 mL, 1.2 mmol) at −78°C under argon. The mixture was stirred at this temperature for 20 min. A soln of the isothiocyanate (1 mmol) in THF (3 mL) was then added dropwise at −78°C. After 1 h at −78°C, the alkyl halide (1.2 mmol) was added and the mixture was stirred at −78°C for 1 h, then at 0°C for 2 h. After addition of ice water, the mixture was extracted with benzene (CAUTION: carcinogen). The organic layer was washed with H₂O, dried (MgSO₄), and concentrated in vacuo. The residue was purified by column chromatography (silica gel) to give triazoles 78.

**Method 4:**

**From N-Alkyl-N-nitrosoamines and Nitriles**

Lithium salts of N-alkyl-N-nitrosoamines react with aryl cyanides to form triazoles 80 in 40–70% yield (Scheme 35). The main limitation of this method is the fact that enolizable nitriles cannot be used.

**Scheme 35** Reaction of Lithium Salts of N-Alkyl-N-nitrosoamines with Aryl Cyanides

![Scheme 35](image)

**1-Methyl-4-phenyl-1H-1,2,3-triazole (80, R¹ = Me; R² = H; Ar¹ = Ph). Typical Procedure:**

**CAUTION:** N-Methyl-N-nitrosomethylamine (N,N-dimethylnitrosamine) is a probable human carcinogen and an eye and skin irritant. It is hepatotoxic and an exp. carcinogen and teratogen. All operations should be performed in a well-ventilated fume hood using appropriate safety precautions and procedures.

Pure N-methyl-N-nitrosomethylamine (1.62 mL, 22 mmol) was added with stirring to a soln of LDA (23 mmol) in anhyd THF (70 mL) [from iPr₂NH (3.22 mL) and 1.6 M BuLi in hexane (14.2 mL)] at −78°C and after 10 min the mixture was treated with PhCN (1.03 mL, 10 mmol). The mixture was maintained at the temperature of dry ice for 10 h and the mixture was treated with a soln of glacial AcOH (1.32 mL, 23 mmol) in THF (5 mL). Working up for references see p 587
with \( \text{CH}_2\text{Cl}_2 \) afforded a crystalline crude product that was recrystallized (CCl₄); yield: 1.15 g (72%); mp 122 °C.

13.13.1.3 By Formation of Two N–C Bonds

13.13.1.3.1 Fragments N–N–N and C–C

The most important and general approach to the synthesis of the 1,2,3-triazole ring system involves azides. A wide variety of azides (organic or inorganic) can be used: alkyl, aryl, hetaryl, acyl, alkoxycarbonyl and sulfonyl azides, azidotrimethylsilane, hydrazoic acid, sodium azide, etc. All are suitable reagents for triazole synthesis.

Azides react with various types of compounds to yield 1,2,3-triazoles or their immediate precursors. The most used are: (i) compounds with C=C bonds (here referred to as alkynes, irrespectively of other functional groups), (ii) compounds with C=C bonds (here referred to as alkenes, and including allenes, enamines, enol ethers, etc.), and (iii) activated methylene compounds.

In spite of the great usefulness of the azides in the triazole synthesis, if the reaction conditions (especially the temperature) are not well controlled, the products obtained may be not the expected triazoles. This is because of the thermal instability of the azides and of some of the intermediates (dihydrotriazoles) formed during the triazole synthesis. It is very important to always consider that most organic azides undergo thermal or photochemical decomposition to nitrenes. The decomposition temperature is dependent on the azide type (Table 2) and some azides, especially cyanogen azide and the lower alkyl azides, are unpredictably explosive. When the decomposition is carried out in the presence of an alkene the corresponding aziridine is usually obtained.

<table>
<thead>
<tr>
<th>Azide Type</th>
<th>Decomposition Temp (°C)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>alkyl azides</td>
<td>180–200</td>
<td>[76]</td>
</tr>
<tr>
<td>aryl azides</td>
<td>140–170</td>
<td>[76]</td>
</tr>
<tr>
<td>sulfonyl azides</td>
<td>120–150</td>
<td>[76]</td>
</tr>
<tr>
<td>alkoxycarbonyl azides</td>
<td>100–130</td>
<td>[76]</td>
</tr>
<tr>
<td>acyl azides</td>
<td>25–80</td>
<td>[76]</td>
</tr>
</tbody>
</table>

13.13.1.3.1.1 Addition of Azides to Alkynes

The thermal 1,3-dipolar cycloaddition of azides to alkynes is often the method of choice for the synthesis of 1,2,3-triazoles since it gives directly the desired product. However, when unsymmetrical alkynes are used, mixtures of the two possible regioisomers are usually obtained. In general, addition to unsymmetrical alkynes tends to give mainly the isomers with the electron-withdrawing groups at the 4-position and the electron-releasing groups at 5-position. The low regioselectivity of these reactions is the major disadvantage of this method as a preparative procedure. The accepted mechanism for these reactions is a concerted 1,3-dipolar cycloaddition. Kinetic data and the regio- and stereoselectivity of these reactions strongly support this mechanism. However, the reactions involving ionic azides (e.g., sodium azide) follow a nonconcerted ionic mechanism. These mechanisms have been discussed and documented in reviews.

N-Unsubstituted 1,2,3-triazoles are prepared by the direct addition of hydrazoic acid or an azide ion to alkynes but it is often more convenient to obtain these compounds by removal of a N-substituent from a 1H- or 2H-triazole.
**Method 1:**

**Addition of Hydrazoic Acid to Alkynes**

Hydrazoic acid reacts with alkynes to give the corresponding N-unsubstituted triazoles 81 (Scheme 36). This method was originally performed by Dimroth and Fester who prepared the parent compound by heating an alcoholic solution of hydrazoic acid with an acetone solution of acetylene at 100°C for 70 hours.\[^{78}\] With alk-1-ynes the reaction is generally carried out in benzene in a closed vessel at temperatures ranging from 90 to 135°C for 30–48 hours.\[^{79}\] The triazoles are obtained in low to moderate yields. Reactions involving alkynes with electron-withdrawing or donating groups are faster and the yields are higher.

**Scheme 36**  Addition of Hydrazoic Acid to Alkynes\[^{44,79–83}\]

<table>
<thead>
<tr>
<th>R(^1)</th>
<th>R(^2)</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>bp (°C)/Torr</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Me</td>
<td>14</td>
<td>35–36</td>
<td>108–109/25</td>
<td>[^{79}]</td>
</tr>
<tr>
<td>H</td>
<td>Bu</td>
<td>56</td>
<td>–</td>
<td>103–105/1</td>
<td>[^{79}]</td>
</tr>
<tr>
<td>H</td>
<td>(CH(_2))(_5)Me</td>
<td>63</td>
<td>27</td>
<td>120–122/2</td>
<td>[^{79}]</td>
</tr>
<tr>
<td>H</td>
<td>(CH(_2))(_9)Me</td>
<td>29</td>
<td>59</td>
<td>148–149/0.6</td>
<td>[^{79}]</td>
</tr>
<tr>
<td>H</td>
<td>Ph</td>
<td>48</td>
<td>148</td>
<td>–</td>
<td>[^{79,80}]</td>
</tr>
<tr>
<td>H</td>
<td>CHO</td>
<td>50</td>
<td>141–142</td>
<td>–</td>
<td>[^{81}]</td>
</tr>
<tr>
<td>H</td>
<td>CO(_2)H</td>
<td>71</td>
<td>222–224</td>
<td>–</td>
<td>[^{44}]</td>
</tr>
<tr>
<td>Ph</td>
<td>CHO</td>
<td>90</td>
<td>186–188</td>
<td>–</td>
<td>[^{82}]</td>
</tr>
<tr>
<td>TMS</td>
<td>CHO</td>
<td>83</td>
<td>171–183</td>
<td>–</td>
<td>[^{83}]</td>
</tr>
<tr>
<td>TMS</td>
<td>Ac</td>
<td>88</td>
<td>159–160</td>
<td>–</td>
<td>[^{83}]</td>
</tr>
<tr>
<td>TMS</td>
<td>CO-t-Bu</td>
<td>79</td>
<td>84–85</td>
<td>–</td>
<td>[^{83}]</td>
</tr>
<tr>
<td>TMS</td>
<td>Bz</td>
<td>85</td>
<td>102</td>
<td>–</td>
<td>[^{83}]</td>
</tr>
</tbody>
</table>

**4-Phenyl-1H-1,2,3-triazole (81, R\(^1\) = H; R\(^2\) = Ph):\[^{79}\]**

**CAUTION:** Hydrazoic acid is highly toxic and explosive. Adequate protection and shielding are necessary during the preparation and handling of this reagent.

A combustion tube containing phenylacetylene (14.7 g, 0.144 mol) and a soln of HN\(_3\) in benzene (50 mL of 14.2% HN\(_3\) in benzene, 0.165 mol) (CAUTION: carcinogen) was sealed and heated in a bath at 110–115°C for 40 h. After cooling to rt almost the entire contents crystallized. The solid was collected by filtration, washed with benzene, and recrystallized twice (benzene). Decolorizing charcoal was used during the first crystallization; yield: 10 g (48%); mp 148°C.

for references see p 587
13.13.1.3.1.2 Method 2: 
Addition of the Azide Ion to Alkynes

The azide ion undergoes addition to alkynes to give triazoles 82 in low to moderate yields (Scheme 37). Better yields are obtained with alkynes bearing electron-withdrawing groups. Almost quantitative yields (>98%) of 5-substituted 1H-1,2,3-triazole-4-carboxaldehydes are obtained from the reaction of alk-2-ynals with sodium azide in dimethyl sulfoxide, at room temperature.\[^{[84]}\] Generally the reaction is carried out in dimethyl sulfoxide or dimethylformamide; sodium azide\[^{[84–87]}\] is frequently used as the azide ion source but lithium azide\[^{[88]}\] and aluminum azide\[^{[89]}\] have also been used. The mechanism of the reaction probably involves the nucleophilic addition of the azide ion to the triple bond followed by 1,5-dipolar cyclization of the resulting vinyl anion. Addition of sodium azide to 1-aryl-5-phenylpent-4-yn-1,3-diones in refluxing dimethylformamide gives the corresponding 4-(3-aryl-1,3-dioxopropyl)-5-phenyl-1H-1,2,3-triazoles 82 (R\(^1\) = Ph; R\(^2\) = COCH\(_2\)Bz, COCH\(_2\)CO-4-Tol, 4-MeOC\(_6\)H\(_4\)COCH\(_2\)CO) in good yields.\[^{[86]}\]

**Scheme 37** Addition of Sodium Azide to Alkynes\[^{[84–86]}\]

<table>
<thead>
<tr>
<th>R(^1)</th>
<th>R(^2)</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>11</td>
<td>–</td>
<td>[^{[85]}]</td>
</tr>
<tr>
<td>H</td>
<td>Ph</td>
<td>40</td>
<td>148</td>
<td>[^{[85]}]</td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>16</td>
<td>140</td>
<td>[^{[85]}]</td>
</tr>
<tr>
<td>H</td>
<td>CO(_2)Me</td>
<td>49</td>
<td>145</td>
<td>[^{[85]}]</td>
</tr>
<tr>
<td>CO(_2)Me</td>
<td>CO(_2)Me</td>
<td>54</td>
<td>132</td>
<td>[^{[85]}]</td>
</tr>
<tr>
<td>Ph</td>
<td>CHO</td>
<td>&gt;98</td>
<td>–</td>
<td>[^{[84]}]</td>
</tr>
<tr>
<td>Bu</td>
<td>CHO</td>
<td>&gt;98</td>
<td>–</td>
<td>[^{[84]}]</td>
</tr>
<tr>
<td>Ph</td>
<td>COCH(_2)Bz</td>
<td>72</td>
<td>87</td>
<td>[^{[86]}]</td>
</tr>
<tr>
<td>Ph</td>
<td>COCH(_2)CO-4-Tol</td>
<td>72</td>
<td>122</td>
<td>[^{[86]}]</td>
</tr>
<tr>
<td>Ph</td>
<td>4-MeOC(_6)H(_4)COCH(_2)CO</td>
<td>60</td>
<td>79</td>
<td>[^{[86]}]</td>
</tr>
</tbody>
</table>

The reaction of propynenitrile with aluminum azide (THF, reflux, 24 h) gives a mixture of the triazoles 83 (32%) and 84 (47%) (Scheme 38).\[^{[88]}\] The formation of the tetrazole ring results from the addition of an azide ion to the cyano group.
Addition of sodium azide to (arylethynyl)triphenylphosphonium halides 85 gives 4-aryl-5-triphenylphosphonio-1,2,3-triazolide ylides 86 in high yields (Scheme 39).\cite{87} These ylides are readily hydrolyzed in aqueous basic solution to give quantitatively triazoles 87 and triphenylphosphine oxide.

Propargyl sulfonates 88 react with lithium azide/copper(I) chloride complex (THF/DMF, −60°C) to give, after acidification, the 5-(1-azidoalkyl)-1H-1,2,3-triazoles 89 in low yields (4–24%); 50–70% of the starting material is recovered (Scheme 40).\cite{88}

**Scheme 38** Addition of Aluminum Azide to Propynenitrile\cite{89}

\[ \text{H} = \equiv \text{CN} + \text{Al(N}_3\text{)}_3 \xrightarrow{} \text{THF, reflux, 24 h} \]

Addition of sodium azide to (arylethynyl)triphenylphosphonium halides 85 gives 4-aryl-5-triphenylphosphonio-1,2,3-triazolide ylides 86 in high yields (Scheme 39).\cite{87} These ylides are readily hydrolyzed in aqueous basic solution to give quantitatively triazoles 87 and triphenylphosphine oxide.

**Scheme 39** Addition of Sodium Azide to (Arylethynyl)triphenylphosphonium Halides\cite{87}

**Scheme 40** Addition of Lithium Azide to Propargyl Sulfonates\cite{88}

4-(3-Aryl-1,3-dioxopropyl)-5-phenyl-1H-1,2,3-triazoles 82 (R1 = Ph; R2 = COCH2Bz, 4-TolCOCH2CO, 4-MeOC6H4COCH2CO); General Procedure:\cite{86}

**CAUTION:** Sodium azide can explode on heating and is highly toxic.

A soln of 1-aryl-5-phenylpent-4-yne-1,3-dione (4 mmol) in DMF (20 mL) was refluxed with NaN₃ (4.6 mmol) for 3 h. The mixture was then poured into cold H₂O (200 mL), acidified with dil H₂SO₄, and the precipitated triazole 82 was collected by filtration, washed with H₂O several times, dried, and recrystallized [benzene/petroleum ether (bp 60–80°C)] as yellow needles.

**13.13.1 Method 3:**

**Addition of Alkyl, Aryl, or Hetaryl Azides to Alkynes**

The addition of alkyl, aryl, and hetaryl azides to alkynes is the most popular method for the synthesis of 1,2,3-triazoles. The number of publications related to this method is so impressive that, although no substantial differences are found in the experimental procedures, for easier systematization of the information available, several variations of the method will be presented according to the type of alkyne used. Once again, it should be emphasized that azides are dangerous compounds, especially alkyl azides which are
treacherously explosive and should be treated with extreme caution. Wherever possible these compounds should only be handled as solutions.

13.13.1.3.1.3.1 Variation 1:
Addition of Azides to Acetylene and to Symmetrically Substituted Alkynes

Azides undergo addition to acetylene and to symmetrically substituted alkynes 90 to give only one 1-substituted 1H-1,2,3-triazole 91, which simplifies the purification step (Scheme 41); this is a general method for the preparation of triazoles 91 and in some cases the yields are excellent. Addition of phenyl azide,[78] arylmethyl azides[90–92] or other alkyl azides[90] to acetylene yields the corresponding 4,5-unsubstituted triazoles 91 (R² = H). This method has also been used for the preparation of dendrimers containing various 1,2,3-triazole rings.[93] The addition of dimethyl acetylenedicarboxylate to per(6-azido-6-deoxy-2,3-di-O-methyl)cyclodextrins yields the corresponding per(4,5-dicarboxy-1,2,3-triazol-1-yl) derivatives.[94] 1,4-Diazidobuta-1,3-dienes react with cyclooctyne at room temperature to give the corresponding bis(triazolyl) derivatives in high yields (86–99%).[95] 1,2-, 1,3-, and 1,4-Bis(azidomethyl)benzenes react with dimethyl, diethyl, and di-tert-butyl acetylenedicarboxylates to afford the corresponding benzobis(triazoles) in good yields.[96] Other interesting bis(triazolyl) derivatives have been prepared by reacting dimethyl acetylenedicarboxylate and bis-azides (produced from the reaction of sodium azide and bis-epoxides).[97]

**Scheme 41** Addition of Azides to Symmetrically Substituted Alkynes[92,98–115]

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>Conditions</th>
<th>Yield (%)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Ph</td>
<td>benzene, 60°C, 2 months</td>
<td>30</td>
<td>[98]</td>
</tr>
<tr>
<td>CF₂CHFCF₃</td>
<td>Ph</td>
<td>180°C, 18 h</td>
<td>88</td>
<td>[99]</td>
</tr>
<tr>
<td>(CF₂)₂CO₂Me</td>
<td>CO₂Me</td>
<td>130°C, 6 h</td>
<td>94</td>
<td>[99]</td>
</tr>
<tr>
<td>Ph</td>
<td>CH₂OH</td>
<td>benzene, 80°C, 12 h</td>
<td>73</td>
<td>[100]</td>
</tr>
<tr>
<td>Ph</td>
<td>CH(OEt)₂</td>
<td>EtOH, 100°C, 28 h</td>
<td>82</td>
<td>[101]</td>
</tr>
<tr>
<td>Ph</td>
<td>CO₂Me</td>
<td>EtOH, reflux, 20 h</td>
<td>92</td>
<td>[102]</td>
</tr>
<tr>
<td>(CH₂)₂Me</td>
<td>CH(OEt)₂</td>
<td>EtOH, 100°C, 43 h</td>
<td>90</td>
<td>[101]</td>
</tr>
<tr>
<td>4-MeOC₆H₄</td>
<td>CO₂Me</td>
<td>benzene, reflux, 24 h</td>
<td>97</td>
<td>[103]</td>
</tr>
<tr>
<td>4-O₂NC₆H₄</td>
<td>CO₂Me</td>
<td>benzene, reflux, 24 h</td>
<td>87</td>
<td>[103]</td>
</tr>
<tr>
<td>4-O₂NC₆H₄</td>
<td>CO₂Me</td>
<td>benzene, reflux, 24 h</td>
<td>80</td>
<td>[104]</td>
</tr>
<tr>
<td>4-AcOC₆H₄</td>
<td>CO₂Me</td>
<td>benzene, reflux, 24 h</td>
<td>87</td>
<td>[103]</td>
</tr>
<tr>
<td>2-AcO₂C₆H₄</td>
<td>Bz</td>
<td>toluene, reflux, 2–30 h</td>
<td>82</td>
<td>[92]</td>
</tr>
<tr>
<td>Bn</td>
<td>CO₂H</td>
<td>acetone, rt to reflux, 1 h</td>
<td>93</td>
<td>[105]</td>
</tr>
<tr>
<td>1-naphthyl</td>
<td>Bz</td>
<td>benzene, reflux, 48 h</td>
<td>70</td>
<td>[106]</td>
</tr>
<tr>
<td>1-naphthyl</td>
<td>CO₂Me</td>
<td>benzene, reflux, 5 h</td>
<td>95</td>
<td>[106]</td>
</tr>
<tr>
<td>1-naphthyl</td>
<td>TMS</td>
<td>CHCl₃, reflux, 96 h</td>
<td>37</td>
<td>[106]</td>
</tr>
<tr>
<td>1-adamantyl</td>
<td>CO₂Me</td>
<td>toluene, reflux, 24 h</td>
<td>77</td>
<td>[107]</td>
</tr>
<tr>
<td>1-adamantyl</td>
<td>CH₂OH</td>
<td>toluene, reflux, 90 h</td>
<td>32</td>
<td>[107]</td>
</tr>
<tr>
<td>1-adamantyl</td>
<td>Ph</td>
<td>toluene, reflux, 500 h</td>
<td>17</td>
<td>[107]</td>
</tr>
</tbody>
</table>
### Variation 2: Addition of Azides to Alk-1-ynes

Azides undergo addition to alk-1-ynes to give mixtures of 1,4- and 1,5-disubstituted 1H-1,2,3-triazoles (Scheme 42). The ratio of the two products is mainly dependent on the structure of alkyne: when R² is an electron-withdrawing group it goes preferentially to position 4 (triazoles 93), however isomers 94 are predominant when R² is an electron-releasing group. The mechanism and kinetics of the cycloaddition of phenyl azide to various 4-substituted phenylacetylenes has been reported. Phenyl azide reacts regioselectively with trifluoromethyl-substituted alkynyl α-amino acids to give the 1,4-disubstituted triazole. It has been shown that cucurbituril substantially accelerates (ca. 10⁵-fold) the reaction of azide-substituted ammonium ions with alkyne-derived ammonium ions. The reaction is regioselective, affording only the 1,4-disubstituted triazole derivatives. This method has been used for the preparation of oligo-1,2,3-triazoles and [n]rotax-

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<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>Conditions</th>
<th>Yield (%)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>(E)-CPH=CHMe</td>
<td>CO₂Me</td>
<td>rt</td>
<td>70</td>
<td>[108]</td>
</tr>
<tr>
<td>cyclohepta-2,4,6-trienyl</td>
<td>CO₂Me</td>
<td>CCl₄, reflux, 1 h</td>
<td>73</td>
<td>[109]</td>
</tr>
<tr>
<td>cyclohepta-2,4,6-trienyl</td>
<td>Bz</td>
<td>benzene, 100°C, 2 h</td>
<td>58</td>
<td>[109]</td>
</tr>
<tr>
<td>CH₃PO(OEt)₂</td>
<td>CO₂Me</td>
<td>toluene, reflux, 30–40 h</td>
<td>92</td>
<td>[110]</td>
</tr>
<tr>
<td>CH₃PO(OEt)₂</td>
<td>Bz</td>
<td>toluene, reflux, 30–40 h</td>
<td>85</td>
<td>[110]</td>
</tr>
</tbody>
</table>

for references see p 587
A catalytic effect is also observed for zinc chloride doped natural phosphate for the cycloaddition of alkyl azides with alk-1-ynes. With this catalyst a significant reduction in the reaction time is observed but the yields and the 1,4-/1,5-substitution ratio of the triazole are not improved. The enzyme acetylcholinesterase, which plays a key role in neurotransmitter hydrolysis in the central and peripheral nervous systems, has been used as a catalyst for the reaction of a tacrine-substituted alkyl azide with a phenanthridinium-substituted terminal alkyne. The 1,5-disubstituted triazole is the predominant isomer. A high-yielding and simple copper(I)-catalyzed reaction sequence leading exclusively to 1,4-disubstituted 1,2,3-triazoles has been described. It involves the reaction of organic azides with alk-1ynes in the presence of the catalyst (0.25–2 mol%) prepared in situ by reduction of copper sulfate with ascorbic acid and/or sodium ascorbate. The reaction proceeds to completion in 6 to 36 hours at room temperature in a variety of solvents, including aqueous tert-butyl alcohol or ethanol and, very importantly, water with no organic cosolvent. The use of microwave-induced 1,3-dipolar cycloaddition of organic azides to alk-1-ynes under solvent-free conditions is also another important development. It allows a substantial decrease in reaction times, reduced pollution, low cost, and simplicity in processing and handling. The addition of O-propargyl glycosides and propargyloxy-calixarenes to a calixarene diazide leads to the formation of interesting 1,2,3-triazole derivatives having glycosyl and calixarene moieties.

### Scheme 42

**Addition of Azides to Alk-1-ynes**

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>Conditions</th>
<th>Yield (%)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>toluene, reflux, 17 h</td>
<td>43</td>
<td>52</td>
</tr>
<tr>
<td>Ph</td>
<td>(CH₂)₃OH</td>
<td>100 ºC, 15 h</td>
<td>63</td>
<td>31</td>
</tr>
<tr>
<td>Ph</td>
<td>CO₂Me</td>
<td>rt, 12 d; 60 ºC, 34 h</td>
<td>88</td>
<td>12</td>
</tr>
<tr>
<td>Bn</td>
<td>Ph</td>
<td>toluene, reflux, 17 h</td>
<td>39</td>
<td>55</td>
</tr>
<tr>
<td>Bn</td>
<td>CONHBn</td>
<td>microwave irradiation, 55 ºC, 30 min</td>
<td>65</td>
<td>22</td>
</tr>
<tr>
<td>(CH₂)₃Ph</td>
<td>piperidino-carbonyl</td>
<td>microwave irradiation, 55 ºC, 30 min</td>
<td>65</td>
<td>22</td>
</tr>
<tr>
<td>CH₃CO₂Et</td>
<td>Ph</td>
<td>toluene, reflux, 48 h</td>
<td>41</td>
<td>36</td>
</tr>
<tr>
<td>1-adamantyl</td>
<td>Ph</td>
<td>toluene, reflux, 35 h</td>
<td>60</td>
<td>21</td>
</tr>
<tr>
<td>1-adamantyl</td>
<td>1-adamantyl</td>
<td>toluene, reflux, 30 h</td>
<td>67</td>
<td>0</td>
</tr>
<tr>
<td>1-adamantyl</td>
<td>CO₂Me</td>
<td>toluene, reflux, 11 h</td>
<td>84</td>
<td>0</td>
</tr>
<tr>
<td>CH₃PO(OEt)₂</td>
<td>Ph</td>
<td>microwave irradiation, 120 ºC, 30 min</td>
<td>45</td>
<td>54</td>
</tr>
<tr>
<td>CH₃PO(OEt)₂</td>
<td>CH₂OH</td>
<td>microwave irradiation, 100 ºC, 30 min</td>
<td>30</td>
<td>69</td>
</tr>
<tr>
<td>CH₃PO(OEt)₂</td>
<td>CO₂Et</td>
<td>microwave irradiation, 100 ºC, 5 min</td>
<td>61</td>
<td>31</td>
</tr>
<tr>
<td>CF₃CFHCF₃</td>
<td>Ph</td>
<td>steel bomb, 130 ºC, 6 h</td>
<td>32</td>
<td>62</td>
</tr>
<tr>
<td>CF₃CFHCF₃</td>
<td>Bu</td>
<td>steel bomb, 120 ºC, 6 h</td>
<td>37</td>
<td>58</td>
</tr>
<tr>
<td>R¹</td>
<td>R²</td>
<td>Conditions</td>
<td>Yield (%)</td>
<td>Ref</td>
</tr>
<tr>
<td>------------</td>
<td>------------</td>
<td>-----------------------------</td>
<td>-----------</td>
<td>-----</td>
</tr>
<tr>
<td>CF₃CFHCF₃</td>
<td>CO₂Me</td>
<td>steel bomb, 120°C, 6 h</td>
<td>70 18</td>
<td>[99]</td>
</tr>
<tr>
<td>CF₃CFHCF₃</td>
<td>TMS</td>
<td>steel bomb, 90°C, 6 h</td>
<td>50 –</td>
<td>[99]</td>
</tr>
<tr>
<td>CH₃C(NO₂)₂Me</td>
<td>CO₃H</td>
<td>CHCl₃, rt, 3 d</td>
<td>89⁺</td>
<td>[130]</td>
</tr>
<tr>
<td>CH≡CH-t-Bu</td>
<td>CO₂Me</td>
<td>rt</td>
<td>54 13</td>
<td>[108]</td>
</tr>
<tr>
<td>4-O₂NC₆H₄</td>
<td>CO₂Et</td>
<td>benzene, reflux, 48 h</td>
<td>60 25</td>
<td>[104]</td>
</tr>
<tr>
<td>CH₃CH₂CO₂Et</td>
<td>Bz</td>
<td>benzene, reflux, 22 h</td>
<td>48 30</td>
<td>[131]</td>
</tr>
<tr>
<td>Cy</td>
<td>Bz</td>
<td>benzene, reflux, 48 h</td>
<td>26 10</td>
<td>[131]</td>
</tr>
<tr>
<td>4-Tol</td>
<td>Bz</td>
<td>benzene, reflux, 26 h</td>
<td>60 11</td>
<td>[131]</td>
</tr>
<tr>
<td>1-naphthyl</td>
<td>Bz</td>
<td>benzene, reflux, 24 h</td>
<td>44 14</td>
<td>[131]</td>
</tr>
<tr>
<td>1-naphthyl</td>
<td>CO₂Et</td>
<td>100°C, 8 h</td>
<td>71 12</td>
<td>[106]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Combined yield of 93 and 94.

The 1,3-dipolar cycloaddition of aryl azides to (trimethylsilyl)acetylene is regioselective and gives, after several days at 25°C, almost quantitative yields of the 1-aryl-4-(trimethylsilyl)-1,2,3-triazoles 96 (Scheme 43).[133] A study has shown that the rate of these cycloadditions increases logarithmically with pressure.[134] For example, the reaction of 4-methoxyphenyl azide with 95 takes 55 days, at atmospheric pressure, to complete consumption of the azide. The same reaction is complete in 1.5 hours if it is conducted at room temperature but under pressure (0.3 GPa). At pressures of about 1 GPa these reactions are almost instantaneous and quantitative.[134]

for references see p 587
Scheme 43 Addition of Aryl Azides to (Trimethylsilyl)acetylene

Addition of Aryl Azides to (Trimethylsilyl)acetylene

\[ \text{Ar}^1\text{N}_3 + \text{H-TMS} \rightarrow \text{TMSH} \]

<table>
<thead>
<tr>
<th>( \text{Ar}^1 )</th>
<th>Time (d)</th>
<th>Yield (%)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>35</td>
<td>96</td>
<td>[133]</td>
</tr>
<tr>
<td>4-Tol</td>
<td>40</td>
<td>95</td>
<td>[133]</td>
</tr>
<tr>
<td>4-MeOC\text{C}_2\text{H}_4</td>
<td>55</td>
<td>95</td>
<td>[133]</td>
</tr>
<tr>
<td>4-Cl\text{C}_2\text{H}_4</td>
<td>25</td>
<td>95</td>
<td>[133]</td>
</tr>
<tr>
<td>4-O_2N\text{C}_2\text{H}_4</td>
<td>20</td>
<td>95</td>
<td>[133]</td>
</tr>
<tr>
<td>4-NCC\text{C}_2\text{H}_4</td>
<td>26</td>
<td>96</td>
<td>[133]</td>
</tr>
<tr>
<td>benzo[\text{b}]thien-2-yl</td>
<td>9</td>
<td>93</td>
<td>[133]</td>
</tr>
<tr>
<td>benzo[\text{b}]thien-3-yl</td>
<td>28</td>
<td>95</td>
<td>[133]</td>
</tr>
</tbody>
</table>

13.13.1.3.1.3.3 Variation 3: Addition of Azides to Unsymmetrical Disubstituted Alkynes

Azides add to unsymmetrical disubstituted alkynes to give mixtures of isomeric triazoles 97 and 98 (Scheme 44). The relative proportions of the two products are strongly dependent on the nature of \( R^2 \) and \( R^3 \).

Scheme 44 Addition of Azides to Unsymmetrical Disubstituted Alkynes

\[ R^1\text{N}_3 + R^2 = R^3 \rightarrow R^2 R^3 \]

<table>
<thead>
<tr>
<th>( R^1 )</th>
<th>( R^2 )</th>
<th>( R^3 )</th>
<th>Conditions</th>
<th>Yield (%)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>CH\text{OH}</td>
<td>CO_2\text{Me}</td>
<td>toluene, 55 °C, 14 d</td>
<td>8</td>
<td>49</td>
</tr>
<tr>
<td>4-MeOC\text{C}_2\text{H}_4</td>
<td>CH\text{OH}</td>
<td>CO_2\text{Me}</td>
<td>benzene, rt, 60 d</td>
<td>31</td>
<td>59</td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>Bz</td>
<td>benzene, 80 °C, 19 h</td>
<td>0</td>
<td>86</td>
</tr>
<tr>
<td>1-naphthyl</td>
<td>Me</td>
<td>CO_2\text{Me}</td>
<td>100 °C, 8 h</td>
<td>9</td>
<td>72</td>
</tr>
<tr>
<td>CH\text{CO}_2\text{-t-Bu}</td>
<td>CF_3</td>
<td>PO(O\text{OiPr})_2</td>
<td>Et_2O, rt, 20 h</td>
<td>68</td>
<td>22</td>
</tr>
<tr>
<td>CH\text{PO(O\text{Et})}_2</td>
<td>Me</td>
<td>PO(O\text{Et})_2</td>
<td>100 °C, 60 h</td>
<td>73</td>
<td>23</td>
</tr>
<tr>
<td>CH\text{PO(O\text{Et})}_2</td>
<td>Ph</td>
<td>CO_2Et</td>
<td>160 °C, 10 min</td>
<td>58</td>
<td>42</td>
</tr>
</tbody>
</table>

A recognition-mediated reaction between 4-(azidomethyl)benzo-15-crown-5 99 and the asymmetric alkyne 100 shows that the regioselectivity of the cycloaddition can be controlled. The mutual recognition between the ammonium cation and the crown ether leads to the formation of triazole 101 and its regioisomer in the ratio of 97:3 (Scheme 45).
Azido sugars have been extensively used to prepare carbohydrate-derived 1,2,3-triazoles. For example, the β-D-galactopyranosyl azide 102 reacts with alkyne 103 to yield mixtures of the nucleoside triazole analogues 104/105 (30%/49%) (Scheme 46). Analogously, the 5-azido-5-deoxy-α-D-xylofuranose 106 reacts with a range of alkynes to give mixtures of 5-(1H-1,2,3-triazol-1-yl)-α-D-xylofuranoses 107/108. 2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl azide reacts with methyl 4-hydroxybut-2-ynoate to yield a mixture of the two expected isomeric triazoles in 75% yield.

Scheme 46  Addition of Azido Sugars to Alkynes [139–141]
13.13.1.3.1.3.4 Variation 4: Using Polymer-Supported Methods

The use of polymer-supported methods to prepare carbohydrate-derived 1,2,3-triazoles is already established. Addition of azidodeoxy carbohydrate derivatives to the monomethyl ether derivative of polyethylene glycol 109 (a soluble polymer-supported alkyne) yields the polymer-supported triazoles 110/111 in a proportion of approximately 2:1 (Scheme 47). Treatment of these polymers with sodium borohydride in hot ethanol gives the corresponding “free” triazoles 112/113 in greater than 75% yield.[143] In a variation of this procedure a succinate ester linkage (instead of an oxalyl ester) is also successfully used to prepare polymer-supported glycosyl triazoles. In this procedure, the “free” glycosyl triazoles can be obtained in high yields (>90%) and high purity by treatment of the polymer with an excess of ammonia in methanol solution, followed by precipitation of the polymer with ether and filtration.[141]

Scheme 47 Addition of Azido Sugars to Soluble Polymer-Supported Alkynes[143]
The complementary method, i.e. reaction of a polymer-supported azido sugar with alkynes, can also be used (Scheme 48). Azide 114 reacts with alkynes to give mixtures of the two regioisomers 115/116 in high yields (R1 = Ph; R2 = H, 50%; R1 = CO2Et; R2 = H, >95%; R1 = CH2OH; R2 = H, >95%). Treatment of these compounds with ammonia in methanol solution, followed by precipitation of the polymer with diethyl ether and filtration gives the corresponding “free” triazoles 117/118.[141]

A solid-phase synthesis of functionalized 1,2,3-triazoles from the reaction of resin-bound azides 119 and terminal alkynes has been reported (Scheme 49).[144] The reaction with methyl propynoate occurs in dimethylacetamide at 60 °C and, after cleavage in trifluoroacetic acid, provides the free acids 120 (R2 = CO2Me), as single isomers, in moderate yields (17–27%). The reaction with phenylacetylene requires higher temperatures (120 °C) and provides 1:1 mixtures (22–25%) of the possible regioisomers 120 (R2 = Ph) and 121 (R2 = Ph) after trifluoroacetic acid cleavage.

---

**Scheme 48** Addition of Alkynes to Soluble Polymer-Supported Azido Sugars[148]

**Scheme 49** Solid-Phase Synthesis of 1H-1,2,3-Triazoles Using Resin-Bound Azides and Terminal Alkynes[144]

---

R1 = H, Me, Et; (CH2)5Me; R2 = CO2Me, Ph
A solid-phase, regioselective, copper(I)-catalyzed, 1,3-dipolar cycloaddition of terminal alkynes to azides has been used to prepare peptido-1,2,3-triazoles. Copper(I) salts are used as catalysts in the reaction of resin-bound terminal alkynes to primary, secondary, and tertiary alkyl azides, aryl azides, and an azido sugar at 25 °C, affording selectively 1,4-disubstituted 1H-1,2,3-triazoles with quantitative conversions and purities ranging from 75 to 99%. [145]

### Variation 5: Intramolecular 1,3-Dipolar Cycloadditions

The intramolecular 1,3-dipolar cycloaddition of an azido group onto a C=C bond gives polycyclic triazoles. Azides 122 and 124, for example, give triazoles 123 (52%) and 125 (59%), respectively, when heated in refluxing toluene (Scheme 50). [146]

![Scheme 50: Synthesis of 1,2,3-Triazoles via Intramolecular 1,3-Dipolar Cycloadditions](image)

Propargyl azides 127 undergo intramolecular cycloaddition reactions yielding N-unsubstituted 1H-1,2,3-triazoles 130 (Scheme 51). The reaction must be carried out in nucleophilic solvents, such as methanol or ethanol, or in the presence of nucleophiles such as azide ion, amines, or thiols, if not, then only polymeric triazole products are obtained. The mechanism of this transformation involves the rearrangement of the propargyl azide to allenyl azide 128 that gives by rapid ring closure the triazafulvene 129. This short-lived intermediate is trapped by nucleophiles to give triazoles 130 in good yields. [147,148] Since propargyl azides can be prepared from propargyl halides or propargyl tosylates 126 (X = halogen, OTs) and sodium azide, various substituted 1,2,3-triazoles can be synthesized in good yields in one-pot procedure from these precursors without the necessity to isolate the potentially hazardous propargyl azides. In the presence of sodium hydroxide the propargyl azides 127 undergo base-catalyzed (prototropic) rearrangement to allenyl azides 131. The immediate cyclization of this intermediate leads to the triazafulvene 132, which can be trapped by nucleophiles to give triazoles 133 in good yields (Scheme 51). [148]
Depending on the reaction conditions, propargyl azides 127 can be selectively converted into triazoles 130 or 133. For example, azide 134 can produce triazole 135 or triazole 136 depending only on the presence or absence of sodium hydroxide (Scheme 52).
The intramolecular 1,3-dipolar cycloaddition of an azide group with a C=C bond has been used extensively for the synthesis of nonclassical polycyclic β-lactams.[149–154]

13.13.1.3.6 Variation 6: Addition of Azides to Alkoxyalkynes

Nitrophenyl azides 138 undergo cycloaddition reactions with 1-methoxyalk-1-ynes 137 at room temperature to give 1H-1,2,3-triazoles 139 in low yields (R1 = Et; X = H, 22%) or the corresponding ring-opened isomeric ß-diazocarboximidates 140 (R1 = Me, 52%; R1 = Et, 75%) (Scheme 53).[155] The reaction of ethoxyacetylene with 4-methoxyphenyl azide and 4-nitrophenyl azide also gives the corresponding 1-aryl-5-ethoxy-1H-1,2,3-triazoles.[103]

Similarly, 5-ethoxy-1H-1,2,3-triazoles 143 are obtained from the reaction of ethoxyacetylene (141) with phenyl azide, substituted phenyl azides[156] and hetaryl azides[114] 142 (Scheme 54). The best yield is obtained with phenyl azide (87%). With 2-nitrophenyl azide, and 4-nitrophenyl azide the yields are very low (6–12%).
Scheme 54  Addition of Azides to Ethoxyacetylene\(^{[114,156]}\)

![Scheme 54](image)

5-Ethoxy-1-(6-methyl-2-oxo-2\(^H\)-pyran-4-yl)-1\(^H\)-1,2,3-triazole (143, \(R^1 = 6\)-methyl-2-oxo-2\(^H\)-pyran-4-yl); Typical Procedure\(^{[114]}\)

A mixture of 4-azido-6-methyl-2\(^H\)-pyran-2-one (0.77 g, 5.09 mmol), ethoxyacetylene (7.13 mmol, from a 50% soln in hexanes) and anhyd THF (18 mL) was left in a closed reactor for 7 d. The resulting precipitate of the product was collected by filtration and the filtrate was left 7 d more at 30°C to give a second crop. The combined precipitates were washed with hexane to afford the pure product; yield: 24% (57% with respect to consumed azide 142); mp 159–161°C.

13.13.1.1.3.1.4 Method 4: Addition of Ethyl Azidoformate and Cyanogen Azide to Alkynes

Ethyl azidoformate (144) undergoes addition to phenylacetylene to give 1,2,3-triazoles. If the reaction is carried out at 50°C (3 weeks) a mixture of the 1,4- and 1,5-disubstituted triazoles is obtained in a ratio of about 53:47 and an overall yield of 36% (Scheme 55)\(^{[157]}\). If the reaction is performed at 130°C the two initially formed triazoles 145/146 isomerize to ethyl 4-phenyl-2\(^H\)-1,2,3-triazole-2-carboxylate (147) and this is the isolated triazole product (16%). Under these reaction conditions, 2-ethoxy-4(or 5)-phenyloxazole 148 (16%) is also obtained\(^{[157,158]}\). The formation of this compound is due to the addition of (ethoxycarbonylnitrene (generated by thermal decomposition of the azide) to phenylacetylene. The reaction of ethyl azidoformate with dimethyl acetylenedicarboxylate and methyl propynoate also gives the corresponding triazoles (23 and 50% yield, respectively) and 2-ethoxyoxazoles (3%)\(^{[158]}\).

