One-Pot, Metal-Free Conversion of Anilines to Aryl Bromides and Iodides

Derek A. Leas,[†] Yuxiang Dong,[†] Jonathan L. Vennerstrom,[†] and Douglas E. Stack*[,‡]

[†]Department of Pharmaceutical Sciences, College of Pharmacy, University of Nebraska Medical Center, Omaha, Nebraska 68198-6125, United States

[‡]Department of Chemistry, University of Nebraska at Omaha, Nebraska 68182, United States

S Supporting Information

ABSTRACT: A metal-free synthesis of aryl bromides and iodides from anilines via halogen abstraction from bromotrichloromethane and diiodomethane is described. This one-pot reaction affords aryl halides from the corresponding anilines in moderate to excellent yields without isolation of diazonium salts. The transformation has short reaction times, a simple workup, and insensitivity to moisture and air and avoids excess halogenation. DFT calculations support a $S_{RN}1$ mechanism. This method represents a convenient alternative to the classic Sandmeyer reaction.
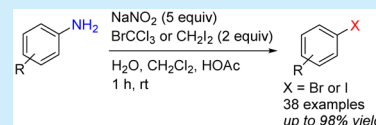
Aryl halides are pivotal intermediates in palladium- and copper-catalyzed cross-coupling reactions.[1] Haloarenes are also important structural motifs in bioactive compounds.[2−5] Ever since Sandmeyer reported that aryldiazonium halides undergo copper halide catalyzed decomposition into haloarenes, multiple reaction variants have been developed such as in situ diazotization,[6] substitutive deamination,[7] phase-transfer catalysis,[8,9] and nucleophilic substitution.[10] Although these previous syntheses of aryl halides from aryl amines produce satisfactory yields, they suffer from numerous competing reactions, time-consuming workup, diazonium salt isolation, and excess halogenation.[7,11−13]

A potentially attractive alternative to conventional aryl halide syntheses is free-radical-mediated halogen abstraction. Halogen abstraction was proposed by Oae et al. in the conversion of anilines, treated with *tert*-butyl thionitrite in the presence of bromoform and iodide, to aryl bromides and iodides.[14] Free-radical generation offers halogen abstraction in solution under mild reaction conditions compatible with sensitive substrates. Recently Burglova et al.[15] described a procedure for one-step deuterium introduction by deamination of anilines (Scheme 1). Using this as a springboard, we explored the conversion of anilines to the corresponding aryl bromides and iodides. We now describe a convenient one-pot method for the metal-free synthesis of aryl bromides and iodides from anilines by halogen

abstraction from $BrCCl_3$ and CH_2I_2 under weakly acidic conditions.

We began model reaction development by exploring the reaction of 4-aminobenzonitrile (**1a**) (Table 1, entry 1) with $NaNO_2$ and a large molar excess of $BrCCl_3$ in the presence of HOAc using a CH_2Cl_2/H_2O two-phase solvent system for 24 h at rt. Under these conditions, 4-bromobenzonitrile (**2a**) was generated in good yield (70%). Using 2 equiv of $BrCCl_3$ and a reaction time of 1 h (Table 1, entry 5), we found that aniline **1a** was converted to aryl halide **2a** in 84% yield. Thus, excess halogen atom source had a small effect on product formation and was optimal at 2 equiv with 5 equiv of $NaNO_2$. Changing the acid source from HOAc to HCl (entry 8) diminished the yield of product **2a** slightly (75%).

