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Ring Halogenations of Polyalkylbenzenes by Ionic Halides and Koser's Reagent

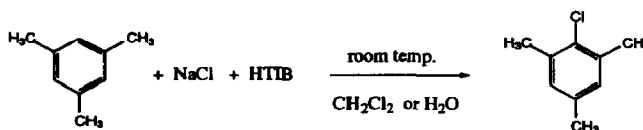
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Abstract. Ring chlorinations of polyalkylbenzenes such as mesitylene have been carried out at room temperature with LiCl or NaCl and stoichiometric amounts of Koser's reagent. Solvents range from water to methylene chloride. The procedures were extended to bromination and iodination.

We wish to report the ring halogenations of certain polymethylbenzenes by mixtures of alkali metal halides and trivalent iodine compounds. Of particular interests are the chlorinations. Such electrophilic chlorinations are usually effected by the time-honored use of chlorine with Lewis acid catalysts such as ferric chloride or antimony pentachloride.^{1,2} This method has been supplemented through the years by thermal treatments of transition metal chlorides.^{3,4} Other techniques center about *in situ* oxidations of chlorides by agents such as hypochlorites,⁵ chlorates,⁶ persulfates,⁷ or nitrates.⁸ Another general source of chlorinating species are those that feature the N-Cl bond. Some are based on chloramine-T,⁹ others utilize N-chlorosuccinimide catalyzed by either p-toluenesulfonic acid¹⁰ or perchloric acid.¹¹ A growing body of work on aromatic chlorination on solid supports has been reviewed recently.¹² The closest report of an electrophilic aromatic chlorination system to that given herein was that of Varvoglis and Gallos who used aluminum chloride or boron chloride with [bis(trifluoroacetoxy)iodo]benzene.¹³

In a procedure typical of our I(III) / chloride method 1,3,5-trimethylbenzene (mesitylene) (1.27 mmol) and [hydroxy(tosyloxy)iodobenzene (HTIB, Koser's reagent) (1.29 mmol) in methanol (10 mL) was treated at room temperature overnight with a stirred lithium chloride (1.7 mmol).¹⁴ The yield of 2-chloro-1,3,5-trimethylbenzene (chloromesitylene) as determined by gas chromatography was 95%. The reaction was not catalytic as shown by the relation of diminished yields and decreasing quantities of HTIB. An unusual range of solvents were used - from methylene chloride to water. Heterogeneity was apparent at either extremus - the inorganic chlorides' limited solubilities in organic solvents and the aromatic compounds' limited solubilities in water. Results for mesitylene are given in Table 1.



Other aromatic compounds were treated in a similar fashion. An 80% yield of chlorodurene was effected with equimolar amounts of 1,2,4,5-tetramethylbenzene (durene), HTIB and lithium chloride in methanol. The corresponding chlorination of 1,4-dimethylbenzene (p-xylene) led to 2-chloro-1,4-dimethylbenzene in 95+% selectivity on a 58% conversion.¹⁵

The isomeric *m*-xylene with sodium chloride and HTIB in methanol underwent a nearly quantitative conversion to 4-chloro-1,3-dimethylbenzene. The same combination of reagents and solvent was used to prepare 1-chloronaphthalene from naphthalene with 96% selectivity on a 55% conversion.

Table 1. Chlorination of Mesitylene with HTIB/Cl⁻

	Mesitylene ^a (mmol)	HTIB (mmol)	Salt (mmol)	Solvent (10mL)	Yield (%) Chloro-mesitylene
1	1.27	1.29	LiCl (1.7)	CH ₃ OH	95
2	0.84	0.89	NaCl (1.11)	CH ₃ OH	93
3	0.84	0.097	LiCl (1.1)	CH ₃ OH	10
4	0.84	0.44	LiCl (1.6)	CH ₃ OH	60
5	0.77	0.80	LiCl (0.90)	CH ₂ Cl ₂	100
6	0.75	0.77	LiCl (1.06)	EtOAc	23
7	0.81	0.84	LiCl (1.03)	Acetone	92
8	0.77	0.77	LiCl (0.89)	CH ₃ CN	95
9	0.87	0.87	NaCl (0.87)	H ₂ O	66

a) All reactions were run at room temperature overnight.

Toluene and benzene were unreactive under these mild conditions. No reaction was observed at room temperature with acetophenone. At the refluxing temperature of methanol that aromatic ketone was chlorinated on the methyl group and not on the ring with HTIB and sodium chloride. This contrasts with the AlCl₃ / PhI(O₂CCF₃)₃ system which could chlorinate fluorenone.¹³ The latter system, however, would be of little value in water due to the aqueous instabilities of both components.