Scheme 55  Addition of Ethyl Azidoformate to Phenylacetylene\(^{[157,158]}\)

![Scheme 55](image)
Ethyl azidoformate reacts with N,N-diethylprop-1-yn-1-amine (149, R₁ = Me) in carbon tetrachloride at room temperature to yield only triazole 150 (R₁ = Me) (Scheme 56). However, if an excess of the ynamine is used, the initially formed triazole isomerizes to ethyl 5-(diethylamino)-4-methyl-2H-1,2,3-triazole-2-carboxylate. Ethyl azidoformate also adds to ynamines 149 (R₁ = Ac, CO₂Me) to give the corresponding triazoles 150 in good yields. Benzoyl azide also adds readily to ynamines. Addition of ethyl azidoformate to ethoxycetylene (no solvent, rt, 35 d) gives a mixture of three isomeric triazoles: ethyl 5-ethoxy-1H-1,2,3-triazole-1-carboxylate, ethyl 4-ethoxy-1H-1,2,3-triazole-1-carboxylate, and ethyl 4-ethoxy-2H-1,2,3-triazole-2-carboxylate in a ratio of 54.5:42:3.5 (by NMR). Addition of 1,4-diazabicyclo[2.2.2]octane converts 1-ethoxycarbonyl isomers into the 2-ethoxycarbonyl derivative.

Scheme 56
Addition of Ethyl Azidoformate to Ynamines

Cyanogen azide (N₃CN) reacts with acetylene at 45°C to give 77% of a 1:1 adduct that is colorless below its melting point (33°C) but is yellow in the melt or in solution. The adduct is a tautomeric mixture of 1H-1,2,3-triazole-1-carbonitrile and N-cyano-α-diazoethylidenimine (see Scheme 3). The cyanogen azide adds to prop-1-yne, but-2-yne, and hex-1-yne are also tautomeric mixtures of the corresponding triazoles and N-cyano-α-diazoimines. Cyanogen azide reacts with ethoxycetylene and N,N-diphenylacetylene to afford only the diazo derivatives, resulting from ring opening of the initially formed 1H-1,2,3-triazole-1-carbonitriles.

13.13.1.1.5 Method 5: Addition of Sulfonyl Azides to Alkynes

Sulfonyl azides 151 undergo addition to electron-rich alkynes (ynamines and alkoxyalynes 152) to yield 1-sulfonyl-1H-1,2,3-triazoles 153 (Scheme 57). However, these compounds are very labile and, in solution, exist in equilibrium with open-chain diazo tautomers. In many cases the diazo tautomer is the sole product. As an example, addition of arenesulfonyl azides 151 (R³ = aryl) to ynamine 152 (R² = Me; Y = NEt₂) gives mainly 1,2,3-triazoles 153 while the reaction of this type of azides with ynamine 152 (R² = Ph; Y = NMe₂) gives the α-diazoamidines 154 (Scheme 57).
**Scheme 57**  Addition of Sulfonyl Azides to Electron-Rich Alkynes

![Chemical structure](image)

<table>
<thead>
<tr>
<th>R¹SO₂N₃</th>
<th>R²Y</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>Me</td>
<td>NET₂</td>
<td>62</td>
<td>84–85</td>
</tr>
<tr>
<td>4-MeOC₆H₄</td>
<td>Me</td>
<td>NET₂</td>
<td>58</td>
<td>54–56</td>
</tr>
<tr>
<td>4-Tol</td>
<td>Me</td>
<td>NET₂</td>
<td>65</td>
<td>49–52</td>
</tr>
<tr>
<td>4-AcHNC₆H₄</td>
<td>Me</td>
<td>NET₂</td>
<td>78</td>
<td>131–132</td>
</tr>
<tr>
<td>4-O₂NC₆H₄</td>
<td>Me</td>
<td>NET₂</td>
<td>–</td>
<td>81</td>
</tr>
<tr>
<td>2,4-Cl₂C₆H₃</td>
<td>Me</td>
<td>NET₂</td>
<td>–</td>
<td>62</td>
</tr>
<tr>
<td>4-MeOC₆H₄</td>
<td>Ph</td>
<td>NME₂</td>
<td>–</td>
<td>79</td>
</tr>
<tr>
<td>4-O₂NC₆H₄</td>
<td>Ph</td>
<td>NME₂</td>
<td>–</td>
<td>70</td>
</tr>
<tr>
<td>4-BrC₆H₄</td>
<td>Ph</td>
<td>NME₂</td>
<td>–</td>
<td>65</td>
</tr>
<tr>
<td>3-O₂NC₆H₄</td>
<td>Ph</td>
<td>NME₂</td>
<td>–</td>
<td>78</td>
</tr>
<tr>
<td>2,5-Cl₂C₆H₃</td>
<td>Ph</td>
<td>NME₂</td>
<td>–</td>
<td>83</td>
</tr>
</tbody>
</table>

Tosyl azide reacts with 3-aminoprop-2-ynimidamides 155 to yield 1H-1,2,3-triazole-4-carboximidamide 156 in good yields (Scheme 58).\(^{[168]}\)

**Scheme 58**  Addition of Tosyl Azide to 3-Aminoprop-2-ynimidamides

![Chemical structure](image)

**Reaction of Arenesulfonyl Azides 151 with Ynamines 152 (Y = Dialkylamino); General Procedure:**\(^{[164]}\)

A soln of the sulfonyl azide (0.01 mol) in THF (10 mL) was added to a soln of the ynamine (0.01 mol) in THF (5 mL) at –78 °C (cooled in dry ice/acetone bath) over 1 h. The soln was then allowed to warm to rt, filtered through anhyd alumina, and the solvent was removed by evaporation under reduced pressure. The resulting solid (or oil) was crystallized (Et₂O/petroleum ether) to afford the appropriate triazole or Æ-diazoamidine.

*For references see p 587*
Azidotrimethylsilane can be successfully used as a safe synthetic equivalent of the highly explosive hydrazoic acid. It undergoes addition to alkynes to give the corresponding 2-(trimethylsilyl)-2H-1,2,3-triazoles \(158\) [via the 1-(trimethylsilyl)-1H-isomers \(157\)] in good yields (Scheme 59). For example, the reaction of azidotrimethylsilane with but-2-yne gives 4,5-dimethyl-2-(trimethylsilyl)-2H-1,2,3-triazole \(158, R^1 = R^2 = Me\) in 78–87\% yield. Similar results are obtained with other alkynes.\[171\] The trimethylsilyl group can be subsequently replaced by a proton under very mild conditions.\[171–173\] In some cases, the N-unsubstituted triazole \(159\) is the isolated product of the cycloaddition reaction.\[174,175\] A related silyl azide, (trimethylsilyl)methyl azide (TMSCH\(_2\)N\(_3\)), also reacts with alkynes to give quantitative yields of the corresponding 1-[(trimethylsilyl)methyl]-1H-1,2,3-triazoles.\[176\]

Azidotributylstannane \(160\) is another synthetic equivalent of hydrazoic acid. It gives 2-substituted triazoles \(162\) by reaction with mono- and disubstituted alkynes by a 1,3-dipolar cycloaddition to give initially the 1-substituted triazoles \(161\) (Scheme 60).\[177–179\] Triazoles \(162\) can be converted into the N-unsubstituted derivatives by treatment with hydrogen chloride. As an example, phenylacetylene reacts with \(160\) (neat, 140°C, 12 h) to give triazole \(162\) \(R^1 = H; R^2 = Ph\) in 61\% yield. On treatment with hydrogen chloride this compound is converted into triazole \(163\) \(R^1 = H; R^2 = Ph\) in 75\% yield.
Method 7: Addition of Azides to Metal Acetylides

Alkyl, aryl, and sulfonyl azides form triazole derivatives with lithium, magnesium, and sodium derivatives of terminal alkynes. The mildness of the conditions required for the additions (0°C or below) suggests that the mechanism of the reaction may be different from that of normal azide addition to alkynes. A plausible mechanism (Scheme 61) involves nucleophilic attack of the acetylenic anion on the terminal nitrogen of the azide, followed by 1,5-anionic cyclization to give the triazolyl anion. The total regioselectivity of the reaction supports this interpretation. The triazolyl anion so formed can be protonated (to give H3O+), carboxylated (to give CO2), or can react with more azide to give a linear triazene which, in turn, can be hydrolyzed to the triazolamine.

Scheme 61 Addition of Azides to Metal Acetylides

Sodium phenylacetylide reacts with tosyl azide (1 equiv) to yield, after acidification, triazole. If an excess of tosyl azide is used, the 4-azidotriazole is obtained (Scheme 62). In both cases the yields are very low. A copper(I)-catalyzed reaction of resin-bound terminal alkynes (probably involving the corresponding copper acetylides) with a range of organic azides has been reported.

for references see p 587
4-Azido-5-phenyl-1-tosyl-1\(^H\)-1,2,3-triazole (171); Typical Procedure\[[184]\]

A slurry of sodium phenylacetylide [prepared from PhC=CH (0.05 mol) and Na (0.05 mol)] in dry Et\(_2\)O (25 mL) was added slowly to a stirred soln of tosyl azide (19.7 g, 0.10 mol) in dry Et\(_2\)O (50 mL) at a rate which maintained the solvent at reflux. As the mixture was stirred for 24 h a brown solid separated (15.2 g, 58%), which corresponds to a sodium salt of an intermediate compound. Part of this compound (5.0 g) was treated with hot glacial AcOH (10 mL) and a light yellow solid was obtained upon cooling. Two recrystallizations (glacial AcOH) afforded pure triazole 171; yield: 0.52 g (16%); mp 170–171 °C (dec).

13.13.1.1.3.1.2 Method 1: Addition of Sodium Azide to C=\(\equiv\)C Bonds

Sodium azide undergoes addition to alkenes with strongly electron-withdrawing substituents to give N-unsubstituted 1,2,3-triazoles in good yields (Scheme 63). The mechanism seems to involve the conjugate addition of the azide ion to the double bond, cyclization of the resulting anion, and aromatization. The synthesis of triazoles 173 by the reaction of sodium azide with \(\alpha\)-nitro acrylic ester 172 (Y = CO\(_2\)Et) and \(\alpha\)-nitro ketone 172 (Y = Bz) are examples of this method.[185] Other nitroalkenes are converted into 1,2,3-triazoles in the same way.[186] Similarly, triazole 175 is obtained, along with two minor dihydrotriazoles, from the reaction of diethyl (4-nitrobenzylidene)malonate (174) with sodium...
ethyl 3-(4-nitrophenyl)acrylate reacts with sodium azide, in aprotic solvents, to give triazole 175 in moderate yields.\[^{187}\] The reaction of \(\beta\)-aryl-\(\alpha\)-(phenylsulfinyl)acrylates 176 with sodium azide gives triazoles 177 in good yields.\[^{188}\] 5-Tosyl-1H-1,2,3-triazole (179) is prepared in 50% yield from the reaction of 1,2-ditoylacetylene (178) with sodium azide.\[^{190,191}\] It has been shown that (E)-2-azidovinyl 4-methylphenyl sulfone is an intermediate in this transformation. Another example of synthesis of 1,2,3-triazoles from the addition of sodium azide to activated alkenes is found in the preparation of (4-oxo-4H-1-benzopyran-2-yl)-1,2,3-triazoles 181 from 2-(2-arylvinyl)-4H-1-benzopyran-4-ones 180.\[^{192}\] Using 180 (\(X = H\)) as starting compounds, triazoles 181 are the only isolated products; the yields are in the range of 48–59%. When 2-(2-aryl-1-bromovinyl)-4H-1-benzopyran-4-ones 180 (\(X = Br\)) are used the triazoles 181 (38–40%) are obtained together with unexpected 1-aryl-5-[(4-oxo-4H-1-benzopyran-2-yl)methyl]tetrazoles (10–12%).

**Scheme 63** Addition of Sodium Azide to Activated Alkenes

\[
\begin{align*}
\text{Ar}^1 & \quad \text{H} & \quad \text{EtO}_2\text{C} & \quad \text{SOPh} & \quad + \quad \text{NaN}_3 & \quad \text{DMF, rt, 24 h} & \quad \text{Ar}^1 & \quad \text{H} & \quad \text{EtO}_2\text{C} & \quad \text{SOPh} & \quad 57\text{–}73\\
\text{Ar}^1 & \quad \text{H} & \quad \text{EtO}_2\text{C} & \quad \text{SOPh} & \quad + \quad \text{NaN}_3 & \quad \text{DMSO, rt, 24 h} & \quad \text{Ar}^1 & \quad \text{H} & \quad \text{EtO}_2\text{C} & \quad \text{SOPh} & \quad 57\text{–}73\\
\text{Ts} & \quad \text{Ts} & \quad + \quad \text{NaN}_3 & \quad \text{DMSO, rt, 24 h} & \quad \text{Ts} & \quad \text{Ts} & \quad 50\\
\end{align*}
\]
Sodium azide also adds to $\alpha$-chloroamines 182 (NR$_2$R$^3$= NMe$_2$, pyrrolidinyl, morpholino) to give 1,2,3-triazoles 184 (via the $\alpha$-azidoenamines 183) in good yields (Scheme 64).

However, with less basic $\alpha$-chloroamines (NR$_2$R$^3$ = NMePh), azirines 185 are the sole reaction products.

**Scheme 64**  Addition of Sodium Azide to $\alpha$-Chloroamines

\[
\text{R}^1 \text{Cl} + \text{NaN}_3 \rightarrow \text{R}^1 \text{N}3 \text{NR}^2 \text{R}^3
\]

$\text{R}^1 = \text{Me, iBu, Ph}$

The addition of sodium azide to (1- and 2-acylvinyl)triphenylphosphonium salts 186 and 189 gives, respectively, acyl or alkoxycarbonyl-1,2,3-triazoles 188 and 191 (via the ylides 187 and 190) (Scheme 65).

**Scheme 65**  Addition of Sodium Azide to (1- and 2-Acylvinyl)triphenylphosphonium Salts

\[
\text{R}^1 \text{O} + \text{Ph}_3\text{P}^+ \text{X}^- + \text{NaN}_3, \text{H}_2\text{O} \rightarrow \text{R}^1 \text{O} + \text{Ph}_3\text{P}^+ \text{N3}^- \text{PPh}_3 \text{R}^1
\]

$\text{R}^1 = \text{iPr, tBu, Cy, cyclopropyl; R}^2 = \text{H, Et}$

**Ethyl 5-(4-Nitrophenyl)-1H-1,2,3-triazole-4-carboxylate (175); Typical Procedure**

**CAUTION:** Sodium azide can explode on heating and is highly toxic.

Diethyl (4-nitrobenzylidene)malonate (174; 2.0 g, 6.82 mmol) was added in one portion to a soln of NaN$_3$ (443 mg, 6.82 mmol) in dry DMSO (10 mL) at 25°C. The mixture immediately became deep orange-brown in color and heat was evolved. After stirring for 2 h, the mixture was poured onto an ice/water slurry (40 g). The resultant mixture was extracted...
with Et₂O (two minor dihydrotriazoles could be obtained from this fraction), the aqueous layer was acidified with dil HCl to pH 1 and extracted with Et₂O. These ethereal extracts were dried (MgSO₄) and evaporated to give a yellow amorphous solid (800 mg) which was recrystallized (CH₂Cl₂) to give pale yellow crystals; yield: 730 mg (41%); mp 174–176°C.

13.13.1.3.1.2 Method 2: Addition of Azides to Activated Alkenes

Azides undergo addition to alkenes with strongly electron-withdrawing substituents to give 4,5-dihydro-1H-1,2,3-triazoles. Frequently these 4,5-dihydro-1H-triazoles are unstable and, by elimination of a stable fragment, aromatize to 1,2,3-triazoles[197–199] or are converted into aziridines by elimination of nitrogen.[200] Generally the addition of azides to these alkenes is regioselective and only one triazole is obtained. However, in some cases mixtures of triazoles are formed. For example, 1-nitroalk-1-enes 192 react with phenyl or methyl azide to give mixtures of the triazoles 193, 194, and 195 (Scheme 66).[197] The relative proportions of these compounds are dependent of the experimental conditions. Nitrotriazoles 195 are obtained by air oxidation of the corresponding 4,5-dihydro-1H-triazoles. The formation of the two regiosomeric triazoles 193 and 194 is explained by the isomerization of the 1-nitroalk-1-enes to 2-nitroalk-1-enes.[197]

Scheme 66 Reaction of Azides with 1-Nitroalk-1-enes[197]

Phenyl azide adds to 1-bromoethenesulfonyl chloride (196), in refluxing chloroform, to yield 4-bromo-1-phenyl-1H-1,2,3-triazole (198) in 45% yield (Scheme 67).[198] The unstable 4,5-dihydro-1H-triazole 197 aromatizes promptly by losing sulfur dioxide and hydrogen chloride.

Scheme 67 Addition of Phenyl Azide to 1-Bromoethenesulfonyl Chloride[198]

Several perfluoroalkyl-substituted 1,2,3-triazoles linked to C6 of d-galactose and d-altrose are synthesized by this method.[199] For example, addition of the monosaccharide azide 199 to the perfluoroalkyl-substituted phenyl vinyl sulfones 200 yields the reversed nucleosides 201 in good yields (Scheme 68). Only a single 1,2,3-triazole derivative is formed in each of these reactions.

for references see p 587
Other sugar-derived 1,2,3-triazoles are prepared by a one-pot substitution–cyclization–oxidation procedure starting from α-arabinose and α-fucose. The key step in this process is an intramolecular 1,3-dipolar cycloaddition of an azide to the C=C bond of an α,β-unsaturated carboxylic ester. The resulting 4,5-dihydro-1H-triazole is readily aromatized by air oxidation.\[201]\ Analogous sugar-derived 4,5-dihydro-1H,1,2,3-triazoles (related to D-glucose and D-galactose) are stable but can be aromatized in good yields to the corresponding triazoles by oxidation with bromine.\[202]\ Maleimides and quinones have also been used as dipolarophiles in reactions with aryl azides,\[203–206\] silyl azides,\[207\] (azidoalkyl)indoles,\[208\] glycosyl azides,\[209\] (1-azidoalkyl)phosphonates\[210\] and α-azidocarboxylic esters.\[210\]

6-Deoxy-1,2:3,4-di-O-isopropylidene-6-[4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl]-α-D-galactopyranose, (201, R1 = C\(_3\)F\(_7\)). Typical Procedure:\[199]\n
A soln of azide 199 (0.85 g, 3.0 mmol) and sulfone 200 (R1 = C\(_3\)F\(_7\); 0.57 g, 2.40 mmol) in toluene (15 mL) was refluxed under argon for 17 h (TLC control). Then the solvent was evaporated under reduced pressure and the residue was purified by column chromatography (toluene/EtOAc 20:1); yield: 0.64 g (72%); mp 128–130 °C; \([\alpha]\)\(_D\) –49.2 (CHCl\(_3\)).

### 13.13.1.3.1.2.3 Method 3: Addition of Azides to Strained Alkenes

Azides react with alkenes to yield 4,5-dihydro-1H-1,2,3-triazoles. Whereas unactivated alkenes are sluggish in their reaction with aryl azides, in contrast strained bicyclic alkenes are particularly reactive.\[206\] For example, the reaction of 4-bromophenyl azide with hex-1-ene (in excess) affords the corresponding 4,5-dihydro-1H-1,2,3-triazole in 89% yield after 5.5 months at room temperature. At elevated temperatures (>80 °C), extensive decomposition of the 4,5-dihydro-1H-1,2,3-triazole is observed.\[211\] No detectable addition product is observed when the same azide and cyclohexene are left for three months at room temperature. Conjugated dienes are, however, much more reactive than the corresponding mono-unsaturated alkenes. For example, the adduct from the reaction of cyclohexa-1,3-diene and 4-bromophenyl azide begins to crystallize after three days at room temperature and, after 18 days, a 77% yield of the corresponding 4,5-dihydro-1H-1,2,3-triazole is obtained.\[211\] On the other hand, phenyl azide and substituted phenyl azides react with norbornene, in refluxing petroleum ether (60–90 °C) for three to four hours, to give the corresponding 1-aryl-4,5-dihydro-1H-1,2,3-triazole in 51–93% yield.\[212,213\] Norbornene and other strained alkenes also react with azidotrimethylsilane to give the corresponding 1-(trimethylsilyl)-4,5-dihydro-1H-1,2,3-triazole adducts in high yields.\[214\] The reaction of norbornene and dicyclopentadiene with several heteraryl methyl azides has been studied.\[212\]
The reaction of azides with norbornadiene is particularly interesting since it allows the synthesis of 4,5-unsubstituted triazoles 204 (Scheme 69). The thermolysis of the intermediate 4,5-dihydro-1H-1,2,3-triazole 203 gives the triazole and cyclopentadiene (via a retro-Diels–Alder reaction). For example, the reaction of norbornadiene with diethyl (azidomethyl)phosphonate \([202, X = \text{PO(OE})_2]\) in tetrahydrofuran at room temperature gives the 4,5-dihydro-1H-1,2,3-triazole 203. X = PO(OEt)\(_2\) in 92% yield. Thermolysis of this compound at 60°C yields the corresponding triazole in 74% yield.\([248]\) Similarly, \(\alpha\)-alkoxy- and \(\alpha\)-alkylsulfanyl-substituted azides, on reaction with norbornadiene in refluxing 1,4-dioxane, also give the corresponding triazoles in high yields.\([215]\) Phenyl azide and substituted phenyl azides also react with norbornadiene to give the corresponding 4,5-dihydro-1H-1,2,3-triazoles which, by thermolysis, yield the corresponding 1-aryl-1H-1,2,3-triazoles.\([213,216,217]\) In the reaction of norbornadiene with azidotrimethylsilane the initially formed 4,5-dihydro-1H-1,2,3-triazole is converted, spontaneously, into 2-(trimethylsilyl)-2H-1,2,3-triazole.\([214]\) Addition of a range of hetaroyl azides to the strained 5-methylenebicyclo[2.2.1]hept-2-ene, at room temperature, afforded carbonyl aziridines as the major product. These compounds are formed by loss of molecular nitrogen from the 4,5-dihydro-1H-1,2,3-triazole adducts.\([218]\)

The oxa and aza analogues of norbornadiene 205 (X = O, NCO\(_2\)Et) also react with phenyl azide to give 1,2,3-triazoles (Scheme 70). While triazole 207 is obtained in quantitative yield from 205 (X = O), the reaction with 205 (X = NCO\(_2\)Et) gives two triazoles: 207 (64%) and 1-phenyl-1H-1,2,3-triazole (36%).\([219,220]\)

Methylenecyclopropane is another interesting strained system that reacts readily with phenyl azide to give stable 4,5-dihydro-1H-1,2,3-triazoles.\([221]\) However, the equivalent reaction with alkyl 2-methylenecyclopropane-1-carboxylates 208 yields 1,2,3-triazoles 210 (Scheme 71).\([128]\) A probable mechanism for the rearrangement of the intermediate 4,5-dihydro-1H-1,2,3-triazoles 209 is shown in Scheme 71.

For references see p 587
**Scheme 71** Reaction of Phenyl Azide with Alkyl 2-Methylenecyclopropane-1-carboxylates

\[
\begin{align*}
R^1O_2C & \quad + \quad PhN_3 \\
\text{100 oC} & \quad 12-24 h \\
\rightarrow & \quad R^1O \quad N \\
\text{Ph} & \quad N
\end{align*}
\]

**Dimethyl 2-(1-Phenyl-1H-triazol-4-yl)butanedioate (210, R\(^1\) = Me; R\(^2\) = H; R\(^3\) = CO\(_2\)Me):**

**Typical Procedure**

A mixture of 208 (R\(^1\) = Me; R\(^2\) = H; R\(^3\) = CO\(_2\)Me; 2 g) and phenyl azide (10 mL) was heated on a steam bath for 12 h. The mixture was cooled and hexane was added to dissolve the remaining phenyl azide. The supernatant layer was decanted and the resulting brown solid was recrystallized (acetone/cyclohexane) to give triazole 210 (R\(^1\) = Me; R\(^2\) = H; R\(^3\) = CO\(_2\)Me); yield: 3.1 g (91%). A pure sample was obtained by recrystallization (EtOAc); mp 114–115°C.

**Method 4: Addition of Azides to Allenes**

Aryl azides undergo addition to allenes to give 4-alkylidene-4,5-dihydro-1H-1,2,3-triazoles in reasonable yields. 4,5-Dihydro-1H-1,2,3-triazoles 212, for example, are obtained in 29–73% yield from the reaction of 2,4-dimethylpenta-2,3-diene (211) (tetramethylallene) with phenyl azide and nitrophenyl azides (Scheme 72).

**Scheme 72** Addition of Aryl Azides to Tetramethylallene

When it is possible, the 4-alkylidene-4,5-dihydro-1H-1,2,3-triazoles aromatize spontaneously to 1,2,3-triazoles, as observed in the reaction of propa-1,2-diene with phenyl azide. In this case a mixture of 5-methyl-1-phenyl-1H-1,2,3-triazole (0.6%), 4-methyl-1-phenyl-1H-1,2,3-triazole (1%), and a diamine (18%) is obtained. Similarly, addition of phenyl azide to methyl buta-2,3-dienoate (213) gives a mixture of the triazoles 214 and 215 (9:1) in 67% yield (Scheme 73). The addition occurs exclusively at the \(\alpha,\beta\)-double bond.
Phenyl azide adds to cyclonona-1,2-diene (216) to give selectively the 4,5-dihydro-1H-1,2,3-triazole 217 (Scheme 74). This stable compound can be isomerized to the corresponding triazole 218 by treatment with a strong base.[223] When optically active (+)-(R)-cyclonona-1,2-diene is used the (+)-(S)-4,5-dihydro-1H-1,2,3-triazole 217 is obtained, suggesting a concerted cycloaddition mechanism.

2,4,6-Trinitrophenyl azide (220) (picryl azide) adds to (aryloxy)allenes 219 to give triazoles 222 or 223, depending on the substituents R1 and R5 (Scheme 75). The reactions proceed via the unisolated 4,5-dihydro-1H-1,2,3-triazoles 221, which undergo an exceptionally facile Claisen rearrangement to triazoles 222.[225] These compounds, unless blocked by a substituent at R1, rapidly tautomerize to the isomeric compounds 223. When R1 and R5 are chloro or methyl the cyclohexadienone derivatives 222 are isolated in 66–85% yield. When R1 or R5 is hydrogen, triazoles 223 are isolated in 67–79% yield.

\[ \text{Ar}^1 = 2,4,6-(\text{O}_2\text{N})_3\text{C}_6\text{H}_2 \]
An interesting one-pot procedure for the conversion of allenyl derivatives into 4,5-unsubstituted 1,2,3-triazoles has been described.[226,227] The method involves a sequential and cascade palladium-catalyzed azide formation (from aryl/hetaryl/vinyl iodides, allene, and sodium azide) followed by a 1,3-dipolar cycloaddition to norbornadiene and finally a retro-Diels–Alder reaction.

**1-Phenyl-1,4,5,6,7,8,9,10-octahydrocyclonona[d][1,2,3]triazole (218); Typical Procedure**[223]

A soln of cyclonona-1,2-diene (216; 1.22 g, 0.01 mol) and phenyl azide (1.19 g, 0.01 mol) in toluene (15 mL) was refluxed for 10 h. The viscous yellow oil, obtained upon solvent evaporation, crystallized when stored at rt for several days. Recrystallization [petroleum ether (bp 60–110°C)] gave 4,5-dihydro-1H-1,2,3-triazole 217; yield: 0.51 g (21%). A soln of the 4,5-dihydro-1H-triazole (1.00 g, 4.14 mmol) in 0.75 M NaOEt in EtOH (40 mL) was refluxed for 3 d. After solvent evaporation, the residue was extracted with Et₂O and the ether extract was washed with H₂O until the aqueous washes were neutral. The Et₂O layer was dried (MgSO₄) and evaporated to give 0.81 g of crude product. Crystallization (petroleum ether/benzene 3:1) afforded white crystalline triazole 218; yield: 0.70 g (70%); mp 77–78°C.

**Method 5: Addition of Azides to α-Acylphosphorus Ylides**

The addition of azides to α-acylphosphorus ylides is a versatile method for the synthesis of 1,2,3-triazoles. Combining different α-acyl- or α-alkoxycarbonyl phosphorus ylides 224 with azides of various types gives a range of substituted triazoles 226 (Scheme 76). The reaction is regioselective, it requires mild conditions (room temperature or refluxing benzene) and generally the triazoles are obtained in good to very good yields.

α-Acylphosphorus ylides are commonly represented in the three resonance forms 224A, 224B, and 224C. However, it has been demonstrated that they exist essentially or exclusively in the cis-enolate configuration 224C. The reaction of these ylides with azides is accelerated by electron-releasing substituents on the ylide and electron-withdrawing substituents on the azide. The polarity of the solvent has only a small effect on the reaction rate. Low entropies of activation are obtained for these reactions. All these kinetic data indicate that the mechanism of these reactions involves a concerted 1,3-dipolar cycloaddition of the azide to the C=C bond in 224C.[228] The resulting 4,5-dihydro-1H-1,2,3-triazoles 225 are converted into triazoles 226 by spontaneous elimination of triphenylphosphine oxide. When acyl or alkoxycarbonyl azides are used, the initially formed 1-substituted triazoles 226 (R¹ = COX) isomerize to the corresponding 2-substituted triazoles 227.[228,231] This synthetic method is, however, not general; with some phosphorus ylides, especially α-ethoxycarbonyl phosphorus ylides (224, R² = OEt), diazo compounds and other products are obtained rather than triazoles.[230–233] With these compounds, in the cases where 1,2,3-triazoles are formed the yields are moderate (when R¹ = Me) or very low (when R¹ = Ph).
Scheme 76  Addition of Azides to α-Acylphosphorus Ylides [228–230,233,234]

\[
\begin{align*}
R_1^O & \quad \text{Scheme 76} & R_2^O & \quad R_3^O \\
\end{align*}
\]

**Table: R1, R2, Conditions, Yield (%)**

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>Conditions</th>
<th>Yield (%)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(MeO)3C6H2</td>
<td>Me</td>
<td>benzene, reflux, 14–16 h</td>
<td>63</td>
<td>[233]</td>
</tr>
<tr>
<td>O(MeO)3C6H2</td>
<td>Ph</td>
<td>benzene, reflux, 14–16 h</td>
<td>52</td>
<td>[233]</td>
</tr>
<tr>
<td>acridin-9-yl</td>
<td>CH3NMe2</td>
<td>benzene, reflux, 2 h</td>
<td>49</td>
<td>[234]</td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>benzene, reflux, 48 h</td>
<td>80</td>
<td>[224]</td>
</tr>
<tr>
<td>Ph</td>
<td>4-O2NC6H4</td>
<td>benzene, reflux, 6 d</td>
<td>67</td>
<td>[228]</td>
</tr>
<tr>
<td>4-O2NC6H4</td>
<td>Me</td>
<td>benzene, reflux, 0.5 h</td>
<td>73</td>
<td>[228]</td>
</tr>
<tr>
<td>4-O2NC6H4</td>
<td>4-O2NC6H4</td>
<td>benzene, reflux, 48 h</td>
<td>98</td>
<td>[228]</td>
</tr>
<tr>
<td>4-MeOC6H4</td>
<td>Ph</td>
<td>benzene, reflux, 72 h</td>
<td>54</td>
<td>[228]</td>
</tr>
<tr>
<td>4-MeOC6H4</td>
<td>4-O2NC6H4</td>
<td>benzene, reflux, 10 d</td>
<td>70</td>
<td>[228]</td>
</tr>
<tr>
<td>T5</td>
<td>Me</td>
<td>CH2Cl2, rt, 0.25 h</td>
<td>98</td>
<td>[230]</td>
</tr>
<tr>
<td>T5</td>
<td>Ph</td>
<td>CH2Cl2, rt, 1 h</td>
<td>98</td>
<td>[230]</td>
</tr>
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<td>T5</td>
<td>4-O2NC6H4</td>
<td>CH2Cl2, rt, 10 h</td>
<td>87</td>
<td>[230]</td>
</tr>
<tr>
<td>Bz</td>
<td>Me</td>
<td>CH2Cl2, rt, 48 h</td>
<td>–</td>
<td>[228]</td>
</tr>
<tr>
<td>4-O2NC6H4CO</td>
<td>Me</td>
<td>CH2Cl2, rt, 24 h</td>
<td>–</td>
<td>[229]</td>
</tr>
<tr>
<td>4-O2NC6H4CO</td>
<td>Ph</td>
<td>CH2Cl2, rt, 24 h</td>
<td>–</td>
<td>[228]</td>
</tr>
<tr>
<td>4-MeOC6H4CO</td>
<td>Me</td>
<td>CH2Cl2, rt, 7 d</td>
<td>–</td>
<td>[228]</td>
</tr>
<tr>
<td>4-MeOC6H4CO</td>
<td>Ph</td>
<td>CH2Cl2, rt, 14 d</td>
<td>–</td>
<td>[229]</td>
</tr>
<tr>
<td>3-O2NC6H4CO</td>
<td>4-O2NC6H4</td>
<td>CH2Cl2, rt, 20 d</td>
<td>–</td>
<td>[229]</td>
</tr>
<tr>
<td>CO2Et</td>
<td>Ph</td>
<td>CH2Cl2, rt, 48 h</td>
<td>–</td>
<td>[229]</td>
</tr>
<tr>
<td>CO2Et</td>
<td>4-O2NC6H4</td>
<td>CH2Cl2, rt, 14 d</td>
<td>–</td>
<td>[229]</td>
</tr>
</tbody>
</table>

*Note: R3 = H for all examples in the table.

For references see p 587
The reaction of a quinuclidin-3-yl α-acylphosphorus ylide with 3-nitrobenzoyl azide in refluxing acetonitrile, followed by column chromatography on basic alumina, affords the corresponding N-unsubstituted 1,2,3-triazole in 52%.\(^{235}\) The reaction of vinyl azides with α-acylphosphorus ylides is a convenient method for the synthesis of 1-vinyl-1H-1,2,3-triazoles.\(^{236}\) The reaction of α-acylphosphorus ylides with azides has been used to prepare a range of 1-[(diethoxyphosphoryl)methyl]-1H-1,2,3-triazoles 230\(^{237}\) and 1,2,3-triazole nucleosides 231\(^{238}\) and 232\(^{239}\) (Scheme 77). Addition of acetyl azide to α-acyl-α-alkylphosphorus ylides or acetylation of those phosphorus ylides and subsequent treatment with sodium azide gives the same 1,2,3-triazoles.\(^{240}\)

### Scheme 77

**Addition of (Diethoxyphosphoryl)methyl Azides and Glycosyl Azides to α-Acylphosphorus Ylides**\(^{237–239}\)

\[
\begin{align*}
\text{R}^1 &= H, \text{Ph}; \text{R}^2 = \text{Me, Ph, CO}_2\text{Et} \\
\text{R}^1 \text{P(OEt)}_2 \text{N}_3 + \text{PPh}_3^+ &\xrightarrow{\text{toluene, } 110^\circ\text{C}, 5-27\text{ h}} \text{61-83\%} \\
\text{R}^1 \text{P(OEt)}_2 \text{N}_3 + \text{PPh}_3^+ &\xrightarrow{\text{toluene, } 110^\circ\text{C, 45 min}} \text{38\%} \\
\text{R}^1 \text{P(OEt)}_2 \text{N}_3 + \text{PPh}_3^+ &\xrightarrow{\text{toluene, } 80^\circ\text{C, 60 h}} \text{59-82\%}
\end{align*}
\]

1-[(Diethoxyphosphoryl)alkyl]-1H-1,2,3-triazoles 230; **General Procedure**\(^{237}\)

A soln of diethyl (azidomethyl)phosphonate 228 (2 mmol) and α-acylphosphorus ylide 229 (2–2.3 mmol) in dry toluene (15 mL) was refluxed for 5–27 h. The solvent was then evaporated in vacuo. The product was separated from the Ph₃PO by flash chromatography to give analytically pure triazole 230.

### Method 6:

**Addition of Azides to Enamines or Enol Ethers**

Azides undergo addition to enamines 233 (R¹ = amino)\(^{241}\) and to enol ethers 233 (R¹ = alkoxy)\(^{242,243}\) under mild conditions, frequently at room temperature, to yield 4,5-dihydro-1H-1,2,3-triazoles 234 (Scheme 78). These reactions are completely regioselective; the amino or alkoxy group in the resulting 4,5-dihydro-1H-1,2,3-triazoles is in the 5-position. In some cases the 4,5-dihydro-1H-1,2,3-triazoles aromatize spontaneously to 1,2,3-triazoles 235, in others the aromatization is effected by heating the compound alone (for enol ether adducts) or by treatment with acid or base (Scheme 78).
The thermal elimination of nitrogen from the 4,5-dihydro-1H-1,2,3-triazoles is a possible competing reaction. Some dihydrotriazoles derived from cyclic enol ethers and enamines fail to give triazoles for this reason. In general, however, yields are very good. The reaction is most effective with azides bearing electron-withdrawing groups such as nitrophenyl, phenylsulfonyl, or ethoxycarbonyl. Sulfonyl azide adducts give N-unsubstituted triazoles, the substituent being lost on aromatization.

13.13.1.3.1.2.6.1 Variation 1: Addition of Azides to Enamines

There are substantial differences in the products obtained from the reactions of enamines with aryl azides or sulfonyl azides. Nitroenamine 236 (X = NO2), for example, reacts with aryl azides to yield the expected triazoles 237 while with tosyl azide it gives the N-unsubstituted triazole 238 (X = NO2) (Scheme 79). With sulfonylenamines 236 (X = SO2Ph, 4-O2NC6H4SO2) the corresponding triazoles 238 are also obtained. Similar results are observed in the reaction of methyl (E)-3-pyrrolidin-1-ylprop-2-enoate (239) with hetaroyl azides 240 (Scheme 79). In all cases methyl 1H-1,2,3-triazole-4-carboxylate is formed in approximately 90% yield. Dienamines also react with 4-nitrophenyl azide to give 1,2,3-triazoles but with tosyl azide only amidines are obtained (formed by decomposition of the intermediate 4,5-dihydro-1H-1,2,3-triazoles).

for references see p 587
An interesting difference in chemical behavior is observed with the two isomeric cyanoenamines 241 and 244 (Scheme 80). Both react with aryl azides to give 4,5-dihydro-1H-1,2,3-triazoles 242 and 245, respectively, which spontaneously aromatize to 1,2,3-triazoles 243 and 246.[246] However, under identical experimental conditions, in one case the elimination of hydrogen cyanide is the favorable process while in the other only amine is eliminated. Both reactions are completely regioselective. The elimination of hydrogen cyanide or amine is independent of the structure of the amine; the process depends only on the relative positions of the amino and cyano groups. These reactions can be done without solvent, at 62–65 °C, and the yields, in both cases, are very good (75–95%).

The synthetic versatility of this method is exemplified in Scheme 81: a range of 1,2,3-triazoles 249 are obtained in good yields from the reaction of (azidomethyl)phosphonates 247 with enamines 248.[124,249,250]

The synthesis of 4-(aminomethyl)-1H-1,2,3-triazoles (Scheme 82) is another interesting application of this method. Enamines 250 (resulting from the reaction of propenal with 2 equivalents of secondary amines) react with aryl azides to give 4,5-dihydro-1H-1,2,3-triazoles 251[251,252] which, upon treatment with base, are converted into triazoles 252. In a similar process, reaction of propenal with benzenethiol, followed by the addition of a secondary amine and an aryl azide gives 4-[(phenylsulfanyl)methyl]-4,5-dihydro-1H-1,2,3-triazoles which, after treatment with base, give mixtures of three triazoles, resulting from the elimination of the amine or the phenylsulfanyl group.[253] Thiopyrano[3,4-d]-1,2,3-triazoles can also be prepared in moderate yields from the reaction of enamines, derived from tetrahydrothiopyran-4-one, and aryl azides.[254]
The reactions of azides with enamines in which tautomerism is possible give mixtures of triazoles (Scheme 83).

Imines with an \( \alpha \)-methylene group can also react with azides via their enamine tautomers. This method has been extended to the solid-phase synthesis of 1,2,3-triazoles. The resin-bound 3-oxobutanamide 253 reacts with primary aliphatic amines yielding 3-aminobut-2-enamides which react with tosyl azide to give the polymer supported triazoles 254 (Scheme 84). Upon treatment with trifluoroacetic acid, the “free” triazoles (as trifluoroacetates) 255 are obtained in purities of up to 82% (\( ^1H \text{NMR, HPLC} \)).
Enamides 256, despite being less reactive than enamines, also react with aryl azides at room temperature (3 days to 10 months) to give 4,5-dihydro-1H-1,2,3-triazoles 257 as stable crystalline products (Scheme 85). In refluxing ethanol, however, the reaction yields the corresponding triazoles as the major product. The reaction of the 4,5-dihydro-1H-1,2,3-triazoles 257 with potassium hydroxide in refluxing methanol yields triazoles 258.[258]

**Scheme 84** Solid-Phase Synthesis of Triazoles via Enamines[257]

**Scheme 85** Reaction of Aryl Azides with Enamides[258]
Variation 2: Addition of Azides to Enol Ethers

As indicated in Section 13.13.1.3.1.2.6, azides react very readily with enol ethers to afford 4,5-dihydro-1H-1,2,3-triazoles in good yields. These reactions are completely regioselective. As an example, 2-ethoxypropene reacts with 4-nitrophenyl azide to give the 4,5-dihydro-1H-1,2,3-triazole 259 in 99% yield; when heated at 150 °C it eliminates ethanol and the corresponding 1,2,3-triazole 260 is formed in quantitative yield (Scheme 86). Cyclic enol ethers, like 2,3-dihydrofuran or 3,4-dihydro-2H-pyran, also react with azides to give the corresponding 4,5-dihydro-1H-1,2,3-triazoles 261. However, when these compounds are heated, nitrogen is evolved and the imino ethers 262 are formed.

