

## Halogenation of Aromatic Compounds by *N*-chloro-, *N*-bromo-, and *N*-iodosuccinimide

Kiyoshi Tanemura,\* Tsuneo Suzuki, Yoko Nishida, Koko Satsumabayashi, and Takaaki Horaguchi†

School of Dentistry at Niigata, The Nippon Dental University, Hamaura-cho, Niigata 951-8580

†Department of Chemistry, Faculty of Science, Niigata University, Ikarashi, Niigata 950-2181

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An efficient and mild method for the halogenation of aromatic compounds using *N*-chloro-, *N*-bromo-, and *N*-iodosuccinimide in the presence of  $\text{NH}_4\text{NO}_3$  or  $\text{FeCl}_3$  in acetonitrile was developed.

Halogenation of aromatic compounds is one of the most important reactions in organic synthesis. The most commonly used reagents for this purpose are bromine and chlorine in the presence of iron halide. In terms of ease of handling in laboratories, *N*-bromo- (NBS) and *N*-chlorosuccinimide (NCS) will be superior halogenating reagents if benzylic halogenation is suppressed. Schmid reported that benzene and toluene gave nuclear brominated derivatives in good yields by the reactions with NBS and  $\text{AlCl}_3$  without solvents under long reflux using a large amount of the catalyst (>1 equiv.), but in unsatisfactory yields (21–61%) of products together with the polysubstituted products by the reactions using  $\text{H}_2\text{SO}_4$ ,  $\text{FeCl}_3$ , and  $\text{ZnCl}_2$ .<sup>1</sup> Lambert et al. reported that nuclear substituted derivatives were obtained in good yields from the reactions of aromatic compounds with NBS in 50% aqueous  $\text{H}_2\text{SO}_4$ ,<sup>2</sup> however, this method requires considerably acidic conditions. Thus, there is a need to develop a practical procedure for the halogenation of aromatic compounds.

In this paper, we report that aromatic compounds react with NCS, NBS, or *N*-iodosuccinimide (NIS) in the presence of  $\text{NH}_4\text{NO}_3$  or  $\text{FeCl}_3$  in  $\text{CH}_3\text{CN}$  to give the corresponding nuclear substituted products.

First, we examined the bromination of toluene with NBS using 0.1 equiv. of various protic and Lewis acids at 60 °C (Table 1). In order to suppress the substitution at benzylic position,<sup>3</sup> a polar solvent,  $\text{CH}_3\text{CN}$  was used. The other solvents such as DMF and DMSO did not give satisfactory results. Nuclear brominated products of toluene were obtained together with the substituted products at the benzylic position. The isomer distribution of *p*- and *o*-bromotoluene varied by the kind of employed catalyst. Interestingly, the reactions using weak acids such as  $\text{NH}_4\text{NO}_3$ ,  $\text{NH}_4\text{Cl}$ , and PyHOTf proceeded faster than that using  $\text{H}_2\text{SO}_4$ , however, the reason is not clear at the present moment. When toluene was treated with NBS at 60 °C for 8 h in the presence of  $\text{NH}_4\text{NO}_3$ , *p*- and *o*-bromotoluene were produced in 62 and 38 relative yields, respectively. A trace amount of benzyl bromide was detected (<1%). The reaction using  $\text{NH}_4\text{Cl}$  gave *p*- and *o*-bromotoluene in 57 and 36 relative yields, respectively within 3 h together with small amounts of *o,p*-dibromotoluene (3%) and benzyl bromide (4%). It was found that  $\text{NH}_4\text{NO}_3$  was the most effective protic acid for nuclear bromination.

In a series of examined Lewis acids,  $\text{FeCl}_3$  showed good results. The reaction completed within 20 min at room temperature to give *p*- and *o*-bromotoluene, and *o,p*-dibromotoluene

**Table 1.** Bromination of toluene with NBS using various catalysts in  $\text{CH}_3\text{CN}$ <sup>a</sup>

Catalyst	Time	Conv. /%	Relative yields/% <sup>b</sup>			
			<i>p</i> -Bromo- toluene	<i>o</i> -Bromo- toluene	<i>o,p</i> -Dibromo- toluene	Benzyl bromide
$\text{H}_2\text{SO}_4$	8 h	68	36	56	0	8
PyHOTf <sup>c</sup>	8 h	82	19	18	4	49
PyHOTs	8 h	65	34	25	0	41
PyHCl <sup>d</sup>	8 h	49	29	16	3	30
$\text{NH}_4\text{OTf}$	8 h	37	25	18	27	30
$\text{NH}_4\text{NO}_3$	8 h	100	62	38	0	trace
$\text{NH}_4\text{Cl}$	3 h	100	57	36	3	4
$\text{AlCl}_3$ <sup>e</sup>	2 h	47	23	8	17	52
$\text{FeCl}_3$ <sup>e</sup>	20 min	100	40	49	11	0
CAN <sup>f</sup>	4 h	87	38	36	0	15
$\text{ZnCl}_2$ <sup>g</sup>	8 h	72	35	33	0	16
$\text{Sc}(\text{OTf})_3$ <sup>h</sup>	8 h	46	35	26	0	33
None	8 h	21	4	4	7	85







