Efficient one-pot transformation of aminoarenes to haloarenes using halodimethylisulfonium halides generated in situ

Woonphil Baik, Wanqiang Luan, Hyun Joo Lee, Cheol Hun Yoon, Sangho Koo, and Byeong Hyo Kim

Abstract: Halodimethylsulfonium halide **1**, which is readily formed in situ from hydrohaloic acid and DMSO, is a good nucleophilic halide. This activated nucleophilic halide rapidly converts aryldiazonium salt prepared in situ by the same hydrohaloic acid and nitrite ion to aryl chlorides, bromides, or iodides in good yield. The combined action of nitrite ion and hydrohaloic acid in DMSO is required for the direct transformation of aromatic amines, which results in the production of aryl halides within 1 h. Substituted compounds with electron-donating or -withdrawing groups or sterically hindered aromatic amines are also smoothly transformed to the corresponding aromatic halides. The only observed by-product is the deaminated arene (usually <7%). The isolated aryldiazonium salts can also be converted to the corresponding aryl halides using **1**. The present method offers a facile, one-step procedure for transforming aminoarenes to haloarenes and lacks the environmental pollutants that usually accompany the Sandmeyer reaction using copper halides.

Key words: aminoarenes, haloarenes, halodimethylsulfonium halide, halogenation, amination.

Résumé : Les halogénures d'halogénodiméthylsulfonium (**1**) qui se forment facilement à partir des acides hydrohaloïques et du DMSO sont de bons halogénures nucléophiles. Sous l'action de ce type d'halogénure nucléophile, les sels d'aryldiazonium préparés in situ à l'aide du même acide hydrohaloïque et de l'ion nitrite peuvent facilement être transformés en chlorures, bromures ou iodures d'aryles, avec de bons rendements. L'action combinée de l'ion nitrite et d'un acide hydrohaloïque dans le DMSO est requise pour la transformation directe des amines aromatiques qui conduit à la formation d'halogénures d'aryles en moins d'une heure. Les composés substitués par des groupes électrodonneurs ou électroattracteurs ainsi que les amines stériquement empêchées sont aussi transformées facilement en halogénures d'aryles correspondants. Le seul produit secondaire observé est l'arène désaminé (généralement moins de 7 %). Sous l'action des produits **1**, les sels d'aryldiazonium isolés peuvent aussi être transformés en halogénures d'aryles correspondants. Cette méthode est présentée comme une procédure facile, en une étape, qui permet de transformer des aminoarènes en halogénoarènes et qui n'est pas entachée des polluants environnementaux qui accompagnent généralement la réaction de Sandmeyer qui utilise des halogénures de cuivre.

Mots clés : aminoarènes, halogénoarènes, halogénure d'halogénodiméthylsulfonium, halogénation, amination.

[Traduit par la Rédaction]

Introduction

Aromatic halides are versatile reagents that can be converted to a wide variety of materials. Representative processes for preparing aromatic halides include: (*i*) direct aromatic halogenation (1), wherein the hydrogen atom is replaced by a halogen atom, and (*ii*) the Sandmeyer reaction (2, 3), which involves the substitution of an amino group by a halogen atom via a diazonium salt. Since aromatic amines are generally more economical to produce, most methods for preparing highly substituted aromatic halides have centered around improving the Sandmeyer reaction. The Sandmeyer reaction is a two-step process: diazotization followed by halogenation (3). The typical Sandmeyer reaction is generally carried out in the presence of more than one equimolar amount of cuprous halide (3*b*–3*d*), and the discharge of excess copper salt can cause environmental pollution. In addition, since the stability and formation of the diazonium salt are the important factors in the Sandmeyer reaction, special conditions such as a low reaction temperature and filtration are necessary (2, 3). Considering the wide range of potential applications for aromatic halides, the development of a simple method that requires a low manufacturing cost while minimizing environmental pollution is required. Some modi-

Received 10 August 2004. Published on the NRC Research Press Web site at http://canjchem.nrc.ca on 9 March 2005.

