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Direct synthesis of anilines and nitrosobenzenes from phenols†

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A one-pot synthesis of anilines and nitrosobenzenes from phenols has been developed using an *ipso*-oxidative aromatic substitution ($^{i}S_{O}Ar$) process. The products are obtained in good yields under mild and metal-free conditions. The leaving group effect on reactions that proceed through mixed quionone monoketals has also been investigated and a predictive model has been established.

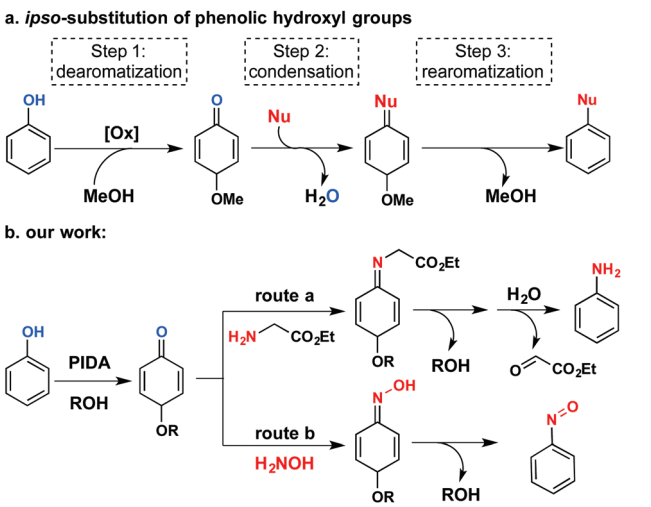
Introduction

Due to their importance and ubiquity, significant efforts have been devoted toward the construction of aryl amines.[1] Transition metal catalyzed approaches, such as the Buchwald–Hartwig[2] coupling and Ullmann-type amination,[3] represent a particularly powerful and well-developed approach using aryl halides as the aryl coupling partner. Despite the success of these methods, there has been increased interest in developing ways to access aryl amines that do not rely on aryl halides that must be pre-synthesized.[4] In this context, phenols represent an ideal starting material because they are one of the most prevalent and diverse classes of natural products.[5,6]

The conversion of phenols to aryl amines, such as anilines, using a metal-catalyzed reaction typically requires high temperature[7] or functionalization of the phenol into a more active derivative (*e.g.*, triflates, tosylates, carbamate derivatives)[8] followed by a cross coupling reaction. Alternatively, aniline derivatives have been constructed directly from phenols using a tandem alkylation, Smiles rearrangement, and hydrolysis approach.[9] However, this strategy is limited because it requires strong base and either high temperatures or phenols bearing electron-withdrawing groups.

Based on our interest in developing carbon–nitrogen bond forming reactions,[10] we sought to explore the direct one-pot synthesis of aryl amines from phenols, specifically the synthesis of anilines and nitrosobenzene derivatives. Our investigations were inspired by a pioneering report by Taylor and Jagdmann in 1978, where they disclosed the conversion of *p*-methoxyphenol to *p*-anisidine, *p*-methoxynitrosobenzene, *p*-methoxyazobenzene and ethyl *p*-methoxyphenylacetate through an *ipso*-oxidative aromatic substitution ($^{i}S_{O}Ar$) process.[11]

Surprisingly, this approach that proceeds through *ipso*-substitution has been largely ignored by the synthetic community,[12] presumably due to use of toxic thallium(III) nitrate[13] as the oxidant and the limited substrate scope; in most cases a single example was reported.[11] However, we felt that this reactivity pattern (Scheme 1a), (*i.e.*, the *ipso* substitution of the phenolic hydroxyl group through an dearomatization/condensation/rearomatization process) warranted further investigation, especially considering the ubiquity of phenols in natural products and pharmaceutically active compounds. Leveraging developments in oxidative dearomatization using



Scheme 1 *ipso*-Oxidative aromatic substitution of phenolic hydroxyl groups.

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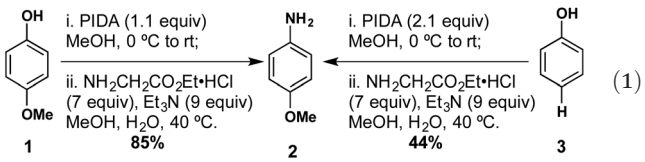
iodine(III) reagents,[14] we envisioned that the use of phenyliodoso diacetate (PIDA) for the oxidative dearomatization of the phenol derivatives would allow access to a broader scope of quinone monoketals, as well as provide a safer alternative to thallium(III) nitrate. Herein, we report our studies that describe the efficient, one-pot synthesis of anilines and nitrosobenzenes from phenols through a tandem dearomatization/condensation/rearomatization process ($^{i}S_{O}Ar$, Scheme 1b).

