Acid Hydrazides, Potent Reagents for Synthesis of Oxygen-, Nitrogen-, and/or Sulfur-Containing Heterocyclic Rings

Poulomi Majumdar,†‡ Anita Pati,†§ Manabendra Patra,‖ Rajani Kanta Behera,‡ and Ajaya Kumar Behera*†

†Organic Synthesis Laboratory, School of Chemistry, Sambalpur University, Jyoti Vihar, Burla 768019, Orissa, India
‡State Key Laboratory of Fine Chemicals, School of Chemical Engineering, Dalian University of Technology, Dalian, 116024, P.R. China
§School of Applied Sciences (Chemistry), KIIT University, Bhubaneswar 751024, India
‖National Institute of Science & Technology, Palur Hill, Berhampur 761068, Orissa, India

CONTENTS
1. Introduction 2942
2. Synthesis of Acid Hydrazides 2943
3. Reactions of Acid Hydrazides 2944
  3.1. Synthesis of Five-Membered Rings with One Heteroatom 2944
    3.1.1. Pyrrole and Their Fused Derivatives 2944
  3.2. Synthesis of Five-Membered Rings with Two Heteroatoms 2945
    3.2.1. Pyrazoles and Their Fused Derivatives 2945
    3.2.2. Imidazoles and Their Fused Derivatives 2947
  3.3. Synthesis of Five-Membered Rings with Three Heteroatoms 2948
    3.3.1. Oxadiazoles and Their Fused Derivatives 2948
    3.3.2. Thiadiazoles and Their Fused Derivatives 2956
    3.3.3. Triazoles and Their Fused Derivatives 2958
  3.4. Synthesis of Six-Membered Rings with One Heteroatom 2962
    3.4.1. Pyran and Their Fused Derivatives 2962
    3.4.2. Pyridine and Their Fused Derivatives 2963
  3.5. Synthesis of Six-Membered Rings with Two Heteroatoms 2965
    3.5.1. Pyridazine and Their Fused Derivatives 2965
    3.5.2. Pyrimidine and Their Fused Derivatives 2966
    3.5.3. Piperazine and Their Fused Derivatives 2968
    3.5.4. Thiazine and Their Fused Derivatives 2968
  3.6. Synthesis of Six-Membered Rings with Three Heteroatoms 2969
    3.6.1. Oxadiazine and Their Fused Derivatives 2969
    3.6.2. Triazine and Their Fused Derivatives 2969
4. Conclusion 2970

1. INTRODUCTION
Heterocycles form by far the largest of the classical divisions of organic chemistry. Moreover, they are of immense importance not only both biologically and industrially but also to the functioning of any developed human society as well. The majority of pharmaceutical products that mimic natural products with biological activity are heterocycles.

Numerous natural drugs such as quinine, papaverine, atropine, codeine, emetine, reserpine, procaine, morphine, and theophylline are heterocycles. The majority of the compounds we are familiar with as synthetic drugs such as chlorpromazine, diazepam, isoniazid, metronidazole, azidothymidine, barbiturates, antipyrene, captoril, and methotrexate are also heterocycles. Some dyes (e.g., mauveine), luminophores (e.g., acridine orange), pesticides (e.g., diazinon) and herbicides (e.g., paraquat) are also heterocyclic in nature. Each of these natural and synthetic heterocyclic compounds can and do participate in chemical reactions in the human body. Moreover, all biological processes are expressed through chemical reactions. Such fundamental manifestations of life as the provision of energy, transmission of nerve impulses, sight, metabolism, and transfer of genetic information are all based on chemical interactions involving participation of many heterocyclic compounds, such as vitamins, enzymes, coenzymes, ATP, DNA, RNA, and serotonin.

Why does nature exploit heterocycles? The appropriate answer to this question is provided by the fact that heterocycles are able to get involved in an extraordinarily wide range of reaction types. Other important practical applications of heterocycles can also be cited, for instance, additives and modifiers in a wide variety of industries including cosmetics, reprography, information storage, plastics, solvents, antioxidants, and vulcanization accelerators. Finally, as an applied science, heterocyclic chemistry is an
inexhaustible resource of novel compounds. There are many common features in chemistry and physics between such related compounds as pyrrole and aniline or between pyridine and nitrobenzene. Nevertheless, nature selected the heterocycles pyrrole and pyridine, and not the homocycles aniline and nitrobenzene, as the basis of most essential biological systems. We now know the reason for this: incorporation of a heteroatom into a cyclic compound imparts new properties. Heterocycles are chemically more flexible and better able to cater the needs of biochemical systems.

Synthesis of various heterocycles has been a research objective for over a century, and a variety of well-established methods are available in the literature. Development of new approaches for their syntheses, employing efficient and atom economical routes, is currently a popular research area. Organic chemists have been engaged in extensive efforts to produce these heterocyclic compounds by developing new and efficient synthetic transformations. Among the new synthetic transformations, uses of hydrazides are among the most attractive precursors for synthesizing heterocyclic compounds.

Moreover, hydrazides include a vast group of organic derivatives of hydrazine containing the functional active group —C(=O)NHNNH2. First representatives, namely, hydrazides of formic acid and acetic acid, were produced as far back as 1895 by Kurzius.1 Great interest in the chemistry of hydrazides and its derivatives is explained by diversity and at times by originality of their properties. Hydrazides find wide applications as drugs, chemical preservers for plants, for manufacturing polymers, glues, etc., in industry, and for many other purposes.2 This class of compounds and their derivatives such as hydrazones have been described as useful synthons of various heterocyclic rings of different ring sizes with one or several heteroatoms that exhibit interesting applications as pharmaceuticals,3,4 herbicides,5 antibacterial agents,6 and dyes.7,8 The synthetic strategy, in general, for various heterocyclic moieties from hydrazide precursors, has been made by cyclization or cycloaddition with numerous reagents. Hydrazide analogues also possess other biological activities like anticonvulsant,9 antidepressant,10 anti-inflammatory,11 antimalarial,12 antimycobacterial,13 antimycobacterial,14 anticancer,15 and antimicrobial16–19 activities.

Hydrazides are rather reactive substances; they are bidentate as ligands. Depending on medium acidity, these reagents form complexes in either amide (type I) or imide (type II) forms20 (Figure 1).

![Figure 1. Hydrazides as ligands.](image)

Isonicotinic acid hydrazide, commercially known as (INH, isoniazid) (Figure 2), has been one of the most effective agents in tuberculosis therapy since 1952, when its action against Mycobacterium tuberculosis was first discovered.21 It appears that INH, like numerous other compounds, has physiological potency in the inhibition of root growth development of levels substantially lower than those that elicit any morphological responses in the tops of established plants.22 It is perhaps from the ranks of such compounds that materials suitable for pre-emergence weed control should be sought. Thus, isonicotinic acid hydrazide has been used in medical practice for more than half a century under the name of isoniazid, and it has not lost its value to the present day.23,24 Further, on this basis, it has given rise to phthiazid, saluzid, and metazid,25 and there continues to be discovered modified analogs such as flurenizid26 with improved pharmacological properties. It is now widely used together with rifampicin and streptomycin for chemotherapy of tuberculosis.

Isocarbozaxid, also known as Marplan (Figure 2), is a powerful monoamine oxidase (MAO) inhibitor.27 As phenelzine, iso carbozaxid is used for depressions which do not respond to other drugs. Iproniazid (Figure 2) is an antidepressant used as psychostimulators.28

The simple indolglyoxylyl hydrazide (Figure 2) is mentioned by Heinzelman and Szmuszkovicz29 as a fairly potent 5-hydroxytryptophan decarboxylase inhibitor (IC50 10−4 M).

The scope of the present review is to provide practical guidance for synthetic chemists. Bearing in mind that the major interest in heterocycles is the synthesis of biologically active compounds, we arranged the material systematically according to the size and shape of the heterocyclic ring, i.e., five- and six-membered heterocyclic rings containing one, two, or three of the same or different heteroatoms (O, N, or S, respectively) from various acid hydrazides. This systematic arrangement may be useful to any chemist searching for bioisosteres of a heterocyclic scaffold, or a heterocyclic substituent will find a whole range of useful structures.

2. SYNTHESIS OF ACID HYDRAZIDES

Usually acid hydrazides are formed by combining hydrazine with various acyl derivatives which include esters, cyclic anhydrides, and acyl halides. A general scheme for formation of acid hydrazides is depicted in (Scheme 1).

**Scheme 1**

\[
\text{R-C-X + NH}_2\text{NH}_2 \rightarrow \text{R-NNH}_2
\]

\(R = \text{alkyl, aryl; } X = \text{OEt, OMe, halides, anhydrides}\)

Cyanoacetic acid hydrazide 2 was obtained in 93% yield by careful addition of hydrazine hydrate to ethyl cyanoacetate 1 in ethanol with stirring at 0 °C (Scheme 2).30

**Scheme 2**

\[
\text{OEt} + \text{NH}_2\text{NH}_2 \rightarrow \text{O-NHNH}_2
\]

\(*(i) 0°C, \text{EtOH}.*

dx.doi.org/10.1021/cr300122t Chem. Rev. 2014, 114, 2942–2977
Treatment of 3-chlorobenzo[\textit{g}]thiophene-2-carbonyl chloride 3 with hydrazine hydrate afforded the corresponding acid hydrazide 4 in 73% yield (Scheme 3).³¹,³²

**Scheme 3**

![Image](84x231 to 276x266)

Reaction of benz[\textit{g}]indole dicarboxylate 5 with hydrazine hydrate in refluxing ethanol and a catalytic amount of pyridine chemoselectively produced only 63% of benz[\textit{g}]indole monocarboxylic hydrazide 6 instead of the expected dicarboxylic hydrazide wherein the C₃-carboethoxy group of these compounds, where the C₃-carboethoxy group has less double-bond character.³⁴ The resistance of the C₃-carboethoxy group of 5 toward nucleophilic attack of the hydrazine hydrate might be attributed to the canonical form ⁵ of these compounds, where the C₃-carboethoxy group has less double-bond character.³⁴⁻³⁶

The cyclic anhydride 8 on hydrolysis with ethanolic hydrochloric acid and subsequent reaction with hydrazine hydrate yielded 92% of 5-chloroanthranilic acid hydrazide 9 (Scheme 5).³⁷

**Scheme 4**

![Image](364x584 to 524x613)

“(i) NH₃·H₂O, EtOH, Py.

“(i) NH₃·H₂O, HCl; (ii) NH₂NH₂

The hydrazides 12 were obtained from the anhydrides 10 and the hydrochlorides of disubstituted hydrazines 11 in the presence of triethylamine and pyridine in an atmosphere of nitrogen (Scheme 6).³⁸

The benzo[\textit{4,5}]imidazo[\textit{2,1-a}]isoindol-11-one 13 on refluxing with hydrazine hydrate at 120 °C yielded 80% of benzimidazolylbenzoyl hydrazide 14 (Scheme 7).³⁹

**Scheme 5**

![Image](389x660 to 500x733)

“(i) EtOH, HCl; (ii) NH₂NH₂·H₂O, EtOH, Py.

“(i) Oil bath, 120 °C.

the heterocycles formed, starting with five- and six-membered rings. These systematic collections in the present review expand the ample possibilities to the synthetic methods accessed by the chemistry for synthesis of heterocyclic compounds and may possibly be useful to pick the route for further research.

3.1. Synthesis of Five-Membered Rings with One Heteroatom

3.1.1. Pyrrole and Their Fused Derivatives. Pyrrole is an important ubiquitous heterocyclic moiety throughout the plant as well as animal kingdom because of its involvement as a subunit of haem, the chlorophyll, vitamin B₁₂, and some bile pigments. Pyrroles have been found to exhibit a wide spectrum of biological activities.⁴⁰⁻⁴² In addition, 2,5-dimethylpyrrole derivatives have shown interesting antiulcer and hypotensive activities.

Also, the indole ring system is a crucial structure in drug discovery and has become an essential component in many pharmacologically active compounds. The extensive number of synthetic routes to and applications of indoles emphasizes the great interest in this area. The most commonly used method for preparation of indoles remains the Fischer indole synthesis discovered in 1883.⁴³,⁴⁴ In spite of extensive studies, important efforts are still focused on providing synthetic routes under mild conditions and with good regiocontrol on the outcome of the reaction.⁴⁶,⁴⁷

Murphy et al.⁴⁸ explored the synthesis of indoles from their recently reported alkylidenated Weinreb amides⁴⁹,⁵⁰ in non-classical Wittig reactions.⁵¹,⁵² Success in this study led the authors to investigate the reactivity of Wittig reagents with acyl hydrazides 16 (Scheme 8).⁴⁸

Reaction of phosphorus ylides with the hydrazide 16c–e and 18 afforded the respective indole derivatives 19–23 in 41–78% yields (Scheme 8).

The authors extended the reactions to N-acetylhydrazide 16a and N-propionyl hydrazide 16b where the unexpected indolin-2-one 26a and 26b were isolated in 76% and 92% yields, respectively (Scheme 9). In these cases, the phosphorane deprotonates 16a/16b to form the enolate of the hydrazide 24a/24b which underwent a Brunner indolin-2-one synthesis,⁵³,⁵⁴ in high yield, to afford 25a/25b before condensation to the final products. The reactivity of cyclohexyl hydrazide 16g mirrored that of the acetyl case 16a and produced 20% of spiroindolin-2-one 27 as well as a low yield of indole 28 (3%) (Scheme 9). They also proposed that conjugate addition of the phosphorane to the α,β-unsaturated hydrazide 16f afforded 29 followed by expulsion of triphenylphosphine. The resulting
cyclopropane 30 then underwent either base-induced deprotonation of one of the gem-dimethyl groups in tandem with ring opening of the cyclopropane to form the enolate or thermal prototropic formation of the enol that is equivalent to 31, followed by deprotonation. The enolate then underwent a Brunner reaction to the indolin-2-one product 32 in 24% yield.

