Thallium in Organic Synthesis. XXII. Electrophilic Aromatic Thallation Using Thallium(III) Trifluoroacetate. A Simple Synthesis of Aromatic Iodides[1-3]

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Abstract: The preparation of thallium(III) trifluoroacetate and its efficacy as a reagent for electrophilic aromatic thallation are described. Arylthallium ditrifluoroacetates, the products of thallation, react rapidly with aqueous potassium iodide to produce thallium(I) iodide and the corresponding aromatic iodide. This extremely simple synthesis of aromatic iodides is generally applicable to a wide range of aromatic and heterocyclic substrates.

Electrophilic substitution of benzenoid compounds represents one of the most exhaustively studied aspects of organic chemistry, both mechanistically and synthetically.[6–8] Within this general context, however, electrophilic aromatic metallation reactions (*i.e.*, where direct formation of a carbon–metal bond occurs) have been least investigated. With the notable exception of mercuration,[9] aromatic metallation reactions such as auration,[10] boration,[11] and plumbation[12] can only be regarded at the moment as chemical curiosities.

Prior to the present study there were, to our knowledge, only two reports in the literature dealing with aromatic thallation. In 1934 Gilman and Abbott[13] reported that treatment of dibenzofuran with thallium(III) chloride in concentrated aqueous solution at 165° resulted in formation of di(4-dibenzofuryl)thallium chloride in 9% yield. More recently, Glushkova and Kocheshkov[14] have shown that the reaction of thallium(III) triisobutyrate with an excess of benzene or an activated aromatic substrate as solvent at 95–115° leads to arylthallium diisobutyrates. The range of aromatic substrates which can be effectively thallated by the latter technique, however, is severely limited by the poor electrophilicity of thallium(III) triisobutyrate. Moreover, the yields of thallated products are only moderate. In view of the restricted nature of these investigations, it is hardly surprising that no synthetic applications of thallation have ever been described.

In this and succeeding papers we describe in detail our investigations into aromatic electrophilic thallation reactions and their utility and versatility in the synthesis of substituted aromatic compounds. The strictly organometallic aspects of this work have been reported elsewhere.[15a] In this and the accompanying paper[15b] attention is concentrated on the preparation of aromatic iodides.

Preparation and Properties of Thallium(III) Trifluoroacetate

Preliminary investigations on the efficacy of thallium(III) triisobutyrate as a thallating reagent, while confirming the results of Glushkova and Kocheshkov,[14] also served to underline the necessity of developing a more powerfully electrophilic and, preferably, more stable reagent.[16] By analogy with mercuration, where Brown and Wirkkala[17] showed that use of trifluoroacetic acid (TFA) as solvent led to a rate increase of 6.9×10^5 relative to acetic acid, we have prepared thallium(III) trifluoroacetate (TTFA) and have found that it fully satisfies our requirements for an extremely reactive thallating reagent.

The salt is easily prepared in 90–100% yield by heating a suspension of thallium(III) oxide in TFA containing 10–20% water. The colorless solution thus obtained can be used directly in thallation reactions. Alternatively, the granular, colorless solid salt can be isolated by evaporation of the TFA and sub-

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[1] Part XXI: A. McKillop, B. P. Swann, and E. C. Taylor, *Tetrahedron Lett.*, 5281 (1970).

[2] We gratefully acknowledge partial financial support of this work by the Smith Kline and French Laboratories, Philadelphia, Pa., and by Eli Lilly and Co., Indianapolis, Ind.

[3] Certain aspects of this work have been described in preliminary communications: A. McKillop, J. S. Fowler, M. J. Zelesko, J. D. Hunt, E. C. Taylor, and G. McGillivray, *Tetrahedron Lett.*, 2423, 2427 (1969).

[4] (a) University of East Anglia; (b) Princeton University; (c) on leave from the University of South Africa; a grant from the Ernest Oppenheimer Memorial Trust and a travel grant from the C.S.I.R. (South Africa) are gratefully acknowledged.

[5] NRCC Postdoctoral Fellow, 1968–1970.