The reaction of enol ethers with heterocyclic azides gives similar results. Aryl azides containing no electron-withdrawing groups add to the enolate ion of acetaldehyde (formed by cycloreversion of tetrahydrofuran in the presence of butyllithium) to give 1-aryl-4,5-dihydro-1H-1,2,3-triazol-5-ols 263 in very good yields (Scheme 87). These compounds are converted into the corresponding 1-aryl-1H-1,2,3-triazoles 264 in good to nearly quantitative yields by treatment with sodium methoxide in methanol or with potassium tert-butoxide in tert-butyl alcohol. In a similar process, benzylic azide and phenyl azide react with the enolate ions of methyl ketones to give mixtures of triazole derivatives. For example, benzylic azide reacts with acetone, in the presence of potassium tert-butoxide, to give a mixture (ca. 1:1) of 1-benzyl-5-methyl-1H-1,2,3-triazole (265) and 1-benzyl-4-isopropenyl-5-methyl-1H-1,2,3-triazole (266) (Scheme 87). When phenyl azide is used, triazole 267 is the main product. Under similar reaction conditions, phenylacetone reacts with organic azides to give triazoles 268 in high yields.

for references see p 587
**Scheme 87** Reaction of Azides with Enolates

\[
\begin{align*}
\text{O}^\text{−} + \begin{array}{c} \text{O} \end{array} & \xrightarrow{\text{THF, rt, } 1-24 \text{ h}} \begin{array}{c} \text{N} \end{array} \quad 70-99\% \\
\begin{array}{c} \text{N} \end{array} & \xrightarrow{\text{NaOR}, R \text{OH, rt, } 0.5-60 \text{ h}} \begin{array}{c} \text{N} \end{array} \quad 65-100\% \\
\end{align*}
\]

\[X = \text{H, 2-SMe, 2-SEt, 4-Me, 2-OMe, 3-OMe, 4-OMe}\]

**1-Benzyl-5-methyl-4-phenyl-1H-1,2,3-triazole** (268, \(R' = \text{Bn}\); Typical Procedure

Benzyl azide (2.48 mL, 0.02 mol) and phenylacetone (2.67 mL, 0.02 mol) were added to \(t\)-BuOK stock soln (20 mL). The mixture turned red and heat evolution was observed after a few min. After 2 h, the mixture was poured into ice water (150 mL). The crystalline product was washed with H\(_2\)O and pentane; crude product yield: 4.22 g (85%). Recrystallization (EtOAc/pentane) gave the pure product; mp 93–94°C.

**13.13.1.3.1.2.7 Method 7: Addition of Azides to Vinyl Acetate**

Azides undergo addition to vinyl esters of lower (C\(_1\)–C\(_4\)) carboxylic acids to yield 1-substituted 1,2,3-triazoles 269 in good yields (Scheme 88). Vinyl acetate is the most readily available and is the preferred vinyl ester substrate. Generally vinyl acetate is also used as solvent and the reaction takes place at 50–150°C. This method has been frequently used for the preparation of 1-aryl- and 1-benzyl-1H-1,2,3-triazoles with biological activities. Heteraryl azides also add to vinyl acetate to give the corresponding triazoles. Similar reaction with isopropenyl acetate yields the 5-methyl-1-substituted 1H-1,2,3-triazoles.
Scheme 88  Reaction of Azides with Vinyl Acetate[114,264–268]

\[
\begin{align*}
R_1N_3 + \text{AcO} & \xrightarrow{50–150^\circ C} \begin{array}{c}
\text{N} \\
\text{N}
\end{array} \quad R_1 \\
\end{align*}
\]

\[269\]

1-(4-Acetylphenyl)-1H-1,2,3-triazole (269, \( R_1 = 4-\text{AcC}_6\text{H}_4 \)); Typical Procedure:[267]

A soln of 4-azidoacetophenone (4.0 g, 24.8 mmol) and vinyl acetate (6 mL) in a closed tube was heated at 80 °C for 24 h. After evaporation of the solvent, the residue was dissolved in CHCl3 and the soln was washed with 2 M NaOH and 2 M HCl. The CHCl3 layer was evaporated in vacuo and the crude residue was recrystallized [benzene (CAUTION: carcinogen)]; yield: 2.86 g (61%); mp 169–171 °C.

13.13.1.3.1.2.8  Method 8:

Addition of Azides to Ketene Acetals

Ketene N,N-, S,S-, S,N, O,O-, and O,N-acetals react with organic azides or sodium azide to yield 1,2,3-triazoles. These reactions are completely regioselective but the yields are strongly dependent on the structure of the ketene acetal.

Aryl azides undergo 1,3-dipolar cycloaddition to 1,1-dimorpholinoethenes [270] to give 4,5-dihydro-1H-1,2,3-triazoles [271] (Scheme 89). When \( R_1 = \text{Me} \) the 4,5-dihydro-1H-1,2,3-triazoles [271] are stable and can be isolated.[253] These compounds are deaminated in almost quantitative yields (95–98%) to the corresponding triazoles [272] by treatment with acetic acid (60 °C, 30 min).[253] When \( R_1 \) is an electron-withdrawing group (COR2, CO2R2, SO2R2, NO2) the 4,5-dihydro-1H-1,2,3-triazoles [271] cannot be isolated or detected; the deamination process to [272] proceeds so rapidly that NMR monitoring of the reaction mixture does not allow detection of signals unequivocally associated with the structure [271].[269]

Scheme 89  Reaction of Aryl Azides with 1,1-Dimorpholinoethenes[253]

\[
\begin{align*}
\text{Ar}^1N_3, \text{toluene} & \xrightarrow{\text{rt or reflux}, 4–50 \text{ h}} \begin{array}{c}
\text{N} \\
\text{N}
\end{array} \quad \text{R}_1 \\
\end{align*}
\]

\[270\]

\[271\]

\[272\]

Cyclic ethene-1,1-diamines [273] react readily with 4-nitrophenyl azide to yield exclusively 1,2,3-triazoles [274] in excellent yields (Scheme 90). However, when phenyl azide or other substituted phenyl azides are used the reaction proceeds much more slowly and mixtures of triazoles [274] and [275] are obtained.[275] The formation of triazoles [274] can be explained by a mechanism where the ethene-1,1-diamines act as nucleophiles and attack the terminal nitrogen of the azide. Cyclization and elimination of one molecule of water yields the

\text{for references see p 587}
triazoles. The formation of triazoles 275 can be explained by a 1,3-dipolar cycloaddition of the azide to the ethene-1,1-diamine, followed by Dimroth rearrangement of the intermediate dihydrotriazole and finally aromatization by deamination.\[270]\]

**Scheme 90**  Reaction of Aryl Azides with Cyclic Ethene-1,1-diamines\[270]\]

2-Nitroethene-1,1-diamines of types 276 or 280, with at least one free NH group, react with 4-chlorobenzensulfonyl azide to give 4-nitro-1,2,3-triazoles 279 and 281, respectively, in low to moderate yields (Scheme 91). The mechanism of formation of these compounds is likely to involve Dimroth rearrangement of the 4,5-dihydro-1H-triazoles 277, resulting from 1,3-dipolar cycloaddition, to 278 followed by elimination of the arylsulfonylamine as show in Scheme 91.\[271]\]

**Scheme 91**  Reaction of 4-Chlorobenzensulfonyl Azide with 2-Nitroethene-1,1-diamines\[271]\]
Aroylketene dithioacetals 282 react with sodium azide via intermediates 283 to afford N-unsubstituted 1,2,3-triazoles 284 in good yields (Scheme 92). Under similar conditions, the reaction with 4,4-bis(methylsulfanyl)but-3-en-2-one does not yield the corresponding triazole.

Scheme 92 Reaction of Aroylketene Dithioacetals with Sodium Azide

![Scheme 92 Reaction of Aroylketene Dithioacetals with Sodium Azide](image)

Tosyl azide reacts smoothly with acylketene S,N-acetals 285 in ethanolic sodium hydroxide solutions to give 1,2,3-triazoles 286 in good yields (Scheme 93). Under similar conditions, the reaction of tosyl azide with cyclic ketene S,N-acetals 288 results in intractable tar, however, in dioxane, at higher temperature, the fused thiazolo[3,2-c][1,2,3]triazole derivatives 289 are obtained in good yields. Detosylation of compounds 286 with concentrated sulfuric acid leads to the corresponding 4-acyl-1,2,3-triazol-5-arnines 287.

Scheme 93 Reaction of Acylketene S,N-Acetals with Tosyl Azide

![Scheme 93 Reaction of Acylketene S,N-Acetals with Tosyl Azide](image)

Ketene O,0-acetals (1,1-bis-enol ethers) 290 react with aryl azides to give triazoles 291 in varying yields (Scheme 94). With temperature control and in the presence of an excess of the ketene acetal, the intermediate 4,5-dihydro-1H-1,2,3-triazole is obtained. The intermediate 4,5-dihydro-1H-1,2,3-triazole obtained from the reaction of ethyl azidoformate and ketene acetics decomposes readily at room temperaturr, the reaction path-

For references see p 587
way depending on the presence of the substituents on the 4-position.\[276] With benzoyl azide the main products are oxazole derivatives.\[275]

Scheme 94  Reaction of Ketene O,O-Acetals with Azides\[154,274]

\[
\begin{array}{c}
\text{R}^1\text{H} \quad + \quad \text{Ar}_1\text{N}_3 \\
\text{EtO} \quad \text{EtO} \\
\end{array}
\]

4-Acyl-5-(tosylamino)-1H-1,2,3-triazoles 286; General Procedure for Reaction of Acylketene S,N-Acetals with Tosyl Azide\[273]

A soln of NaOH (4.80 g, 0.12 mol) in EtOH (10 mL) was added slowly (5 min) to an ice-cooled and stirred suspension of the ketene S,N-acetal 285 (0.01 mol) and tosyl azide (2.36 g, 0.012 mol) in EtOH (10 mL), and the mixture was further stirred at rt for 10 h. It was then poured over crushed ice (150 g), acidified with 20% AcOH (30 mL), and extracted with CHCl₃ (3 x 50 mL). The organic extract was washed with H₂O (3 x 50 mL), dried (Na₂SO₄), and evaporated to give crude triazoles 286, which were further purified by recrystallization (EtOH).

13.13.1.3.1.3  Reaction of Azides with Active Methylene Compounds

The base-catalyzed condensation of azides with active methylene compounds (the Dimroth reaction) is a versatile method for the preparation of 1H-1,2,3-triazoles. It was first described by Dimroth in 1902.\[277,426] Depending on the functional groups present in the active methylene compound used, the substituent in the 5-position of the triazole can be an alkyl or aryl group, a hydroxy group, an alkoxycarbonyl group, or an amino group. Although the reactions are stepwise,\[278] they are completely regioselective. The mechanism of the Dimroth reaction can be envisaged as a nucleophilic attack by the carbanion on the terminal nitrogen of the azide, followed by cyclization to a dihydrotriazole and aromatization. In accord with this mechanism, the reaction goes least readily with azides bearing electron-releasing groups. The reactions are generally carried out with alkoxides in alcohols at room temperature or under reflux. However, in some cases better results are obtained using potassium tert-butoxide in tetrahydrofuran,\[279] sodium amide in diisopropyl ether,\[280] or potassium carbonate in dimethyl sulfoxide.\[281]

13.13.1.3.1.3.1  Method 1:  Reaction of Azides with 1,3-Diketones, 3-Oxo Esters, or 3-Oxooamides

Organic azides react with 1,3-diketones, 3-oxo esters, or 3-oxoamides to yield, generally in good yields, 1H-1,2,3-triazoles with a carbonyl group in position 4 (Scheme 95). The reaction with aryl or hetaryl azides gives better yields. With simple vinyl azides\[282] and 2-azidovinyl ketones\[283] the expected 1-vinyl-1,2,3-triazoles are obtained. However, when 1-azidovinyl ketones are reacted with 3-oxo esters in the presence of triethylamine the initially formed 1-vinyl-1,2,3-triazoles undergo further reaction with another molecule of the oxo ester.\[284] In hexamethylphosphoronic triamide, 4-nitrophenyl azide reacts smoothly with acyclic 1,3-diketones and 3-oxo esters to afford the corresponding triazoles 293 in almost quantitative yields.\[285] However, with five- and six-membered cyclic 1,3-diones it gives mainly the corresponding diazo derivatives. 1,3-Dicarbonyl compounds react with tosyl azide in hexamethylphosphoronic triamide to give only the corresponding diazo compounds, usually in high yields.\[285]
Scheme 95  Reaction of Azides with 1,3-Diketones, 3-Oxo Esters, or 3-Oxo-amides\[135,267,281,286–295\]

\[ R_1N_3 + \overset{N}{\overset{N}{\overset{N}{\overset{R_1}{\overset{\text{base}}{O}}}}} \overset{\text{Conditions}}{\overset{R_3}{\overset{R_2}{\overset{\text{Yield}^a (\%)}}{\overset{\text{Ref}}{O}}}} \]

\[ R^2 = \text{alkyl, aryl}; R^3 = \text{alkyl, aryl, OR}_4, \text{NR}_4R_5 \]

<table>
<thead>
<tr>
<th>R(^1)</th>
<th>R(^2)</th>
<th>R(^3)</th>
<th>Conditions</th>
<th>Yield(^a) (%)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-O(_2)NC(_6)H(_4)</td>
<td>Me</td>
<td>Me</td>
<td>NaOEt, EtOH, rt, 5 h</td>
<td>83</td>
<td>[267]</td>
</tr>
<tr>
<td>3-HO-4-Me(_2)O(_2)CC(_6)H(_3)</td>
<td>Ph</td>
<td>Ph</td>
<td>Et(_3)N, MeOH, reflux, 15 h</td>
<td>60</td>
<td>[286]</td>
</tr>
<tr>
<td>2-O(_2)NC(_6)H(_4)</td>
<td>Me</td>
<td>OEt</td>
<td>NaOEt, EtOH, 0(^\circ)C, 2 h</td>
<td>56</td>
<td>[287]</td>
</tr>
<tr>
<td>Ph</td>
<td>Me</td>
<td>OMe</td>
<td>Et(_3)N, MeOH, 70(^\circ)C, 10 d</td>
<td>68</td>
<td>[135]</td>
</tr>
<tr>
<td>3,5-Cl(_2)C(_6)H(_3)CH(_2)</td>
<td>Me</td>
<td>OEt</td>
<td>K(_2)CO(_3), DMSO, 35(^\circ)C, 18 h</td>
<td>89</td>
<td>[241]</td>
</tr>
<tr>
<td>2-O(_2)N-4-ClC(_6)H(_4)</td>
<td>Me</td>
<td>NHPh</td>
<td>NaOEt, EtOH, rt, 18 h</td>
<td>80</td>
<td>[287]</td>
</tr>
<tr>
<td>4-(HO(_2)CCH(_2)O)C(_6)H(_4)</td>
<td>Me</td>
<td>NET(_2)</td>
<td>NaOEt, EtOH, reflux, 16 h</td>
<td>65</td>
<td>[288]</td>
</tr>
<tr>
<td>4-pyridyl</td>
<td>4-O(_2)NC(_6)H(_4)</td>
<td>OEt</td>
<td>NaOEt, EtOH, rt, 24 h</td>
<td>86</td>
<td>[249]</td>
</tr>
<tr>
<td></td>
<td>Me</td>
<td>Me</td>
<td>NaOEt, EtOH, rt, 4 h</td>
<td>90</td>
<td>[248]</td>
</tr>
<tr>
<td></td>
<td>Ph</td>
<td>OEt</td>
<td>NaOEt, EtOH, rt, 4 h</td>
<td>71</td>
<td>[291]</td>
</tr>
<tr>
<td>MeO</td>
<td>4-O(_2)NC(_6)H(_4)</td>
<td>OEt</td>
<td>NaOEt, EtOH, 0–3(^\circ)C, 6 h</td>
<td>n.r.</td>
<td>[242]</td>
</tr>
<tr>
<td>Cl</td>
<td>Me</td>
<td>NHPh</td>
<td>NaOEt, EtOH, 0(^\circ)C to rt, 6 h</td>
<td>n.r.</td>
<td>[230]</td>
</tr>
<tr>
<td>acridin-9-yl</td>
<td>Me</td>
<td>Me</td>
<td>NaOMe, MeOH, rt, 24 h</td>
<td>62</td>
<td>[294]</td>
</tr>
<tr>
<td>acridin-9-yl</td>
<td>Me</td>
<td>OMe</td>
<td>KOH, MeOH, rt, 12 h</td>
<td>75</td>
<td>[254]</td>
</tr>
</tbody>
</table>

\(^a\) Yields determined by NMR

\( R^3 = \text{alkyl, aryl, OR}_4, \text{NR}_4R_5 \)

for references see p 587
Aryl azides react with 2-substituted 1H-indane-1,3(2H)-diones to give fairly stable tricyclic 4-acyl-4,5-dihydro-1H-triazol-5-ols in good yields.[296] With tosyl azide the isolated products are isoquinolinediones.[296] Ethyl 2-oxocyclododecanecarboxylate (294) reacts with phenyl azide, in the presence of 1 equivalent of sodium ethoxide, to give the 1H-1,2,3-triazol-5-ol 295 in 48% yield (Scheme 96).[297]

Scheme 96 Reaction of Ethyl 2-Oxocyclododecanecarboxylate with Phenyl Azides[297]

3-Oxoamides react with sulfonyl azides in a different way than with alkyl or aryl azides. In this case, the sulfonyl azide acts as a diazo transfer agent and the nitrogen of the amide function is involved in the formation of the 1,2,3-triazole ring. As indicated in Scheme 97, in the presence of sodium ethoxide, tosyl azide reacts with 3-oxoamides 296 to give the sodium salts of 4-acyl-1H-1,2,3-triazol-5-ols in almost quantitative yields. However, attempts to convert salts 297 into the corresponding hydroxy derivatives leads to the formation of diazoamides 298.[298]

Scheme 97 Reaction of Tosyl Azide with 3-Oxoamides[298]

Dimethyl 3-oxopentanedioate (299) reacts with aryl[299] and glycosyl azides[300] to yield selectively triazoles 300 (Scheme 98).
Diethyl 2-oxobutanedioate, ethyl 2,4-dioxo-4-phenylbutanoate, and ethyl 4-(2-furyl)-2,4-dioxobutanoate, all as sodium salts, react with aryl azides to afford triazoles in low yields (Scheme 99).\(^{301}\)

**Scheme 98** Reaction of Dimethyl 3-Oxopentanedioate with Azides

\[
\begin{align*}
\text{R}^1 & \quad \text{Conditions} \quad \text{Yield (\%)} \quad \text{Ref} \\
\text{Ph} & \quad \text{Et}_2\text{N, MeOH, reflux, 4 d} \quad 62 \quad [299] \\
4-\text{ClC}_6\text{H}_4 & \quad \text{Et}_2\text{N, MeOH, reflux, 1 d} \quad 76 \quad [299] \\
4-\text{O}_2\text{NC}_6\text{H}_4 & \quad \text{Et}_2\text{N, MeOH, reflux, 1 d} \quad 94 \quad [299] \\
4-\text{AcC}_6\text{H}_4 & \quad \text{Et}_2\text{N, MeOH, reflux, 1 d} \quad 82 \quad [299] \\
\text{BzO} & \quad \text{K}_2\text{CO}_3, \text{DMSO, rt, 15 h} \quad 95 \quad [100] \\
\text{BzO} & \quad \text{K}_2\text{CO}_3, \text{DMSO, rt, 24 h} \quad 93 \quad [100] \\
\text{BnO} & \quad \text{K}_2\text{CO}_3, \text{DMSO, 45 °C, 24 h} \quad 80 \quad [100]
\end{align*}
\]

**Scheme 99** Reaction of 2-Oxobutanedioate and 2,4-Dioxobutanoate Derivatives with Azides\(^{301}\)

**Method 2:**

**Reaction of Azides with Malonic Esters, Malonamides, or Acetamides**

The base-catalyzed reaction of organic azides with malonic acid derivatives is one of the best methods for the synthesis of 1\(H\)-1,2,3-triazol-5-ols 303 with an alkoxy (or aryloxy) carbonyl or carbamoyl functions in the 4-position (Scheme 100). As observed with other active methylene compounds, these reactions are stepwise and completely regioselective.

for references see p 587
Scheme 100  Reaction of Azides with Diethyl Malonate[281,302–304]

\[
\text{R}_1\text{N}_3 + \text{EtO}_2\text{C-}CO_2\text{Et} \xrightarrow{\text{base}} \left[ \begin{array}{c}
\text{EtO}_2\text{C} \\
\text{HO} \\
\text{N} \\
\text{NR}_1 \\
\text{EtO}_2\text{C} \\
\text{HO} \\
\text{N} \\
\text{NR}_1
\end{array} \right]
\]

<table>
<thead>
<tr>
<th>R(^1)</th>
<th>Conditions</th>
<th>Yield (%)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bn</td>
<td>K(_2\text{CO}_3), DMSO, 35 °C, 44 h</td>
<td>77</td>
<td>[281]</td>
</tr>
<tr>
<td>Bn</td>
<td>NaOMe, MeOH, reflux, 15 h</td>
<td>88</td>
<td>[302]</td>
</tr>
<tr>
<td>3,5-C(_2\text{Cl}_2\text{H}_3)(_2\text{CH}_2)</td>
<td>K(_2\text{CO}_3), DMSO, 40 °C, 72 h</td>
<td>96</td>
<td>[281]</td>
</tr>
<tr>
<td>4-MeOC(_6\text{H}_4)(_2\text{CH}_2)</td>
<td>K(_2\text{CO}_3), DMSO, 35 °C, 72 h</td>
<td>92</td>
<td>[281]</td>
</tr>
<tr>
<td>4-MeOC(_6\text{H}_4)(_2\text{CH}_2)</td>
<td>NaOEt, EtOH, reflux, 18 h</td>
<td>67</td>
<td>[303]</td>
</tr>
<tr>
<td>4-pyridyl</td>
<td>NaOMe, MeOH, rt, 24 h</td>
<td>75</td>
<td>[304]</td>
</tr>
</tbody>
</table>

Malonamides 304 (X = CONHR\(^1\)) give an unusual reaction with phenyl azide from which 1H-1,2,3-triazol-5-ols 306 are isolated; aniline is also formed (Scheme 101).[305] A mechanism has been suggested involving cyclization of the triazene intermediate 305 with displacement of aniline. Similar behavior is observed in the reaction of N-methylphenylacetamide (304, X = Ph; R\(^1\) = Me) with phenyl azide.[305] However, with phenylacetamide (304, X = Ph; R\(^1\) = H) a mixture of two triazoles is obtained: the corresponding triazole 306 (R\(^1\) = H; X = Ph) and 1,4-diphenyl-1H-1,2,3-triazol-5-ol. With malonic esters and amides substituted at the central carbon, triazole formation is accompanied by decarboxylation and 4-alkyl- or 4-aryl-1H-1,2,3-triazol-5-ols are obtained.[305,306]

Scheme 101  Reaction of Phenyl Azide with Malonamides and Phenylacetamide[305]

\[
\text{PhN}_3 + X \text{CONHR}^1 \xrightarrow{\text{NaOEt}} \left[ \begin{array}{c}
\text{X} \\
\text{NH}^1
\end{array} \right]
\]

N-Arylsulfonylmalonamide derivatives 307 and malonohydrazides 309 react with tosyl azide to give selectively 1-(arylsulfonyl)- and 1-(arylmethyleneamino)-1H-1,2,3-triazol-5-ols 308 and 310, respectively, in moderate to good yields (Scheme 102).[307] The mechanism of the reaction involves a diazo group transfer followed by subsequent cyclization of the intermediate diazomalonate derivative.
Scheme 102  Reaction of Tosyl Azide with Malonohydrazides and N-Tosylmalonamides

\[
\begin{align*}
R^1R^2N & \xrightarrow{\text{TsN₃, NaOEt, EtOH}} R^1R^2N^+ \text{SO₂Ar¹} \\
R¹ = H, Me; R² = Ts, 4-O₂NC₆H₄; Ar¹ = 4-Tol, Ph
\end{align*}
\]

62-68%

The reaction of phosphonyl and phosphinyl acetamides with tosyl azide, in the presence of potassium tert-butoxide, yields 1H-1,2,3-triazolols, presumably via diazo derivatives (Scheme 103).

Scheme 103  Reaction of Tosyl Azide with Phosphonyl and Phosphinyl Acetamides

\[
\begin{align*}
\text{R}^1\text{R}^2\text{P} \xrightarrow{\text{TsN₃, NaOEt, EtOH}} & \text{R}^1\text{R}^2\text{P} \text{CONH}_2 \\
\text{R}¹ = \text{OEt} & 56\% \\
\text{R}¹ = \text{Ph} & 70\%
\end{align*}
\]

1-(Arylmethyleneamino)-1H-1,2,3-triazol-5-ol Sodium Salts

The malonohydrazide (2 mmol) was suspended in a soln of NaOEt (0.136 g, 2 mmol) in EtOH (12 mL) and tosyl azide (0.40 g, 2 mmol) was added dropwise at 0–5 °C. The mixture was stirred for 2 h after which the precipitate was collected by filtration and dried.

Method 3:
Reaction of Azides with Acetonitrile Derivatives

Organic azides react with acetonitrile derivatives to give 1-substituted 1H-1,2,3-triazol-5-amines in good yields (Scheme 104). However, to avoid Dimroth rearrangement of the products, the reactions must be carried out at low temperatures (0–20 °C).

In the reactions of acetonitrile derivatives with 2-substituted aryl azides (e.g., 2-nitrophenyl azide, 2-azidobenzoic acid, or 2-azidobenzonitrile), the 1H-1,2,3-triazol-5-amine can react further by condensation of the amino group with the ortho substituent on the 1-phenyl group, resulting in the formation of fused 1,2,3-triazoles.

Best yields are obtained with aryl, hetaryl, and benzyl azides but some good results have also been obtained with alkyl azides.
### Scheme 104 Reaction of Azides with Acetonitrile Derivatives

$$R^1N_3 + R^2CN \rightarrow R^1N=NR^2\text{ (315)}$$

**R** = aryl, CN, CO<sub>2</sub>R<sub>3</sub>, CONR<sub>3</sub>R<sub>4</sub>, PO(OEt)<sub>2</sub>

<table>
<thead>
<tr>
<th><strong>R&lt;sup&gt;1&lt;/sup&gt;</strong></th>
<th><strong>R&lt;sup&gt;2&lt;/sup&gt;</strong></th>
<th><strong>Conditions</strong></th>
<th><strong>Yield (%)</strong></th>
<th><strong>Ref</strong></th>
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<tr>
<td>(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;5&lt;/sub&gt;Me</td>
<td>Ph</td>
<td>t-BuOK, THF, rt, 12 h</td>
<td>98</td>
<td>[279]</td>
</tr>
<tr>
<td>Me</td>
<td>t-Bu</td>
<td>LDA, Et&lt;sub&gt;2&lt;/sub&gt;O, –78 to 0°C, 1 d</td>
<td>35</td>
<td>[115]</td>
</tr>
<tr>
<td>Bn</td>
<td>Bn</td>
<td>NaNH&lt;sub&gt;2&lt;/sub&gt;, iPr&lt;sub&gt;2&lt;/sub&gt;O, reflux, 7 d</td>
<td>24</td>
<td>[280]</td>
</tr>
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<td>CH&lt;sub&gt;3&lt;/sub&gt;SPh</td>
<td>2-FC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;, DMSO, rt, 16 h</td>
<td>29</td>
<td>[116]</td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>NaOMe, MeOH, 0°C to rt, 24 h</td>
<td>99</td>
<td>[317, 318]</td>
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<tr>
<td>4-pyridyl</td>
<td>Ph</td>
<td>NaOMe, MeOH, rt, 24 h</td>
<td>82</td>
<td>[104]</td>
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<tr>
<td>4-&lt;sub&gt;O&lt;/sub&gt;2NC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;Me</td>
<td>NaOMe, MeOH, rt, 24 h</td>
<td>89</td>
<td>[304]</td>
</tr>
<tr>
<td>Bn</td>
<td>Ph</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;, DMSO, rt to 40°C, 24 h</td>
<td>84</td>
<td>[281]</td>
</tr>
<tr>
<td>Bn</td>
<td>t-BuOK</td>
<td>THF, rt, 12 h</td>
<td>78</td>
<td>[279]</td>
</tr>
<tr>
<td>Bn</td>
<td>CN</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;, DMSO, rt to 40°C, 18 h</td>
<td>48</td>
<td>[279]</td>
</tr>
<tr>
<td>Bn</td>
<td>CONH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>NaOEt, ETOH, reflux, 5 h</td>
<td>84</td>
<td>[281]</td>
</tr>
<tr>
<td>Bn</td>
<td>CONH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>NaOEt, ETOH, reflux, 1 h</td>
<td>81</td>
<td>[119]</td>
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<tr>
<td>Bn</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td>NaOEt, ETOH, reflux, 3 h</td>
<td>25</td>
<td>[119]</td>
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<td>Bn</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;H</td>
<td>NaOEt, ETOH, reflux, 4 h</td>
<td>20</td>
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<tr>
<td>Ph</td>
<td>CONH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>NaOMe, MeOH, rt, 24 h</td>
<td>88</td>
<td>[120]</td>
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<tr>
<td>Ph</td>
<td>CONMe&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Et&lt;sub&gt;2&lt;/sub&gt;O, NaOMe, MeOH, 0°C, 24 h</td>
<td>74</td>
<td>[217]</td>
</tr>
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<td>4-HO&lt;sub&gt;2&lt;/sub&gt;CC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>CONH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>NaOMe, MeOH, rt, 7 d</td>
<td>61</td>
<td>[120]</td>
</tr>
<tr>
<td>2-&lt;sub&gt;O&lt;/sub&gt;2NC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>CONH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>NaOEt, ETOH, 0°C to rt, 23 h</td>
<td>55</td>
<td>[122]</td>
</tr>
<tr>
<td>3,3-dimethylbut-1-enyl</td>
<td>CONH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>NaOMe, MeOH, reflux, 30 min</td>
<td>62</td>
<td>[282]</td>
</tr>
<tr>
<td>1-naphthyl</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td>NaOEt, ETOH, 0°C to rt, 6 h</td>
<td>94</td>
<td>[123]</td>
</tr>
<tr>
<td>4-pyridyl</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td>NaOEt, ETOH, 0°C to rt, 16 h</td>
<td>86</td>
<td>[123]</td>
</tr>
<tr>
<td>4-quinolyl</td>
<td>CONH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>NaOEt, ETOH, 0°C to rt, 21 h</td>
<td>91</td>
<td>[123]</td>
</tr>
<tr>
<td>4-quinolyl</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td>NaOEt, ETOH, 0°C to rt, 21 h</td>
<td>79</td>
<td>[123]</td>
</tr>
</tbody>
</table>

**Ref** = 1,2,3-Triazoles
The reaction of cyanoacetamide with glycosyl azides, in aqueous dimethylformamide with potassium hydroxide and at room temperature gives 5-amino-1-glycosyl-1H-1,2,3-triazole-4-carboxamide shows that this type of cycloaddition has a two-step mechanism. Also using cyanoacetamide and glycosyl azides, a study of the influence of the reaction conditions (the nature of the solvent and base) on the retention or inversion of the configuration of the anomeric carbon has been described. A range of 1-(substituted benzyl)-5-amino-1H-1,2,3-triazole-4-carboxamides has been prepared from the reaction of cyanoacetamide with benzyl azides.

Treatment of 2-oxocyclododecanecarbonitrile (316) with phenyl azide in the presence of a catalytic amount of sodium ethoxide for four days at room temperature leads to the formation of 1H-1,2,3-triazol-5-amine (317) and lactam (318) in 60 and 10% yield, respectively (Scheme 105). A mechanism for the formation of these two compounds has been proposed.

**Scheme 105**  
Reaction of 2-Oxocyclododecanecarbonitrile with Phenyl Azide

Sulfonyl azides do not generally give triazoles with activated methylene compounds. However, in aqueous alkaline solutions, sulfonyl azides, and also azidoformates and N,N-dimethylcarbamoyl azide, react with malononitrile to yield N-unsubstituted 1,2,3-triazoles (319, 320, and 321, respectively, in good to excellent yields, as indicated in Scheme 106. For references see p 587
13.13.1.3.1.4  **Method 4:**
**Reaction of Aryl Azides with Alkoxides**

Aryl azides react with sodium ethoxide or propoxide to afford 1-aryl-1H-1,2,3-triazoles 322 in moderate yields (Scheme 107). Two equivalents of azide are required, the second being reduced to aniline. The mechanism of this reaction probably involves the formation of an aldehyde by hydride transfer from the alkoxide to one mole of aryl azide. The attack of the carbanion of the aldehyde so produced on a second mole of the azide leads to the triazole. The reaction of tosyl azide with sodium butoxide yields only butyl toluenesulfonate.

**Scheme 107**  Reaction of Aryl Azides with Alkoxides

1-Aryl-4-methyl-1H-1,2,3-triazoles 322 (R1 = H); Typical Procedure for Condensation of Aryl Azides with Sodium Propoxide:

The appropriate aryl azide (0.03 mol) was added to a cold soln of NaOPr (0.04 mol) and the mixture was refluxed on a water bath for 24 h. The brownish product was acidified with concd HCl, steam-distilled, made alkaline, and steam-distilled again. The residual soln was extracted with Et2O; when the extract was evaporated, the 1-aryl-4-methyl-1H-1,2,3-triazole 322 (R1 = Me) separated and was crystallized (petroleum ether or EtOH/H2O).
13.13.1.4 By Formation of One N–N Bond

13.13.1.4.1 Fragment N–N – C–C–N

13.13.1.4.1.1 Method 1: Cyclization of α-Diazoamides

α-Diazoamides can be cyclized to 1H-1,2,3-triazoles by treatment with base[298,308,309,329] or by other methods. Some reactive α-diazoamides cyclize spontaneously to the corresponding triazoles; one example is indicated in Scheme 108. The intermediate α-diazoamides 324, generated in situ from the reaction of ethyl N-(diazoacetyl)glycinate (323) with benzoyl bromides, cyclize spontaneously to triazoles 325.[330]

Scheme 108  Cyclization of Ethyl N-(3-Aryl-2-diazo-3-oxopropanoyl)glycinates[330]

![Scheme 108](image)

Reaction of α-diazoamide 326 with phosphorus pentachloride gives methyl 1-benzyl-5-chloro-1H-1,2,3-triazole-4-carboxylate (328) through the intermediate imidoyl chloride 327 (Scheme 109).[331] N-Unsubstituted 5-halo-1H-1,2,3-triazoles are also obtained in good to excellent yields by treatment of diazomalononitrile derivatives with hydrogen halides.[1]

Scheme 109  Cyclization of a Diazomalonamide[331]

![Scheme 109](image)

13.13.1.4.1.2 Method 2: Thermolysis of α-Azidoacetophenone (Phenylsulfonyl)hydrazones

α-Azidoacetophenone (phenylsulfonyl)hydrazones 330, prepared by the reaction of the corresponding α-bromoacetophenone (phenylsulfonyl)hydrazones with sodium azide, are converted into 4-aryl-1H-1,2,3-triazoles 332, in good yields on heating in refluxing benzene (Scheme 110). The reaction proceeds probably via the elimination of benzene-sulfonic acid from the intermediate 2-(phenylsulfonyl)-2,5-dihydro-1H-1,2,3-triazoles 331.[332] The α-bromoacetophenone (phenylsulfonyl)hydrazones 329 react with benzyl-

for references see p 587
ideneaniline to yield 4-aryl-1-phenyl-1H-1,2,3-triazoles (19–25%) and substituted 2,3,4,5-tetrahydro-1,2,4-triazines (20–45%).[333]

Scheme 110  Thermolysis of α-Azidoacetophenone (Phenylsulfonyl)hydrazones[332,333]

\[
\begin{align*}
\text{Ar}^1 &\xrightarrow{\text{Br}} \text{SO}_2\text{Ph} \\
\text{N} &\xrightarrow{\text{NaN}_3, \text{DMF}} 82-94\% \\
\text{N} &\xrightarrow{\text{SO}_2\text{Ph}} 71-96\% \\
\text{Ar}^1 &\xrightarrow{\text{N}_2, \text{PhSO}_2\text{H}} 82-94\% \\
\end{align*}
\]

\[\text{Ar}^1 = 4-\text{XC}_6\text{H}_4; X = \text{H}, \text{Br}, \text{Cl}, \text{NO}_2, \text{Me}, \text{Ph}, \text{N} \equiv \text{NPh}\]

13.13.1.4.1 Method 3: Cyclization of α-Hydroxyimino Hydrazones

Cyclic α-hydroxyimino hydrazones 334 and 337 (prepared from α-hydroxyimino ketones 333 and 336, respectively) on heating at 170–190°C for three hours in diethylene glycol containing potassium hydroxide yield the N-unsubstituted 1,2,3-triazoles 335 and 338 (Scheme 111). The yield of triazole significantly decreases as the size of the ketone ring increases from five- to six- to seven-membered, that is as the rings become more flexible and the hydrazone and oxime groups less coplanar.[334,335] Under the same conditions, acyclic α-hydroxyimino hydrazones do not give triazoles; in this case, the normal Wolff–Kishner reduction products are obtained.

Scheme 111  Cyclization of α-Hydroxyimino Hydrazones[334,335]

\[
\begin{align*}
\text{HO}_\text{N} &\xrightarrow{\text{H}_2\text{NNH}_2} \text{OH} \xrightarrow{\text{KOH, diethylene glycol}} 15-52\% \\
\text{OH} &\xrightarrow{\text{KOH, diethylene glycol}} 170-190\;^\circ\text{C}, 3\;\text{h} 32\% \\
\end{align*}
\]

Glyoxal O-benzylloxime hydrazone 340, generated in situ by addition of glyoxal O-benzylloxime 339 to a 10-fold excess of hydrazine, gives 1-(benzyloxy)-1H-1,2,3-triazole 341 by oxidative cyclization (Scheme 112). Copper(II) sulfate is the best oxidant but manganese dioxide and nickel peroxide can also be used.[336]
3,8-Dihydroindeno[1,2-d][1,2,3]triazole (335, n = 1); Typical Procedure[335]:

1H-Indene-1,2(3H)-dione 1-hydrazone 2-oxime (334, n = 1; 930 mg, 5.3 mmol) and KOH (1.23 g, 22 mmol) in purified diethylene glycol (50 mL) was heated, with a stream of N₂ bubbling through it, until the temperature reached 170–190 °C (ca. 30 min). Heating was maintained at this temperature for 3 h and N₂ was bubbled through the soln for the entire time. The mixture was then cooled, diluted with 1 M aq KOH (400 mL), and extracted with CH₂Cl₂ (4 × 200 mL). The alkaline soln was acidified with HCl and the pH was adjusted to 7 with NaHCO₃. The soln was again extracted with CH₂Cl₂ (4 × 200 mL). Each extract was back-washed with sat. aq NaCl (2 × 100 mL). These organic extracts were combined, dried (Na₂SO₄), filtered, and evaporated in vacuo to yield a weakly acidic fraction (584 mg) which was sublimed (100 °C/0.2 Torr) to yield triazole 335 (n = 1); yield: 432 mg (52%); mp 144 °C.

13.13.1.4.1.4 Method 4: Cyclization of α-Hydroxyimino Aroyl- or Arylsulfonylhydrazones

Oxidation of α-hydroxyimino aroylhydrazones 342 with lead(IV) acetate in acetic acid gives 1-(aryloxy)-4,5-dimethyl-1H-1,2,3-triazoles 344 in moderate yields (Scheme 113). This transformation probably involves an intramolecular [1,3]-aroyl migration in the intermediate 343.[337]

α-Hydroxyimino tosylhydrazones 345 are converted into 4-aryl-5-methyl-1H-1,2,3-triazol-1-ols 347 in good yields by thermal cyclization of salts 346 (Scheme 114).[24] The α-diazo oximes 348 are probable intermediates in this transformation. Attempts to prepare 4,5-dimethyl-1H-1,2,3-triazol-1-ol by this method failed.[24]
Scheme 114  Cyclization of α-Hydroxyimino Tosylhydrazones[24]

\[
\begin{align*}
\text{Ar}^1 & = \text{Ph, 4-MeOC}_{6}H_{4}\\
\end{align*}
\]

1-(Aryloxy)-4,5-dimethyl-1\textit{H}-1,2,3-triazole 344 by Oxidation of α-Hydroxyimino Aroylhydrazones; General Procedure[337]

A soln of 342 (1 mmol) in AcOH/CH\textsubscript{2}Cl\textsubscript{2} (1:5, 30 mL) was added over 20 min to a stirred soln of Pb(OAc)\textsubscript{4} (4 mmol) in dry CH\textsubscript{2}Cl\textsubscript{2} (30 mL). The soln was stirred at 0°C for 30 min and then 10% aq Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} was added. The organic layer was separated, washed with brine, dried, and evaporated. The resulting residue was either chromatographed or recrystallized from the appropriate solvent.

13.13.1.1.4.1.5 Method 5:
Cyclization of 1,2-Diketone Bis(hydrazones) Derivatives

1,2-Diketone bis(hydrazones) and some of their derivatives such as bis( semicarbazones), bis(arylsulfonylhydrazones), and bis(acylhydrazones) are converted into 1\textit{H}-1,2,3-triazol-1-amines. The cyclization of these compounds is carried out by oxidation or by treatment with acids or bases.

13.13.1.1.4.1.5.1 Variation 1:
Cyclization of 1,2-Diketone Bis(hydrazones)

Oxidation of bis(hydrazones) 349 with manganese dioxide or mercury(II) oxide gives 1\textit{H}-1,2,3-triazol-1-amines 350 (Scheme 115). Although two isomeric triazoles would be expected from unsymmetrical bis(hydrazones), compounds 349 give only the 4-aryl-1,2,3-triazol-1-amines.\[338\] Other vicinal bis(hydrazones) have been converted into 1\textit{H}-1,2,3-triazol-1-amines.\[339-342\] The major disadvantage of this method is that unless the conditions are carefully controlled, complete oxidation of the bis(hydrazones) occurs and the isolated products are alkynes. Pyrolysis of cyclooctane-1,2-dione bis(hydrazone) yields the corresponding N-unsubstituted 1\textit{H}-1,2,3-triazole.\[342\]
13.13.1.4.1.5.2 Variation 2: Cyclization of 1,2-Diketone Bis(arylsulfonylhydrazones)

Vicinal bis(arylsulfonylhydrazones) 351 can be cyclized using either acid or base to give 1-(arylsulfonylamino)-1H-1,2,3-triazoles. When unsymmetrical 1,2-diketones are used, the two possible triazoles 352 and 353 are obtained (Scheme 116). Benzil bis(tosylhydrazone) cyclizes to 4,5-diphenyl-1-(tosylamino)-1H-1,2,3-triazole by oxidation with either mercury(II) or lead(IV) acetates in acetic acid. This type of triazole is also obtained by thermal or photochemical decomposition of the dianions of the bis(tosylhydrazones) of 1,2-diketones. The 1-(arylsulfonylamino)-1H-1,2,3-triazoles are converted into 1H-1,2,3-triazol-1-amines by treatment with sulfuric acid.

