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Practical bromination of arylhydroxylamines with $SOBr_2$ towards *ortho*-bromo-anilides

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ABSTRACT

A facile approach for synthesizing *ortho*-bromoanilides from readily available aryhydroxylamines and thionyl bromide is demonstrated in this work. Mild reaction conditions and broad scope of substrates ranging from heterocyclic structures to pharmaceutics-potential motifs are used in the reactions of this paper. Efficient bromination of *ortho* C—H bonds of the aryhydroxylamines has been achieved. *Ortho*-bromoanilide products were obtained in good to excellent yields, and model scaled-up reactions of this synthetic approach are shown in this work.

Introduction

Aryl halides are very valuable chemicals in modern organic chemistry since their widespread applications in transition-metal catalyzed cross-coupling reactions as key substrates to afford diverse C—C, C—N, C—O and C—S bonds [1]. In addition, aryl halides have also been widely used in transition-metal-free transformations, such as nucleophilic aromatic substitution [2], generation of highly reactive organometallic reagents (e.g. aryllithium, arylmagnesium reagents) and benzyne species. Furthermore, aryl halides serve as key components of a wide range of natural products [3], pharmaceuticals [4], as well as functional materials [5]. Among these aryl halides, halogenated anilines are particularly attractive due to their frequent appearance in dyes and pigments [6]. Since the aryl bromides have higher reactivity and represent easier conversion to more desirable targets than the corresponding aryl chloride, therefore the development of mild, efficient and regioselective bromination of anilides is still highly desired.

Electrophilic aromatic substitution/bromination, employing bromine [7], *N*-bromosuccinimides [8], peroxides/HBr [9] and DMSO/HBr [10] as brominating reagents, is the dominant strategy to aryl bromides (Scheme 1a). While powerful, these approaches were suffering from several limitations: (1) the employment of highly toxic or hazardous reagents; (2) only the activated arenes were amenable to these protocols; (3) the formation of undesirable byproducts, for instance, the overbromination products and multiple regioisomers. Transition metal-catalyzed directed regioselective C—H bromination was found to be an efficient approach to *ortho*-brominated aromatic compounds [11]. Unfortunately these transformations usually require the employment of expensive metal catalysts, such as palladium, rhodium, and long-time heating at high temperature for completion (Scheme 1b). Recently, a variety of Lewis basic organocatalysts were successfully applied to the electrophilic bromination of aryl compounds that represents a more environmentally friendly route than the metal catalyst system [12]. However, these strategies often suffer from the specific catalysts and the narrow substrate scope. Thus, it is still attractive to develop a metal and oxidant free alternative protocol for the rapid access to bromoarenes under mild conditions.

In 2006, Shi and co-workers elegantly reported a palladium-catalyzed *ortho*-selective halogenation of acetanilides employing CuX_2 (X = Cl, Br) as halogen source (Scheme 1c) [11a]. A milder palladium-catalyzed *ortho*—C—H halogenation of anilides with NXS (X = Cl, Br) in the presence of *p*-toluenesulfonic acid (PTSA) was developed by Bedford and co-workers in 2011 (Scheme 1c) [11f]. Recently, we demonstrated that arylhydroxylamines can be *O*-alkenylated or *O*-arylated with a series of electrophiles, and the transient intermediates can undergo a cascade [3,3]-sigmatropic rearrangement and re-aromatization to afford structurally diverse indoles [13] or biaryl products [14], respectively. As part of our continuous interest in arylhydroxylamines, we are pleased to describe herein a transition metal-free facile approach to *ortho*-bromoanilides by treatment of

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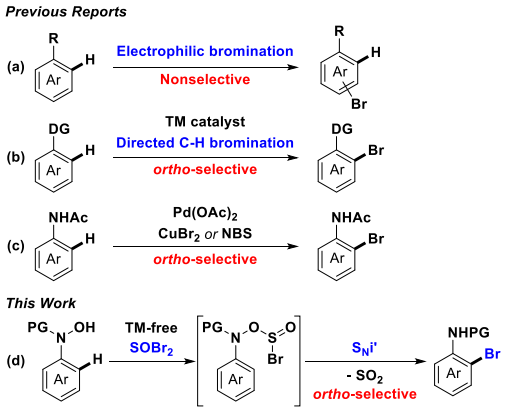


Scheme 1. Synthetic routes to aryl bromides and *ortho*-bromoanilides.

