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PII: S0040-4039(20)30402-0  
DOI: <https://doi.org/10.1016/j.tetlet.2020.151959>  
Reference: TETL 151959

To appear in: *Tetrahedron Letters*

Received Date: 5 March 2020  
Revised Date: 15 April 2020  
Accepted Date: 17 April 2020

Please cite this article as: Phuc Tran, D., Nomoto, A., Mita, S., Dong, C-p., Kodama, S., Mizuno, T., Ogawa, A., Metal- and Base-free Synthesis of Aryl Bromides from Arylhydrazines, *Tetrahedron Letters* (2020), doi: <https://doi.org/10.1016/j.tetlet.2020.151959>

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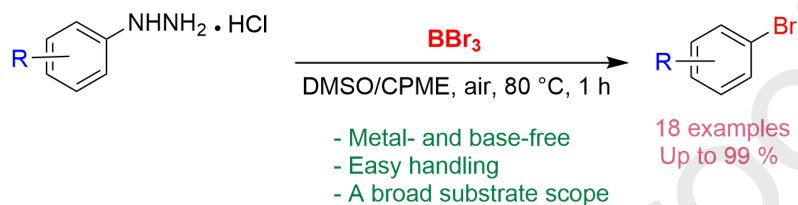


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### Metal- and Base-free Synthesis of Aryl Bromides from Arylhydrazines

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## Metal- and Base-free Synthesis of Aryl Bromides from Arylhydrazines

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### ARTICLE INFO

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Article history:

Received

Received in revised form

Accepted

Available online

### ABSTRACT

An efficient method was developed to synthesize brominated aromatic compounds from arylhydrazine hydrochlorides by using BBr<sub>3</sub> in DMSO/CPME (cyclopentyl methyl ether) under air at 80 °C for 1 h without the use of bases or metal catalysts. In particular, this method could be carried out satisfactorily using electron-withdrawing groups to afford aryl bromides in a moderate to excellent yields.

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### Keywords:

Aryl Bromide

Arylhydrazine

Metal-free

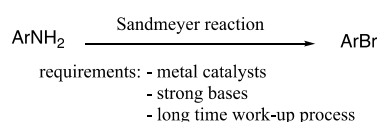
Base-free

### Introduction

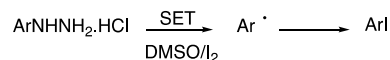
Aryl bromides are one of the most essential and useful chemicals as they serve as fundamental substrates in building blocks for organic synthesis reactions such as Heck reaction<sup>1</sup> and cross coupling reactions<sup>2</sup>. Brominated aromatic compounds are found in many natural organisms, and some of them have biomedical value<sup>3</sup>.

A common bromination method from anilines is the Sandmeyer reaction. Although various bromination reactions using anilines have been developed, they require metal-based catalysts, a strong basic medium, or a long time for the workup process<sup>4</sup>. To overcome these disadvantages, the development of metal- and base-free synthesis of aryl bromides is strongly desired. Recently, we effectively synthesized aryl iodides from arylhydrazine<sup>5</sup> without using a metal catalyst or base. Arylhydrazines<sup>6</sup>, upon oxidation with I<sub>2</sub>, were converted to arenediazonium salts, which undergo SET (single-electron transfer) to form aryl radicals *in situ*. Based on the aryl radicals formation from arylhydrazines, we recently developed a series of arylation reactions of heteroarenes<sup>7</sup> and organochalcogenides<sup>8</sup>. We expected that the use of a suitable brominating reagent instead of I<sub>2</sub> will lead to successful formation of the corresponding aryl bromides from arylhydrazines. Dimethyl sulfoxide (DMSO) was used as a solvent, which can dissolve arylhydrazine hydrochloride salts and will oxidize hydrogen bromide, similar to HI<sup>9</sup>.