When CCl_4 was used as the halogen source (entry 10), benzonitrile was formed, suggesting hydrogen abstraction from CH_2Cl_2 is faster than chlorine abstraction. CBr_4 and CH_2I_2 afforded the corresponding halide products **2a** and **3a** in moderate to good yields (Table 1, entries 12 and 13). When we ran the reaction under Ar (Table 1, entry 14), the yield of **2a** increased only slightly (90% vs 84%). Increasing the reaction temperature from rt to 70 °C (Table 1, entry 15) eroded the yield (64%) due to generation of benzonitrile (7%), 4-nitrobenzonitrile (5%), and 4,4′-(1-triazene-1,3-diyl)bis-benzonitrile (21%). Although a single-phase CH_3CN/H_2O system (Table 1, entry 9) gave a yield similar to that of the biphasic CH_2Cl_2/H_2O system (Table 1, entry 5), the latter is preferred due to the solubilizing power of CH_2Cl_2, easy diazotization in the water layer, and convenient separation of final products from inorganics and salts.[9,15]
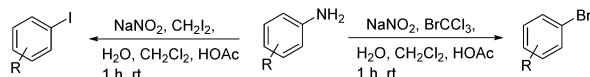
We investigated the scope of the new reaction using the conditions from entries 5 and 13 (Table 1) to synthesize a range of aryl bromides and iodides (Figure 1). The reaction

Scheme 1. Aromatic Deamination
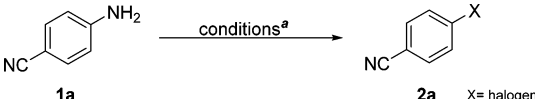

(a) Previous work by Burglova et al.
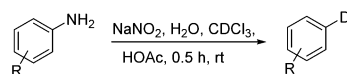
(b) This work

Table 1. Optimization of the Reaction Conditions

entry	NaNO$_2$ (equiv)	halogen source (equiv)	acid (equiv)	solvent system	time (h)	temp (°C)	yield[b] (%)
1	5.7	BrCCl$_3$ (57)	HOAc (20)	CH$_2$Cl$_2$/H$_2$O	24	23	70
2	5.7	BrCCl$_3$ (57)	HOAc (20)	CH$_2$Cl$_2$/H$_2$O	1	23	68
3	5	BrCCl$_3$ (5.3)	HOAc (20)	CH$_2$Cl$_2$/H$_2$O	1	23	70
4	10	BrCCl$_3$ (5)	HOAc (20)	CH$_2$Cl$_2$/H$_2$O	1	23	75
5	**5**	**BrCCl$_3$ (2)**	**HOAc (20)**	**CH$_2$Cl$_2$/H$_2$O**	**1**	**23**	**84**
6	2.5	BrCCl$_3$ (2)	HOAc (20)	CH$_2$Cl$_2$/H$_2$O	1	23	57
7	1.5	BrCCl$_3$ (2)	HOAc (20)	CH$_2$Cl$_2$/H$_2$O	1	23	52
8	5	BrCCl$_3$ (2)	HCl (20)	CH$_2$Cl$_2$/H$_2$O	1	23	75
9	5	BrCCl$_3$ (2)	HOAc (20)	CH$_3$CN/H$_2$O	1	23	80
10	5	CCl$_4$ (2)	HOAc (20)	CH$_2$Cl$_2$/H$_2$O	1	23	4[c]
11	5		HOAc (20)	CH$_2$Cl$_2$/H$_2$O	1	23	0
12	5	CBr$_4$ (2)	HOAc (20)	CH$_2$Cl$_2$/H$_2$O	1	23	50
13	**5**	**CH$_2$I$_2$ (2)**	**HOAc (20)**	**CH$_2$Cl$_2$/H$_2$O**	**1**	**23**	**81**
14	5	BrCCl$_3$ (2)	HOAc (20)	CH$_2$Cl$_2$/H$_2$O	1	23	90[d]
15	5	BrCCl$_3$ (2)	HOAc (20)	CH$_2$Cl$_2$/H$_2$O	1	70	64[e]