Michael and co-workers\(^5\) reported a dicationic platinum (bpy)Pt(II) catalyzed intramolecular hydrohydrazination of olefins 33–35 that proceeded through N−H activation of an alkenyl hydrazide followed by olefin insertion into a Pt−N bond. Reaction optimization revealed Pt(bpy)Cl\(_2\) (10 mol %) and AgOTf (20 mol %) in DMF−\(_d\) when NR\(_2\) = NPhthal, 120 °C when NR\(_2\) = NHAc. Yields given are isolated yields after 1 day unless otherwise noted. (a) 2 days.

### 3.2. Synthesis of Five-Membered Rings with Two Heteroatoms

#### 3.2.1. Pyrazoles and Their Fused Derivatives

The term pyrazole was given by Ludwig Knorr in 1883. Pyrazole was first described by Buchner in 1889, who discovered it during decomposition of pyrazole 3,4,5-tricarboxylic acid. In 1959, the first natural pyrazole, 1-pyrazolyl-alanine, was isolated from seeds of watermelons. Interest in pyrazoles stemmed from their application in drugs and dyes, as antioxidants in fuels, as anesthetics, and in agricultural fields. In medicine, derivatives of pyrazoles are used for their antiinflammatory,\(^5\) antipyretic, analgesic, muscle relaxing,\(^6\) antiarrhythmic, tranquilizing, psychogenic, anticonvulsant, monoamine oxidase inhibiting, anti diabetic,\(^6\) and antibacterial\(^6\) activities. The following are a few drugs: antipyrine, used as an analgesic and febrifuge; tartrazine, most commonly used as a yellow dye for food; phenylbutazone (butazolidin), an antiinflammatory drug used in treatment of arthritis. Therefore, it became of interest to synthesize new pyrazole derivatives of possible biological activities.

It was reported that treatment of hydrazide 2 with ethyl benzoylacetic acid yielded N′-(2-cyanoacetyl)-3-oxo-2-phenylpyrrole 39, which underwent cyclocondensation with 3-hydrazino-5,6-diphenyl-1,2,4-triazine 40 in absolute ethanol to produce compound 41, which on reaction with dilute hydrochloric acid gave 55% of 1-(1-(5,6-diphenyl-1,2,4-triazin-3-yl)-5-phenyl-1H-pyrazol-3-yl)pyrazolidine-3,5-dione 42 (Scheme 11).\(^6\)

#### Scheme 11\(^a\)

\(^{a}(i)\) EtOH, reflux, 140–150 °C, 4 h; (ii) dilute HCl, reflux, 5 h.
A series of pyrazole derivatives using cyanoacetic acid hydrazide was synthesized by a number of research groups (Schemes 12−19). Elnagdi and coworkers\(^6^4\) reported the reaction of 2-(1-phenylethylidene)malononitrile and ethyl 2-cyano-3-phenylbut-2-enoate with hydrazide\(^2\) to furnish pyrazoline\(^43\) and pyrazolidinone derivative\(^44\), respectively, with 75% yield (Scheme 12).

Reaction of hydrazide\(^2\) with alkylisocyanate yielded alkylcarbamoyl derivative\(^45\), which upon treatment with 2 N sodium hydroxide furnished the cyclized pyrazole derivative\(^46\) in 48−92% yields (Scheme 13).\(^6^5\)

Condensation of hydrazone derivative\(^47\) obtained from hydrazide\(^2\) and cyclohexanone with aromatic aldehyde in ethanolic triethylamine gave the 3-aryl-4,5,6,7-tetrahydro-1\(H\)-indazoles\(^48\) in 75−78% yield (Scheme 14).\(^6^6\)

Pyrazole derivative\(^50\) was produced in 75% yields on condensation of hydrazide\(^49\) with benzaldehyde via 1,5-dipolar cyclization of the initially formed adduct followed by rearrangement via elimination of \(\text{HN} = \text{C} = \text{S}\) (Scheme 15).\(^6^7\) Shams et al.\(^6^7\) further subjected pyrazole\(^50\) to a reaction with methylene carbonitrile reagents \((\text{XCH}_2\text{CN}; \text{X} = \text{CN} \text{ and } \text{CO}_2\text{Et})\) affording the respective pyranopyrazole derivatives\(^51\) in 86% \((\text{X} = \text{CN})\) and 65% \((\text{X} = \text{COOEt})\) yield via \(\beta\)-attack on the benzylidene moiety followed by cyclization through the pyrazole oxo function (Scheme 15).

Shams et al.\(^6^7\) also treated hydrazide\(^49\) with salicylaldehyde to produce the coumarin derivative\(^52\), which on subsequent reaction with methylene carbonitrile reagents \((\text{XCH}_2\text{CN}; \text{X} = \text{CN} \text{ and } \text{CO}_2\text{Et})\) afforded the respective pyrazole derivatives\(^53\) in 80% \((\text{X} = \text{CN})\) and 72% \((\text{X} = \text{COOEt})\) yield via a \(\beta\)-dipolar attack of the hydrazinocarbonyl moiety of\(^52\) on the methylene carbonitrile dipole (Scheme 16).

Condensation of hydrazide\(^2\) with isatin was reported at room temperature and furnished the isolated intermediate \((2\text{E})-2\text{-cyano}-2\text{-}(2\text{-oxo}-1\text{-},2\text{-dihydro}-3\text{-H}-\text{indol}-3\text{-ylidene})\text{acetohydrazide}\(^57\), which was cyclized on heating to give \((2\text{E})\text{-3-(3-amino-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene)-1,3-dihydro-2H-indol-2-one}\(^58\). Compound\(^58\) was also directly obtained on refluxing hydrazide\(^2\) with isatin in ethanol containing a catalytic amount of triethylamine (Scheme 18).\(^6^9\)

Condensation of hydrazide\(^2\) with isatin was reported at room temperature and furnished the isolated intermediate \((2\text{E})\text{-2-cyano-2-(2-oxo-1,2-dihydro-3H-indol-3-ylidene})\text{acetohydrazide}\(^57\), which was cyclized on heating to give \((2\text{E})\text{-3-(3-amino-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene)-1,3-dihydro-2H-indol-2-one}\(^58\). Compound\(^58\) was also directly obtained on refluxing hydrazide\(^2\) with isatin in ethanol containing a catalytic amount of triethylamine (Scheme 18).\(^6^9\)

4-Amino-3-hydroxypyrazole derivatives\(^6^0\) and\(^6^1\) \((80-86\% \text{ yields})\) were prepared from reaction of the hydrazide\(^2\) with ketones in the presence of a basic catalyst via cyclization of hydrazone derivatives\(^47\) and\(^59\) (Scheme 19).\(^7^0\)

Hydrazide\(^62\) furnished the intramolecular cyclized pyrazolo derivative\(^63\) in 82% \((\text{R} = 4\text{-BrC}_6\text{H}_4)\) and 70% \((\text{R} = 2\text{-5-Me}_2\text{C}_6\text{H}_3)\) yields upon refluxing in glacial acetic acid (Scheme 20).\(^7^1\)
Lam et al. reported the synthesis of 5-aminopyrazole and applied it for preparation of pyrazolo[5,1-d][1,2,3,5]tetrazine-4(3H)-ones. In this strategy, hydrazide was reacted with (1-ethoxyethylidene)malononitrile at room temperature to provide benzyl 5-amino-4-cyano-3-methyl-1H-pyrazole-1-carboxylate. The authors attempted to obtain compound by diazotizing followed by reaction with an amine but resulted instead in formation of (Scheme 21). Further investigation confirmed that the diazotization of 65 did not proceed readily, and the carbobenzyloxy group on N1 of compound 65 was readily removed during the reaction with isopropylamine to provide 66 in 90% yield. Subsequent diazotization of 66 with 4 M HCl and sodium nitrite in water at 0–5 °C gave nonisolable and was treated overnight with phenylisocyanate, which provided 7-methyl-4-oxo-3-phenyl-3,4-dihydropyrazolo[5,1-d][1,2,3,5]tetrazine-8-carbonitrile in 72% yield (Scheme 21). The authors also developed a SPS of 5-aminopyrazole. The pyrazole was obtained in 75% yield by treatment of acetic acid hydrazide with phenylacetyl chloride followed by cyclization of the resulting intermediate in basic medium. On the other hand, fusion of hydrazide and ethyl carboxylate at 200 °C gave 85% of pyrazole without isolation of intermediate (Scheme 22).

Catalyst-free cyclocondensation of allenic ketones with hydrazides afforded the 1-acyl-5-hydroxypyrazolines with high regioselectivity, which were further converted into 1-acyl pyrazoles via BF3·Et2O-catalyzed dehydration in good to excellent yields:

3.2.2. Imidazoles and Their Fused Derivatives. The imidazole ring system is one of the most important substructures found in a large number of natural products and pharmacologically active compounds. For example, the amino acid histidine, the hypnotic agent etomidate, the antiulcerative agent cimetidine, the proton pump inhibitor omeprazole, the fungicide ketoconazole, and the benzodiazepine antagonist flumazenil are imidazole derivatives. Therefore, there is a continuous need for developing concise and practical synthetic methods for preparation of imidazole and related compounds.
Diazotization of 3-aminothieno[2,3-b]pyridine carbonyl hydrazide derivative 79 gave the corresponding 3-amino-5-[(1-naphthylamino)carbonyl]thieno[2,3-b]pyridine-2-carbonyl azide derivative 80, which was subjected to Curtius rearrangement\(^{82,83}\) to give 72% of N-1-naphthyl-2-oxo-2,3-dihydro-1H-imidazo-[4',5':4,5]thieno[2,3-b]pyridine-7-carboxamide derivative 81 (Scheme 25).\(^{84}\)

Imidazole 84 was synthesized in 50% yield from reaction of hydrazide 69 with oxazolone 82 via cyclization of acid hydrazido derivative 83 in basic medium (Scheme 26).\(^{74}\)

Condensation of o-phenylenediamines 85 with hydrazide 86 to melting reactants at 240 °C afforded 2-hydroxy-7-[benzimidazol-2-yl]methyl-5-methylpyrazolo[1,5-a] pyrimidines 87 in 60–80% yields (Scheme 27).\(^{85}\)

Shams et al.\(^{67}\) reported the reaction of cyanoacetic 2-[[benzoylmino]thioxomethyl] hydrazide 49 with α-haloketones (XCH₂COR; A: X = Cl, R = OEt; b: X = Cl, R = Me; c: X = Br, R = Ph) to afford the respective imidazolothione derivatives 88 (a, 75%; b, 88%; c, 70%) which on subsequent treatment with malononitrile afforded the pyran systems 89 (a, 82%; b, 82%; c, 88%) via nucleophilic attack on the carbonitrile reagent followed by 1,6-dipolar intramolecular cyclization (Scheme 28).

**Scheme 25\(^{a}\)**

\(^{a}\)(i) AcOH, NaN\textsubscript{3}O/H\textsubscript{2}O, stirred, 6 h; (ii) xylene, reflux 18 h.

**Scheme 26\(^{a}\)**

\(^{a}\) (i) aq EtOH (80%), reflux, 6 h; (ii) 2N NaOH, reflux, 4 h.

**Scheme 27**

\(^\text{R}_1, \text{R}_2 = a: \text{H}, b: \text{Me}, c: \text{H}, d: \text{H}, \text{NO}_2\)

**Scheme 28\(^{a}\)**

\(^{a}\)(i) EtOH, reflux, 5 h; (ii) 1,4-dioxane, TEA, 4 h.

### 3.3. Synthesis of Five-Membered Rings with Three Heteroatoms

#### 3.3.1. Oxadiazoles and Their Fused Derivatives

Oxadiazoles are commonly utilized pharmacophores due to their metabolic profile and ability to engage in hydrogen bonding. In particular, marketed antihypertensive agents such as tiodazosin\(^{86}\) and nesapidil\(^{87}\) as well as antibiotics such as furamizole\(^{88}\) contain the oxadiazole nucleus. 2-Amino-1,3,4-oxadiazoles have demonstrated biological activity as muscle relaxants\(^{89}\) and antimicrobials,\(^{90}\) while 2,5-diaryl-1,3,4-oxadiazoles are known to be platelet aggregation inhibitors.\(^{91}\) S-Aryl-2-hydroxymethyl-1,3,4-oxadiazoles have shown diuretic, analgesic, antiinflammatory, anticonvulsive, and antiemetic properties, and 2-hydroxyphenyl-1,3,4-oxadiazoles behave as hypnotics and sedatives.\(^{92}\) Widespread use of 1,3,4-oxadiazoles as a scaffold in medicinal chemistry as demonstrated by these examples establishes this moiety as a member of the privileged structures class.

Rebek et al.\(^{94}\) reported the hydrolysis of the ethyl ester 90 with LiOH, followed by coupling with N-acyl hydrazides 91 mediated by EDCI/HOBt which led to formation of intermediates 92 in good yields. Dehydration of N,N'-diacyl hydrazides 92 using POCl\textsubscript{3} yielded 45–53% of α-helix mimetic oxadiazole-phenyl sca

**Scheme 29\(^{a}\)**

\(^{a}\) (i) LiOH, THF/H\textsubscript{2}O; (ii) EDCI, HOBut, DCM; (iii) POCl\textsubscript{3}, MeCN, reflux, 12 h.
refluxing afforded 92% of [1,2,4]triazolo[4,3-α]piperazines \(^{97}\) (Scheme 30).\(^{95}\)

**Scheme 30**

\[\text{reaction steps} \]

\(^{\text{a}}\)(i) POCl₃, reflux, 80 °C, 17 h; (ii) MeOH, -20 °C; (iii) MeOH, reflux.