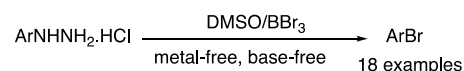
a) A common bromination method using anilines



b) Our previous work to synthesize aryl iodides



c) This our work to synthesis aryl bromide

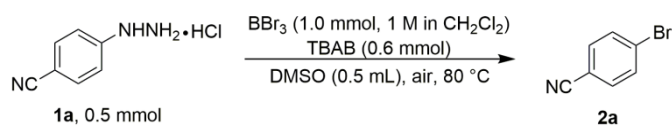


**Scheme 1:** Brominated aromatic compounds

Herein, we study a method to synthesize brominated aromatics from arylhydrazine hydrochlorides by using BBr<sub>3</sub>/DMSO without the use of bases or metal catalysts (Scheme 1).

### Results and discussion

Initially, the reaction of 4-benzonitrile hydrazine hydrochloride (**1a**, 0.5 mmol) with tetrabutylammonium bromide (TBAB) (0.6 mmol) and boron tribromide (BBr<sub>3</sub>) (1.0 mmol, 1 M in CH<sub>2</sub>Cl<sub>2</sub>) in 0.5 mL of normal grade DMSO (not dehydrated, 99.0% purity) as a solvent at 80 °C in the air is the model reaction to achieve the optimal conditions (Table 1).



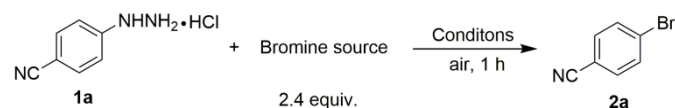
Entry	TBAB (mmol)	BBr <sub>3</sub> (mmol)	Time (h)	Yield <sup>a</sup> (%)
1	0.6	1.0	5	72
2	0.6	1.0	14	61
3 <sup>b</sup>	0.6	1.0	5	73
4 <sup>c</sup>	0.6	1.0	3	71
5	0	1.0	3	83
6	0	0.8	3	77
7	0	1.2	3	89
8	0	1.5	3	89
9	0	1.2	5	79
10	0	1.2	1	81

<sup>a</sup>Yield was determined by <sup>1</sup>H NMR (CDCl<sub>3</sub>, 1,3,5-trioxane as an internal standard).

<sup>b</sup>Reaction temperature is 90 °C.

<sup>c</sup>Reaction temperature is 100 °C.

**Table 2.** Effect of brominating reagents and conditions on bromination.



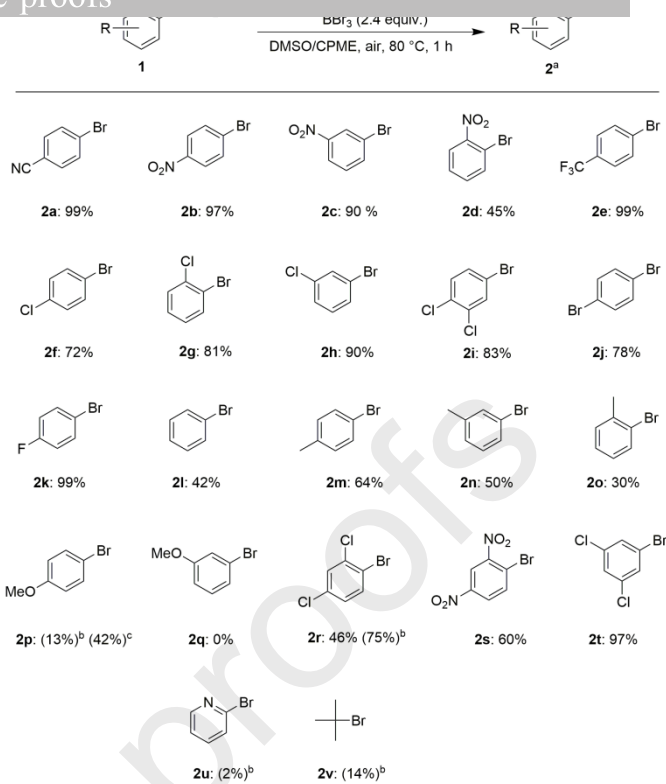
Entry	Bromine source	Conditions	Yield <sup>a</sup> (%)
1	PBr <sub>3</sub>	DMSO (0.5 mL), 80 °C	24
2	BrCCl <sub>3</sub>	DMSO (0.25 mL), CH <sub>2</sub> Cl <sub>2</sub> (0.25 mL), 80 °C	46
3	Br <sub>2</sub>	DMSO (1.5 mL), 80 °C	47
4	BBr <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub> (0.4 mL), 60 °C	N.D.
5	BBr <sub>3</sub>	DMSO (0.2 mL), CH <sub>2</sub> Cl <sub>2</sub> (0.2 mL), 80 °C	49
6	BBr <sub>3</sub>	CPME (0.2 mL), DMSO (0.2 mL), 80 °C	99
7	BBr <sub>3</sub>	Et <sub>2</sub> O (0.2 mL), DMSO (0.2 mL), 80 °C	48
8	BBr <sub>3</sub>	THF (0.2 mL), DMSO (0.2 mL), 80 °C	99