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 doi: 10.1139/V05-026

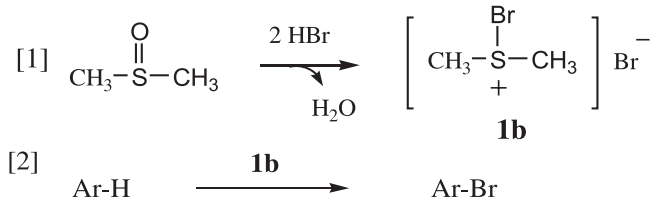
Table 1. Transformation of *p*-nitroaniline to *p*-bromoaniline under various conditions.[a]

Entry	HBr (equiv.)	KNO_2 (equiv.)	Solvent	Conditions	Yield (%)[b] 3	4	2
1	1.5	1.5	DMSO	12 h, 80 °C	35 (6)[c]	tr	40
2	4.0	4.0	DMSO	10 min, 35 °C	86 (7)[c]	0	tr
3	4.0	4.0	H_2O	24 h, 35 °C	0	~10	(Salt)[d]
4	4.0	4.0	DMF[e]	12 h, 35 °C	0	~5	Sluggish
5	3.0	0	DMSO	24 h, rt	0	26	tr
6	0	4.0	DMSO	24 h, 35 °C	0	0	98

[a]Reactions were performed by adding 10.0 mmol of *p*-nitroaniline and the indicated amount of HBr to KNO_2 in 50 mL of solvent.
[b]Yields were determined by GLC analysis by comparison to dodecane as an internal standard.
[c]The deaminated product, nitrobenzene.
[d]The aryldiazonium salt was formed.
[e]Other solvents (THF, HMPA, hexane, and benzene) were also examined, but none gave the desired product.

fied Sandmeyer reactions (4) that involve a diazonium salt have been developed for the purpose of simplicity. Unlike the sodium nitrite and acidic conditions needed for the preparation of diazonium salt, alkyl nitrite is a useful in situ diazotizing agent for the one-step preparation of aromatic halides (4*a*–4*d*). This method also uses anhyd. $CuCl_2$ (4*a*–4*b*) or $CuBr_2$ (4*a*–4*b*) and I_2 with CH_2I_2 for iodination (4*d*). Iodination suffers in this case in that it is difficult to separate the product from excess diiodomethane. A similar direct replacement of the aromatic amino group by iodine or bromine through reactions with gaseous nitrogen dioxide, but without an added metal activator, has been reported (4*h*, 4*k*). Although there are specific advantages to each of these methods, none of the modified variations has received wide application. To simplify the reaction and minimize the environmental problems and manufacturing cost, several factors should be considered: (*i*) the development of in situ diazotization for a single-step reaction, and (*ii*) the development of an activated halogen nucleophile that can replace CuX_2, I_2, CH_2I_2, etc.

Bromodimethylsulfonium bromide **1b** has been used as a bromide nucleophile in the substitution of hydrogen atom(s) of aromatic compounds (5–7). As shown in eqs. [1] and [2], when HBr is added with DMSO as the solvent, bromodimethylsulfonium bromide **1b** is formed instantly, and replacement of a hydrogen atom of the benzene ring by bromide occurs simultaneously (5).

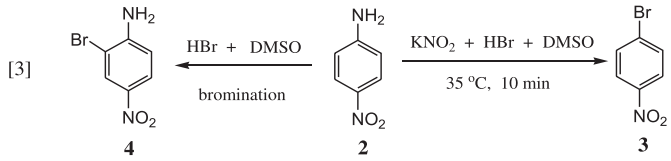


Despite the synthetic utility of **1b** in the bromination of arenes, it has not been investigated as an activated halogen nucleophile in the replacement of a diazonium group. An aromatic amine would be converted to a diazonium salt by the addition of nitrite salt and hydrohaloic acid, while at the same time an activated halide nucleophile **1** (X = Cl (**1a**), X = Br (**1b**), X = I (**1c**)) would be prepared readily in situ from the same hydrohaloic acid and DMSO. Thus, the transformation of an amine group to a halogen group in aromatic compounds may occur in a single-step process via concurrent diazotization–displacement using the combination of NO_2^-–HX–DMSO. Therefore, we sought to use **1** in the halogenation of the diazonium salt that is prepared in situ using the same halohydric acid and nitrite ion.

Results and discussion

Bromination and (or) chlorination

Preliminary studies on the bromination of *p*-nitroaniline were carried out using KNO_2 and 48% aq. HBr[2] in DMSO. *p*-Nitroaniline **2** with KNO_2 (4 equiv.) and HBr (4 equiv.) in DMSO at 35 °C afforded *p*-bromonitrobenzene **3** in 86% yield within 10 min along with a 7% yield of nitrobenzene (Table 1 and eq. [3]). None of the brominated product, 2-bromo-4-nitroaniline **4**, was observed. However, when *p*-nitroaniline was reacted with a mixture of HBr and DMSO in the absence of KNO_2, 2-bromo-4-nitroaniline **4** was observed in 26% yield, as reported by Chauhan and co-workers (6). The transformation to *p*-bromonitrobenzene was not observed without the nitrite ion. With stoichiometric amounts of HBr and KNO_2 in DMSO, 35% of *p*-bromonitrobenzene and 40% of the starting material were observed, but even after 24 h the brominated product was only formed in a trace amount (~2%). Presumably, the diazonium salt that is instantly formed by the action of KNO_2 and HBr prevents the bromination of *p*-nitroaniline.



