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Metal-Free Functionalization of *N,N*-Dialkylanilines via Temporary Oxidation to *N,N*-Dialkylaniline *N*-Oxides and Group Transfer

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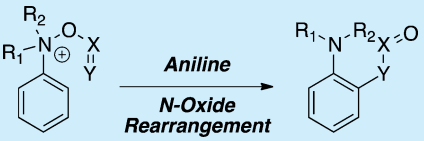
Supporting Information

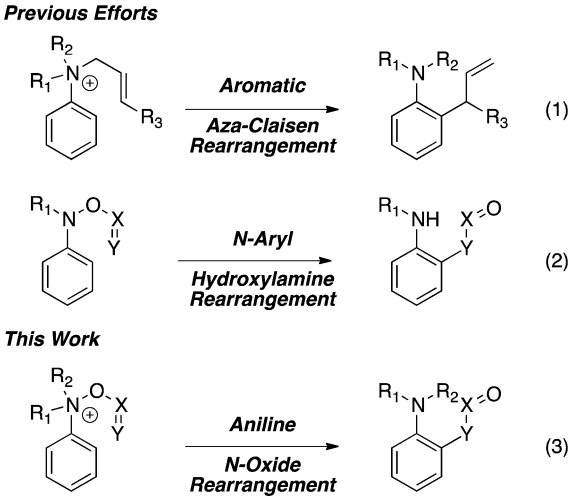
ABSTRACT: A simple set of protocols for the controlled elaboration of anilines is reported allowing access to a diverse array of aminophenols, aminoarylsulfonates, alkylated anilines, and aminoanilines in 29−95% yield in a single laboratory operation from easily isolable, bench-stable *N,N*-dialkylaniline *N*-oxides. The introduction of new C−O, C−C, and C−N bonds on the aromatic ring is made possible by a temporary increase in oxidation level and excision of a weak N−O bond.



Engaging anilines at nitrogen and executing a group transfer from nitrogen to carbon is an attractive method for the controlled functionalization of electron-rich aromatic rings, which are otherwise more problematic to manipulate.[1] The aniline and aminophenol substructures are embedded in many synthetic building blocks, ligands and other catalyst frameworks, as well as a myriad of biologically active compounds.[2] Efficient access to these structures is of value to chemists in many fields, yet methods that allow selective and controlled elaboration of anilines remain rare.

The all-carbon aza-Claisen rearrangement of alkylated anilines is an inefficient process and does not provide a synthetically useful means of aromatic functionalization (Scheme 1, eq 1).[3] The introduction of weak, excisable *N*−*O* bonds into the operative bond network affords the opportunity to exploit this important scaffold for complexity generating reactions.[4] The rearrangement of various acylated *N*-arylhydroxylamines in this pursuit to give protected hydroxyanilines has a long history dating to the mid-1950s, and various pericyclic, ion-pair, and radical-type mechanisms have been examined (Scheme 1, eq 2).[4,5] A small number of carbon−carbon bond formations utilizing these substrates have also been described over the same time period, but substrate scope is generally limited to migrating groups that can support an anion.[6] A recent series of investigations greatly expanded the landscape of carbon−heteroatom bond formations in *N*-arylhydroxylamine rearrangements, allowing access to hydroxy- and aminoanilines, as well as cyclized products.[7] These transformations are described as concerted [3,3]-sigmatropic rearrangements and in most cases require prolonged exposure to elevated temperature, microwave heating, or other potentially deleterious reaction conditions. Most of these transformations are efficient but require judicious choice of nitrogen-protective groups and can also be sensitive to the electronic nature of the aromatic ring.

Scheme 1. Aromatic Rearrangements Featuring *N* → *C* Group Transfer



We had need of several substituted anilines and sought to overcome some of the limitations of the *N*-arylhydroxylamine rearrangements and provide a single platform on which one could execute a variety of bond formations on anilines under mild reaction conditions at low temperature (Scheme 1, eq 3). Herein, we describe C−O, C−C, and C−N bond formations under exceptionally mild reaction conditions that function by virtue of an increase in oxidation level from aniline to aniline *N*-oxide. Aniline *N*-oxides are conveniently generated from the corresponding anilines, easily isolated and handled, and are generally bench stable.[8,9] Following an *O*-acylation event, group transfer from nitrogen to carbon excises the weak *N*−*O* bond and gives an iminium ion, and after loss of a proton, aromaticity and electron density at nitrogen are restored. These bond formations proceed in seconds to minutes at low temperature. The transformation of *N,N*-dialkylaniline-*N*-oxides into oxygenated anilines was explored in the classical Boyland−Sims oxidation,[10] with several mechanistic inquiries described in the literature.[11]

