Ring Halogenations of Polyalkylbenzenes with *N*-Halosuccinimide and Acidic Catalysts

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1-Bromo-2,5-pyrrolidinedione (NBS) and 1-chloro-2,5-pyrrolidinedione (NCS) with catalytic quantities of *p*-toluenesulfonic acid have been used for ring halogenations of polyalkylbenzenes. [Hydroxy(tosyloxy)iodo]benzene was effective as a catalyst with NBS but not NCS. Competition experiments with 1-iodo-2,5-pyrrolidinedione (NIS) were run to indicate selectivities in substrates, halogen sources and catalysts. With this information a mixed halogenated compound, 2-bromo-4-iodo-1,3,5-trimethylbenzene was prepared in high yield.

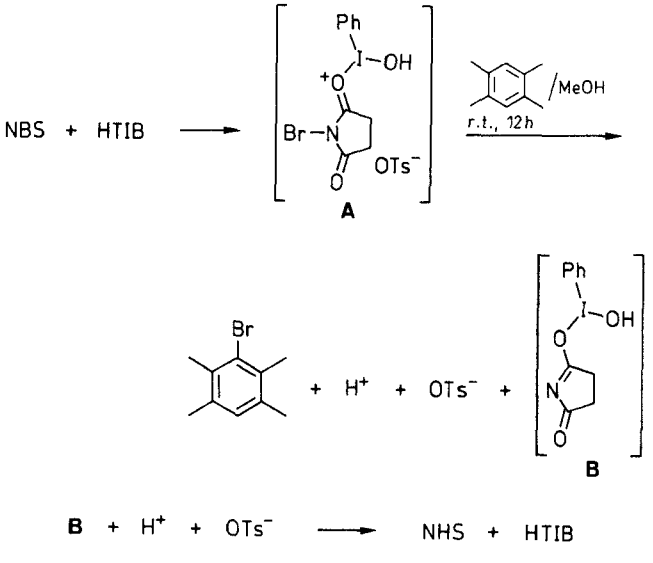
Iodinations of the rings of polyalkylbenzenes by means of either 1-iodo-2,5-pyrrolidinedione (*N*-iodosuccinimide, NIS) and catalytic quantities of [hydroxy(tosyloxy)iodo]-benzene (Koser's reagent, HTIB) or iodine and HTIB in stoichiometric quantities, have been reported lately.[1] The use of these combinations of reagents stemmed from their uses in the conversions of secondary alkynols to α-iodo enones.[2] More recently, they have been adapted to the conversions of specialized tertiary alkynols to β-iodo enones.[3] Such preparations of vinyl iodide or aromatic iodides are complementary to their ever increasing utilizations in synthetic methodologies involving couplings catalyzed by complexes of palladium, nickel or copper.

As to the scope of these reagents, the mildness of the reaction's conditions stand in stark contrast to heretofore conventional methods for aromatic iodinations.[4] In other areas NIS has been activated for iodinations with stoichiometric or greater quantities of acids. Two examples can be cited for specialized aromatics and two for non-aromatic compounds. Murti examined NIS in acidic media in a kinetic study of the iodination of substituted acetanilides.[5] Das and Kundu employed a solvent mixture of trifluoroacetic acid and its anhydride for NIS in the iodination of dialkoxypyrimidines and -uracils.[6] For the coupling of carbohydrate fragments, Fraser-Reid used NIS and a saturated solution of trifluoromethanesulfonic acid in dichloromethane.[7] This method was supplemented by a coupling combination of NIS and stoichiometric amounts of silver trifluoromethanesulfonate for thioglycerides and assorted sugars.[8] The utility of NIS and a catalytic amount of an acid has been demonstrated clearly by van Boom who used NIS and catalytic trifluoromethanesulfonic acid to couple thioglycerides with glycosyl acceptors and 1,1-thioorthoesters with glycosides.[9,10]

In this paper we wish to report results of facile and mild halogenations of the rings of polyalkylbenzenes with 1-bromo-2,5-pyrrolidinedione (*N*-bromosuccinimide, NBS) and 1-chloro-2,5-pyrrolidinedione (*N*-chlorosuccinimide, NCS) along with appropriate comparisons with NIS and its variants. Aromatic bromination of benzene and toluene with NBS and stoichiometric amounts of aluminum chloride, iron(III) chloride and other strong Lewis acids were reported some years ago.[11] Analogous chlorination under acidic conditions were demonstrated with *tert*-butyl hypochlorite.[12] These pivotal works were supplemented by aromatic halogenations of benzene, toluene and chlorobenzene with NBS and NCS in vigorously stirred solutions of aqueous sulfuric acid (25–67%) at 45–80°C.[13] Extensions of such systems to polyalkylbenzenes have not received attention.[14] Specialized nuclear brominations with NBS, such as with phenols[15] or guaiazulene,[16] continue to receive sporadic attention.

