Synthetic Methods

Copper-Catalyzed Mild Nitration of Protected Anilines

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Abstract: A practical copper-catalyzed direct nitration of protected anilines, by using one equivalent of nitric acid as the nitrating agent, has been developed. This procedure features mild reaction conditions, wide structural scope (with regard to both N-protecting group and arene substitution), and high functional-group tolerance. Dinitration with two equivalents of nitric acid is also feasible.

Nitroarenes are important intermediates for the synthesis of pharmaceuticals, dyes, and materials, among other valuable chemicals.[10] The synthetic versatility of the nitro group makes these compounds useful precursors for the construction of heterocyclic frameworks.[2] Most commonly, nitroarenes are prepared by means of the classical direct electrophilic nitration of arenes with excess nitric acid or mixed strong-acid systems, such as H2SO4/HNO3. Although this method constitutes an important process in both academia and industry,[11,12] the harsh reaction conditions represent a limitation in terms of tolerance towards oxidation or to acid-sensitive functional groups. Moreover, from a bulk-scale standpoint, disposal of acidic waste after the reaction is often problematic.

In recent years, metal nitrate salts [e.g., Ca(NO3)2, Bi(NO3)3·6H2O, AgNO3, or Ni(NO3)3·6H2O] have emerged as new nitrating agents.[13] These salts eliminate the need for strong acidic conditions, although the price for this improvement is the generation of significant amount of metal waste, which is derived from stoichiometric use of the metal nitrate salts. Additionally, these reagents are often expensive or difficult to prepare. Chelation-assisted ortho-nitration of aromatic C–H bonds under Pd,[7] Rh,[8] and Cu[9] catalysis has also been developed using AgNO3, NaNO2, or AgNO3 as nitrating agents, but this strategy is limited in scope. In work by Liu and co-workers,[9] Cu(NO3)2·3H2O (1.5 equiv) was found to be an efficient nitrating agent for the ortho-nitration of 2-phenylpyridines. An isolated example of ortho-nitration by using HNO3 (2 equiv) in the presence of Cu(OAc)2 (50 mol %) is also described.[9] Strong Lewis acids, such as lanthanide triflates, have been found to be efficient catalysts for the nitration of a range of simple aromatic compounds by using stoichiometric quantities of nitric acid.[10] However, generally these conditions are not compatible with aniline derivatives because they do not remain active in the presence of the basic nitrogen.

Very recently, Arms and co-workers have described the selective nitration of N-sulfonyl anilines with tert-butyl nitrite.[11] Although good yields are obtained with electron-neutral or electron-rich substrates, this protocol was not well-suited for aniline derivatives containing strong electron-withdrawing substituents, which generally provided incomplete conversions. Additionally, the use of common N-protecting groups different from sulfonamides, such as amides or carbamates, proved to be incompatible.

Despite these advances, there is a great need for more general, practical, safe, and green methods for the catalytic nitration of anilines. A method using one equivalent of inexpensive HNO3 is ideal because the only stoichiometric byproduct of the reaction is water. Herein, we present a practical Cu-catalyzed nitration of anilines that uses one equivalent of HNO3. This protocol expands the scope of the reaction in terms of N-derivatives (sulfonamides, carbamates, amides, and ureas) and arene substitution, including strongly electron-deactivated substrates with CF3, CN, or NO2 groups.

In previous studies on Cu-catalyzed C–H halogenation of aniline derivatives,[12] we accidentally observed partial nitration of aniline when using Cu(NO3)2·xH2O as the catalyst. In fact, full conversion of N-(2-pyridyl) sulfonyl aniline (1) was achieved when using one equivalent of Cu(NO3)2·xH2O under otherwise similar conditions. Unfortunately, the reaction was not regioselective and a mixture of 3:1 of o-/p- regioisomers 2 was obtained (Scheme 1).[13]

Therefore, N-(2-pyridyl)sulfonyl p-toluidine (3) was chosen as a model substrate for optimization studies aiming to develop a catalytic, rather than stoichiometric (with respect to copper), version of this process (Table 1). Firstly, it was deemed appropriate to find a solvent that would be more attractive to industry. We found that the Cu-promoted nitration of 3 occurs smoothly in MeCN[14] to afford the desired product 5 with >99% yield (entry 1). Next, we focused on developing a Cu-catalyzed protocol. In an initial attempt, we used NH4NO3 as an stoichiometric NO2 source and 10% of Cu(NO3)2·xH2O in the presence of O2 as an external oxidant, but only 13% yield of the desired product 5 was achieved (entry 2). However, changing the nitro source to one equivalent of HNO3 (entry 3) or iAmONO (entry 4) afforded desired product 5 in excellent yield (>99% and 94% by NMR spectroscopy, respectively). Based on these results, HNO3 was chosen for further studies. Control experiments determined that nitroaniline derivative 5 is not produced in the absence of a Cu catalyst[15] (entry 5), and that the reaction requires aerobic conditions (1 atm O2) to achieve reactivity under catalytic conditions (entry 6), thus highlighting the crucial role of catalyst and oxidant in this reaction.

