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Para-Selective Halogenation of Nitrosoarenes with Copper(II) Halides

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Supporting Information

ABSTRACT: The para-selective direct bromination and chlorination of nitrosoarenes with copper(II) bromide and chloride is reported. Under mild reaction conditions, a range of halogenated arylnitroso compounds are obtained in moderate to good yields with high regioselectivity. Additionally, the versatility of the method is demonstrated by the development of a one-pot procedure to obtain the corresponding para-halogenated aniline- and nitrobenzene derivatives.

Arylnitroso compounds are versatile building blocks that can undergo a broad range of transformations. Moreover, nitroso compounds are readily synthesized by nitrosation or by redox reactions of nitrogen-containing starting materials. Most of the known transformations of arylnitroso compounds are operating on the nitroso group itself, with addition, N- or O-nitroso aldol, annulation, and cycloaddition, and nitroso–ene reactions being the most important examples. Additionally, the nitroso group can easily be reduced or oxidized to obtain amines, hydroxylamines, or nitro compounds. In contrast, there are far fewer examples of aromatic functionalization reactions of nitrosoarenes.

Given the wide applicability of halogenated aromatics, the development of regioselective halogenation methods has received considerable attention. Conveniently, the use of Cu(II) salts has been devised as a mild and selective alternative to classical methods, both by organometallic pathways (C–H functionalization, ortho-directing) and by oxidative methods (for electron-rich arenes, para-directing). Interestingly, the electron-withdrawing nitroso group has been recognized to be selectively para-directing in the classical halogenation with Br₂ and Cl₂. For nitrosobenzene, the para-halogenated product was obtained in yields ~40% or less. This procedure requires a careful control of the reaction temperature (~5 °C), and a repeated removal of HX formed. Moreover, azoxyarenes and nitro compounds were formed as byproducts, along with unreacted starting material.

Even though this reactivity has been recognized as unique, no other methods for the halogenation of nitrosoarenes have, to the best of our knowledge, been reported. Exploiting the unique reactivity of nitrosoarenes, and with the use of Cu(II) halides as mild, convenient, and less hazardous alternatives to elemental Cl₂/Br₂, we herein report on a general and regioselective halogenation method (Scheme 1b) and the subsequent one-pot oxidation/reduction protocol to obtain functionalized anilines, nitrosoarenes, and nitroarenes.

During the initial screening of reaction conditions for the chlorination of nitrosobenzene (1a) with CuCl₂, a number of interesting observations were encountered (Scheme 2).

Scheme 2. Relevant Findings in the Screening of Conditions

In the presence of 1.0 equiv of CuCl₂ in MeCN at 40 °C, the para-chlorinated nitrosoarene 2a was obtained as a single regioisomer in 24% yield (by crude ¹H NMR) after 18 h, along with 19% of unreacted starting material 1a (Scheme 2, conditions A). Upon increasing the loading of CuCl₂ to 2.0 equiv, ~90% conversion of 1a was observed after 8 h, and the NMR yield of 2a was 49% (Scheme 2, conditions B). Around 7% of azoxyarene was observed, whereas the remainder of the starting material was not accounted for. Using CuCl₂ in a catalytic amount (10 mol %) with NCS as an oxidant, 2a was formed in 19% yield after 24 h at 50 °C (Scheme 2, conditions C). However, a similar yield (17%) was obtained in the absence of CuCl₂, and the use of NCS led to a significant amount of nitrobenzene (33% yield) as a byproduct, demonstrating the need for a mild oxidant, such as Cu(II) halides.

When a stoichiometric amount of CuCl₂ was used (Scheme 2, conditions A and B), a long induction period was observed, which led us to suspect that radicals may be involved. Thus, we investigated the effect of TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl) on the system.

Scheme 1. Halogenation of Arylnitroso Compounds

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brominated nitrosoarenes were obtained in comparable yields (Scheme 2, conditions D). No conversion was observed without BHT after 24 h at rt. In order to improve the yield of the halogenation reaction, several solvents, dilution, slow addition, and a lower reaction temperature were screened. In addition, a number of published halogenation methods were investigated for comparison. None of the efforts led to a more efficient reaction than the use of Cu(II) halides in a stoichiometric amount; see the Supporting Information (Table S-1) for a selection of reaction conditions investigated. We settled for a general method using 2.2 equiv of the Cu(II) halide and 1 mol % of BHT and investigated the scope of this transformation. We were pleased to find that the general reaction conditions were applicable for a wide range of substituted nitrosoarenes, yielding the monochlorinated products with high regioselectivity (Scheme 3).