Reaction of isatoic anhydrides \(^{98}\) with appropriate hydrazides in acetic acid led to formation of 1-(2-substituted amino-benzoyl)-2-aroylhydrazines, which underwent cyclization in the presence of polyphosphoric acid (PPA) to form 2,5-diaryl-substituted 1,3,4-oxadiazoles \(^{99}\) in 35−42% yields (Scheme 31).\(^{96}\)

**Scheme 31**

\[\text{reaction steps} \]

\(^{\text{a}}\)(i) AcOH; (ii) PPA.

Cyclodehydration of semicarbazides for synthesis of the oxadiazole moiety has been reported by various researchers (Schemes 32−38). Oxidative cyclization of oxalyldiphenylthiosemicarbazides \(^{101}\) in the presence of alkaline I₂/KI solution afforded bis-2-(5-phenylamino-1,3,4-oxadiazole) \(^{102}\) in 57−67% yields (Scheme 32).\(^{97}\)

**Scheme 32**

\[\text{reaction steps} \]

\(^{\text{a}}\)(i) CHCl₃, reflux, 1 h; (ii) H₂SO₄, stirring.

**Scheme 33**

\[\text{reaction steps} \]

\(^{\text{a}}\)(i) Hg(OAc)₂, AcOH.

Li et al.\(^{102}\) adapted a similar procedure for synthesis of 1,3,4-oxadiazoles \(^{117}\) in 83−94% yields by treating 4-(3-methylbenzoyl)-1-(2-phenoyacetyl)thiosemicarbazide \(^{116}\) with mercuric acetate in glacial acetic acid (Scheme 37). The thiosemicarbazides \(^{119}\) obtained by nucleophilic addition reaction of 1-(4-chlorophenyl)-4-hydroxy-1H-pyrazole-3-carboxylic acid hydrazide \(^{118}\) with phenyl isothiocyanate underwent cyclization to 1,3,4-oxadiazole \(^{120}\) in low yield (31%) by boiling the former with mercuric oxide in absolute ethanol (Scheme 38).\(^{103}\)

**Scheme 34**

\[\text{reaction steps} \]

\(^{\text{a}}\)(i) EtOH, Δ; (ii) EtOH, KOH/KI, I₂.

**Scheme 35**

\[\text{reaction steps} \]

\(^{\text{a}}\)(i) EtOH, Δ; (ii) EtOH, NaOH/KI, I₂.

**Scheme 36**

\[\text{reaction steps} \]

\(^{\text{a}}\)(i) Hg(OAc)₂, AcOH.

1-Cinnamoyl-4-phenyl semicarbazide \(^{110}\), synthesized by reaction of phenyl isocyanate with the cinnamic acid hydrazide \(^{109}\), was subjected to acid-catalyzed intramolecular cyclization with sulfuric acid to afford 78% of 2-cinnamoyl-5-aminophenyl 1,3,4-oxadizoles \(^{111}\) (Scheme 35).\(^{100}\)

**Scheme 37**

\[\text{reaction steps} \]

\(^{\text{a}}\)(i) POCl₃, reflux, 80 °C, 17 h; (ii) MeOH, -20 °C; (iii) MeOH, reflux.

**Scheme 38**

\[\text{reaction steps} \]

\(^{\text{a}}\)(i) MeOH, −20 °C; (ii) MeOH, reflux.
pentoxide to yield 44% of 1,3,4-oxadiazole 125. In an alternative route, compound 125 was obtained in 56% yield by thermal cyclization of ethoxyformaldehyde hydrazone 126 generated on refluxing the mixture of 123 and triethyl orthoformate (Scheme 40).104

Acetic acid anhydride was also used by a group of researchers for formation of oxadiazole derivatives (Schemes 41−43). Cyclocondensation of benzalhydrazone derivative 128 with acetic anhydride furnished acetyl oxadiazoles 129 in 49−75% yields (Scheme 41).105 Similarly, the 1,3,4-oxadiazoline 131 was prepared in 70% yield exclusively by cyclization of the intermediate 130 (Scheme 42).103

Dehydrative ring closure of the N-acetyl derivative 133, obtained from refluxing hydrazone 132 in acetic acid anhydride, with phosphorus oxychloride in acetonitrile furnished the corresponding oxadiazole derivatives 134 in very low yields (25−28%) (Scheme 43).106 Various 1,3,4-oxadiazoles prepared by reaction of different aryl-substituted hydrazones of respective 4-fluorobenzoic acid hydrazone and 4-pyrryl-1-yl benzoic acid hydrazone with acetic anhydride were also reported by Kocyigit-Kaymakcoglu et al.107 and Vagdevi et al.108

The hydrazone 135 on nucleophilic displacement reaction with methyl oxalyl chloride in the presence of triethylamine produced a diacyl hydrazide intermediate 136, which underwent cyclization upon treatment with p-toluenesulfonyl chloride (TsCl) to yield 1,3,4-oxadiazole derivative 137 in 75−94% yields (Scheme 44).109,110 Subsequent addition of the requisite

![Scheme 37](image1)

**(i)** Hg(OAc)$_2$/AcOH, reflux.

**Scheme 38**

![Scheme 38](image2)

**(i)** HgO, EtOH.

**Scheme 39**

![Scheme 39](image3)

**(i)** P$_2$O$_5$, xylene, reflux.

**Scheme 40**

![Scheme 40](image4)

**(i)** reflux; (ii) P$_2$O$_5$, toluene; (iii) reflux; (iv) $\Delta$.
side chain (R₁) to the methyl ester was accomplished via a metal–halogen exchange of the corresponding alkylbromide to give the α-ketooxadiazole 138 in 20–73% yields (Scheme 44).<sup>109,110</sup> 

Cyclocondensation of acid hydrazides 106, 118, 123, and 139–151 with carbon disulfide in alcoholic KOH or NaOH under reflux conditions gave the respective oxadiazole derivatives 152–167 (Table 1). The dicarbohydrazide 168 was reacted with carbon disulfide and ethanolic KOH to obtain the corresponding oxadiazole derivative 169 in 48% yield (Scheme 45).<sup>124</sup>

Table 1. Synthesis of Oxadiazoles 152–167 from Acid Hydrazides and Carbon Disulfide<sup>1</sup>

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>R</th>
<th>Product</th>
<th>Ref.</th>
<th>Yield %</th>
<th>Sl. No.</th>
<th>R</th>
<th>Product</th>
<th>Ref.</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R₁</td>
<td><img src="image1.png" alt="Image" /></td>
<td>34</td>
<td>61-68</td>
<td>9</td>
<td><img src="image2.png" alt="Image" /></td>
<td>116</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Image" /></td>
<td>103</td>
<td>83.3</td>
<td>69</td>
<td>10</td>
<td><img src="image4.png" alt="Image" /></td>
<td>117</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="Image" /></td>
<td>104</td>
<td>59</td>
<td></td>
<td>11</td>
<td><img src="image6.png" alt="Image" /></td>
<td>118</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="Image" /></td>
<td>105</td>
<td>83</td>
<td>70</td>
<td>12</td>
<td><img src="image8.png" alt="Image" /></td>
<td>119</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td><img src="image9.png" alt="Image" /></td>
<td>112</td>
<td>65-68</td>
<td>70-84</td>
<td>13</td>
<td><img src="image10.png" alt="Image" /></td>
<td>120</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td><img src="image11.png" alt="Image" /></td>
<td>113</td>
<td>71</td>
<td></td>
<td>14</td>
<td><img src="image12.png" alt="Image" /></td>
<td>121</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td><img src="image13.png" alt="Image" /></td>
<td>114</td>
<td>74</td>
<td></td>
<td>15</td>
<td><img src="image14.png" alt="Image" /></td>
<td>122, 123</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td><img src="image15.png" alt="Image" /></td>
<td>115</td>
<td>60</td>
<td></td>
<td>16</td>
<td><img src="image16.png" alt="Image" /></td>
<td>108</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup>(i) CS₂, alcoholic KOH, or NaOH.
The dipotassium salt of galactaric acid bis-hydrazidocarbodithioic acid 171, obtained on condensation of galactaric acid bis-hydrazide 170 with carbon disulfide in the presence of ethanolic potassium hydroxide at ambient temperature, underwent base-catalyzed dehydrosulfurative cyclization on heating with ethanolic potassium hydroxide to form 82% of 1,4-bis(5-thioxo-1,3,4-oxadiazolin-2-yl)-galacto-tetritol structure 172 (Scheme 46).125

2,5-Diaryl-1,3,4-oxadiazoles 173, obtained in 39–53% yields, were synthesized by refluxing the hydrazides 145 with trimethyl orthobenzoate (Scheme 47).126

Thermal cyclodehydration of hydrazide 1,4-bis(4-aryl)-hydrazide 174 in N-cyclohexyl-2-pyrolidone (CHP) yielded the oxadiazole-containing monomer, 2,5-bis(aryl)-1,3,4-oxadiazoles 175, with 70–88% yields (Scheme 48).127

Cyclization of hydrazides 176 in dry DMF at 0 °C containing triethylamine followed by addition of 1,1’-carbodiimidazole (CDI) afforded the N-boc-protected benzylamine oxadiazole intermediates 177. The final N-boc deprotection in the presence of 4 M HCl afforded the [1,3,4]oxadiazol-2-one benzylamine building blocks 178 in 88–91% yields (Scheme 49).128

Schiﬄs bases 180 underwent cyclization in the presence of iodobenzene diacetate (IBD) to yield 70–75% of oxadiazoles 181 (Scheme 50).129

A group of researchers have utilized triethylorthoformate to synthesize oxadiazole derivatives. Indole carbohydrazide 141 was heated with triethylorthoformate to form 69% of oxadiazole derivative 182 (Scheme 51).131 Similarly, reaction of 183 with triethylorthoformate underwent smooth cyclization to yield 82% of 4-amino-5-benzoyl-3-oxdiazolo[1,3,4]isoxazole 184 (Scheme 51).130
One-pot solvent-free synthesis of 1,3,4-oxadiazoles 185 by condensation of acid hydrazide and triethyl orthoalkanes under microwave irradiation was reported by Varma et al.131 (Scheme S2). This green protocol was catalyzed efficiently by solid sodium trifluoromethanesulfonate (Scheme S2).

**Scheme S2**

```
R + H, F, OMe R₁ + H, Et, Ph
```

*(i) NaFon NRS0, MWI.

A group of researchers used cyanogen bromide as a source of nitrogen as in conjugated polymers with oxadiazole structures to electroluminescence. Hence, recently, there has been much study on applying conjugated polymers with oxadiazole structures to eletrooptics. Various conjugated polymers with 1,3,4-oxadiazole structures show diverse characteristics such as thermal and chemical stability in addition to mechanical strength and rigidity, allowing them to be used in carbon fibers, high-performance fibers, reinforcing materials, and gas separation membranes.145,146 It is understood that oxadiazole shows such characteristics because its structures resemble the characteristics of phenyl structures.147

Sureshbabu et al.134 reported the synthesis of S-linked 1,3,4-oxadiazole-tethered N°-protected peptidomimetics under sonication using acid hydrazides as synthetic precursor.

A group of researchers used cyanogen bromide as a source of single carbon for synthesis of the amino oxadiazole derivatives (Schemes 55 and 56). Treatment of hydrazide 143 with cyanogen bromide at 80–85 °C produced oxadiazole 188 in 73% yield (Scheme S5).115 Similarly, 2-oxo-2H-chromen-4-yl acetohydrazide when treated with cyanogen bromide generated the amino oxadiazole derivative 189 in 78–87% yields (Scheme S6).135 Kagthara and co-workers also utilized cyanogen bromide for condensation of benzoyl hydrazide 14 to form 90% of 1,3,4-oxadiazoles.39

A series of 1,3,4-oxadiazole derivatives was formed from condensation of acid hydrazides with aromatic acids in phosphorus oxychloride (Table 2).

Adapting a similar procedure, Husain et al.142 also reported the synthesis of 1,3,4-oxadiazole derivatives from acid hydrazides. Schwarz and co-workers143 reported the synthesis of oxadiazole from acyl hydrazides 190. When POCl₃ was employed in refluxing acetonitrile to effect cyclodehydration of 190a, smooth conversion to a new heteroaromatic product was observed, which was considered to be either compound 194a or 192, via a second dehydration. Two mechanistic possibilities for double dehydration of 190a were considered (Scheme S7). In scenario A, cyclodehydration to an hydrazido-oxazole 191 would be followed by attack of the carbonyl and dehydration to afford 1H-pyrazolo[4,3-d]oxazole 192, which is ruled out.144 However, scenario B proceeded through formation of the oxadiazole amide 193a, and subsequent dehydration of this intermediate by POCl₃ afforded exclusively imidazo[5,1-b][1,3,4]oxadiazole 194a in 76% isolated yield. Following the same path, imidazo[5,1-b][1,3,4]oxadiazole 194b was obtained in 73% yield. In addition, when 2-methylalanine was employed as the core subunit in acyclic precursor 195 only the oxadiazole amide 196 was obtained in 65% yield as cyclodehydration to the imidazo-oxadiazole was precluded by the presence of a quaternary carbon atom (Scheme S8).143 Similarly, methylation of the amide nitrogen as in 197 afforded a substrate unable to participate in the second dehydration event, resulting in exclusive formation of 32% of 198.