The molar ratio of HBr to aromatic amine for this reaction should be from about 3:1 to about 5:1; preferably, about 4:1. A higher molar ratio of HBr will lead to the formation of brominated product as a by-product. For example, with 7 equiv. of HBr and 4 equiv. of KNO_2 in DMSO, *p*-bromoaniline was transformed to 76% *p*-dibromobenzene and 15%

[2]Due to safety and handling considerations, aqueous hydrohaloic acid or hydrohaloic acid in glacial acetic acid solution is preferred. It is generally available commercially and contains about 48%–57% by weight H_2O solution or acetic acid.

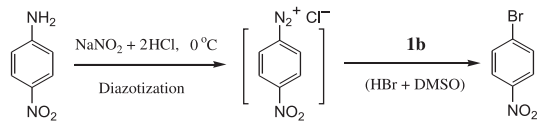
Table 2. Transformation of Ar-NH_2 by KNO_2 and HX in DMSO.[a]

Entry	Substrate	Time (min)	Product	Yield (%)[b]
1	*o*-$O_2NC_6H_4NH_2$	15	*o*-$O_2NC_6H_4Br$	82 (78)
2	*o*-$O_2NC_6H_4NH_2$	30	*o*-$O_2NC_6H_4Cl$	79 (73)
3	*p*-CH_3CO $C_6H_4NH_2$	10	*p*-CH_3CO C_6H_4Br	88
4	*p*-CH_3CO $C_6H_4NH_2$	60	*p*-CH_3CO C_6H_4Cl	69
5	5-Cl-2-$O_2NC_6H_4NH_2$	10	5-Cl-2-$O_2NC_6H_4Br$	77
6	3,5-$(O_2N)_2C_6H_4NH_2$	10	3,5-$(O_2N)_2C_6H_4Br$	83 (80)
7	3,5-$(O_2N)_2C_6H_4NH_2$	60	3,5-$(O_2N)_2C_6H_4Cl$	69
8	2-MeO-5-$O_2NC_6H_4NH_2$	20	2-MeO-5-$O_2NC_6H_4Br$	81
9	*p*-HOOC $C_6H_4NH_2$	20	*p*-HOOC C_6H_4Br	78
10	*p*-HOOC $C_6H_4NH_2$	120	*p*-HOOC C_6H_4Cl	67
11	4-CH_3-2-$O_2NC_6H_4NH_2$	10	4-CH_3-2-$O_2NC_6H_4Br$	81
12	2,6-$(CH_3)_2C_6H_4NH_2$	30	2,6-$(CH_3)_2C_6H_4Br$	79
13	2,6-$(CH_3)_2C_6H_4NH_2$	120	2,6-$(CH_3)_2C_6H_4Cl$	69
14	2,6-$F_2C_6H_4NH_2$	20	2,6-$F_2C_6H_4Br$	85
15	*p*-$CH_3OC_6H_4NH_2$	10	*p*-$CH_3OC_6H_4Br$	85
16	4-Aminobenzophenone	10	4-Bromobenzophenone	89 (85)
17	4-Aminobenzophenone	60	4-Chlorobenzophenone	77
18	4-Aminoacetophenone	15	4-Bromoacetophenone	91
19	4-Aminobiphenyl	20	4-Bromobiphenyl	85 (78)
20	1-Aminonaphthalene	20	1-Bromonaphthalene	61
21	2-Aminoanthraquinone	20	2-Bromoanthraquinone	80
22	2-Amino-3-nitropyridine	30	2-Bromo-3-nitrophridine	54
23	5-Aminoisoquinoline	30	5-Bromoisoquinoline	61 (54)
24	1-Aminoisoquinoline	120	1-Chloroisoquinoline	51
25	3-Aminoquinoline	30	3-Bromoquinoline	59

[a]Reactions were performed by adding 10.0 mmol of the aniline and 40.0 mmol of 48% aq. HBr (or 37% aq. HCl) in 25 mL of DMSO to 40.0 mmol of KNO_2 in 25 mL of DMSO. The reaction temperature was 35 °C.

