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The Iodination of Benzene with Iodine in the Thallium(III) Trifluoroacetate-Trifluoroacetic Acid System

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Molecular iodine in the system of thallium(III) trifluoroacetate-trifluoroacetic acid has been found to possess a high potency for aromatic iodination. Under controlled conditions, benzene and also mesitylene were step-by-step mono-, di-, and triiodinated, whereupon whole iodine was consumed for the iodination by the oxidation process of the thallium(III) salt. In the course of the iodination of benzene, an intermediate has been revealed to consist of thalliated benzenes, which were transformed into iodinated benzenes by the electrophilic attack of iodine.

Recently, Taylor *et al.*[1,2] reported a new aromatic iodination process, one which involves thalliation with thallium(III) trifluoroacetate to aryl thallium(III) ditrifluoroacetate, followed by iodination with potassium iodide to aryl iodide. On the other hand, the iodination with molecular iodine in the presence of thallium(III) trifluoroacetate in carbon tetrachloride was additionally described in their experimental section,[2] which attracted our attention for practical purposes. This iodination, however, was not investigated in the mechanistic aspect.

In this paper we will describe our finding that molecular iodine in the system consisting of thallium(III) trifluoroacetate and trifluoroacetic acid possesses a high potency for direct aromatic iodination.

Results and Discussion

A preliminary test for the aromatic iodination with molecular iodine was carried out in order to examine the effect of metal trifluoroacetate on the iodination of benzene. Several metal trifluoroacetates, such as Fe(III),[3] Cu(II),[3] Ag(I), Hg(II), and Tl(III) salts, were prepared, and the iodination was carried out in the presence of these metal salts in a large excess of benzene at its refluxing temperature. The results are summarized in Table 1. As can be seen, Tl(III), Ag(I), and Hg(II) salts showed a considerable effect in the reaction, while the other salts were almost inert. Among these three salts, particularly thallium(III) trifluoroacetate exhibited a noticeable result. The yield in this case was 83% for a two-molar-equivalent formation from a one-molar equivalent of iodine, suggesting that an oxidation-reduction process is involved.

Table 1. Effect of metal trifluoroacetates on the iodination of benzene

$$C_6H_6 \xrightarrow[M(CF_3CO_2)_n\text{-}C_6H_6]{I_2{}^{a)}} C_6H_5I$$

M(n)	Fe(III)	Cu(II)	Ag(I)	Hg(II)	Tl(III)
Yield[b] (%)	trace	trace	48	48	83
Solubility[c] of $M(CF_3CO_2)_n$	p.s.	p.s.	s.	s.	p.s.

a) A mixture of I_2 (2.5 mmol), $M(CF_3CO_2)_n$ (3.75 m mol) and benzene (10 ml) was refluxed for 2.5 hr. b) Yield is based on the formation of 2 mol of iodobenzene from 1 mol of iodine, and determined by glc using nitrobenzene as an internal standard. c) s., soluble; p.s., partly soluble.

Table 2. Solvent effect on the iodination of benzene[a]

Solvent	Reaction temp. (°C)	Yield[b] (%) of iodobenzene
MeCN	80	13
$CHCl_3$	63	34
CCl_4	76	87
DMF	85	0
Dioxane	85	0
MeOH	65	3
CF_3CO_2H	68	100

a) A mixture of C_6H_6 (5.5 mmol), I_2 (2.5 mmol), and $Tl(CF_3CO_2)_3$ (2.75 mmol) in solvent (8 ml) was heated for 2.5 hr. b) Similar to the b) of Table 1.

On the basis of these results, further study was centered on the behavior of thallium(III) trifluoroacetate toward the iodination. Experiments with this thallium salt in various solvents were carried out, generally at the refluxing temperature of the solvents used. The results are summarized in Table 2. As can be seen, trifluoroacetic acid, carbon tetrachloride and benzene showed marked effects on the iodination. The effect of trifluoroacetic acid was most remarkable, affording an almost quantitative yield of iodobenzene even at room temperature (30 °C) in a 15 min reaction period. The formation of thallium(I) salt equivalent to the reacted thallium(III) trifluoroacetate was confirmed as thallium(I) chromate by the quantitative analysis of the reaction mixture. Therefore, the reaction can be represented by the following overall equation:

$$Tl(CF_3CO_2)_3 + I_2 + 2C_6H_6 \longrightarrow Tl(CF_3CO_2) + 2C_6H_5I + 2CF_3CO_2H \qquad (1)$$