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[15] (a) A. McKillop, J. D. Hunt, and E. C. Taylor, *J. Orgonometal. Chem.*, 24, 77 (1970); (b) E. C. Taylor, F. Kienzle, R. L. Robey, A. McKillop, and J. D. Hunt, *J. Amer. Chem. Soc.*, 93, 4845 (1971).

[16] Thallium(III) triisobutyrate decomposes fairly rapidly on storage.

[17] H. C. Brown and R. A. Wirkkala, *J. Amer. Chem. Soc.*, **88**, 1447, 1453, 1456 (1966).

Table I. Experimental Data for Representative Arylthallium Ditrifluoroacetates, $ArTl(OCOCF_3)_2$

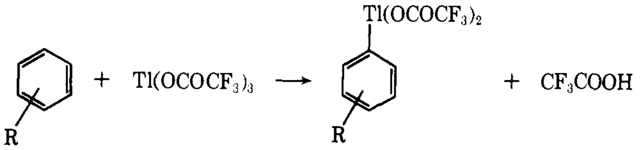
Ar	Yield, %[a] A B	Mp, °C[b]	Mol formula	Anal. Calcd C	Anal. Calcd H	Anal. Found C	Anal. Found H
C_6H_5	96 (48)	184–189	$C_{10}H_5F_6O_4Tl$	23.66	0.99	23.74	0.81
$4\text{-}FC_6H_4$	70 (30)	103–108	$C_{10}H_4F_7O_4Tl$	22.85	0.72	22.94	0.92
$4\text{-}ClC_6H_4$	80 (85)	147–159 dec	$C_{10}H_4ClF_6O_4Tl$	22.16	0.74	22.28	0.58
$4\text{-}CH_3C_6H_4$	75 (75)	174–190	$C_{11}H_7F_6O_4Tl$	25.33	1.35	25.60	1.32
$2,4\text{-}(CH_3)_2C_6H_3$	100 (78)	162–187	$C_{12}H_9F_6O_4Tl$	26.91	1.69	26.84	1.83
$2,5\text{-}(CH_3)_2C_6H_3$	91 (80)	140–144	$C_{12}H_9F_6O_4Tl$	26.91	1.69	26.61	1.74
$2,4,6\text{-}(CH_3)_3C_6H_2$	94 (34)	155–157	$C_{13}H_{11}F_6O_4Tl$	28.41	2.02	28.30	1.40
$2\text{-}COOHC_6H_4$	76 (79)	215–220 dec	$C_{11}H_5F_6O_6Tl$	23.95	0.95	24.03	1.08

[a] The figures in column A are based on yields of aromatic iodo compounds obtained on treatment of the arylthallium ditrifluoroacetates with aqueous potassium iodide (see Table II). The yields in column B refer to isolated arylthallium ditrifluoroacetates, obtained by filtration of the thallation reaction mixture. [b] The melting points of these compounds cannot be used as reliable criteria of purity, since they vary erratically according to the rate of heating, amount of sample, degree of compactness, and crystal size. In some cases the indistinct and broad melting point range may be due to a mixture of positional isomers (see Table II).

sequently used in inert solvents such as acetonitrile. TTFA shows no distinct melting point and decomposes slowly when heated above 100°. Although the solid salt is water sensitive, it can be stored at room temperature in stoppered flasks, protected from light, for long periods without appreciable decomposition. Solutions of TTFA in TFA, on the other hand, are relatively stable to water; as much as 20% water by volume can be added to 0.8 *M* solutions of TTFA in TFA before appreciable hydrolysis of the salt takes place.

Electrophilic Aromatic Thallation

Preparation of Arylthallium Ditrifluoroacetates. Direct thallation of a wide range of aromatic substrates is readily accomplished simply by addition of the aromatic compound to a solution of TTFA in TFA. Reaction with substrates which are activated toward electrophilic substitution is generally complete within a few minutes at room temperature. Thallation of mildly deactivated substrates such as the halobenzenes requires longer reaction times at room temperatures (*ca.* 48 hr) or 30 min at reflux temperature (73°), while deactivated compounds such as benzoic acid or α,α,α-trifluorotoluene are thallated after 21- and 98-hr reflux, respectively. For acid-sensitive substrates such as thiophene, solid TTFA in acetonitrile is the condition of choice. In the majority of cases studied the arylthallium ditrifluoroacetates formed[18] crystallize directly from the reaction mixture and are isolated by simple filtration.