Scheme 3. Chlorination of Nitrosoarenes<sup>a</sup>

For ortho-substituted nitrosoarenes, para-chlorinated products were obtained in moderate to high yields depending on the electronic character of the substituent. The highest isolated yield, 74%, was obtained for the o-methyl derivative. This reaction was also performed on an 11.0 mmol scale to obtain 1.18 g of the chlorinated product (69% yield). The less electron-rich nitrosoarenes were obtained in lower yields and required longer reaction times and/or elevated temperatures (Scheme 3, 2d–f). No reaction was observed in an attempted chlorination of o-nitrotroisobenzene (<i>1g</i>). <i>Meta</i>-substituted nitrosoarenes afforded the corresponding products in moderate to good yields (2h–j), whereas for the <i>para</i>-substituted substrates, a prolonged reaction time was required, and the products were identified as the ortho-chlorinated nitroso derivatives 2j–l.

Upon replacing CuCl<sub>2</sub> with CuBr<sub>2</sub>, the analogous para-brominated nitrosoarenes were obtained in comparable yields (Scheme 4). The most important difference was an increased reactivity observed with CuBr<sub>2</sub> as exemplified in the bromination of nitrosobenzene (<i>1a</i>), where traces (<5%) of the 2,4-dibrominated product were observed, and by the short reaction times required for dimethyl-substituted nitrosoarenes <i>1i</i> and <i>1j</i> to avoid decomposition. In some cases, we observed di- or tribrominated anilines as byproducts (<10%). Moreover, the nitro-substituted substrate <i>1g</i>, which was unreactive in the chlorination (Scheme 3, 2g), was brominated in an acceptable yield (3g, 40% yield). This result is remarkable as similar halogenation methods for arenes only work for electron-rich substrates or require directing groups. The bromination was also scalable, giving 3b in 57% yield (<i>1.25 g</i>). The attempted halogenation of OMe-, Me<sub>2</sub>N-, CHO-, and acyl-substituted nitrosoarenes led to an intractable mixture of products. When CuBr<sub>2</sub> (0.1 equiv) and NBS (1.5 equiv) were used, comparable yields of 3a and 3b were obtained. However, for CF<sub>3</sub>-containing substrate <i>1f</i>, only 5% yield of 3f was obtained under the catalytic conditions. No formation of 3b was observed using NBS without CuBr<sub>2</sub>. Further, we were interested in comparing the reaction outcome for a series of dimethyl-substituted nitrosoarenes (<i>1i</i>, <i>1j</i>, <i>1m</i>, and <i>1n</i>). As seen in Schemes 3 and 4, the reactions of 2,5-dimethylated nitrosoarene <i>1i</i> afforded the <i>para</i>-halogenated products 2i and 3i in excellent selectivity. Quite unexpectedly, substrate <i>1j</i> gave an isomeric mixture of <i>ortho</i>-halogenated products 2j and 3j with a preference for functionalization at the least hindered position (Schemes 3 and 4, 2j and 3j). However, the halogenation of substrates <i>1m</i> and <i>1n</i> led to rather unexpected outcomes (eqs 1 and 2).

For nitrosoarene <i>1m</i>, being substituted in the <i>para</i>-position and in one of the <i>ortho</i>-positions with respect to the nitroso group, the benzylc products <i>2m</i> and <i>3m</i> were selectively obtained instead of the expected <i>ortho</i>-halogenated products. We
speculate that the ortho-position may be less reactive on the basis of the geometry and direction of the nitroso group,13 favoring a quinomethide-type of reactivity. The ortho-disubstituted substrate 1n was in contrast completely unreactive under the applied reaction conditions, possibly due to a low solubility of dimerized mixture to obtain anilines.

As seen in Schemes 3 and 4, moderate yields were generally obtained. For certain substrates, e.g., nitrosobenzene, the formation of azoxyarenes was observed, and in most cases ~10% of the starting material remained unreacted. Formation of polymeric material and sublimation, generally observed for nitrosoarenes, are other possible reasons for the moderate isolated yields. In order to probe for possible regioisomeric products and to acquire more information on the mass balance, the chlorination of 1b was monitored by 1H NMR (Figure 1).

