RSC Advances

COMMUNICATION

View Article Online

A facile, regioselective and controllable bromination of aromatic amines using a CuBr₂/Oxone[®] system[†]

Cite this: DOI: 10.1039/c3ra41664j

Received 7th April 2013, Accepted 29th May 2013

DOI: 10.1039/c3ra41664j

www.rsc.org/advances

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A combination of cupric bromide and Oxone[®] serves as a facile, mild and effective reagent for the bromination of aromatic amines. Primary, secondary and tertiary aromatic amines are all suitable substrates. The reaction possesses high regioselectivity and functional group tolerance, and mono- and multi-brominated products can be obtained controllably in moderate to excellent yields.

Halogenation of aromatic compounds continues to be an important reaction in synthetic organic chemistry. Bromoarenes are particularly versatile intermediates for a variety of transformations that range from the synthesis of functionalized aromatic molecules¹ to any organometallic reagents utilized in modern transition metal-catalyzed couplings.² The classical electrophilic bromination of aromatic compounds involves the use of molecular bromine and mineral acids. However, this leads to obvious drawbacks such as harsh conditions (e.g., strongly acidic), hazardous waste, and problems associated with bromine-economy. Furthermore, aromatic amines, due to their high reactivity, tend to suffer from poor regioselectivity and polybromination is a common problem.³ Over the past decade, a wide range of mild, regio-specific protocols for the bromination of activated aromatic compounds have been developed with varying degrees of success.⁴⁻¹⁴ Representative methods include: the use of brominatother than ing molecular bromine like agents *N*-bromosuccinimide,⁴ hexamethylenetetramine-bromine complex,⁵ PVPP-Br₂ complex⁶ and bromide/DMSO systems;⁷ the use of a combination of a bromide salt and oxidant such as NH₄Br/ $H_2O_2,^8 \quad \text{MPHT/H}_2O_2,^9 \quad \text{KBr/peroxodisulfate},^{10} \quad \text{KBr/Oxone}^{\text{(R)}},^{11}$ NH₄Br/Oxone[®],¹² and LiBr/O₂;¹³ as well as the use of CuBr₂ alone.¹⁴ However, these methods, aiming largely at the bromination of electron-rich substrates such as phenols, aryl alkyl ethers, and polyalkyl-substituted arenes, involved only a few types and

narrow range of aromatic amines. In the studies that specialized in the halogenation of aromatic amines, in 2002 Smith et al.15 reported a bromination method for anilines using n-BuLi/R₃SnCl/ Br₂ at -78 °C, while in 2001 Tour *et al.*¹⁶ employed BnNEt₃ICl₂ as a halogenating reagent for the iodination of anilines. Accordingly, we desired to develop an improved protocol for the halogenation of aromatic amines, which should be mild, regioselective, substitution-controllable and, in particular, general (i.e., suitable for primary, secondary, and tertiary arylamines). Herein, we report our work on the oxidative bromination of aromatic amines. After a comprehensive evaluation of the existing methods, we decided on the use of a brominating system consisting of a bromide salt and an oxidant for the bromination of aromatic amines. Cupric bromide was selected as the preferred bromine source since it has long been known to affect the bromination of alkenes and alkynes, cause the α -bromination of carbonyl compounds,¹⁷ and was recently used for the mono-bromination of some electron-rich arenes.14

As a starting point, N-phenyl-1-naphthylamine was chosen as a model substrate in order to optimize the reaction conditions (Table 1). Upon the use of cupric bromide alone (0.5 molecules of CuBr₂ are equal to 1 equivalent of Br atoms), monobromination took place, but the reaction did not go to completion (Table 1, run 1). However, the use of excess CuBr₂ had a disappointing outcome where a substantial amount of the dibrominated product was produced, while the monobrominated product was isolated in only a low yield (run 2). We then examined protocols using CuBr₂ plus an additional oxidizing agent. Several commonly used oxidants were tested. H2O2 (30% aqueous solution) and TPHP (70% aqueous solution) totally suppressed the reaction (runs 3 and 4), while m-CPBA and DTBP did not work well (comparing runs 5 and 6 with run 1). To our pleasure, a rapid, clean conversion was observed using Oxone[®] as the additional oxidant,18 with a high 75% isolated yield of the monobrominated product obtained (run 7). The effect of O_2 on the reaction could be excluded since a similar yield was obtained when the reaction was carried out under a nitrogen atmosphere (run 8 vs. run 7). A brominating system consisting of a catalytic amount of cupric bromide and other bromine sources (such as KBr or NH4Br)

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[†] Electronic supplementary information (ESI) available. See DOI: 10.1039/c3ra41664j