From a synthetic standpoint, it is remarkable that this protocol allows for simultaneous scale-up, lower catalyst loading, and lower temperature. For example, a one-gram-scale nitr-
A broad range of common protecting groups (PG) were next examined in the nitration reaction of 4-aminobenzenitrile derivatives 4 and 7–14 in Scheme 2) with HNO3 (1.0 equiv) under our optimized conditions (10 mol% of Cu, 100 °C). Additionally, Figure 1 shows the reaction profile for each case from a measure of conversion (%) versus time (min). All of the sulfonamide groups evaluated enabled a very fast nitration reaction (>90% conversion in 20 min). Among the sulfonyl groups tested, the N=SO2Py showed the best reactivity–selectivity balance, affording 6 as the only product (no dinitration was detected by 1H NMR spectroscopy), which was isolated in 98% yield. For the other two sulfonyl groups tested (PG = Ts (4-toluenesulfonyl), 4-Ns (4-nitrobenzenesulfonyl)), reaction times longer than 30 min resulted in a small amount (5–12%) of competitive dinitration at the positions ortho to the amino group. Nevertheless, high yields of the corresponding nitro derivatives can be achieved if the reaction is stopped after 30 min [97% for 12 (PG = Ts) and 94% for 16 (PG = Ns)].

The N,N-dimethyl urea 9 was even more reactive, reaching full conversion to mononitrated product 17 after just 10 min. The product was isolated in 99% yield by simple precipitation. This protocol also proved to be compatible with carbamates and amides. Although conversions below 55% were observed in the nitration of benzamide 10 and methyl carbamate 11 after 2 h, the reaction occurred cleanly and good yields of the corresponding mononitrated products, 18 and 19, were obtained after 12 h (86 and 89%, respectively). In the case of the Fmoc-protected derivative, partial decomposition of the starting material prevented an accurate measure of its kinetic profile (substrate 12, not recorded in Figure 1). Despite this shortcoming, the corresponding nitro derivative 20 was obtained in synthetically useful yield (12 h, 57%). In contrast, more electrophilic benzamides 13 and 14 showed very poor reactivity (products 21 and 22 were obtained in 23 and 12% yield, respectively, after 16 h).

Once the compatibility of the catalyst system with standard nitrogen protecting groups was demonstrated, we examined the scope in terms of arenne substitution. As shown in Scheme 3, a wide range of protected p-substituted anilines underwent nitration at the ortho-position in acceptable to good yields (25 examples, 54–98%). Substrates bearing strong electron-withdrawing groups (CF3, CN, CO2Me, and COMe) showed a similar reactivity to those with electron-donating groups (OMe, Me) in terms of yield reaction. It is also important to stress the high functional-group tolerance (ether, ketone, ester, nitro, cyano, or acetol), especially to halogen substitution (F, Cl, Br, or I, products 50–53, 61, 64, 66, and 69–72), thus providing

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**Table 1. Optimization of the reaction conditions.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Nitrating agent</th>
<th>Product</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1[a]</td>
<td>CH3 (3)</td>
<td>Cu(NO3)2·xH2O</td>
<td>5</td>
<td>&gt; 99</td>
</tr>
<tr>
<td>2</td>
<td>CH3 (3)</td>
<td>(NH4)NO3·H2O</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>CH3 (3)</td>
<td>HNO3</td>
<td>5</td>
<td>&gt; 99 (95)[c]</td>
</tr>
<tr>
<td>4</td>
<td>CH3 (3)</td>
<td>iAmONO</td>
<td>5</td>
<td>94</td>
</tr>
<tr>
<td>5[b]</td>
<td>CH3 (3)</td>
<td>HNO3</td>
<td>5</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>6[b]</td>
<td>CH3 (3)</td>
<td>HNO3</td>
<td>5</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>7[b]</td>
<td>CH3 (3)</td>
<td>HNO3</td>
<td>5</td>
<td>94 (93)[c]</td>
</tr>
<tr>
<td>8</td>
<td>CN (4)</td>
<td>HNO3</td>
<td>6</td>
<td>&gt; 99 (94)[c]</td>
</tr>
<tr>
<td>9[b]</td>
<td>CN (4)</td>
<td>HNO3</td>
<td>6</td>
<td>&lt; 5</td>
</tr>
</tbody>
</table>