[b]Yields were generally determined by GLC analysis by comparison to an internal standard. Isolated yields after column chromatography or recrystallization are given in parentheses.

tribromobenzene. Thus, the use of excess HBr results in dibromobenzene, which is further brominated to give the tribromobenzene. The molar ratio of nitrite to aromatic amine should be about 3:1 to 5:1. The use of low molar ratios may cause a drop in product yields. To investigate the role of DMSO in the transformation of *p*-nitroaniline to *p*-bromonitrobenzene, other solvents were studied. However, none of the other solvents (H_2O, DMF, THF, HMPA, hexane, benzene, etc.) gave the desired product under the same conditions. The formation of the diazonium salt was observed in H_2O, and the reaction was very sluggish in DMF. No further reaction was seen in the absence of DMSO. Thus, DMSO has two roles; first, it reacts with HBr to form bromodimethylsulfonium bromide **1b**, and second, it readily dissolves nitrite ion. In fact, the reaction is too fast to observe the formation of the diazonium salt. To prove that the reaction proceeds via aryldiazonium salt under our conditions, isolated diazonium salt that was prepared by the general method (8) using sodium nitrite and HCl was treated with a premixed solution of HBr and DMSO as shown in eq. [4]. As expected, *p*-bromonitrobenzene was produced in 52% yield. According to this two-step protocol (diazotization–replacement), the activated bromodimethylsulfonium bromide **1b** directly converted the diazonium salt to provide the aryl bromide compound.

[4] 

The present method is characterized by the simultaneous in-situ formation of the activated bromide **1b** and aryldiazonium salt of the same HBr at room temperature and the smooth one-pot transformation of aminoarenes to monohaloarenes without further halogenated by-products.

The reaction is carried out by dissolving KNO_2 in DMSO and then adding *p*-nitroaniline and HBr to the resulting mixture at ambient temperature. The order in which the nitrite ion, hydrobromic acid, and an aromatic amine are added is not critical to the reaction.

The general applicability of this procedure for several other aminoarenes was then investigated, and the results are presented in Table 2. As can be seen, clean transformation occurs in good to excellent yields. The products were checked for purity by GLC and ^1H NMR. All of the products were also checked by GC–MSD to ensure the absence of any brominated by-products.

Reactions of sterically hindered aminobenzenes took place in reasonable yields within 1 h. Furthermore, anilines, even those with electron-withdrawing substituents, such as an aldehyde, ketone, nitro group, or carboxylic group, also showed good reactivity. For example, with 2,4-dinitroaniline

Table 3. Effect of CuX in the transformation of Ar-NH_2 by KNO_2 and HX in DMSO.[a]

Entry	Substrate	Time (min)	Product	Yield (%)[b]
1	*p*-$CH_3COC_6H_4NH_2$	10	*p*-$CH_3COC_6H_4Br$	94
2	*p*-$CH_3COC_6H_4NH_2$	20	*p*-$CH_3COC_6H_4Cl$	82
3	3,5-$(O_2N)_2C_6H_4NH_2$	10	3,5-$(O_2N)_2C_6H_4Br$	91
4	3,5-$(O_2N)_2C_6H_4NH_2$	20	3,5-$(O_2N)_2C_6H_4Cl$	88
5	*p*-HOOC $C_6H_4NH_2$	10	*p*-HOOC C_6H_4Br	83
6	*p*-HOOC $C_6H_4NH_2$	30	*p*-HOOC C_6H_4Cl	77
7	2,6-$F_2C_6H_4NH_2$	10	2,6-$F_2C_6H_4Br$	97
8	1-Aminonaphthalene	20	1-Bromonaphthalene	76
9	2-Amino-3-nitropyridine	30	2-Bromo-3-nitrophridine	74
10	5-Aminoisoquinoline	30	5-Bromoisoquinoline	81
11	1-Aminoisoquinoline	30	1-Chloroisoquinoline	79

[a]Reactions were performed by adding 2.0 mmol of CuX (0.2 equiv.) under the same conditions as in Table 2.
[b]Yields were generally determined by GLC analysis by comparison to an internal standard.

or 2,6-dimethylaniline, transformation took place to predominantly produce 1-bromo-2,4-dinitrobenzene or 1-bromo-2,6-dimethylbenzene, respectively. Furthermore, bromination or side-chain bromination was not observed, which suggests a highly effective transformation that is fully controlled by electronic and steric factors. However, in most cases, deaminated product was observed in trace (~7%) yields, and this was not affected by the amount of either HX or KNO_2. Conventional diazotization of electron-deficient anilines such as dinitroanilines is usually carried out using concentrated sulfuric acid as the reaction medium (4*c*, 8). Thus, the present method is especially attractive for anilines bearing electron-withdrawing groups. In addition, the present method was effective for preparing highly halogen-substituted benzenes. For example, 2,4-difluoroaniline reacts with KNO_2–HBr–DMSO to give 1-bromo-2,4-difluorobenzene in 87% yield within 30 min. For electron-rich anilines, the yields were also modest to high. However, conversion of aromatic diamines to the corresponding dibromo or monobromo products was unsatisfactory.