Durene (1,2,4,5-tetramethylbenzene) and mesitylene (1,3,5-trimethylbenzene) were selected as the primary substrates for the NBS reactions in light of their utility in the NIS work. Firstly, a simple treatment of durene with bromine in carbon tetrachloride afforded less than 5% bromodurene at room temperature, whereas mesitylene was brominated in 89% conversion with a 100% selectivity to bromomesitylene.

Bromine in methanol and NBS in methanol were effective for the formation of bromodurene in 67 to 78% yields without catalysts. These control reactions are incorporated in Table 1, which is a presentation of time-yield data as a function of several reagent combinations. All reagents gave satisfactory to excellent yields but catalysts were clearly desirable. The best catalyst is *p*-toluenesulfonic acid (TsOH) from the standpoint of highest yield and fastest time. Its selection was arrived at by the examination of the induction times of the other combinations involving HTIB. The use of TsOH was suggested by the sharp increase in the conversions with HTIB between the thirtieth and the forty-fifth minutes. The dramatic effect shown in the entry for TsOH is underscored further by the observation that within two minutes the conversion to bromodurene was 44%.



Scheme 1

Table 1. Bromination of Durene in Methanol[a]

Time (min) Reagent [Catalyst]	Bromodurene yields (%) 15	30	45	21 × 60
Br_2 [−]	17	23	33	67
NBS [−]	8	8	8	76
NBS [HTIB]	14	21	55	76
NBS + NHS [HTIB]	8	10	15	73
NBS [HTIB + NIS]	12	30	75	87
NBS [TsOH]	90	95	97	99

[a] Conditions: Durene (1 mmol), reagent (1 mmol) and catalyst (0.1 mmol) in MeOH (10 mL) at r.t.

Table 2. Mixed Halogenations of Durene with NXS[a]

Time (min)	Components in Mixture (%) Durene	Iododurene	Bromodurene
3	93	5	2
20	81	11	6
45	39	18	41
65	30	19	50
30 × 60	20	29	48

[a] Conditions: Durene (2 mmol), NBS (1 mmol), NIS (1 mmol) and HTIB (0.2 mmol) in MeOH (10 mL) at r.t.

Table 3. Mixed Halogenation of Mesitylene with NXS[a]

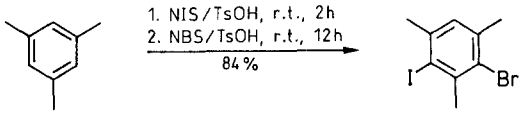
Time (min)	Components in Mixture (%) Mesitylene	Iodomesitylene	Bromomesitylene
55	47	43	10
90	41	44	15
120	35	45	19
180	24	48	26
290	18	48	33
24 × 60	3	49	46

[a] Conditions: mesitylene (2 mmol), NBS (1 mmol), NIS (1 mmol) and HTIB (0.2 mmol) in MeOH (10 ml) at r.t.

The Scheme for the catalytic effect of HTIB indicates an attack on the carbonyl oxygen of NBS to stimulate the heterolytic cleavage of the bromine to nitrogen bond. A similar activation by the protic acid, TsOH, formed in the bromodurene-forming step is possible. It is just such a species that was considered by Lambert, Ellis and Parry in their discussion of the sulfuric acid system.[13] The experiment involving succinimide (NHS) as a molar component would indicate that NHS played no part in providing a catalytic species. To be sure, it was somewhat inhibitory to the rate but did not lower the overall yield of bromodurene after 21 hours. The addition of NIS as a cocatalyst did improve both rates and yield. The complex of NIS and HTIB could be similar to structure **A** in Scheme 1 and could deliver an activating iodonium species to NBS. An interaction with the solvent to afford protons via hypoiodites is another possibility for the enhancement by NIS.

A competition experiment with stoichiometric quantities of NIS and NBS with catalytic HTIB and two moles of durene was carried out to test the relative reactivities of these halogenating agents. The results are shown in Table 2 and indicate a greater reactivity for NBS. Again, an interesting surge was noted for NBS prior to the forty fifth minute. No chlorination took place with NCS and HTIB so that reagent could not be incorporated into the comparison.

A similar competition experiment was run with mesitylene and the results are given in Table 3. Here both iodomesitylene and bromomesitylene approached their maximum values of 50%, but the NIS was clearly more reactive.