Various conjugated polymers with 1,3,4-oxadiazole structures show diverse characteristics such as thermal and chemical stability in addition to mechanical strength and rigidity, allowing them to be used in carbon fibers, high-performance fibers, reinforcing materials, and gas separation membranes.145,146 It is understood that oxadiazole shows such characteristics because its structures resemble the characteristics of phenyl structures.147

Sureshbabu et al.134 reported the synthesis of S-linked 1,3,4-oxadiazole-tethered N°-protected peptidomimetics under sonication using acid hydrazides as synthetic precursor.

A group of researchers used cyanogen bromide as a source of single carbon for synthesis of the amino oxadiazole derivatives (Schemes 55 and 56). Treatment of hydrazide 143 with cyanogen bromide at 80–85 °C produced oxadiazole 188 in 73% yield (Scheme S5).115 Similarly, 2-oxo-2H-chromen-4-yl acetohydrazide when treated with cyanogen bromide generated the amino oxadiazole derivative 189 in 78–87% yields (Scheme S6).135 Kagthara and co-workers also utilized cyanogen bromide for condensation of benzoyl hydrazide 14 to form 90% of 1,3,4-oxadiazoles.39

A series of 1,3,4-oxadiazole derivatives was formed from condensation of acid hydrazides with aromatic acids in phosphorus oxychloride (Table 2).

Adapting a similar procedure, Husain et al.142 also reported the synthesis of 1,3,4-oxadiazole derivatives from acid hydrazides. Schwarz and co-workers143 reported the synthesis of oxadiazole from acyl hydrazides 190. When POCl₃ was employed in refluxing acetonitrile to effect cyclodehydration of 190a, smooth conversion to a new heteroaromatic product was observed, which was considered to be either compound 194a or 192, via a second dehydration. Two mechanistic possibilities for double dehydration of 190a were considered (Scheme S7). In scenario A, cyclodehydration to an hydrazido-oxazole 191 would be followed by attack of the carbonyl and dehydration to afford 1H-pyrazolo[4,3-d]oxazole 192, which is ruled out.144 However, scenario B proceeded through formation of the oxadiazole amide 193a, and subsequent dehydration of this intermediate by POCl₃ afforded exclusively imidazo[5,1-b][1,3,4]oxadiazole 194a in 76% isolated yield. Following the same path, imidazo[5,1-b][1,3,4]oxadiazole 194b was obtained in 73% yield. In addition, when 2-methylalanine was employed as the core subunit in acyclic precursor 195 only the oxadiazole amide 196 was obtained in 65% yield as cyclodehydration to the imidazo-oxadiazole was precluded by the presence of a quaternary carbon atom (Scheme S8).143 Similarly, methylation of the amide nitrogen as in 197 afforded a substrate unable to participate in the second dehydration event, resulting in exclusive formation of 32% of 198.

Various conjugated polymers with 1,3,4-oxadiazole structures show diverse characteristics such as thermal and chemical stability in addition to mechanical strength and rigidity, allowing them to be used in carbon fibers, high-performance fibers, reinforcing materials, and gas separation membranes.145,146 It is understood that oxadiazole shows such characteristics because its structures resemble the characteristics of phenyl structures.147 Hence, recently, there has been much study on applying conjugated polymers with oxadiazole structures to eletrooptics. Specifically, related to development of the multilevel structure of OLED (ITO/HTL/EL/ETL/metal) it is studied and developed widely as ETL.148 In view of this, Lee et al.149 synthesized oxadiazole polymer 202 (80% yield) with bipyridyl groups via thermal dehydrative cyclization of precursor polymer 201 using phosphorus oxychloride, which have an n-type semiconducting property due to electron deficiency and chelating efficiency because of the bipyridine scaffold (Scheme S9).

1-(5-Chloro-2-methoxyphenyl)-5-methyl-1H-pyrazole-4-carboxyhydrazide 203 on reaction with proper substituted benzoyl chlorides in the presence of pyridine yielded compounds 204, 205, and 206.
which when heated with phosphorus oxychloride gave the respective oxadiazoles 205 in 66–80% yields (Scheme 60).150

N’-(2-Cyano-3-(2,4-dichlorophenyl)acryloyl)benzohydrazide underwent ring closure upon refluxing with phosphorus oxychloride to give the oxadiazole derivative 206 in 75% yield (Scheme 61).151

Condensation of hydrazinoisonicotinic acid hydrazide 144 with p-fluorobenzaldehyde yielded the benzylidene derivative 207, which on further treatment with anhydrous sodium acetate in refluxing glacial acetic acid gave oxadiazole 208 in 85% yield. Acetylation of 208 with acetic anhydride afforded 70% of the oxadiazole derivative 209. On the other hand, treatment of compound 207 with acetic acid in the presence of sodium acetate and bromine gave oxadiazole 210 in 85% yield (Scheme 62).116

Dehydrative ring closure of the intermediate 211 with thionyl chloride furnished the corresponding oxadiazole derivatives 212 in 28–30% yield (Scheme 63).106

Table 2. Synthesis of 1,3,4-Oxadiazoles from Acid Hydrazides and Aromatic Acids

<table>
<thead>
<tr>
<th>SL. No.</th>
<th>Hydrazide</th>
<th>Aromatic acids</th>
<th>Product</th>
<th>Ref</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>ROOCH</td>
<td>R</td>
<td>136</td>
<td>59-74</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>ROOCH</td>
<td>R</td>
<td>39</td>
<td>68-79</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>PhCOOH</td>
<td>R</td>
<td>105</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Ar = 4-OC6H4</td>
<td>R</td>
<td>137</td>
<td>66-80</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>ROOCH</td>
<td>R</td>
<td>138</td>
<td>81-87</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>ROOCH</td>
<td>R</td>
<td>139</td>
<td>63-89</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>Ar = 4-OC6H4</td>
<td>R</td>
<td>140</td>
<td>70-81</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>Me</td>
<td>R</td>
<td>141</td>
<td>65</td>
</tr>
</tbody>
</table>

哪有 phosphorus oxychloride 蒸发的 respective oxadiazoles 205 in 66–80% yields (Scheme 60).150

N’-(2-Cyano-3-(2,4-dichlorophenyl)acryloyl)benzohydrazide underwent ring closure upon refluxing with phosphorus oxychloride to give the oxadiazole derivative 206 in 75% yield (Scheme 61).151

Condensation of hydrazinoisonicotinic acid hydrazide 144 with p-fluorobenzaldehyde yielded the benzylidene derivative 207, which on further treatment with anhydrous sodium acetate in refluxing glacial acetic acid gave oxadiazole 208 in 85% yield. Acetylation of 208 with acetic anhydride afforded 70% of the oxadiazole derivative 209. On the other hand, treatment of compound 207 with acetic acid in the presence of sodium acetate and bromine gave oxadiazole 210 in 85% yield (Scheme 62).116

Dehydrative ring closure of the intermediate 211 with thionyl chloride furnished the corresponding oxadiazole derivatives 212 in 28–30% yield (Scheme 63).106

Table 2. Synthesis of 1,3,4-Oxadiazoles from Acid Hydrazides and Aromatic Acids

<table>
<thead>
<tr>
<th>SL. No.</th>
<th>Hydrazide</th>
<th>Aromatic acids</th>
<th>Product</th>
<th>Ref</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>ROOCH</td>
<td>R</td>
<td>136</td>
<td>59-74</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>ROOCH</td>
<td>R</td>
<td>39</td>
<td>68-79</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>PhCOOH</td>
<td>R</td>
<td>105</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Ar = 4-OC6H4</td>
<td>R</td>
<td>137</td>
<td>66-80</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>ROOCH</td>
<td>R</td>
<td>138</td>
<td>81-87</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>ROOCH</td>
<td>R</td>
<td>139</td>
<td>63-89</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>Ar = 4-OC6H4</td>
<td>R</td>
<td>140</td>
<td>70-81</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>Me</td>
<td>R</td>
<td>141</td>
<td>65</td>
</tr>
</tbody>
</table>
Treatment of the hydrazide 183 with ethyloxalyl chloride in the presence of anhydrous pyridine produced the corresponding ethyl{2-[(4-amino-5-benzoylisoxazol-3-yl)carbonyl]hydrazine}(oxo)acetate 213, which was readily cyclized to ethyl-5-(4-amino-5-benzoylisoxazol-3-yl)[1,3,4]oxadiazole-2-carboxylate (68% yield) under acidic conditions with thionyl chloride (Scheme 64).154

Badri et al.155 reported an efficient, one-pot, solution-phase preparation of 2,5-disubstituted-1,3,4-oxadiazoles 219 (60–81% yields) directly from the acyl hydrazide and aromatic aldehydes using 1,4-bis(triphenylphosphonium)-2-butene peroxodisulfate as an oxidant under nonaqueous and aprotic conditions (Scheme 66).

The two enantiomers of N-protected hydrazides of phenylglycine 220 were subjected to heating with an excess of triethyl orthoesters (R3 = H, Me, Et, Ph) to yield the acyclic derivatives of 1-(alkanecarbonyl)-2-ethoxymethylenehydrazines 221 as the only products. Introduction of an acidic solvent (glacial acetic acid) to the reaction mixture resulted in formation of 2,5-disubstituted-1,3,4-oxadiazoles 222 in low to moderate yields (38–80%) (Scheme 67).156

Kulikov and co-workers157 reported the synthesis of 4-amino1,2,5-oxadiazole 226 on treatment of potassium salt of dinitroacetic acid hydrazide 223 with N2O4 via intermediate formation of azidocarbonyl-formonitrile oxide and diazide 225. The low-yield diazide 225 underwent Curtius rearrangement of one of two azidocarbonyl groups to give a low yield of amino 1,2,5-oxadiazole 226 (16%) (Scheme 68).

Use of hydrazides as amine components in the Petasis 3-component coupling reaction (CCR) had been investigated by...
Hydrazido alcohols 227 were obtained from reaction of hydrazides, boronic acids, and hydroxaldehyde. The resulting hydrazido alcohols 227 were selectively converted into oxazolidinone 228 and oxadiazolone 229 ring systems 229 via triphosgene-mediated cyclization processes by slow addition of 1 equiv of bis(trichloromethyl)carbonate (BTC) and fast addition of a large excess of BTC, respectively.

### 3.3.2. Thiadiazoles and Their Fused Derivatives

Thiadiazoles are a class of heterocycles which have attracted significant interest in medicinal chemistry, and they have a wide range of pharmaceutical and biological activities including antibacterial,159−162 antifungal,161,162 antitubercular,163−165 analgesic,166 antiinflammatory,161,162,166 and leishmanicidal167 agents.

4-Bromobenzoyl isothiocyanate on treatment with aryloxyacetic acid hydrazides 115 gave 1,4-disubstituted thiosemicarbazides 230, which when refluxed with glacial acetic acid underwent intramolecular dehydrative cyclization to afford the corresponding substituted 1,3,4-thiadiazoles 231 in 90−97% yields (Scheme 69).

The diacyl hydrazide 136 underwent cyclization upon treatment with Lawesson’s reagent, i.e., 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-phosphetene-2,4-disulfide, to yield methyl 1,3,4-thiadiazole-2-carboxylates, which underwent subsequent addition of the requisite side chain (R1) to the methyl ester via a metal−halogen exchange of the corresponding alkylbromide to give the α-ketothiadiazoles 232 in low to moderate yields (Scheme 70).

### Chemical Reviews

**Table 3. BTC-Mediated Oxadiazolone and Oxazolidinone Formation**

<table>
<thead>
<tr>
<th>entry</th>
<th>R1</th>
<th>R2</th>
<th>Oxadiazolone product (yield %)*</th>
<th>Oxazolidinone product (yield %)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>H</td>
<td>85</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Ph</td>
<td>86</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>MeO</td>
<td>Ph</td>
<td>87</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>MeO</td>
<td>MeO</td>
<td>88</td>
<td>88</td>
</tr>
</tbody>
</table>

*Isolated yield after flash column chromatography.

The diacyl hydrazide 136 underwent cyclization upon treatment with Lawesson’s reagent, i.e., 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-phosphetene-2,4-disulfide, to yield methyl 1,3,4-thiadiazole-2-carboxylates, which underwent subsequent addition of the requisite side chain (R1) to the methyl ester via a metal−halogen exchange of the corresponding alkylbromide to give the α-ketothiadiazoles 232 in low to moderate yields (Scheme 70).

### Scheme 70a

*Lawesson’s reagent; (ii) R1Li or R1MgBr.

2-(3-Chloro-1-benzo[2-γ]-1,3,4-thiadiazole 233 was obtained in 53% yield on treatment of 3-chloro-2-(N-formyl acid hydrazide)benzo[b]thiophene 121 with phosphorus pentasulphide under refluxing xylene solution (Scheme 71).

### Scheme 71a

*P2S5, xylene, reflux.

Refluxing acetylhydrazine 124 with phosphorus pentasulphide in toluene formed 1,3,4-thiadiazole 234 in 61% yield, while dehydrocyclization of thiosemicarbazide 235 with phosphoryl trichloride gave the thiadiazole 236 with 53−54% yields (Scheme 72).

### Scheme 72a

*P2S5, toluene; (ii) POCl3.

Refluxing terephthalic acid hydrazide 237 with phenyl/benzyl isothiocyanate in DMF in the presence of sodium hydride and concentrated hydrochloric acid formed nonisolable intermediate 238, which was subsequently refluxed with phosphoryl chloride to give bis-thiadiazoles 239 with yields as follows: Ar = Ph (87%) and PhCH2 (92%) (Scheme 73).