Having demonstrated the superiority of the aminoarenes, we then turned our attention to the evaluation of heterocyclic amine compounds. Reactions with aminopyridines also showed good transformations to their corresponding bromopyridines without any noticeable side reactions (Table 2, entries 22~25). Typically, during the reactions with aminopyridines, such as 5-aminoisoquinoline, 1-aminoisoquinoline, 2-amino-3-nitropyridine, or aminoquinoline, complete conversion was observed even though the pyridinium salt was formed by the action of HBr. We believe that the positively charged nitrogens of the pyridinium salt and the diazonium salt exert some electronic and inductive effects to enhance the electrophilicity of the carbon atom of the ring.

We successfully performed this transformation on a semi-preparatory scale (1000 g)[3] and a microscale (<0.1 g). In any case, this one-pot procedure is superior to the classical or modified Sandmeyer reactions in terms of yield, convenience, cost, and reaction time. In addition, the ease with which the product can be purified due to the use of the water-miscible solvent DMSO and aq. HX allows a large-scale preparation in an efficient one-pot reaction.

The versatility of halodimethylsulfonium halide, especially chlorodimethylsulfonium chloride **1a**, is also demonstrated in Table 2. Upon treatment of 37% aq. HCl with KNO_2 in DMSO, the amino group is transformed to give a chlorinated arene. The yields were relatively low compared to the bromination, indicating that the pK_a values of HX may affect the stabilities of both the halodimethylsulfonium halide and the diazonium salt.

In an attempt to increase the product yield for some aminoarenes and aminopyridines, we examined the effect of a copper halide. The typical conversion of arenediazonium ions to aryl halides requires a quantitative amount of Cu(II) halide (Sandmeyer reaction). We observed that the addition of 0.2 equiv. of CuBr (or CuCl) to the reaction mixture under our conditions increased the yield and reduced the reaction time (Table 3).

Iodination

Since some reactions, such as the Ullmann (9, 10), Suzuki (11), and Heck reactions (12), are facile for iodoarenes, a simple and reliable preparation method is still under investigation. Attractive methods have been proposed by several groups (4*d*–4*j*), such as using "isoamyl nitrite" as the diazotizing agent and "diiodomethane" as both a solvent and halogen source (4*d*). However, it can be difficult to separate the product from excess diiodomethane and the use of sterically hindered anilines is problematic. To evaluate the sequence using iododimethylsulfonium iodide **1c**[4] prepared in situ by HI and DMSO, the conversion of anilines to iodobenzenes was also investigated. Most of the conversions to iodobenzenes were successful under these conditions. Furthermore, the yields were excellent with a very short reaction time and in most cases by-products were not observed. We were surprised by the high transformation efficiency of sterically hindered and electron-withdrawing group substi-

[3]A high-speed mechanical stirrer with a multiblade paddle was adequate for dissolving KNO_2 for the preparatory-scale reaction.
[4]It is likely that the mechanism of the formation of halodimethylsulfonium halides (**1c**) iododimethylsullfonium iodide, involves reversible formation of a sulfur dichloride (R_2SCl_2) intermediate. See ref. 5*b*. Bromodimethylsulfonium iodide prepared from HBr, DMSO, and I^- via the formation of bromodimethylsulfonium bromide was treated followed by the replacement of bromide with a more nucleophilic iodide, as shown in eq. [6].

Table 4. Transformation of Ar-NH_2 to Ar-I using halodimethylsulfonium iodide.[a]