Scheme 2

The competitive aspects of such experiments can be converted into a cooperative endeavor. If the mesitylene was reduced to one mole in the joint presence of NIS and NBS the principal product was 2-bromo-4-iodo-1,3,5-trimethylbenzene in 63% yield. The yield was improved to 84% and the purity of the mixed halide product enhanced, when mesitylene/NIS mixture (1 : 1) was treated with TsOH as a catalyst (0.2) in methanol for two hours followed by addition of NBS and TsOH (1 : 0.2) for a subsequent overnight standing at room temperature (Scheme 2). The addition of NBS prior to the addition of NIS afforded only bromomesitylene. An addition of NCS/TsOH (1 : 0.1) to a reaction solution of the mixed dihalogen compound formed by NIS/NBS sequences was followed by an 18 hour refluxing protected from light led to only trace amounts of 2-bromo-4-chloro-6-iodo-1,3,5-trimethylbenzene.

A competition experiment with durene (1 mmol), mesitylene (1 mmol) and NBS (1 mmol) with HTIB (0.1 mmol) indicated roughly a 3 to 1 preference for mesitylene after 18 hours. That ratio held throughout that period. A parallel reaction using NIS showed a 90 : 2 ratio for mesitylene achieved after 3 hours. These differences in reactivities are combined in Table 4, which contains the two sets of competition experiments.

Table 4. Mixed Aromatics with NXS and HTIB[a]

Time (min)	Conversion (%) to Haloaromatics NBS		NIS	
	Bm[b]	Bd[b]	Im[b]	Id[b]
15	9	2	27	0
30	10	3	48	2
45	11	3	55	2
60	12	4	61	2
18 × 60	68	26	90	2

[a] Conditions: durene (1 mmol), mesitylene (1 mmol), NXS (1 mmol) and HTIB (0.1 mmol) in MeOH (10 mL) at r.t.

[b] Bm = bromomesitylene; Bd = bromodurene; Im = iodomesitylene; Id = iododurene.

The remarkable effect of the *p*-toluenesulfonic acid was also examined by these competitive techniques. These data are given in Table 5. Again, both NBS and NIS reaction rates are accelerated greatly by TsOH. Of interest to brominations are the higher selectivities of NBS/TsOH versus NBS/HTIB in addition to the previously noted enhanced rates. The synthetic utility of the NBS/catalytic TsOH combination was shown by its ability to convert mesitylene into bromomesitylene almost quantitatively upon overnight standing in methanol. This combination was able as well to transform *p*-xylene into 2-bromo-1,4-dimethylbenzene in 63% conversion and 100% selectivity.

Table 5. Mixed Aromatics with NXS and TsOH[a]

Time (min)	Conversion (%) to Haloaromatics			
	NBS		NIS	
	Bm[b]	Bd[b]	Im[b]	Id[b]
15	66	4	55	2
30	66	4	72	2
45	67	4	84	2
60	68	4	92	2
17 × 60	71	4	98	5

[a] Conditions: durene (1 mmol), mesitylene (1 mmol), NXS (1 mmol) and TsOH (0.1 mmol) in MeOH (10 mL) at r.t.
[b] Bm = bromomesitylene; Bd = bromodurene; Im = iodomesitylene; Id = iododurene.

The combination of NBS/catalytic TsOH was equally effective for mesitylene in acetonitrile with quantitative conversion to bromomesitylene. Durene's conversion, however, was poor (22%) in acetonitrile and there was no conversion at all in ethyl acetate.

The clear preference of any of the four reagent combinations for mesitylene over durene is most likely due to the relative stabilizations of the sigma complexes in addition to the presence of one more site of attack as shown in the Figure. The mesitylene system's cations are all tertiary whereas those of durene have one less tertiary. To explore this point further, *m*-xylene's behavior was examined since it should resemble durene. When *m*-xylene (1 mmol) was treated with NIS (1 mmol) and HTIB (0.1 mmol) in methanol (10 mL) at room temperature overnight, the reaction mixture consisted of 4-iodo-1,3-dimethylbenzene (85%) and *m*-xylene (15%). The corresponding reaction with *p*-xylene had a reaction mixture containing 2-iodo-1,4-dimethylbenzene (10%) and *p*-xylene (90%).

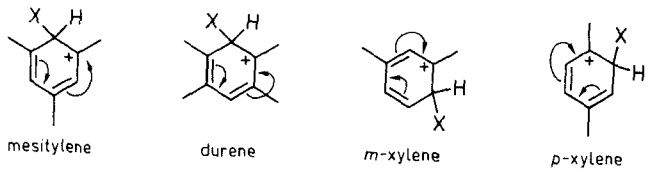


Figure. Sigma complexes of halonium reactions with alkyl aromatics.