The effectiveness of the iodination in trifluoroacetic acid in the presence of thallium(III) trifluoroacetate was further realized for the polyiodination of benzene. The di-, tri-, and tetraiodinations of benzene were performed step-by-step with appropriate amounts of iodine and thallium(III) trifluoroacetate, as is shown in Table 3. 1,4-Diiodobenzene, 1,2,4-triiodobenzene, and 1,2,4,5-tetraiodobenzene were obtained in fair yields by this method. Despite the high efficiency of this method for iodination, though, the insolubility of the polyiodobenzenes in the reaction medium appears

Table 3. Iodination of benzene and mesitylene[a)]

Substrate	Molar ratio			Solv.	Temp. (°C)	Time (hr)	Product	Yield (%)
	Sub	: I_2	: $Tl(TFA)_3$					
C_6H_6	1.1	: 0.5	: 0.55	TFA	30	0.25	C_6H_5I	94[b)]
C_6H_6	1.1	: 0.5	: 0.55	TFA	68	2.5	C_6H_5I	100[b)]
C_6H_6	1.1	: 0.5	: 0.55	CCl_4	76	2.5	C_6H_5I	87[b)]
C_6H_6	1.0	: 1.0	: 1.1	TFA	68	2.5	p-$C_6H_4I_2$	86[b)]
C_6H_6	1.0	: 1.0	: 1.1	CCl_4	76	2.5	C_6H_5I p-$C_6H_4I_2$	89[b)] 2[c)]
C_6H_6	1.0	: 1.5	: 1.7	TFA	68	12.5	1,2,4-$C_6H_3I_3$ 1,2,4,5-$C_6H_2I_4$	70[c)] 13[c)]
C_6H_6	1.0	: 2.0	: 2.2	TFA	68	20	1,2,4-$C_6H_3I_3$ 1,2,4,5-$C_6H_2I_4$	38[c)] 41[c)]
1,3,5-$C_6H_3Me_3$	1.0	: 0.5	: 0.55	TFA	68	0.5	$C_6H_2IMe_3$ $C_6HI_2Me_3$	60[c)] 11[c)]
1,3,5-$C_6H_3Me_3$	1.0	: 1.0	: 1.1	TFA	68	0.75	$C_6HI_2Me_3$	92[c)]
1,3,5-$C_6H_3Me_3$	1.0	: 1.5	: 1.7	TFA	68	1.5	$C_6I_3Me_3$	82[c)]

a) A mixture of benzene or mesitylene (3 mmol), I_2 and $Tl(CF_3CO_2)_3$ in solvent (8 ml) was allowed to react. b) Yield is determined by glc using nitrobenzene as an internal standard. c) Yield is based on the product actually isolated.

to resist further penta- or hexa-iodination. The use of carbon tetrachloride instead of trifluoroacetic acid as a solvent failed in the diiodination of benzene. By the same procedure as has been described for benzene, mesitylene was iodinated step-by-step to give mono-, di-, and triiodomesitylene in good yields (Table 3).

In view of the above iodination results, iodine in the system of thallium(III) trifluoroacetate-trifluoroacetic acid has been revealed to be a powerful iodinating agent. The effect of trifluoroacetic acid was recognized from the fact that iodine in thallium(III) acetate-acetic acid did not work even for the monoiodination of benzene.

It is obvious that the overall reaction (1) for the iodination of benzene involves successive iodination with iodine formed through the oxidation of I^- with Tl^{3+} [Eq. (3)] after the initial iodination [Eq. (2)]. The iodine formed in Eq. (3) retraces the same path over again:

$$C_6H_6 + I_2 \xrightarrow{Tl(CF_3CO_2)_3} C_6H_5I + HI \qquad (2)$$

$$2HI + Tl(CF_3CO_2)_3 \longrightarrow Tl(CF_3CO_2) + I_2 + 2CF_3CO_2H \qquad (3)$$

The formation of less than a half molar equivalent of iodobenzene in the use of silver(I) and mercury(II) trifluoroacetates seems to be due to the inertness of these salts for the oxidation of I^- to iodine.