Table 1 Screening of the reaction conditions^a



Run	Br source (mmol)	source nol) Oxidant (mmol) So		Time (h)	$\operatorname{Yield}^{b}(\%)$	
1	$CuBr_{2}(0.5)$	None	MeCN	12	45	
2	$CuBr_2$ (1–2)	None	MeCN	12	~ 40	
3	$CuBr_2(0.5)$	$30\% H_2O_2$ (1.2)	MeCN	12	Trace	
4	$CuBr_2$ (0.5)	70% $TPHP^{c}$ (1.2)	MeCN	12	None	
5	$CuBr_2(0.5)$	m-CPBA ^d (1.2)	MeCN	12	46	
6	$CuBr_2(0.5)$	$\text{DTBP}^{e}(1.5)$	MeCN	12	49	
7	$CuBr_2(0.5)$	$Oxone^{(R)}$ (1.2)	MeCN	3	75	
8^{f}	$CuBr_2(0.5)$	$Oxone^{\mathbb{R}}$ (1.2)	MeCN	3	74	
9^g	$CuBr_2(0.05)$	$Oxone^{\mathbb{R}}$ (1.2)	MeCN	6	60	
10	$CuBr_{2}(0.5)$	$Oxone^{\mathbb{R}}$ (1.2)	H_2O	3	None	
11	$CuBr_2(0.5)$	$Oxone^{\mathbb{R}}$ (1.2)	MeOH	3	32	
12	$CuBr_2(0.5)$	$Oxone^{\mathbb{R}}$ (1.2)	Dioxane	3	71	
13	$CuBr_2(0.5)$	$Oxone^{\mathbb{R}}$ (1.2)	DCE^{h}	8	68	
14	CuBr (1.0)	$Oxone^{\mathbb{R}}$ (1.2)	MeCN	3	55	
15	KBr (1.0)	$Oxone^{\mathbb{R}}$ (1.2)	MeCN	8	26	
16	$NH_4Br(1.0)$	$Oxone^{\mathbb{R}}$ (1.2)	MeCN	12	41	
17	$TBAB^{i}$ (1.0)	$Oxone^{(R)}$ (1.2)	MeCN	12	43	
18	CuBr ₂ (0.5)	Oxone [®] (0.5)	MeCN	3	62	

^{*a*} Conditions: **1a** (1 mmol), solvent (8 mL), room temperature, in air, monitored by TLC. ^{*b*} Isolated yields. ^{*c*} *t*-Butyl hydroperoxide. ^{*d*} *m*-Chloroperbenzoic acid. ^{*e*} Di(*t*-butyl) peroxide. ^{*f*} The reaction mixture was degassed and run under an N₂ atmosphere. ^{*g*} 5 mol% of CuBr₂ and 1.5 equiv. KBr or NH₄Br. ^{*h*} 1,2-Dichloroethane. ^{*i*} Tetrabutyl ammonium bromide.

seemed effective (run 9), but the Cu-catalyzed bromonation suffered from a relatively slower conversion rate and a complex product distribution. The nature of the solvent used has a notable effect on the reaction; protonic solvents, such as H_2O and methanol, which are usually used with Oxone[®], are poor (runs 10 and 11), whereas polar non-protonic solvents (runs 7, 12 and 13) are a more suitable reaction medium. Cuprous bromide (run 14), despite being slightly inferior to cupric bromide (run 7), performed better than other bromide salts (runs 15, 16 and 17), indicating that the presence of copper cations is favorable for this reaction. Additionally, the use of a suitable amount of the oxidant Oxone[®] is necessary for an efficient transformation (see run 18 *vs.* run 7). Based on a comprehensive assessment of the experiments mentioned above, we chose run 7 (Table 1) as our standard conditions.

Next, we examined the substrate scope of this monobromination reaction (Table 2). Most of the primary arylamines afforded good to excellent yields of the desired product (Table 2, runs 1–6, 8, and 9). Bromination of aniline proceeded with clean conversion and a high yield of 72% (run 1). In the case of 1-naphthylamine, the reaction was slow at room temperature, but heating resulted in a complicated mixture (run 7). The mono-bromination of anilines took place preferentially at the *para* position unless the position was blocked. For example, *p*-substituted anilines (run 4 and 8) and 2-naphthylamine (run 6) were brominated at their *ortho* positions.