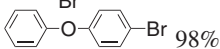















<sup>a</sup>Reaction conditions: Toluene 10 mmol, NBS 10 mmol, Catalyst 1 mmol,  $\text{CH}_3\text{CN}$  6.3 mL, Temp. 60 °C. <sup>b</sup>Determined by <sup>1</sup>H NMR spectroscopy. <sup>c</sup>10% of *p*-bromobenzyl bromide was obtained. <sup>d</sup>*p*- and *o*-Bromobenzyl bromide were obtained in 2 and 20% yields, respectively. <sup>e</sup>At 25 °C. <sup>f</sup>*p*- and *o*-Bromobenzyl bromide were obtained in 8 and 3% yields, respectively. <sup>g</sup>*p*- and *o*-Bromobenzyl bromide were obtained in 9 and 7% yields, respectively. <sup>h</sup>6% of *p*-bromobenzyl bromide was obtained.

in 40, 49, and 11% relative yields, respectively. Benzyl bromide was not detected at all. In the case of  $\text{AlCl}_3$ , conversion was low because NBS was consumed by the reaction with  $\text{AlCl}_3$ . In the absence of the catalyst, benzylic bromination proceeded very slowly. For the bromination of aromatic compounds using NBS, the actual active agent is not free bromine but possibly the protonated or Lewis acid-coordinated NBS.<sup>2</sup> Further study is necessary to establish the mechanism.

The results of bromination of various substrates with NBS using  $\text{NH}_4\text{NO}_3$  and  $\text{FeCl}_3$  in  $\text{CH}_3\text{CN}$  are summarized in Table 2.<sup>4</sup> The reactions of more active compounds than benzene with NBS in the presence of 0.1 equiv. of  $\text{NH}_4\text{NO}_3$  led to the corresponding monobrominated products in good yields. Diphenyl ether, which was sensitive for acids, reacted with NBS catalyzed by  $\text{NH}_4\text{NO}_3$  to give the *p*-brominated product in 98% yield. When diphenyl ether was treated with bromine at room temperature without a catalyst in  $\text{CCl}_4$ , the same product was obtained in a lower yield (63%).<sup>5</sup> For benzene and less active compounds than benzene, the reactions were performed in the presence of  $\text{FeCl}_3$  to give the corresponding brominated products in good yields. The reaction of nitrobenzene was conducted at 150 °C without the solvent to afford *m*-bromobenzene in 95% yield. Bromination at the benzylic positions was hardly observed in the substrates possessing methyl and ethyl groups.

Furthermore, this method can be applied to the chlorination

**Table 2.** Bromination of various substrates by NBS in CH<sub>3</sub>CN<sup>a</sup>




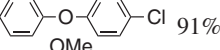





















Substrate	Catalyst/mmol	Temp/°C <sup>b</sup>	Time	Products/Yield/% <sup>c</sup>
	NH <sub>4</sub> NO <sub>3</sub> (1)	25	10 min	 94%
	NH <sub>4</sub> NO <sub>3</sub> (1)	25	10 min	 97%
	NH <sub>4</sub> NO <sub>3</sub> (1)	25	10 min	 96%
PhOPh	NH <sub>4</sub> NO <sub>3</sub> (1)	25	30 min	 98%
	NH <sub>4</sub> NO <sub>3</sub> (1) <sup>d</sup>	60	8 h	 53%  32%
	FeCl <sub>3</sub> (1) <sup>e</sup>	20	20 min	 39%  48%
	NH <sub>4</sub> NO <sub>3</sub> (1)	60	8 h	 53%  30%
	FeCl <sub>3</sub> (1)	100	8 h	 85%
	FeCl <sub>3</sub> (10)	100	2 h	 57%  38%
	FeCl <sub>3</sub> (10)	100	7 h	 99%
	FeCl <sub>3</sub> (10) <sup>f</sup>	150	2 h	 95%