Dipotassium salt of galactaric acid bis-hydrazidocarbodithioic acid 171 underwent acid-catalyzed dehydrocyclization with...
sulfuric acid in methanol at room temperature to give 1,4-bis(5-thioxo-1,3,4-thiadiazolin-2-yl)-galacto-tetritol 240 (82% yield) (Scheme 74).125

1,3,4-Thiadiazoles 243 were obtained in 47–93% yields by cyclization of thiosemicarbazides 242 with orthophosphoric acid (Scheme 75).170

Hydrazide 146, when heated with either ammonium thiocyanate or potassium thiocyanate, afforded the 4-methyl-9,10-diphenylpyrazido-[3′,4′,3,4]-pyrazol[5,1-c]-1,2,4-triazine-3-carbothiosemicarbazide 244. The cyclodehydration of 244 in the presence of acetyl chloride led to formation of 2-acetylamino-1,3,4-thiadiazole derivative 245 in 57% yield (Scheme 76).118 Similarly, Para et al.171 also reported the synthesis of different amino-1,3,4-thiadiazoles from different 3,4,5-n-trialkoxynbenzoylthiosemicarbazides in the presence of acetyl chloride.

Condensation of acetyl isothiocyanate with hydrazide 2 gave thiocarbamoyl derivative 261, which underwent intramolecular cyclization in refluxing acetic acid to produce 55% of N-[5-(cyanomethyl)-1,3,4-thiadiazol-2-yl]acetamide 262 (Scheme 77).176

N-Acetyl derivative 133 of pyridazinyl-2-acetylderivative hydrazide 132 on reaction with phosphorus pentasulfide afforded thiadiazolo compound 263 with 26–30% yields along with other compounds.

**Scheme 73**

![Scheme 73](image)

"(i) NaH/DMF, conc HCl; (ii) POCl3.

**Scheme 74**

![Scheme 74](image)

"(i) CS2, EtOH/KOH; (ii) H2SO4/MeOH.

**Scheme 75**

![Scheme 75](image)

"(i) H3PO4.

**Scheme 76**

![Scheme 76](image)

"(i) NH2SCN or KSCN; (ii) AcCl.

**Scheme 77**

![Scheme 77](image)

"(i) AcOH.

**Table 4. Synthesis of 1,3,4-Thiadiazoles 254–260 by Dehydrative Cyclization of Thiosemicarbazides**

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Ar</th>
<th>Product</th>
<th>Ref.</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
<td><img src="image" alt="Image" /></td>
<td></td>
<td>54-98</td>
</tr>
<tr>
<td>2.</td>
<td><img src="image" alt="Image" /></td>
<td><img src="image" alt="Image" /></td>
<td></td>
<td>59-72</td>
</tr>
<tr>
<td>3.</td>
<td><img src="image" alt="Image" /></td>
<td><img src="image" alt="Image" /></td>
<td></td>
<td>70-75</td>
</tr>
<tr>
<td>4.</td>
<td><img src="image" alt="Image" /></td>
<td><img src="image" alt="Image" /></td>
<td></td>
<td>80-97</td>
</tr>
<tr>
<td>5.</td>
<td><img src="image" alt="Image" /></td>
<td><img src="image" alt="Image" /></td>
<td></td>
<td>84-97</td>
</tr>
<tr>
<td>6.</td>
<td><img src="image" alt="Image" /></td>
<td><img src="image" alt="Image" /></td>
<td></td>
<td>97-97</td>
</tr>
<tr>
<td>7.</td>
<td><img src="image" alt="Image" /></td>
<td><img src="image" alt="Image" /></td>
<td></td>
<td>98-98</td>
</tr>
</tbody>
</table>
with oxadiazolo derivative 134 as a minor product. Similarly, the intermediate 211 when treated with phosphorus pentasulphide furnished 30–35% of thiadiazoles 264 along with oxadiazolo derivative 212 as a minor product. On the other hand, treatment of hydrazide 132 with formic acid yielded 265, which on dehydrative ring closure by treatment with phosphorus pentasulphide in xylene afforded thiadiazole derivative 266 in low yields (23–25%) (Scheme 78).106

Scheme 78**

**(i) P$_2$S$_5$, xylene; (ii) HCOOH.

3.3.3. Triazoles and Their Fused Derivatives. 1,2,4-Triazoles and their derivatives represent an interesting class of compounds possessing a wide spectrum of biological activities. A large number of 1,2,4-triazole-containing ring systems exhibit antibacterial,177–182 antifungal,179–183 antitubercular,184–186 antinflammatory,189–191 anticancer,192,193 anticonvulsant,194,195 antiviral,196,197 insecticide,198 antidepressant,199 and central nervous system (CNS)195 activities. Moreover, there are a number of antimicrobial compounds containing a 1,2,4-triazole ring in their structures such as Fluconazole, Itraconazole, Voriconazole, Ravuconazole, and Posaconazole that are important antifungal drugs.200

Reaction of 2-nitrobenzylamine with 1,1′-carbonyldiimidazole and benzhydrazide formed the 1-benzoyl-4-(2-aminobenzyl)semicarbazide. Catalytic hydrogenation of the nitro group in the presence of 10% palladium on charcoal gave the corresponding 1-benzoyl-4-(2-amino benzyl)semicarbazide derivative 267. Cyclization of amino derivative 267 in 5% potassium carbonate led to formation of 75% of 4-(2-amino benzyl)-3-phenyl-4,5-dihydro[1,2,4]triazol-5-one (Scheme 79).201

3-Ethylsulfanyl-5-cyanomethyl-4-phenyl-1,2,4-triazole 269 was prepared in 90% yield by reaction of 1-cyanoacetyl-4-phenylthiocarbazide with ethyl iodide in DMF and in the presence of anhydrous potassium carbonate at room temperature (Scheme 80).202

Scheme 79**

**(i) H$_2$/Pd; (ii) K$_2$CO$_3$.

Scheme 80**

**(i) EtI, K$_2$CO$_3$/DMF.

Scheme 81**

**(i) AcONa, AcOH.

Francis et al.37 studied the synthesis of 3-(2-amino-5-chlorophenyl)-5-phenyl-1,2,4-triazole 271 (62% yield) on reaction of 2-amino-5-chlorobenzohydrazide 9 with benzamide (Scheme 82).

Scheme 82**

**(i) PhCl, EtOH, reflux.

Reaction of acid hydrazide 4, 103, 108, 112, 118, 123, 139, 247, 249, and 272–278 with isothiocyanate derivatives resulted in formation of the corresponding thiosemicarbazides 279, 104, 107, 113, 119, 280, 281, 251, 253, and 282–288. Alkaline cyclization of the thiosemicarbazides using sodium hydroxide afforded the 1,2,4-triazolin-3-thiones 289–304 (Table 5).

Hydrazide 2 treated with different ethoxycarbonylhydrazones 305 to generate respective 3-alkyl-4-carboxethyamino-5-cyano methyl-4H-1,2,4-triazole derivatives 306 in 58–73% yields (Scheme 83).212

Reaction of 2 with lactim ether produced 89% of 1-cyanomethyl-4H,5,6-dihydro-1,2,4-triazolo[4,3-α]-benz[f] azepine 308 (Scheme 84).213

Hydrazinolysis of 1,3,4-oxadiazole 111 moiety 154 yielded 48% of 4-amino-4H,1,2,4-triazole-3-thiol structure 309 (Scheme 85).104 A series of 1,2,4-triazole derivatives prepared following a similar procedure was reported by Mohan 214 Dhiman,215 Mostafa,216 Demirbaş,217 Seleim,218 and Vainilavicius et al.219

Reaction of terephthalic acid hydrazide 237 with phenyl/ benzyl isothiocyanate and phenyl isocyanate in DMF in the presence of sodium hydride gave the nonsoluble intermediates

dx.doi.org/10.1021/cr300122t Chem. Rev. 2014, 114, 2942–2977
Table 5. Synthesis of 1,2,4-Triazolin-3-thiones 289–304 by Alkaline Cyclization of Thiosemicarbazides

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Ar</th>
<th>Product</th>
<th>Yield</th>
<th>Ref.</th>
<th>Sl. No.</th>
<th>Ar</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
<td>289</td>
<td>32 48</td>
<td></td>
<td>9.</td>
<td></td>
<td>297</td>
<td>175 94-99</td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td>290</td>
<td>98 67-90</td>
<td></td>
<td>10.</td>
<td></td>
<td>272</td>
<td>203 70-85</td>
</tr>
<tr>
<td>3.</td>
<td></td>
<td>291</td>
<td>34 53-64</td>
<td></td>
<td>11.</td>
<td></td>
<td>298</td>
<td>204 2 89-92</td>
</tr>
<tr>
<td>4.</td>
<td></td>
<td>292</td>
<td>101 63</td>
<td></td>
<td>12.</td>
<td></td>
<td>299</td>
<td>205 05 89-92</td>
</tr>
<tr>
<td>5.</td>
<td></td>
<td>301</td>
<td>103 85-90</td>
<td></td>
<td>13.</td>
<td></td>
<td>300</td>
<td>206 67-85</td>
</tr>
<tr>
<td>6.</td>
<td></td>
<td>294</td>
<td>104 61-71</td>
<td></td>
<td>14.</td>
<td></td>
<td>302</td>
<td>207 91-98</td>
</tr>
<tr>
<td>7.</td>
<td></td>
<td>295</td>
<td>33 83</td>
<td></td>
<td>15.</td>
<td></td>
<td>276</td>
<td>208 76-87</td>
</tr>
<tr>
<td>8.</td>
<td></td>
<td>296</td>
<td>173 60</td>
<td></td>
<td>16.</td>
<td></td>
<td>270</td>
<td>209 70</td>
</tr>
</tbody>
</table>

Scheme 83

\[ \text{NHCOEi} + \text{NCOEi} \rightarrow \text{NHCOEi} \]

Scheme 84

\[ \text{N} + \text{O} \rightarrow \text{N} \]

Scheme 85a

a(i) CS2, alcholic KOH.

238 and 312, respectively, which upon cyclization with NaOH furnished the corresponding bis-1,2,4-triazoles 310 and 5,5’- (1,4-phenylene)bis(4-phenyl-3-oxo-1,2,4-triazole) 313 in 65–69% and 64% yields, respectively. Furthermore, reaction of 238 with ethyl iodide at room temperature catalyzed by anhydrous
Potassium carbonate yielded 58–62% of the triazole product 311 (Scheme 86).169

Refluxing hydrazide 49 in acetic acid initially produced 1,3,4-thiadiazole derivative 314, which underwent ring opening under the prevailing reaction conditions and then ring closing of the intermediate 315 to afford the 1,2,4-triazole thione 316 in 86% yield (Scheme 87).67

Three-component condensation reaction of acid hydrazides, S-methyl isothioamide hydroiodides 317, and ammonium acetate on the surface of silica gel under microwave irradiation gave the corresponding 3,5-disubstituted-1,2,4-triazoles 318 in 66–91% yields (Scheme 88).220

Condensative cyclization with concomitant dehydrosulfuration and dehydration of the salt of galactaric acid bis-hydrazidocarbodithioic acid 171 has been accomplished by heating with ammonium acetate to give 71% of the 1,4-bis(5-thioxo-1,2,4-triazolin-3-yl)-galacto-tetritol 320b (77% yield) were achieved on heterocyclization of the dithioate 171 with acetamide and methylamine, respectively (Scheme 89).125

The thiosemicarbazide 244 was cyclized under a basic condition to produce the 1,2,4-triazole-3-thione derivative 321 in 83% yield (Scheme 90).118 A series of 1,2,4-triazole derivatives following a similar procedure was reported by Mohan214 and Zhang et al.136

Reaction of thiosemicarbazides 242 with triethylamine in ethanol underwent smooth cyclization through dehydration to afford 1,2,4-triazole-5(4H)-thione 322 in 82–97% yields (Scheme 91).170

Condensation of 3,4,5,6-tetrahydro-7-methoxy-2H-azepine 323 with diethoxycarbonyl acetic acid hydrazide in methylene chloride at room temperature provided the amidrazone 324. Subsequently, the Horner–Emmons reaction was carried out with benzaldehyde in NaOEt/EtOH at room temperature to give 3-phenyl-N′-(4,5,6,7-tetrahydro-3H-azepin-2-yl)acrylhydrazide 325. Cyclodehydration of 325 was accomplished in refluxing toluene with a catalytic amount of acetic acid to afford trans-3-styryl-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepine 326 in 71% yield (Scheme 92).221

Condensative cyclization with concomitant dehydrosulfuration and dehydration of the salt of galactaric acid bis-hydrazidocarbodithioic acid 171 has been accomplished by heating with ammonium acetate to give 71% of the 1,4-bis(5-thioxo-1,2,4-triazolin-3-yl)-galacto-tetritol 320b (77% yield) were achieved on heterocyclization of the dithioate 171 with acetamide and methylamine, respectively (Scheme 89).125

The thiosemicarbazide 244 was cyclized under a basic condition to produce the 1,2,4-triazole-3-thione derivative 321 in 83% yield (Scheme 90).118 A series of 1,2,4-triazole derivatives following a similar procedure was reported by Mohan214 and Zhang et al.136

Reaction of thiosemicarbazides 242 with triethylamine in ethanol underwent smooth cyclization through dehydration to afford 1,2,4-triazole-5(4H)-thione 322 in 82–97% yields (Scheme 91).170

Condensation of 3,4,5,6-tetrahydro-7-methoxy-2H-azepine 323 with diethoxycarbonyl acetic acid hydrazide in methylene chloride at room temperature provided the amidrazone 324. Subsequently, the Horner–Emmons reaction was carried out with benzaldehyde in NaOEt/EtOH at room temperature to give 3-phenyl-N′-(4,5,6,7-tetrahydro-3H-azepin-2-yl)acrylhydrazide 325. Cyclodehydration of 325 was accomplished in refluxing toluene with a catalytic amount of acetic acid to afford trans-3-styryl-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepine 326 in 71% yield (Scheme 92).221

Compound 327 was reacted with cyanoacetic acid hydrazide to obtain the corresponding 3-alkyl-4-tert-butoxycarbonylamino-
5-cyanomethyl-1H-1,2,4-triazoles 329 in 37–81% yields via the intermediates 328. Compounds 329 were converted to the corresponding 3-alkyl-4-amino-5-cyanomethyl-1H-1,2,4-triazole hydrochlorides 330 in good yields in the presence of 6 N HCl, which on further treatment with 2 N KOH led to formation of 3-alkyl-4-amino-5-cyanomethyl-1H-1,2,4-triazoles 331 (44–79% yields) (Scheme 93).