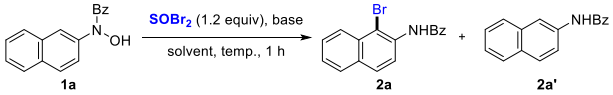
arylhydroxylamines with thionyl bromide under mild conditions (Scheme 1d).

Results and discussion

At the outset of investigation, the reaction between *N*-hydroxy-*N*-(naphthalen-2-yl)benzamide **1a** and thionyl bromide was examined in THF at −20 °C using Na_2CO_3 as base. We delightedly found that the expected *N*-(1-bromonaphthalen-2-yl)benzamide **2a** was isolated in 31% yield and 60% of *N*-(naphthalen-2-yl)benzamide **2a′** was also isolated (Table 1, entry 1). In order to inhibit the undesired side product **2a′**, we screened various solvents (Table 1, entries 2–8) and found that dichloromethane was the optimal option (Table 1, entry 8). The influence of base was next investigated, and revealed that the employment of different bases had limited effect on the yield of the desirable product (Table 1, entries 9–14). Reducing the amount of base resulted in a slightly improvement in yield from 69% to 74% (Table 1, entries 15 and 16). After extensive screening of temperatures, we found that adding thionyl bromide at 0 °C and then slowly warming it to room temperature can improve the results (Table 1, entries 17–19). We were pleased to find that the isolated yield of **2a** can be increased up to 97% in dichloromethane in the absence of base at 0 °C to room temperature for 1 h and only trace amount of **2a′** was detected (Table 1, entry 20).

With the optimized reaction conditions in hand, we began to examine the scope of this *ortho*-bromination protocol under standard conditions as shown in Table 2. A variety of protecting-group onto the nitrogen atom of the 2-naphthyl hydroxylamine, such as Bz-, Ac-, Piv-, -CO_2Me, Cbz-, Fmoc-, TFA-, except for Boc, were amenable to this transformation to furnish the corresponding *ortho*-bromoanilides in good to excellent yields with excellent regioselectivity (Table 2, entries 1–8). These results also revealed that the benzoyl group was the optimal protecting-group of the arylhydroxylamines (Table 2, entry 1). For substrates bearing OMe, OBn, Br and aryl functional group on the naphthalene ring, the desired products **2i-2q** were obtained with high yields (Table 2, entries 9–17). Furthermore, phenylhydroxylamines with various substituents on the phenyl ring were next investigated, affording the corresponding *ortho*-brominated products in moderate to high yields and excellent regioselectivity under standard conditions (Table 2, entries 18–32). Notably, substrates bearing electron-withdrawing groups, such as Cl, Br, I, CF_3, were tolerated albeit with moderate yields, indicating the feasibility of this transformation with electron-deficient system (Table 2, entries 19–21, 24 and 32). When *N*-(3-fluorophenyl)-*N*-hydroxybenzamide **1ab** was tested, bromination occurred at the 6-position and 2-position of benzene ring, and the ratio of regioisomers was 2 to 1. Its regioselectivity might be due to the influence of steric and electronic effect, and **2ab** and **2ab′** could be separated by column chromatography (Table 2, entry 28). Moreover, this method was tolerant of

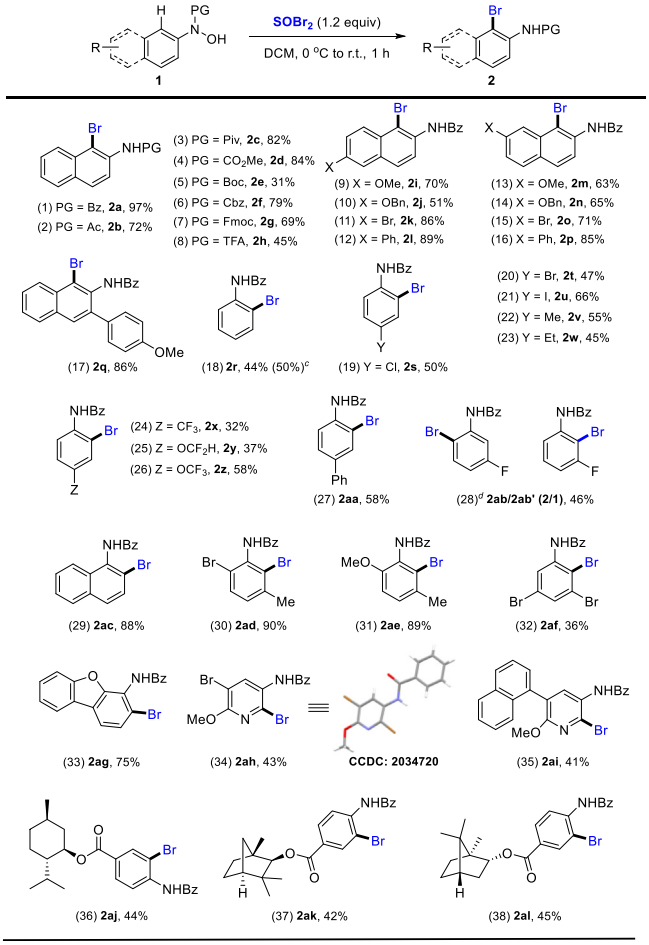
Table 1
Optimization of the reaction conditions.[a]