[a] Conditions: 3 or 4 (0.20 mmol), nitrating agent (0.20 mmol), Cu(NO3)2·xH2O (10 mol%), MeCN (0.2 m), O2 (1 atm), 100 °C, 1 h. [b] Conversion yields by 1H NMR spectroscopy. [c] Under Ar with a stoichiometric amount of Cu. [d] Isolated yield. [e] Without Cu. [f] Under Ar atmosphere. [g] 1 gram scale, 1 mol% Cu catalyst, 40 °C. [h] 1 mol% Cu catalyst. iAmONO = iso-amylnitrite.

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**Scheme 2. Evaluation of N-protecting groups in the nitration of 4-aminobenzonitrile.**

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**Figure 1. Reactivity profile (conversion %) versus time (min) of different protecting groups (PG) in the nitration of 4-aminobenzonitrile derivatives.** Conversions determined by 1H NMR spectroscopy.
products suitable for further elaboration. Even an iodo substituent was tolerated on the aniline coupling partner, however, substantial protodehalogenation was observed and was responsible for the lowest yields of this series (50 and 69 were obtained in 55 and 54 %, respectively). A CO$_2$H group also proved to be suitable (58, 75 %), with only a small amount of nitrodecarboxylated product being detected in the reaction mixture.

For the Fmoc protecting group, which provided a modest yield in the case of the 4-aminobenzonitrile derivative, it was compatible with anilines bearing an electron-donating substituent (67, 89 % yield). The dramatic increase in the reactivity of electron-rich aniline derivatives allowed the use of the previously unreactive pentafluorobenzamide protecting group (65, 56 %). Complete ortho regioselectivity, with regard to the amino group, was observed in substrates in which the para-position was blocked, even in those cases where the blocking substituent has a strong ortho-directing effect, such as the OMe group (48, 55, 60, 62, 65, 67, and 68; 56–98 % yield). Gratifyingly, ortho-substituted aniline derivatives underwent nitration at the para-position with complete regiocontrol and no apparent sensitivity to electronic properties of the substituent (Scheme 4).


led to a 3:1 mixture of para and ortho regioisomers (83). When one ortho-position and the para-position were blocked, nitration occurred at the free ortho-position in good yield (84, 85 %). Unfortunately, meta-substitution was not effective in controlling the regioselectivity, as exemplified in the nitration of m-methoxy N-tosyl aniline 85, which afforded a 1.0:1.5 mixture of mono-nitrated regioisomers at the C2 and C4 positions (o-86 and p-86) in good overall yield (Scheme 5, see the Supporting Information for an additional example). Heteroaromatic substrates were also amenable to the reaction, as demonstrated in the nitration of 6-aminoquinoline derivative 87, which occurred cleanly at C5 to give 88 in 84 % yield (no other regioisomer was detected by NMR spectroscopy in the crude mixture). Importantly, the reaction in the absence of Cu catalysis provided a complex mixture of products (Scheme 6).

Scheme 5. Nitration of meta-substituted aniline derivative 85.


Capitalizing on the high reactivity of our nitration protocol, especially in the case of strongly electronically deactivated aniline derivatives, we next evaluated the application of this protocol...
tocil to accessing dinitrated anilines by using two equivalents of HNO₃. To our delight, the efficiency of this catalytic system was also conserved when the aniline possessed a nitro substituent, enabling a mild dinitration procedure. Indeed, a representative set of protected para-substituted anilines underwent ortho dinitration in synthetically useful yields (89–93, 73–85 % yield, Scheme 7), regardless of the electronic nature of the substituent or the identity of the protecting group at the nitrogen atom (sulfonamide or urea). Again, compatibility to halogen substitution (Cl; products 91, 94, and 95, 58–85 %) provides a useful handle for further derivatization. Even strong electron-withdrawing groups were tolerated at the aromatic ring (e.g., CF₃, or CN; 92 and 93, 76 and 78 %, respectively). The presence of a substituent at the ortho-position allowed dinitration at both the unsubstituted ortho- and para-positions (94, 58 %), whereas the 4-chloro-2-nitro-disubstitution led to nitration at the available ortho-position (95, 72 %, 1.0 equiv of HNO₃). The m-methoxy-substituted aniline derivative 85 underwent dinitration cleanly at the less hindered ortho-position and at the para-position (96, 83 %).