Entry	Substrate	Halide	Time (min)	Product	Yield (%)[b]
1	*o*-$O_2NC_6H_4NH_2$	**1c**	15	*o*-$O_2NC_6H_4I$	89
2	2-CH_3O-5-O_2N-$C_6H_4NH_2$	**1c**	10	2-CH_3O-5-O_2N-C_6H_4I	93 (88)
3	5-Cl-2-$O_2NC_6H_4NH_2$	**1c**	10	5-Cl-2-$O_2NC_6H_4I$	95 (91)
4	3,5-$(O_2N)_2C_6H_4NH_2$	**1c**	10	3,5-$(O_2N)_2C_6H_4I$	89
5	4-CH_3-2-$O_2NC_6H_4NH_2$	**1c**	10	4-CH_3-2-$O_2NC_6H_4I$	81
6	2,6-$(CH_3)_2C_6H_4NH_2$	**1c**	10	2,6-$(CH_3)_2C_6H_4I$	87
7	2,6-$F_2C_6H_4NH_2$	**1c**	20	2,6-$F_2C_6H_4I$	84
8	*p*-$CH_3OC_6H_4NH_2$	**1c**	10	*p*-$CH_3OC_6H_4I$	85
9	2-CH_3O-5-O_2N-$C_6H_4NH_2$	**1c′**	30	2-CH_3O-5-O_2N-C_6H_4I	81 (73)
10	2,6-$F_2C_6H_4NH_2$	**1c′**	30	2,6-$F_2C_6H_4I$	74
11	4-Aminobenzophenone	**1c′**	30	4-Iodobenzophenone	90
12	2-Aminoanthraquinone	**1c**	20	2-Iodoanthraquinone	90
13	1-Aminonaphthalene	**1c**	30	1-Iodonaphthalene	59
14	1-Aminonaphthalene	**1c′**	30	1-Iodonaphthalene	65
15	1-Aminonaphthalene	**1c** (CuI)[c]	30	1-Iodonaphthalene	93 (88)
16	2-Amino-3-nitropyridine	**1c**	60	2-Iodo-3-nitrophridine	59
17	2-Amino-3-nitropyridine	**1c** (CuI)[c]	60	2-Iodo-3-nitrophridine	89 (81)

[a]**1c**: Reactions were performed by adding 10.0 mmol of the aniline and 40.0 mmol of 57% aq. HI in 25 mL of DMSO to 40.0 mmol of KNO_2 in 25 mL of DMSO. **1c′**: 48% aq. HBr and KI were used instead of HI. The reaction temperature was 35 °C.
[b]Yields were generally determined by GLC analysis by comparison to an internal standard. Isolated yields after column chromatography or recrystallization are given in parentheses.
[c]CuI (0.1 equiv.) was added.

tuted anilines in Table 4 (entries 3–6), where 1-iodo-2,6-dinitrobenzene and 1-iodo-2,6-dimethylbenzene were formed in respective yields of 89% and 87% with a very short reaction time. The reported yield of 1-iodo-2,6-dinitrobenzene for the route with isoamyl nitrite in diiodomethane is only 36% at 105 °C (6). The present method is highly attractive for the preparation of aryl iodides because of the simple one-pot conversion and high yields.

Similar to the formation of bromodimethylsulfonium bromide **1b** from HBr and DMSO, iododimethylsulfonium iodide **1c** is prepared by HI and DMSO (eq. [5]). To confirm the halogen source of halodimethylsulfonium halide, bromodimethylsulfonium iodide **1c′**, prepared from HBr, DMSO, and KI via the formation of bromodimethylsulfonium bromide **1b**, was examined (eq. [6]). As shown in Table 4 (entries 9–11), similar results were obtained using HBr–KI–KNO_2–DMSO, which indicates that bromodimethylsulfonium iodide **1c′** also acts as an excellent halogen source for the replacement of aryldiazonium salt.

[5] $CH_3SOCH_3 \xrightarrow[H_2O]{2HI} [CH_3SCH_3]^+ I^-$ **1c**

[6] $CH_3SOCH_3 \xrightarrow[H_2O]{2\ HBr} [CH_3SCH_3]^+ Br^- \xrightarrow{I^-} [CH_3SCH_3]^+ I^-$ **1c′**

Fluorination

In addition to our study of the direct transformation of aryldiazonium salt to fluoroarenes, some halodimethylsulfonium fluorides were also investigated. Similar reaction protocols were used with various fluoride sources, however, the conversion of aminoarenes to fluoroarenes was not successful even in the presence of CuF. Presumably, the weak nucleophilicity and low acidity of HF may not lead to the formation of halodimethylsulfonium fluoride.

Conclusions

We have described an efficient protocol for the transformation of aminoarenes to iodo-, bromo-, or chloroarenes using in-situ-generated halodimethylsulfonium halides. The present method offers several advantages: (*i*) the amino group in an aromatic compound can be transformed to a halide in reasonable to high yields regardless of a substituent effect; (*ii*) the process is simple and consists of a single step; (*iii*) the reaction time is very short (generally 10~60 min), and the reaction temperature is mild (e.g., at 35 °C); (*iv*) the cost of the hardware is very low; and (*v*) the reaction can minimize environmental pollution.

