

Halogenation Using *N*-Halogenocompounds. I. Effect of Amines on *ortho*-Bromination of Phenols with NBS

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(Received December 11, 1992)

Synopsis. Primary and secondary amines, especially diisopropylamine and dibutylamine, catalyzed *ortho*-dibromination of phenol and *ortho*-monobromination of 2-substituted phenols with NBS in dichloromethane to give selectively 2,6-dibromophenol and 2-bromo-6-substituted phenols, respectively. The effective intermediates are inferred to be *N*-bromoamines. The scope and limitations of the bromination are also presented.

Several methods for direct *ortho*-bromination and *ortho*-dibromination of phenols have been reported.^{1–4)} Pearson et al.⁵⁾ found that treatment of phenols with bromine in the presence of a large excess of *t*-butylamine at -70°C gave 2-bromo- or 2,6-dibromophenols in good yields. Recently, Schmitz et al.⁶⁾ showed that the reaction between phenol and *N,N*-dibromomethylamine efficiently affords 2,6-dibromophenol. However, the former reaction requires very low temperatures and the latter uses an unstable brominating agent. We wish to report here the practical *ortho*-bromination of phenols using *N*-bromosuccinimide (NBS) in the presence of primary or secondary amines at room temperature.

Results and Discussion

Phenol was treated with NBS (2 molar amounts) in the presence of primary amines (2 molar amounts) at room temperature in dichloromethane. The results are summarized in Table 1. Our aim was selective preparation of 2,6-dibromophenol. It is well-known that bromination of phenol with bromine in carbon disulfide leads to exclusive *para*-substitution.⁷⁾ Addition of every primary amine was effective for obtaining the desired product selectively. In the absence of amines, the yield of 2,6-dibromophenol was much lower than that of 2,4,6-tribromophenol. The selective *ortho*-dibromination of phenols was also observed when secondary amines were added. Particularly, diisopropylamine and dibutylamine showed high *ortho*-selectivity. These phenomena show that primary and secondary amines promote *ortho*-bromination of phenols. Addition of tertiary amines, such as triethylamine, tripropylamine, tripen-tylamine, and 1,4-diazabicyclo[2.2.2]octane was ineffective in the *ortho*-selectivity. Probably the bromination in this system is related to the *N*-bromoamines⁸⁾ described later and the steric effect of amines seems not to be important.

Table 2 shows the relation between the yields of the

products and the amounts of added diisopropylamine which showed the highest *ortho*-selectivity. The distribution of the products was only slightly influenced by the added amount of the amine in the bromination. Even a 0.1 molar amount of diisopropylamine was sufficiently effective. From these results, it was concluded that the amine worked catalytically in the selective *ortho*-bromination of phenol.

An attempt to *ortho*-monobrominate phenol by the use of one molar amount of NBS and 0.1 molar amount of diisopropylamine failed; the yield of the *ortho*-monobromide was comparable to that of the *ortho*-dibromide (ca. 30%) (Table 2, Run 6). This result means that *ortho*-selectivity was achieved, but mono-selectivity was not realized in this system. In the reaction between phenol and NBS, *ortho*-monobromophenol was prepared more efficiently without amines (*ortho/para* = 75/20) (Table 2, Run 7) rather than in the presence of diisopropylamine.

ortho-Bromination of 2-substituted phenols (e.g. 2-bromophenol, 2-chlorophenol, *o*-cresol) by NBS (1 molar amount) in the presence of diisopropylamine (0.1 molar amount) or in the absence of the amine was carried out (Table 3). The results were compared with the bromination with bromine. It was apparent that bromine gave *para*-bromides exclusively. In the case of NBS, the addition of a catalytic amount of the amine remarkably raised the ratio of the *ortho*-monobrominated phenols. *o*-Cresol was considerably *ortho*-brominated by NBS even without the amine. In Tables 2 and 3, the isolated yields of the *ortho*-bromides are shown in parentheses. Our method is satisfactory for synthesizing *ortho*-bromophenols.

To study the reasons why *ortho*-selectivity appears in the bromination of phenols using NBS and amines, *N*-bromodibutylamine (NBB)⁹⁾ was prepared as a brominating agent and allowed to react with phenol. One molar amount of NBB did not give *ortho*-monobromophenol selectively, but gave a mixture of *ortho*-monobromophenol (30.8%) and *ortho*-dibromophenol (28.8%), and a considerable amount of phenol (35.7%) was recovered. However, 2,6-dibromophenol was obtained in an 81.7% yield when two molar amounts of NBB were used. *N*-Bromoamines such as NBB were very unstable and decomposed in less than a day at room temperature.