Results and discussion

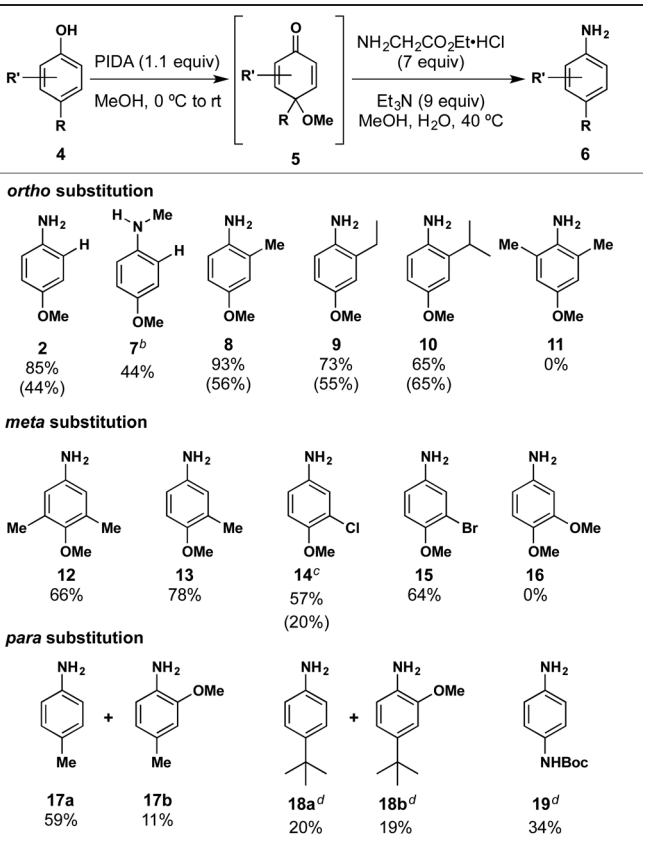
We began our studies using 4-methoxyphenol, as its PIDA oxidation is high yielding in methanol. After oxidation, the quinone monoketal was reacted directly with an excess of the inexpensive ethyl glycinate hydrochloride, triethylamine, and 5% water. Under these conditions *p*-anisidine could be synthesized directly from *p*-methoxyphenol (**1**) in 85% yield (eqn (1)). Phenol (**3**) could also be used as a starting material, although a lower yield (44%) was obtained due to the known poor efficiency of the PIDA double oxidation.[15] The reaction could be conducted on gram scale (57% isolated yield), which allowed the loading of ethyl glycinate to be reduced from seven to two equivalents (see ESI† for details). Notably, neither the condensation intermediate nor Schiff base were isolated; the reaction proceeded completely to *p*-anisidine *in situ*.



(1)

With reaction conditions in hand for the one-pot transformation, we next investigated the scope (Table 1). Initially, the steric tolerance at the *ortho* position was probed using both mono- and di-*ortho* substituted phenols (**8–11**). Given that the reaction presumably proceeds through an imine intermediate, we were delighted to discover that the reaction tolerated *ortho* substitution on the phenol. While 2-*tert*-butylphenol proved to be too bulky for condensation to occur (not shown), the 2-methyl, 2-ethyl, and 2-isopropyl derivatives all proceeded smoothly to the aniline product (**8–10**). Unsurprisingly, the oxidation of 4-methoxy-2,6-dimethylphenol produced a quinone monoketal but this intermediate was also unreactive under our conditions, suggesting that one of the *ortho* positions must be unsubstituted in order for the imine intermediate to form. The *meta* position tolerated a wider-range of substituents, with dimethyl, methyl, chloro, and bromo 4-methoxyphenols all proceeding to the aniline in good yield (**12–15**). Electron rich quinone monoketals derived from 3,4-dimethoxyphenol did not result in the desired aniline (**16**) formation. In this case, the quinone was consumed *via* a 1,4-addition reaction with methanol or ethyl glycinate (not shown; similar decomposition products were observed with 2-*tert*-butylphenol described above).[16] Phenols bearing an alkyl group at the 4-position also participated in the reaction

Table 1 Scope of aniline synthesis from phenol derivatives[a]

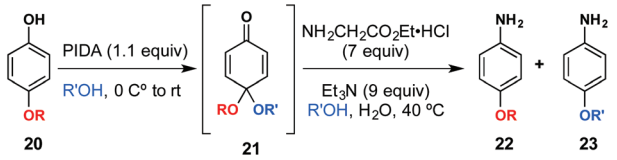


[a] Reactions conducted on 2 mmol scale. Yields determined by ^{1}H NMR using dimethyl terephthalate (DMT) as an internal standard. Yields in parentheses are from reactions with 4-unsusbstituted phenols and 2.1 equiv. of PIDA. [b] $MeNHCH_2CO_2Et{\cdot}HCl$ was used as the nitrogen source. [c] 1 mmol scale. [d] Isolated yield.

