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Reaction of 1,3,5-Tri-*tert*-Butylbenzene with 2,4,6,8-Tetraiodo-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione

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Abstract—Reactions of 1,3,5-tri-*tert*-butylbenzene with 2,4,6,8-tetraiodo-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione in acetic and trifluoroacetic acids involve substitution of one or two *tert*-butyl groups in the aromatic ring with formation of mono-, di-, and triiodo-substituted derivatives. No iodo derivatives are formed in acetonitrile.

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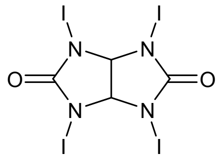
Iodo derivatives of trialkylbenzenes are convenient models for studying steric effects of substituents and deformations of the benzene ring. Direct iodination of trimethylbenzene (mesitylene) readily occurs with formation of iodo derivatives in high yield, whereas introduction of iodine into benzene ring containing *tert*-butyl groups involves some specificity. Monosubstituted *tert*-butylbenzene undergoes smooth iodination [1–6], while iodination of di-*tert*-butylbenzenes is not selective, and it leads to the formation of a considerable amount of *ipso*-substitution products [1, 5]. This is especially typical of 1,4-di-*tert*-butylbenzene [1, 5]. Direct iodination of 1,3,5-tri-*tert*-butylbenzene (**I**) was not studied.

tert-Butyl groups in compound **I** can be replaced even in the bromination process, in particular in acid medium. According to [7], the bromination of **I** with acetyl hypobromite generated *in situ* by reaction of bromine with silver perchlorate in acetic acid yields not only 1,3,5-tri-*tert*-butyl-2-bromobenzene but also acetoxylation product, 2,4,6-tri-*tert*-butylphenyl acetate and products of replacement of one *tert*-butyl group by the halogen atom or acetoxy group, the substrate conversion being 55%. Even more complex mixture of compounds, including *ipso*-substitution and diarylation products, was obtained in the bromination of **I** with 2,4,6,8-tetrabromo-2,4,6,8-tetraazabicyclo-[3.3.0]octane-3,7-dione [8].

The calculated (PM3) enthalpies of electrophilic (S_E) and *ipso*-iodination (S_i) of compound **I**, ΔH = 500.90 and –258.95 kJ/mol, respectively, indicate that *ipso*-iodination is thermodynamically more favorable than electrophilic iodination. We examined the behavior of compound **I** in reaction with 2,4,6,8-tetraiodo-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione (**II**) in acetonitrile and organic acids, acetic (in the presence of sulfuric) and trifluoroacetic. We previously showed that tetraiodoglycoluril **II** is a soft iodinating agent which readily reacts with polyalkylbenzenes in the temperature range from 0 to 20°C [9].

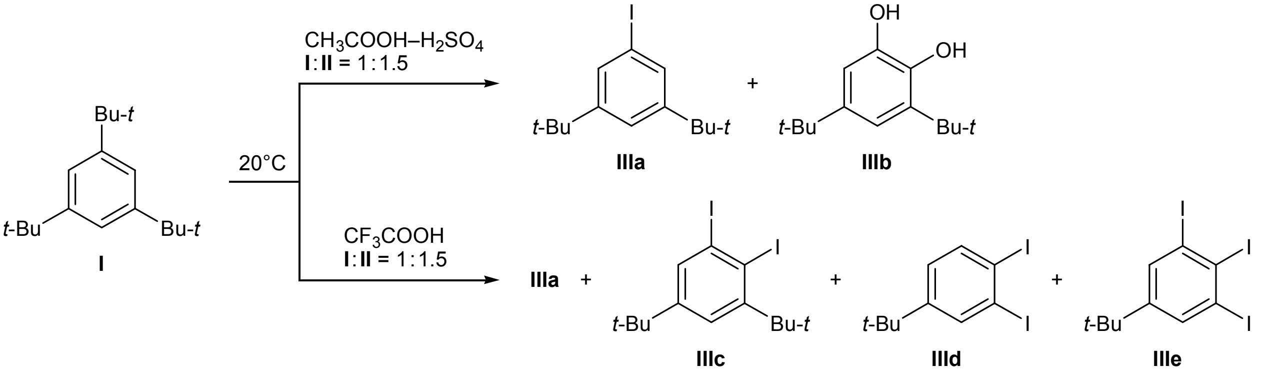


II

In order to avoid *ipso*-substitution, we tried to react trialkylbenzene **I** with glycoluril **II** in acetonitrile in the absence of acid. However, stirring of the reaction mixture for 24 h at room temperature (~20°C), followed by heating for 5 h under reflux, did not result in any transformation of the substrate (GC–MS data).

The iodination occurred in acid medium, namely in acetic acid containing sulfuric acid, but the process was necessarily accompanied by *ipso*-substitution of one *tert*-butyl group even in 10 min. The reaction of **I** with **II** at a molar ratio of 1 : 0.25 resulted in 18.3% conversion of the substrate into 1,3-di-*tert*-butyl-5-iodobenzene (**IIIa**), whereas the other part of **I** remained unchanged. In the presence of excess reagent (ratio **I** : **II** 1 : 1.5), the reaction mixture contained compound **IIIa** and a hydroxy derivative, assumingly,

Scheme 1.