Treatment of hydrazone 332 of N-triazino-2-acetic acid hydrazide 69 with FeCl₃–ethanol afforded 1,3,4-oxadiazole 333, which on condensation with phenylhydrazine through ANRORC (addition of the nucleophile, ring opening, and ring closure) gave 65% of 1,2,4-triazole 334 (Scheme 94).

The intermediate acylamidrazones 336 were obtained from reactions of acetamidine or benzamidine 335 with an malonodihydrazide 100b or terephthalobishydrazide 237 in the presence of sodium ethoxide and underwent thermal cyclization to form the corresponding 1,2,4-triazoles 337 in moderate to high yields (R₁, R₂ = Me, CH₂ (92%); Me, Ph (89%); Ph, CH₂ (93%); Ph, Ph (88%)) (Scheme 95).

[1,2,4]Triazolo[2,3-a]isoquinoline derivative 339 was obtained as the sole product in fairly good yield (80%) upon treatment of compound 338 with semicarbazide hydrochloride (Scheme 96) via nucleophilic ring opening and nitrogen attack at the carbonyl group of the δ-lactone (tetrahedral mechanism) followed by 1,5-exo-trig cyclization with elimination of water.

Hydrazides 343 underwent the standard combinatorial transformations including cyclo-α-methyl amide coupling with 344 in refluxing 2-propanol to form 1,2,4-triazoles 345 (Scheme 97) in moderate to good yields.

Hydrazides 343 and orthoesters in ethanol–acetic acid solution had been studied to obtain a series of 4-acylamino-1,2,4-triazoles 349 as the final products in 25–64% yields by Zielinski and co-workers via intermediates 347 and 348 (Scheme 98).

2-Benzothiazolylthioacetyl hydrazide generally when reacted with CS₂ in ethanolic KOH unexpectedly formed s-triazolo[3,4-b]benzothiazole-3-thiol 342 instead of 5-substituted-1,3,4-oxadiazol-2-thiol 340. Alternatively, the authors successfully obtained 342 through the isolated intermediate 2-benzothiazolyldihydrazide 341 generated via intramolecular addition–elimination reaction of the substrate 2-benzothiazolhydrazide in the presence of ethanolic KOH. Hydrazine 341 reacted with KOH and CS₂ further to convert into s-triazolo[3,4-b]-benzothiazole-3-thiol 342 (Scheme 97).

The intermediate acylamidrazones 336 were obtained from reactions of acetamidine or benzamidine 335 with a malonodihydrazide 100b or terephthalobishydrazide 237 in the presence of sodium ethoxide and underwent thermal cyclization to form the corresponding 1,2,4-triazoles 337 in moderate to high yields (R₁, R₂ = Me, CH₂ (92%); Me, Ph (89%); Ph, CH₂ (93%); Ph, Ph (88%)) (Scheme 95).

The intermediate acylamidrazones 336 were obtained from reactions of acetamidine or benzamidine 335 with a malonodihydrazide 100b or terephthalobishydrazide 237 in the presence of sodium ethoxide and underwent thermal cyclization to form the corresponding 1,2,4-triazoles 337 in moderate to high yields (R₁, R₂ = Me, CH₂ (92%); Me, Ph (89%); Ph, CH₂ (93%); Ph, Ph (88%)) (Scheme 95).

Hydrazides 343 underwent the standard combinatorial transformations including cyclo-α-methyl amide coupling with 344 in refluxing 2-propanol to form 1,2,4-triazoles 345 (Scheme 97) in moderate to good yields.

Reaction of α-hydroxyacid hydrazides 346 and orthoesters in ethanol–acetic acid solution had been studied to obtain a series of 4-acylamino-1,2,4-triazoles 349 as the final products in 25–64% yields by Zielinski and co-workers via intermediates 347 and 348 (Scheme 98).

The intermediate acylamidrazones 336 were obtained from reactions of acetamidine or benzamidine 335 with a malonodihydrazide 100b or terephthalobishydrazide 237 in the presence of sodium ethoxide and underwent thermal cyclization to form the corresponding 1,2,4-triazoles 337 in moderate to high yields (R₁, R₂ = Me, CH₂ (92%); Me, Ph (89%); Ph, CH₂ (93%); Ph, Ph (88%)) (Scheme 95).
Quan et al.\textsuperscript{228} incorporated triazole into benzo[\textit{b}][1,4]thiazin-3(4\textit{H})-one\textsuperscript{350} at the third and fourth positions to give compound\textsuperscript{351} (96\% yield) (Scheme 100).

\textbf{Scheme 100}\textsuperscript{a}

\textsuperscript{a}(i) \textit{Cyclohexanol}.

A convenient and efficient one-step, base-catalyzed synthesis of 3,5-disubstituted 1,2,4-triazoles\textsuperscript{353} in 34\texttextordmasquera – 83\% yields by condensation of a nitrile\textsuperscript{352} and a hydrazide was reported by Yeung and co-workers\textsuperscript{229} (Scheme 101).

\textbf{Scheme 101}\textsuperscript{a}

\textsuperscript{a}(i) \textit{K}_2\textit{CO}_3, 150 \textdegree C, MW.

Microwave-assisted organic synthesis (MAOS) condition was employed to obtain 86\texttextordmasquera – 97\% of 1,2,4-triazolo[4,3-\textit{b}]pyridazines\textsuperscript{354} by condensation of 3,6-dichloropyridazine with aryl hydrazides in the presence of a catalytic amount of\textit{AcOH} or\textit{HCl} (Scheme 102).\textsuperscript{230}

Fusion of the hydrazide derivative\textsuperscript{248} with urea (\(X = \textit{O}\)) and/or thiourea (\(X = \textit{S}\))\textsuperscript{355} afforded the corresponding triazolo phthalazines\textsuperscript{356} (yield \(X = \textit{O}\) (43\%) and \(X = \textit{S}\) (51\%)\)), respectively (Scheme 103).\textsuperscript{174}

\textbf{Scheme 103}

\textsuperscript{a}(i) \textit{K}_2\textit{CO}_3, 150 \textdegree C, MW; (ii) \textit{CuI}/\textit{CS}_2\textit{CO}_3, 80 \textdegree C; (iii) \textit{POCl}_3, oil bath (120\texttextordmasquera – 130 \textdegree C), reflux, 3 h.

Patel et al.\textsuperscript{231,232} developed a tandem and convergent approach to nitrogen-containing azoles by exploiting the thiophilic property of copper(I) iodide used in a catalytic quantity (Scheme 105).\textsuperscript{231} Phenyl isothiocyanate in DMSO was treated with aniline and stirred at 80 \textdegree C to generate in situ 1,3-diphenylthiourea. Thiourea underwent oxidative desulfurization upon treatment with CuI/\textit{Cs}_2\textit{CO}_3 to give the intermediate carbodiimide, which undergoes nucleophilic attack by the formic acid hydrazide to give the acylureidrazone intermediate, which on subsequent dehydrative cyclization and aromatization leads to formation of 3-amino [1,2,4]triazoles\textsuperscript{361} in 90\% yield.

\textbf{Scheme 105}\textsuperscript{a}

\textsuperscript{a}(i) \textit{DMSO}, 80 \textdegree C; (ii) \textit{CuI}/\textit{CS}_2\textit{CO}_3, 80 \textdegree C; (iii) \textit{POCl}_3, oil bath, 3 h.

3.4. Synthesis of Six-Membered Rings with One Heteroatom

3.4.1. Pyran and Their Fused Derivatives. Pyrans and their derivatives are of considerable interest due to their pharmacological activities\textsuperscript{239} such as spasmyltic, diuretic,
anticoagulant, anticancer, and antianaphylactic activity. Moreover, pyrans are useful intermediates for synthesis of various compounds. Furthermore, pyrans represent building blocks of a series of natural products, and consequently, numerous methods have been reported for synthesis of these compounds.

Treatment of bisdithiolobenzoquinone 363 with 2 in a 1:2 molar ratio in refluxing ethanol containing piperidine as a catalyst gave 63% of dispiro[di-pyrano-(2,4-′:6,4″)-bidithiolo-(4,5-b:4′,5′-e)-4,8-benzoquinone] derivative 364 (Scheme 107).

Pyrano[2,3-d]-thiazole derivatives 367 was obtained in 86–91% yields from addition of two molecules of 2-cyanomethyl-2-thiazolin-4-one 366a (X = CN) to one molecule of each of the benzylidene derivatives of cyanoacetic acid hydrazide 365 with loss of one molecule of hydrazine. Analogously, 366b (X = CO₂Et) reacted with 365 to give 84–86% of the pyrano[2,3-d]-thiazoles 368 (Scheme 108).

A yield of 78% of 3-Methyl-6-oxo-4-phenyl-1,6-dihydropyran-[2,3-c]pyrazole-5-carbonitrile 369 was prepared via cyclocondensation of 2 with 4-benzylidene-3-methyl-2-pyrazolin-5-one (Scheme 109).

### 3.4.2. Pyridine and Their Fused Derivatives.

The pyridine nucleus is an important heteroaromatic class of compounds with a wide range of activities, and it is present in many drugs, vitamins, food-flavoring agents, plant products, dyes, rubber products, adhesives, insecticides, and herbicides. In view of these findings, it was contemplated to design and synthesize some new pyridine derivatives.

Reaction of N-arylmethylene-2-cyanoacetohydrazides 370 when treated with benzylidenemalononitrile afforded 72% of [1,2,4]triazolo[1,5-a]pyridin-5(3H)-one derivative 371 (Scheme 110).

Anthranilonitrile was fused with different N-aryldienes 370 of cyanoacetohydrazide 2 in the presence of triethylamine to afford triazo[4,3-a]quinoline derivatives 374 in 60–75% yields through the initial Thorpe-Ziegler addition of the methylene group of 370 to the CN group of anthranilonitrile to afford the acyclic intermediates 372 followed by loss of a water molecule to afford the intermediates 373, which in turn undergo further cyclization via addition of the NH to the activated C=N to give the final products 374 (Scheme 111).

Refluxing hydrazone derivative 47 and appropriate arylidenes of activated nitriles in ethanolic piperidine yielded spiro[cyclohexane-1,2-′-[1,2,4]triazolo[1,5-a]pyridine]-5′-(1′H)-one derivatives 375 (Scheme 112).

One-pot synthesis of [1,2,4]triazolo[1,5-a]pyridin-5(1H)-one derivatives 377 was reported in 82–89% yields by reaction of 2 with malononitrile and aromatic aldehyde (Scheme 113). Treatment of 2 with 3-acetyl- and 3-carboethoxycoumarin 378 in ethanol containing a catalytic amount of piperidine under reflux afforded pyrazolo[3,4-b]pyridine-1,6-dione 379 and 380 in 70% and 60% yields, respectively (Scheme 114).
Cyclocondensation of hydrazide 2 with (4-methoxybenzylidene)malononitrile in ethanol in the presence of triethylamine afforded 1-aminopyridine derivative 381, which underwent hydrolysis followed by ring opening and recyclization on refluxing in 95% aqueous ethanol and triethylamine to give 70% of 1,4-diamino-5-cyano-2-(4-methoxyphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid 382 (Scheme 115).²⁵¹

Martin and co-workers reinvestigated cyclocondensation of 2 with (4-methoxybenzylidene)malononitrile either at room or reflux temperature in absolute or 96% ethanol to achieve 1,6-diamino-4-(4-methoxyphenyl)-3,5-dicyano-2-pyridone 383 (Scheme 116).²⁵²

Treatment of 390 with malononitrile gave the pyridine adducts 392 in 78−88% yields via formation of the intermediate 391 (Scheme 121).²⁵⁸ The reaction pathway in later is believed to be through intramolecular cycloaddition of the amidic −NH group to the terminal −C≡N function.

Condensation of 393 with aromatic aldehydes furnished the acrylonitriles 394 (Scheme 122). Treatment of the latter compounds with malononitrile gave the aminopyridine deriv-
tives 395 in 68−72% yields. Further support for the proposed structure 395 was prepared independently through addition of acetonitrile derivative to the activated double bond in benzylidene malononitrile derivatives under Michael reaction conditions (Scheme 122).\textsuperscript{259} Similarly, Mohareb et al.\textsuperscript{260} reported the synthesis of pyridines from α-cyanoacinnamonic acid or ethyl α-cyanoacetate.

Reaction of compound 396 with either acetylacetone or ethyl acetoacetate gave the 6-oxopyridine derivatives (yields X = Me (55%) and OEt (54%)) (Scheme 123).\textsuperscript{261} A similar method was adapted by Abu-Hashem et al.\textsuperscript{262} to prepare pyridine derivatives.