<sup>a</sup>Reaction conditions: Substrate 10 mmol, NBS 10 mmol, CH<sub>3</sub>CN 5 mL.  
<sup>b</sup>Bath temp. <sup>c</sup>Isolated yields. <sup>d</sup>A trace amount of benzyl bromide was obtained. <sup>e</sup>6% of 2,4-dibromotoluene was obtained. <sup>f</sup>Without solvent.

of aromatic compounds. The results are shown in Table 3. Wide ranges of substrates were treated with FeCl<sub>3</sub> in CH<sub>3</sub>CN to afford the corresponding chlorinated compounds in good yields. In particular, the use of NH<sub>4</sub>NO<sub>3</sub> was effective for acid sensitive substrates. For example, 2-chlorothiophene<sup>6</sup> (59%) and a small amount of 2,5-dichlorothiophene<sup>6</sup> (10%) were isolated from the reaction of thiophene using this method, while only polymeric materials were produced from the reactions with NCS in the presence of 0.1 equiv. of FeCl<sub>3</sub> in CH<sub>3</sub>CN at room temperature. The yield (96%) for chlorination of diphenyl ether using NH<sub>4</sub>NO<sub>3</sub> was higher than that using 0.1 equiv. of FeCl<sub>3</sub> in CH<sub>3</sub>CN (25 °C, 5 h, 71%).

Finally, we conducted a brief examination of iodination. The reactions of anisole, diphenyl ether, and toluene with NIS catalyzed by 0.1 equiv. of FeCl<sub>3</sub> in CH<sub>3</sub>CN gave *p*-iodoanisole (25 °C, 0.5 h, 99%), *p*-iodophenyl phenyl ether (25 °C, 0.5 h, 99%), and *o*- (43%) and *p*-iodotoluene (60 °C, 1 h, 41%), respectively. Benzene reacted with NIS in the presence of 1 equiv. of FeCl<sub>3</sub> at 100 °C for 5 h in CH<sub>3</sub>CN to give iodobenzene in 89% yield. Chlorobenzene and methyl benzoate, which were less active than benzene, did not react with NIS at 100 °C in the presence of 1 equiv. of FeCl<sub>3</sub> in CH<sub>3</sub>CN.

**Table 3.** Chlorination of various substrates by NCS in CH<sub>3</sub>CN<sup>a</sup>

Substrate	Catalyst/mmol	Temp/°C <sup>b</sup>	Time	Products/Yield /% <sup>c</sup>
	NH <sub>4</sub> NO <sub>3</sub> (1)	60	1 h	 59%  10%
PhOPh	NH <sub>4</sub> NO <sub>3</sub> (1)	100	7 h	 91%
	FeCl <sub>3</sub> (1)	25	30 min	 93%
	FeCl <sub>3</sub> (1)	25	30 min	 93%
	FeCl <sub>3</sub> (1)	25	1 h	 86%  12%
	FeCl <sub>3</sub> (1)	100	3 h	 84%  47%
	FeCl <sub>3</sub> (1)	100	3 h	 37%  52%
	FeCl <sub>3</sub> (1)	100	3 h	 32%  52%
	FeCl <sub>3</sub> (10)	100	2 h	 75%  5%
	FeCl <sub>3</sub> (10)	100	7 h	 35%  45%
	FeCl <sub>3</sub> (10)	100	17 h	 95%
	FeCl <sub>3</sub> (10) <sup>d</sup>	150	3 h	 91%

<sup>a</sup>Reaction conditions: Substrate 10 mmol, NCS 10 mmol, CH<sub>3</sub>CN 5 mL. <sup>b</sup>Bath temp. <sup>c</sup>Isolated yields. <sup>d</sup>Without solvent.

In conclusion, we devised an efficient and mild method for nuclear halogenation of aromatic compounds. NBS and NCS are readily available and NH<sub>4</sub>NO<sub>3</sub> and FeCl<sub>3</sub> are cheap. This method is especially useful for chlorination of aromatic compounds since molecular chlorine is a toxic gas and not easy to handle, and for iodination since it normally requires a strong oxidizing agent.

#### References and Notes

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- A typical experimental procedure is as follows: A mixture of 1,4-dimethoxybenzene (1.38 g, 10 mmol), NBS (1.78 g, 10 mmol), and NH<sub>4</sub>NO<sub>3</sub> (80 mg, 1 mmol) in dry CH<sub>3</sub>CN (5 mL) was stirred at 25 °C for 10 min. The reaction mixture was poured into water (50 mL) and extracted with ether. The extracts were washed with water, dried, and evaporated. The residue was chromatographed (hexane-acetone = 10:1) on silica gel to give 2-bromo-1,4-dimethoxybenzene (2.04 g, 94%).
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