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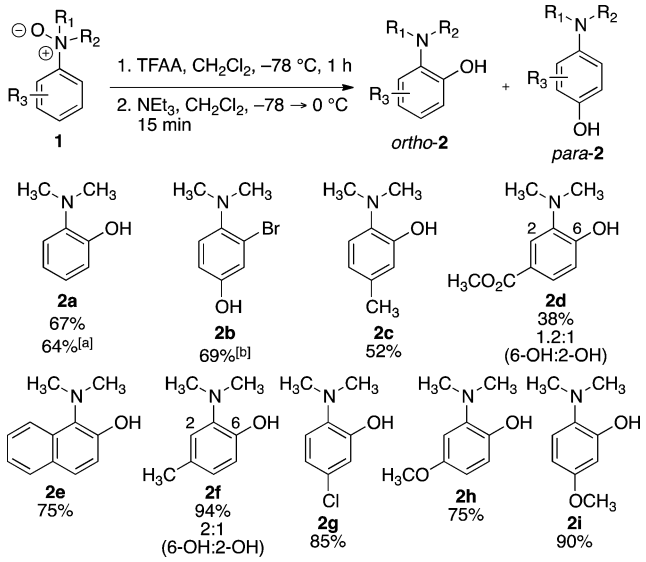
Milder, more controlled transformations in this context were probed briefly in the past, and in these early mechanistic studies, reaction yields varied widely (6−90%) with side products attributed to the multiple mechanistic pathways that are available (concerted rearrangements, ion-pair, and radical pathways).[12] To our knowledge, there are only two prior examples of carbon−carbon bond formations in this context, the reaction of *N,N*-dimethylaniline-*N*-oxide with diketene and acetylene dicarboxylates.[13] In that work, spectroscopic data supported mechanisms in which *O*-acylation/alkylation events are followed by fragmentations into radical pairs, which recombined to give the alkylated products. The alkylated products were accompanied by several side products and thus other mechanistic possibilities could not be excluded.[14]

We describe efficient access to a variety of aminophenols by sequential treatment of *N,N*-dialkylaniline *N*-oxides with trifluoroacetic anhydride and triethylamine in dichloromethane at −78 °C (Scheme 2). The intermediate trifluoroacetate esters

Scheme 2. Hydroxylation of *N,N*-Dialkylaniline *N*-Oxides*

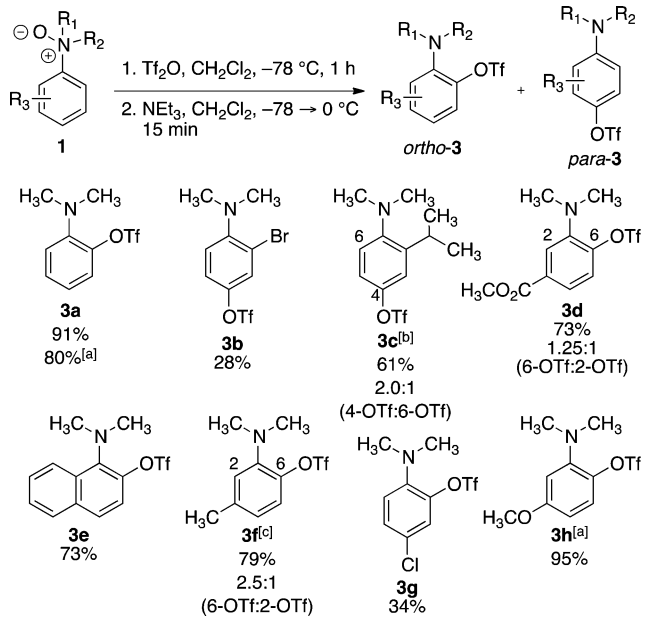


*Yields of isolated products; reactions were performed on a 1.0 mmol scale. [a]Reaction conducted on a 10.0 mmol scale. [b]The 2-bromo-6-hydroxy-*N,N*-dimethylaniline product was detectable in the crude product mixture but inseparable from the 2-bromo-*N*-methylaniline side product.