Experimental section

General

All reagents were used without further purification. Mass spectra were obtained at a 70 eV via GC–MSD coupling. ^1H NMR spectra were recorded on a 300 MHz spectrometer in $CDCl_3$ solution. GLC analyses were performed using a capillary column (25 m × 0.2 mm i.d.). Melting points were determined on a Mel-Temp II apparatus and were uncorrected. All known products were identical in all respects (mp, IR, MS, and NMR) to those previously reported.

General procedure for microscale production — Use of bromodimethylsulfonium bromide prepared by HBr and DMSO

A solution of 48% aq. HBr (2.49 mL, 20.0 mmol) dissolved in DMSO (25 mL) was added dropwise to a solution of aminoarene (5 mmol) in a mixture of 25 mL of DMSO and KNO_2 (1.70 g, 20.0 mmol) at 35 °C with stirring. The added mixture was stirred at 35 °C for the time given in Table 2 and then transferred to a solution of K_2CO_3 (5 g) in 100 mL of ice water. The reaction mixture was then taken up in ether, and the ethereal extracts were washed with water and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure gave the crude product. The crude product was further purified by column chromatography (or recrystallization) to give the product, the mp, and spectral data (^{1}H NMR and GC–MS) all of which were in full agreement with those of an authentic sample.

General procedure for preparative-scale production

A mixture of 2.5 L of DMSO and KNO_2 (85.1 g, 1.0 mol) was vigorously stirred at 60 °C to rapidly dissolve KNO_2, and aminoarene (0.25 mol) was then added.[3] The resulting solution was then cooled to room temperature. Aqueous HBr solution (48%, 124.5 mL, 1.0 mol) diluted with 2.0 L of DMSO was added dropwise at a rate of 20 mL/min, and the mixture was then warmed to 35 °C. The DMSO solution of HBr added to the reaction mixture can be carried off through a long condenser tube. After the usual workup, the crude product was purified by recrystallization.

Preparation of 4-bromoanisole

A mixture of 4-methoxyaniline (0.25 mol, 30.75 g), KNO_2 (85.1 g, 1.0 mol), HBr solution (48%, 124.5 mL, 1.0 mol), and 4.5 L of DMSO was stirred at 60 °C for 2 h. The product was recovered by the standard procedure, yielding 37.87 g of pure 4-bromoanisole (81%).

General procedure for microscale production — Use of iododimethylsulfonium iodide prepared by HI and DMSO

Aminoarene (5.0 mmol) was added to a solution of KNO_2 (1.70 g, 20.0 mmol) in DMSO (25 mL) at 35 °C. Aqueous HI (57%, 2.64 mL, 20 mmol) in DMSO (25 mL) was added, and the reaction mixture was stirred for the time given in Table 4. After the reaction was completed, the cooled reaction mixture was neutralized with 10% aq. Na_2CO_3 and extracted with methylene chloride (3 × 10 mL). The combined methylene chloride extracts were washed with brine and dried over magnesium sulfate. The solvent was removed in vacuo and the residue was chromatographed to give the product, the mp, and spectral data (^{1}H NMR and GC–MS) all of which were in full agreement with those of an authentic sample.

General procedure for microscale production — Use of bromodimethylsulfonium iodide prepared by HBr, KI, and DMSO

To a solution of aminoarene (5.0 mmol) in a mixture of 25 mL of DMSO and KNO_2 (1.70 g, 20 mmol) was added dropwise a solution of 47% HBr (2.49 mL, 20 mmol) and KI (4.15 g, 25 mmol) dissolved in DMSO (25 mL) at 35 °C. When the addition was complete, the mixture was further stirred at 35 °C for an additional 10 min and then transferred to a solution containing K_2CO_3 (5 g) in 100 mL ice water. The reaction mixture was then taken up in ether, and the ethereal extracts were washed with water and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure gave the crude product.

Acknowledgments

This work was supported by the Regional Research Center program of the Ministry of Science and Technology (MOST) and KOSEF-Kyungkido.