The mechanism of the *ortho*-dibromination of phenol is considered as follows: First, *N*-bromoamines are gen-

Table 1. Dibromination of Phenol with NBS in the Presence of Primary, Secondary, and Tertiary Amines^{a)}

Amine ^{b)}	Product yield (%) ^{c)}					Recovd. (%)
	2,6-Dibromophenol	2,4,6-Tribromophenol	2-Bromophenol	2,4-Dibromophenol	4-Bromophenol	
—	11.0	35.4	21.9	17.2	14.6	0.2
<i>i</i> -PrNH ₂	69.3	10.5	14.4	0.7	1.4	3.8
<i>n</i> -BuNH ₂	78.9	11.6	4.0	1.1	0.6	3.8
<i>i</i> -BuNH ₂	65.4	16.0	11.2	0.7	0.5	6.2
<i>i</i> -BuNH ₂	73.5	12.4	11.0	1.1	0.4	1.6
<i>n</i> -C ₅ H ₁₁ NH ₂	73.8	11.9	9.1	0.9	0.5	3.9
<i>n</i> -C ₆ H ₁₃ NH ₂	73.7	11.2	9.2	1.1	0.7	4.1
<i>n</i> -C ₇ H ₁₅ NH ₂	73.6	11.3	9.9	1.0	0.5	3.7
<i>n</i> -C ₈ H ₁₇ NH ₂	71.9	12.7	9.9	1.0	0.6	3.8
<i>n</i> -C ₉ H ₁₉ NH ₂	79.7	11.0	6.2	1.0	0.5	1.6
(<i>n</i> -Pr) ₂ NH	72.1	11.7	9.0	1.2	0.7	5.2
(<i>i</i> -Pr) ₂ NH	81.8	10.7	3.2	1.4	0.8	2.2
(<i>n</i> -Bu) ₂ NH	79.3	7.9	6.8	1.3	0.7	3.9
Piperidine	75.9	6.8	11.0	4.4	0.5	1.4
Morpholine	68.5	16.8	8.3	0.3	0.8	7.2
Et ₃ N	13.6	34.8	16.1	17.4	9.6	8.5
(<i>n</i> -Pr) ₃ N	10.6	38.0	13.3	17.8	11.2	9.0
(<i>n</i> -C ₅ H ₁₁) ₃ N	18.1	34.2	11.4	17.5	13.5	5.4
1,4-Diazabicyclo [2.2.2]octane	1.6	57.5	4.6	7.2	12.3	16.7

a) Reactions were carried out at room temperature. b) Molar ratio of PhOH : NBS : amine = 1 : 2 : 2. c) Yields of the products were determined by GC.

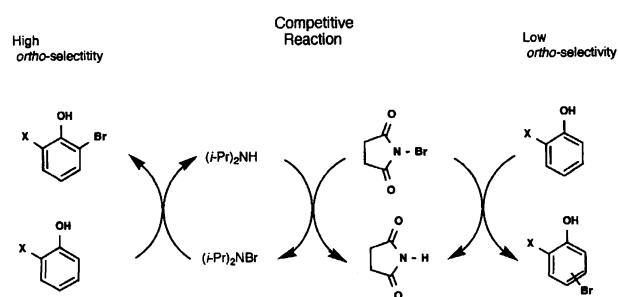
Table 2. Dibromination of Phenol with NBS in the Presence of Various Amounts of (*i*-Pr)₂NH^{a)}

Molar ratio		Product yield (%) ^{b)}					Recovd. (%)
Run	NBS/amine/PhOH	2,6-Dibromophenol	2,4,6-Tribromophenol	2-Bromophenol	2,4-Dibromophenol	4-Bromophenol	
1	2.0/0.1/1.0	79.4(78) ^{c)}	12.4	3.6	—	0.2	4.3
2	2.0/0.5/1.0	80.8	8.0	8.3	—	0.7	2.1
3	2.0/1.0/1.0	80.5	11.1	4.7	0.3	0.3	3.1
4	2.0/2.0/1.0	81.8	9.7	3.2	1.4	0.8	3.1
5	2.0/4.0/1.0	79.5	9.2	5.6	0.6	1.2	3.9
6	1.0/0.1/1.0	33.1	2.0	26.7	0.2	0.3	37.7
7	1.0/—/1.0	1.0	1.5	74.5	1.4	20.4	2.5

a) Reactions were carried out at room temperature. b) Yields of the products were determined by GC. c) Isolated yield.

erated from the reaction between NBS and amines,⁸⁾ then they form strong hydrogen bonding with phenols to cause bromination at one *ortho*-position of phenol and regeneration of the amines. A catalytic amount of the amines is enough because of the regeneration of the amines. The repetition of the above process causes one more substitution at the other *ortho*-position of 2-bromophenol. In the cases of 2-substituted phenols the *ortho*-bromination can occur only once (Scheme 1). Because the tertiary amines cannot be brominated by NBS, they do not influence the *ortho*-bromination of phenols. Though the hydrogen bonding between the phenolic OH and NBS will be formed, the bonding is inferred to be weaker than that between the OH and the *N*-bromoamines. The nucleophilicity (or basicity) of the nitrogen atom of *N*-bromoamines is stronger than that of NBS. This is why traces of *N*-bromoamines can react with phenols continuously.

In conclusion, this method for selective *ortho*-bromi-



Scheme 1.

nation of phenols is practical and quite easy to perform.