4,5-Diphenyl-1-(tosylamino)-1H-1,2,3-triazole (352, R¹ = R² = Ph; Ar¹ = 4-Tol);
Typical Procedure:[345]
Benzil bis(tosylhydrazone) (74 g, 0.14 mol) was added rapidly to a stirred soln of KOH (9 g, 0.16 mol) in ethylene glycol (400 mL) at 120 °C. After 10 min the soln was cooled to 40 °C and H₂O was added slowly, with rapid stirring, until a precipitate began to appear. The mixture was then acidified with 2 M HCl and more H₂O was added until the total volume was 1 L. The precipitate was then collected by filtration, dried, and washed well with petroleum ether to leave the triazole; yield: 43 g (81%); mp 232–233 °C (EtOH).

13.13.1.4.1.5.3 Variation 3: Cyclization of 1,2-Diketone Bis(semicarbazones)

The 1,2-diketone bis(semicarbazones) 354 undergo cyclization on treatment with lead(IV) acetate to give 1-ureido-1H-1,2,3-triazoles 355 (Scheme 117). These compounds are hydrolyzed with concentrated hydrochloric acid to give the corresponding 1H-1,2,3-triazol-1-amines 356.[350]

For references see p 587
Scheme 117  Cyclization of 1,2-Diketone Bis(semicarbazones)\(^{[350]}\)

![Scheme 117](image)

<table>
<thead>
<tr>
<th>(R^1)</th>
<th>(R^2)</th>
<th>1-Ureido-1(H)-1,2,3-triazole 355 Yield (%)</th>
<th>mp (°C)</th>
<th>1(H)-1,2,3-Triazol-1-amine 356 Yield (%)</th>
<th>mp (°C)</th>
<th>Ref</th>
</tr>
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<tbody>
<tr>
<td>Me</td>
<td>Me</td>
<td>30</td>
<td>225–226</td>
<td>65</td>
<td>89–91</td>
<td>([350])</td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>40</td>
<td>209–211</td>
<td>55</td>
<td>126–128</td>
<td>([350])</td>
</tr>
<tr>
<td>Ph</td>
<td>Me</td>
<td>34</td>
<td>207–208</td>
<td>55</td>
<td>142–144</td>
<td>([350])</td>
</tr>
<tr>
<td>4-Tol</td>
<td>Me</td>
<td>40</td>
<td>203–204</td>
<td>58</td>
<td>164–165</td>
<td>([350])</td>
</tr>
<tr>
<td>4-BrC(_6)H(_4)</td>
<td>Me</td>
<td>38</td>
<td>204–205</td>
<td>50</td>
<td>169–171</td>
<td>([350])</td>
</tr>
<tr>
<td>4-Tol</td>
<td>H</td>
<td>32</td>
<td>224–226</td>
<td>52</td>
<td>123–124</td>
<td>([350])</td>
</tr>
</tbody>
</table>

1-Ureido-1\(H\)-1,2,3-triazoles 355; General Procedure\(^{[350]}\)
Pb(OAc)\(_4\) (0.021 mol) was added to a suspension of bis(semicarbazone) 354 (0.02 mol) in CH\(_2\)Cl\(_2\) (100 mL) and the mixture was stirred at rt for 3 h. The mixture was filtered and the precipitate was treated with MeOH. The methanolic soln upon evaporation gave the 1-ureido-triazole which was recrystallized (MeOH or EtOH).

Variation 4: Cyclization of 1,2-Diketone Bis(acylhydrazones)

1,2-Diketone Bis(acylhydrazones) undergo oxidative cyclization to 1\(H\)-1,2,3-triazol-1-amine derivatives 360–362 (via intermediate 358/359) (Scheme 118). Lead(IV) acetate is the oxidant most used for this transformation. With bis(arylhydrazones) 357 (\(R^2\) = aryl) the principal products are imides 360 and amides 361.\(^{[351–355]}\) On the other hand, oxidation of bis(arylacetylhydrazones) 357 (\(R^2\) = arylmethyl) yields mainly 1-(arylacetylamino)-1,2,3-triazoles 362 (\(R^2\) = arylmethyl) in moderate yields.\(^{[356]}\) Oxidation of bis(acylhydrazones) 357 (\(R^2\) = Me) with lead(IV) acetate gives amides 361 (\(R^2\) = Me) as the primary products but partial hydrolysis to monoacetylamino derivatives 362 may occur in some cases during the workup.\(^{[357]}\) Lead(IV) acetate oxidation of mixed arylhydrazones of biacetyl affords pairs of isomeric triazoles (of the imide 360 type) in different proportions.\(^{[358]}\)
**Scheme 118** Cyclization of 1,2-Diketone Bis(acylhydrazones)\[357\]

![Chemical structure](attachment:image.png)

**Lead(IV) Acetate Oxidation of Bis(acylhydrazones)\[357\]**; **General Procedure:**\[357\]

To a stirred suspension of the bis(acylhydrazone) (2 mmol) in CH$_2$Cl$_2$ (20 mL) was added Pb(OAc)$_4$ (2.4 mmol) dissolved in CH$_2$Cl$_2$ (20 mL). The slight excess of the oxidant was checked throughout the experiment by the use of KI/starch paper and maintained, if necessary, by the addition of extra amounts of Pb(OAc)$_4$. When all the starting material was consumed the mixture was filtered and the filtrate was extracted successively with aq Na$_2$S$_2$O$_3$ and Na$_2$CO$_3$. The dried soln was evaporated under reduced pressure and the residue was chromatographed (medium pressure, silica gel, petroleum ether/EtOAc, gradient elution). The isolated products were further purified by recrystallization.

**Method 6:**

**Cyclization of (1,2-Diphenylethene-1,2-diyl)bis(trityldiazene)**

(1,2-Diphenylethene-1,2-diyl)bis(trityldiazene) (363) cyclizes readily to the 1H-1,2,3-triazol-1-amine derivative 365 when treated with acetic acid or left in suspension in ordinary unpurified chloroform for several days (Scheme 119).\[359\] The dipolar compound 364 is a probable intermediate in this transformation. Treatment of compound 365 with benzoyl chloride yields 1-benzoylamino)-4,5-diphenyl-1H-1,2,3-triazole. The synthetic usefulness of this method is still to be demonstrated. See also Section 13.13.2.1.3.1.2 for the cyclization of 1,2-diketone bis(arylhydrazones) to 2H-triazoles.

**Scheme 119** Cyclization of (1,2-Diphenylethene-1,2-diyl)bis(trityldiazene)\[359\]

![Chemical structure](attachment:image.png)

**4,5-Diphenyl-N-trityl-1H-1,2,3-triazol-1-amine (365)**\[359\]

A suspension of (1,2-diphenylethene-1,2-diyl)bis(trityldiazene) (363; 0.5 g, 0.69 mmol) in 90% AcOH (10 mL) was evaporated to one half of the original volume on a hot plate. The solid dissolved with disappearance of the red color in a few minutes. Upon cooling, the
white crystalline triazolamine 365 was separated; yield: 0.30 g (90%). Recrystallization (petroleum ether/benzene) gave crystals; mp 265–267°C.

13.13.1.5 By Formation of One N–C Bond

13.13.1.5.1 Fragment N–N–N–C–C

13.13.1.5.1.1 Method 1:
Cyclization of Linear Triazenes and Tetrazenes

Triazenes are a recognized intermediate in the synthesis of 1,2,3-triazoles starting from an azide and an activated methylene compound (see Section 13.13.1.1.3.1.3, Scheme 95). Stable triazene compounds can also be cyclized to 1,2,3-triazoles.[360–364] For example, 1-aryl-3-(cyanomethyl)triazenes 366 cyclize in aprotic media with Lewis base catalysis to give 1-aryl-1H-1,2,3-triazol-5-amins 367 (Scheme 120). If the reaction is carried out in protic media the cyclization is followed by Dimroth rearrangement and the isolated products are the isomeric N-aryl-1H-1,2,3-triazol-5-amins 368.[365] Treatment of chloroform solutions of triazenes 366 with suspended basic alumina for several days yields the 1H-1,2,3-triazol-5-amins 367 essentially free from isomers 368. However, refluxing the triazenes (X = 4-NO2 or 4-CN) in absolute ethanol for 1–2 hours gives triazoles 368 with no trace of the isomeric triazoles 367. In a similar process, 1-aryl-1H-1,2,3-triazol-5-ols are prepared by cyclization of 1-aryl-3-(ethoxycarbonylmethyl)triazenes.[364]

Scheme 120  Cyclization of Linear Triazenes[363]

\[
\begin{align*}
\text{alumina, CHCl}_3 & \quad \text{rt, 7 d} \quad \text{56–92%} \\
\end{align*}
\]

The 1,2,3-triazole system can also be formed by the isomerization of 1-(arylazo)aziridines 369 (Scheme 121). This isomerization is catalyzed by iodide ions and the product is a 1-aryl-4,5-dihydro-1H-1,2,3-triazole 371.[365] The isomerizations probably occur by a nucleophilic attack of iodide ion on the aziridinyl carbon to yield the ion 370, which subsequently displaces an iodide ion by the negatively charged nitrogen. Although the 4,5-dihydro-1H-1,2,3-triazoles 371 are obtained in high yields, this is a dangerous method since some 1-(arylazo)aziridines 369 explode violently on standing at room temperature for 20–30 minutes.[365]
Anodic oxidation of 1-aryl-3,3-dimethyltriazenes in acetonitrile gives 2-aryl-5-methyl-2\(H\)-1,2,3-triazole-4-carbonitriles in low yields.\(^{[366]}\) Methyl 1-benzyl-1\(H\)-1,2,3-triazole-4-carboxylate is obtained in 2\% yield, together with several other products, by photolysis of a tetraz-2-ene;\(^{[367]}\) this method has very limited synthetic interest.

1-Aryl-1\(H\)-1,2,3-triazol-5-amines 367 by Cyclization of 1-Aryl-3-(cyanomethyl)triazenes; General Procedure\(^{[363]}\)

The triazene 366 (250 mg) was dissolved in the minimum volume of CHCl\(_3\) (25–50 mL) and basic alumina (2.5 g) was added. The suspension was stirred at rt for 7 d. The mixture was filtered to remove alumina and the filtrate evaporated to dryness in vacuo. The residue was the 1\(H\)-1,2,3-triazol-5-amine 367.

13.13.1.5.1.2 Method 2: Cyclization of Vinyl Azides

In the presence of a base, vinyl azides (e.g., 372) cyclize to 1\(H\)-1,2,3-triazoles, such as 374 (Scheme 122).\(^{[85,190]}\) A probable mechanism for such transformation involves the formation of the anion of the vinyl azide, which then cyclizes to the aromatic triazole anion (e.g., 373). Protonation affords the final product.

Methyl 3,3-diazido-2-cyanoacrylate (375) reacts with amines to give vinyl azides 376, which undergo 1,5-cyclization to form triazoles 378 (via 4\(H\)-1,2,3-triazoles 377) in good yields (Scheme 123).\(^{[368]}\) Under controlled reaction conditions (catalytic amount of the amine and absence of moisture) vinyl azides 376 are converted into methyl 1,2,3-triazole-2-carboxylates 379.\(^{[369]}\)
Scheme 123  Reaction of Methyl 3,3-Diazido-2-cyanoacrylate with Amines\textsuperscript{[368,369]}

\[
\begin{align*}
N & \quad N \\
R_1R_2NH, CH_2Cl_2 & \quad 0 \text{ oC to rt, 12 h}
\end{align*}
\]

\[
\begin{align*}
& \quad 375 \\
& \quad 376 \\
& \quad 377 \\
& \quad 378 \\
\end{align*}
\]

\[
\begin{align*}
& \quad 379 \quad NR_1R_2 = \text{pyrrolidin-1-yl} \quad 90\% \\
& \quad NR_1R_2 = \text{piperidino} \quad 68\%
\end{align*}
\]

NR\textsuperscript{1}R\textsuperscript{2} = NEt\textsubscript{2}, pyrrolidin-1-yl, piperidino, morpholino, thiomorpholino, 4-methylpiperazin-1-yl, 4-benzylpiperazin-1-yl

13.13.1.5.1.3  Method 3: Cyclization of (Z)-2-(Formyloxy)vinyl Azides

(Z)-2-(Formyloxy)vinyl azides are converted into 1H-1,2,3-triazoles by using triethyl phosphite (Scheme 124).\textsuperscript{[370]} Addition of triethyl phosphite to formate 380 immediately initiates an exothermic reaction producing a deep orange solution. Evaporation of the solvent and purification by silica gel chromatography gives triazole 382. It has been shown by NMR that N-formyltriazole 381 (which can be isolated) is the initial product of cyclization. 4-Phenyl-1H-1,2,3-triazole is prepared by cyclization of formate 383 following the same methodology.\textsuperscript{[370]}

Scheme 124  Cyclization of (Z)-2-(Formyloxy)vinyl Azides\textsuperscript{[370]}

\[
\begin{align*}
& \quad 380 \\
& \quad 381 \\
& \quad 382 \quad 46\%
\end{align*}
\]
13.13.2 Synthesis by Ring Transformation

There are several heterocyclic compounds that, by chemical modification or just by isomerization, are converted into $^{1}H$-1,2,3-triazoles or $^{2}H$-1,2,3-triazoles (see also Section 13.13.2.2). Despite some synthetically interesting exceptions, in most cases the starting heterocycles are not readily available and the routes are unlikely to be general. The following are examples of transformations of this type that lead to $^{1}H$-1,2,3-triazole derivatives: (a) diazotization of isoxazol-4-amines to give triazol-1-ols, $^{[371,372]}$ (b) diazotization of 5-aminothiazol-2-ols to give triazol-4-ols, $^{[373]}$ (c) diazotization of 3-aminopyrimidinium salts to give 4-(3-oxoprop-1-enyl)-1,2,3-triazole derivatives, $^{[374,375]}$ (d) base-induced rearrangement of sydnoneimines to give triazol-4-ols, $^{[376]}$ (e) reaction of ethyl 2-amino-4,5-dihydrofuran-3-carboxylates with phenyl azide to give $^{1}H$-1,2,3-triazol-5-amines, $^{[377]}$ (f) thermolysis of 5-diazo-6-methoxyuracils results in the formation of 4-acyl-1,2,3-triazole derivatives, $^{[378–380]}$ (g) reaction of 1,2,4-triazin-3-ones with $N$-chlorinating agents, $^{[381]}$ (h) treatment of 1,2,4-triazin-3-one 2-oxides with acetic anhydride, $^{[382]}$ (i) reduction or oxidation of triazolotriazoles, $^{[383,384]}$ (j) diazotization of 7-aminocephalexins sulfoxides, $^{[385]}$ (k) thermolysis of mesoionic oxatrizololones in the presence of alkynes, $^{[386]}$ (l) reaction of 1,3,3-trimethyl-2-methylene-2,3-dihydro-$^{1}H$-indole with aryl azides, $^{[387]}$ (m) reaction of isothiazole dioxides with sodium azide, $^{[388]}$ (n) reaction of triazolo[1,5-$a$]pyridines with aniline, $^{[389]}$ (o) permanganate oxidation of substituted benzotriazoles, $^{[390–392]}$ (p) hydrolytic cleavage of 1,2,3-triazolo[4,5-$d$]pyrimidines, $^{[393–395]}$ and (q) reaction of 4-oxo-$^{4}H$-pyridino[1,2-$a$]pyrimidine-3-diazonium salts with primary alcohols $^{[396]}$.

The chemical transformation of 1,2,3-thiadiazoles into $^{1}H$-1,2,3-triazoles is a synthetically useful method. For example, base-catalyzed isomerization of 1,2,3-thiadiazol-5-amine derivatives affords $^{1}H$-1,2,3-triazole-5-thiols in high yields. $^{[397–401]}$ Also, thermolysis of 5-alkyl- or 5-[allyl(alkoxycarbonyl)amino]-1,2,3-thiadiazoles $^{384}$ in a sealed glass tube in the absence of solvent gives 5-(alkylsulfanyl)-$^{1}H$-1,2,3-triazoles $^{385}$ (Scheme 125).$^{[402]}$

Another example of this approach is the conversion of 5-chloro-1,2,3-thiadiazole-4-carbaldehyde $^{386}$ into $^{1}H$-1,2,3-triazole-4-carbothioamides $^{390}$ (Scheme 126).$^{[403]}$ A wide variety of amine derivatives can be used in this method. A probable mechanism for this transformation involves intermediates $^{387–389}$ and is indicated in Scheme 126. Other examples of conversion of 5-chloro-1,2,3-thiadiazole derivatives into $^{1}H$-1,2,3-triazoles are reported.$^{[404,405]}$

### Scheme 125

Thermolysis of 5-(Alkoxycarbonylamino)-1,2,3-thiadiazoles $^{[402]}$

```
```

R$^{1}$O$_{2}$C

R$^{2}$S

$^{384}$

$^{220\,^\circ C, 15\,min}$

$^{\text{CO}_{2}}$

R$^{2}$S

$^{385}$

R$^{1}$ = Me, Et, CH$_{2}$CH$_{2}$CH$_{3}$; R$^{2}$ = Me, Et

The reaction of diazoalkanes with 3,5-dichloro-2H-1,4-oxazin-2-ones 391 and 3-chloro-2H-1,4-benzoxazin-2-ones 395 is another interesting method for the synthesis of 1H-1,2,3-triazole derivatives (Schemes 127 and 128). The intermediate bicyclic or tricyclic triazolo-fused compounds 393 and 396 are converted into the monocyclic 1H-1,2,3-triazoles 394 or 397 by reaction with nucleophiles (amines, methanol, water). The first step of this procedure involves the selective attack of the diazoalkane to the imidoyl chloride function (e.g., giving 392) followed by ring closure. Reactions with diazomethane give higher yields (68–91%) of the fused triazoles than reactions with diazooethane or diazopropane (41–52%). The reaction conditions required for the ring cleavage of the lactone function in compounds 393 are dependent on the nucleophile: with propylamine or diethylamine it takes one hour at room temperature, with aniline it requires three hours at reflux and with methanol or water it takes 12 hours at reflux. The triazoles 394 obtained from this two-step procedure have the interesting α-chloro ketone substituent at N1, which may be used for the elaboration of other heterocycles.
Scheme 127  Reaction of Diazoalkanes with 3,5-Dichloro-2H-1,4-oxazin-2-ones\[406,407\]

\[ R'^1\}_{O\text{O}} Cl N + R'\text{CHN}_2 \xrightarrow{\text{Et}_2\text{O, } 0\text{ °C, } 3\text{ d}} R'^2\text{ClN}_2 \]

<table>
<thead>
<tr>
<th>Compound</th>
<th>( R^1 )</th>
<th>( R^2 )</th>
<th>( \text{Nu} )</th>
<th>Yield(^{a,b} ) (%)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>393</td>
<td>Me</td>
<td>H</td>
<td>-</td>
<td>91</td>
<td>[407]</td>
</tr>
<tr>
<td>393</td>
<td>Ph</td>
<td>H</td>
<td>-</td>
<td>81</td>
<td>[407]</td>
</tr>
<tr>
<td>393</td>
<td>2,6-Cl_2C_6H_4</td>
<td>H</td>
<td>-</td>
<td>72</td>
<td>[407]</td>
</tr>
<tr>
<td>393</td>
<td>2,6-Cl_2C_6H_4</td>
<td>Me</td>
<td>-</td>
<td>n.r.</td>
<td>[407]</td>
</tr>
<tr>
<td>393</td>
<td>Me</td>
<td>Et</td>
<td>-</td>
<td>n.r.</td>
<td>[407]</td>
</tr>
<tr>
<td>394</td>
<td>Me</td>
<td>H</td>
<td>OMe</td>
<td>95</td>
<td>[407]</td>
</tr>
<tr>
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<td>Ph</td>
<td>H</td>
<td>OMe</td>
<td>80</td>
<td>[407]</td>
</tr>
<tr>
<td>394</td>
<td>Me</td>
<td>H</td>
<td>NEt_2</td>
<td>87</td>
<td>[407]</td>
</tr>
<tr>
<td>394</td>
<td>Me</td>
<td>Et</td>
<td>OMe</td>
<td>28(^c)</td>
<td>[407]</td>
</tr>
<tr>
<td>394</td>
<td>2,6-Cl_2C_6H_4</td>
<td>Me</td>
<td>OMe</td>
<td>25(^c)</td>
<td>[407]</td>
</tr>
<tr>
<td>394</td>
<td>2,6-Cl_2C_6H_4</td>
<td>H</td>
<td>NHP_H</td>
<td>84</td>
<td>[407]</td>
</tr>
<tr>
<td>394</td>
<td>Me</td>
<td>H</td>
<td>OH</td>
<td>55</td>
<td>[407]</td>
</tr>
</tbody>
</table>

\(^a\) n.r. = not reported.
\(^b\) Yield of 394 from 393 or 393 from 391 unless otherwise stated.
\(^c\) Yield of 394 from 391.

Scheme 128  Reaction of Diazoalkanes with 3-Chloro-2H-1,4-benzoxazin-2-ones\[406,407\]

\[ R'\text{O} \_\text{Cl} N + R''\text{CHN}_2 \xrightarrow{\text{Et}_2\text{O, } 0\text{ °C, } 3\text{ d}} R'^2\text{N}_2 \]

\[ \text{NuH} \rightarrow \text{NuH} \]

\[ \text{R'}\text{O} \_\text{Cl} N \]

---

Methyl 1H-1,2,3-Triazole-5-carboxylates 394 and 397 (Nu = OMe); General Procedure: \[407\]

CAUTION: Diazomethane is explosive by shock, friction, or heat, and is highly toxic by inhalation.

Compound 391 or 395 (10 mmol) was slowly added to a Et₂O soln of CH₂N₂ (40 mmol) at 0°C. In the cases of MeCHN₂ and EtCHN₂, iPr₂O was used as solvent and, to avoid violent reactions, the initial temperature was −78°C. Afterwards the temperature was brought to 4°C and, after stirring for 3 d, the excess of diazo compound and the solvent was evaporated. Then the residue was recrystallized (CHCl₃/hexane) yielding 393 or 395. This compound (10 mmol) was dissolved in MeOH (50 mL), the soln was brought to reflux temperature, and the solvent was evaporated after 15 min (for 393) or 12 h (for 396). The residue was recrystallized (CHCl₃/hexane) yielding 394 or 397.

Aromatization

4,5-Dihydro-1H-1,2,3-triazoles (triazolines) are intermediates of 1,2,3-triazoles in many synthetic methods, especially those involving the addition of azides to C=CR bonds. In most cases 4,5-dihydro-1H-1,2,3-triazoles aromatize spontaneously to the corresponding triazoles but when they are stable compounds they can be aromatized by oxidation, elimination, or isomerization reactions. This subject is discussed in a review. \[4\] Some illustrative examples are described below.

Method 1: By Oxidation Reactions

The oxidative dehydrogenation of 4,5-dihydro-1H-1,2,3-triazoles 398 to triazoles 399 is carried out mainly with potassium permanganate or nickel peroxide (Scheme 129). Very good results are obtained when the reaction is carried out with potassium permanganate in a two-phase system (benzene/water) using tetrabutylammonium chloride as a phase-transfer catalyst.\[59,408,409\] If the reaction is run in a single phase in anhydrous benzene alone, the products are not triazoles but imines.\[410\] The oxidation of 4,5-dihydro-1H-1,2,3-triazoles bearing sterically crowded ortho-substituted phenyl groups in the 5-position with potassium permanganate gives low yields of the corresponding triazoles. In these cases much better results are obtained with nickel peroxide.\[58,411\]
Scheme 129 Oxidative Dehydrogenation of 4,5-Dihydro-1H-1,2,3-triazoles

\[
\begin{align*}
R^1 & \quad R^2 & \quad \text{Method} & \quad \text{Time (h)} & \quad \text{Yield (%)} & \quad \text{Ref} \\
4\text{-pyridyl} & \quad \text{Ph} & \quad A & \quad 2 & \quad 65 & \quad [408] \\
4\text{-pyridyl} & \quad 4\text{-Tol} & \quad A & \quad 2 & \quad 73 & \quad [408] \\
4\text{-pyridyl} & \quad 4\text{-ClC}_6\text{H}_4 & \quad A & \quad 3 & \quad 72 & \quad [408] \\
3\text{-pyridyl} & \quad 3\text{-O}_2\text{NC}_6\text{H}_4 & \quad A & \quad 8 & \quad 58 & \quad [408] \\
2\text{-quinoyl} & \quad \text{Ph} & \quad A & \quad 7 & \quad 40 & \quad [408] \\
2\text{-quinoyl} & \quad 4\text{-ClC}_6\text{H}_4 & \quad A & \quad 5.5 & \quad 57 & \quad [408] \\
4\text{-O}_2\text{NC}_6\text{H}_4 & \quad 4\text{-O}_2\text{NC}_6\text{H}_4 & \quad A & \quad 8 & \quad 38 & \quad [408] \\
2\text{-ClC}_6\text{H}_4 & \quad 4\text{-MeOC}_6\text{H}_4 & \quad B & \quad 4 & \quad 63 & \quad [54] \\
2\text{-ClC}_6\text{H}_4 & \quad 3,4\text{-ClC}_6\text{H}_3 & \quad B & \quad 3 & \quad 63 & \quad [54] \\
2,4\text{-ClC}_6\text{H}_3 & \quad \text{Ph} & \quad B & \quad 4 & \quad 65 & \quad [54] \\
2,4\text{-ClC}_6\text{H}_3 & \quad 4\text{-F}_3\text{CC}_6\text{H}_4 & \quad B & \quad 4 & \quad 70 & \quad [54] \\
2,6\text{-ClC}_6\text{H}_3 & \quad \text{Ph} & \quad B & \quad 4 & \quad 50 & \quad [54] \\
2,6\text{-ClC}_6\text{H}_3 & \quad 3\text{-ClC}_6\text{H}_4 & \quad B & \quad 3 & \quad 52 & \quad [54] \\
2,6\text{-ClC}_6\text{H}_3 & \quad 4\text{-BrC}_6\text{H}_4 & \quad B & \quad 3 & \quad 74 & \quad [54] \\
\end{align*}
\]

The oxidation of 1-aryl-4-methylene-5-morpholino-4,5-dihydro-1H-1,2,3-triazoles with 3-chloroperoxybenzoic acid affords 1-aryl-1H-1,2,3-triazole-4-carbaldehydes (Scheme 130). The corresponding carboxylic acids are also produced as byproducts.\(^{[412]}\) 4,5-Dihydro-1H-1,2,3-triazoles also react with halomethyl radicals to yield 1,2,3-triazole derivatives.\(^{[413]}\) Oxidation of 4,5-dihydro-1H-triazole with bromine gives triazole in 83% yield (Scheme 130).\(^{[202]}\)

Scheme 130 Oxidation of 4,5-Dihydro-1H-1,2,3-triazoles with 3-Chloroperoxybenzoic Acid\(^{[412]}\) or Bromine\(^{[202]}\)

13.13. Monocyclic N-Unsubstituted and 1-Substituted 1,2,3-Triazoles

FOR REFERENCES SEE P 587
1,5-Disubstituted 1H-1,2,3-Triazoles \(399\) by Nickel Peroxide Oxidation; General Procedure\[58\]

To a soln of the 4,5-dihydro-1H-1,2,3-triazole \(398\) (5 mmol) in benzene (100 mL) (CATION: carcinogen) was added dried, finely powdered NiO\(_2\) (0.06 mol) and the mixture was refluxed with vigorous magnetic stirring for 3–4 h. The mixture was then allowed to cool to rt and filtered under gravity. The residual NiO\(_2\) was washed with hot CHCl\(_3\), and the combined filtrates were subjected to rotary evaporation. The resulting oily residue was cooled and triturated with petroleum ether, or an Et\(_2\)O/petroleum ether mixture, when it solidified to a clean, crystalline mass, and the colored impurities remained in soln. Many of the triazoles at this point were quite pure, giving reasonably sharp melting points. Recrystallization (acetone/petroleum ether) gave analytically pure samples.

13.13. Method 2: By Elimination Reactions

Several methods for the synthesis of 1,2,3-triazoles involve spontaneous or induced elimination reactions. Typical examples are the reactions of azides with enamines, enol ethers, or enolates, and the thermal elimination of stable molecules from 4,5-dihydro-1H-1,2,3-triazoles via retro-Diels–Alder reactions (see, for example, Schemes 69 and 70).\[213,214,217,220,414\] The elimination of morpholine from compound \(404\) on heating in formic acid (Scheme 131) is another example. In this process the piperidine ring is cleaved reductively, with carbon dioxide evolution, and the triazole \(405\) is obtained.\[415\] In some cases the elimination reaction corresponds to an isomerization, as exemplified in the conversion of 4,5-dihydro-1H-triazole \(406\) into triazole \(407\) (Scheme 131).\[387\] The base-catalyzed dehydration of 4,5-dihydro-1H-1,2,3-triazol-5-ols (by treatment with hot methanolic potassium hydroxide) also gives high yields of the corresponding triazoles.\[263\] In a related method, 1-benzyl-4,5-difluoro-4,5-bis(trifluoromethyl)-4,5-dihydro-1H-1,2,3-triazole is converted into 1-benzyl-4,5-bis(trifluoromethyl)-1H-1,2,3-triazole in 69% yield by defluorination with tetrakis(dimethylamino)ethene.\[416\]
Synthesis by Substituent Modification

Substitution of Existing Substituents

Of Hydrogen

Method 1: Lithiation

1-Substituted 1,2,3-triazoles undergo lithiation with butyllithium or lithium diisopropylamide preferentially at the 5-position at –20 to –78°C. The resulting lithiated species react with carbon, silicon, halogen, and sulfur electrophiles to yield a range of 1,5-disubstituted 1,2,3-triazoles. This subject has been reviewed comprehensively.[417] At room temperature, the lithiated species rapidly undergo fragmentation to nitrogen and lithium ketenimines.[418,424]

The lithiation of 1-[2-(trimethylsilyl)ethoxy]methyl]-1H-1,2,3-triazole (408, R1 = SEM) followed by addition of an electrophile, gives moderate yields of 1,5-disubstituted 1,2,3-triazoles 410 (R1 = SEM) (Scheme 132).[419] The 2-(trimethylsilyl)ethoxymethyl (SEM) group is a particularly interesting N1 protecting group for lithiation: it is readily attached to the triazole, it helps the stabilization of the intermediate triazol-5-ylithium species by intramolecular coordination, and it is removed under very mild conditions (by heating with dilute hydrochloric acid or by treatment with tetrabutylammonium fluoride in refluxing tetrahydrofuran). In a similar way, 5-substituted 1-benzyloxy-1H-1,2,3-triazoles 410 (R1 = OBn) are obtained in excellent yields from lithiation of 1-(benzyloxy)-1H-1,2,3-triazole (408, R1 = OBn), followed by reaction with an electrophile.[336] Removal of the benzylox group by catalytic hydrogenation affords the corresponding 1H-1,2,3-triazol-1-ols in 98–100% yield. Compound 408 (R1 = OBn) is also converted into 5-acyl- and 5-aryl-1,2,3-triazoles through a lithiation–transmetalation strategy.[420] Lithiation of 1-methyl-1H-1,2,3-triazole with butyllithium or lithium 2,2,6,6-tetramethylpiperidide occurs at the 4-position and after quenching with aldehydes and carboxylic amides the corresponding 4-(1-hydroxyalkyl) and 4-acyl derivatives are obtained in good yields (71–86%).[421]

Scheme 132 Lithiation of 1H-1,2,3-Triazoles and Quenching with Electrophiles[336,419]

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>Electrophile</th>
<th>Yield (%)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEM</td>
<td>CH(OH)Ph</td>
<td>PhCHO</td>
<td>45</td>
<td>[419]</td>
</tr>
<tr>
<td>SEM</td>
<td>Bz</td>
<td>EtOCH2</td>
<td>21</td>
<td>[419]</td>
</tr>
<tr>
<td>SEM</td>
<td>Me</td>
<td>Mel</td>
<td>30</td>
<td>[419]</td>
</tr>
<tr>
<td>SEM</td>
<td>SPh</td>
<td>PhSSPh</td>
<td>80</td>
<td>[419]</td>
</tr>
<tr>
<td>SEM</td>
<td>Cl</td>
<td>Cl,CCL3</td>
<td>50</td>
<td>[419]</td>
</tr>
<tr>
<td>SEM</td>
<td>TMS</td>
<td>TMSCl</td>
<td>37</td>
<td>[419]</td>
</tr>
<tr>
<td>OBn</td>
<td>D</td>
<td>D2O</td>
<td>90</td>
<td>[336]</td>
</tr>
<tr>
<td>OBn</td>
<td>Me</td>
<td>Mel</td>
<td>93</td>
<td>[336]</td>
</tr>
</tbody>
</table>

For references see p 587
The lithiation of 1,2,3-triazoles is also carried out with 4,5-dibromotriazoles (both 1H- and 2H-) via a bromine–lithium exchange reaction. For example, 4,5-dibromo-1-(methoxymethyl)-1H-1,2,3-triazole (411) reacts with butyllithium, in diethyl ether or tetrahydrofuran at −80 to −70°C, at position 5 and the resulting lithiated derivative 412 is quenched with aqueous ammonium chloride, carbon dioxide, methyl chloroformate, benzophenone, or dimethyl or diphenyl disulfide to give high yields of the corresponding 5-substituted 1,2,3-triazoles 413 (Scheme 133).

### Scheme 133  Lithiation of 4,5-Dibromo-1-(methoxymethyl)-1H-1,2,3-triazole

![Scheme 133](image)

<table>
<thead>
<tr>
<th>R⁺</th>
<th>Electrophile</th>
<th>Yield (%)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>OBn</td>
<td>CHO</td>
<td>DMF</td>
<td>87</td>
</tr>
<tr>
<td>OBn</td>
<td>CO₂Me</td>
<td>CICO₂Me</td>
<td>76</td>
</tr>
<tr>
<td>OBn</td>
<td>CONMe₂</td>
<td>CICONMe₂</td>
<td>97</td>
</tr>
<tr>
<td>OBn</td>
<td>Cl</td>
<td>Cl₂CCl₃</td>
<td>88</td>
</tr>
<tr>
<td>OBn</td>
<td>Br</td>
<td>Br₂</td>
<td>86</td>
</tr>
<tr>
<td>OBn</td>
<td>I</td>
<td>I₂</td>
<td>96</td>
</tr>
<tr>
<td>OBn</td>
<td>SMe</td>
<td>MeSSMe</td>
<td>67</td>
</tr>
<tr>
<td>OBn</td>
<td>TMS</td>
<td>TMSCl</td>
<td>93</td>
</tr>
<tr>
<td>OBn</td>
<td>SnBu₃</td>
<td>Bu₃SnCl</td>
<td>91</td>
</tr>
</tbody>
</table>

5-Substituted 1-Benzoxy-1H-1,2,3-triazoles 410 (R⁺ = OBn) by Lithiation Followed by Reaction with an Electrophile; General Procedure.

Under N₂ at −78°C, a 0.1 M soln of 408 (R⁺ = OBn) in dry THF was treated dropwise with 1.6 M BuLi in hexane (1.2 equiv). After 5 min the electrophile was added (neat or dissolved in THF) and stirring was continued at −78°C for 1 h and at rt 1 h. The mixture was then quenched with sat. NH₄Cl and the product was extracted with CH₂Cl₂. The organic phase was washed with H₂O, dried (MgSO₄), concentrated, and purified by flash chromatography (EtOAc/heptane 1:2).
13.13.1.4.1.1.2 Method 2: N-Trimethylsilylation

1H-1,2,3-Triazole (414, R¹ = H)\(^{[421,430]}\) and 4-methyl-1H-1,2,3-triazole (414, R¹ = Me)\(^{[430]}\) react with chlorotrimethylsilane to give selectively 2-trimethylsilyl derivatives 415 (Scheme 134). Refluxing a mixture of 1H-1,2,3-triazole and hexamethyldisilazane for six hours gives an 81% yield of 1-(trimethylsilyl)-1H-1,2,3-triazole (416) and 2-(trimethylsilyl)-2H-1,2,3-triazole (417) in a 1:5 ratio.\(^{[422]}\) 1,2,3-Triazole N-oxides are C-silylated at ring and exocyclic α-positions in high yields in a one-pot procedure involving treatment with trimethylsilyl trifluoromethanesulfonate, iodotrimethylsilane, or tert-butyldimethylsilyl trifluoromethanesulfonate in the presence of 1,2,2,6,6-pentamethylpiperidine, diisopropylethylamine, or lithium tetramethylpiperidide.\(^{[423]}\)

Scheme 134 N-Trimethylsilylation of 1H-1,2,3-Triazoles\(^{[421,430]}\)

![Diagram of Scheme 134]

2-(Trimethylsilyl)-2H-1,2,3-triazole (415, R¹ = H)\(^{[421]}\)

TMSCI (10.7 mL, 84 mmol) was added to a soln of 1H-1,2,3-triazole (4.7 mL, 80 mmol) and Et₃N (12.1 mL, 87 mmol) in benzene (80 mL) ([CAUTION: carcinogen] under N₂ with ice cooling, and the mixture was stirred for 30 min and then refluxed at 80°C for 2 h. After filtration, the filtrate was evaporated to afford a residue, which was distilled under atmospheric pressure to give a colorless oil; yield: 9.72 g (86%); bp 148°C; ¹H NMR (CDCl₃, δ): 7.73 (s, 2H, hetaryl), 0.51 (s, 9H, TMS).

13.13.1.4.1.3 Method 3: Carboxylation

Carboxylation of C-lithio\(^{[424,425]}\) or Grignard\(^{[190,181]}\) derivatives of triazoles gives the corresponding carboxylic acids (Scheme 135). The lithiated species 412 (Scheme 133) is quenched with carbon dioxide to give 4-bromo-1-(methoxymethyl)-1H-1,2,3-triazole-5-carboxylic acid in 72% yield.\(^{[462]}\) The 2-methoxymethyl analogue of 412 yields methyl 4-bromo-2-(methoxymethyl)-2H-1,2,3-triazole-3-carboxylate in 71% when quenched with methyl chloroformate.\(^{[462]}\) Similarly, lithiation of 1-benzzyloxy-1H-1,2,3-triazole and quenching the resulting 5-lithiated species with methyl chloroformate or dimethylcarbamoyl chloride yields the corresponding 5-carboxylate (76%) or N,N-dimethyl carboxamide (97%) (see Scheme 132).\(^{[136]}\)

5-Amino-1H-1,2,3-triazole-4-carboxylic acid is obtained in low yield (14%) by heating 1H-1,2,3-triazol-4-amine with aqueous potassium hydrogen carbonate for 16 hours at 100°C.\(^{[624]}\)

for references see p 587
**Scheme 135**  Carboxylation of 1,4-Diphenyl-1H-1,2,3-triazole[424]

![Chemical structure of 1,4-Diphenyl-1H-1,2,3-triazole and its carboxylation product]

**1,4-Diphenyl-1H-1,2,3-triazole-5-carboxylic Acid (419); Typical Procedure:[424]**

To a stirred solution of 1,4-diphenyl-1H-1,2,3-triazole (418; 0.04 mol) in anhyd THF (80 mL) was added dropwise over 15 min, 1.6 M BuLi in hexane (26 mL) at −20 to −60 °C under N₂. When the addition was completed the mixture was stirred and cooled for an additional 0.5–1 h and then the mixture was poured onto solid CO₂. Acidification of an aqueous solution of the salt yielded the carboxylic acid 419; yield: 62%; mp 169–170°C (dec).

**13.13.1.4.1.4 Method 4: Acylation**

N-Unsubstituted 1,2,3-triazoles can be N-acylated by acyl halides and anhydrides with dry benzene or pyridine as the solvent. Substitution takes place at the 1-position but the acyl group may migrate to the 2-position on heating or on treatment with base.[173,429,430] Thus, acetylation with acetyl chloride gives 1-acetyl derivatives that rearrange to the 2-isomers above 120°C; acetylation by heating the triazoles with acetic anhydride gives the 2-acetyl derivatives directly. An alternative route to 1-acetyl-1H-1,2,3-triazoles is the reaction of 2-trimethylsilyl derivatives (e.g., 420) with acetyl chloride, giving products such as 421 (R₁ = Me) (Scheme 136).[173,430] This method can be used to prepare a range of 1-acyl-1H-1,2,3-triazoles, intermediates in the synthesis of oxazoles.[431]

**Scheme 136**  Acylation of 2-(Trimethylsilyl)-2H-1,2,3-triazole[173,430]

![Chemical structure of the reaction of 2-(trimethylsilyl)-2H-1,2,3-triazole with acetyl chloride]

Reaction of 4,5-diphenyl-1H-1,2,3-triazole with benzoyl chloride in pyridine gives the corresponding 1-benzoyl derivative.[432] The 1H-1,2,3-triazol-4-ols 422 react with benzoyl chloride in pyridine to yield the dibenzoyl derivatives 423 in high yields (Scheme 137).[433]

**Scheme 137**  Benzoylation of 1H-1,2,3-Triazol-4-ols[433]

![Chemical structure of the benzoylation reaction]

The reaction of 1,2,3-triazole with thiobenzoyl chloride (CCl₄, Et₃N, rt) yields a mixture of 1- and 2-thiobenzoyl-1,2,3-triazoles (22:78).[434] Similar results are obtained if the sodium salt of 1,2,3-triazole is used. However, only 1-thiobenzoyl-1,2,3-triazole is formed in 40% yield in the reaction of thiobenzoyl chloride with 2-(trimethylsilyl)-2H-1,2,3-triazole (CCl₄,
0°C.\cite{434} Reaction of 1,2,3-triazole with isocyanates affords the corresponding urea derivatives.\cite{435}

1,2,3-Triazoles are also C-acylated. In this case, the corresponding lithiated species are reacted with appropriate electrophiles (acyl halides, esters, amides) (see Section 13.13.1.4.1.1.1).