Reactions were carried out on 0.5 mmol scale.

<sup>a</sup>Yield was determined by <sup>1</sup>H NMR (CDCl<sub>3</sub>, 1,3,5-trioxane as an internal standard).

After 5 h of reaction, the desired product, 4-bromobenzonitrile (**2a**), was formed in 72% yield (entry 1). Prolonging the reaction time resulted in a lower yield (61%, entry 2). When the reaction was conducted at a higher temperature, the yield of **2a** did not increase (entries 3 and 4). Intriguingly, the use of 1.0 mmol of BBr<sub>3</sub> in the absence of TBAB increased the yield of **2a** (83%) (entry 5). Next, we changed the ratio of **1a** and BBr<sub>3</sub> (entries 5-10) and found that **2a** was obtained in a good yield (81%) in the presence of 2.4 equiv. of BBr<sub>3</sub> (1.2 mmol) for 1 h (entry 10).

Other brominating reagents under different reaction conditions were also attempted for the bromination (Table 2). Because PBr<sub>3</sub> has high oxophilicity and bromine content, it serves as a useful brominating reagent to convert alcohols to the corresponding alkyl bromides<sup>10</sup>. The use of PBr<sub>3</sub> (2.4 equiv.) in 0.5 mL DMSO at 80 °C led to only 24% yield of **2a** (Table 2, entry 1). BrCCl<sub>3</sub> is a useful brominating reagent for converting arylamines to aryl bromides through the S<sub>RN</sub>1 mechanism under basic conditions<sup>4b</sup>.



Reactions were carried out on 0.5 mmol scale in DMSO/CPME (0.2 mL/0.2 mL).

<sup>a</sup> Isolated yield.

<sup>b</sup> Determined by <sup>1</sup>H NMR.

<sup>c</sup> BrCCl<sub>3</sub> instead of BBr<sub>3</sub>.

**Scheme 2.** Scope of aryl bromides.

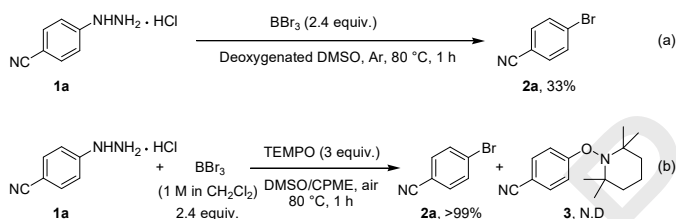
Bromination using BrCCl<sub>3</sub> afforded **2a** in moderate yield with the formation of dimethyl sulfide (entry 2). When Br<sub>2</sub><sup>11</sup>, a commonly used bromine reagent, was used, a similar moderate yield of **2a** was obtained (entry 3). Using CH<sub>2</sub>Cl<sub>2</sub> as solvent, no **2a** was formed (entry 4). The use of a mixed solvent of DMSO and CH<sub>2</sub>Cl<sub>2</sub> led to the formation of **2a** (49%) (entry 5). Considering the effects of air and moisture, the reaction was conducted under argon with deoxidized DMSO, but **2a** was formed in 33% yield (Scheme 3, reaction (a)). Interestingly, a use of cyclopentyl methyl ether (CPME) as a solvent extremely improved the yield of **2a** (99%) (entry 6). To examine the effect of other ethereal solvents, diethyl ether (Et<sub>2</sub>O) and tetrahydrofuran (THF) were also used. The use of THF resulted in the formation of **2a** with an excellent yield (99%), whereas the yield of **2a** decreased to 48% in the case of Et<sub>2</sub>O. Therefore, ethereal solvents such as CPME and THF are suitable as co-solvents for the bromination. Hence, CPME is chosen for the bromination because it is usually used in chemical industries. In comparison with the mixture of DMSO and BBr<sub>3</sub> which reacted strongly with formation of dimethyl sulfide, the presence of CPME will make it more gently. Thus, the optimal reaction conditions include BBr<sub>3</sub> (2.4 equiv.), DMSO/CPME (0.2 mL/0.2 mL), under air, for 1 h.