Run	Amine 1	Product 2 (yield)	Run	Amine	Product 2 (yield)
1	$\sqrt[]{-NH_2}$ 1b	Br - NH ₂ 2b 72% ^b	12	$\sqrt[]{-NH}$ 1m	Br
2	$ \underbrace{ \sum_{l \in \mathbb{N}}^{Cl} }_{l c} $	$\frac{CI}{2c 74\%}$	13	HN HN 1a	2a 75%
3	$\overbrace{1d}{ Id} $	Br NH ₂ 2d 76%	14		2n 67% ^b
4	CI-NH2 1e	$\frac{1}{2e} \frac{e^{Br}}{90\%}$	15	С) 10	20 78%
5	$ \underbrace{ - }_{NH_2} $	Br	16	⟨	$\frac{1}{2p} \frac{1}{65\%}$
6	lg	2g 82% ^c	17	⟨ → – _N 1q	$ \begin{array}{c} \text{Br} & \swarrow & N \\ \mathbf{2q} \ \mathbf{78\%} \end{array} $
7	NH ₂	NH ₂ Br 2h 25%	18	or lr	2r 85% ^c
8	o ₂ NNH ₂ 1i	0 ₂ N- 3i 75%	19	$\sim \sim $	$ \begin{array}{c} \stackrel{\text{Br}}{\longrightarrow} \\ \stackrel{\text{N}}{\longrightarrow} \\ 2s \ 69\%^c \end{array} $
9	NH2 1j	Br N NH2 2j 74%	20		[₽] ¹ ¹ ¹ ¹ ¹ ¹ ¹ ¹
10		Br H 2k 73%	21		u 80%
11	NHAc 11	Br NHAc 21 None			

^{*a*} Conditions: amine (1 mmol), cupric bromide (0.5 mmol), Oxone[®] (1.2 mmol), acetonitrile (8 mL), room temperature, in air, 3 h; isolated yields. ^{*b*} 50 mmol scale bromination carried out, 24 h. ^{*c*} 0.5 h, 0–5 °C.

Furthermore, this method can be extended to the bromination of heteroaromatics like 2-aminopyridine (run 9) and carbazole (run 10) which gave high isolated yields. Note that deactivated *N*-acyl aniline was not suitable for this bromination (run 11). Secondary aromatic amines can be brominated smoothly (runs 12–15): 4-Bromo-*N*-methylaniline was obtained in 76% yield (run 12); both

N-phenyl-1-naphthylamine (run 13) and *N*-phenyl-2-naphthylamine (run 15) gave the desired products selectively monobrominated at the *para* position of phenyl group; and using diphenylamine gave a 67% yield of the *p*-monobrominated product (run 14), with a small amount of 4,4'-dibromodiphenylamine. Tertiary aromatic amines are also suitable substrates for monobromination (run 16–21). *N*,*N*-Dialkylanilines were *para* or *ortho* (if the *para* position was blocked) brominated in good to excellent yields (runs 16–19). Moreover, sensitive functional groups like aldehydes survived under the reaction conditions (runs 18 and 19). The monobromination of triarylamines resulted in high yields of the desired products (runs 20 and 21).

Mixed polybromination of the aromatic amines was anticipated to be a potential concern to address. However, under the monobromination conditions mentioned above no appreciable amount of multibrominated product was observed for any of the substrates studied. On the other hand, a controllable multibromination reaction would be desirable for use in synthetic chemistry. For this purpose, diphenylamine (1n) was chosen as a test substrate. The starting material, **1n**, was first treated using a large excess of cupric bromide (2.5 equivalents) and Oxone[®] (6 equivalents) (Scheme 1). It was found that when the reaction was quenched after less than 0.5 h, 4,4'-dibromodiphenylamine (3n) was obtained in a 69% isolated yield and no mono-brominated product (2n) remained. When the reaction time was increased up to 2 h, a mixture of 3n, 4n and 5n was observed qualitatively using TLC. Finally, if the reaction time was prolonged to over 5 h, exhaustive bromination was achieved, giving an 84% yield of 2,2',4,4'-tetrabromodiphenylamine (5n). Alternatively, and also conveniently, specific multi-brominated products can be afforded solely, or as the main product formed, by precise control of the number of equivalents of CuBr2 used. For example, 3n is obtained in 75% yield using 1 equiv. of CuBr₂ plus Oxone[®] (2.5 equiv.) at room temperature for 3 h. 4n is obtained in 53% yield using 1.5 equiv. of CuBr₂ plus Oxone[®] (4 equiv.) at room temperature for 16 h. Finally, 5n is obtained in 87% yield using 4 equiv. of CuBr₂ plus Oxone[®] (10 equiv.) at room temperature for 10 h. Interestingly, the treatment of diphenylamine with only cupric bromide (3-5 equivalents) (i.e., in the absence of Oxone[®]) always afforded a mixture of 3n and 4n, whether reaction times were short or long, with none of 5n being detected. In none of the reactions described above did we observe the formation of penta- or hexabromodi-



Scheme 1

Table 3 Polybromination of aromatic amines under controlled conditions^a





^{*a*} Conditions: amine (1 mmol), CuBr₂ (2.5 mmol), Oxone^(R) (6 mmol), acetonitrile (10 mL), room temperature, 5 h; isolated yields. ^{*b*} 0.5 h. ^{*c*} 2 h. ^{*d*} 16 h.

phenylamine, even after prolonged reaction times. Accordingly, a controllable multi-bromination of aromatic amines can be achieved by simple control of the equivalents of the brominating reagents used and/or the reaction times. Some representative cases of multi-bromination are shown in Table 3.