From the reaction profile above, it can be concluded the reaction took off after a fairly long induction period (in MeCN-d₃ at 20 °C (Figure 1), the reaction was found to require slightly longer time). Moreover, 1H NMR analysis showed that only 80% of the material could be identified as 1b or 2b in the crude reaction mixture. The 1H NMR yield (64%) was slightly lower than the isolated yield (74%), which also indicates that complexation of 2b (and/or 1b) with copper could account for some of the remaining material. Furthermore, by comparison with a reference sample of the ortho-chlorinated product, neither 1H NMR nor HPLC analysis of the crude reaction mixture could verify formation of the ortho-regioisomer in any traceable amounts.

In order to demonstrate the versatility of our method, we envisioned that a series of halogenated arenes within the whole landscape of nitrogen oxidation states could be accessed by a one-pot halogenation—reduction step (Figure 2).

The in situ reduction of the halogenated nitrosoarenes was achieved by the addition of NaBH₄, to the halogenation reaction mixture to obtain anilines 4b, 5b, and 5f in good yields. Aniline 4f was found to be unstable under the reaction conditions (Figure 2). Interestingly, the reduction of the nitroso group was found to be more efficient in the presence of the copper salts already present in the reaction mixture from the halogenation step.17 Furthermore, the oxidation of the nitroso group could efficiently be achieved in one-pot sequence using Oxone (40–68% yield, 6b, 6f, 7b, and 7f). No regioisomeric products were obtained in the one-pot oxidation or reduction reactions, which further support the high regioselectivity of our halogenation protocol.

Furthermore, we were interested in comparing our results with the halogenation of a selection of electron-rich arenes (8a–c) with CuX₂ (Scheme 5).

We found that the brominated derivatives of phenol (8a) and methoxybenzene derivatives 8b,c could be obtained in high yields. Although the corresponding chlorination using CuCl₂ worked reasonably well for 8a and 8c upon heating, anisole (8b) did not react at all. These results are very similar to the ones reported in the literature for the halogenation of electron-rich arenes with Cu(II) salts under oxidative conditions.13c,g When comparing the halogenation of nitrosoarenes 1 with the results presented in Scheme 5, one can point out a couple of important differences. First, the electron-deficient nitrosoarenes 1 typically required shorter reaction times compared to the electron-rich arenes 8. Moreover, no induction period was observed for the halogenation of electron-rich substrates 8 as was seen for the nitrosoarenes 1, which may indicate different overall mechanistic pathways.

Based on the observation that nitrosoarenes with EWGs generally required more forcing reaction conditions compared to nitrosoarenes with EDGs, we speculate that the mechanism involves a rate-determining step in which a positive charge is built up. Moreover, since the nitrosoarenes reacted unexpectedly rapid (compared to arenes 8), it is not unlikely that the nitroso group is temporarily converted into a more reactive functional group during the course of the reaction. Indeed the electrophilic bromination of nitrosoarenes with Br₂ has been proposed to be initiated by a HBr addition across the N–O bond.15 A similar hydroxylamine type of intermediate could also be envisioned in our case as we could observe azoxybenzene derivatives (formed by the condensation of hydroxylamine with a nitrosoarene) as byproducts in the reaction. The second equivalent of the Cu(II) halide, which was necessary to obtain full conversion, may be important for reoxidizing any hydroxylamine type of intermediates or for the stoichiometric generation of X₂ or HX, which are likely to be involved (Scheme 6, A). Alternative mechanisms, such as a nucleophilic attack of a halide anion on a Bamberger-type18 of nitrenium intermediate (B), or pathways involving radical species (C), cannot be ruled out. Whether BHT is involved in any important redox reactions, or serves as a radical scavenger to prevent unproductive radical pathways, remains unclear.

![Figure 1. Chlorination of 1b, monitored by 1H NMR (blue, 1b; red 2b).](image1)

![Figure 2. One-pot synthesis of halogenated anilines and nitroarenes: step 1, halogenation; step 2, oxidation/reduction (see the Supporting Information for details). (a) Product was not stable.](image2)
Scheme 6. Proposed Halogenation Intermediates

In short, we have developed an operationally simple para-selective method for the bromination and chlorination of a wide range of nitrosoarenes with Cu(II) halides. The resulting nitroso derivatives were, in a one-pot procedure, conveniently transformed into the corresponding anilines and nitroarenes. Thus, with a limited set of starting compounds and with an easy-to-execute method, a range of halogenated, nitrogen-functionalized products can be obtained in high regioisomeric purity and decent yields.

ASSOCIATED CONTENT
Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03198.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES


(14) See the Supporting Information for details.