13.13.1.4.1.5 Method 5: Formylation

As shown in Scheme 132, C-lithiated 1,2,3-triazole species are quenched with dimethylformamide to afford the corresponding formyl derivatives in excellent yields;\cite{336} however other attempts to quench 1,2,3-triazolylithium compounds with dimethylformamide have failed.\cite{419,462} The Vilsmeier–Haack formylation of 1H-1,2,3-triazol-5-amines 424 gives the corresponding 1H-1,2,3-triazole-4-carbaldehydes 425 in good yields (Scheme 138). These compounds are hydrolyzed by dilute hydrochloric acid to the corresponding 5-amino derivatives 426.\cite{436} The Vilsmeier–Haack formylation of 1-benzyl-1,2,3-triazol-5-ols affords the corresponding 5-chloro-1H-1,2,3-triazole-4-carbaldehydes in 60–94% yields.\cite{302} 1H-1,2,3-Triazole-4-carbaldehydes are also prepared from the corresponding carbonitriles by catalytic hydrogenation (10% Pd/C, aq 0.1 M HCl)\cite{437} or by Raney nickel/formic acid reduction.\cite{438}

**Scheme 138** Vilsmeier–Haack Formylation of 1H-1,2,3-Triazol-5-amines\cite{446}

5-Amino-1-methyl-1H-1,2,3-triazole-4-carbaldehyde (426, R1 = Me); Typical Procedure:\cite{436}

POCl3 (0.16 g, 1 mmol) was added to 1-methyl-1H-1,2,3-triazol-5-amine (424, R1 = Me; 0.05 g, 0.5 mmol) in DMF (1 mL) at 0°C. The mixture was then heated at 85°C for 1 h, cooled, and poured onto ice (15 g). The mixture was adjusted to pH 7 and extracted with CHCl3 (3 × 20 mL). The extract was dried (K2CO3) and the solvent was removed in vacuo. The residue was recrystallized (benzene/cyclohexane 1:4) (CAUTION: carcinogen) to give 5-[(dimethylamino)methylene]amino)-1-methyl-1H-1,2,3-triazole-4-carbaldehyde (425, R1 = Me); yield: 75%; mp 136°C. This compound was refluxed for 20 min with 1 M HCl (16 equiv). The soln was neutralized and extracted with CHCl3. Evaporation of the dried (K2CO3) extract gave 426 (R1 = Me); yield: 65%.

13.13.1.4.1.6 Method 6: Arylation

1,2,3-Triazoles can be N-arylated by reaction with activated aryl halides. Reaction of 1H-1,2,3-triazole with 1-fluoro-2-nitrobenzene\cite{439} or 1-fluoro-4-nitrobenzene\cite{440} gives mixtures of the corresponding 1- and 2-nitrophenyl-1,2,3-triazoles. However, with 1-fluoro-2,4-dinitrobenzene and 2-chloro-1,3,5-trinitrobenzene only the 1-substituted derivatives are obtained (Scheme 139).\cite{440} Reaction of 1H-1,2,3-triazole with 2-chloro-1,3,5-trinitrobenzene (427, X = Cl), 2-fluoro-1,3,5-trinitrobenzene (427, X = F) or 1,2,3,5-tetranitrobenzene (427, X = NO2) in dioxane, dimethylformamide, or dimethyl sulfoxide for two days at room temperature gives 1-(2,4,6-trinitrophenyl)-1H-1,2,3-triazole (428) exclusively, except in one case.\cite{471} When the reaction is carried out with 2-fluoro-1,3,5-trinitrobenzene...
(427, X = F) in dimethyl sulfoxide, the 2-(2,4,6-trinitrophenyl)-2H-1,2,3-triazole is also formed; the final product composition depends on the way in which the reagents are mixed.

**Scheme 139** Arylation of 1H-1,2,3-Triazole with 2,4,6-Trinitrophenyl Derivatives[440]

1-(4-Tolyl)-1H-1,2,3-triazole is obtained in 11% yield from the reaction of 1H-1,2,3-triazole and 4-tolylboronic acid in the presence of anhydrous copper(II) acetate and pyridine.[441] A mixture of 9-(1H-1,2,3-triazol-1-yl)acridine (429) (49%) and 9-(2H-1,2,3-triazol-2-yl)acridine (430) (26%) is obtained from the reaction of the anion of 1H-1,2,3-triazole, generated using sodium hydride in dry dimethylformamide, with 9-chloroacridine (Scheme 140).[442] Deprotonation of triazole 431 with potassium hexamethyldisilazanide followed by the addition of pentafluoropyridine gives the 2-(4-pyridyl)-substituted triazole 432 in 49% yield (Scheme 140).[174]

**Scheme 140** Arylation of 1H-1,2,3-Triazoles with 9-Chloroacridine[442] and Pentafluoropyridine[174]

1,2,3-Triazoles are also C-arylated. The palladium-catalyzed reaction of the 1,2,3-triazol-5-ylzinc iodide species 433 with appropriate aryl and hetaryl iodides gives the 5-aryl-1- or 5-hetaryl-1H-1,2,3-triazoles 434 (Scheme 141).[420]
1-(2,4,6-Trinitrophenyl)-1H-1,2,3-triazole (428):[471]

A soln of 1H-1,2,3-triazole (4.20 g, 60 mmol), 2-fluoro-1,3,5-trinitrobenzene (427, X = F; 13.40 g, 60 mmol) and dry DMF (100 mL), protected from atmospheric moisture, was stirred at rt for 3 d. This soln was then poured with stirring into H₂O (2 L). The precipitated product was collected by filtration, washed with H₂O, and dried. The product was then dissolved in a minimal amount of acetone (~400 mL), and to this stirred soln was added H₂O (1.5 L), dropwise at first, until crystallization was induced, at which time the flow was increased to a slow, steady stream. The precipitated product was again collected by filtration, washed with H₂O, and dried to give white crystals; yield: 14.6 g (90%); mp 214 °C (dec).

13.13.1.4.1.1.7 Method 7: Alkylation

1,2,3-Triazoles can be N- and C-alkylated. N-alkylation is readily achieved by one of the following methods: (i) reaction with alkyl halides, dimethyl sulfate, methyl tosylate, or methyl fluorosulfonate (ii) by reaction with alcohols in acidic media, (iii) by addition to aziridines, (iv) by conjugate addition to activated alkenes and alkynes, and (v) by the Mannich reaction. Alkylation with alkyl halides requires the use of a base; generally a sodium alkoxide, sodium hydride, or sodium hydroxide are employed.

Alkylation of N-unsubstituted 1,2,3-triazoles under basic, neutral or weakly acidic conditions generally affords mixtures of the N-alkyl derivatives. The 1,2,3-triazole itself and the symmetrical 4,5-disubstituted triazoles give mixtures of 1- and 2-alkyl isomers while unsymmetrical 4,5-substituted triazoles frequently give all the three possible monoalkyl derivatives. Some selectivity for 1-alkylation is observed when silver or thallium salts of the triazoles are reacted with iodoalkanes. Selective alkylation at N1 is obtained by reaction of a 2-(trimethylsilyl)-2H-1,2,3-triazole with primary alkyl halides in the presence of tetrabutylammonium fluoride.

It has been shown that 1H-1,2,3-triazole reacts with propan-2-ol in concentrated sulfuric acid to yield 1-isopropyl-1H-1,2,3-triazole (80%) as the sole reaction product. The scope of this method is still to be demonstrated.
Alkylation of 1-methyl- and 1-benzyl-1H-1,2,3-triazole gives only the 1,3-disubstituted triazolium salts.\[455\] The 2-alkyl-2H-1,2,3-triazole 1-oxides are quantitatively methylated at the N-oxygen by trimethylxonium tetrafluoroborate to yield the corresponding 1-methoxytriazolium tetrafluoroborates.\[456\] 1-Alkyl-1H-1,2,3-triazol-5-ols on reaction with diazomethane or iodomethane are alkylated at the alcohol oxygen, N2, and N3.\[330,331\] 1H-1,2,3-Triazole-4-thiol is converted selectively into the 4-(methylsulfanyl) derivative by reaction with a small excess iodomethane, in the presence of an equimolar amount of ethanolic potassium hydroxide (1.8 M).\[447\] Addition of diazomethane to the 4-(methylsulfanyl)triazole gives a mixture of the three possible N-methylated 4-(methylsulfanyl)triazoles.\[447\]

The alkylation of ethyl 4-(4-hydroxyphenoxy)-1H-1,2,3-triazole-5-carboxylate (435) under alkaline conditions exclusively yields the N2 and N3 alkylation products (Scheme 142). Alkylation at N1 or at the hydroxy group is not observed.\[457\] While alkylation of 435 with benzyl or 4-methoxybenzyl chlorides gives a 1:1 mixture of the two isomers, with 4-bromophenacyl bromide preferential substitution at N2 is observed (14% and 65% respectively to 436 and 437). Alkylation with trityl chloride shows a marked steric preference for the less hindered N2 position, with isomer 437 (R1 = Tr) being formed almost exclusively.

**Scheme 142** Alkylation of Ethyl 4-(4-Hydroxyphenoxy)-1H-1,2,3-triazole-5-carboxylate\[457\]

\[
\begin{align*}
\text{HO-} & \hspace{1cm} \text{EtO}_2\text{C} \\
& \text{N} \hspace{1cm} \text{N} \\
& \text{H} \hspace{1cm} \text{NEtO}_2\text{C} \\
\end{align*}
\]

1. K₂CO₃, DMF
2. R₁X, 20 – 40 °C

\[
\begin{align*}
\text{HO-} & \hspace{1cm} \text{EtO}_2\text{C} \\
& \text{N} \hspace{1cm} \text{N} \\
& \text{N} \hspace{1cm} \text{NEtO}_2\text{C} \\
\end{align*}
\]

R₁ = CH₂Ar¹, CH₂COAr¹, Tr; X = Cl, Br

N-Unsubstituted triazoles also react with compounds of other types to yield N-substituted derivatives. For example, they react with nitrilimines (generated in situ) to yield a mixture of 1- and 2-(benzohydrazonoyl)-1,2,3-triazoles, as illustrated in Scheme 143,\[458\] and react with 1-O-acetyl ribofuranose derivatives (by an acid-catalyzed fusion procedure) to afford mixtures of triazole nucleosides 438 and 439 (Scheme 144).\[459\]

**Scheme 143** Reaction of Triazoles with Nitrilimines\[458\]

\[
\begin{align*}
\text{N} \hspace{1cm} \text{N} \\
& \text{PhC=NN} = \text{Ph} \\
\end{align*}
\]

[benzene reflux, 10 h]

\[
\begin{align*}
\text{N} \hspace{1cm} \text{N} \\
& \text{PhC=NN} = \text{Ph} \\
\end{align*}
\]

41%

\[
\begin{align*}
\text{N} \hspace{1cm} \text{N} \\
& \text{PhC=NN} = \text{Ph} \\
\end{align*}
\]

33%
C-Alkylation of triazoles is achieved by lithiation followed by addition of an alkyl halide. For example, reaction of 1-phenyl-1H-1,2,3-triazole with butyllithium and addition of iodomethane gives 5-methyl-1-phenyl-1H-1,2,3-triazole (440, R1 = H) in 94% yield (Scheme 145).[424] It is interesting to note that under similar reaction conditions, 4-methyl-1-phenyl-1H-1,2,3-triazole yields 4,5-dimethyl-1-phenyl-1H-1,2,3-triazole (440, R1 = Me), while its isomer 5-methyl-1-phenyl-1H-1,2,3-triazole gives only the 5-ethyl derivative 441. Lithiation of 1,4-diphenyl- and 1,5-diphenyl-1H-1,2,3-triazole, followed by iodomethane quench, gives the corresponding derivatives 440 (R1 = Ph) and 442 in 78 and 99% yield, respectively, reflecting the higher steric hindrance in the 1,4-diphenyl isomer. For other examples of C-alkylation of triazoles see Section 13.13.1.4.1.1.1.

The reaction of 1,2,3-triazole, 1-methyl-, 2-methyl-, 4-methyl-, and 4,5-dimethyl-1,2,3-triazole with chlorine, bromine, iodine, hypochlorite, hypobromite, and hypiodite has been studied.[460] 1H-1,2,3-Triazole reacts with bromine to afford 4,5-dibromo-1H-1,2,3-triazole (443) in almost quantitative yield (Scheme 146).[461,462] The intermediate monobromo...
motriazole cannot be trapped; apparently it is brominated faster than the starting material. The 4,5-dibromo-1H,1,2,3-triazole is also obtained in 90–95% yield by bromodecarboxylation of 1,2,3-triazole-4-carboxylic acid.[462]

Scheme 146 Bromination of 1H-1,2,3-Triazole

1-Methyl- and 4-methyl-1H-1,2,3-triazole react with bromine to give, respectively, the 4-bromo-1-methyl- and 5-bromo-4-methyl-1H-1,2,3-triazole in good yields. The isomeric 2-methyl-2H-1,2,3-triazole, less reactive toward halogenation, reacts with bromine only in the presence of a catalyst (iron filings) and yields 4,5-dibromo-2-methyl-2H-1,2,3-triazole; the monobrominated product is not obtained.[460] 4-Bromo- and 5-bromo-1H-1,2,3-triazoles are obtained indirectly by bromination of a triazole with a removable group at N1, as shown in Scheme 147.[463]

Scheme 147 Bromination of 1H-1,2,3-Triazoles with a Removable Substituent at N1

2- and 3-Substituted 1,2,3-triazole 1-oxides 444 and 447 are halogenated selectively in position 5 in excellent yields (Scheme 148).[456,464,465] Since compounds 445 and 448 are deoxygenated almost quantitatively (see Section 13.13.1.4.1.4.4), this is a useful route for the synthesis of 1- and 2-substituted 4-halo-1,2,3-triazoles. The chlorination/deoxygenation of 2-(4-tolyl)-2H-1,2,3-triazole 1-oxides to give 446 is carried out in one step by reaction with gaseous hydrogen chloride.[466]
**Scheme 148**  Halogenation of 1,2,3-Triazole 1-Oxides\[456,464–466\]

\[
\begin{align*}
\text{NaOCl, Cl}_2, \text{or Br}_2 & \\
\text{rt} & \\
72\text{--}100\% & \\
\end{align*}
\]

R\(^1\) = Me, Bn, Ph; R\(^2\) = H, Me; X = Cl, Br

1-Methoxy-2-phenyl-2\(H\)-1,2,3-triazol-1-ium tetrafluoroborates 449 react with potassium hydrogen fluoride to yield 4-fluoro-2-phenyl-2\(H\)-1,2,3-triazoles 450 (Scheme 149).\[465\]

**Scheme 149**  Fluorination of 1-Methoxy-2-phenyl-2\(H\)-1,2,3-triazol-1-ium Tetrafluoroborates\[465\]

\[
\begin{align*}
\text{KHF}_2, \text{MeCN}, \text{rt}, 3 \text{ d} & \\
61\text{–}64\% & \\
\end{align*}
\]

R\(^1\) = H, Me

Mesoionic compound 451 reacts with bromine in acetic acid to give the 5-bromo derivative 452 (Scheme 150).\[362\]

**Scheme 150**  Bromination of Mesoionic Triazole Compounds\[362\]

\[
\begin{align*}
\text{Br}_2, \text{AcOH}, \text{rt}, 2 \text{ h} & \\
68\% & \\
\end{align*}
\]

C-Lithiated 1,2,3-triazole species are quenched with bromine or iodine to afford the corresponding halogenated derivatives in excellent yields.\[336\] Using hexachloroethane as the electrophile, the chlorinated derivatives are obtained.\[336,419\]

*for references see p 587*
Reaction of 1H-1,2,3-triazole with iodine monochloride yields 1-iodo-1H-1,2,3-triazole (453). Melting a mixture of this compound with 3,5-dimethyl-1H-1,2,4-triazole for 5–10 minutes gives 4,5-diiodo-1H-1,2,3-triazole (454) (Scheme 151).\[467\] 1H-1,2,3-Triazole gives 1,4,5-tribromo-1H-1,2,3-triazole when treated with an excess of sodium hypobromite.\[460\]

**Scheme 151  Iodination of 1H-1,2,3-Triazole\[467\]**

\[
\begin{align*}
\text{N} & \text{N} & \text{I} \\
\text{N} & \text{I} & \text{Cl, NaOEt} \\
\text{EtOH, rt} & 110 \degree C, 5–10 \text{ min} & 75% \\
\text{453} & \text{454}
\end{align*}
\]

2-Phenyl-2H-1,2,3-triazol-4-ol reacts with bromine to give the corresponding 5-bromo derivative in high yield.\[474\] A method for the selective conversion of 2,4,5-triphenyl-2H-1,2,3-triazole into 2-(2-chlorophenyl)-4,5-diphenyl-2H-1,2,3-triazole has been reported.\[468\]

4,5-Dibromo-1H-1,2,3-triazole (443); Typical Procedure:\[462\]

Br₃ (15 mL, an excess) was added dropwise to a stirred soln of 1H-1,2,3-triazole (15.0 g, 217 mmol) in H₂O (100 mL) warmed to 40–45°C and the resulting soln was stirred for a further 1 h. The precipitate was collected by filtration and further Br₃ (10 mL) was added to the filtrate, then it was kept at rt overnight, after which a second crop of product had precipitated. The combined amounts of product were washed with H₂O (3 × 50 mL), dried, and recrystallized (aq MeOH) to give the product; yield: 47.8 g (97%); mp 192–194°C.

**13.13.1.4.1.9 Method 9: N-Amination**

4,5-Diphenyl-1H-1,2,3-triazole is aminated by reaction with hydroxylamine-O-sulfonic acid yielding the corresponding triazol-1-amines and triazol-2-amines in approximately equal amounts (Scheme 152).\[3\]

**Scheme 152  N-Amination of 4,5-Diphenyl-1H-1,2,3-triazole\[3\]**

\[
\begin{align*}
\text{Ph} & \text{N} & \text{Ph} \\
\text{Ph} & \text{N} & \text{Ph} \\
\text{H₂NOSO₃H} & \text{NH₂} & +
\end{align*}
\]

1H-1,2,3-Triazole is oxidized by peracids to 1H-1,2,3-triazol-1-ol (Scheme 153). Best yields are obtained with 3-chloroperoxybenzoic acid or hydrogen peroxide plus formic acid.\[338,468\] Yields of 65% are obtained by adding the oxidant (hydrogen peroxide/formic acid) portionwise over 30 days followed by continuous extraction of the triazolol with diethyl ether over three weeks.\[136\] The autoxidation of an N-unsubstituted 1,2,3-triazole to the corresponding triazol-2-ol has been reported.\[542\]
13.13 Method 11: Nitration

Direct nitration of 1H-1,2,3-triazole to give 4-nitro-1H-1,2,3-triazole is not possible. However, this compound is obtained in moderate yield from the reaction of 1-morpholino-2-nitroethene and tosyl azide. Attempts to introduce a nitro group in the triazole ring of 1-phenyl- and 4-phenyl-1H-1,2,3-triazole are unsuccessful since nitration occurs only in the phenyl ring. For example, the reaction of 4-phenyl-1H-1,2,3-triazole with a mixture of nitric acid and sulfuric acid at 0°C gives the 4-(4-nitrophenyl) derivative in 50% yield; at 90°C the 4-(2,4-dinitrophenyl) derivative is obtained in 35% yield. Similarly, the 3-phenyl-1,2,3-triazole 1-oxide is nitrated with fuming nitric acid, at room temperature, at the para phenyl position.

The nitration of 2-phenyl-2H-1,2,3-triazole with a mixture of fuming nitric acid and concentrated sulfuric acid at 20°C gives a mixture of 2-(4-nitrophenyl)-2H-1,2,3-triazole (454) and 4-nitro-2-(4-nitrophenyl)-2H-1,2,3-triazole (455) (Scheme 154). However, if the nitration is carried out with nitric acid in acetic anhydride at 15°C, only triazole 454 is obtained.

While 2-(2,4,6-trinitrophenyl)-2H-1,2,3-triazole is nitrated at C4 of the triazole ring, the isomeric 1-(2,4,6-trinitrophenyl)-1H-1,2,3-triazole is resistant to nitration, even under forcing conditions. Nitration of 2-phenyl-2H-1,2,3-triazol-4-ol with nitric acid in glacial acetic acid affords 5-nitro-2-phenyl-2H-1,2,3-triazol-4-ol in 60% yield. Under similar conditions, 2-phenyl-2H-1,2,3-triazol-4-ol 1-oxide also gives the corresponding 5-nitro derivative. Nitration of 4-(2,4,6-trinitroanilino)-1H-1,2,3-triazole with a mixture of nitric acid and sulfuric acid, at 20–25°C, affords the corresponding 5-nitro derivative in 30% yield.

Nitration of 2-methyl-2H-1,2,3-triazole with a mixture of fuming nitric acid and concentrated sulfuric acid, at room temperature, affords 2-methyl-4-nitro-2H-1,2,3-triazole (456) in 98% yield (Scheme 155). Under more vigorous conditions (10 h at 100°C) this compound is further nitrated to 2-methyl-4,5-dinitro-2H-1,2,3-triazole (457) (97%). Nitration of 2-methyl-2H-1,2,3-triazole 1-oxide at room temperature gives a mixture of the 4- and 5-nitro derivatives. At 100°C both compounds are further nitrated to 2-methyl-4,5-di-nitro-2H-1,2,3-triazole 1-oxide. Nitration of 2-phenyl-2H-1,2,3-triazole 1-oxide at room temperature gives initially (detectable after 1 min of reaction time) a mixture of 2-(4-nitrophenyl)-2H-1,2,3-triazole 1-oxide, 5-nitro-2-phenyl-2H-1,2,3-triazole 1-oxide, and 5-nitro-2-
(4-nitrophenyl)-2H-1,2,3-triazole 1-oxide. The final product, 2-(2,4-dinitrophenyl)-5-nitro-2H-1,2,3-triazole 1-oxide, is formed after approximately two hours.\textsuperscript{[465]}

[Scheme 155] Nitration of 2-Methyl-2H-1,2,3-triazole\textsuperscript{[456]}

2-Methyl-4-nitro-2H-1,2,3-triazole (456); Typical Procedure: 2-Methyl-2H-1,2,3-triazole (1 mmol), concd H\textsubscript{2}SO\textsubscript{4} (1.02 mL), and fuming HNO\textsubscript{3} (d 1.55; 0.51 mL) were stirred at rt for 3 h. H\textsubscript{2}O (5 mL) was added. Extraction with CH\textsubscript{2}Cl\textsubscript{2} (5 mL, 2 x 3 mL), drying (K\textsubscript{2}CO\textsubscript{3}), and removal of the solvent gave the crude product (98%). Recrystallization (ligroin) gave crystals; mp 99–101 °C.

13.13.1.4.1.2 Of Metals

13.13.1.4.1.2.1 Method 1: Desilylation

N-Trimethylsilyl substituents are readily removed under very mild conditions: treatment with aqueous methanol, ethanol, or aqueous acid. Triazole derivatives containing both N- and C-trimethylsilyl substituents, such as 458, are selectively desilylated: methanol cleaves N−Si bonds (e.g., to give 459), while methanol/hydrochloric acid cleaves Si−C bonds as well, both with protonation (Scheme 156).\textsuperscript{[172]}

[Scheme 156] Selective Desilylation of 4-Phenyl-2,5-bis(trimethylsilyl)-2H-1,2,3-triazole\textsuperscript{[72]}

Removal of the trimethylsilyl group from 460 is readily carried out with 10% aqueous potassium hydroxide in boiling methanol to give triazoles 461 in almost quantitative yields (Scheme 157).\textsuperscript{[72]} Heating 4-substituted 5-(trimethylsilyl)-1H-1,2,3-triazoles with potassium fluoride and concentrated hydrochloric acid (2 drops) in refluxing ethanol gives the 4-substituted 1H-1,2,3-triazoles in high yields.\textsuperscript{[52]}

[Scheme 157] Desilylation of 5-(Alkylsulfonyl)-5-(trimethylsilyl)-1,2,3-triazoles\textsuperscript{[72]}
13.13.1 Monocyclic N-Unsubstituted and 1-Substituted 1,2,3-Triazoles

13.13.1.4.1.3 Of Carbon Functionalities

13.13.1.4.1.3.1 Method 1: Decarboxylation

Most 1,2,3-triazolecarboxylic acids lose carbon dioxide when heated above their melting point. This reaction has been known since the 19th century.\cite{477–479} A reasonable number of examples of this transformation are found in the literature.\cite{23,105,282,331,430,480} 1H-1,2,3-Triazole (464, R¹ = H) is obtained in 93% by heating 1H-1,2,3-triazole-4-carboxylic acid (462, R¹ = H) in an oil bath at 220 °C for a few minutes (Scheme 158).\cite{44} 1,5-Disubstituted 1,2,3-triazole-4-carboxylic acids decarboxylate slowly in boiling benzene\cite{481} or toluene.\cite{482}

5-Amino-1-benzyl-1H-1,2,3-triazole-4-carboxylic acid is decarboxylated to the corresponding triazolamine, in 60–84% yield, by refluxing in N,N-dimethylaniline for 15 minutes.\cite{319,428} 5-Amino-1-methyl-1H-1,2,3-triazole-4-carboxylic acid decarboxylates in refluxing butan-1-ol (3 h, 65% yield)\cite{393} while 5-amino-1H-1,2,3-triazole-4-carboxylic acid and 5-amino-1-cyclohexyl-1H-1,2,3-triazole-4-carboxylic acid are decarboxylated to the corresponding triazolamines, in 57 and 63% yield, respectively, by heating in 1 M hydrochloric acid for one hour.\cite{428} 1H-1,2,3-Triazol-4,5-dicarboxylic acids generally lose two moles of carbon dioxide on heating above their melting point (Scheme 158).\cite{105,478} For example, 1-benzyl-1H-1,2,3-triazole is obtained in essentially quantitative yield by thermal decarboxylation of 1-benzyl-1H-1,2,3-triazole-4,5-dicarboxylic acid.\cite{105} However 1-phenyl-1H-1,2,3-triazole-4,5-dicarboxylic acid preferentially decarboxylates at the 5-position, giving the corresponding 4-carboxylic acid.\cite{475} 1-(1-Naphthyl)-1H-1,2,3-triazole-4,5-dicarboxylic acid decarboxylates in refluxing toluene (24 h) to give 1-(1-naphthyl)-1H-1,2,3-triazole in 90% yield.\cite{106}

\begin{center}
\textbf{Scheme 158} Decarboxylation of 1H-Triazolocarboxylic Acids\cite{44,105,474}
\end{center}

\begin{center}
\begin{align*}
\text{HO}_2\text{C} & \quad \text{N} & \quad \text{N} & \quad \text{R}^1 \\
462 & \quad \text{N} & \quad \text{N} & \quad \text{R}^1 \\
\text{HO}_2\text{C} & \quad \text{N} & \quad \text{N} & \quad \text{R}^1
\end{align*}
\end{center}

\begin{center}
1H-1,2,3-Triazole (464, R¹ = H); Typical Procedure.\cite{44}
\end{center}

1H-1,2,3-Triazole-4-carboxylic acid (462, R¹ = H; 40 g, 0.35 mol) was heated in an oil bath. At a bath temperature of 220 °C a vigorous evolution of CO₂ took place. The reaction was over in a few min and the 1,2,3-triazole was distilled; yield: 22.8 g (93%); bp 205–206 °C/ 760 Torr.

13.13.1.4.1.3.2 Method 2: Deformylation

1,4-Diphenyl-1H-1,2,3-triazole-5-carbaldehyde (465) is deformylated in almost quantitative yield by treatment with sodium methoxide in refluxing methanol (Scheme 159). Under the same conditions, the isomer 1,5-diphenyl-1H-1,2,3-triazole-4-carbaldehyde is re-
covered quantitatively. Alternatively, quantitative deformylation of \(465\) is accomplished, on treatment with a large excess of hydrazine (100-fold) in refluxing ethanol to give 1,4-diphenyl-1H-1,2,3-triazole \(466\) via hydrazone \(467\) (Scheme 159).

**Scheme 159** Deformylation of 1,4-Diphenyl-1H-1,2,3-triazole-4-carbaldehyde

\[
\begin{align*}
\text{OHC} & \quad \text{NaOMe, MeOH, reflux, 12 h} \\
\text{Ph} & \quad \text{93%} \\
\text{H}_2\text{NNH}_2, \text{EtOH} & \quad \text{reflux, 4 h} \\
\text{Ph} & \quad \text{100%} \\
\end{align*}
\]

**1,4-Diphenyl-1H-1,2,3-triazole (466): Typical Procedure:**

A soln of freshly cut Na (0.23 g, 10 mmol) and 1,4-diphenyl-1H-1,2,3-triazole-5-carbaldehyde \(465\) (1.00 g, 4 mmol) in anhyd MeOH (50 mL) was refluxed for 12 h in a vessel provided with a dry ice condenser, after which time 25–30 mL of liquid was distilled. On cooling the soln remaining in the reaction vessel the product was obtained; yield: 0.83 g (93%).

**Method 3: Deacylation**

1- and 2-Acyltriazoles are readily hydrolyzed in water or dilute acid; the rate constants for hydrolysis and aminolysis of several \(N\)-acetyl-1,2,3-triazoles have been measured. 2-Benzoyl-4-(benzoyloxy)-2H-1,2,3-triazoles \(468\) are hydrolyzed selectively to the corresponding 4-benzoyloxy derivatives \(469\) (Scheme 160).

**Scheme 160** Selective Hydrolysis of 2-Benzoyl-4-(benzoyloxy)-2H-1,2,3-triazoles

\[
\begin{align*}
\text{BzO} & \quad \text{H}_2\text{O, acetone} \quad \text{reflux, 4-11 h} \\
\text{R} & \quad \text{R}^1 = \text{H} \quad 89\% \\
\text{R} & \quad \text{R}^1 = \text{Ph} \quad 89\% \\
\end{align*}
\]

\(O\)-Aryl-1H-1,2,3-triazole-1-carboximidates \(470\) are hydrolyzed to the corresponding \(N\)-unsubstituted derivatives \(471\) by reaction with concentrated hydrochloric acid at room temperature (Scheme 161); they are also hydrolyzed in aqueous sodium hydroxide (100°C, 15 min).
Scheme 161  Hydrolysis of O-Aryl-1H-1,2,3-triazole-1-carboximidates\[^{49}\]

\[
\begin{align*}
\text{Ar}^1O & \quad \text{HN} \quad \text{Ar}^1 \quad \text{HN} \\
\text{R}^1 & \quad \text{O} \quad \text{Ar}^1 & \quad \text{HN} \\
470 & \quad \text{HCl} \quad 20^\circ\text{C, 5 h} & \quad 471 \\
\text{R}^1 = \text{H, CO}_2\text{Et}; \text{Ar}^1 = \text{Ph, 4-Tol, 4-MeOC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4
\end{align*}
\]

13.13.1.4.1.3.4  Method 4: Dearylation

N-Aryl substituents that are activated by nitro groups are removed by nucleophilic displacement by hydrazine\[^{483}\] or by potassium hydroxide.\[^{484}\] Oxidative removal of a 4-aminophenyl substituent at N1 by potassium permanganate has also been reported.\[^{485}\] Oxidation of 2,4-bis(2,4-diaminophenyl)-2H-1,2,3-triazole (472) gives 1H-1,2,3-triazole-4-carboxylic acid (Scheme 162).\[^{486}\]

Scheme 162  Oxidative Dearylation of 2,4-Bis(2,4-diaminophenyl)-2H-1,2,3-triazole\[^{486}\]

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{NH}_2 \\
\text{H}_2\text{N} & \quad \text{NH}_2 & \quad \text{KMnO}_4, \text{NaOH} \quad 100^\circ\text{C} & \quad \text{HO}_2\text{C} \\
\text{80\%} & \quad (\text{Scheme 162}) & \quad \text{80\%}
\end{align*}
\]

13.13.1.4.1.3.5  Method 5: Dealkylation

N-Benzyl-1,2,3-triazoles are frequently used as precursors of N-unsubstituted triazoles. The benzyl group is removed by reduction with sodium in liquid ammonia,\[^{105,319,432,487}\] catalytic hydrogenation,\[^{96,105,457,488}\] or chromic acid oxidation.\[^{280}\] The 4-methoxybenzyl group is readily removed by solvolysis in trifluoroacetic acid\[^{303}\] at 65 °C or with 47% hydrobromic acid\[^{336}\] at 120 °C (Scheme 163). The related 3-bromo-4-methoxybenzyl group is removed by treatment with concentrated sulfuric acid at 120 °C.\[^{463}\] Triazoles having a 2-acetoxybenzyl group in N1 are dealkylated, in low yield, simply by refluxing in piperidine or in diethanolamine.\[^{93}\] 2-Benzyl-2H-1,2,3-triazole and 1-benzyl-1H-1,2,3-triazole 3-oxides are N-debenzylated by treatment with iodotrimethylsilane, concentrated hydrobromic acid, or concentrated sulfuric acid.\[^{449}\]

for references see p 587
Triazoles having a 2-(trimethylsilyl)ethoxymethyl group at N1 (e.g., 474) are dealkylated in good yields under mild conditions, namely by action of dilute aqueous hydrochloric acid or by treatment with tetrabutylammonium fluoride in tetrahydrofuran (Scheme 164).\(^1\) The cleavage of 1-cycloheptatrienyltriazoles 475 is carried out by passing hydrogen chloride through a solution of the triazole in diethyl ether (Scheme 165).\(^1\) The cleavage is probably facilitated by the stability of the tropylium ion.

1-Benzylxoy-1H-1,2,3-triazoles (e.g., 476) are debenzylated in almost quantitative yields to the corresponding 1,2,3-triazol-1-ols by catalytic hydrogenation (Scheme 166).\(^1\)
1H-1,2,3-Triazoles by Removal of the 4-Methoxybenzyl Group from Triazoles 473; General Procedure:\[^{[490]}\]

A soln of the N-protected triazole (ca. 1 g) in TFA (15–30 mL) was stirred at 60–65 °C for 1–7 h; the course of the reaction was monitored by RP–HPLC. The TFA was removed in vacuo and H₂O was added to the residue. The product was isolated from the water-insoluble material by column chromatography (CHCl₃). In the case of compounds 473 (R¹ = CO₂Et; R² = OH, CN) the product was obtained by evaporation of the filtered aqueous phase.

13.13.1.4.1.4 Of Heteroatoms

13.13.1.4.1 Method 1: Substitution of Halogens by Nucleophiles

Heating 5-bromo-1-methyl-1H-1,2,3-triazole with ethanolic ammonia for 10 hours at 100 °C in a sealed tube affords the corresponding 5-amino derivative in low yield (22% of the hydrochloride). The 4-bromo-1-methyl-1H- and 4-bromo-2-methyl-2H-1,2,3-triazoles do not react with ammonia under the same conditions.\[^{[44]}\] 5-Bromo-1-methyl-1H-1,2,3-triazole also reacts with aniline to yield the corresponding 5-anilino derivative in 54%\[^{[44]}\]. The displacement of the chloro group in triazoles 477 (R¹ = Bn)\[^{[457,491,756]}\] and 477 (R¹ = 4-MeOC₆H₄CH₂)\[^{[303,491,756]}\] by nucleophiles, such as cyanide, aryloxide, and arenethiolate, gives good yields of the corresponding derivatives 478 (Scheme 167). Similarly, 1,4-diphenyl-1H-1,2,3-triazole-5-carbonitrile is prepared in 75% yield from the reaction of the corresponding 5-chloro derivative with sodium cyanide in dimethyl sulfoxide (140 °C, 4 h).\[^{[438]}\]

Scheme 167 Displacement of a Chlorine by Nucleophiles\[^{[303,457,491,756]}\]

Heating 1-aryl-5-chloro-1H-1,2,3-triazoles 479 with hydrazine gives directly 5-(substituted amino) 1H-1,2,3-triazol-1,5-diamines 481 (Scheme 168). The 5-hydrazinotriazoles 480 are presumably formed first but rearrange spontaneously under the reaction conditions.\[^{[492]}\] Heating 5-chloro-1-phenyl-1H-1,2,3-triazole with an aqueous solution of sodium hydrosulfide at 100 °C in a sealed tube produces a bis(1-phenyl-1H-1,2,3-triazol-5-yl) sulfide.\[^{[404]}\] Curiously, when the same reaction is carried out at room temperature the product is N-phenyl-1,2,3-thiadiazol-5-amine.\[^{[404]}\]

for references see p 587
Reaction of 1-Aryl-5-chloro-1H,1,2,3-triazoles with Hydrazine

\[ R^1 = \text{H, Ph; } Ar^1 = \text{Ph, 4-ClC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4, 4-\text{pyridyl} \]

Attempted displacement of bromine from 4,5-dibromo-1H,1,2,3-triazole by dimethylamine under vigorous conditions (sealed tube, 260 °C, 140 h) yields only the dimethylamine salt of the dibromotriazole. The halo group in 4-chloro- and 4-bromo-3-substituted 1H,1,2,3-triazole 1-oxides is readily displaced by methoxide ions at 20 °C while the 5-chloro analogues require heating at 140 °C. The displacement of bromine from bromo- and dibromo-1,3-disubstituted 1,2,3-triazolium salts by methoxide, hydroxide, and sulfide has been studied extensively. The 5-bromo-1,2-disubstituted 1,2,3-triazolium fluorsulfonates react with hydroxide or methoxide ions to form 1,2-disubstituted 1,2,3-triazol-5-ones. Intramolecular displacement of chlorine in 4-acyl-5-chloro-1H,1,2,3-triazoles gives access to interesting polycyclic triazole derivatives.

**Method 2:** Substitution of Hydroxy Groups by Halogens

Reaction of the 1H,1,2,3-triazol-5-ol 482 with phosphorus pentachloride in toluene at 40 °C gives the 5-chloro derivative 483 in 65% yield (Scheme 169).

**Method 3:** Substitution of Diazonium Groups by Nucleophiles

Displacement of nitrogen from diazonium salts derived from 1,2,3-triazol-4-amines and 1,2,3-triazol-5-amines is achieved in the same manner as for other aromatic diazonium salts. For example, a range of 4-substituted 5-azido-1-phenyl-1H,1,2,3-triazoles 486 is prepared in high yield by diazotization of the corresponding 5-amino derivatives 484 followed by addition of excess sodium azide to the diazonium ions 485 (Scheme 170). In a similar process, 5-amino-1H,1,2,3-triazole-4-carboxamide is converted into the 5-ido derivative in 33%. Diazotization of 1-methyl-1H,1,2,3-triazol-4-amine with sodium nitrite/hydrobromic acid gives directly the 4-bromo derivative in 41% yield.
**Scheme 170** Substitution of Diazonium Groups by Nucleophiles[^498,^499]

\[
\begin{align*}
\text{NaNO}_2, \text{H}_2\text{O}, \text{HCl} & \quad \rightarrow \\
\text{5 to 0 °C} & \quad \rightarrow \\
\text{NaBH}_4, \text{H}_2\text{O} & \quad \rightarrow
\end{align*}
\]

\[
\begin{align*}
\text{R}^1 & = \text{Ph, XC}_6\text{H}_4, \text{CHO, CONH}_2, \text{CN, PO(OEt)}_2, \text{SO}_2\text{Ph} \\
\end{align*}
\]

**CAUTION:** Sodium azide can explode on heating and is highly toxic.

An aqueous soln of NaNO\(_2\) (0.76 g, 11 mmol) was added slowly to a well stirred soln of 5-amino-1-phenyl-1\(^{\text{H}}\)-1,2,3-triazole-4-carbaldehyde (484, \(R^1 = \text{CHO}\); 1.88 g, 10 mmol) in concd HCl (120 mL) at −5 to 0 °C. Then, a 10-fold excess of NaN\(_3\) in H\(_2\)O was added dropwise at about −30 °C. After dilution with H\(_2\)O, the mixture was extracted with Et\(_2\)O and the combined extracts were dried (MgSO\(_4\)). The solvent was evaporated and the residue was chromatographed (silica gel, CH\(_2\)Cl\(_2\)). Crystallization (CH\(_2\)Cl\(_2\)/Et\(_2\)O) gave pure compound; yield: 62%; mp 97 °C (dec).

**Method 4:** Deoxygenation

Triazole N-oxides, such as 487, 489, and 491, are deoxygenated to triazoles (e.g., 488, 490, and 492) in almost quantitative yield by refluxing in phosphorus trichloride (Scheme 171)[^456,^464,^465] or by reduction with zinc in acidic media (Scheme 172).[^466,^501] 2-Aryl-1\(^{\text{H}}\)-1,2,3-triazole 1-oxides are converted directly into 2-aryl-4-chloro-1\(^{\text{H}}\)-1,2,3-triazoles by reaction with gaseous hydrogen chloride[^466] or by heating with concentrated hydrochloric acid in a sealed tube.[^465]

**Scheme 171** Deoxygenation of Triazole N-Oxides with Phosphorus Trichloride[^456,^464,^465]

\[
\begin{align*}
\text{X} & = \text{Cl, Br} \\
\end{align*}
\]
13.13.1.4.1.5 Method 5: Dehalogenation

1-Substituted 5-bromo-1H-1,2,3-triazole 3-oxides 493 are debrominated in virtually quantitative yield when heated at 100 °C for 1 hour with sodium sulfite (Scheme 173).[464]

Scheme 173  Debromination of 5-Bromo-1H-1,2,3-triazole 3-Oxides[464]

R₁ = Me, Ph, Bn

1-Methyl-1H-1,2,3-triazole 3-Oxide (494, R₁ = Me); Typical Procedure[464]
5-Bromo-1-methyl-1H-1,2,3-triazole 3-oxide (493, R₁ = Me; 0.56 g, 3.1 mmol), Na₂SO₃ (1.19 g, 9.4 mmol), and H₂O (5.6 mL) were refluxed for 1 h. The H₂O was removed and the residue was extracted with boiling MeCN (3 × 10 mL). Removal of the MeCN afforded 494 (R₁ = Me); yield: ~100%; mp 123–124 °C.