The scope of bromination was investigated using the conditions of entry 6 (Table 2) and a range of aryl bromides could be synthesized in moderate to excellent yields (Scheme 2). The reaction was carried out satisfactorily with electron-withdrawing groups (EWG) such as cyano (**2a**), nitro (**2b**, **2c**, **2d**, **2s**), trifluoromethyl (**2e**), and halo groups (**2f**, **2j**, **2k**).

The bromination of arylhydrazines bearing the substituent groups at the *para* position afforded excellent yields of 4-

bror

1-bromo-4-fluorobenzene (**2k**). The bromination of arylhydrazines consisting *meta* substituents also provided very good yields of 1-bromo-3-nitrobenzene (**2c**, 90%), and 1-bromo-3-chlorobenzene (**2h**, 90%). In contrast, the *ortho* substituents resulted in moderate yields of 1-bromo-2-nitrobenzene (**2d**, 45%) and 2-bromotoluene (**2o**, 30%) due to their steric hindrance. In particular, in the case of the chloro substituent, the effectivity of electron-withdrawing ability at the *meta* position is higher than that at the *para* position; thus, the yield of **2h** is higher than that of **2f**. The disubstituted phenylhydrazine hydrochlorides also tolerated the optimal conditions to generate the corresponding aryl bromides. While 1-bromo-2,4-dinitrobenzene (**2s**) was obtained in moderate yield (60%), 1-bromo-3,4-dichlorobenzene (**2i**), 1-bromo-2,4-dichlorobenzene (**2r**), and 1-bromo-3,5-dichlorobenzene (**2t**) were synthesized in good yields (83%, 75%, and 97%, respectively). Moreover, the bromination of substrates bearing a methyl group could afford the corresponding products (**2m**, **2n**, and **2o**). Unfortunately, the bromination of *p*- or *m*-methoxyphenyl hydrazine hydrochloride barely occurred (**2p**, **2q**), presumably because of the complexation of the methoxy group and BBr<sub>3</sub>. When BrCCl<sub>3</sub> was used instead of BBr<sub>3</sub>, *p*-methoxyphenyl bromide (**2p**) was obtained in 42% yield. When the 2-hydrazinopyridine hydrochloride was used as a substrate, the complexation between pyridine and BBr<sub>3</sub> inhibited the desired bromination (**2u**). Moreover, *tert*-butyl bromide as an alkyl bromide was formed in only 14% yield (**2v**).



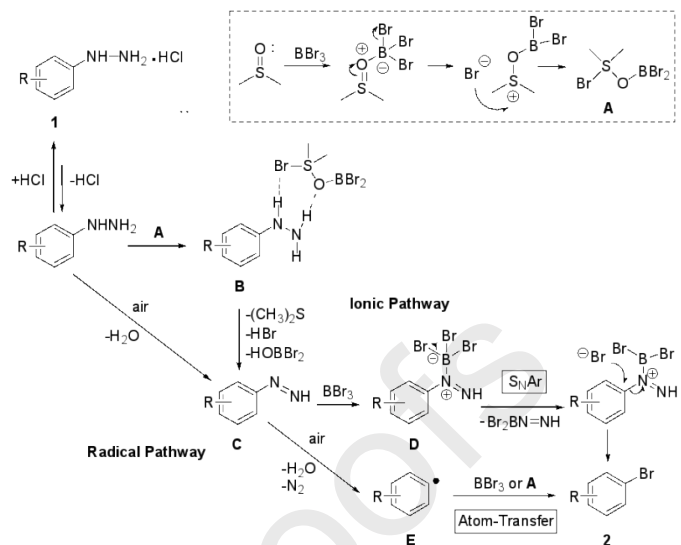
Scheme 3. Control experiments.