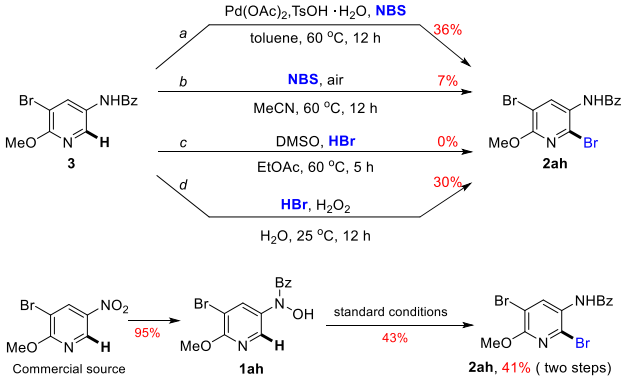
entry	solvent	base	temp.	**2a**,yield[b]	**2a'**,yield[b]
1	THF	Na_2CO_3	−20 °C	31%	60%
2	DCE	Na_2CO_3	−20 °C	54%	23%
3	Et_2O	Na_2CO_3	−20 °C	42%	35%
4	$CHCl_3$	Na_2CO_3	−20 °C	62%	16%
5	CCl_4	Na_2CO_3	−20 °C	9%	4%
6	EtOAc	Na_2CO_3	−20 °C	17%	51%
7	PhCl	Na_2CO_3	−20 °C	49%	32%
8	DCM	Na_2CO_3	−20 °C	69%	20%
9	DCM	pyridine	−20 °C	34%	36%
10	DCM	Et_3N	−20 °C	32%	20%
11	DCM	K_2CO_3	−20 °C	58%	36%
12	DCM	$NaHCO_3$	−20 °C	60%	28%
13	DCM	K_3PO_4	−20 °C	57%	26%
14	DCM	DIPA	−20 °C	52%	14%
15[c]	DCM	Na_2CO_3	−20 °C	72%	24%
16[d]	DCM	Na_2CO_3	−20 °C	74%	20%
17[d]	DCM	Na_2CO_3	−10 °C	72%	18%
18[d]	DCM	Na_2CO_3	0 °C	71%	20%
19[d]	DCM	Na_2CO_3	0 °C to r.t.	83%	6%
20	**DCM**	**None**	**0 °C to r.t.**	**97%**	**2%**

[a] Unless otherwise noted, all reactions were carried out under the following conditions: **1a** (0.2 mmol), $SOBr_2$ (1.2 eq.), base (2.0 eq.), solvent (1 mL), 1 h.
[b] Yields of isolated products.
[c] 1.0 equivalents of base was employed.
[d] 0.5 equivalents of base was employed. DCE = 1,2-dichloroethane; DCM = Dichloromethane; DIPA = Diisopropylamine.

Table 2
Substrate scope.[a,b].



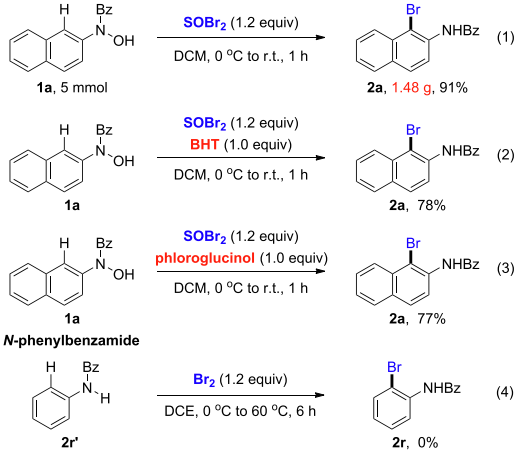
[a]Reaction conditions: **1** (0.2 mmol), $SOBr_2$ (0.24 mmol), DCM (1 mL) at 0 °C to r.t. under N_2 for 1 h. For substrates **2r-2al**, 4 Å MS (100 mg) was employed as additive. [b]Yields of isolated products. [c]Yield in the parenthesis is the isolated yield of *N*-phenylbenzamide. *N*-(4-bromophenyl)benzamide was not detected in this transformation. [d]The regioselectivity was determined by the ratio of isolated yield of **2ab** and **2ab′**. Combined yield of the pure regioisomers. Bz = benzoyl; Ac = Acetyl; Boc = *t*-Butyloxy carbonyl; Cbz = benzoxycarbonyl; Piv = pivaloyl; Fmoc = 9-fluorenylmethyloxycarbonyl; TFA = Trifluoroacetyl; Bn = benzyl.