are hydrolyzed on workup to give the phenols directly in 52−94% yield. These conditions strongly favor *ortho* functionalization, with the exception that substrates bearing a single *ortho* substituent modestly favor the 4-hydroxy-*N,N*-dialkylaniline product (e.g., Scheme 2, product **2b**). We have not conclusively determined the mechanism of the group transfer, and studies are ongoing. As in the prior investigations, possibilities include concerted [3,3]-sigmatropic rearrangements, ion-pair, and radical pathways. In any case, we were not surprised to observe that substrates with no open *ortho* or *para* positions (i.e., 2,4,6-trimethyl-*N,N*-dimethylaniline) give no hydroxylated product. Substrates bearing a *meta* substation give mixtures of *ortho* hydroxylation products, favoring the less sterically encumbered product (1.2−2:1). The reaction functions well with both electron-donating and -withdrawing substitutents with two notable exceptions, substrates bearing *o*-methyl or *p*-carbonyl substituents. In the case of *o*-methyl substitution, the acylation event is followed by nonspecific decomposition via what appears to be a deprotonation that gives an aza-xylylene.[15] In the case of *p*-carbonyl substitution, the acylation event is followed by deprotonation of the *N*-methyl to give an iminium ion that hydrolyzes on workup to result in the corresponding *N*-methylaniline product.[16]

Trifluoromethanesulfonic anhydride (triflic anhydride, Tf_2O) and *p*-toluenesulfonyl chloride (tosyl chloride) also serve as viable acylation/oxygenation agents (Schemes 3 and 4).[7]

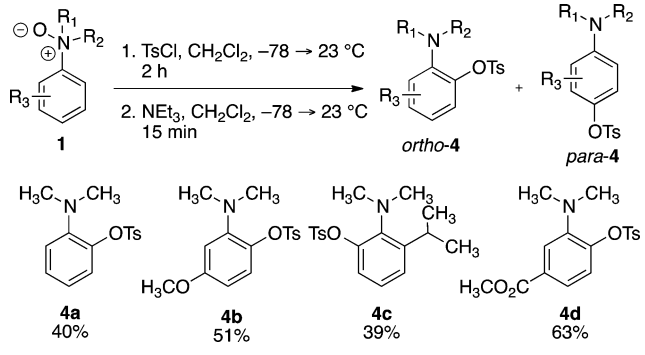
Scheme 3. Trifluoromethanesulfonylation of *N,N*-Diallkylaniline *N*-Oxides*



*Yields of isolated products; reactions were performed on a 1.0 mmol scale. [a]Reaction was performed on a 10.0 mmol scale. [b]Reaction was performed for 2 h at −78 °C prior to addition of triethylamine. [c]Product was isolated as a mixture of regioisomers.

Sequential treatment of *N,N*-dialkylaniline *N*-oxides with triflic anhydride or tosyl chloride and triethylamine in cold dichloromethane gives a variety of aryl sulfonates in moderate to excellent yields. As above, we observed the same regiochemical preferences for functionalization and the same liabilities with

Scheme 4. *p*-Toluenesulfonylation of *N,N*-Diallkylaniline *N*-Oxides[a]



[a]Yields of isolated products; reactions were performed on a 1.0 mmol scale.

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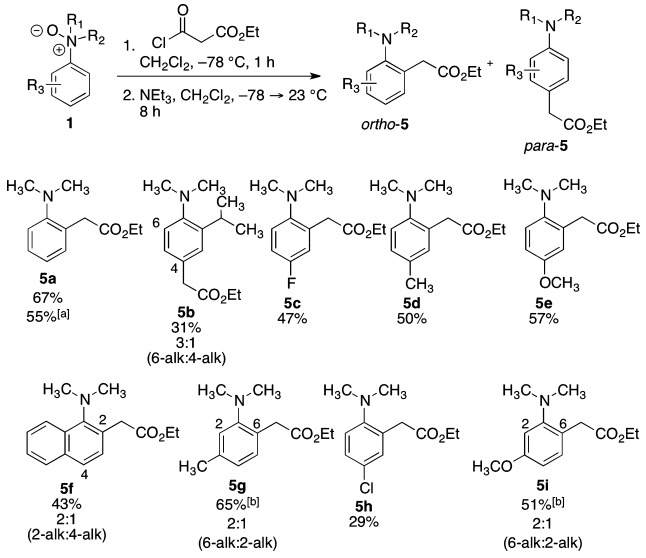
respect to methyl and carbonyl substitution. Additionally, the sulfonylated aniline *N*-oxides are more vulnerable to the unproductive elimination reaction pathway that gives rise to *N*-methylanilines. This reaction pathway dominates in substrates bearing strong electron donors at the *para* position (e.g., *N*,*N*-dimethyl-*p*-anisidine), but strong electron donors are tolerated at the *meta* position (e.g., *N*,*N*-dimethyl-*m*-anisidine gives products **3h** and **4b** in 95% and 51% yield, respectively).