13.13.1.4.2 Addition Reactions

13.13.1.4.2.1 Method 1: Conversion into N-Oxides

1-Substituted 1,2,3-triazole 3-oxides 496 are prepared by oxidation of 1-substituted triazoles 495 with 3-chloroperoxybenzoic acid (Scheme 174). The yields are good but decrease when electron-withdrawing substituents are present, particularly if situated adjacent to the nitrogen to be oxidized. Phenyl groups at this position also lead to decreased yields. The low yield in these cases is not a serious drawback since unchanged starting material is readily recovered.[464,489] Oxidation of 1-(arylmethyl)-1H-1,2,3-triazoles with peracetic acid does not give the expected N-oxides but 1-arylmethyloxy derivatives.[91] Attempts to obtain 2-phenyl-2H-1,2,3-triazole 1-oxide by oxidation of 2-phenyl-2H-1,2,3-triazole with a range of oxygen donators are unsuccessful.[465]
1-Substituted 1H-1,2,3-Triazole 3-Oxides 496; General Procedure[^464]

The 1-substituted triazole 495 (1.0 g) was dissolved with heating in EtOAc (1 mL). After cooling to 20°C, MCPBA (1.2 molar equiv) was added. The mixture was stirred for 120 h, diluted with CH2Cl2 (10 mL) and washed with aq 1 M NaOH (8 mL). The aqueous soln was extracted with CH2Cl2 (2 × 8 mL). The combined organic phase was dried, the CH2Cl2 was removed, EtOAc (10 mL) was added, and the suspension was filtered through silica gel (2 g). Washing with further EtOAc (2 × 10 mL) and removal of the solvent gave unchanged starting material. Subsequent extraction of the silica gel (EtOAc/MeOH 1:1; 5 × 10 mL) and removal of the solvents gave the crude product.

### Rearrangement of Substituents

Appropriately substituted 1,2,3-triazoles may undergo thermal, photochemical, acid-catalyzed, or base-catalyzed isomerizations. As shown in many of the previous methods, frequently these isomerizations occur spontaneously during the synthesis of the triazole ring. Isomerizations are also observed during reactions involving substitution or modification of substituents on a 1,2,3-triazole (see, for example, Scheme 168). The most important isomerization reaction in 1,2,3-triazoles is the Dimroth rearrangement, illustrated in Scheme 175 for 1H-1,2,3-triazol-5-amines. This type of isomerization is also observed in other heterocyclic systems. The interconversion of compounds 497 and 498 is mainly controlled by the nature of R1, but it is also influenced by the basicity of the solvent used. Isomers 498 are favored when R1 is an aryl group, a large rigid group, or an electron-withdrawing group. Isomers 497 are favored when R1 is an alkyl group[^21].

This type of isomerization is also observed in 1-substituted 4-(iminomethyl)-1H-1,2,3-triazoles (Scheme 176). For example, imines 500 and 501 (R1 = H) are interconvertible when heated in dimethyl sulfoxide at 80°C. The equilibrium position depends on the electronic properties of the R2 substituent, favoring 501 when R2 is alkyl, benzyl, and 4-methoxyphenyl, and 500 when R2 is 4-chlorophenyl and 4-nitrophenyl[^469]. An interesting application of this isomerization is the synthesis of 1-alkyl-1H-1,2,3-triazole-4-carbaldehydes 502 from 1-phenyl-1H-1,2,3-triazole-4-carbaldehyde (499, R1 = H).[^502] This type of isomerization is also applied to the conversion of 1-phenyl-1H-1,2,3-triazole-4-carbaldehydes 499 (R1 = Me, Ph) into 4-oxo-substituted 1-alkyl-1H-1,2,3-triazoles 502 (R1 = Me, Ph).[^503]

---

[^464]: Scheme 174 Preparation of 1-Substituted 1H-1,2,3-Triazole 3-Oxides[^464,469]

1. R1 = Me, Ph, Bn, 4-MeOC6H4CH2; R2 = H, Me, Cl; R3 = H, Me, Ph, Cl, Br, OMe
2. MCPBA, EtOAc
3. rt, 5 d
4. 6−85%

**Scheme 174** Preparation of 1-Substituted 1H-1,2,3-Triazole 3-Oxides[^464,469]

**Scheme 175** Dimroth Rearrangement in 1H-1,2,3-Triazol-5-amines

---

[^502]: for references see p 587
Despite the failure of hydrazone and oxime derivatives 500 (R^1 = H; R^2 = NH_2, NHPh, OH) to isomerize to 501,[502] phenylhydrazone 504 (prepared from aldehyde 503) are converted into derivative 505 (Scheme 177). Similarly, phenylhydrazone 507 (R^1 = NHPh) and oxime 507 (R^1 = OH) are converted into amides 508.[504] Triazole 506 [and 1-benzyl, 1-(4-chlorobenzyl), and 1-(4-methoxybenzyl) analogues] are converted into carboxamides of type 508 (R^1 = Me, Et) by reaction with methylamine or ethylamine followed by rearrangement of the resulting imines on heating above their melting points.[502]

Another interesting type of isomerization in 1,2,3-triazoles corresponds to the migration of alkyl groups between nitrogens. This is not a very common transformation, but some examples have been reported.[505,506,757] Triazole 509, for example, isomerizes to 510 when treated with boron trifluoride (Scheme 178). [506,757]
Migration of alkyl groups is also observed in 1,3-disubstituted 1,2,3-triazolium-4-thiolates 511. Heating these compounds in an organic solvent at 180 °C results in transfer of alkyl groups with the formation of (alkylsulfanyl)-1,2,3-triazoles (Scheme 179). When R¹ and R² are different alkyl groups, four compounds 512–515 are obtained. The formation of compounds 514 and 515 clearly indicates that this is an intermolecular reaction. If 511 has only one alkyl group, only one product is formed. For example, 1-methyl-3-phenyl-1,2,3-triazolium-4-thiolate (511; R¹ = Me; R² = Ph) is quantitatively converted into 5-(methylsulfanyl)-1-phenyl-1H-1,2,3-triazole (513; R¹ = Me; R² = Ph).[495]

1-Ethyl-1H-1,2,3-triazole-4-carbaldehyde (502, R¹ = H; R² = Et); Typical Procedure:[502]

To a soln of 499 (R¹ = H; 1 g, 5.8 mmol) in MeOH (20 mL), was added 70% aq EtNH₂ (0.57 mL, 1.5 equiv), and the whole was stirred overnight at rt. The soln was concentrated and the resulting precipitate 500 (R¹ = H; R² = Et) was collected by filtration and dried; yield: 0.6 g (52%); mp 35 °C. This compound (0.6 g, 3 mmol) was heated overnight in DMSO (2 mL) at 80 °C. The soln was poured into ice water and the precipitate 501 (R¹ = H; R² = Et) was collected; yield: 0.5 g (83%); mp 83 °C. Compound 501 (0.5 g, 2.5 mmol) was dissolved in a mixture of H₂O/MeOH (1:1; 20 mL) containing 10% of HCO₂H and the soln was heated overnight at 80 °C. After addition of H₂O (20 mL), the soln was extracted with CHCl₃, and the extracts were washed with H₂O and dried (MgSO₄). The solvent was removed and the resulting oil (0.3 g) was chromatographed (silica gel, CH₂Cl₂/Et₂O 9:1) to give 502 (R¹ = H; R² = Et); yield: 0.15 g (48%).

for references see p 587
Product Subclass 2: Monocyclic 2-Substituted 1,2,3-Triazoles

Synthesis by Ring-Closure Reactions

By Formation of One N—N and One N—C Bond

Fragments C—C—N—N and N

Method 1: From N-Aminophthalimide and Conjugated Azoalkenes

2-(Phenylazo)propene \((517, R^1 = \text{Me}; R^2 = \text{H})\) and 1-(phenylazo)cyclopentene \([517, R^1, R^2 = (\text{CH}_2)_3]\) react with N-aminophthalimide \((516)\), in the presence of lead(IV) acetate, to give 2-phenyl-2\(H\)-1,2,3-triazoles \(520\) in moderate yields (Scheme 180).\(^{[508]}\) A probable mechanism for this reaction involves the initial formation of the azimine intermediate \(518\), 1,5-electrocyclization to the 2,5-dihydro-1\(H\)-triazole \(519\), and, finally, 1,2-elimination of phthalimide.

**Scheme 180**

2\(H\)-1,2,3-Triazoles from N-Aminophthalimide and Conjugated Azoalkenes\(^{[508]}\)

By Formation of Two N—C Bonds

Fragments N—N—N and C—C

Method 1: Addition of Azidotrimethylsilane and Azidotributylstannane to Alkynes

Azidotrimethylsilane and azidotributylstannane undergo addition to alkynes to give 2-(trimethylsilyl)- or 2-(tributylstannyl)-2\(H\)-1,2,3-triazoles, resulting from the isomerization of the initially formed 1-substituted derivatives These reactions are discussed in Section 13.13.1.1.3.1.1.6 (Schemes 59 and 60). A palladium-catalyzed three-component coupling reaction of azidotrimethylsilane, alkynes, and allyl methyl carbonate has been described.\(^{[509]}\) It affords selectively 2-allyl-2\(H\)-1,2,3-triazoles \(521\) in low to moderate yields (Scheme 181). A \(\pi\)-allylpalladium azide complex, which undergoes the 1,3-dipolar cycloaddition with the alkyne, has been proposed as a key intermediate in this reaction.
Scheme 181  2-Allyl-2H-1,2,3-triazoles from Azidotrimethylsilane, Alkynes, and Allyn Methyl Carbonate\cite{509}

\[
\text{TMSN}_3 + \text{RCO}_2\text{Me} \xrightarrow{\text{Pd}^2(\text{dba})_3, \text{EtOAc}} \text{R}^1 = \text{H, Et, (CH}_2)_n\text{Me; } \text{R}^2 = \text{AcO} \\
\text{R}^1 = \text{Ph; } \text{R}^2 = \text{CN, CHO, AcO, CO}_2\text{Me, PO(OEt)}_2\text{, SO}_2\text{Ph, NEt}_2
\]

Method 2: Addition of Acyl or Alkoxycarbonyl Azides to $\alpha$-Acytophosphorus Ylides

Acyl and alkoxycarbonyl azides undergo addition to $\alpha$-acylphosphorus ylides \cite{229,231} to yield 2-substituted 2H-1,2,3-triazoles, which result from the spontaneous isomerization of the initially formed 1-substituted triazoles (Scheme 182). For the discussion of this type of reaction and examples see Section 13.13.1.1.3.1.2.5 (Scheme 76).

Scheme 182  2H-1,2,3-Triazoles from Acyl or Alkoxycarbonyl Azides and $\alpha$-Acytophosphorus Ylides\cite{229,231}

By Formation of One N–N Bond

Fragment N–N–C–C–N

Method 1: Cyclization of $\alpha$-Hydroxyimino Hydrazones

The intramolecular elimination of water from $\alpha$-hydroxyimino hydrazones is a general method for the synthesis of 2H-1,2,3-triazoles (Scheme 183). Generally acetic anhydride\cite{510–514} is the reagent of choice, but other reagents are also used, namely phosphorus pentachloride\cite{515}, urea\cite{516}, or bromine.\cite{513} As an example, 2H-1,2,3-triazole 524 (R$^1$ = R$^2$ = Ph; R$^3$ = 4-O$_2$NC$_6$H$_4$) is obtained in 57% yield by refluxing the corresponding hydroxyimino hydrazone 523 with acetic anhydride for 40 minutes.\cite{289}

Scheme 183  Cyclization of $\alpha$-Hydroxyimino Hydrazones\cite{229}

This method has been applied to the synthesis of a range of 2,2'-diaryl-5,5'-dimethyl-4,4'-bi-2H-1,2,3-triazoles 526 from $\alpha$-hydroxyimino hydrazones 525 (Scheme 184).\cite{517}

for references see p 587

Another interesting example of the application of this method is the synthesis of 2-aryl-2H-1,2,3-triazoles starting from dehydro-ascorbic acid 527 (Scheme 185). On boiling with acetic anhydride, the dehydro-ascorbic acid 3-(hydroxyimino)-2-arylhydrazones 528 are converted into the acetylated triazole derivatives 529, whereas the unacetylated triazole derivatives 530 are obtained upon reaction with bromine in water.\cite{512} Treatment of triazole 529 (Ar1 = Ph) with ammonia gives the 2H-1,2,3-triazole-4-carboxamide 531 in quantitative yield.\cite{512} Compound 529 (Ar1 = 3-BrC6H4) is obtained in 85% yield by treating the corresponding 3-(hydroxyimino)-2-arylhydrazone 528 with acetic anhydride in pyridine overnight at room temperature.\cite{514}

![Scheme 184](image1)

**Scheme 184** Synthesis of 4,4'-Bi-2H-1,2,3-triazoles\cite{517}

\[ \text{PhN} \text{N} \text{N} \text{N} \text{PhN} \xrightarrow{\text{PCl5, CHCl3, rt, 1 h}} \text{X} \]

X = H, 2-Cl, 3-Cl, 4-Cl, 4-NO2, 2-Br, 3-Br, 4-Br

If the α-hydroxyimino hydrazone is N-unsubstituted, dehydration with acetic anhydride gives a 2-acetyl-2H-1,2,3-triazole, which is readily hydrolyzed to the corresponding N-unsubstituted triazole (Scheme 186) (see also Section 13.13.1.1.4.1.3).\cite{510}
Dehydration of amide derivatives \(532\) in refluxing thionyl chloride gives 2-phenyl-2\(H\)-1,2,3-triazole-4-carboxamides \(533\) in good yields (Scheme 187). \(^{[518]}\)

In acetic acid, the nitro(arylhydrazono)acetaldehyde oximes \(534\) are converted into the 2-aryl-2\(H\)-1,2,3-triazol-4-ol 1-oxides \(536\), probably via the intermediate \(535\) (Scheme 188). \(^{[466,501]}\)

Oxidation of (arylhydrazono)acetaldehyde oximes \(537\) with copper(II) sulfate \(^{[465,466,519]}\) in aqueous pyridine, with mercury(II) oxide, \(^{[520]}\) or with N-iodosuccinimide \(^{[521]}\) leads to the formation of 2-aryl-2\(H\)-1,2,3-triazole 1-oxides \(538\) (Scheme 189).

Cyclization of the oxomalonaldehyde derivatives \(540\) and \(541\) [produced from bis(oxyimino) hydrazone \(539\)] with cesium carbonate in tetrahydrofuran affords 2-aryl-2\(H\)-1,2,3-triazoles \(542\) and \(543\) in moderate to excellent yields (Scheme 190). \(^{[519,522,523]}\) These triazoles are hydrolyzed to the 4-formyl derivative or converted into a range of other interesting 4-substituted 2-aryltriazoles.
**Scheme 190** Oxidation of \(\alpha\)-Acetoxylimino Arylhydrazones with Cesium Carbonate\(^{[519,522,523]}\)

\[
\begin{align*}
\text{Ac}_2\text{O, rt} & & \text{Ac}_2\text{O, heat} \\
\text{rt, 30 min} & & \text{5−10 min}
\end{align*}
\]

\(\text{Ar}^1 = \text{Ph}, 2-\text{FC}_{6}\text{H}_4, 2-\text{ClC}_{6}\text{H}_4, 2,6-\text{Cl}_2\text{C}_{6}\text{H}_3, 3,4-\text{Cl}_2\text{C}_{6}\text{H}_3, 2,4,6-\text{Cl}_3\text{C}_{6}\text{H}_2, 2,6-\text{Cl}_2-4-\text{F}_3\text{C}_{6}\text{H}_2\)

Oxidation of both hydroxyimino arylhydrazones 544 and 545 with lead(IV) acetate yields 2-aryl-2\(H\)-1,2,3-triazole 1-oxides 546 in moderate to excellent yields (Scheme 191).\(^{[524]}\)

**Scheme 191** Oxidation of \(\alpha\)-Hydroxyimino Arylhydrazones with Lead(IV) Acetate\(^{[524]}\)

**Method 2:**

**Cyclization of 1,2-Diketone Bis(arylhydrazones)**

The oxidation of 1,2-diketone bis(arylhydrazones) to 2-aryl-2\(H\)-1,2,3-triazoles (Scheme 192) is a very general reaction and it has been used extensively for the preparation of sugar “osotriazoles” from osazones. This subject has been reviewed.\(^{[525]}\) The nitrogen eliminated is that attached to the 1-position for sugar osazones; a possible mechanism for the reaction is shown in Scheme 192.\(^{[3]}\) Many oxidizing agents have been used, especially copper sulfate and other copper(II) salts,\(^{[526−529]}\) and nitrous acid.\(^{[530,531]}\) As an example, oxidation of the phenyl-\(\alpha\)-glucosazone [547, \(R^1 = \text{H}; R^2 = (\text{CHOH})_3\text{CH}_2\text{OH}\)] with copper(II) sulfate gives the corresponding triazole 550 in 59% yield.\(^{[526−528]}\) In a similar way, glyoxal is converted into 2-phenyl-2\(H\)-1,2,3-triazole in 59% overall yield via osazone 547 (\(R^1 = R^2 = \text{H}\)).\(^{[522]}\) Oxidation of the tetra-\(O\)-acetylphenylosazones from \(\text{D}\)-glucose, \(\text{D}\)-galactose, and \(L\)-sorbose
with nitrous acid gives the corresponding 2-phenyl-2H-1,2,3-triazole tetraacetates in approximately 80% yield.\[530\]

**Scheme 192** Oxidation of 1,2-Diketone Bis(phenylhydrazones)\[525\]

This type of reaction can be extended to 1,2-diketone bis(phenylhydrazones) 547 \( (R^1 = R^2 = \text{alkyl or aryl}) \). Oxidation of these compounds with potassium dichromate in acetic acid,\[532\] nickel peroxide,\[533\] manganese(IV) oxide,\[534\] or with other oxidants yields a variety of products; the products formed depend upon the reaction conditions. In some cases, 2-substituted 2H-1,2,3-triazoles are obtained in low to moderate yields. As indicated in Scheme 192, a probable mechanism for the formation of triazoles involves the oxidation of the bis(phenylhydrazones) to bis(phenylazo)ethene derivatives 548, which can exist in the mesoionic form 549.\[535,536\] Loss of phenylnitrene from this species yields triazoles 550. The bis(phenylazo)ethene derivatives 548 are isolated in high yields,\[533\] and can be converted into 2-phenyl-2H-1,2,3-triazoles by acid treatment\[537\] or by irradiation with UV light.\[538\] Mesoionic species 549 have been trapped by dipolarophiles in 1,3-dipolar cycloadditions to yield new interesting 1,2,3-triazole derivatives.\[535,539,540\] N-Benzoyl analogues of mesoionic species 549 are isolated in good yields as stable crystalline compounds.\[541\] 1,2-Bis(arylazo)cycloalkenes (548, \( R^1, R^2 = \text{ring with six or more carbons} \)) when heated or treated with acid undergo intramolecular rearrangements, via 1,2,3-triazolium imide 1,3-dipoles of type 549, to yield 2-aryl-2H-1,2,3-triazoles bearing a 2-aminoaryl group in the cycloalkene ring.\[542\]

1,2-Diketone bis(hydrazones) also cyclize to 1,2,3-triazoles solely by thermolysis: heating biacetyl bis(hydrazone) at 170°C gives 4,5-dimethyl-1H-1,2,3-triazole (25%) and heating biacetyl bis(phenylhydrazone) at 300°C yields 2-phenyl-4,5-dimethyl-2H-1,2,3-triazole in 51% yield.\[543\]

Oxidation of phenylhydrazones of aromatic aldehydes 551 with manganese(IV) oxide in refluxing benzene also affords triazoles 553 and other isolated products (Scheme 193).\[534\] The dimerization of the phenylhydrazones to 552 appears to be the key step in this transformation. Triazoles 553 are obtained in low to moderate yields. The oxidation of arylhydrazones derived from 2-acetylpyridine and 2-benzoylpyridine with lead(IV) acetate leads to the formation of fused 1,2,3-triazolium systems.\[544\]
Method 3: Cyclization of $\alpha$-Imino Hydrazones

The oxidative cyclization of 1,2-diketone imine hydrazones 554 with ammoniacal copper sulfate yields 2$H$-1,2,3-triazoles 555. N-Substituted imines 556 give 1,2-disubstituted triazolium salts 557 when N-bromosuccinimide is used as the oxidant (Scheme 194).\cite{545,546}

A related reaction is the oxidative cyclization of (carbamimidoyl)(phenylazo)acetamide 558 (X = O) and (phenylazo)malonimidamide 558 (X = NH) to triazoles 559 (Scheme 195).\cite{547}
Method 4: Cyclization of 1,2-Bis(N-alkoxy-N-nitrosoamines)

1,2-Bis(N-alkoxy-N-nitrosoamines) 560 are smoothly converted into 1-alkoxy-4,5-dihydro-1H,1,2,3-triazole 2-oxides 561, in high yields, under reflux in methanol. Reaction of these compounds with sodium methoxide affords 4H-1,2,3-triazole 2-oxides or 2H-1,2,3-triazol-2-ols 563 (Scheme 196).[548,549]

Scheme 196 Cyclization of 1,2-Bis(N-alkoxy-N-nitrosoamines)[548,549]

13.13.2 Synthesis by Ring Transformation

Thermal or basic treatment of arylhydrazones 565 of 3-acylisoxazoles 564 affords 4-acyl-2-aryl-2H-1,2,3-triazoles 566 (Scheme 197). For example, hydrazone 565 (R1 = R2 = Me; Ar1 = 2-ClC6H4) is converted into the corresponding triazole 566 by warming it to fusion in a test tube plunged in a silicone oil bath at ca. 240°C.[517] Hydrazone 565 (R1 = R2 = Ph; Ar1 = 4-O2NC6H4) is converted quantitatively into the corresponding triazole 566 when it is melted in the presence of copper powder or by treatment with ammonia.[550] Copper(II) acetate can also be used as catalyst for this transformation.[551] The kinetics of the transformation of hydrazones 565 into triazoles 566 catalyzed by amines[552] or in the presence of borate buffers,[553] has been studied.

Scheme 197 Synthesis of 2-Aryl-2H-1,2,3-triazoles from Arylhydrazones of 3-Acylisoxazoles[510,510]

4-(Arylazo)isoxazol-5-ones 568 (produced from 4-arylisoxazol-5-ones 567) are converted into 2-aryl-2H-1,2,3-triazoles 569 when refluxed in propan-2-ol, in the presence of a tertiary amine, or in 1-(dimethylamino)propan-2-ol (Scheme 198).[554]
Arylhydrazones of 3-acyl-1,2,4-oxadiazoles yield 4-(acylamino)-2-aryl-2H-1,2,3-triazoles 571 by thermal or basic rearrangement (Scheme 199). For example, hydrazone 570 (R1 = 3-O2NC6H4; Ar1 = 4-O2NC6H4) is converted into the corresponding triazole in 60% yield when it is melted in the presence of copper powder. The same triazole is obtained in 90% yield by treatment of hydrazone 570 (R1 = 3-O2NC6H4; Ar1 = 4-O2NC6H4) with ammonia. Phenylhydrazone 570 (R1 = Ar1 = Ph) gives the corresponding triazole 571 in almost quantitative yield when treated with either equimolar or catalytic amounts of copper(II) acetate monohydrate in methanol at room temperature for two hours. A kinetic study of the rearrangement of arylhydrazones 570 (R1 = Ph; Ar1 = XC6H4) into triazoles 571 has been reported. The effect of β-cyclodextrin on the mononuclear rearrangement of 570 (R1 = Ar1 = Ph) into 571 (R1 = Ar1 = Ph), in aqueous borate buffer at pH = 9.6, at temperatures ranging from 293.15 to 313.15 K, has also been reported. The 2,4-dinitrophenylhydrazone of 3-benzoyl-1,2,4-oxadiazol-5-amine 570 (R1 = NH2; Ar1 = 2,4-(O2N)2C6H3) is converted rapidly into the 4-ureido-2H-1,2,3-triazole 571 (R1 = NH2; Ar1 = 2,4-(O2N)2C6H3), in dimethyl sulfoxide at room temperature or by heating above its melting point.

When refluxed in ethanol, in the presence of sodium ethoxide, the 1,2,5-oxadiazole phenylhydrazone 572 rearranges to triazoles 573 and 574 (Scheme 200). The two isomeric oximes 573 (E, 80%) and 574 (Z, 10%) can be separated by column chromatography.

4-(Alkylamino)-3-nitro-1,2,5-oxadiazole 2-oxides 575 react with primary aliphatic amines to afford 2-alkyl-4-(alkylamino)-5-nitro-2H-1,2,3-triazole 1-oxides 577, via intermediates 576, in low to moderate yields (Scheme 201). Compounds 577 are also prepared in a one-pot procedure from 3,4-dinitro-1,2,5-oxadiazole 2-oxide.
Scheme 201 Synthesis of 2-Alkyl-5-nitro-2H-1,2,3-triazole 1-Oxides from 4-(Alkylamino)-3-nitro-1,2,5-oxadiazole 2-Oxides\textsuperscript{[558–560]}

\[
\begin{align*}
\text{Oxidation of 4-(arylhydrazono)-4H-pyrazole-3,5-diamines 578 with lead(IV) acetate (2 equiv) provides 2-aryl-2H-1,2,3-triazole-4-carbonitriles 579 in moderate yields (Scheme 202). Plausible mechanisms for this transformation have been proposed.} & \text{[561]} \\
\end{align*}
\]

Scheme 202 Synthesis of 2-Aryl-2H-1,2,3-Triazoles from 4-(Arylhydrazono)-4H-pyrazole-3,5-diamines\textsuperscript{[561]}

\[
\begin{align*}
\text{Photolysis of 2-methyl-5-phenyl-2H-tetrazole (582) produces, among other minor products, 2-methyl-4,5-diphenyl-2H-1,2,3-triazole (583) in low yield (Scheme 204).} & \text{[563]} \\
\end{align*}
\]

Scheme 203 Synthesis of 2H-1,2,3-Triazole 1-Oxides from 2-Methyl-4-nitro-1-phenyl-1H-imidazole\textsuperscript{[562]}

\[
\begin{align*}
\text{4,6-Disubstituted 2-methyl-2,5-dihydro-1,2,3-triazines 584 are oxidized by 3-chloroperoxybenzoic acid (2 equiv) to give 4-substituted 2-methyl-2H-1,2,3-triazoles 585 in good yields if at least one of the substituents is a phenyl group (Scheme 205).} & \text{[564,565]} \\
\end{align*}
\]

for references see p 587
The 1,2,3,4-tetrazine 587, generated from the reaction of an (alkylazo)alkene 586 and dimethyl azodicarboxylate, is unstable and on workup yields 2,5-dihydro-1H-1,2,3-triazole 588 (Scheme 206). This isomerization is probably acid catalyzed since by addition of trifluoroacetic acid 587 is converted in near quantitative yield into triazole 589.\(^\text{[566]}\) The same triazole is also obtained cleanly when 588 alone is treated with trifluoroacetic acid under the same conditions.

[1,2,3]Triazolo[1,5-b]pyridazinium salts 590, when treated with morpholine, undergo opening of the pyridazine ring to yield mixtures of the triazoles 591 and 592 (Scheme 207).\(^\text{[567]}\) The ratio of these products varies significantly depending on whether R\(^1\) is an alkyl or an aryl group. Reaction of triazolopyridazinium salts 590 with alkoxides or thiolates affords the 4-vinyl-2H-1,2,3-triazoles 593 and 594, respectively, as the sole products.\(^\text{[567]}\)
Irradiation of 2-aryl-2H-benzotriazoles 595 with UV light, in an aerated solvent, results in the oxidation of the benzo ring and formation of 2-aryl-2H-1,2,3-triazole-4,5-dicarboxylic acids 597 (Scheme 208). The 2aryl-2H-benzotriazole-4,7-diones 596 are plausible intermediates since photooxidation of compound 596 (R1 = R2 = H), obtained by oxidation of 595 (R1 = R2 = H) with potassium dichromate, also leads to 597 (R1 = R2 = H). Oxidation of 2-phenyl-2H-benzotriazole (595, R1 = R2 = H) with potassium permanganate also gives the dicarboxylic acid 597 (R1 = R2 = H) (in 50% yield) but oxidation of 595 (R1 = OMe; R2 = Me) under similar conditions, results in the formation of a tricarboxylic acid 597 (R1 = OMe; R2 = CO2H) in 48% yield. 

**Scheme 207**  Synthesis of 2H-1,2,3-Triazoles from Triazolopyridazinium Salts

- **R1 = Me, 4-ClC6H4; Ar1 = 4-BrC6H4**
- **NaOMe, MeOH, rt**
- **R1 = Me** 72%
- **R1 = 4-ClC6H4** 82%

- **R1 = Me; 4-ClC6H4, Ar1 = 4-BrC6H4**
- **BnSH, KOH, EtOH, 5-10 oC**
- **R1 = Me** 95%
- **R1 = 4-ClC6H4** 90%
Scheme 208  Photooxidation of 2-Aryl-2\textsubscript{H}-benzotriazoles\textsuperscript{[568]}

\[
\text{O}_2, \text{EtOH} \quad \text{hv}, \text{rt}, 12.5 \text{ d}
\]

R\textsubscript{1} = R\textsubscript{2} = H   93%

13.13.2.3  Synthesis by Substituent Modification

Since substituent modification reactions in 1\textsubscript{H}- and 2\textsubscript{H}-1,2,3-triazoles are, in many cases, very similar, the synthesis of new 2\textsubscript{H}-1,2,3-triazoles by substituent modification of monocyclic 2-substituted 2\textsubscript{H}-1,2,3-triazoles is covered in Section 13.13.1.4.

13.13.3  Product Subclass 3:  
N-Unsubstituted and 1-Substituted Benzotriazoles

13.13.3.1  Synthesis by Ring-Closure Reactions

13.13.3.1.1  By Formation of Two N–N Bonds

13.13.3.1.1.1  Method 1:  
From Benzene-1,2-diamines and Nitrous Acid

The diazotization of benzene-1,2-diamine derivatives is the most common synthetic route to benzotriazoles. This is a very general method, which can also be applied to the cyclization of other 1,2-diaminocarbocycles\textsuperscript{[569]} and 1,2-diaminoheterocycles.\textsuperscript{[570–574]} In almost all the cases the diazotization is carried out with nitrous acid (generated in situ from sodium nitrite and a mineral acid) but other reagents can also be used. Esters of nitrous acid with primary or secondary alcohols, preferentially methyl nitrite\textsuperscript{[575]} or diphenylnitrosamine,\textsuperscript{[576]} also react with benzene-1,2-diamine derivatives to afford benzotriazoles in high yields. Molecules consisting of a benzene-1,2-diamine group linked to a fluorophore moiety are used as probes for nitric oxide (NO) detection; fluorescent benzotriazoles are formed in this reaction.\textsuperscript{[577–579]}

The structure of the products obtained from the action of nitrous acid on an aromatic 1,2-diamine, or on one of its alkyl, aryl, or acyl derivatives, was the subject of a very interesting scientific dispute, which occurred between the 1870s and 1910. The symmetrical structure 598 (Scheme 209), proposed by Griess,\textsuperscript{[580,581]} was shown to be incorrect and structure 599, suggested by Kekulé, was confirmed as the correct one.\textsuperscript{[582,583]}

A range of diversely substituted benzotriazole derivatives 601 is prepared by diazotization of the corresponding benzene-1,2-diamine derivatives 600, a few examples are shown in Scheme 210.

**Scheme 210**  
Diazotization of Benzene-1,2-diamine Derivatives

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>Conditions</th>
<th>Yield (%)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>NaNO₂, AcOH, H₂O, 5–80°C, 1 h</td>
<td>75–81</td>
<td>[584]</td>
</tr>
<tr>
<td>H</td>
<td>5,6-Cl₂</td>
<td>NaNO₂, HCl, H₂O, 0 °C</td>
<td>50</td>
<td>[545]</td>
</tr>
<tr>
<td>H</td>
<td>5,6-(NO₂)₂</td>
<td>NaNO₂, HCl, H₂O, 5–25°C, 1 h</td>
<td>83</td>
<td>[546]</td>
</tr>
<tr>
<td>Me</td>
<td>6-Cl</td>
<td>NaNO₂, HCl, H₂O, 10°C</td>
<td>29</td>
<td>[545]</td>
</tr>
<tr>
<td>2,4,6-(O₂N)₃C₆H₂</td>
<td>4,6-(NO₂)₂</td>
<td>NaNO₂, H₂SO₄, H₂O, 5–25°C, 1 h</td>
<td>63</td>
<td>[546]</td>
</tr>
<tr>
<td>Ac</td>
<td>5,6-Me₂</td>
<td>NaNO₂, AcOH, H₂O, 10–50°C</td>
<td>63</td>
<td>[547]</td>
</tr>
<tr>
<td>Ac</td>
<td>5-NHAc-6-OMe</td>
<td>NaNO₂, HCl, H₂O, 5°C, 2 h</td>
<td>97</td>
<td>[548]</td>
</tr>
<tr>
<td>CSCHMeNHboc</td>
<td>6-NO₂</td>
<td>NaNO₂, AcOH, H₂O, 0°C, 30 min</td>
<td>79</td>
<td>[549]</td>
</tr>
<tr>
<td>benzotriazol-2-yl</td>
<td>H</td>
<td>NaNO₂, AcOH, H₂O</td>
<td>&gt;90</td>
<td>[590]</td>
</tr>
<tr>
<td>CO₂Et</td>
<td>7-Cl-4-OEt-5-CO₂Me</td>
<td>NaNO₂, H₂SO₄, H₂O, 5°C, 15 min</td>
<td>68</td>
<td>[591]</td>
</tr>
<tr>
<td>SO₂Ph</td>
<td>5-Me</td>
<td>NaNO₂, HCl, H₂O, rt</td>
<td>100</td>
<td>[592]</td>
</tr>
<tr>
<td>HN</td>
<td>H</td>
<td>NaNO₂, HCl, H₂O, 0°C to rt, 2 h</td>
<td>96</td>
<td>[322]</td>
</tr>
<tr>
<td>6-methyl-3-pyridyl</td>
<td>H</td>
<td>NaNO₂, HCl, H₂O, 0°C</td>
<td>63</td>
<td>[593]</td>
</tr>
<tr>
<td>acridin-9-yl</td>
<td>5,6-Me₂</td>
<td>NaNO₂, HCl, H₂O, 0°C, 1 h</td>
<td>85</td>
<td>[579]</td>
</tr>
</tbody>
</table>

Benz[b]1,2-d:4,5-d’bistriazoles are synthesized, in one step, by diazotization of benzene-1,2,4,5-tetraamine derivatives (Scheme 211). 1,7-Bis(2,4,6-trinitrophenyl)bentriazobistriazole 603 is obtained in 60% yield from the bis(acetylamino) derivative 602, while the 1,7-di-acetyl analogue 605 is prepared in 93% from 1,5-bis(acetylamino)-2,4-dinitrobenzene (604).

*FOR PERSONAL USE ONLY*

An alternative method for the conversion of benzene-1,2-diamine derivatives into benzotriazoles consists of their reaction with benzonitrile oxide, followed by diazotization of the resulting N-substituted benzamide oximes 607 to 1-benzohydroximoyl-1H-benzotriazoles 608 (Scheme 212). These compounds are hydrolyzed in refluxing concentrated hydrochloric acid to afford benzotriazoles 609 in quantitative yields. There is no obvious advantage of this method over direct diazotization of diamines 606, except the fact that compounds 607 can also be converted into benzimidazoles by treatment with hydrochloric acid.
5,6-Dinitro-1H-benzotriazole [601, R¹ = H; R² = 5,6-(NO₂)₂]; Typical Procedure[586]
A slurry of 4,5-dinitrobenzene-1,2-diamine (7.0 g, 35 mmol) in concd HCl (300 mL) was treated dropwise with a 10% aq NaNO₂ (90 mL) at 5–10°C. After the resulting mixture had stirred at 25°C for 1 h it was chilled to 0°C and the product was collected by filtration, washed with H₂O, and air-dried to provide analytically pure crystals of the monohydrate of 5,6-dinitrobenzotriazole; yield: 6.6 g (83%); mp 144°C. Anhyd product was obtained when the monohydrate was dried in an oven at 80°C overnight.

13.13.3.1.2
By Formation of One N–N and One N–C Bond

13.13.3.1.2.1
Fragments C–C–N and N–N

13.13.3.1.2.1.1
Method 1:
From Arylamines and 2-Azido-3-ethyl-1,3-benzothiazolium Tetrafluoroborate

The benzothiazolium tetrafluoroborate 610 reacts with 2-naphthylamine to afford naphtho[1,2-d][triazole 612 in 70% yield (Scheme 213).[599] Since salt 610 is a good diazo-transfer reagent,[600] diazoamino derivative 611 is a probable intermediate in this reaction. Compound 610 also reacts with amino-heterocycles to yield heterocycle-fused 1,2,3-triazoles in good yields.[599]

Scheme 213
Synthesis of 1H-Naphtho[1,2-d][1,2,3]triazole from 2-Naphthylamine[599]

1H-Naphtho[1,2-d][1,2,3]triazole (612); Typical Procedure[599]
To a soln of 2-naphthylamine (0.615 g, 5 mmol) in 0.4 M HCl in EtOH (40 mL) at rt was added 2-azido-3-ethyl-1,3-benzothiazolium tetrafluoroborate (610; 1.5 g, 5.1 mmol) in one portion and the mixture was stirred for 1 h. The solvent was evaporated and aq 2 M NH₄ (20 mL) was added to the residue. The mixture was stirred, filtered, and extracted with CHCl₃ (2 × 5 mL). The organic phase was discharged. The aqueous phase was neutralized and the resulting solid was filtered, washed with H₂O, and dried; yield: 0.60 g (70%); mp 175–180°C.

for references see p 587
Fragments C—C—N—N and N

Method 1:
From α-Diazo Ketones and Amines

Benzoyl trifluoromethanesulfonate (614) smoothly transforms 10-diazophenanthren-9(10H)-one (613) into diazonium salt 615, which reacts with isopropylamine to give the phenanthrotriazole 616 in 86% overall yield (Scheme 214).[38]

Scheme 214  Synthesis of Phenanthro[9,10-d][1,2,3]triazole from a α-Diazo Phenanthrenone[38]
Scheme 215  Synthesis of Benzotriazoles from Azides and Dehydrobenzene[601–604]

\[
\begin{array}{c}
\text{CO}_2\text{H} \\
\text{NH}_2
\end{array}
\xrightarrow{\text{BaONO}}
\begin{array}{c}
\text{R}^1 \text{N}_3
\end{array}
\xrightarrow{R^1 N_2}
\begin{array}{c}
\text{NNN}
\end{array}
\]

\(R^1 = \text{alkyl, aryl, glycosyl, acyl, sulfonyl}\)

<table>
<thead>
<tr>
<th>(R^1)</th>
<th>Conditions</th>
<th>Yield (%)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>((\text{CH}_3)_2\text{Me})</td>
<td>(\text{CH}_2\text{Cl}_2, \text{acetone, reflux, 2 h})</td>
<td>70</td>
<td>[601]</td>
</tr>
<tr>
<td>(\text{Ph})</td>
<td>(\text{CH}_2\text{Cl}_2, \text{acetone, reflux, 2 h})</td>
<td>52</td>
<td>[601]</td>
</tr>
<tr>
<td>4-(\text{OHCC}_6\text{H}_4)</td>
<td>(\text{CH}_2\text{Cl}_2, \text{acetone, reflux, 2 h})</td>
<td>50</td>
<td>[601]</td>
</tr>
<tr>
<td>4-(\text{AcC}_6\text{H}_4)</td>
<td>(\text{CH}_2\text{Cl}_2, \text{acetone, reflux, 2 h})</td>
<td>50</td>
<td>[601]</td>
</tr>
<tr>
<td>4-(\text{O}_2\text{NC}_6\text{H}_4)</td>
<td>(\text{CH}_2\text{Cl}_2, \text{reflux, 1.5 h})</td>
<td>62</td>
<td>[602]</td>
</tr>
<tr>
<td>1-napthyl*</td>
<td>(\text{CH}_2\text{Cl}_2, \text{acetone, reflux, 3 h})</td>
<td>75</td>
<td>[603]</td>
</tr>
<tr>
<td>acridin-9-yl</td>
<td>(\text{CH}_2\text{Cl}_2, \text{acetone, reflux, 2 h})</td>
<td>47</td>
<td>[601]</td>
</tr>
<tr>
<td>(\text{Bz})</td>
<td>(\text{CH}_2\text{Cl}_2, \text{acetone, reflux, 2.5 h})</td>
<td>73</td>
<td>[604]</td>
</tr>
<tr>
<td>4-(\text{MeOC}_6\text{H}_4) &amp; (\text{CO}_2\text{H})</td>
<td>63</td>
<td>[602]</td>
<td></td>
</tr>
<tr>
<td>4-(\text{AcC}_6\text{H}_4) &amp; (\text{SO}_2\text{Ph})</td>
<td>60</td>
<td>[602]</td>
<td></td>
</tr>
<tr>
<td>4-(\text{ClC}_6\text{H}_4) &amp; (\text{SO}_2\text{Ph})</td>
<td>52</td>
<td>[602]</td>
<td></td>
</tr>
</tbody>
</table>

* Isopentyl nitrite was used.

The synthesis of 1-(2-methyl-1-naphthyl)-1\(H\)-naphtho[2,3-d][1,2,3]triazole (620) from the reaction of a naphthyl azide with 2,3-dehydronaphthalene (619), produced from 3-amino-2-naphthoic acid (618), is an interesting extension of this method (Scheme 216).[603]

Scheme 216  Synthesis of Naphthotriazoles from Azides and 2,3-Dehydronaphthalene[603]

\[
\begin{array}{c}
\text{CO}_2\text{H} \\
\text{NH}_2
\end{array}
\xrightarrow{\text{Me(\text{CH}_2)\text{ONO}}}
\begin{array}{c}
\text{DME, reflux, 1.5 h}
\end{array}
\xrightarrow{\text{R^1 N_2}}
\begin{array}{c}
\text{NNN}
\end{array}
\]

\(R^1 = \text{aryl, alkenyl, alkoxy, acyl, sulfonyl}\)

21%
**1-(1-Naphthyl)-1H-benzotriazole (617, R\(^1\) = 1-naphthyl); Typical Procedure:**

A stirred soln of 1-naphthylazide (8.45 g, 50 mmol) and isopentyl nitrite (13.5 mL, 100 mmol) in \(\text{CH}_2\text{Cl}_2\) (400 mL) was refluxed and treated with a soln of 2-aminobenzoic acid (13.7 g, 100 mmol) in acetone (100 mL) over 2 h. Heating was continued for a further 1 h, after which the mixture was cooled and evaporated under reduced pressure to leave a brown oil. Chromatography (silica gel) afforded the benzotriazole as a white crystalline solid; yield: 9.15 g (75%); mp 114–115°C.