(**17a** and **18a**), although *ortho*-methoxylation by-products (**17b** and **18b**) were also produced; the formation of regioisomers is a consequence of the PIDA oxidation. The reaction can be extended to amino phenols, resulting in the diamine (**19**) in moderate yield. Finally, we evaluated the possibility of generating substituted anilines. Although less efficient when compared to ethyl glycinate, ethyl sarcosinate can be used as the nitrogen source, generating the *N*-methyl aniline **7** in moderate yield. It is worth noting that column chromatography can be avoided in most cases, with purification through an acid/base extraction yielding the desired aniline with good purity.

Based on the presumed mechanism of the transformation, we next turned our attention to exploring reactions that proceed through a mixed quinone monoketal. Whereas previous studies focused on the rearomatization of pre-formed mixed quinone monoketals,[17] we were interested in the product distribution generated directly from phenols *via* the *in situ* $^{i}S_{O}Ar$ protocol. To evaluate the leaving group preference, we studies seven different phenolic starting materials which formed mixed quinone monoketal intermediates *in situ via* a PIDA oxidation in methanol (Table 2, entries 1–7). Consistent

Table 2 Alkoxide effect on product formation *via* mixed quinone monoketals[a]



Entry	R	R′OH	% Yield	% Yield
1	iPr	MeOH	**24** R = iPr, 75	**2** R′ = Me 10
2	Et	MeOH	**25** R = Et, 72	**2** R′ = Me, 21
3	4-MeOBn	MeOH	**26** R = 4-MeOBn, 37	**2** R′ = Me, 45
4	Bn	MeOH	**27** R = Bn, 33	**2** R′ = Me, 52
5	4-NO_2Bn	MeOH	**28** R = 4-NO_2Bn, 5	**2** R′ = Me, 57
6	CH_2CF_3	MeOH	0	**2** R′ = Me, 76
7	Ac	MeOH	0	**2** R′ = Me, 21
8[b]	Bn	TFE	**27** R = Bn, 44	0
9[b]	Me	TFE	**2** R = Me, 43	0
10	Me	EtOH	**2** R = Me, 16	**25** R′ = Et, 67
11	Et	EtOH	**25** R = Et, 82	NA
12	Me	iPrOH	**2** R = Me, 5	**24** R′ = iPr, 11

[a] Reactions conducted on 2 mmol scale. Yields determined by ^{1}H NMR using dimethyl terephthalate (DMT) as an internal standard. [b] 0.5 mmol scale.

with previous observations,[17] there is a clear correlation between the electronic character of the alkoxide in structure **21**, OR *vs.* OR′, that is retained in the final product: the more electron rich alkoxide relative to methoxide is retained preferentially in the final product (entries 1 and 2). Not surprisingly, diminished selectivity is observed with 4-methoxybenzyloxide and benzyloxide, which are more electronically similar to methoxide (entries 3 and 4). In line with these observations, the formation of 4-methoxyaniline becomes the predominant product if the alkoxy group is more electron deficient than methoxide (entries 5–7).

Conducting the PIDA oxidation in solvents other than methanol provides an alternative pathway to access the mixed quinone monoketals (entries 8–12). For example, 2,2,2-trifluoroethanol (TFE) can be used as a solvent for the ^iS_OAr reaction, and while the product yields are low due to the poor efficiency of the PIDA oxidation in TFE, the starting alkoxy group is exclusively retained in the product (entries 8 and 9). To our satisfaction, the reaction works well in ethanol affording 4-ethoxyaniline in good yield (entries 10 and 11). Interestingly, the yield of 4-ethoxyaniline (**25**) was nearly identical when the reaction was conducted in methanol *vs.* ethanol (entries 2 and 10). This observation is consistent with the product-determining step being elimination of the least basic alkoxide and suggests that isolation of the mixed quinone monoketal is not necessary. From a synthetic point of view, this is attractive because it provides two complimentary routes to access anilines such as **25**. This approach was extended to an isopropyl derivative (entry 12), however it was challenging to determine the generality due to the poor reaction efficiency in isopropanol.[18]

In general, the product distribution observed in Table 2 correlates directly with pK_a in that the alkoxy group having the lower pK_a is preferentially eliminated. Although similar observations have been reported previously,[17] direct correlation of this trend to pK_a has not been demonstrated. Toward that end, we have formulated a Hammett-like treatment for the mixed quinone monoketals listed in Table 2 (entries 1 to 5). To do so, we defined σ_{ROH} as the difference between the pK_a of methanol and the conjugate acid of the alkoxy substituent appended to the starting material, **20** (eqn (2)). We also defined "alkoxide retention" as a quotient corresponding to the yield of 4-alkoxy aniline **22** divided by the sum of the yields for products **22** and **23** (eqn (3)). Thus, the quotient accesses the tendency of the original substituent to be retained in the product rather than be eliminated from structure **21**. Consequently, the larger the quotient, the less likely the original substituent will be eliminated.