Hydrazides with methyl 2-diazo-3-oxobutanoate was converted into 1,2,4-triazines 398 in the presence of copper(II) acetate as the catalyst followed by treatment with ammonium acetate in acetic acid. Subsequent hetero-Diels−Alder reaction\textsuperscript{263−267} of triazines 398 with norbornadiene gave pyridines 399 in 40−94% yields (Scheme 124).\textsuperscript{268}

A palladium-catalyzed addition of hydrazides to 2-chloropyridine in DMF and a phosphine ligand Josiphos 400 formed 1,2,4-triazolo[4,3-a]pyridines in 47−91% yields, which occurred chemoselectively at the terminal nitrogen atom of the hydrazide, followed by dehydration in acetic acid under microwave irradiation (Scheme 125).\textsuperscript{269}

Interaction of compound 2-cyano-N′-[1-(2,5-dimethoxypyphenyl)]ethylideneacetylhydrazide with ethyl α-cyanoacinnamate derivatives, malononitrile, and ethyl cyanoacetate gave the dihydropyridine derivatives 403, 404, and 405 in 59−81%, 82%, and 77% yields, respectively (Scheme 126).\textsuperscript{270}

3.5. Synthesis of Six-Membered Rings with Two Heteroatoms

3.5.1. Pyridazine and Their Fused Derivatives. The pyridazinone derivatives show wide biological activity. They constitute the pyridazinone class of herbicides, which are carotenoid biosynthesis inhibitors,\textsuperscript{271} and also act as fungicide and insecticides.\textsuperscript{272} Even more important, the pyridazin-3(2\textsubscript{H})-one ring is present in many compounds that possess a variety of pharmacological properties and therefore play the role of a pharmacophore viz. cardiotonic,\textsuperscript{273} antihypertensive,\textsuperscript{274} antinociceptive,\textsuperscript{275} antifungal,\textsuperscript{276} and antiulcer\textsuperscript{277} agents.

Reflexing hydrazone derivatives 406 of indole-2-carboxylic acid hydrazide 275 in acetyl chloride afforded the corresponding indolo[2,3-d]pyridazine derivatives 407 in 76−81% yields. Acetylation of indole-2-carboxylic acid hydrazide 275 in acetic acid afforded 2-acetylhydrazinocarbonylindole 408, which underwent cyclization in POCl\textsubscript{3} to form 43% of indolo[3,2-b]pyridazine derivative 409. On the other hand, reflexing 275 in formic acid afforded the N-formyl derivative 410. By ring closure of 410 upon heating, indolo[3,2-b]pyridazine derivative 411 was obtained in 43% yield (Scheme 127).\textsuperscript{278}

Reaction of 2 with 2-phenyl-1,1,3-tricyano-3-bromopropene in a basic medium gave the nonisolable acyclic intermediate 412, which underwent cyclization via addition of the active methylene to the CN group to afford the 69% of pyrrolo[1,2-b]pyridazine derivative 413 (Scheme 128).\textsuperscript{279}

Reflexing hydrazide 2 with aceanthraquinone in acetic acid produced 414, which when treated with potassium hydroxide was converted into 10,11-dihydro-10-oxo-aceanthryleno[1,2-
One-pot reaction of 2 with biacetyl yielded pyridazin-3-one derivative 417 in quantitative yield (94%) via cyclocondensation of the unisolated hydrazone derivative 416 (Scheme 130). Oxidation of hydrazones 332a, b of N-triazino-2-acetic acid hydrazide 69 using SeO₂ led to formation of arylpyridazine-3(2H)-ones 419 in 90−95% yields. Also, hydrazone 332c underwent cyclization in sodium ethoxide, resulting in formation of pyridazine-3(2H)-one 420 in 78% yield (Scheme 131). Ethynylbenzoates on heating with hydrazine hydrate in ethanol directly led to the cyclization products 422 (67−90%) without intermediate accumulation of hydrazides 421 (Scheme 132). On refluxing, N-amino lactams 422 underwent rearrangement to give a 6-exo product benzopyridazinones 423a and 423b in 65% and 75% yields, respectively. Only lactam 422c with a strong acceptor nitro substituent did not undergo recyclication even under more prolonged heating with KOH (Scheme 132). 3.5.2. Pyrimidine and Their Fused Derivatives. Pyrimidine is a key structural component in life molecules, and its derivatives are considered privileged structures in medicinal chemistry. It is therefore logical to explore the synthesis of pyrimidine heterocycles.

Oxidation of hydrazones 332a, b of N-triazino-2-acetic acid hydrazide 69 using SeO₂ led to formation of arylpyridazine-3(2H)-ones 419 in 90−95% yields. Also, hydrazone 332c underwent cyclization in sodium ethoxide, resulting in formation of pyridazine-3(2H)-one 420 in 78% yield (Scheme 131). Ethynylbenzoates on heating with hydrazine hydrate in ethanol directly led to the cyclization products 422 (67−90%) without intermediate accumulation of hydrazides 421 (Scheme 132). On refluxing, N-amino lactams 422 underwent rearrangement to give a 6-exo product benzopyridazinones 423a and 423b in 65% and 75% yields, respectively. Only lactam 422c with a strong acceptor nitro substituent did not undergo recyclication even under more prolonged heating with KOH (Scheme 132). 3.5.2. Pyrimidine and Their Fused Derivatives. Pyrimidine is a key structural component in life molecules, and its derivatives are considered privileged structures in medicinal chemistry. It is therefore logical to explore the synthesis of pyrimidine heterocycles.

Oxidation of hydrazones 332a, b of N-triazino-2-acetic acid hydrazide 69 using SeO₂ led to formation of arylpyridazine-3(2H)-ones 419 in 90−95% yields. Also, hydrazone 332c underwent cyclization in sodium ethoxide, resulting in formation of pyridazine-3(2H)-one 420 in 78% yield (Scheme 131). Oxidation of hydrazones 332a, b of N-triazino-2-acetic acid hydrazide 69 using SeO₂ led to formation of arylpyridazine-3(2H)-ones 419 in 90−95% yields. Also, hydrazone 332c underwent cyclization in sodium ethoxide, resulting in formation of pyridazine-3(2H)-one 420 in 78% yield (Scheme 131).
carried out in dry tetrahydrofuran, afforded the pyrimidinone derivative 432 in 71% yield. 1-N-Amino-3-cyanobarbituric acid 433 was synthesized in 70% yield by reaction of chlorocarbonylisocyanate with 2 (Scheme 134). 292

Scheme 134<sup>a</sup>

![Scheme 134](image)

<sup>a</sup>(i) Dioxane/TEA.

Reactions of hydrazide 434 with ethyl 2-cyano-3-mercaptop-3-(phenylamino)acrylate under PTC conditions produced 40% of bis[ethyl(4-oxo-3-phenyl-1(H)thieno(2,3'-)pyrimidin-2-ylidene) cyanoacetate 435 via nucleophilic attack of the NH group of the N,S-acetal at the carbonyl carbon with elimination of a hydrazine molecule followed by intramolecular cyclization through elimination of an H2S molecule (Scheme 135). 293

Scheme 135<sup>a</sup>

![Scheme 135](image)

<sup>a</sup>(i) K2CO3, TBAB.

Cinnamoyl isothiocyanate reacts with 2 to give the corresponding cinnamoyl thiourea 436, which underwent cyclization to give the corresponding 1-(5-oxo-4,5-dihydro-1H-pyrazol-3-yl)-6-phenyl-2-thioxotetrahydropyrimidin-4(1H)-one 437 in 60% yield (Scheme 136). 294

Scheme 136<sup>a</sup>

![Scheme 136](image)

<sup>a</sup>(i) NaOEt.

Knoevenagel condensation of salicylaldehyde with cyclopentylidene hydrazide leads to formation of the coumarine imine 441, which on attack by the second molecule of salicylaldehyde generated pyrimidin-4(5H)-one derivative 442 in 70% yield. Base-catalyzed rearrangement of 442 gave the pyrimidin-4(5H)-one derivative 443 in 71% yield (Scheme 138). 296

Scheme 138<sup>a</sup>

![Scheme 138](image)

<sup>a</sup>(i) EtOH, H2O; (ii) piperidine.

Condensation of the anhydride with the hydrazides of arenecarboxylic acids in the presence of p-toluenesulfonic acid gave the 2-aryl-3-amino-4-quinazolones 444 (yield Ar = Ph (37%) and 4-NO2C6H4 (39%)) (Scheme 139). 297

Scheme 139<sup>a</sup>

![Scheme 139](image)

<sup>a</sup>(i) AcOH, PTSA, boiling. 9 h.

Acylation of anthranilic acid hydrazide 145 with 2 equivalent of ethoxyl chloride formed diester 445, which readily underwent cyclization in the presence of acetic anhydride to ethyl 3-[ethoxy(oxo)acetylamin]-4-o xo-3,4-dihydroquinazoline-2-carboxylate 446 with 51% yield. On the other hand, ethyl 4-oxo-3-(2,5-dioxopyrroloidin-1-yl)-3,4-dihydroquinazoline-2-carboxylate 450 was synthesized starting from 4-[2-(2-amino benzoyl)hydrazino]-4-oxobutanoic acid 447, which on reaction with ethoxyl chloride gave oxamate 448. Oxamate 448 on heating in acetic acid afforded the derivative 449, which on further treatment with acetic anhydride furnished 68% of quinazolin-4-one 450. Ethyl 4-oxo-3-(2,5-dioxopyrroloidin-1-yl)-3,4-dihydroquinazoline-2-carboxylate 450 can also be obtained in 73% yield directly from ester 448 without isolation of ester intermediate 449 by the action of acetic anhydride (Scheme 140). 299,300 Compound 451 was obtained in 83% yield by successive acylation of hydrazide 145 with succinic and phthalic anhydrides in acetic acid (Scheme 140).

Cyclization of 2-amino-3,5-dibromobenzohydrazide with carbon disulfide afforded 51% of quinazolin-4-one derivative 452 (Scheme 141). 302

Reactions of 3-amino-4-(4-methoxyphenyl)-6-pyridin-3-ylthieno[2,3-b]-pyridine-2-carboxydrazide 453 with formic acid, dimethylformamide-dimethylacetel, and acetic anhydride were carried out separately to afford the corresponding pyridothenopyrimidines 454, 455, and 456, respectively, in 70–87% yields (Scheme 142). 303

![Scheme 137](image)

<sup>a</sup>(i) Ac2O, 138 °C; (ii) HCOOH, 100 °C.
Reaction of 2-isothiocyanato-3-cyano-4,5,6,7-tetrahydrobenzo[b]-thiophene with formic acid hydrazide (R = H) and acetic hydrazide (R = Me) afforded the respective 5-thioxo-4,6,8,9,10,11-hexahydro-benzo[b]thiopheno[2,3-d]-1,2,4-triazolo[1,5-c]pyrimidines 457 (yield R = H (76%) and Me (78%)). Formation of 457 proceeds by attack of the terminal amino group of hydrazide onto the isothiocyanate then to the nitrile function for cyclization and subsequent attack of the imino group onto the amide for annelation (Scheme 143).304

Imidate derivatives of pyrazole 458 were reacted with the appropriate (para-substituted)benzoic acid hydrazide in refluxing 2-methoxyethanol to afford the intermediates 459, which subsequently were subjected to a thermally induced cyclization in diphenyl ether at 260 °C to give 460. Hydrolysis of 460 in 20% HCl gave rise to the corresponding hydrolyzed intermediates 461, which were consequently converted into the 5-amino-7- or 8-(substituted)-2-[(para-substituted)phenyl]pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine derivatives 462 (17−54% yields) in the presence of 1-methyl-2-pyrrolidinone, cyanamide, and p-toluene sulfonic acid monohydrate (Scheme 144).305

3.5.3. Piperazine and Their Fused Derivatives. Piperazines are a significant class of organic compounds for clinical chemistry.306 Piperazines have been reported in gene transfer reactions, and quaternary piperazinium salts have shown spasmylytic, antihelmintic, and germicidal activity. Some piperazine derivatives possess high biological activity for multidrug resistance in cancer and malaria.306,307,308,309

3,4-Di(pyrrol-1'-yl)thieno[2,3-b]thiophene-2,5-dicarbohydra-zide 463 was converted to 2,5-dicarbazido-3,4-di(pyrrol-1'-yl) thieno(2,3-λ)thiophene 464 on treatment with nitrous acid, which was easily decomposed at 170 °C through a Curtius rearrangement, and subsequent ring closure produced the corresponding bis[thienopyrrolopiperazine] 466 in 90% yield via the intermediacy of isocyanate derivative 465 (Scheme 145).293

3.5.4. Thiazine and Their Fused Derivatives. Among the heterocycles, 1,3-thiazines are a class of compounds with biological activity, such as antimicrobial,310 antitumor,311 antioxidant,312 calcium channel modulators,313 and antipyretic.314,315 In view of these observations it was considered of interest to synthesize some new thiazine derivatives of biological importance.

Scheme 140

Scheme 141

Scheme 142

Scheme 143

Scheme 144

Scheme 145
Treatment of 3,4-diaminothieno(2,3-b)thiophene-2,5-dicarbonyldiazide 434 with S,S-acets under PTC conditions afforded bis[(coxo-1H-thieno(2,3-b)]-1,3-thiazin-2-ylidine] malononitrile 467 (29% yield) via nucleophilic attack of the SH group of the S,S-acetal at the carbonyl group with elimination of a hydrazine molecule and subsequent intramolecular cyclization via elimination of hydrogen sulfide molecule (Scheme 146).293

Scheme 146a

(i) K2CO3, TEBAC, MeCN, Δ.

Reactions of acetophenone with [hydroxyl(tosyloxy)iodo]-benzene (HTIB) formed 470, which on condensation with benzoic acid hydrazides afforded the acid hydrazones 471 which underwent requisite cyclization on addition of K2CO3 to yield 2,5-diphenyl-6H-1,3,4-oxadiazine 472 in 58−71% yields (Scheme 147).323

Scheme 147a

(i) K2CO3, TEBAC, MeCN, Δ.