[a]Reaction conditions: **1a** (1.7 mmol), NaNO$_2$, halogen source, and solvent system (5 mL each of organic solvent and H$_2$O) were added to a reaction flask and stirred (5 min). Acid source was slowly added in one portion with stirring, and the reaction was covered with a balloon for the specified time. [b]Isolated yield is listed unless stated otherwise. [c]Yield determined by GC/MS. [d]Under Ar atmosphere. [e]The reaction was conducted under atmosphere in a sealed vessel.
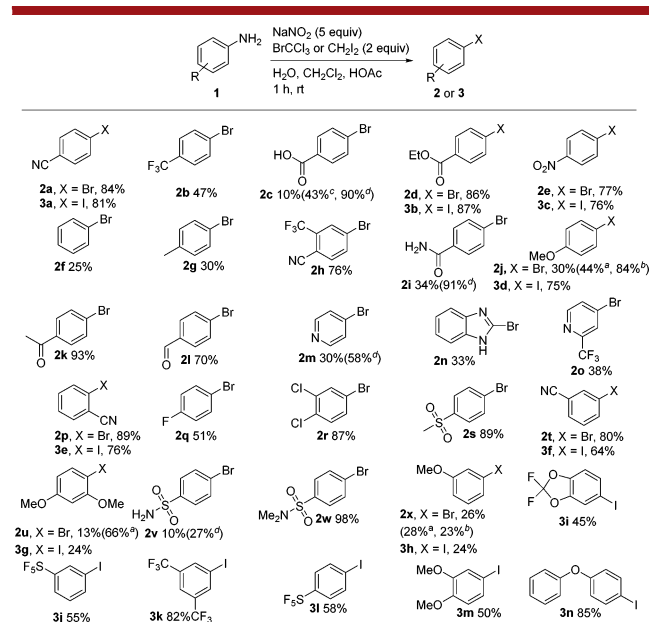

Figure 1. Aniline substrate scope. Key: (a) 23 °C, 24 h.; (b) 70 °C, 24 h, in a sealed vessel; (c) CH$_3$CN, 23 °C, 1 h; (d) CH$_3$CN, 70 °C, 24 h, in a sealed vessel.

Figure 2. Aqueous phase byproducts.

worked well with electron-withdrawing groups (EWG) such as trifluoromethyl (**2b**, **2h**, **3k**), ester (**2d**, **3b**), nitro (**2e**, **3c**), ketone (**2k**), aldehyde (**2l**), sulfone (**2s**), and pentafluorosulfanyl (**3j** and **3l**).

Bromination of *p*-anisidine afforded **2j** in 30% yield and generated several byproducts in the aqueous phase (Figure 2) including the hydrogen abstraction product anisole (**4a**) and the dimeric triazene **4b**, diazo **4c**, and biphenyl **4d**. However, when we added 2 equiv of NaN$_3$ prior to reaction workup, GC/MS analysis of the reaction mixture revealed generation of **2j*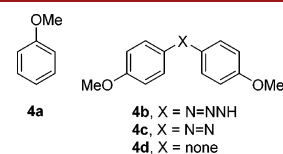* and 1-azido-4-methoxybenzene (**5a**, SI). This indirectly demonstrates that a large amount of 4-methoxybenzenediazonium remains unreacted in the aqueous layer, indicating that the electron-donating *p*-methoxy group deters the diazonium from decaying into the aryl radical intermediate. Hence, diazonium decomposition can be considered the rate-limiting step (RLS) for this reaction. When we extended the reaction time from 1 to 24 h, the yield of **2j** increased to 44%. Increasing the reaction temperature to 70 °C improved the yield of **2j** to 84%. These results suggest the lower yields obtained for electron-rich anilines can be attributed to the high stability of the diazonium intermediate at rt. *m*-Anisidine generated **2x** and **3h** in low yields (26% and 24%). Extending the reaction time and increasing the temperature did not increase reaction yields. We detected no azide reaction product after addition of NaN$_3$ to the aqueous layers, suggesting extensive byproduct formation in these reactions.

Unexpectedly, for electron-rich anilines, reaction yields tended to increase when CH$_2$I$_2$ was used as the halogen source (**3d** vs **2j**, **3g** vs **2u**), although for the latter reaction, the major product was 1,3-dimethoxybenzene. Other relatively electron-rich anilines afforded the corresponding iodides **3i**, **3m**, and **3n** in moderate to good yields. We hypothesize that the reaction generates iodide (eq 1) in situ, which can catalyze aryl radical formation as iodide is a better reducing agent than acetate. The presence of iodide is also supported by the observation that the solution developed a burgundy iodine color as a result of iodide oxidation.[16,17]