To understand the bromination mechanism, some control experiments were investigated (Scheme 3). Although, under argon, **2a** was formed in 33% yield (reaction (a)), atmospheric exposure led to **2a** in almost quantitative yield (entry 6 in Table 2). Therefore, air plays as an important role in bromination.<sup>13</sup> To clarify whether the bromination involves a radical pathway, 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) was added to the bromination of **1a** (reaction (b)). The almost quantitative formation of **2a** even in the presence of TEMPO without the formation of 4-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)benzonitrile **3** strongly suggests the present bromination reaction might not involve a radical process at least in the key steps.

To get more information about the mechanism, we investigated a Hammett linear free energy relationship study of the bromination using four kinds of arylhydrazines **2b**, **2e**, **2l**, and **2m** (for the detailed experiments, see Supporting Information). The determined  $\rho$  value,  $\rho = +0.63$ , is inconclusive to determine the mechanism; namely, a radical pathway such as an atom-transfer reaction<sup>14,15</sup> and an ionic pathway such as an aromatic nucleophilic substitution (S<sub>N</sub>Ar) are both possible<sup>16</sup>.

In our previous study of the iodination of arylhydrazines with I<sub>2</sub><sup>5</sup>, however, a TEMPO trapping experiment indicated the formation of **3**, suggesting a radical pathway. In addition, Stack's report concerning the bromination of anilines to give aryl bromides also described a successful trapping of aryl radical by

pathway.<sup>4b</sup>



Scheme 4. Possible pathways.

Proposed pathways, which include both ionic and radical mechanisms, are shown in Scheme 4. First, the starting material, arylhydrazine hydrochloride (**1**) generates arylhydrazine in equilibrium. Dimethyl sulfoxide (DMSO) serves as a Lewis base and reacts with a Lewis acid, BBr<sub>3</sub>, to form **A** as a key species, which can be generated both under argon and under air. In the case of argon atmosphere, **A** interacts with the hydrogen atoms of hydrazine (see **B**) to form diazene **C**, where DMSO acts as an oxidizing agent. Under air, **A** might play a similar role as the case under argon, and moreover, air-oxidation of arylhydrazine to **C** might be accelerated by the formation of **B**, although air can directly oxidize arylhydrazine to **C**. In an ionic pathway, **C** undergoes coordination with BBr<sub>3</sub> or **A** (see **D**) and then aromatic nucleophilic substitution (S<sub>N</sub>Ar) to afford **2**. In a radical pathway, air-oxidation of **C** leads to aryl radical **E**, which abstracts bromine atom from BBr<sub>3</sub> or **A** to afford **2** (atom-transfer reaction)<sup>17</sup>. If **E** abstracts Br from **A**, the concomitantly formed Br<sub>2</sub>BO• might contribute to the formation of arylhydrazine to **C**.

## Conclusion

A metal- and base-free synthetic method of aryl bromides from arylhydrazine hydrochlorides is developed. Various aryl bromides can be successfully prepared without using any metal catalysts or bases.

## Acknowledgments

D.P.T. is grateful for the support of the Ministry of Education, Culture, Sports, Science and Technology (MEXT) Scholarship Program. This research was supported by JSPS KAKENHI (B, 19H02791) and (B, 19H02756), from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and by Kyoto-Advanced Nanotechnology Network.

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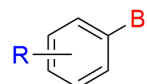
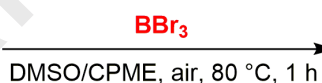
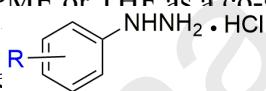
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- The use of CPME or THF as a co-solvent improved the
- Arylhydrazine converted to a



- Metal- and base-free
- Easy handling
- A broad substrate scope

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