This result follows from the lesser stabilization afforded to the sigma complex of the *para* isomer. A competition experiment of *m*-xylene and durene was run and the results are given in Table 6. The durene was iodinated at a somewhat faster pace than *m*-xylene but both achieved high conversions. With NBS, however, there was almost exclusive bromination of the durene ring. This result is given in Table 7.

Table 6. Mixed Aromatics with NIS and HTIB[a]

Time (min)	Components in Mixture (%)			
	m-xylene	iodoxylene[b]	durene	iododurene
1	50	0	50	0
15	49	1	44	6
30	45	5	41	9
45	43	7	38	12
60	40	10	36	14
165	35	15	30	20
19 × 60	27	23	25	25

[a] Conditions: durene (1 mmol); *m*-xylene (1 mmol), NIS (1 mmol), HTIB (0.1 mmol) in MeOH (10 mL) at r.t.
[b] 4-Iodo-1,3-dimethylbenzene.

Table 7. Mixed Aromatics with NBS and HTIB[a]

Time (min)	Components in Mixture (%)			
	m-xylene	bromoxylene[b]	durene	bromodurene
1	50	0	48	2
15	50	0	46	4
30	50	0	44	6
60	49	1	38	12
100	47	3	17	33
19 × 60	47	3	15	35

[a] Conditions: durene (1 mmol); *m*-xylene (1 mmol), NBS (1 mmol), HTIB (0.1 mmol) in MeOH (10 mL) at r.t.
[b] 4-Bromo-1,3-dimethylbenzene.

In light of the aforementioned ineffectiveness of HTIB as a catalyst for the chlorination by NCS, TsOH was used as the acidic component. The lesser reactivity of NCS versus NIS and NBS was noted previously for the silver nitrate catalyzed halogenations of steroidal alkynols.[17]

Table 8. Reaction of Mesitylene and NCS/TsOH[a]

TsOH/mesitylene	Temp. (°C)	Time (h)	Yield (%) chloromesitylene
0	r.t.	18	0
0.1	r.t.	18	22
0	reflux	1	0
0.1	reflux	1	75
0.1	reflux	3	81
0.5	r.t.	18	62
1.0	r.t.	18	68
1.5	r.t.	18	75
2.0	r.t.	18	80

[a] Conditions: mesitylene (1 mmol), NCS (1 mmol), and indicated amounts of TsOH in MeOH (10 mL).

Table 9. Spectroscopic Data of Halogenated Alkylaromatics

Halo Compound	MS *m/z* (%)	^{1}H NMR ($CDCl_3$) δ	IR ν (cm^{-1}) (1100–700 cm^{-1})
3-halo-1,2,4,5-tetramethylbenzene			
Cl	170/168 (M^+, 12/41), 133 (M–Cl, 100)	2.35 (s, 6H), 2.41 (s, 6H), 6.94 (s, 1H)	1096 (s), 1000 (s), 866 (s), 819 (s), 752 (m)
Br	214/212 (M^+, 43/45), 133 (M–Br, 100)	2.37 (s, 6H), 2.46 (s, 6H), 6.96 (s, 1H)	1090 (s), 1005 (s), 985 (s), 868 (s), 800 (s)
I	260 (M^+, 29), 133 (M–I, 100)	2.33 (s, 6H), 2.46 (s, 6H), 6.91 (s, 1H)	1004 (s), 975 (s), 873 (s), 727 (s)
2-halo-1,3,5-trimethylbenzene			
Cl	156/154 (M^+, 16/48), 119 (M–Cl, 100)	2.33 (s, 3H), 2.43 (s, 6H), 6.96 (s, 2H)	1052 (s), 1036 (s), 1008 (m), 952 (m), 847 (s)
Br	200/198 (M^+, 25/29), 119 (M–Br, 100)	2.31 (s, 3H), 2.45 (s, 6H), 6.96 (s, 2H)	1005 (s), 935 (m), 835 (s)
I	246 (M^+, 31), 119 (M–I, 83), 91 (100)	2.30 (s, 3H), 2.49 (s, 6H), 6.93 (s, 2H)	1031 (m), 1005 (s), 950 (m), 845 (s)
4-halo-1,3-dimethylbenzene			
Br	186/184 (M^+, 24/23), 105 (M–Br, 100)	2.34 (s, 3H), 2.44 (s, 3H), 6.88 (d, 1H), 7.09 (s, 1H), 7.40 (d, 1H)	1017 (s), 913 (m), 865 (m), 800 (s), 763 (s)
I	232 (M^+, 100), 105 (M–I, 83)	2.37 (s, 3H), 2.49 (s, 3H), 6.80 (d, 1H), 7.17 (s, 1H), 7.77 (d, 1H)	1000 (s), 910 (m), 865 (m), 797 (s)

When mesitylene was treated with an equimolar amount of NCS and a tenth molar amount of TsOH in methanol at reflux for three hours, 2-chloro-1,3,5-trimethylbenzene (chloromesitylene) was formed in 81% yield. No other products were detected. A similar yield could be obtained by a standing at room temperature overnight with two equivalents of TsOH. Further data on these combinations are given in Table 8.