Although the reaction mechanism remains unclear, some experiments are consistent with the hypothesis that the reaction proceeds through a radical pathway. For example, the model nitration of toluidine derivative 3 with HNO₃ was completely suppressed in the presence of one equivalent of galvinoxyl as a radical scavenger (see the Supporting Information for details). Also, N-alkylation resulted incompatible; no reaction was observed when using a N-Me-N-SO₂Py-protected aniline (see the Supporting Information). This N-substitution would prevent the formation of an amidyl radical intermediate (11) (that can be delocalized onto the aromatic ring) upon one-electron oxidation by the CuII species. This carbon-centered radical could react with Cu(NO₃)₂ or be intercepted by a nitrogen dioxide radical, which could be produced by thermal decomposition of Cu(NO₃)₂ (a plausible reaction pathway is outlined in Scheme 8).(17, 18)

Taking advantage of the flexibility of this methodology with regard to the nature of the aniline protecting group, Scheme 9 shows varied possibilities for the amino deprotection without affecting the nitro-group functionality (products 97–100, 83–99 %). On the other hand, because the nitroaniline derivatives can be considered as orthogonally protected diamino benzenes, their versatility as valuable building blocks towards the construction of more complex heterocyclic ring systems was demonstrated (Scheme 10). Either of the two masked amino groups can be easily converted into the free NH₂ in a selective fashion. Thus, catalytic hydrogenation of the nitro group of 5 or 55 furnished the corresponding diamino benzene deriva-

Scheme 7. Formation of dinitrated products. Isolated yields. [a] 2 h, 50 °C. [b] 30 mol % of the Cu catalyst, 24 h. [c] 1.0 equiv of HNO₃.

Scheme 8. Plausible mechanistic pathway.

Scheme 9. Strategies for the amino deprotection.

Scheme 10. Synthetic application of the nitroaniline derivatives.

tives 101 (PG = SO2Py, 95 %) and 102 (PG = Ts, 87 %) in high yields.

These products can be further derivatized into the corre-555sponding 1H-benzo[d]imidazol-2(3H)-ones 103 and 104 by using triphosgene (Scheme 10). Subsequent deprotection of the N-Ts protecting group afforded the unprotected heteroar-560ene 105 in 81 % yield. Interestingly, heterocyclic product 103 is well-suited for a subsequent nitration reaction under our Cu-565atalyzed methodology, occurring selectively at the para-posi-

In summary, we have developed a reliable Cu-catalyzed pro-
cedure for the selective nitration of para-substituted and ortho-substituted aniline derivatives by using one equivalent of HNO3, which produces water as the only stoichiometric by-

Keywords: anilines · benzimidazoles · copper · nitration · nitric acid

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2) a) K. Schofield, Aromatic Nitrations, Cambridge University Press, Cam-
4) For a review on recent advances in the synthesis of nitrocompounds, see: G. Yan, M. Yang, Org. Biomol. Chem. 2013, 11, 2554.
6) For the synthesis of ortho-nitroacetanilidines from anilines using Bi(NO3)3/ 

7) For the selective nitration of product 104 (77 % yield). Additionally, the product catalyzed cyclization through the cascade sulfonamidation–oxidation of the glyoxalate-derived imine 107(16) obtained in situ from condensation of aniline 101 with ethyl glyoxalate, led to the for-

This selectivity was not improved by using other typical N-protected groups. For further information, see the Supporting Information.

For a Cu-catalyzed ortho-selective C–Hamination of protected anilines, see: a) A. M. Martínez, R. Rodríguez, R. Gómez Arrayáys, J. C. Carre-
10) For other copper salts, such as CuO or CuOAc2, were similarly applicable in the model nitration of 3 to give 5 (see the Supporting Information for details).
12) For the thermal decomposition of Cu(NO3)2·3H2O releasing nitrogen dioxide, see: a) I. V. Morozov, K. O. Znamenkov, Y. M. Korenev, O. A. Shyakhutdin, Thermochim. Acta 2003, 403, 173; b) H. Wayne Richardson, Copper Compounds in Vollmann’s Encyclopedia of Industrial Chemistry 2005, Wiley-VCH, Weinheim. See also ref. [9]. The applicability of other Cu salts as precatalysts, such as Cu(OAc)2 or CuCl (easily oxidable under O2), is fe-

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