3,5-di-*tert*-butylbenzene-1,2-diol (**IIIb**, 14.8%), and 46.7% of **I** remained intact (Scheme 1). By replacing AcOH–H_2SO_4 by CF_3COOH (molar ratio **I**:**II** 1:0.25) we succeeded in increasing the conversion of **I**, but the major product was 3,5-di-*tert*-butyl-5-iodobenzene (**IIIa**) (see table). The higher activity of the system **II**–CF_3COOH follows not only from the higher conversion of substrate **I** into iodo derivative **IIIa** but also from the formation of a number of other iodination products with different degrees of substitution as the amount of iodinating agent **II** increased.

In the reaction mixture obtained from compound **I** and 1.5 equiv of **II** in CF_3COOH we detected by GC–MS 1,3-di-*tert*-butyl-5-iodobenzene (**IIIa**, 28.7%), 3,5-di-*tert*-butyl-1,2-diiodobenzene (**IIIc**, 15.9%), 4-*tert*-butyl-1,2-diiodobenzene (**IIId**, 1.6%), and (assumingly), 5-*tert*-butyl-1,2,3-triiodobenzene (**IIIe**, 53.8%) (Scheme 1, see table). Neither expected 1,3,5-tri-*tert*-butyl-2-iodobenzene nor acetylation products were detected.

EXPERIMENTAL

Gas chromatographic–mass spectrometric analysis was performed on an Agilent-7890A gas chromatograph coupled with an Agilent-5975C mass-selective

Reaction of 1,3,5-tri-*tert*-butylbenzene (**I**) with 2,4,6,8-tetraiodo-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione (**II**) in AcOH–H_2SO_4 and CF_3COOH (20°C, 10 min; GC–MS data)

Solvent, molar ratio **I**:**II**	Compound no.	Fraction, %	Mass spectrum, *m*/*z* (I_{rel}, %)
AcOH–H_2SO_4, 1:0.25	**I**	81.7	246 (11) $[M]^+$, 231 (100), 57 (19), 41(7)
	IIIa	18.3	316 (32) $[M]^+$, 301 (100), 273 (7), 159 (11), 127 (7), 115 (7), 57 (16), 41(8)
AcOH–H_2SO_4, 1:1.5	**I**	46.7	246 (11) $[M]^+$, 231 (100), 57 (19), 41 (7)
	IIIa	38.5	316 (32) $[M]^+$, 301 (100), 273 (7), 159 (11), 127 (7), 115 (7), 57 (16), 41(8)
	IIIb	14.8	222 (19) $[M]^+$, 207(100), 191 (5), 179 (5), 96 (6), 82 (7), 57(16)
CF_3COOH, 1:0.25	**I**	36.1	246 (11) $[M]^+$, 231 (100), 57 (19), 41 (7)
	IIIa	63.9	316 (30) $[M]^+$, 301 (100), 273 (6), 159 (11), 127 (6), 115 (5), 57 (15), 41 (6)
CF_3COOH, 1:1.5	**IIIa**	28.7	316 (30) $[M]^+$, 301 (100), 273 (6), 159 (11), 127 (6), 115 (5), 57 (15), 41(6)
	IIIc	15.9	442 (88) $[M]^+$, 427 (100), 399 (45), 285 (11), 143 (6), 129 (8), 115 (17), 91 (5), 57 (24), 41 (11)
	IIId	1.6	386 (57) $[M]^+$, 371 (100), 343 (17), 254 (5), 244 (13), 127 (6), 117 (17), 89 (7)
	IIIe	53.8	512 (79) $[M]^+$, 497 (100), 469 (21), 370 (21), 258 (9), 234 (10), 215 (5), 127 (7), 115 (19), 74 (8), 41 (7)

detector (HP-5MS capillary column, 5.30 m × 0.25 mm, film thickness 0.25 μm; electron impact, 70 eV). Commercial 1,3,5-tri-*tert*-butylbenzene, mp 70–71°C (Aldrich), was used. 2,4,6,8-Tetraiodo-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione (**II**) was prepared according to the procedure described in [10].

Reaction of 1,3,5-tri-*tert*-butylbenzene (I) with 2,4,6,8-tetraiodo-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione (II). *a*. Compound **II**, 0.97 g (1.5 mmol), was added to a solution of 0.247 g (1 mmol) of **I** in 5 ml of acetonitrile, and the mixture was stirred for 24 h at room temperature and heated for 5 h under reflux. According to the GC–MS data, the mixture contained only initial compound **I**.

b. Compound **II**, 0.162 g (0.25 mmol), was added to a solution of 0.247 g (1 mmol) of **I** in 5 ml of acetic acid, 0.5 ml of sulfuric acid was then added dropwise on cooling with ice–water, and the mixture was stirred for 10 min at 20°C.

c. Compound **II**, 0.97 g (1.5 mmol), was added to a solution of 0.247 g (1 mmol) of **I** in 5 ml of acetic acid, 0.5 ml of sulfuric acid was then added dropwise on cooling with ice–water, and the mixture was stirred for 10 min at 20°C.

d. Compound **II**, 0.162 g (0.25 mmol), was added to a solution of 0.247 g (1 mmol) of **I** in 5 ml of trifluoroacetic acid, and the mixture was stirred for 10 min at 20°C.

e. Compound **II**, 0.97 g (1.5 mmol), was added to a solution of 0.247 g (1 mmol) of **I** in 5 ml of trifluoroacetic acid, and the mixture was stirred for 10 min at 20°C.

When the reaction was complete, the mixture was diluted with 20 ml of water and extracted with methylene chloride (3 × 10 ml), the extracts were washed with water and a 5% solution of $NaHCO_3$ until neutral reaction, dried over Na_2SO_4, and evaporated under reduced pressure, and the residue was analyzed by GC–MS (see table).

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