A problem is how Reaction (2) proceeds mechanistically under these conditions. The aromatic thalliation has been reported by Taylor *et al.*[4)] to proceed smoothly in trifluoroacetic acid by the use of thallium(III) trifluoroacetate.

$$C_6H_6 + Tl(CF_3CO_2)_3 \longrightarrow C_6H_5Tl(CF_3CO_2)_2 + CF_3CO_2H \qquad (4)$$

The rapidity of this reaction is enough to consider phenyl thallium bis-trifluoroacetate as an intermediate for the iodination. In order to confirm this consideration, phenyl thallium bis-trifluoroacetate was allowed to react with one half and with one molar equivalent of iodine in trifluoroacetic acid under the conditions used for the above-mentioned iodination. The reaction proceeded with sufficient rapidity to give mainly iodobenzene in the former case and mainly 1,4-diiodobenzene in the latter, in yields of 78 and 86% respectively. These reactions can be written as follows:

$$C_6H_5Tl(CF_3CO_2)_2 + \frac{1}{2}I_2 \longrightarrow C_6H_5I + \frac{1}{2}Tl(CF_3CO_2) + \frac{1}{2}Tl(CF_3CO_2)_3 \qquad (5)$$

$$C_6H_5Tl(CF_3CO_2)_2 + I_2 \longrightarrow C_6H_4I_2(p\text{-}) + Tl(CF_3CO_2) + CF_3CO_2H \qquad (6)$$

A possible pathway of Reaction (5) can be represented by the following equations:

$$C_6H_5Tl(CF_3CO_2)_2 + I_2 \longrightarrow C_6H_5I + TlI(CF_3CO_2)_2 \qquad (7)$$

$$TlI(CF_3CO_2)_2 + CF_3CO_2H \longrightarrow Tl(CF_3CO_2)_3 + HI \qquad (8)$$

$$HI + \frac{1}{2}Tl(CF_3CO_2)_3 \longrightarrow \frac{1}{2}Tl(CF_3CO_2) + \frac{1}{2}I_2 + CF_3CO_2H \qquad (9)$$

The reaction is presumed to be initiated by Eq. (7), which is regarded as an electrophilic substitution attacked by iodine, thus affording iodobenzene. The succeeding stages, (8) and (9), involve oxidation of I^- to iodine by the action of Tl^{3+}. By the summation of Eqs. (7), (8), and (9), an overall Eq. (5) is given. In Reaction (5) it is supposed that the iodobenzene and thallium(III) trifluoroacetate formed react further in an equimolar ratio to form thalliated iodobenzene ($C_6H_5I + Tl(CF_3CO_2)_3 \rightarrow IC_6H_4Tl(CF_3CO_2)_2 + CF_3CO_2H$). Actually, when iodobenzene was refluxed with an equimolar amount of thallium(III) trifluoroacetate in trifluoroacetic acid for 2.5 hr, a loss of about two-thirds the iodobenzene was observed by glc.

This is consistent with the above finding that Reaction (5) gave only a moderate yield of iodobenzene. Also, Reaction (6) must have proceeded through the *para*-thalliated iodobenzene.

It may be concluded that the iodination of benzene [Eq. (1)] in the system of thallium(III) trifluoroacetate–trifluoroacetic acid proceeds by the pathway of (4), (7), (8), and (9), which are summed up by Eq. (1). It should be emphasized that the iodination reaction described here involves two important stages; one is the electrophilic substitution of phenyl thallium di-trifluoroacetate with iodine, and the other is the oxidation of the resultant iodide anion to iodine with thallium(III) salt. This mechanism is quite different from that of the iodination of aryl thallium di-trifluoroacetate with potassium iodide reported by Taylor *et al.*[2] They speculated that the reaction proceeds *via* aryl thallium diiodide:

$$\mathrm{ArTl(CF_3CO_2)_2} + 2\mathrm{KI} \longrightarrow$$
$$[\mathrm{ArTlI_2}] \longrightarrow \mathrm{ArI} + 2\mathrm{CF_3CO_2K} + \mathrm{TlI}.$$

Experimental

Metal Trifluoroacetates. The Tl(III),[2,4] Hg(II),[5] and Ag(I) trifluoroacetates[6] were prepared according to the methods of the literature. The Fe(III) and Cu(II) trifluoroacetates were prepared as follows.

Into a solution of $\mathrm{Fe(CF_3CO_2)_2}$, which had been prepared by the addition of iron powder to an aqueous trifluoroacetic acid solution (more than 3 molar equivalents), 30% $\mathrm{H_2O_2}$ was added; the resulting solution of the Fe(III) salt was then concentrated to dryness.