The catalytic nature of the reaction was exemplified further when acetonitrile was used as a solvent in place of methanol. At a TsOH to mesitylene ratio of 0.1 the yield after a three hour refluxing was greater than 95%.

Other aromatic compounds such as anisole, benzene, toluene, *p*-xylene and durene did not react with NCS/TsOH in methanol or acetonitrile at room temperature. Three hour refluxing in methanol, however, was proved useful for durene to give chlorodurene (82%).

Several other acidic catalysts were examined and were found to afford no or minimal conversions. Among these are the aforementioned HTIB, silver nitrate, trifluoroacetic acid and [(bis(trifluoroacetoxy)iodo]benzene.

A 2% (v/v) mixture of trifluoromethanesulfonic acid and methanol was used as a reaction medium suitable for a 95% conversion of mesitylene to its chlorinated derivative at refluxing temperature. This result hearkens back to the use of NCS in 50 to 60% sulfuric acid for the ring chlorination of benzene, toluene and chlorobenzene, which was an earlier effort to utilize NCS for such purposes.[13]

In general, the broad range of acids and acid catalysts for ring halogenations by *N*-halosuccinimides stretches from strong mineral acids with NCS through the TsOH with NBS to the mild HTIB with NIS. Thereby a background is provided for one-pot synthesis of mixed halogenated aromatics.

Melting points are uncorrected and were taken on a Hoover-Thomas melting point apparatus. IR spectra were obtained with a Perkin-Elmer 137 IR spectrophotometer. ^{1}H NMR was recorded of $CDCl_3$ solutions on a GE-300 spectrometer, operated in the Fourier transform mode at 300 MHz. GC analyses were carried out on a Perkin-Elmer Sigma 3 B gas chromatograph with a methyl silicone column (0.25 mm × 50 m) and operated at the following conditions: injection temperature (250 °C), initial temperature (80 °C), ramp rate (16 °C/min), solvent elution time (60 seconds). GC/MS analyses were performed with a Hewlett-Packard 5992 with an OV-1 column (0.25 mm × 15 m) and were operated with the same conditions as for the GC analyses. Reagents were obtained from the Aldrich Chemical Co. and solvents were received from the J. T. Baker Co. All products were known compounds. Spectral data are given in Table 9.

3-Bromo-1,2,4,5-tetramethylbenzene; Typical Procedure for Analyses:

A solution of durene (139.9 mg, 1.02 mmol), NBS (181.9 mg, 1.01 mmol) and HTIB (47.1 mg, 0.115 mmol) in MeOH (10 mL) was protected from light and allowed to stand overnight. The reaction mixture was diluted with Et_2O (100 mL) and washed with 5% NaS_2O_3 (25 mL) and H_2O (50 mL). The ether layer was dried ($MgSO_4$). The solvent was reduced to 15 mL, whereupon one sample was injected into the gas chromatograph and another sample into the GC/MS spectrometer.

2-Bromo-4-iodo-1,3,5-trimethylbenzene; Typical Procedure for Preparations:

Mesitylene (185 mg, 1.54 mmol), NIS (366 mg, 1.63 mmol) and TsOH (39 mg, 0.2 mmol) were dissolved in MeOH (10 mL). After 2 h at r.t. in the dark NBS (312 mg, 1.76 mmol) and more TsOH (45 mg, 0.24 mmol) were added. The mixture then stood at r.t. overnight in the dark. After the work up as above, the ether was evaporated to a residue (422 mg, 84% yield) of white crystals, mp 36–37 °C. After a recrystallization from MeOH the crystals melted at 41–43 °C (Lit.[18], 42–43 °C) and weighed 274 mg (55%).

MS: *m/z* (%) = 326/324 (M^+, 92/100), 199/197 (M-I, 25/27), 117 (M-HBrI, 63).

^{1}H NMR ($CDCl_3$): δ = 2.33 (s, 3 H), 2.38 (s, 3 H), 2.79 (s, 3 H), 6.98 (s, 1 H).

IR (Nujol): ν = 1206 (m), 1015 (s), 947 (s), 850 (s) cm^{-1}.

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