Reactions of acetophenone with [hydroxyl(tosyloxy)iodo]-benzene (HTIB) formed 470, which on condensation with benzoic acid hydrazides afforded the acid hydrazones 471 which underwent requisite cyclization on addition of K2CO3 to yield 2,5-diphenyl-6H-1,3,4-oxadiazine 472 in 58−71% yields (Scheme 147).323

Scheme 148a

(i) MeCN; (ii) K2CO3.

The hydrazide-hydrazone derivatives 473 of 2 underwent cyclization in sodium ethoxide solution to give the 2-(5-(4-bromoaryl)-6H-1,3,4-oxadiazin-2-yl)acetonitrile derivatives 474 (yields X = Br (81%) and NO2 (77%)) (Scheme 149).318

Scheme 149a

(i) 1,4-Dioxan, reflux 2 h; (ii) NaOEt/EtOH, reflux on water bath for 4 h, HCl till pH 6.

3.6.2. Triazine and Their Fused Derivatives. 1,2,4-Triazines and their derivatives have been widely studied in terms of their synthetic methodologies and reactivity since some of these derivatives were reported to have promising biological activities.324 Synthesis of 1,2,4-triazines and their derivatives is well documented,325−328 and their methods of preparation are numerous and varied.

1,2,4-Triazines 475 were obtained in 61−93% yields from the one-pot condensation reaction of acid hydrazide, ammonium acetate, and dicarbonyl compounds on the surface of silica gel in the presence of triethylamine under microwave irradiation (Scheme 150).329 Lindsley et al.330 also reported a one-pot 3-

Scheme 150a

(i) NH4OAc, SiO2, TEA, MW.

component condensation under microwave irradiation of an acyl hydrazide-tethered indole to form a triazine, unnatural β-carboline alkaloids in good isolated yields from ammonium acetate followed by an inverse-electron demand Diels–Alder reaction.

Nucleophilic addition reaction of 3-thiophen-2-yl-acryloylisothiocyanate with hydrazide 2 afforded thiocarbamoyl derivative 476, which gave 55% of pyrazolo[1,5-a][1,3,5]triazine derivative 477 on treatment with 5% potassium hydroxide (Scheme 151).331

Scheme 151a

(i) 5% KOH.

Reaction of hydrazide 49 with salicylaldehyde afforded the coumarin derivative 478, which on further treatment with phenacyl bromide afforded 70% of 1,2,4-triazine-3-thione derivative 479. The reaction is assumed to follow a 1,4-dinucleophilic attack by the aminothioxomethylhydrazine moiety on the α-haloketone (Scheme 152).57

Scheme 152a

Ar = Ph, 4-MeC6H4, 4-MeOC6H4, 4-BzC6H4, 4-CIC6H4, 4-NO2C6H4, Ar′ = Ph, 4-BzC6H4.
1,2,4-Triazine 480 was synthesized in 63% yield by condensation of hydrazide 149 with chloroacetamide (Scheme 153).121

Coupling of 393 with pyrazole-5-diazonium chloride yielded polycondensed heterocyclic pyrazolo[5,1-c]-1,2,4-triazine 482 (60% yield) via the nonisolable hydrazone intermediate 481 (Scheme 154).259

Reaction of hydrazone derivative 396 with diazonium chlorides formed the triazine derivative 483 in 54–82% yields (Scheme 155).261

Condensation of N’-(2,4-dinitrophenyl)-3-oxo-3-phenylpropenylhydrazide with triazine gave the corresponding hydrazone 484, which underwent cyclization on heating with glacial acetic acid in the presence of anhydrous sodium acetate to form pyrazole derivative 485. Alkylation of 485 using ethyl bromoacetate led to formation of 65% of 2-(2,4-dinitrophenyl)-6-(5,6-diphenyl-1,2,4-triazin-3-yl)-7-phenyl-2,3-dihydropyrazolo[5,1-c][1,2,4]triazin-4(6H)-one 486 (Scheme 156).63

Neunhoeffer et al.332 reported the cyclization of amino acid hydrazides for synthesis of five- and six-membered polyfunctional heterocyclic compounds that have been published in the last three decades. Many pharmaceutically active heterocycles have been obtained based on the reaction of acid hydrazides particularly concerning Gewald reaction, Curtius rearrangement, Dimroth rearrangement, Horner–Emmons reaction, and Reid–Heindel reaction. Essentially esters, organic acid halides, lactones, lactams, and cyclic anhydrides are potential resources for generation of variety of acid hydrazides as key synthon components for preparation of numerous diverse heterocycles. Reaction of hydrazides with most other various reagents like isocyanate, isothiocyanate, carbonyldi, aldhe, ketones, both cyclic and acyclic, for synthesis of heterocycles

4. CONCLUSION

This review describes the high synthetic potential of various acid hydrazides for synthesis of five- and six-membered polyfunctional heterocyclic compounds that have been published in the last three decades. Many pharmaceutically active heterocycles have been obtained based on the reaction of acid hydrazides particularly concerning Gewald reaction, Curtius rearrangement, Dimroth rearrangement, Horner–Emmons reaction, and Reid–Heindel reaction. Essentially esters, organic acid halides, lactones, lactams, and cyclic anhydrides are potential resources for generation of variety of acid hydrazides as key synthon components for preparation of numerous diverse heterocycles.
occurs through nucleophilic addition, substitution, addition—elimination, and ANRORC (addition of the nucleophile, ring opening, and ring closure) mechanisms under basic, acidic, or neutral reaction conditions. Most of these reagents are accessible from easily or commercially available low-cost starting materials. This review has also demonstrated the salient feature to development of an environmentally benign microwave-irradiated experimental procedure for heterocyclic synthesis from this basic acid hydrazide unit. The synthetic methods illustrated in this review can be extended to the synthesis of natural heterocycles and also suggest that acid hydrazides can be a promising building block in combinatorial synthesis of functionalized heterocyclic compounds used for design of novel highly effective pharmaceutical drugs with a broad spectrum of bioresponses. In certain cases, reports on the low yield of bioactive heterocycles in this review could be overcome by prospective synthetic chemists with this continued investigation and new approaches for broad methodology and elaborated experimental techniques could be explored for its enhancement for preparation of a library of such polyfunctional heterocycles to provide a useful aid to medicinal chemistry.

**AUTHOR INFORMATION**

**Corresponding Author**

*E-mail: ajaykumar.behera@yahoo.com.*

**Notes**

The authors declare no competing financial interest.

**Biographies**

Poulomi Majumdar obtained her M.Sc. degree from Ranvenshaw College, Utkal University, India, in 2006, and M.Phil. degree from School of Chemistry, Sambalpur University, India, with specialization in Organic Synthesis in 2007. As a Project Fellow, UGC Research Project, she received her Ph.D. degree under the supervision of Dr. A.K. Behera from the same University in July, 2012, in the area of Organic Synthesis. Currently, she is working as Postdoctoral fellow in the Molecular photophysics and photochemistry group of Prof. Jianzhang Zhao, Dalian University of Technology, China. Her scientific research interest includes synthesis of heterocycles, spiroheterocycles, fluorescent molecular probes and phosphorescent transition metal complexes including their study on photophysical properties with steady-state and timeresolved spectroscopy followed by DFT calculations.

Anita Pati was born in Sambalpur, Odisha, India, in 1977. She obtained her M.Sc. degree in 2002, and M.Phil. degree in 2003, from Sambalpur University, India. During her Ph.D. she worked with Prof. R. K. Behera in the area of organic synthesis and after receiving her Ph.D. degree from Sambalpur University in August 2010, she joined the group of Dr. Dillip Kumar Chand and Dr. Santosh J. Gharpure, Indian Institute of Technology Madras, Chennai, India, to pursue her postdoctoral research work in the area of supramolecular Chemistry. After the successful completion of her postdoctoral research training, presently she is working as an Assistant Professor in the School of Applied Sciences (Chemistry), KIIT University, Bhubaneswar. Her research interest includes organic synthesis, new synthetic methods and supramolecular chemistry.

Manabendra Patra was born in Cuttack, India. He received his M.Sc. (1991) and M.Phil. (1993) degrees from the PG Department of Chemistry, Sambalpur University, India. He studied micellar chemistry during his M.Phil. work. He obtained his Ph.D. degree on polymer kinetics under the guidance of Professor B. K. Sinha from Sambalpur University in 1999. In the same year he joined the group of Professor Rajani Kanta Behera as a Research Associate working on organic synthesis. At present, he is an Assistant Professor at the National Institute of Science and Technology, Berhampur, Orissa. His research interest is in on surface chemistry and organic synthesis.
Rajani K. Behera was born in 1952 in Kalahandi District of Odisha, India. He received his M.Sc. degree in 1974 and Ph.D. degree in 1980 from Sambalpur University. After working at Government College, he became a Lecturer at Sambalpur University and subsequently became a Reader in 1991 and Professor in 1999. He worked with Professor G. R. Newkome at the University of South Florida on the synthesis of dendrimers from 1988 to 1991. He has one patent in the United States and another in Canada to his credit. His research interests include synthesis of heterocycles, macromolecules, and dendrimers.

Ajaya Kumar Behera was born in Nayagarh District of Odisha, India, in 1962. He received his M.Sc. degree from Utkal University in 1984 and M.Phil. and Ph.D. degrees from Berhampur University in 1990 and 1996, respectively. After working for a few years at Government College, he joined the PG Department of Chemistry, Sambalpur University, in 1997 as Senior Lecturer and became Reader in 2003. His research interest includes synthesis of pharmacologically active heterocycles, spiroheterocycles, and natural products.

ACKNOWLEDGMENTS
This research was supported by grants from University Grants Commission (UGC), New Delhi.

ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>bpy</td>
<td>2,2′-bipyridine</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butyloxy carbonyl</td>
</tr>
<tr>
<td>t-Bu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>BTC</td>
<td>bis(trichloromethyl) carbonate</td>
</tr>
<tr>
<td>BTPBP</td>
<td>1,4-bis(triphenylphosphonium)-2-butene peroxodisulfate</td>
</tr>
<tr>
<td>BSH</td>
<td>bis(trimethylsilyl)acetamide</td>
</tr>
<tr>
<td>CCR</td>
<td>component coupling reaction</td>
</tr>
<tr>
<td>CDI</td>
<td>1,1′-carbonyldimidazole</td>
</tr>
<tr>
<td>CDK</td>
<td>cyclin-dependent kinase</td>
</tr>
<tr>
<td>CHP</td>
<td>N-cyclohexyl-2-pyrrolidone</td>
</tr>
<tr>
<td>conc</td>
<td>concentrate</td>
</tr>
<tr>
<td>cycl</td>
<td>cyclization</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>dil</td>
<td>dilute</td>
</tr>
<tr>
<td>DMA</td>
<td>dimethylacetal</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethyl formamide</td>
</tr>
<tr>
<td>EDCI</td>
<td>ethylenediamine chloride</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>ETL</td>
<td>electron transport layer</td>
</tr>
<tr>
<td>h</td>
<td>hour</td>
</tr>
<tr>
<td>HOBr</td>
<td>1-hydroxy benzotriazole</td>
</tr>
<tr>
<td>HTIB</td>
<td>[hydroxy(tosyloxy)iodo]benzene</td>
</tr>
<tr>
<td>HTL</td>
<td>hole transport layer</td>
</tr>
<tr>
<td>HMDS</td>
<td>hexamethyldisilazane</td>
</tr>
<tr>
<td>IBD</td>
<td>iodobenzene diacetate</td>
</tr>
<tr>
<td>IBX</td>
<td>iodoxybenzoic acid</td>
</tr>
<tr>
<td>INH</td>
<td>isonicotinic acid hydrazide</td>
</tr>
<tr>
<td>ITO</td>
<td>indium tin oxide</td>
</tr>
<tr>
<td>MAO</td>
<td>monoamine oxidase</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>min</td>
<td>minute</td>
</tr>
<tr>
<td>MW</td>
<td>microwave</td>
</tr>
<tr>
<td>NMP</td>
<td>N-methyl-2-pyrrolidone</td>
</tr>
<tr>
<td>OLED</td>
<td>organic light-emitting diode</td>
</tr>
<tr>
<td>PEG</td>
<td>polyethylene glycol</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PPA</td>
<td>polyphosphoric acid</td>
</tr>
<tr>
<td>PTC</td>
<td>phase transfer catalyst</td>
</tr>
<tr>
<td>PTSA</td>
<td>p-toluensulfonic acid</td>
</tr>
<tr>
<td>PTSCI</td>
<td>p-toluene sulphonyl chloride</td>
</tr>
<tr>
<td>i-pr</td>
<td>isopropyl</td>
</tr>
<tr>
<td>py</td>
<td>pyridine</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>SPS</td>
<td>solid-phase synthesis</td>
</tr>
<tr>
<td>TEA</td>
<td>triethylamine</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TEBAC</td>
<td>triethyl benzylammonium chloride</td>
</tr>
<tr>
<td>Δ</td>
<td>heating</td>
</tr>
</tbody>
</table>

REFERENCES

(1) Smith, P. A. S. Organic Reactions; Foreign Literature Publishers: Moscow, 1951; p 322.
(9) Kumar, P.; Narasimhan, B.; Sharma, D. ARKIVOC 2008, 159.


(32) Jørgensen, P. T.; Ostermayer, F.; Schröter, H. Ger Offen 2,313,409, 1974; Chem. Abstr. 1975, 82, 4191m.


(35) Fischer, E.; Bourdon, P. Chem. Ber. 1883, 16, 2241.