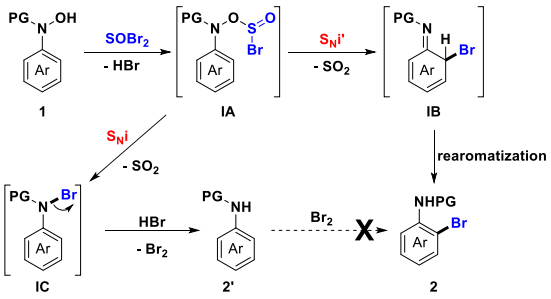
Scheme 2. Various synthetic routes to *ortho*-bromoanilide **2ah**.

heterocyclic arylhydroxylamines, such as dibenzofuran and pyridine aromatics (Table 2, entries 33–35). The excellent *ortho*-regioselectivity and structure of the product was determined by X-ray analysis of **2ah** (Table 2, entry 34). In addition, this transformation could also be applied to the modification of nature products relevant molecules, such as menthol, fenchol and borneol derivatives (Table 2, entries 36–38).

To further evaluate the compatibility of the current method is not trivial compared with the literature reported protocols [10c,11f,15], *N*-(2,5-dibromo-6-methoxypyridin-3-yl)benzamide **2ah** was selected as the target product (Scheme 2). Utilizing our



Scheme 3. Gram scale reaction and control experiment. BHT = butylated hydroxytoluene.



Scheme 4. Proposed mechanism.

optimized reaction conditions, the desired *ortho*-bromoanilide **2ah** could be obtained with a two-step yield of 41%, while the literature methods gave lower yields. These results indicated that our method provided a complementary tool to access *ortho*-bromoanilides that were difficult to prepare.

To demonstrate the potential synthetic application of this transformation, the gram scale reaction of substrate **1a** as representive was carried out under standard reaction conditions. We delightfully found that 91% yield of **2a** can be obtained with excellent regioselectivity (Scheme 3, Eq. 1). To gain some mechanistic insights of this transformation, control experiment was conducted in the presence of BHT and phloroglucinol, and resulted in no significant change in the isolated yield of **2a** (Scheme 3, Eq. 2 and 3). This result concluded that the free radical mechanism could be ruled out in this reaction (Scheme 3, Eq. 2 and 3).

Based on the aforementioned results, we proposed the reaction mechanism involving the intramolecular substitution (S_Ni') as shown in Scheme 4. Nucleophilic attack of arylhydroxylamine to $SOBr_2$ gives the bromosulphite **IA**, which could subsequently undergo a S_Ni' type reaction process to afford intermediate **IB**, followed by the 1,3-proton migration/rearomatization to furnish the final *ortho*-bromoanilide **2**. Alternatively, the bromosulphite **IA** may undergo a classical S_Ni type reaction to afford highly reactive *N*-bromoanalide **IC**, which could be rapidly protonated by HBr to furnish the side product **2′** and Br_2. It was noteworthy that the side product **2′** can not be converted into the corresponding *ortho*-bromoanilide **2** in the presence of Br_2 (Scheme 3, Eq. 4) [16]. These results revealed that the classical electrophilic bromination mechanism is not likely and the S_Ni' type reaction pathway is more reasonable. We speculated that the addition of base may neutralizes HBr in the system and produces water, which could cause the hydrolysis of $SOBr_2$ and lead to the decrease in yield of the reactions.

Conclusion

In summary, we have presented a facile, efficient and practical *ortho*-bromination of arylhydroxylamines with readily available thionyl bromide under mild conditions. This protocol was demonstrated to be general, and a variety of structurally diverse *ortho*-bromoanilides have been prepared in moderate to good yields with excellent regioselectivity. The development of new *ortho*-functionalization of arylhydroxylamines and mechanistic investigations are currently ongoing in our laboratory.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153074.

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