$$ICH_2OAc + H_2O \rightarrow HI + CH_2O + HOAc \qquad (1)$$
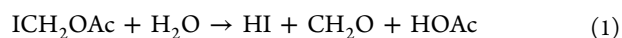
4-Bromobenzoic acid (**2c**) was produced in only 10% yield (Figure 1); multiple byproducts were detected via GC/MS, such as the triazene and azo dimers and the hydrogen abstraction product benzoic acid. Adding NaN$_3$ to the aqueous layer produced a large amount 4-azidobenzoic acid (**5b**, SI), suggesting that the unreacted diazonium intermediate is not highly soluble in CH$_2$Cl$_2$. When a water/CH$_3$CN solvent system (Table 1, entry 9) was used, **2c** was produced in 43% yield. Moreover, when the temperature was increased to 70 °C for 24 h, the yield of **2c** increased to 90%. This result indicates that the low initial yield of **2c** was due to poor solubility and later decomposition of the diazonium intermediate in the organic layer. Amide **2i** was also produced in low yield (34%) using the CH$_2$Cl$_2$/water solvent system at rt. However, when we used the water/CH$_3$CN solvent system (Table 1, entry 9) at 70 °C for 24 h, the yield of **2i** increased to 91%.

4-Bromobenzonitrile (**2a**), 2-bromobenzonitrile (**2p**), and 3-bromobenzonitrile (**2t**) were produced in yields ranging from 80 to 89%. 2-Bromobenzimidazole (**2n**) was produced in 33% yield from the corresponding amine. The unsubstituted 4-aminosulfanilamide gave only low yields (10−27%) of the aryl bromide reaction product **2v**, whereas the fully substituted 4-amino-*N*,*N*-dimethylbenzenesulfonamide afforded the corresponding reaction product **2w** in high (98%) yield. Pyridines **2m** and **2o** were produced in relatively low yields due to dimerization side products.

For this reaction, it appears that electron-deficient anilines afford higher yields than electron-rich anilines. However, increased reaction times and temperatures can improve the yields for electron-rich anilines. Additionally, a H$_2$O/CH$_3$CN solvent system can increase yields of aryl halides from anilines with low solubility in CH$_2$Cl$_2$.

To gain insight into the mechanistic details of this conversion, the reaction of **1a** was conducted in the presence of 2 equiv of TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxyl); under these conditions 4-((2,2,6,6-tetramethylpiperidin-1-yl)-oxy)benzonitrile (Scheme 2, **6a**) was formed in 50% yield. These results indicate the reaction proceeds through an aryl free radical resulting from homolytic bond cleavage of the diazonzium cation.

Scheme 2. Aryl Radical Trapping Experiment
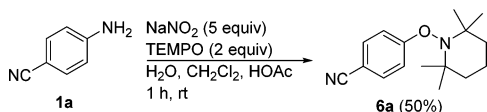
On the basis of the overall understanding of Sandmeyer-type reactions and previous mechanistic investigations,[9,18,19] we propose an S$_{RN}$1-like mechanism (Scheme 3). First, the aniline reacts with NaNO$_2$ to produce diazonium salt intermediate **A**. Then, a single-electron transfer from acetate causes diazonium decomposition to afford N$_2$, aryl radical **B**, and acetoxy radical **C**. Subsequently, radical **B** abstracts halide from the halogen source to produce the trichloromethyl radical, which then either combines with the remaining acetoxy radical **C** to generate active ester **D** or dimerizes to produce hexachloro-ethane **E**. Active ester **D** decomposes in aqueous conditions, and although we could not directly detect **D**, we were able to detect minute amounts of phenyl acetate and large amounts of **E** during the reaction, data which supports this mechanism.[9]