**13.13.3.1.2 Method 2: From Azides and Quinones**

As described in Section 13.13.1.3.1.2.3, organic azides undergo addition to alkenes with electron-withdrawing groups to yield dihydrotriazoles or triazoles. When benzoquinones or naphthoquinones are used, benzotriazole derivatives are obtained. From the reaction of benzo-1,4-quinone and phenyl azide, mono- or bis-addition products 621, and 622 and 623, respectively, are formed, depending on the number of equivalents of azide used (Scheme 217). Phenyl azide adds to 2-methylbenzo-1,4-quinone to give only one monoadduct.

![Scheme 217 Reaction of Benzo-1,4-quinone with Phenyl Azide](image)

Naphtho-1,4-quinone reacts with methyl azide (sealed tube, 105°C, 20 h) to afford triazole 624 (\(R^1 = \text{Me}\)) in 48% yield. Similar reactions of naphtho-1,2-quinone and 6-bromo-naphtho-1,2-quinone with methyl azide or phenyl azide do not give any triazole derivatives. Naphtho-1,4-quinone reacts with (azidoalkyl)phosphonates and with ethyl azidoacetate to afford triazole derivatives 624 in good yields (Scheme 218).

![Scheme 218 Reaction of Naphtho-1,4-quinone with Allyl Azides](image)

**1-Substituted 1H-Naphtho[2,3-d][1,2,3]triazole-4,9-diones 624; General Procedure:**

A soln of naphtho-1,4-quinone (0.47 g, 3 mmol) in THF was added dropwise, with stirring, to a soln of diethyl (1-azidoalkyl)phosphonate or ethyl azidoacetate (3 mmol) in THF.
(15 mL) and the mixture was refluxed for 20 h. The solvent was evaporated and the residue was purified by flash chromatography (silica gel, Et₂O/hexane) to give the triazole.

### 13.13.3.1.4 By Formation of One N–N Bond

#### 13.13.3.1.4.1 Fragment N–N–C–C–N

#### 13.13.3.1.4.1.1 Method 1: Cyclization of 2-Nitrophenylhydrazines

When treated with a base, 2-nitrophenylhydrazines cyclize to benzotriazol-1-ols (Scheme 219). Benzotriazol-1-ol exists in tautomeric equilibrium with 1H-benzotriazole 3-oxide. The position of the equilibrium depends on the solvent; e.g., in water the N-oxide form predominates. In some circumstances, the use of 2,4-dinitrophenylhydrazide to prepare 2,4-dinitrophenylhydrazones may lead to the formation of 6-nitrobenzotriazol-1-ol. The cyclization of 2-nitrophenylhydrazines can also be carried out with polyphosphoric acid (e.g., conversion of 625 into 626, Scheme 220). Benzotriazol-1-ols are powerful explosives and decompose violently at 200–210°C to carbonaceous material. A large variety of benzotriazol-1-ol derivatives are used extensively as coupling reagents.

#### Scheme 219 Cyclization of 2-Nitrophenylhydrazines in Alkaline Media

![Scheme 219](image)

#### Scheme 220 Cyclization of 2-Nitrophenylhydrazines with Polyphosphoric Acid

![Scheme 220](image)

1-Methyl-7-nitro-1H-benzotriazole 3-Oxide (626): Typical Procedure

A mixture of 1-(2,6-dinitrophenyl)-1-methylhydrazine (0.4 g, 1.9 mmol) and PPA (15 g) was gently warmed and stirred for 10 min. The resulting brown soln was cooled and poured into H₂O (100 mL). The soln was extracted with CHCl₃ (3 × 30 mL) and the yellow organic extract was chromatographed (basic alumina, 100–200 mesh, 100 g). The unchanged hydrazine was eluted with CHCl₃. A second fraction was collected, concentrated under reduced pressure, and recrystallized (EtOH) to give 626 as yellow plates; yield: 0.15 g (41%); mp 242–243°C.

#### 13.13.3.1.4.1.1 Variation 1: Reaction of 1-Chloro-2-nitrobenzenes or 1,2-Dinitrobenzenes with Hydrazine

1,2-Dinitrobenzenes 627 (X = NO₂) and 1-chloro-2-nitrobenzenes 627 (X = Cl) react with hydrazine to yield benzotriazol-1-ols 629 via the 2-nitrophenylhydrazines 628 (Scheme 221). The yields of the reactions are highly dependent on the substituents on the

---

For references see p 587
starting material. In some cases the substitution of the nitro group is the most favorable process, the corresponding arylhydrazines are then the main products.\([619]\) The synthesis of benzotriazol-1-ols from 1-methoxy-2-nitrobenzenes (627, \(X = OMe\)) has also been described.\([609,617]\)

**Scheme 221** Benzotriazol-1-ols from 1,2-Dinitrobenzenes or 1-Chloro-2-nitrobenzenes and Aqueous Hydrazine\([617,619–621]\)

<table>
<thead>
<tr>
<th>(X)</th>
<th>(R^1)</th>
<th>Yield (%)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>(NO_2)</td>
<td>4,6-Cl(_2)</td>
<td>60</td>
<td>([617])</td>
</tr>
<tr>
<td>(NO_2)</td>
<td>4,6-Br(_2)</td>
<td>–(a)</td>
<td>([617])</td>
</tr>
<tr>
<td>Cl</td>
<td>H</td>
<td>90</td>
<td>([619])</td>
</tr>
<tr>
<td>Cl</td>
<td>4,5-Cl(_2)</td>
<td>85</td>
<td>([619])</td>
</tr>
<tr>
<td>Cl</td>
<td>4,5,6-Cl(_3)</td>
<td>67</td>
<td>([619])</td>
</tr>
<tr>
<td>Cl</td>
<td>4,5,6,7-Cl(_4)</td>
<td>40</td>
<td>([619])</td>
</tr>
<tr>
<td>Cl</td>
<td>6-CF(_3)</td>
<td>90</td>
<td>([620])</td>
</tr>
<tr>
<td>Cl</td>
<td>6-OMe</td>
<td>6</td>
<td>([620])</td>
</tr>
<tr>
<td>Cl</td>
<td>6-CONH(_2)</td>
<td>39</td>
<td>([620])</td>
</tr>
<tr>
<td>Cl</td>
<td>6-SO(_2)NHMe</td>
<td>79</td>
<td>([620])</td>
</tr>
<tr>
<td>Cl</td>
<td>6-SO(_2)NHBn</td>
<td>96</td>
<td>([621])</td>
</tr>
</tbody>
</table>

\(a\) Yield not reported.

Polymer-supported benzotriazol-1-ol derivatives 633\([621]\) and 637\([622]\) are prepared, respectively, from the reaction of polymer-supported 1-chloro-2-nitrobenzenes 632 and 636 and hydrazine (Scheme 222). Precursor 632 is obtained from the reaction of the aminomethylated polystyrene 630 and the benzenesulfonyl chloride 631 while 636 is prepared by Friedel–Crafts alkylation of polystyrene 634, using 4-chloro-3-nitrobenzyl alcohol (635). The polymeric reagent 633 is highly efficient for the synthesis of amides.\([621,623]\)

**Scheme 222** Polymer-Supported Benzotriazol-1-ol Derivatives\([621,622]\)
**Benzotriazol-1-ols** \(^{629}\); General Procedure.\(^ {6317}\)

The appropriate 1-chloro-2-nitrobenzene (5 g) was dissolved in hot EtOH (15–20 mL) and 85% aq hydrazine (5 g) was added. The mixture was refluxed for 3 h and cooled. The precipitate was collected by filtration, dissolved in hot H\(_2\)O, and the benzotriazol-1-ol derivative was precipitated with aq HCl. The crude product was decolorized with charcoal and recrystallized (EtOH/MeOH 1:1).

**Method 2:**

**Cyclization of (2-Aminophenyl)hydrazine Derivatives**

Oxidative cyclization of 1-(acetylamino)-2-hydrazino-3-nitrobenzene with chlorine affords 4-nitro-1\(H\)-benzotriazole in 80% yield (Scheme 223).\(^ {624}\)

**Scheme 223** Cyclization of 1-(Acetylamino)-2-hydrazino-3-nitrobenzene\(^ {624}\)

**Method 3:**

**Cyclization of (2-Aminophenyl)triazene Derivatives**

Polymer-bound 1-(2-aminophenyl)triazenes \(^{638}\) are cleaved smoothly with trifluoroacetic acid in dichloromethane at room temperature within minutes to give 1-substituted benzotriazoles \(^{639}\) in excellent yields (Scheme 224).\(^ {625}\)

**Scheme 224** Benzotriazoles from Polymer-Bound 1-(2-Aminophenyl)triazenes\(^ {625}\)

\(R^1 = \text{CH}_2\text{CHCH}_2\), cyclopropyl, cyclopentyl, 4-MeOC\(_6\)H\(_4\)CH\(_2\)R

---

for references see p 587
13.13.3.2 Synthesis by Ring Transformation

13.13.3.2.1 Method 1:
From 4,5-Dimethylene-4,5-dihydro-1H-triazoles

4,5-Dimethyl-4,5-dihydro-1H-triazoles 641, generated from 640 by 1,4-elimination of bromine, are trapped in low to moderate yields by dienophiles in Diels–Alder reactions (Scheme 225).[626] Benzotriazole 642 is obtained when 641 is generated in the presence of dimethyl acetylenedicarboxylate; adduct 643 is formed when N-methylmaleimide is used as the dienophile. This adduct is converted into the benzotriazole derivative 644 by treatment with N-bromosuccinimide.

Scheme 225 Benzotriazoles from 4,5-Dimethyl-4,5-dihydro-1H-triazoles[626]

13.13.3.2.2 Method 2:
Transformation of 1,3-Dihydro-2H-benzimidazol-2-ones

The reaction of 1,3-dihydro-2H-benzimidazol-2-one (645) with sodium nitrite and water, in a autoclave at high temperature, gives the sodium salt of benzotriazole, which, by acidification gives 1H-benzotriazole in high yield (Scheme 226).[627] This reaction can be extended to 1,3-dihydro-2H-benzimidazol-2-ones with substituents on positions 4–7.

Scheme 226 Benzotriazoles from 1,3-Dihydro-2H-benzimidazol-2-ones[627]
13.13.3.2.3  **Method 3:**
Transformation of 1,2,4-Benzotriazin-3(2H)-ones

1,2,4-Benzotriazin-3(2H)-one 646 and phenanthrotiazin-3-one 647 are converted into 1H-benzotriazole and phenanthrotriazole 648, respectively, on treatment with ethereal chloramine at room temperature (Scheme 227).[381] Treatment of benzotriazin-3-one 646 with lead(IV) acetate in refluxing benzene affords 1-acetyl-1H-benzotriazole in good yield.[381]

**Scheme 227**  Benzotriazoles from 1,2,4-Benzotriazin-3(2H)-ones[381]

![Scheme 227](image)

13.13.3.2.4  **Method 4:**
Transformation of 1,2,3,4-Benzotetrazine 1,3-Dioxides

The reduction of 1,2,3,4-benzotetrazine 1,3-dioxides 649 with sodium hydrosulfite or tin(II) chloride affords benzotriazoles 651 in almost quantitative yields (Scheme 228).[628] It has been suggested that this transformation proceeds via the intermediate N-nitroso-benzotriazoles 650.

**Scheme 228**  Benzotriazoles from 1,2,3,4-Benzotetrazine 1,3-Dioxides[628]

![Scheme 228](image)

R¹ = H, Br; R² = H, Br, NO₂

*for references see p 587*
**Synthesis by Substituent Modification**

**Substitution of Existing Substituents**

**Of Hydrogen**

**Method 1: N-Trimethylsilylation**

Benzotriazole reacts with hexamethyldisilazane to give 1-(trimethylsilyl)-1H-benzotriazole (652) in 95% yield (Scheme 229). [169,434,629,630]

**Scheme 229** N-Trimethylsilylation of 1H-Benzotriazole

```
N
N
\[ \text{heat} \quad 95\% \]

652
```

**Method 2: Carboxylation**

Heating an intimate mixture of 1H-benzotriazol-5-ol with a large excess of anhydrous potassium carbonate in a nickel-lined steel autoclave, with carbon dioxide under pressure, affords 5-hydroxy-1H-1,2,3-benzotriazole-4-carboxylic acid (653) in 49% yield (Scheme 230). [631,632]

**Scheme 230** Carboxylation of 1H-Benzotriazol-5-ol

```
\text{K}_2\text{CO}_3, \text{CO}_2
\quad \text{180} - \text{190}^\circ \text{C, 16 h}

653
```

Benzotriazole reacts with chloroformates 654, in alkaline solutions, to afford selectively the corresponding alkyl 1H-benzotriazole-1-carboxylates 655 (Scheme 231). [633–635]

**Scheme 231** N-Alkoxycarbonylation of 1H-Benzotriazole

```
\text{aq NaOH}
\quad 58-100\%

R^1 = \text{Me, Et, Ph, Bn}
```

**Ethyl 1H-1,2,3-Benzotriazol-1-carboxylate (655, R^1 = Et); Typical Procedure:** [634]

Ethyl chloroformate (6.0 g, 0.056 mol) was slowly added to a stirred and cooled aqueous soln of 1H-benzotriazole (6.0 g, 0.05 mol) and NaOH (2.0 g, 0.05 mol). After completion of the addition, the mixture was stirred for an additional 15 min, and the precipitated white solid was then collected by filtration, washed with H₂O, dried, and recrystallized (Et₂O); yield: 9.1 g (95%); mp 70–71 °C.
**13.13.3.3.1.3 Method 3: Acylation**

Benzotriazoles react with acyl chlorides and anhydrides to afford the 1-acyl derivatives 656 (Scheme 232).[587]  

Scheme 232  Acylation of 1H-Benzotriazole[587]  

1-Acyl-1H-benzotriazoles 656 (R¹ = aryl, 2-arylvinyl) are prepared in moderate to good yields from the reaction of 1H-benzotriazole and acyl chlorides in pyridine or in aqueous sodium hydroxide.[634] Other benzotriazole derivatives 656 (R¹ = alkyl, aryl) are obtained in high yields (87–99%) from the reaction of 1H-benzotriazole and acyl chlorides in anhydrous dichloromethane and triethylamine at 0 °C.[636,637] 1-Acyl-1H-benzotriazoles 656 (R¹ = Me, Et, Bu, Ph) are prepared in good yields by fusion of 1H-benzotriazole and acyl chlorides at 80–100 °C.[630] When the acyl chlorides are not available, 1-acyl-1H-benzotriazoles are also conveniently prepared from 1-mesy1-1H-benzotriazole and the respective carboxylic acids in yields of 80–95%.[630] 1-Acyl-1H-benzotriazoles are also prepared in excellent yields (94–95%) from the reaction of 1-(trimethylsilyl)-1H-benzotriazole and acyl chlorides.[629]  

5,6-Dimethyl-1H-benzotriazole reacts with acetic anhydride (reflux for 30 min) to give the 1-acetyl derivative in 93% yield.[587] The same compound also reacts with benzoyl chloride and 4-nitrobenzoyl chloride, in the presence of aqueous sodium hydroxide, to yield the 1-acetyl derivatives in 82 and 50% yield, respectively.[587]  

1H-Benzotriazole reacts with trifluoroacetic anhydride in tetrahydrofuran, at room temperature, to give 1-(trifluoroacetyl)-1H-benzotriazole (656, R¹ = CF₃) in almost quantitative yield.[638] This compound is a convenient trifluoroacetylation reagent for amines and alcohols. 1H-Benzotriazol-5-amine reacts with trifluoroacetic anhydride in dimethylformamide, at room temperature, to give selectively 5-[trifluoroacetyl]amino]benzotriazole in 85% yield.[638]  

Thiobenzoyl chloride reacts with benzotriazole or 1-(trimethylsilyl)-1H-benzotriazole to yield 1-(thiobenzoyl)-1H-benzotriazole in 64 and 44% yield, respectively.[434]  

1H-Benzotriazole reacts with aryl isocyanates to yield 1-(aryliminocarbonyl)-1H-benzotriazoles.[640]

**13.13.3.3.1.4 Method 4: N-Formylation**

1H-1,2,3-Benzotriazole-1-carbaldehyde (657) is conveniently prepared from 1H-benzotriazole and formic acid in the presence of dicyclohexylcarbodiimide (Scheme 233).[641] This compound is a stable N- and O-formylating agent for a variety of amines and alcohols. The diethyl acetal of compound 657 is prepared directly in 90% yield from the reaction of 1H-benzotriazole and triethyl orthoformate.[642]
**Scheme 233**  N-Formylation of 1H-Benzotriazole\[^{[641]}\]

\[
\text{N-H} + \text{HCO}_2\text{H} \xrightarrow{\text{DCC, CH}_2\text{Cl}_2, \text{rt, 15 h}} \text{CHO}
\]

1H-1,2,3-Benzotriazole-1-carbaldehyde (657); Typical Procedure:\[^{[641]}\]

To a mixture of 1H-benzotriazole (14.85 g, 0.125 mol) and HCO\_2\text{H} (6.9 g, 0.15 mol) in anhyd CH\_2Cl\_2 (250 mL) was added DCC (36.05 g, 0.175 mol). The mixture was stirred at rt for 15 h, the precipitate filtered and the solvent removed in vacuo. Recrystallization of the residue gave pure 657 as white needles; yield: 13 g (71%); mp 94–96 °C.

**13.13.3.1.1.5 Method 5: Arylation**

1H-Benzotriazole reacts with activated aryl halides and hetaryl halides to yield the 1-aryl- or 1-hetaryl-1H-benzotriazole derivatives as the main (or sole) products. With 1-chloro-2-nitrobenzene (658, R¹ = R² = H) it gives a mixture of 659 (R¹ = R² = H; 39%) and 660 (R¹ = R² = H; 16%), which can be separated by column chromatography (Scheme 234).\[^{[643]}\]

The reaction with 1-chloro-2,4-dinitrobenzene (658, R¹ = NO\_2; R² = H) in refluxing toluene, in the absence of any added base, affords exclusively the 1H-isomer 659 (R¹ = NO\_2; R² = H) in 96% yield\[^{[644]}\] but if it is carried out in refluxing ethanol, in the presence of anhydrous sodium acetate, it gives a mixture of 659 (R¹ = NO\_2; R² = H) and 660 (R¹ = NO\_2; R² = H) in the ratio of approximately 23:10.\[^{[645]}\] With 2-chloro-1,3,5-trinitrobenzene (658, R¹ = R² = NO\_2) or 2-fluoro-1,3,5-trinitrobenzene the 1H-isomer 659 (R¹ = R² = NO\_2) is the sole product.\[^{[586]}\] 2-Fluoro-1,3,5-trinitrobenzene reacts with mono- and dinitrobenzotriazoles\[^{[586]}\] to afford the corresponding 1-(2,4,6-trinitrophenyl) derivatives; with benzo[1,2-d:4,5-d’]bistriazole it gives a mixture of 1,5- and 1,7-bis(2,4,6-trinitrophenyl)benzo[1,2-d:4,5-d’]bistriazoles.\[^{[595]}\]

**Scheme 234**  N-Arylation of 1H-Benzotriazole\[^{[641,644]}\]

\[
\text{N-H} + \text{ClO}_2\text{N} \xrightarrow{\text{R¹ = R² = H, NO}_2} \text{O}_2\text{N}
\]

1H-Benzotriazole reacts with 2-bromopyridine and 2-bromopyrimidine, in the absence of added base, to give the corresponding 1-substituted benzotriazole derivatives in high yields.\[^{[642,644]}\] The reaction of 1H-benzotriazole with 2-chloro-3-nitropyridine and 4-chlo-
ro-3-nitropyridine in dimethyl sulfoxide at 80 °C, in the presence of sodium carbonate, also affords the corresponding 1-substituted benzotriazole derivatives. Under microwave irradiation, benzo- and naphthotriazoles react with 4-chloropyridine and 4-chloroquinoline derivatives to give the 1-substituted derivatives in good yields (Scheme 235).

Scheme 235  N-Arylation of Benzotriazoles under Microwave Irradiation

A palladium(0)-catalyzed N-arylation of benzotriazole with aryl iodides with both electron-donating and electron-withdrawing groups and heteraryl halides has been reported. The reaction is carried out in dimethylformamide at 150 °C, under phase-transfer conditions, in the presence of potassium carbonate and copper salts. The 1-aryl-1H-benzotriazole derivatives are obtained in excellent yields (75–98%). 1H-Benzotriazole is also N-arylated in water by diaryliodonium salts (Ar12IBF4) yielding the 1-aryl derivatives in almost quantitative yields. This is also a palladium- and copper-catalyzed reaction.

The polymer-supported benzotriazole reacts with 4-tolylboronic acid in the presence of copper(II) acetate and pyridine, under microwave irradiation, to yield the corresponding N-toly derivatives. Cleavage of these products with trifluoroacetic acid gives the two regioisomeric benzotriazoles (1:1) in 55% yield (Scheme 236).

Scheme 236  N-Arylation of a Polymer-Supported Benzotriazole

1-(2,4-Dinitrophenyl)-1H-benzotriazole (659, R1 = NO2; R2 = H); Typical Procedure:

A mixture of 1-chloro-2,4-dinitrobenzene (658, R1 = NO2; R2 = H; 6.08 g, 30 mmol), 1H-benzotriazole (21.44 g, 180 mmol), and toluene (30 mL) was refluxed for 9 d. The mixture was treated with 20% KOH (200 mL), extracted with CHCl3 (5 × 500 mL), dried (MgSO4), and evaporated to afford a yellow solid; yield: 8.20 g (96%); mp 182–184 °C.

for references see p 587
13.13.3.1.6 Method 6: 
Alkynylation

Potassium benzotriazol-1-ide, prepared from 1H-benzotriazole and potassium tert-butoxide, reacts with alkynyl(phenyl)iodonium tosylates 667 to give 1-(2-arylethylnyl)-1H-benzotriazoles 668 in good yields (Scheme 237). The reaction with oct-1-ynyl(phenyl)iodonium tosylate 667, R1 = (CH2)5Me affords a mixture of two 1-alk-1-enyl-1H-benzotriazole derivatives. An alternative one-pot synthesis of 1-(substituted ethynyl)-1H-benzotriazoles 668 (R1 = alkyl or aryl) has been published.

![Scheme 237](image)

13.13.3.1.7 Method 7: 
Alkenylation

A simple and convenient method for the stereoselective synthesis of 1-(alk-1-enyl)-1H-benzotriazole derivatives, directly from benzotriazole, has been reported. It involves the reaction of alkenyl(phenyl)iodonium salts with 1H-benzotriazole in the presence of a base (Scheme 238). In the reaction with alkenyl(phenyl)iodonium salts 669 (R1 = Ph) and 671, retention of configuration is observed in the products 670 and 672, but with 669 (R1 = Bu) complete inversion of configuration occurs. This method is particularly efficient for the preparation of 1-(alk-1-enyl)-1H-benzotriazoles with amino-, acyl-, and alkoxy carbonyl substituents, which are difficult to prepare by other methods. Other nonselective or less convenient methods for the synthesis of 1-(alk-1-enyl)-1H-benzotriazoles are also known.

![Scheme 238](image)
Method 8: Alkylation

1H-Benzo[d]triazole reacts with dimethyl sulfate,\textsuperscript{[657,658]} diazomethane,\textsuperscript{[657]} and iodomethane\textsuperscript{[658]} to give mixtures of 1- and 2-methylbenzo[d]triazole. The 1-methyl isomer is always the main product, except in the reaction with diazomethane where the 1-methyl/2-methyl ratio is 5:17.\textsuperscript{[657]} Methylation of 4-nitrobenzo[d]triazole and 5-methylbenzo[d]triazole with diazomethane leads to the formation of the 2-methyl derivatives.\textsuperscript{[585]} Methylation of 5,6- and 4,7-dichlorobenzo[d]triazole with dimethyl sulfate gives the 1-methyl isomer as the main product.\textsuperscript{[585]}

The alkylation of 1H-benzo[d]triazole is frequently carried out with alkyl halides in the presence of a base; the 1-alkyl isomer 673 is generally the main product and, in some cases, 1,3-dialkyl-1H-benzotriazolium salts 675 are also formed (Scheme 239). Sodium hydride\textsuperscript{[659]} and sodium alkoxides\textsuperscript{[660,661]} are frequently used as the base but higher yields may be obtained using sodium hydroxide in dimethylformamide.\textsuperscript{[662]} Alkylations with alkyl halides using phase-transfer catalysis with 18-crown-6,\textsuperscript{[663]} polyethylene glycols or their dialkyl ethers,\textsuperscript{[664]} or quaternary ammonium salts\textsuperscript{[665–667]} also give excellent yields. Many other reaction conditions have also been used, namely aqueous sodium hydroxide,\textsuperscript{[668]} triethylamine in toluene,\textsuperscript{[669]} potassium carbonate in tetrahydrofuran,\textsuperscript{[670]} potassium fluoride and alumina in acetonitrile,\textsuperscript{[661]} or just by refluxing the benzotriazole and the alkyl halide in benzene or toluene in the absence of any added base.\textsuperscript{[644,671]} 1H-Benzo[d]triazole can also be alkylated with alkyl halides in the absence of solvent, either in basic media under solvent-free phase-transfer catalysis conditions or in the absence of base by conventional or microwave heating.\textsuperscript{[672]}

Addition of bromocyclopentane and bromocycloheptane to the anion of benzotriazole (generated with sodium ethoxide in ethanol) yields the expected mixtures of 1- and 2-cycloalkylbenzo[d]triazoles. However, under the same conditions, bromocyclohexane gives only cyclohexene and benzotriazole, cyclohexyl tosylate affords only the 2-cyclohexyl-2H-benzo[d]triazole 674 (R\textsuperscript{1} = Cy), while with tricyclohexyl phosphate the 1-cyclohexyl-1H-benzo[d]triazole is formed with the complete absence of the N2 isomer.\textsuperscript{[673]}

A high-yielding route to produce selectively 1-ethyl-1H-benzo[d]triazole involves the carbonylation of 1H-benzo[d]triazole with ethyl chloroformate (see Section 13.13.3.3.1.1.2) followed by alkylation or the resulting compound with triethyloxonium tetrafluoroborate and then methanolation (Scheme 240).\textsuperscript{[634]} This gives pure 1-ethyl-1H-benzo[d]triazole in 89% overall yield from 1H-benzo[d]triazole. Another method for the selective synthesis of
1-alkyl-1H-benzotriazoles involves the reaction of 1-(trimethylsilyl)-1H-benzotriazole with alkyl halides.\textsuperscript{[629]}

**Scheme 240**  
A Selective Route to 1-Ethyl-1H-benzotriazole\textsuperscript{[634]}

\[
\begin{align*}
\text{EtOCOCl} & \quad \text{aq NaOH} \quad \rightarrow \quad \text{et} \quad \text{CO}_2\text{Et} \\
+ \quad \text{N} & \quad \text{N} \quad \text{Et}_3\text{O}^+ \quad \text{BF}_4^- \\
\rightarrow \quad \text{N} & \quad \text{N} \quad \text{Et} \quad \text{CO}_2\text{Et} \\
+ \quad \text{N} & \quad \text{N} \quad \text{Et} \quad \text{BF}_4^- \\
\end{align*}
\]

The reaction of 1H-benzotriazole with dibromoalkanes may give the two monosubstituted derivatives or the three possible disubstituted isomers, depending on the molar ratio of the dibromoalkane to 1H-benzotriazole.\textsuperscript{[661,668]} 1H-Benzotriazole reacts with 1 equivalent of bis(bromomethyl)benzene (1,2-, 1,3-, or 1,4-), 4,4'-bis(bromomethyl)biphenyl and 4',4''-bis(bromomethyl)-1,3-terphenyl,\textsuperscript{[674]} and 2,6-bis(bromomethyl)pyridine\textsuperscript{[675]} to yield, in each case, only the bis(benzotriazol-1-yl) isomer. Addition of another equivalent of the bis(bromomethyl) derivative affords, in each case, only one dicationic benzotriazolophane (see schemes in Section 13.13.5.2.2). 1H-Benzotriazole also reacts with dichloromethane and chloroform, in the presence of a phase-transfer catalyst, to yield mixtures of all possible isomers of di- and tri(benzotriazol-1-yl and -2-yl)methane.\textsuperscript{[676,677]}

1H-Benzotriazole reacts with diarylmethanols, in the presence of a catalytic amount of 4-toluenesulfonic acid and azeotropic removal of water, to give mixtures of the corresponding 1- and 2-diarylmethylbenzotriazole derivatives (Scheme 241).\textsuperscript{[669,678]}

**Scheme 241**  
Alkylation of 1H-Benzotriazole with Diarylmethanols\textsuperscript{[669,678]}

\[
\begin{align*}
\text{N} & \quad \text{N} \quad \text{Ar}_1 \quad \text{Ar}_2 \\
+ \quad \text{TsOH}, \text{benzene} \quad \text{reflux} \quad \rightarrow \quad \text{Ar}_1 \quad \text{Ar}_2 \\
\rightarrow \quad \text{N} & \quad \text{N} \quad \text{Ar}_1 \quad \text{Ar}_2 \\
\end{align*}
\]

1H-Benzotriazole reacts with 2-(chloromethyl)oxirane (epichlorohydrin) in benzene to yield the two compounds resulting from oxirane ring opening.\textsuperscript{[679]} Using 2 equivalents of benzotriazole (and triethylamine) or sodium benzotriazolide the reaction gives a complex mixture of products resulting from the oxirane ring opening and simultaneous substitution of chlorine by a benzotriazolyl group (Scheme 242).\textsuperscript{[680]}
Scheme 242  Alkylation of 1H-Benzotriazole with 2-(Chloromethyl)oxirane

\[
\begin{align*}
&\text{1H-Benzotriazole} + \text{2-(Chloromethyl)oxirane} \\
&\text{Et}_3\text{N, toluene reflux, 7 h} \\
&\text{Bt1} = \text{OH} + \text{Bt2} \\
&\text{Bt2} = \text{Cl} + \text{OH} + \text{Bt2} \\
&\text{Bt1} + \text{OH} + \text{Bt2} \\
&\text{Bt1} + \text{OH} + \text{Bt2} \\
&\text{Bt1} + \text{OH} + \text{Bt2} \\
&\text{Bt1} + \text{OH} + \text{Bt2}
\end{align*}
\]

1H-Benzotriazole gives conjugate addition reactions with \(\alpha,\beta\)-unsaturated carbonyl compounds to yield only 1-alkyl derivatives (reactions carried out without solvent and in the presence of a few drops of pyridine or benzyltrimethylammonium hydroxide solution). Under similar conditions, and in striking contrast, 4,5,6,7-tetrahalogenated benzotriazoles afford only the 2-alkyl derivatives. This difference is due mainly to the steric effect of the 4,7-substituents, which direct this type of addition to the 2-position. This was confirmed by using 4,7-dichloro-1H-benzotriazole and 5,6-dichloro-1H-benzotriazole, which give only 2- and 1-substituted derivatives, respectively. Heating a mixture of 1H-benzotriazole and N,2-dimethylpropenamide at 150°C for six days gives only the N1 Michael addition product in 45% yield. 1H-Benzotriazole reacts with acrylamide in basic medium (pyridine–sodium methoxide) to afford only the N1 Michael addition product in 96% yield. However, it was shown by NMR analysis that the crude product of this reaction is a 35:65 mixture of the N1 and N2 addition products, but after 24 hours only the signals of the N1 isomer are observed. This means that the Michael addition yields a kinetic mixture which slowly equilibrates to the most stable isomer (the thermodynamic product). In an aqueous micellar medium, mixtures of N1 and N2 addition products are obtained from the reaction of benzotriazole with 1,3-diphenylprop-2-en-1-one (chalcone) (Scheme 243), acrylonitrile, and diethyl maleate.

Scheme 243  Reaction of 1H-Benzotriazole with 1,3-Diphenylprop-2-en-1-one

\[
\begin{align*}
&\text{1H-Benzotriazole} + \text{1,3-Diphenylprop-2-en-1-one} \\
&\text{NaOH, H}_2\text{O, CTAB, rt, 1 d} \\
&\text{CTAB = cetyltrimethylammonium bromide}
\end{align*}
\]

1H-Benzotriazole reacts with aliphatic aldehydes to yield isolable crystalline 1-hydroxy-alkyl benzotriazole derivatives (Scheme 244). In solution these condensation products dissociate into their components and equilibrate between the 1- and 2-positions of the benzotriazole ring. The reaction with aromatic aldehydes or ketones does not afford the corresponding condensation products.

For references see p 587
1H-Benzotriazole reacts with an aldehyde or ketone and an amine to yield the condensation products 676 generally in very high yields (Scheme 245). The aminomethylation of 1H-benzotriazole by the Mannich reaction[453,685] is an example of this very general reaction: both aliphatic and aromatic aldehydes can be used, ketones (particularly cyclic ones), ammonia, and primary and secondary amines (aliphatic, aromatic, and heteroaromatic) all give the expected products.[8] 1-Chloro- and 1-bromo-1H-benzotriazoles 677 (X = Cl, Br) undergo electrophilic addition to alkenes to afford 1- and 2-(2-haloalkyl)benzotriazoles, with trans configuration, in good yields.[686,687] 1-Bromo-1H-benzotriazole is much more reactive than the chloro derivative. For example, the addition of 677 (X = Br) to cyclohexene (giving products 678 and 679) is essentially instantaneous in dichloromethane at room temperature compared with a reaction time of approximately 4 hours for 677 (X = Cl), despite the low solubility of 677 (X = Br) (Scheme 246). N,4,5,6,7-Pentachlorobenzotriazole, although extremely insoluble in organic solvents, also undergoes rapid addition to alkenes.[687] 1-Chloro-1H-benzotriazole also gives addition products with enamines and enol ethers.[642] The reaction of 1H-benzotriazol-1-ol derivatives with alkyl halides in the presence of a base affords mainly the 1-alkoxy derivatives 680, but the N-alkyl derivatives 681 can also be formed (Scheme 247). For example, methylation of 1H-benzotriazol-1-ol with iodomethane, in methanol/sodium methoxide, affords a mixture of the O- and N-methyl derivatives.[609,615,688] However, using the same conditions, 4-nitro-1H-benzotriazol-1-ol and 6-nitro-1H-benzotriazol-1-ol give only the 1-methoxy compounds.[615,688] Reaction of 1H-benzotriazol-1-ol with 1-acetoxy-4-iodobutane in acetonitrile, with potassium carbonate as base, gives only the O-alkyl derivative in 95% yield.[670] A range of 1-alkoxy-4,5-dichloro-1H-benzotriazole derivatives is prepared by reaction of the sodium salt of 4,5-dichloro-1H-benzotriazol-1-ol with the appropriate alkyl halides.[690] Several 1-alkoxy-4-nitro-
1H-benzotriazole derivatives are prepared by alkylation of the 1-hydroxy derivative with alkyl halides under phase-transfer conditions.\cite{691}

**Scheme 247**  
Alkylation of 1H-Benzotriazol-1-ols with Alkyl Halides\textsuperscript{[684–691]}

\[ \text{R}^1\text{H} \text{N} = \text{N}\text{OH} \stackrel{\text{R}^2\text{X}, \text{base}}{\rightarrow} \text{R}^1\text{H} \text{N} = \text{N}\text{R}^2 + \text{R}^2\text{O}^- \]

**Alkylation of 1H-Benzotriazole with Alkyl Halides; General Procedure:**\textsuperscript{[662]}
To a flask provided with a CaCl\textsubscript{2} guard tube and magnetic stirrer was introduced finely ground NaOH (40 mmol), DMF (8–10 mL), 1H-benzotriazole (10 mmol), and the alkyl halide (10 mmol). After stirring for 15–60 min, the mixture was poured into H\textsubscript{2}O (50–70 mL) to give a solid or oily product. Solids were collected by filtration, washed with H\textsubscript{2}O (25 mL), and dried, while the oily products were extracted with CHCl\textsubscript{3} (3\times 10 mL), washed with H\textsubscript{2}O (5\times 10 mL), dried (MgSO\textsubscript{4}), and the solvent evaporated under reduced pressure. 1-Alkyl- and 2-alkylbenzotriazole isomers were separated by column chromatography (hexane/CHCl\textsubscript{3} 2:1).

**13.13.3.3.1.9 Method 9:** Halogenation

Benzotriazole is rapidly converted into crystalline 1-chloro-1H-1,2,3-benzotriazole (682, X = Cl) by treatment with sodium hypochlorite in aqueous acetic acid (Scheme 248).\textsuperscript{[692]} Similar reaction with sodium hypoiodite in aqueous sodium hydroxide gives 1-iodo-1H-benzotriazole in 43% yield.\textsuperscript{[687]} Alternatively 1-iodo-1H-benzotriazole is obtained in 94% yield by treatment of 1-chloro-1H-benzotriazole in dichloromethane with 1 equivalent of iodine.\textsuperscript{[687]} Similarly, 1-bromo-1H-benzotriazole is prepared in 80% yield by the addition of 1-chloro-1H-benzotriazole to a solution of bromine in dichloromethane.\textsuperscript{[687]} Addition of sodium hypochlorite to a solution of 4,5,6,7-tetrachloro-1H-benzotriazole in glacial acetic acid, at room temperature, rapidly affords N,4,5,6,7-pentachloro-1H-benzotriazole (because of the extreme insolubility of this compound, the position of the fifth chlorine at N1 or N2 was not assigned unambiguously).\textsuperscript{[687]}

**Scheme 248**  
Synthesis of 1-Chloro- and 1-Iodo-1H-benzotriazole\textsuperscript{[687,692]}

\[ \text{NH} \text{N} + \text{NaOX} \rightarrow \text{NH} \text{N} \xrightarrow{\text{AcOH, H}_2\text{O, rt}} \%	ext{X} = \text{Cl} 100\% \%	ext{X} = \text{I} 43\% \]

1H-Benzotriazole is chlorinated to 4,5,6,7-tetrachloro-1H-benzotriazole (683, X = Cl) in 87% yield by refluxing with aqua regia (a mixture of concentrated hydrochloric acid and concentrated nitric acid) for three hours (Scheme 249).\textsuperscript{[16]} Under similar conditions, 2-methyl-2H-benzotriazole gives 4,5,6,7-tetrachloro-2-methyl-2H-benzotriazole in 50% yield but chlorination of 1-methyl-1H-benzotriazole with aqua regia requires three days to give 4,5,6,7-tetrachloro-1-methyl-1H-benzotriazole in 57% yield.\textsuperscript{[685]} Refluxing 4-nitro-1H-benzotriazole with aqua regia for three days affords 4,5,6,7-tetrachloro-1H-benzotriazole (62%), and 2,5-dimethyl-2H-benzotriazole gives 4,5,6,7-tetrachloro-2-methyl-2H-benzotriazole (yield not reported); in these systems the substituents on the benzenic ring are replaced by chlorine.\textsuperscript{[539]}

---

1-Chloro-1H-benzotriazole (682, X = Cl); Typical Procedure:[692]

2 M NaOCl (50 mL, 0.1 mol) was added dropwise at rt to a stirred soln of 1H-benzotriazole (10 g, 0.08 mol) in aq AcOH (1:1). After dilution with H2O the resulting solid was collected and recrystallized once (CH2Cl2/petroleum ether) to give pure (682, X = Cl) as colorless needles; yield: 13 g (~100%); mp 104–108°C.

4.5.6.7-Tetrachloro-1H-benzotriazole (683, X = Cl); Typical Procedure:[16]

A soln of 1H-benzotriazole (4.76 g, 0.040 mol) in a mixture of concd HCl (525 mL) and concd HNO3 (175 mL) was refluxed for 3 h, cooled, and diluted to precipitate the product; yield: 9.0 g (87%). Recrystallization (MeNO2) gave a white crystalline solid; mp 256–260°C.

13.13.3.3.1.10 Method 10: Sulfonylation

1H-Benzotriazole reacts with trifluoromethanesulfonic anhydride, in dry dichloromethane and dry pyridine at −78°C, to afford 1-(trifluoromethylsulfanyl)-1H-benzotriazole in 87% yield.[642]

5.6-Dimethyl-1H-benzotriazole reacts with benzenesulfonyl chloride, in the presence of 10% aqueous sodium hydroxide solution, to yield the 1-phenylsulfonyl derivative in 72% yield.[587] Naphthotriazoles also give only the 1-phenylsulfonyl derivatives.[582]

1H-Benzotriazol-4-amine reacts with an equimolar amount of 4-toluenesulfonyl chloride in pyridine at room temperature to give 4-(tosylamino)-1H-benzotriazole (684, ArI = 4-Tol) (Scheme 250).[699] Under similar experimental conditions, 5-methyl-1H-benzotriazol-4-amine gives the 1-tosyl-1H-benzotriazole derivative 685 as the only isolated product. With an excess of arenesulfonyl chloride both starting benzotriazol-4-amines afford the bis-sulfonylated derivatives 686.[699] The reaction of benzotriazol-5-amines with arenesulfonyl chlorides has also been reported.[529] 1-Mesy1- and 1-(phenylsulfonyl)-1H-benzotriazole are prepared in good yields from the reaction of the corresponding sulfonyl chlorides and 1-(trimethylsilyl)-1H-benzotriazole[630] or 1-(tributylstannyl)-1H-benzotriazole.[699]
1H-Benzotriazol-1-amines are valuable precursors to didehydrobenzenes under notably mild conditions, using either lead(IV) acetate\(^{[694]}\) or N-bromosuccinimide.\(^{[695]}\) Treatment of 1H-benzotriazole with hydroxylamine-O-sulfonic acid in hot (70–75 °C) aqueous potassium hydroxide solution gives a mixture of 1H-benzotriazol-1-amine (687) and 2H-benzotriazol-2-amine in an approximately 3:1 ratio (Scheme 251).\(^{[694]}\) The formation of the 2-amino isomer is avoided by changing the reaction conditions (temperature and solvent). The 1-amino isomer is obtained selectively in 62% yield when the reaction is carried out in dioxane containing 5% water and the reaction mixture is maintained below 50 °C. Better yields (69%) of the 1-isomer, uncontaminated by the 2-isomer, are obtained in dimethylformamide containing 5% water.\(^{[696]}\) In ethanol the conversion is nearly quantitative, but a 2:1 mixture of the two isomers is formed, the 2-amino derivative being the main product.\(^{[696]}\)

N-Amination of 1H-naphtho[2,3-d][1,2,3]triazole and 1H-naphtho[1,2-d][1,2,3]triazole in aqueous potassium hydroxide with hydroxylamine-O-sulfonic acid gives mainly the 1-amino derivatives (27 and 18% yields, respectively).\(^{[697]}\) N-Amination of benzo[1,2-d:4,5-d’]-bistriazole (688) under similar conditions gives a mixture of five products: the two monoamino derivatives and the three possible diamino derivatives (Scheme 252).\(^{[698]}\) The combined yields of diamino and monoamino products are 45 and 48%, respectively.
tion of a 1,2,3-triazolo[4,5-d][1,2,3]triazole with O-(mesitylsulfonyl)hydroxylamine affords the 1-amino and 2-amino derivatives in 22 and 46% yield, respectively. N-Amination of 4-cyanoazuleno[1,2-d]-1,2,3-triazole with 1-(aminoxy)-2,4-dinitrobenzene gives a 3:2 mixture of two isomeric N-amino derivatives in 54% yield.