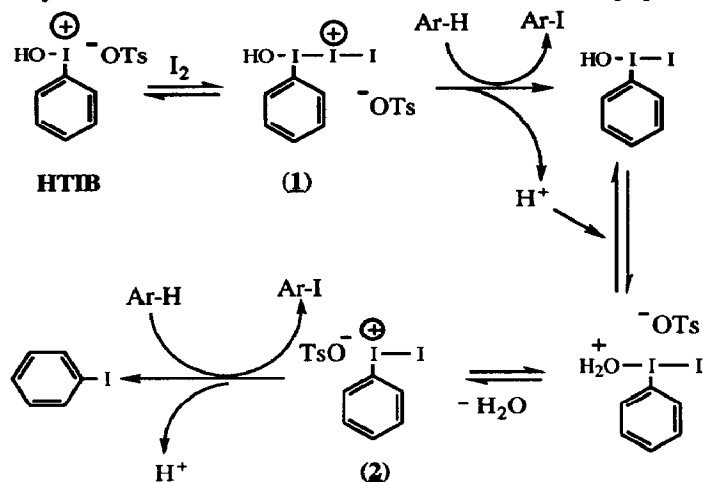
Replacements of HTIB in these reactions were tested. Sodium chloride and (diacetoxyiodo)benzene in equimolar amounts with mesitylene in methanol formed chloromesitylene in 90% yield. That reactant mixture in water afforded a low (25%) conversion but high (95%) selectivity of chloromesitylene. The use of [bis(trifluoroacetoxy)iodo]benzene, sodium chloride and mesitylene in equimolar quantities in methanol afforded the chloromesitylene in 95% yield. Iodine pentoxide and sodium chloride in methanol led to only a 10% yield of chloromesitylene; in water there was no reaction with this combination.

The aqueous instability of (diacetoxyiodo)benzene was in contrast to the behavior of HTIB, whereby HTIB was allowed to stand 20 hours in water prior to the addition of sodium chloride and mesitylene. Chloromesitylene was formed in 92% selectivity on a 90% conversion. The other product in these water reactions was dichloromesitylene. This was a possible outcome of the somewhat larger solubility of chloromesitylene versus mesitylene.

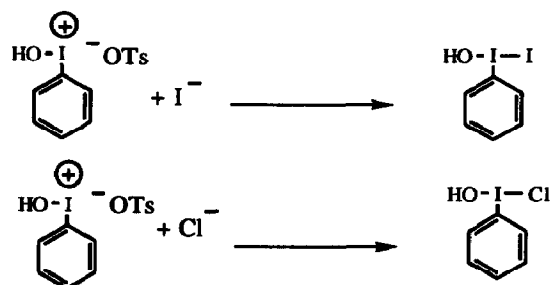
Chlorides could be replaced with bromides and iodides but not fluorides. Mesitylene was converted to bromomesitylene (2-bromo-1,3,5-trimethylbenzene) in 95% yield upon treatment with HTIB and 20% molar excess of sodium bromide in methanol. A similar result was obtained in acetonitrile. The conversion in acetone dropped to 24% but the selectivity to bromomesitylene was 100%. The use of 2 moles of HTIB and sodium bromide in methanol led to a 90% yield of 2,4-dibromo-1,3,5-trimethylbenzene. Lithium bromide could replace the sodium salt in these reactions. For example, equimolar amounts of mesitylene, HTIB and lithium bromide in methanol afforded a 90% yield of bromomesitylene. An equimolar mixture of *p*-xylene, HTIB and sodium bromide afforded an 82% yield of 2-bromo-1,4-dimethylbenzene.

The iodides differed somewhat, but provided insights on a possible mode of action of these halide-HTIB duos. Equimolar amounts of sodium iodide, HTIB and mesitylene afforded 2-iodo-1,3,5-trimethylbenzene in 100% selectivity on an 83% conversion in methylene chloride. Iodomesitylene was prepared from mesitylene, *N*-iodosuccinimide and catalytic *p*-toluenesulfonic acid¹⁰ and was then treated with NaI / HTIB in methylene chloride to give a 55% yield of diiodomesitylene. In methanol, however, there was no product other than iodine with equimolar amounts of reactants. When the quantity of HTIB was doubled, the yield of iodomesitylene rose to 90%. Since the iodide has significant solubility in methanol, the heterogeneity of iodides is required to prevent attack of the iodonium species by iodide rather than substrate. These results harken back to previous work wherein equimolar amounts of iodine, HTIB and mesitylene in methanol led to a 91% yield of 2,4-diiodo-1,3,5-trimethylbenzene.¹⁶ This unanticipated delivery of two atoms of iodine was verified by the use of half molar quantities of iodine and HTIB with one mole of mesitylene to obtain iodomesitylene in 95% yield without any diiodomesitylene.

A possible pathway for these events that invokes two different iodinating species is as follows:



If species **2** were present and able to iodinate, it could be formed by another route, the addition of ionic iodide to the ionized HTIB followed by dehydration. This postulate is in keeping with the present iodide results. Analogous pathways would apply to the chloride and bromide reactions, whereby $\text{PhI}(\text{OH})\text{Cl}$ and $\text{PhI}(\text{OH})\text{Br}$ would be involved in the halogenations.



Finally, a sequential process from mesitylene to 2-bromo-3-chloro-5-iodo-1,3,5-trimethylbenzene was carried out with NaCl/HTIB in methanol, followed by NaI/HTIB and NaBr/HTIB in CH₂Cl₂. With each step lasting 18 hours, the final mixture contained the trihalogenated product (8%), the chloriodomesitylene (76%), bromochloromesitylene (7%) and chloromesitylene (9%). A reversal in order of halogenations (Br -I- Cl) afforded only bromiodomesitylene (85%).

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- 15) Conversion is the molar percent of unaccounted or unrecovered starting material to the total starting material. Selectivity is the molar percent of a specific product to the unaccounted or unrecovered starting material. Yield of a product is selectivity times conversion. All products were known compounds and were determined by GC/MS.
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