References

1. (*a*) E.B. Merkushev. Synthesis, 923 (1988); (*b*) R.C. Larock. Comprehensive organic transformations. 2nd ed. Wiley, New York. 1999. pp. 619–626.
2. (*a*) D.S. Wulfman. The chemistry of diazonium and diazo groups. *Edited by* S. Patai. Wiley, New York. 1978. Chap. 8; (*b*) R.C. Larock. Comprehensive organic transformations. 2nd ed. Wiley, New York. 1999. pp. 678–679; (*c*) J.K. Kochi. J. Am. Chem. Soc. **79**, 2942 (1957); (*d*) S.C. Dickerman, D.J. Desouza, and N. Jacobson. J. Org. Chem. **34**, 710 (1969); (*e*) C.J. Galli. J. Chem. Soc. Chem. Perkin Trans. 2, 897 (1984).
3. (*a*) H.H. Hodgen. Chem. Rev. **40**, 251 (1947); (*b*) L.A. Bigelow. *In* Organic syntheses, collective volumes. Vol. 1. Wiley, New York. 1941. p. 135; (*c*) W.W. Hartman and M.R Brethen. *In* Organic syntheses, collective volumes. Vol. 1. Wiley, New York. 1941. p. 162; (*d*) J.L Hartwell. *In* Organic syntheses, collective volumes. Vol. 3. Wiley, New York. 1955. p. 185.
4. (*a*) M.P. Dolye, B. Siegried, and J.F. Dellaria. J. Org. Chem. **42**, 2426 (1977); (*b*) M.P. Dolye, M.A. Van Lente, R. Mowat, and W.F. Fobare. J. Org. Chem. **45**, 2570 (1980); (*c*) M.P. Dolye and W.J. Bryker. J. Org. Chem. **44**, 1572 (1979); (*d*) W.B. Smith and O.C. Ho. J. Org. Chem. **55**, 2543 (1990); (*e*) V. Nair and S.G. Richardson. J. Org. Chem. **45**, 3969 (1980); (*f*) L. Friedman and J.F. Chlebowski. J. Org. Chem. **33**, 1636 (1967); (*g*) J.G. Lee and H.T. Cha. Tetrahedron Lett. **33**, 3167 (1992); (*h*) H. Suzuki and N. Nonoyama. Tetrahedron Lett. **39**, 4533 (1998); (*i*) C. Giordano, L. Coppi, and M. Paiocchi. US Patent 5 142 093, 1992; (*j*) M.J. Evers, L.E. Christiaens, M.R. Guillaume, and M.J. Renson. J. Org. Chem. **50**, 1779 (1985); (*k*) M.S. Newman and W. Fones. J. Am. Chem. Soc. **69**, 1221 (1947).
5. (*a*) G. Majetich, R. Hicks, and S. Reister. J. Org. Chem. **62**, 4321 (1997); (*b*) K. Mislow, T. Simmons, J. Melillo, and A. Ternary. J. Am. Chem. Soc. **86**, 1452 (1964); (*c*) D. Landini and F. Montari. J. Chem. Soc. Chem. Commun. 86 (1968).
6. S.K. Srivastava, P.M.S. Chauhan, and A.P. Bhaduri. J. Chem. Soc. Chem. Commun. 2679 (1996).
7. (*a*) G. Megyeri and T. Keve. Synth. Commun. **19**, 3415 (1989); (*b*) T. Fletcher and H. Pan. J. Am. Chem. Soc. **78**, 4812 (1956).
8. W.W. Hartman and M.R. Brethen. Organic syntheses, collective volumes. Vol. 1. Wiley, New York. 1941. pp. 162.
9. For reviews, see: (*a*) P.E. Fanta. Synthesis, 9 (1974); (*b*) M. Goshaev, O.S. Otroshchenko, and A.S. Sadykov. Russ. Chem. Rev. **41**, 1046 (1972); (*c*) G. Bringmann, R. Walker, and R. Weirich. Angew. Chem. Int. Ed. Engl. **29**, 977 (1990).
10. (*a*) T.D. Nelson and A.I. Meyers. J. Org. Chem. **59**, 2655 (1994); (*b*) J.C. Salfeld and E. Baume. Tetrahedron Lett. **7**,

3365 (1966); (*c*) A.G. Mack, H. Suschitzy, and B.J. Wakefield. J. Chem. Soc. Perkin Trans. 1, 1682 (1980).
11. (*a*) For reviews, see: N. Miyaura and A. Suzuki. Chem. Rev. **95**, 2457 (1995); (*b*) V. Fiandanese, L. Mazzone, and F. Naso. J. Chem. Soc. Chem. Commun. 2523 (1995).
12. (*a*) J.J. Bozell and C.E. Vogt. J. Am. Chem. Soc. **110**, 2655 (1988); (*b*) R.C. Larock and P.L. Johnson. J. Chem. Soc. Chem. Commun. 1368 (1989); (*c*) R.C. Larock and B.E. Baker. Tetrahedron Lett. **30**, 2603 (1989).