It must be pointed out that dealkylation and bromination may be observed when *N*,*N*-dialkylaniline reacts with the CuBr₂/ Oxone[®] system under heating conditions.¹⁹ For example, by elevating the temperature and prolonging the reaction time, a mono *N*-dealkylation-bromination would be the main reaction (Scheme 2).

Lastly, a very preliminary attempt was made to perform the chlorination of aromatic amines under similar conditions by replacing cupric bromide with cupric chloride. The chlorination reaction of aromatic amines is inferior to the corresponding bromination (Table 4), and further studies to improve the reaction conditions are under way in our laboratory.

We propose a possible mechanism for the monobromination of the aromatic amines in Scheme 3. A radical cation $PhNR_2^+$ is formed *via* a single electron transfer from $PhNR_2$ to Cu^{2+} and is immediately trapped by the nucleophile (Br⁻) forming a radical, which then transfers a further electron to Cu^{2+} to form a cationic species. Finally, the cationic species releases H⁺ to give the product. CuBr formed in the first step of the reaction is oxidized by Oxone[®] in the second step, to regenerate the CuBr₂ reactant. There is some supportive evidence for this proposed mechanistic pathway in the literature,^{11,20} and is also in good agreement with





Table 4 Chlorination of aromatic amines using ${\rm CuCl_2/Oxone^{I\!\!R}}$ system^a



^{*a*} Conditions: amine (1 mmol), $CuCl_2 \cdot 2H_2O$ (0.5 mmol), $Oxone^{(\mathbb{R})}$ (1.2 mmol), acetonitrile (8 mL), in air, room temperature, 18 h; isolated yield.

our experimental observations. For example, it was found that the presence of a Cu^{2+} species is always favorable for this transformation (Table 1, runs 1, 7, 9, and 14 *vs.* runs 15–17). Furthermore, a radical-trapping experiment using (2,2,6,6-tetramethylpiperidinyl)-*N*-oxyl (TEMPO) in the model reaction showed that the starting amine was consumed completely to afford a complicated distribution of products, with only extremely small amounts of mono- or multi-brominated aromatic amines detected. This also implies that the mechanistic pathway involving a radical cation is feasible.

In conclusion, we have developed a simple, mild and efficient protocol for the bromination of aromatic amines, with high regioselectivity and functional group tolerance. This reaction covers a wide range of substrates and, in particular, provides a controllable synthesis for various levels of brominated aromatic amines by simple adjustment of the reaction conditions. Thus, this method represents an attractive synthetic route to expensive low-volume aromatic bromoamines. It is noteworthy that this reaction could have the potential to become a catalytic reaction, *i.e.*, a copper-catalyzed bromination of aromatic amines (see run 9 of Table 1). This study is under way in our group and will be published in due course.

Experimental section

General procedure for mono-bromination of aromatic amines

An oven-dried 50 mL three necked flask was charged with amine (1 mmol), cupric bromide (0.5 mmol), and Oxone[®] (1.2 mmol). After acetonitrile (8 mL) was added *via* syringe, the mixture was stirred for 3 h at room temperature until the starting amine was completely consumed (monitored by TLC). Saturated sodium carbonate (5 mL) was added, with stirring for 5 min, and then 10 mL of water added. The aqueous layer was extracted with ethyl



 $(ii) \qquad 2\mathsf{KHSO}_5^{\bullet}\mathsf{KHSO}_4^{\bullet}\mathsf{K}_2\mathsf{SO}_4 + 2\mathsf{CuBr} + 2\mathsf{HBr} \longrightarrow 2\mathsf{KHSO}_5^{\bullet}\mathsf{KHSO}_4^{\bullet}\mathsf{K}_2\mathsf{SO}_4 + 2\mathsf{CuBr}_2 + 2\mathsf{H}_2\mathsf{O}$



acetate (15 mL \times 3). The combined organic layers were washed with brine, dried over anhydrous MgSO₄, and evaporated under reduced pressure. The residue was purified by column chromatography.

General procedure for multi-bromination of aromatic amines

An oven-dried 50 mL three necked flask was charged with amine (1 mmol), cupric bromide (2.5 mmol) and Oxone[®] (6 mmol), then acetonitrile (10 mL) was added *via* syringe. The reaction mixture was stirred at room temperature. The reaction was monitored by TLC and quenched according to the time mentioned in the above text. The mixture was then filtered through a pad of silica gel and the filtrate washed with ethyl acetate (20 mL \times 2). The combined organic phases were evaporated under reduced pressure and the residue purified by column chromatography.

Acknowledgements

The authors thank National Natural Science Foundation of China (Project Nos. 20872142 and 21102150) for financial support of this work.

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