Scheme 3. Proposed Mechanism
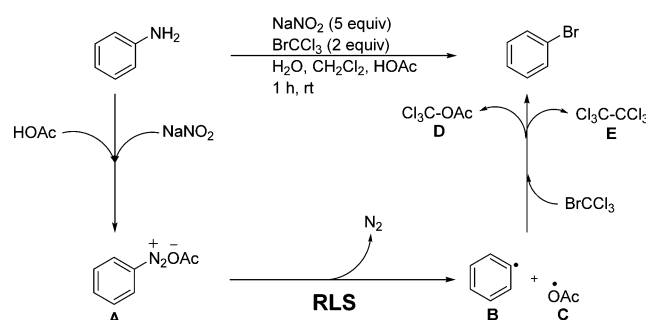
To assess the proposed reaction mechanism (Scheme 3) and to gain further insight into the origin of the effect of aryl substituents on diazonium degradation, we performed a computational study. We have already described that substantial quantities of unreacted diazonium (**A**, Scheme 3) intermediates remain in the aqueous layer for electron-rich anilines, consistent with the low yields for these substrates. Thus, one can consider the RLS to be that of diazonium degradation via homolytic bond cleavage to form a phenyl free radical (Scheme 3).

To explore the substituent effects of this reaction, a linear free energy relationship (LFER) study using DFT calculations was conducted. Relative thermodynamic stabilities of substituted diazonium cations and phenyl radicals compared to the unsubstituted phenyl counterparts were modeled using the UB3LYP functional. Relative free energy differences between substituted and unsubstituted substrates were obtained using the exchange reaction in Scheme S1. A combination of 12 para-substituted electron-donating and -withdrawing groups (EWG) were modeled on aryl radical and diazonium aromatic rings. Hammet plots were prepared by plotting the log (K_R/K_H), derived from the relative free energy differences, calculated using the exchange reaction in Scheme S1, versus Hammett substituent constants[20−22] σ_p (Figure 3) and σ_p^+ (Figure S1). Full computational details, calculations, and thermodynamic data are contained in the SI.
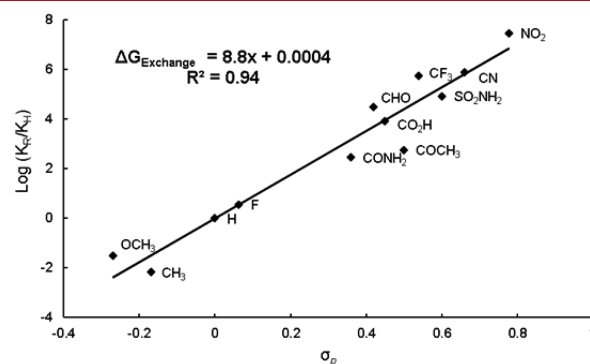
Figure 3. Hammet plot of calculated log (K_R/K_H) values vs σ_p values in CH$_2$Cl$_2$ solvent.

As seen by the linear correlations in Figure 3 and Figure S1, the etiology of the substituent effects on the degradation of aryl diazoniums to the corresponding aryl radicals is affected in a consistent way. The relative free energy differences of the exchange reaction divided by −1.36 kcal/mol represent the log (K_R/K_H) used in LFER plots (derivation is shown in the SI). The RLS (Scheme 3) involves a substantial decrease in positive

charge in going from diazonium cation to the free radical and should display a LFER with a large positive slope, ρ. Figure 3 shows the log (K_R/K_H) versus σ_p Hammet substituent constants with good linear correlation ($R^2 = 0.94$), indicating the *para* EWG substituents are generating partial positive character on the *ipso* aryldiazonium carbon with a combination of both inductive and resonance effects. The slope in Figure 3 is greater than that of Figure S1, $\rho = 8.8$ and 6.3, respectively, indicating greater substituent sensitivity to both inductive and resonance effects (contained in the σ_p constants) as opposed to just resonance effects.

We next evaluated the bond lengths in order to establish whether a correlation is present between aryl-substituent and aryldiazonium bond distance since increased bond lengths favor homolytic bond cleavage. Figure S2 shows the change in bond lengths versus σ_p for the substituted diazonium cations which revealed good correlation, $R^2 = 0.91$. Moreover, when we plotted the change in C−N aryldiazonium bond frequency versus σ_p (Figure S3), the electron-rich aromatic rings have higher frequency C−N bond vibrations relative to electron deficit aromatic rings, supporting a mechanism where the RLS involves homolytic bond cleavage.