Experimental

Both melting points and boiling points were not corrected. ¹H NMR spectra were determined with a VARIAN VXR-300 spectrometer. GC analyses were performed by using an SE-30 column (3 m×3 mm i.d.).

General Procedure for *ortho*-Bromination of Phe-

Table 3. Bromination of 2-Substituted Phenols with NBS and Br₂^{a)}

Substrate X	Agent ^{b)}	(i-Pr) ₂ NH/PhOH	Product distribution (%) ^{c)}			Recovd. (%)
Br	Br ₂	—	13.7	81.3	2.4	2.6
Br	NBS	—	18.4	22.5	29.4	29.6
Br	NBS	0.1	82.0(80) ^{d)}	—	5.7	12.3
Cl	Br ₂	—	7.1	77.1	1.4	14.3
Cl	NBS	—	27.1	17.7	24.8	30.4
Cl	NBS	0.1	84.2(83) ^{d)}	—	8.1	8.4
Me	Br ₂	—	2.7	94.0	0.3	2.9
Me	NBS	—	75.4	21.1	1.5	2.0
Me	NBS	0.1	96.5(91) ^{d)}	0.4	1.5	1.5

a) Reactions were carried out at room temperature. b) Molar ratio of agent : PhOH = 1 : 1. c) Yields of the products were determined by GC. d) Isolated yield.

nols with NBS. The dibromination of phenol is typical. A solution of phenol (188 mg, 2 mmol) in CH₂Cl₂ (4 ml) was mixed with a solution of an amine (0.2 mmol) in CH₂Cl₂ (1 ml). To the mixture was added a solution of NBS (712 mg, 4 mmol) in CH₂Cl₂ (20 ml) over 30 min and the mixture was stirred for 1 h at room temperature. The reaction mixture was acidified to pH 1 with concd sulfuric acid and water (40 ml). The organic layer was separated, dried with MgSO₄, and concentrated under reduced pressure. The residue was then submitted to GC analysis (Tables 1, 2, and 3).

The retention times of the *ortho*-, *para*-, di-, and tribromides were identical to those of authentic samples. 2,6-Dibromophenol, 2-bromo-6-chlorophenol, and 2-bromo-6-methylphenol were prepared by our method. Other *para*-, di-, and tribromides were prepared according to the literature.^{4,6,10)} 2-Bromophenol and 4-bromo-2-chlorophenol were purchased.

Bromination of Phenol with NBB. Bromine (9.6 g, 3.1 ml) was added to sodium hydroxide (6.0 g, 0.15 mol) dissolved in water (50 ml) under cooling in an ice-water bath. Dibutylamine (6.5 g, 0.05 mol) was added dropwise to the above solution at 5 °C and the mixture was stirred for 10 min. Dichloromethane (30 ml) was added to the mixture, and the organic layer was washed with water (10 ml×2), dried with MgSO₄, and concentrated in vacuo at room temperature to give NBB as an orange oil (10.0 g, 96%) which was used without purification. The crude product was assayed by iodometric titration. Analysis showed the existence of 36.0% active bromine, as compared with the theoretical value of 38.8% for C₈H₁₈BrN.

To a solution of phenol (0.19 g, 2 mmol) in CH₂Cl₂ (5 ml) was added a solution of NBB (0.82 g, 4 mmol) in CH₂Cl₂ (15 ml) over 10 min and the mixture was stirred for 25 min at room temperature. To the reaction mixture was then added concd sulfuric acid (10 ml). The organic layer was dried with MgSO₄, concentrated in vacuo, and analyzed by GC.

Independent Synthesis of Authentic *ortho*-Bromo-

phenols. 2,6-Dibromophenol Using the same procedure as described above, phenol (940 mg, 10 mmol) was converted into the desired product. The crude product was purified by column chromatography on silica gel followed by recrystallization from hexane to give 2,6-dibromophenol (1.96 g, 78%): Colorless needles, mp 59.5–60.5 °C (lit.⁶⁾ mp 55–56 °C); ¹H NMR (CDCl₃) δ=5.90 (1H, s, OH), 6.72 (1H, t, *J*=7.7 Hz, 4-H), and 7.46 (2H, d, 3- and 5-H).

2-Bromo-6-chlorophenol. Colorless prisms (83%); mp 55.0–56.0 °C (from hexane) (lit.⁶⁾ mp 52–55 °C); ¹H NMR (CDCl₃) δ=5.90 (1H, s, OH), 6.78 (1H, t, *J*=8.0 Hz, 4-H), 7.31 (1H, dd, *J*=1.3 and 8.0 Hz, 5-H), and 7.48 (1H, dd, 3-H).

2-Bromo-6-methylphenol. Colorless liquid (91%); bp 207–208 °C (lit.⁴⁾ bp 206–207 °C); ¹H NMR (CDCl₃) δ=2.30 (3H, s, CH₃), 5.60 (1H, s, OH), 6.73 (1H, t, *J*=8.1 Hz, 4-H), and 7.08 (1H, d, 5-H), and 7.31 (1H, d, 3-H).

These *ortho*-bromophenols and other authentic samples were used to prepare GC calibration curves.

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