Importantly, the elevated reactivity of *N*,*N*-dialkylaniline *N*-oxides allows facile carbon−carbon bond formation under exceptionally mild reaction conditions: *O*-acylation events that give C−C π-systems in their wake result in efficient and clean *N* → *C* group transfer, and following rearrangement, a decarboxylation gives the final alkylated products. Ethyl malonyl chloride,[17] a substrate that will present a π-system by virtue of its existence predominantly as an enol tautomer, functions successfully in this context (Scheme 5). We have noted the same

Scheme 5. Alkylation of *N*,*N*-Dialkylaniline *N*-Oxides with Ethyl Malonyl Chloride*



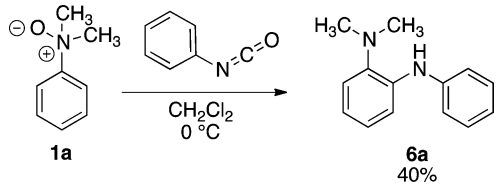
*Yields of isolated products; reactions were performed on a 1.0 mmol scale. [a]Reaction was performed on a 10.0 mmol scale. [b]Product was isolated as a mixture of regioisomers.

regiochemical preferences as in the above carbon−heteroatom bond formations and the same liability with respect to demethylation to give *N*-methylanilines. Moreover, the carbon−carbon bond formation event appears to be quite facile, occurring at low temperature in a matter of minutes; the slowest event of the reaction sequence appears to be the decarboxylation. The reaction functions well for both electron-donating and -withdrawing substitutents, and *C*-alkylated products are obtained cleanly in 29−67% yield.

Methods for the direct amination of anilines are exceptionally rare.[7] We have successfully executed a group transfer to give a new C−N bond using *N*,*N*-dialkylaniline *N*-oxides and phenyl isocyanate as a nitrogen source (Scheme 6), which to our knowledge is only the second example of the introduction of a new C−N bond on an aromatic ring utilizing an aniline *N*-oxide.[13b,18] Studies to increase the efficiency of this transformation are ongoing.

The elevated reactivity of *N*,*N*-dialkylaniline *N*-oxides facilitates clean, efficient, controlled, and scalable introduction

Scheme 6. Amination of *N*,*N*-Dimethylanline *N*-Oxide (1a)



of carbon−heteroatom and carbon−carbon bonds onto the aromatic ring in the absence of metals, Lewis acids, or other exotic reagents. Our future efforts are directed toward unraveling the mechanistic details of these reactions, expanding the scope of new bond forming reactions of aniline-*N*-oxides, and the application of these methods to natural product synthesis. These studies will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectral data for compounds **1**−**6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(9) Substrates with benzylic or allylic substitution at nitrogen readily undergo [1,2]- and [2,3]-Meisenheimer rearrangements; see: (a) Meisenheimer, J. *Ber.* **1919**, *52B*, 1667−1677. (b) Meisenheimer, J.; Greeske, H.; Willmersdorf, A. *Ber.* **1922**, *55B*, 513−532. (c) Kleinschmidt, R. F.; Cope, A. C. *J. Am. Chem. Soc.* **1944**, *66*, 1929−1933. (d) Pine, S. H. *Org. React.* **1970**, *18*, 403−464. (e) Oae, S.; Ogino, K. *Heterocycles* **1977**, *6*, 583−675. (f) Hoffmann, R. W. *Angew. Chem., Int. Ed.* **1979**, *18*, 563−572. (g) Brückner, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. *6*, pp 873−908. (h) Markó, I. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. *3*, pp 913−974. (i) Albini, A. *Synthesis* **1993**, 263−277. (j) Sweeney, J. B. *Chem. Soc. Rev.* **2009**, *38*, 1027−1038.

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