The picture that emerges from the DFT calculations is one in which *para* EWGs weaken the *ipso* carbon−diazonium bond, prompting homolytic bond cleavage to produce an aryl radical which then abstracts a halogen atom. In cases such as **3d** and **3n**, we hypothesize that iodide generated in situ catalyzes the formation of aryl radicals. Overall, the results from Figures 1, 3, S1, and S2 demonstrate that the yield of aryl halide product is tuned in response to the electron-withdrawing and electron-donating ability of the aryl-ring substituents.

In conclusion, we have developed a Sandmeyer-type synthesis of aryl halides from anilines. This metal-free transformation is operationally simple, tolerates a variety of functional groups, and can be conducted under mild acidic conditions without the exclusion of air.

ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00771.

Experimental procedures; spectra for all new compounds; computational details of for the production of Figure 3 (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: dstack@unomaha.edu.

ORCID Ⓓ

Jonathan L. Vennerstrom: 0000-0003-0075-2336
Douglas E. Stack: 0000-0002-8253-860X

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

REFERENCES

(1) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442−4489.
(2) Cabrita, M. T.; Vale, C.; Rauter, A. P. *Mar. Drugs* **2010**, *8*, 2301−2317.
(3) Wilcken, R.; Zimmermann, M. O.; Lange, A.; Joerger, A. C.; Boeckler, F. M. *J. Med. Chem.* **2013**, *56*, 1363−1388.
(4) Lu, Y.; Liu, Y.; Xu, Z.; Li, H.; Liu, H.; Zhu, W. *Expert Opin. Drug Discovery* **2012**, *7*, 375−383.
(5) Xu, Z.; Yang, Z.; Liu, Y.; Lu, Y.; Chen, K.; Zhu, W. *J. Chem. Inf. Model.* **2014**, *54*, 69−78.
(6) Cadogan, J. I. G.; Roy, D. A.; Smith, D. M. *J. Chem. Soc. C* **1966**, 1249−1250.
(7) Doyle, M. P.; Siegfried, B.; Dellaria, J. F., Jr. *J. Org. Chem.* **1977**, *42*, 2426−2431.
(8) Bartsch, R. A.; Yang, I. W. *Tetrahedron Lett.* **1979**, *20*, 2503−2504.
(9) Korzeniowski, S. H.; Blum, L.; Gokel, G. W. *Tetrahedron Lett.* **1977**, *18*, 1871−1874.
(10) Lucas, H. J.; Kennedy, E. R. *Org. Synth.* **1943**, *2*, 351.
(11) Hodgson, H. H.; Walker, J. *J. Chem. Soc.* **1933**, 1620−1621.
(12) Karimi Zarchi, M. A.; Mousavi, S. Z. *J. Polym. Res.* **2014**, *21*, 1−9.
(13) Ku, H.; Barrio, J. R. *J. Org. Chem.* **1981**, *46*, 5239−5241.
(14) Oae, S.; Shinhama, K.; Kim, Y. H. *Chem. Lett.* **1979**, *8*, 939−942.
(15) Burglova, K.; Okorochenkov, S.; Hlavac. *Org. Lett.* **2016**, *18*, 3342−3345.
(16) Abeywickrema, A. N.; Beckwith, A. L. J. *J. Org. Chem.* **1987**, *52*, 2568−2571.
(17) Meyer, G. J.; Roessler, K.; Stoecklin, G. *J. Am. Chem. Soc.* **1979**, *101*, 3121−3123.
(18) Wang, S.; Qiu, D.; Mo, F.; Zhang, Y.; Wang, J. *J. Org. Chem.* **2016**, *81*, 11603−11611.
(19) Kochi, J. K. *J. Am. Chem. Soc.* **1957**, *79*, 2942−2948.
(20) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195.
(21) McDaniel, D. H.; Brown, H. C. *J. Org. Chem.* **1958**, *23*, 420−427.
(22) Swain, C. G.; Lupton, E. C., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 4328−4337.