$$\sigma_{ROH} = pK_a(MeOH) - pK_a(ROH) \quad (2)$$

$$\text{Alkoxide retention} = (\text{yield of 4-alkoxy aniline})/\text{total yield} \quad (3)$$

The resulting modified Hammett plot, illustrated in Fig. 1, reveals that, the more electron poor the alkoxide, the more likely it is to be eliminated during the rearomatization process, which is consistent with the negative rho value (ρ = −0.49). Importantly, this analysis can be applied to mixed quinone monoketals in other systems (see ESI† for details), and be used to design a synthesis where the 4-alkoxy group is retained or exchanged in the product.

Encouraged by the direct conversion of phenols into anilines and based on our interest in nitroso chemistry,[10a,b,d] we sought to extend our methodology to a one pot synthesis of nitrosobenzene derivatives using hydroxylamine (Table 3). Treatment of the substituted quinone adducts generated *in situ* with hydroxylamine sulphate and pyridine (2 equiv.) resulted in moderate to good yields of the desired nitroso compounds (**32**, **34**–**38**). The reaction works well for the conversion of 4-methoxyphenol into 4-methoxynitrosobenzene (**32**), however this methodology does not tolerate *ortho* substitution (**33**). The reaction works well for *meta*-substituted derivatives such as dimethyl, methyl, chloro, and bromo 4-methoxyphenols (**34**–**37**). As with the aniline derivatives, the reaction of

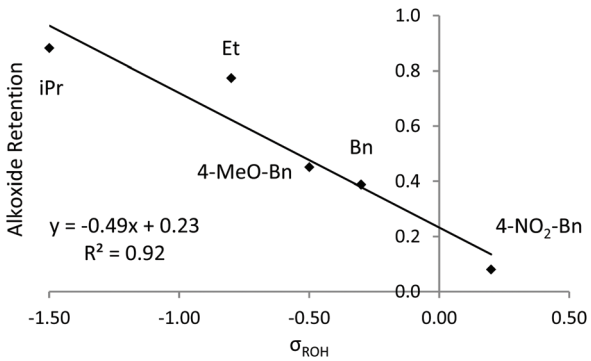
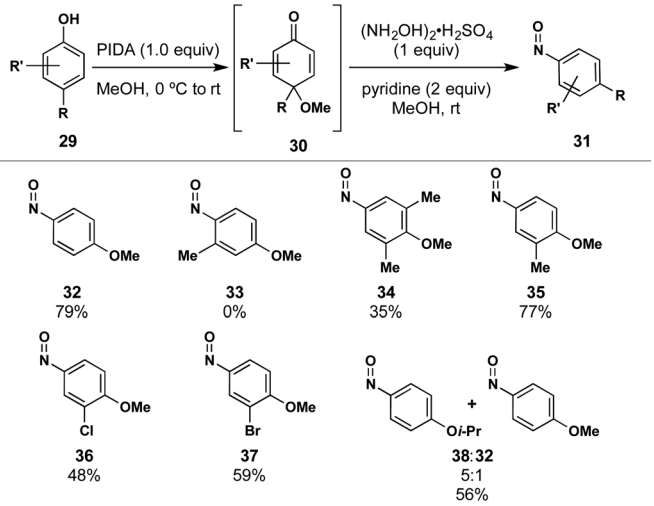


Fig. 1 Modified Hammett plot for the reaction of mixed quinone monoketals.

Table 3 Scope of nitrosobenzene derivatives from phenol derivatives[a]



[a] Reactions conducted on 0.25 mmol scale. Isolated yield after purification by column chromatography.

4-isopropoxyphenol in methanol gives a distribution of products (5 : 1, **38** : **32**), where the major product corresponds to retention of the more electron rich alkoxide group. This one-pot protocol provides a direct approach to access electron rich nitroso derivatives from readily available phenols.

Conclusions

We have described a one-pot, metal-free synthesis of nitrogen-containing aryl compounds using the underdeveloped $^{i}S_{O}Ar$ reaction. The mild access to a variety of electron-rich anilines complements the existing methods from electron-poor phenols. The scope of nitrosobenzenes was explored, providing access to these useful intermediates directly from phenols. Our analysis of leaving groups in mixed quinone monoketals allows the prediction of products and has applications beyond the chemistry described herein. The exploration of the scope, limitations, and mixed quinone monoketals lays the foundation for a powerful method to form aryl-nitrogen bonds from phenols.

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