

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

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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 NH_4NO_3 or 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 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 H_2SO_4 , FeCl_3 , and ZnCl_2 .¹ Lambert et al. reported that nuclear substituted derivatives were obtained in good yields from the reactions of aromatic compounds with NBS in 50% aqueous H_2SO_4 ,² 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 NH_4NO_3 or FeCl_3 in CH_3CN 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,³ a polar solvent, CH_3CN 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 NH_4NO_3 , NH_4Cl , and PyHOTf proceeded faster than that using H_2SO_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 NH_4NO_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 NH_4Cl 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 NH_4NO_3 was the most effective protic acid for nuclear bromination.

In a series of examined Lewis acids, 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 CH_3CN ^a

Catalyst	Time	Conv. /%	Relative yields/% ^b			
			<i>p</i> -Bromo- toluene	<i>o</i> -Bromo- toluene	<i>o,p</i> -Dibromo- toluene	Benzyl bromide
H_2SO_4	8 h	68	36	56	0	8
PyHOTf^c	8 h	82	19	18	4	49
PyHOTs	8 h	65	34	25	0	41
PyHCl^d	8 h	49	29	16	3	30
NH_4OTf	8 h	37	25	18	27	30
NH_4NO_3	8 h	100	62	38	0	trace
NH_4Cl	3 h	100	57	36	3	4
AlCl_3^e	2 h	47	23	8	17	52
FeCl_3^e	20 min	100	40	49	11	0
CAN^f	4 h	87	38	36	0	15
ZnCl_2^g	8 h	72	35	33	0	16
$\text{Sc}(\text{OTf})_3^h$	8 h	46	35	26	0	33
None	8 h	21	4	4	7	85

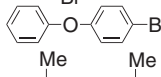
^aReaction conditions: Toluene 10 mmol, NBS 10 mmol, Catalyst 1 mmol, CH_3CN 6.3 mL, Temp. 60 °C. ^bDetermined by ¹H NMR spectroscopy. ^c10% of *p*-bromobenzyl bromide was obtained. ^d*p*- and *o*-Bromobenzyl bromide were obtained in 2 and 20% yields, respectively. ^eAt 25 °C. ^f*p*- and *o*-Bromobenzyl bromide were obtained in 8 and 3% yields, respectively. ^g*p*- and *o*-Bromobenzyl bromide were obtained in 9 and 7% yields, respectively. ^h6% 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 AlCl_3 , conversion was low because NBS was consumed by the reaction with 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.² Further study is necessary to establish the mechanism.

The results of bromination of various substrates with NBS using NH_4NO_3 and FeCl_3 in CH_3CN are summarized in Table 2.⁴ The reactions of more active compounds than benzene with NBS in the presence of 0.1 equiv. of NH_4NO_3 led to the corresponding monobrominated products in good yields. Diphenyl ether, which was sensitive for acids, reacted with NBS catalyzed by NH_4NO_3 to give the *p*-brominated product in 98% yield. When diphenyl ether was treated with bromine at room temperature without a catalyst in CCl_4 , the same product was obtained in a lower yield (63%).⁵ For benzene and less active compounds than benzene, the reactions were performed in the presence of 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 CH₃CN^a

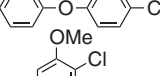
Substrate	Catalyst/mmol	Temp/°C ^b	Time	Products/Yield/% ^c
	NH ₄ NO ₃ (1)	25	10 min	 94%
	NH ₄ NO ₃ (1)	25	10 min	 97%
	NH ₄ NO ₃ (1)	25	10 min	 96%
PhOPh	NH ₄ NO ₃ (1)	25	30 min	 98%
	NH ₄ NO ₃ (1) ^d	60	8 h	 53%  32%
	FeCl ₃ (1) ^e	20	20 min	 39%  48%
	NH ₄ NO ₃ (1)	60	8 h	 53%  30%
C ₆ H ₆	FeCl ₃ (1)	100	8 h	 85%
	FeCl ₃ (10)	100	2 h	 57%  38%
	FeCl ₃ (10)	100	7 h	 99%
	FeCl ₃ (10) ^f	150	2 h	 95%

^aReaction conditions: Substrate 10 mmol, NBS 10 mmol, CH₃CN 5 mL.^bBath temp. ^cIsolated yields. ^dA trace amount of benzyl bromide was obtained. ^e6% of 2,4-dibromotoluene was obtained. ^fWithout solvent.

of aromatic compounds. The results are shown in Table 3. Wide ranges of substrates were treated with FeCl₃ in CH₃CN to afford the corresponding chlorinated compounds in good yields. In particular, the use of NH₄NO₃ was effective for acid sensitive substrates. For example, 2-chlorothiophene⁶ (59%) and a small amount of 2,5-dichlorothiophene⁶ (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 FeCl₃ in CH₃CN at room temperature. The yield (96%) for chlorination of diphenyl ether using NH₄NO₃ was higher than that using 0.1 equiv. of FeCl₃ in CH₃CN (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 FeCl₃ in CH₃CN 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 FeCl₃ at 100 °C for 5 h in CH₃CN 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 FeCl₃ in CH₃CN.

Table 3. Chlorination of various substrates by NCS in CH₃CN^a

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

^aReaction conditions: Substrate 10 mmol, NCS 10 mmol, CH₃CN 5 mL. ^bBath temp. ^cIsolated yields. ^dWithout solvent.

In conclusion, we devised an efficient and mild method for nuclear halogenation of aromatic compounds. NBS and NCS are readily available and NH₄NO₃ and FeCl₃ 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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- 3 S. D. Ross, M. Finkelstein, and R. C. Petersen, *J. Am. Chem. Soc.*, **80**, 4327 (1958).
- 4 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 NH₄NO₃ (80 mg, 1 mmol) in dry CH₃CN (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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