Scheme 252  N-Amination of Benzo[1,2-d:4,5-d']bistriazole

1H-Benzotriazol-1-amine (687): Hydroxylamine-O-sulfonic acid (94.9 g, 0.84 mol) was added portionwise to a stirred soln of 1H-benzotriazole (50.0 g, 0.42 mol) and KOH (117.6 g, 2.1 mol) in DMF (250 mL) and H2O (12 mL) such that the temperature of the mixture remained below 50°C (ca. 1.0 g·min−1). After the addition was complete, the mixture was cooled to rt and stirring continued for a further 1 h. The resulting precipitate was removed by vacuum filtration and washed thoroughly with Et2O. The filtrate was evaporated to dryness using a rotary evaporator attached to a rotary pump. The temperature of the water bath was kept below 50°C; above this, rearrangement to the corresponding 2-amino isomer became significant. The residue was dissolved in a minimum of 2 M HCl and the resulting soln kept at −2°C overnight during which time 1H-benzotriazol-1-amine hydrochloride crystallized and was removed by filtration. The solid was dried under vacuum and showed mp 131–134°C and was >95% pure according to 1H NMR data. The free amine was obtained by direct basification of the solid salt using aq 2 M NaOH followed by extraction with Et2O (3 × 100 mL). The combined extracts were dried and evaporated to leave 687 as a colorless solid; yield: 38.8 g (69%); mp 84°C.

13.13.3.3.1.1.2  Method 12: Nitration

Nitration of 1H-benzotriazole with a mixture of concentrated nitric and sulfuric acids, at room temperature, gives 4-nitro-1H-benzotriazole in 50% yield while 5-methyl-1H-benzotriazole gives the 4-nitro derivative 689 (R1 = Me) in 90% yield under similar experimental conditions (Scheme 253). Nitration of 5-chloro-1H-benzotriazole (at 60°C) affords derivative 689 (R1 = Cl) in 83% yield. Nitration of 1H-benzotriazole-5-carboxylic acid at 90°C gives derivative 690 (R1 = CO2H) while 5-nitro-1H-benzotriazole at 115°C affords a mixture of 690 (R1 = NO2, 30%) and 691 (67%).
Nitration of 1-methyl-1H-benzotriazole affords 1-methyl-7-nitro-1H-benzotriazole\[701\] while 2-methyl-2H-benzotriazole gives 2-methyl-5-nitro-2H-benzotriazole.\[585\] Nitration of 1-(1,2,3-triazolyl)-1H-benzotriazole derivatives with potassium nitrate in concentrated sulfuric acid at 60°C affords the corresponding 5-nitro derivatives in high yields (ca. 80%). If the 5-position is occupied, nitration occurs at the 4-position.\[322\] 1-Phenyl- and 2-phenylbenzotriazoles give the corresponding 4-nitrophenyl derivatives by nitration with potassium nitrate in concentrated sulfuric acid at 60°C.\[702,703\] Nitration of 1-(2,4,6-trinitrophenyl)-1H-benzotriazole with a mixture of concentrated nitric and sulfuric acids, at reflux for 2 hours, gives the 5,7-dinitro derivative in 73% yield.\[704\] Nitration of 2-(2-hydroxy-5-methylphenyl)-2H-benzotriazole with a mixture of concentrated nitric and acetic acids, at 70°C for 10 minutes, gives the 2-(2-hydroxy-5-methyl-3-nitrophenyl) derivative in 84% yield.\[704\] Nitration of 1,5-bis(2,4,6-trinitrophenyl)benzo[1,2-d:4,5-d’]bistriazole with a mixture of nitric acid and sulfuric acid gives the 4-nitro derivative in 21% yield.\[595\]

5-Methyl-4-nitro-1H-benzotriazole (689, R1 = Me): Typical Procedure:\[699\]

To 5-methyl-1H-benzotriazole (5 g, 37.5 mmol) in concd H2SO4 (20 mL) was added a mixture of HNO3 (70%, 5 mL) and concd H2SO4 (5 mL) at below 20°C, and the resulting mixture was allowed to stand overnight. The soln was poured onto ice, and the resulting precipitate was collected by filtration, washed with H2O, and recrystallized (EtOH) to give microcrystals; yield: 6.0 g (90%); mp 254–255°C.

### 13.13.3.3 N-Unsubstituted and 1-Substituted Benzotriazoles

**Method 13:**

**Azo Coupling**

N-Unsubstituted, 1- and 2-substituted activated benzotriazoles (with a hydroxy or amino group) all react with arenediazonium salts to yield (arylazo)benzotriazoles.\[631,701,705\] A range of benzo[1,2-d:3,4-d’]bistriazoles 695 are prepared by oxidation of the 4-(arylazo)benzotriazol-5-amines 694 (see Section 13.13.4.1.2.1.1) obtained from the reaction of 2aryl-2H-benzotriazol-5-amines 692 with diazonium salt 693 (Scheme 254).\[706\]
Both 1H-benzotriazol-5-ol and 5-hydroxy-1H-benzotriazole-4-carboxylic acid afford the same azo dye 696 when reacted with diazonium salts (Scheme 255). The complementary synthetic route to (arylazo)benzotriazoles, i.e. diazotization of benzotriazol-5-amine followed by reaction with an activated aromatic compound can also be used successfully.

**Scheme 255  Azo Coupling with Activated Benzotriazoles**

**4-(4-Chlorophenylazo)-1H-benzotriazol-5-ol (696): Typical Procedure**

4-Chloroaniline (6.38 g, 0.05 mol) was dissolved in 2.5 M HCl (100 mL) and diazotized by the addition of 5 M NaNO₂ (10 mL) at 10°C. This soln was filtered and diluted to 200 mL to make a 0.25 M soln. Part of this soln (8 mL, 2 mmol) was added with stirring to a soln of 1H-benzotriazol-5-ol (0.286 g, 2.12 mmol) dissolved in a mixture of H₂O (40 mL), 1 M NaOH (4 mL) and 1 M Na₂CO₃ (2 mL). A deep orange soln was formed immediately. After 15 min stirring, the soln was acidified by the addition of 5 M HCl (1 mL). The reddish-orange precipitate formed was collected by filtration, washed, and dried at 100°C; yield: 0.47 g (85%); mp 247–249°C.
13.13.3.2 Of Carbon Functionalities

13.13.3.2.1 Method 1: Decarboxylation

When refluxed in water, 5-hydroxy-1H-benzotriazole-4-carboxylic acid decarboxylates to afford 1H-benzotriazol-5-ol in 76% yield (Scheme 256). Its isomer, 5-hydroxy-1H-benzotriazole-6-carboxylic acid does not decarboxylate under the same conditions.

\[ \text{Scheme 256 Decarboxylation of Benzotriazoles} \]

13.13.3.2.2 Method 2: Deacylation

1-Acetyl-5-methyl-1H-benzotriazole and 1-acetyl-6-methyl-1H-benzotriazole are deacetylated in boiling acetic acid/water (1:1) for eight to nine hours. 1-Acetyl-6-(acetylamino)-5-methyl-1H-1,2,3-benzotriazole is selectively hydrolyzed to 6-(acetylamino)-5-methyl-1H-1,2,3-benzotriazole which then is hydrolyzed to 5-methyl-1H-benzotriazol-6-amine.

\[ \text{Scheme 257 Deacetylation of 1-Acetyl-1H-benzotriazoles} \]

1-Substituted benzotriazol-5-amines are obtained in 85% yield by deacylation of the corresponding 5-[(trifluoroacetyl)amino]-1H-benzotriazoles in methanol/potassium carbonate. 1-Acetyl-5,6-dimethyl-1H-benzotriazole (697) is slowly deacetylated when dissolved in ethanol/water (3:1) at room temperature (Scheme 257). Compound 698 is hydrolyzed in 6 M hydrochloric acid to the propanoic acid derivative 699.

\[ \text{Scheme 258 Deacetylation of 1,7-Diacetyl-1,7-dihydrobenzo[1,2-d:4,5-d’]bistriazole} \]

1,7-Diacetylbenzobistriazole 700, dissolved in ethanol/water (1:1), is deacetylated in almost quantitative yield by acid treatment (Scheme 258).

For references see p 587.
**1,5-Dihydrobenzo[1,2-d:4,5-d’]bistriazole (688); Typical Procedure:**

A mixture of 1,7-diacetyl-1,7-dihydrobenzo[1,2-d:4,5-d’]bistriazole (700; 0.73 g, 3 mmol), 50% aq EtOH (100 mL), and concd H₂SO₄ (1 mL) was refluxed for 1 h, then the reflux condenser was removed and most of the EtOH was allowed to evaporate. The resultant mixture was chilled and filtered to remove the product, which was washed with H₂O and dried at 100 °C to give pure 688; yield: 0.46 g (96%); explosion temperature 370 °C when heated at 20 °C·min⁻¹.

### 13.13.3.3 Of Heteroatoms

#### 13.13.3.3.1 Method 1: Deoxygenation

2H-Benzotriazole 1-oxides of type 701 are readily deoxygenated to 2H-benzotriazoles 702 or 703 by reduction with zinc dust in alkaline ethanolic solutions,[710] zinc powder and sulfuric acid,[711] hydrazine hydrate in a high-boiling ether,[712] or by using baker’s yeast in sodium hydroxide solution[713] (Scheme 259). If the reduction with zinc is carried out with heating, the 5-chloro-2H-benzotriazole 1-oxides 701 (R₁ = Cl) are simultaneously deoxygenated and dechlorinated (see Section 13.13.3.3.3.2).[710]

**Scheme 259** Deoxygenation of 2-Aryl-2H-benzotriazole 1-Oxides[710,713]

2-Alkyl-2H-benzotriazole 704 is deoxygenated to 705 by reduction with tin(II) chloride (Scheme 260).[714]

**Scheme 260** Deoxygenation of 2-Alkyl-2H-benzotriazole 1-Oxides[714]

Refluxing 1-nonyl-1H-benzotriazole 3-oxide (706) in neat acetic anhydride gives the deoxygenated 1-nonyl-1H-benzotriazole (707; yield not reported) (Scheme 261).[715]
Polymer-supported 1H-benzotriazol-1-ol 708 is readily converted into the corresponding NH derivative 709 by reductive cleavage of the 1-hydroxy moiety with either phosphorus trichloride or samarium(II) iodide (Scheme 262).[622]

A simultaneous deoxygenation and dehalogenation, to give products 711, is observed during the reduction of 5-chloro-2H-benzotriazole 1-oxides 710 with zinc dust in alkaline ethanolic solution and heating on a steam bath for five hours (Scheme 263).[710]

1-Alkyl-1H-benzotriazoles react with dimethylidioxirane to give the corresponding 1-alkyl-1H-benzotriazole 3-oxides 712. In contrast, under similar conditions, 2-alkyl-2H-benzotriazoles 713 are converted into the corresponding trans-4,5,6,7-diepoxyl-4,5,6,7-tetrahydro-2H-benzotriazoles 714 (Scheme 264).[715]
Scheme 264  Oxidation of Benzotriazoles with Dimethyldioxirane

\[
\begin{align*}
R^1 & = \text{Me, Et, Pr, (CH}_2\text{)}_5\text{Me, (CH}_2\text{)}_8\text{Me, Bn, CH}_2\text{CH}_2\text{Ph, CHPhMe, CH}_2\text{CO}_2\text{Et, CH}_2\text{OPh, CH}_2\text{C}=\text{CH, CH}_2\text{CN} \\
\end{align*}
\]

2-Methyl-2\(H\)-benzotriazole is converted into its 1-oxide derivative, in very low yield, by oxidation with 3-chloroperoxybenzoic acid (Scheme 265). Most of the starting benzotriazole is recovered unchanged.

Scheme 265  Oxidation of Benzotriazoles with 3-Chloroperoxybenzoic Acid

13.13.4  Product Subclass 4:  
2-Substituted Benzotriazoles

13.13.4.1  Synthesis by Ring-Closure Reactions

13.13.4.1.1  By Formation of Two N—N Bonds

13.13.4.1.1.1  Fragments N—C—C—N and N

13.13.4.1.1.1.1  Method 1:  
From Benzene-1,2-diamine and Nitrobenzenes

Benzene-1,2-diamine reacts with nitrobenzenes to yield 2-aryl-2\(H\)-benzotriazoles and 2-aminoazobenzenes (Scheme 266). The latter compounds can be converted into 2-aryl-2\(H\)-benzotriazoles (see Scheme 267).
13.13.4.1.2 By Formation of One N–N Bond

13.13.4.1.2.1 Fragment \( \text{N} \rightarrow \text{C} \rightarrow \text{C} \rightarrow \text{N} \)

13.13.4.1.2.1.1 Method 1: Cyclization of 2-Aminoazobenzenes

2-Aminoazobenzenes are converted into 2-aryl-2\(H\)-benzotriazoles by oxidation with copper sulfate in ammonia or pyridine solution (Scheme 267). Using ammoniacal copper sulfate, 2,4-diaminoazobenzene (715, \( R_1 = 4-\text{NH}_2; R_2 = \text{H} \)) is converted quantitatively into 2-phenyl-2\(H\)-benzotriazole-5-amine,[717] and 2,2’-diaminoazobenzene (715, \( R_1 = \text{H}; R_2 = 2-\text{NH}_2 \)) is oxidized to 2-(2-aminophenyl)-2\(H\)-benzotriazole (716; \( R_1 = \text{H}, R_2 = 2-\text{NH}_2 \)) with copper sulfate in pyridine in 65% yield.[643]

Scheme 267 Oxidative Cyclization of 2-Aminoazobenzenes[643,717]

\[
\text{R}_1 \text{N} \quad \text{N} \quad \text{N} \quad \text{NH}_2 \\
\begin{array}{c}
\text{CuSO}_4, \text{H}_2\text{O} \\
\text{NH}_3 \text{ or py} \\
\text{rt to reflux, 2 h}
\end{array}
\begin{array}{c}
\text{R}_1 \text{N} \quad \text{N} \\
\text{R}_2
\end{array}
\]

Similarly, 1-(2-nitrophenylazo)-2-naphthylamine 717 is converted into the naphthotriazole 718 by oxidative cyclization with copper sulfate in pyridine (Scheme 268).[643] The same naphthotriazole is obtained in 70% yield by refluxing the azo compound in thionyl chloride.[643]

Scheme 268 Oxidative Cyclization of 1-(2-Nitrophenylazo)-2-naphthylamine[643]

\[
\begin{array}{c}
\text{A: CuSO}_4, \text{py, reflux, 4 h} \\
\text{B: SOCl}_2, \text{benzene, reflux, 18 h}
\end{array}
\begin{array}{c}
\text{O}_2\text{N} \\
\text{A: 83%} \\
\text{B: 70%}
\end{array}
\]

2-(Arylazo)anilines 719 and 1-(arylazo)-2-naphthylamines 721 are converted into the corresponding 2\(H\)-benzotriazoles 720 and 2\(H\)-naphthotriazoles 722, respectively, by refluxing in dimethylformamide, with a current of bubbling air, in the presence of copper(II) acetate (Scheme 269).[718] This procedure[718,719] and the one using copper sulfate as oxidant,[547,720,721] can also be applied to the synthesis of heterocycle-fused 1,2,3-triazoles.

for references see p 587
A range of benzo[1,2-d:3,4-d′]bistriazoles is prepared by oxidation of 4-(arylazo)benzotriazol-5-amines (see Scheme 254 in Section 13.13.3.1.1.13). [706]

2-(2-Aminophenyl)-2H-benzotriazole (716, R1 = H; R2 = 2-NH2): Typical Procedure: [643]

2,2′-Diaminoazobenzene (4.4 g, 0.02 mol) was dissolved in pyridine (50 mL) and treated with anhyd CuSO4 (12.8 g, 0.08 mol) added in portions with stirring. After 30 min at rt, the mixture was refluxed for 2 h, cooled, and poured into cold H2O (200–250 mL) with stirring. The dark solid which separated was collected by filtration and washed with H2O. Three recrystallizations (2 × EtOH and 1 × hexane), with concomitant treatment with activated carbon, yielded well-defined, yellow crystals; yield: 65%; mp 97–98 °C.

13.13.4.1.2.1 Method 2:
Cyclization of 2-Azidoazobenzenes

The synthesis of 2H-benzotriazoles by thermal extrusion of nitrogen from 2-azidoazobenzenes has been known since the 19th century. [722,723] This is a very convenient method since a range of 2-azidoazobenzenes can be prepared from simple precursors (Scheme 270). [724,725] The kinetics of the thermal decomposition of 2-azidoazobenzenes 723 to 2-aryl-2H-benzotriazoles 724 has been investigated. [726] The reaction of 723 with boron trifluoride or trifluoride in benzene at room temperature also gives benzotriazoles 724 in high yields (90–94%). [727]
The benzotriazolo[2,1-a]benzotriazole 727 is prepared in good yield by the thermal or photochemical decomposition of 2,2'-diazidoazobenzene (725). This transformation requires the elimination of 2 equivalents of nitrogen and this can be performed at 175 °C (Scheme 271). However, since the nitrogen is liberated in two distinct stages, 1 equivalent at approximately 60 °C and the second equivalent at approximately 170 °C, it is possible to convert 725 into 2-(2-azidophenyl)-2H-benzotriazole (726) in good yield. Benzotriazole 726 is also formed when a benzene solution of 725 is exposed to sunlight for three days. Similarly, 726 is converted into 727 when exposed to sunlight for ten days.

2,4-Bis(arylazo)-1-azido- and 1-(arylazo)-2-azidonaphthalene derivatives 728 and 730 are converted into 2H-naphtho[1,2-d][1,2,3]triazoles 729 by thermal decomposition (Scheme 272).
Scheme 272  Thermolysis of (Arylazo)azidonaphthalenes\[729\]

\[
\begin{align*}
N & \quad N_3 \\
N & \quad N_3 \\
R^1 & \quad N_3 \\
N & \quad N_3 \\
R^1 & \quad N_3 \\
\text{heat} & \quad - N_2 \\
R^1 & \quad N_2Ar^1 \quad 78-81\% \\
R^1 & \quad H \quad 60-85\%
\end{align*}
\]

1-(2-Azidophenyl)-3-methyl-3-phenyltriazene (731) is converted into 2-[methyl(phenyl)amino]-2H-benzotriazole (732) when refluxed in m-xylene (Scheme 273). \[725\]

Scheme 273  Thermolysis of a (2-Azidophenyl)triazene Derivative\[725\]

\[
\begin{align*}
N & \quad N \quad N \\
N & \quad N \\
N & \quad N \\
\text{m-xylene, reflux, 1 h} & \quad - N_2 \\
N & \quad N \quad N \\
N & \quad N \\
N & \quad N \\
63\%
\end{align*}
\]

2-Azidoazobenzenes 734 are intermediates in the conversion of 2-nitro-, 2-chloro-, and 2-bromoazobenzenes 733 into 2-aryl-2H-benzotriazoles 735 (Scheme 274). This transformation is accelerated by the addition of a suitable metal catalyst (e.g., CuBr). \[730\]

Scheme 274  Synthesis of 2-Aryl-2H-benzotriazoles from 2-Nitro-, or 2-Haloazobenzenes and Sodium Azide\[730\]

\[
\begin{align*}
X = \text{NO}_2, \text{Cl, Br} \\
N & \quad N \\
N & \quad N \\
R^1 & \quad NAr^1 \\
N & \quad N \\
N & \quad N \\
R^1 & \quad NAr^1 \\
\text{NaNO}_2, \text{DMSO or DMF} & \quad 125^\circ \text{C, 4-10 h} \\
N & \quad N \\
N & \quad N \\
R^1 & \quad NAr^1 \\
N & \quad N \\
N & \quad N \\
R^1 & \quad NAr^1 \\
- N_2 \\
- N_2 \\
N & \quad N \\
N & \quad N \\
R^1 & \quad NAr^1 \\
N & \quad N \\
N & \quad N \\
R^1 & \quad NAr^1 \\
N & \quad N \\
N & \quad N \\
R^1 & \quad NAr^1 \\
N & \quad N \\
N & \quad N \\
R^1 & \quad NAr^1 \\
N & \quad N \\
N & \quad N \\
R^1 & \quad NAr^1 \\
\text{X = NO}_2, \text{Cl, Br}
\end{align*}
\]

2-(2-Azidophenyl)-2H-benzotriazole (726); Typical Procedure\[643\]

A soln of 725 (5 g, 18.9 mmol) in acetone or benzene (CAUTION: carcinogen) was refluxed for 2 h. \(N_2\) was evolved, and the orange color was discharged. The solvent was removed by distillation, and the crystalline residue was recrystallized (petroleum ether or aq acetone) to afford light yellow needles; yield: 70%; mp 78–79\(^\circ\)C.
Method 3:
Cyclization of 2-Nitroazobenzenes

2-Nitroazobenzenes \( \text{736} \) give reductive cyclization reactions to afford 2-aryl-2\( \text{H} \)-benzotriazole 1-oxides \( \text{737} \) or 2-aryl-2\( \text{H} \)-benzotriazoles \( \text{738} \), depending on the reducing agent and the reaction conditions (Scheme 275). For example, reduction of azo compounds \( \text{736} \) with glucose\(^{[710]} \) or with hydroxylamine\(^{[731]} \) in ethanolic sodium hydroxide solution, at reflux, affords 2\( \text{H} \)-benzotriazole 1-oxides \( \text{737} \) in good yields. 2-Nitroazobenzenes react with thiourea \( S,S \)-dioxide in ethanolic sodium hydroxide to give, depending on the reaction conditions, either the corresponding 2-aryl-2\( \text{H} \)-benzotriazoles \( \text{738} \) or their 1-oxides \( \text{737} \).\(^{[732]} \) Several other reducing agents can be used for the conversion of 2-nitroazobenzenes into 2-aryl-2\( \text{H} \)-benzotriazoles or their 1-oxides, namely sodium sulfide, sodium hydrosulfide,\(^{[723]} \) ammonium sulfide,\(^{[734]} \) sodium dithionite,\(^{[735]} \) hydrazine hydrate,\(^{[711,712]} \) zinc dust with sodium hydroxide,\(^{[710]} \) molybdenum-promoted Raney nickel,\(^{[736]} \) hydrogen in the presence of a catalyst,\(^{[737,738]} \) and carbon monoxide in an alkaline medium in the presence of a copper–amine complex catalyst.\(^{[739]} \)

\[ \text{Scheme 275} \quad \text{Reductive Cyclization of 2-Nitroazobenzenes}^{[710]} \]

2-Nitroazobenzenes \( \text{739} \) cyclize selectively to give 2aryl-2\( \text{H} \)-benzotriazole 1-oxides \( \text{740} \) by reduction with baker’s yeast (\textit{Saccharomyces cerevisiae}) in sodium hydroxide solution (Scheme 276). Using twice the amount of baker’s yeast, a larger amount of sodium hydroxide, and a longer reaction time, gives 2-aryl-2\( \text{H} \)-benzotriazoles \( \text{741} \) as the sole product in good yields.\(^{[713]} \)
13.13.4.1.2.1.4  Method 4: Cyclization of 1-Substituted 2-(2-Nitroaryl)hydrazines

Under reductive conditions, 1-aryl-2-(2-nitroaryl)hydrazines 743 cyclize to 2-aryl-2H-benzotriazoles 744 (Scheme 277). Frequently benzotriazoles 744 are prepared directly from the reaction of 1-halo-2-nitrobenzene derivative 742 (X = Cl, Br), or a 1,2-dinitrobenzene derivative 743 (X = NO2), and an excess of an arylhydrazine. Under acidic conditions, hydrazines 743 are dehydrated to 2-aryl-2H-benzotriazole 1-oxides 745 (Scheme 277). Most 1-aryl-2(2,4,6-trinitrophenyl)hydrazines 743 [R1 = 4,6-(NO2)2; Ar1 = Ph, 4-Tol, C6F5] are readily cyclized by refluxing in anhydrous ethanolic hydrogen chloride. However, cyclization of 1,2-bis(2,4,6-trinitrophenyl)hydrazine to 4,6-dinitro-2-(2,4,6-trinitrophenyl)-2H-benzotriazole 1-oxide requires more vigorous conditions. Cyclization proceeds smoothly and nearly quantitatively by gentle heating a suspension of that hydrazine derivative in concentrated sulfuric acid for 30–60 minutes.

Scheme 277  Cyclization of 1-Aryl-2-(2-nitroaryl)hydrazines[609,445,741]
2-Methyl-6-nitro-2H-benzotriazole 1-oxide (747) is prepared by acid-catalyzed dehydration of 1-methyl-2-(2,4-dinitrophenyl)hydrazine (746) or by addition of iodomethane to a solution of 2,4-dinitrophenylhydrazine (Scheme 278).[743]

Scheme 278  Acid-Catalyzed Dehydration of 1-Methyl-2-(2,4-dinitrophenyl)hydrazine[743]

The 2-nitrophenylhydrazine derivative 748 gives the 2-alkyl-2H-benzotriazole 1-oxide 749 when treated with pyridine (Scheme 279).[714]

Scheme 279  Base-Catalyzed Conversion of a 2-Nitrophenylhydrazine Derivative into a 2-Alkyl-2H-benzotriazole 1-Oxide[714]

13.13.4.1.2.1.5  Method 5:
Cyclization of Vicinal Diazides

2,3-Diazidonaphtho-1,4-quinone (750) reacts with triphenylphosphine to form almost quantitatively the phosphorane 751 (Scheme 280). This compound undergoes an aza-Wittig reaction with aldehydes (e.g., to give 753) and is readily hydrolyzed to the triazol-2-amine 752, which is a stable and high-melting compound.[744]
Synthesis by Ring Transformation

Method 1: Isomerization of 4-(Arylazo)-2,1,3-benzoxadiazoles

Addition of a diazonium salt to 5-(dimethylamino)-2,1,3-benzoxadiazole 1-oxide (754) gives the 4-arylazo derivative 755, which isomerizes to the 2-aryl-2H-benzotriazole 756 (Scheme 281).[745]

Method 2: Transformation of 1,3,3-Trialkyl-2-(2,4-dinitrophenyl)diaziridines

1-(2,4-Dinitrophenyl)diaziridines bearing an NH group 757 (R1 = H), upon heating in toluene for ca. 3 hours, rearrange to the corresponding 2,4-dinitrophenylhydrazones. However, heating 1,3,3-trialkyl-2-(2,4-dinitrophenyl)diaziridines or 1,3-dialkyl-2-(2,4-dinitrophenyl)diaziridines 757 (R1 = H) does not give hydrazones but affords instead 2-alkyl-6-nitro-2H-benzotriazole 1-oxides 759 (via intermediates 758) in almost quantitative yields (Scheme 282).[643]
Scheme 282  Transformation of 1,3,3-Dialkyl-2-(2,4-dinitrophenyl)diaziridines\[743]\]

\[
\begin{align*}
\text{Scheme 282} & \quad \text{Transformation of 1,3,3-Dialkyl-2-(2,4-dinitrophenyl)diaziridines} \[743]\]
\end{align*}
\]

\[
N\begin{array}{c}
R^1 \\
R^2 \\
R^3 \\
\end{array} \rightarrow \text{toluene, reflux} \to \\
3-14 \text{ h} \\
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{O} \\
\end{array} \\
758 \\
759
\]

\[
\text{R}^1 = \text{Me, iPr, Cy; R}^2, \text{R}^3 = (\text{CH}_2)_5 \quad \text{R}^2 = \text{Me, Et; R}^3 = \text{H, Me}
\]

13.13.4.2.3  Method 3:  Transformation of 1-(2-Nitrophenyl)-1\text{H}-tetrazoles

5-Aryl-1-(2-nitrophenyl)-1\text{H}-tetrazoles\[746,747]\] and 1-aryl-5-(2-nitrophenyl)-1\text{H}-tetrazoles\[748]\] decompose when heated to give nitrogen, carbon dioxide, and 2-aryl-2\text{H}-benzotriazoles; the former react much faster than the latter. For example, decomposition of 1-(2-nitrophenyl)-5-phenyl-1\text{H}-tetrazole (760) in refluxing nitrobenzene is complete after one hour while decomposition of 5-(2-nitrophenyl)-1-phenyl-1\text{H}-tetrazole (763) requires 19 hours (Scheme 283).\[748]\] It has been shown that the thermal decomposition of these tetrazoles to 2-aryl-2\text{H}-benzotriazoles (e.g., 762) proceeds via 2-nitrophenyl(phenyl)carbodiimides (e.g., 761; Ph may be replaced by a substituted-phenyl ring). A sequence of electrocyclic ring closing and opening reactions is proposed as the mechanism of the conversion of carbodiimides 761 to 2-aryl-2\text{H}-benzotriazoles.\[746,747]\] There are several other precursors (both cyclic and acyclic) of diarylcarbodiimides with an ortho nitro group and, consequently, they can be used in the synthesis of 2-aryl-2\text{H}-benzotriazoles.\[746,747]\]

Scheme 283  Transformation of 1(5)-(2-Nitrophenyl-5(1)-phenyltetrazoles into 2-Phenyl-2\text{H}-benzotriazoles\[748]\]

\[
\begin{align*}
\text{N} \equiv \text{N} & \quad \text{PhNO}_2, \text{reflux} \to \text{N} \equiv \text{N}\text{Ph} \\
\text{N} \equiv \text{N} & \quad \text{PhNO}_2, \text{reflux} \to \text{N} \equiv \text{N}\text{Ph}
\end{align*}
\]

The carbodiimides 765 are suggested as probable intermediates in the reaction of the phosphoramidate 764 with aryl isocyanates to yield the 2-aryl-2,4-dihydroimidazo[4,5-d][1,2,3]triazoles 766 (Scheme 284).\[749]\]

for references see p 587
Scheme 284  Synthesis of 2-Aryl-2,4-dihydroimidazo[4,5-d][1,2,3]triazoles via Carbobdiamides\cite{749}

\[
\begin{align*}
\text{Et}_3\text{N} & \quad \text{MeCN, 60 °C} \\
\text{Ar}_1\text{NCO} & \\
\text{N} & \\
\text{N} & \\
\text{NO}_2 & \\
\text{P(OEt)}_3 & \\
\rightarrow & \\
\text{Et}_3\text{N} & \\
\text{N} & \\
\text{N} & \\
\text{NO}_2 & \\
\text{ClO}_4^- & \\
\rightarrow & \\
\text{Et} & \\
\text{N} & \\
\text{N} & \\
\text{NAr}_1 & \\
\end{align*}
\]

13.13.4.3  Synthesis by Substituent Modification

Since substituent modification reactions in 1H- and 2H-benzotriazoles are, in many cases, very similar, the synthesis of new 2H-benzotriazoles by substituent modification is covered in Section 13.13.3.3.

13.13.5  Product Subclass 5: 1,2,3-Triazolium Salts

13.13.5.1  Synthesis by Ring-Closure Reactions

13.13.5.1.1  By Formation of One N—N and One N—C Bond

13.13.5.1.1.1  Method 1: From Diarylnitrilimines and Alkyl Isocyanides

Diarylnitrilimines 768 (generated in situ from 767 and triethylamine) react with alkyl isocyanides to form the triazolium salts 769 (Scheme 285)\cite{444,750}. Depending on the reaction conditions, other heterocyclic compounds are obtained, namely 1,2,4-triazolium salts, pyrazole derivatives, and quinoxaline derivatives. Experiments with tert-butyl isocyanide and phenyl isocyanide failed to give the respective triazolium salts 769.

Scheme 285  Reaction of Diarylnitrilimines with Alkyl Isocyanides\cite{444,750}

\[
\begin{align*}
\text{Ar}_1^+ & \quad \text{NHAr}_2^- \\
\text{Cl} & \\
\text{MeCN, rt} & \\
\Rightarrow & \\
\text{Ar}_1^+ & \\
\text{N} & \\
\text{N} & \\
\text{NAr}_2^- & \\
\text{1. R}_1\text{NC, MeCN, rt, 24 h} & \\
\Rightarrow & \\
\text{Ar}_1^+ & \\
\text{N} & \\
\text{N} & \\
\text{Ar}_2^+ & \\
\text{ClO}_4^- & \\
\Rightarrow & \\
\text{R}_1 & \\
\text{N} & \\
\text{NAr}_2^+ & \\
\end{align*}
\]

R\(^{-1}\) = Me, iPr, Cy; Ar\(^{-1}\) = Ph, 4-Tol; Ar\(^{+}\) = Ph, 4-Tol
Synthesis of 2H-Triazol-1-ium Salts 769; General Procedure.

**CAUTION:** Perchlorate salts are potential explosives.

Et$_3$N (2 mmol) was added at rt to a soln of the N-arylbenzohydrazonoyl chloride 767 (2 mmol) and the alkyl isocyanide (2 mmol) in dry MeCN (50 mL); the mixture was allowed to stand for 24 h. Removal of the solvent gave a crystalline residue which was washed with Et$_2$O and dissolved in the minimum amount of H$_2$O (some insoluble material was filtered off). Then 10% aq HClO$_4$ was added to cause precipitation of crude 769 as a greenish-white solid. Chromatography (acidic alumina, acetone), followed by addition of Et$_2$O to the concentrated eluate, afforded colorless plates.

### By Formation of One N—C Bond

#### Fragment N—N—N—C—C

#### Method 1: Cyclization of α-Imino Hydrazones

The oxidation of substituted α-imino hydrazones 770 with N-bromosuccinimide affords 1,2-disubstituted 2H-triazol-1-ium salts 771 (Scheme 286).

**Scheme 286** Oxidative Ring Closure of Substituted α-Imino Hydrazones

\[
\begin{align*}
\text{R}^1 \text{N} & + \text{R}^2 \text{N} \rightarrow \text{R}^1 \text{R}^2 \text{N} - \text{N} \\
\text{Ar}^1 = \text{alkyl, aryl; R}^2 = \text{alkyl, CN; R}^3 = \text{H, halo, alkyl}}
\end{align*}
\]

#### Method 2: Cyclization of (3-Aryl-1-methyltriaz-2-enyl)acetic Acid Derivatives

Cyclization of ethyl (1-methyl-3-phenyltriaz-2-enyl)acetate 772 (Ar$^1$ = Ph; X = OEt) with thionyl chloride/pyridine gives the mesoionic compound 773 (Ar$^1$ = Ph) together with a small amount of the sulfide 774 (Scheme 287).

Under similar reaction conditions, cyclization of amide 772 (Ar$^1$ = Ph; X = NH$_2$) gives only sulfide 774. Similar results are obtained when Ar$^1$ = 4-tolyl. Treatment of acetonitrile derivatives 775 with dry hydrogen chloride affords 4-amino-3-aryl-1-methyl-3H-1,2,3-triazol-1-ium chlorides 776. Cyclization of 775 with acetyl chloride gives the acetamido derivatives 777. The yields from all these transformations are low.

**Scheme 287** Cyclization of (3-Aryl-1-methyltriaz-2-enyl)acetic Acid Derivatives

\[
\begin{align*}
\text{Ar}^1 = \text{Ph, 4-Tol; X = OEt, NH}_2
\end{align*}
\]
This type of chemistry has been applied to the synthesis of the mesoionic 1,3-diaryl-1,2,3-triazoles \(778\) (Scheme 288).[752]

Scheme 288  Cyclization of (3-Aryl-1-methyltriaz-2-enyl)acetic Acid Derivatives[752]

Alkylation of 1-alkyl-1,2,3-triazoles \(779\) gives 1,3-disubstituted 3H-1,2,3-triazol-1-ium salts \(780\)[455] while alkylation of 2-substituted 2H-1,2,3-triazoles \(781\) affords 1,2-disubstituted 2H-1,2,3-triazol-1-ium salts \(782\) (Scheme 289).[450] 2-Substituted 1,2,3-triazoles are much more difficult to alkylate than the isomeric 1-substituted 1H-triazoles; this difference in reactivity agrees with the fact that 1-substituted triazoles are much more basic than the isomeric 2-substituted compounds.[450] While 1-substituted 1,2,3-triazoles react readily with methyl 4-toluenesulfonate,[448,449] producing 1,3-disubstituted 1,2,3-triazoliun 4-toluensulfonates in high yields, 2-substituted 1,2,3-triazoles, when treated with methyl 4-toluensulfonate, iodomethane, or dimethyl sulfate do not react, or they give the triazolium salts in low yield only.[450] 2,4-Diphenyl-2H-1,2,3-triazole is, however, converted into the triazolium salt, in 80% yield, by methylation with dimethyl sulfate.[444] Methyl fluorosulfonate is a successful methylating reagent for 2-substituted 1,2,3-triazoles (Scheme 289).[450] The reaction is carried out in the absence of a solvent and the required temperature is dependent on the substituents \(R^1\) and \(R^2\) in triazole \(781\). For example, 2-methyl-2H-1,2,3-triazole reacts with methyl fluorosulfonate at 0°C, 2-phenyl-2H-1,2,3-triazole reacts at room temperature, and the reaction with 4,5-dibromo-2-methyl-2H-1,2,3-triazole only occurs at 60°C.[450]
1-Phenyl-1H-1,2,3-triazole adds fairly rapidly to vinylsulfonyl chloride, in the absence of a base, to yield quantitatively the sulfonate \( \text{783} \) (Scheme 290).

**Scheme 290**  \[ \text{Addition of 1-Phenyl-1H-1,2,3-triazole to Vinylsulfonyl Chloride} \[198\]

1-Ethyl-1H-1,2,3-triazole reacts with tetracyanoethene oxide, at 0°C, to yield 3-ethyl-3H-1,2,3-triazol-1-ium-1-dicyanomethanide (\( \text{784} \)) in 73% yield (Scheme 291).

**Scheme 291**  \[ \text{Reaction of 1-Ethyl-1H-1,2,3-triazole with Tetracyanoethene Oxide} \[753\]

13.13.5.2.2  **Method 2:**  
**Alkylation of N-Alkylbenzotriazoles**

As discussed in Section 13.13.3.3.1.1.8, during the alkylation of benzotriazole with alkyl halides, in some cases,\[672\] the 1,3-dialkylbenzotriazolium salts are also formed (Scheme 239). 1-Substituted 3-methyl-3H-benzotriazol-1-ium iodides \( \text{785} \) are prepared in low to good yields by the reaction of 1-substituted 1H-benzotriazoles with iodomethane (Scheme 292).\[754\]

For references see p 587
Alkylation of 1-\{dialkylamino\}methyl-1H-benzotriazoles 786 leads to the formation of (1H-benzotriazol-1-ylmethyl)ammonium salts 787 (Scheme 293).\textsuperscript{755} This reaction is limited to iodomethane, iodoethane, and 1-(chloromethyl)-1H-benzotriazole. Methyl 4-toluene sulfonate can also be used but reacts only with 1-(pyrrolidin-1-ylmethyl)-1H-benzotriazole [786, R1,R2 = (CH2)4]. In some cases, the 1,3-dialkylbenzotriazolium salts 790 are obtained. Indeed, when 1-(pyrrolidin-1-ylmethyl)-1H-benzotriazole [786, R1,R2 = (CH2)4] is heated with benzyl bromide in a sealed tube at 60–80 °C, 1,3-dibenzyl-3H-benzotriazol-1-ium bromide (790, R1 = Bn; X = Br) is obtained in 65% yield.\textsuperscript{755} The explanation for the formation of salts 790 depends on the fact that compounds 786, in solution, are in equilibrium with the ion pair 788, which reacts with the alkylating agent to form successively 1-alkyl-1H-benzotriazole 789 and then 790.

Ethyl 1H-benzotriazole-1-carboxylate reacts with triethylxonium tetrafluoroborate to yield the corresponding 3-\{ethoxycarbonyl\}1-ethyl-3H-benzotriazol-1-ium salt (see Scheme 240).\textsuperscript{634}

Alkylation of benzotriazole with bis(bromomethyl)benzenes (1,2-, 1,3- or 1,4-) in two steps affords the benzotriazolophanes 791 (Scheme 294).\textsuperscript{674} The symmetrical benzotriazolophanes 792, 793, and 794 are prepared in a similar manner.\textsuperscript{674,675}

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The unsymmetrical benzotriazolophanes 796 and 797 are obtained by alkylation of the precyclophane 795 with the corresponding bis(bromomethyl)benzene derivatives (Scheme 295).[^675]

[^675]: 1,2,3-Triazolium Salts
1-Ethyl-1\textsubscript{H}-benzotriazole reacts with tetracyanoethene oxide, at room temperature, to yield 3-ethyl-3\textsubscript{H}-benzotriazol-1-ium-1-dicyanomethanide \textbf{798} (Scheme 296).\textsuperscript{[753]}

\textbf{Scheme 296}  Reaction of 1-Ethyl-1\textsubscript{H}-benzotriazole with Tetracyanoethene Oxide\textsuperscript{[753]}

References


1,2,3-Triazoles


1,2,3-Triazoles


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