Copper(I) oxide freshly prepared from $\mathrm{CuSO_4 \cdot 5H_2O}$ and NaOH was dissolved in aqueous trifluoroacetic acid, and the resulting solution was concentrated to dryness to give $\mathrm{Cu(CF_3CO_2)_2}$.

These metal trifluoroacetates were used after having been thoroughly dried over $\mathrm{P_2O_5}$ *in vacuo.*

Iodination Procedure. The iodinations shown in Table 1, Table 2, and Table 3 were carried out as follows.

To the solvent (in Table 1 benzene itself was used) placed in a flask, metal trifluoroacetate and iodine were added. The mixture was immediately refluxed or warmed at the fixed temperature. Ag(I) and Hg(II) trifluoroacetates were easily soluble in benzene, but the other Fe(III), Cu(II) and Tl(III) salts were only partly soluble. In the run with Ag(I) trifluoroacetate, AgI was precipitated as the reaction proceeded (Table 1). In the iodinations in several solvents (Table 2), acetonitrile, DMF, methanol, and trifluoroacetic acid gave a homogeneous reaction solution, but chloroform and carbon tetrachloride were able to dissolve Tl(III) trifluoroacetate to only a limited extent. When 1,4-di-, 1,2,4-tri- or 1,2,4,5-tetraiodobenzene, and mono-, di- or triiodomesitylene were formed (Table 3), these products were deposited during the reaction because of their low solubility. In the polyiodination of benzene in trifluoroacetic acid, a mixture of tri- and tetraiodobenzene made a mass such as was formed in the reaction mixture. Therefore, in these cases the reaction required a longer period. In general, monoiodobenzene was quantitatively analyzed from the reaction mixture by glc, using a column of silicone DC 550 and with nitrobenzene as the internal standard.

All the iodinated benzenes except iodobenzene were isolated by the following procedure. After the evaporation of trifluoroacetic acid from the reaction mixture, the residue (in the case of tri- and tetraiodobenzene) or its benzene solution (in the case of 1,4-diiodobenzene) was washed with 10% nitric acid and then with aqueous sodium bisulfite to remove the metal trifluoroacetate and unreacted iodine. The crystals obtained as 1,4-diiodobenzene by the evaporation of benzene were almost pure, colorless crystals: mp 128 °C (lit,[7] mp 128—129 °C). Its IR spectrum was consistent with that of an authentic specimen. The 1,2,4-tri and 1,2,4,5-tetraiodobenzene were obtained as a mixture, which was separated by alumina-column chromatography. The 1,2,4-triiodobenzene was obtained by elution with *n*-hexane, and then 1,2,4,5-tetraiodobenzene was eluted with benzene. 1,2,4-Triiodobenzene: colorless crystals, mp 91 °C (lit,[7] mp 90—91 °C). 1,2,4,5-Tetraiodobenzene: colorless crystals, mp 250—251 °C (lit,[7] mp 252—253 °C). Their IR spectra were consistent with those of authentic specimens.

The monoiodomesitylene was obtained in the same manner as has been described for 1,4-diiodobenzene. Monoiodomesitylene: colorless crystals, mp 31—32 °C (lit,[8] mp 32—34 °C). Most of the di- and tri-iodomesitylenes were deposited from the reaction mixture; filtration gave almost pure crystals. Diiodomesitylene: colorless crystals mp 80—81 °C (lit,[8] mp 81—82 °C). Triiodomesitylene: colorless crystals, mp 206 °C (lit,[8] mp 206—208 °C).

Reaction of Phenyl Thallium bis-Trifluoroacetate with Iodine in Trifluoroacetic Acid. To a solution of 1.27 g (0.0025 mol) of phenyl thallium bis-trifluoroacetate in 8 ml of trifluoroacetic acid, 0.32 g (0.0012 mol) of iodine was added, after which the mixture was refluxed for 1 hr. The brown color of the iodine disappeared about 10 min after the beginning of refluxing. When the reaction mixture was cooled, crystals came out; these were collected (0.04 g) and identified with 1,4-diiodobenzene. The reaction mixture was carefully concentrated, and after the resulting residue has been washed with 10% nitric acid it was dissolved in benzene. The benzene solution was subjected to glc, using nitrobenzene as the internal standard. The yield of iodobenzene was 78%. Using 0.64 g (0.0025 mol) of iodine, the reaction was carried out in the way described above; 1,4-diiodobenzene was thus obtained in an 86% yield, while the formation of only a trace of monoiodobenzene was detected by glc.

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