The arylthallium ditrifluoroacetates prepared in this manner are colorless, stable, crystalline solids. They are in general soluble in methanol, ethanol, glyme, acetonitrile, tetrahydrofuran, and dimethyl sulfoxide, but show a tendency to decompose or undergo symmetrization to the more stable diarylthallium trifluoroacetates[15a] if the solutions are stored for long periods. Yields and experimental data for representative arylthallium ditrifluoroacetates are summarized in Table I.

The orientation of the carbon–thallium bond in arylthallium ditrifluoroacetates is most readily determined by examination of the well-defined nmr spectra shown by these compounds. In general, Tl–H coupling constants are numerically very large, a phenomenon which has been qualitatively rationalized on the basis of a Fermi contact interaction as a result of the large effective nuclear charge on the thallium atom.[19,20] Detailed nmr studies[20] on $RTlX_2$ compounds have established that in benzene and substituted benzenes, Tl–H coupling constants are ~130 times greater than the corresponding H–H coupling constants. Consequently, nmr provides an unambiguous method for determination of the orientation of the carbon–thallium bond in arylthallium ditrifluoroacetates.[15a]

Synthesis of Aromatic Iodides

Over 30 years ago Challenger and his coworkers[21] reported that treatment of phenylthallium dichloride with inorganic nucleophiles resulted in anion exchange.

$$C_6H_5TlCl_2 + 2X^- \longrightarrow C_6H_5TlX_2 + 2Cl^-$$

An unusual reaction was noticed, however, when X^- was iodide. Thus, treatment of phenylthallium dichloride with potassium iodide gave some iodobenzene and thallium(I) iodide as the only products of reaction. Neither conditions nor yields for this interesting observation were described, and the inaccessibility of arylthallium dihalides precluded further investigation into the generality or potential synthetic utility of this reaction. The ease of cleavage of the carbon–thallium bond has also been demonstrated by Glushkova and Kocheshkov,[14] who determined the orientation of the carbon–thallium bond in arylthallium diisobutyrates by fission of this bond with molecular iodine, and identification of the resulting iodides.

With the development of TTFA and the resultant ease of preparation of arylthallium ditrifluoroacetates, their reaction with inorganic nucleophiles was reinvestigated.[15a] We were immediately able to confirm Challenger's original observation on the action of

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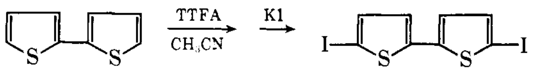
(18) Although polymercuration is common (see ref 9), polythallation has thus far been observed in only one instance (A. McKillop and E. C. Taylor, unpublished observations), *viz.*

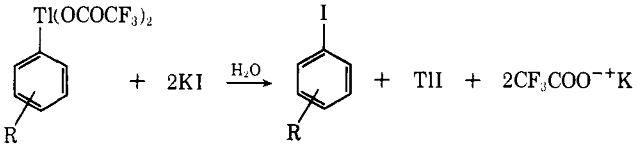


(19) J. P. Maher and D. F. Evans, *J. Chem. Soc.*, 5534 (1963).

(20) J. P. Maher and D. F. Evans, *ibid.*, 637 (1965).

(21) (a) F. Challenger and B. Parker, *ibid.*, 1462 (1931); (b) F. Challenger and O. V. Richards, *ibid.*, 405 (1934).

potassium iodide on ArTlX$_2$ compounds, and to show that this is indeed a general organothallium reaction. Thus treatment of arylthallium ditrifluoroacetates with aqueous potassium iodide solution results in almost instantaneous precipitation of thallium(I) iodide and formation of the corresponding aromatic iodide in high yield.



The overall process of thallation followed by treatment with iodide ion thus constitutes an extremely simple synthesis of aromatic iodides. The procedure is effective with a wide range of aromatic substrates, proceeds rapidly at room temperature in aqueous solution, and does not normally require isolation of the intermediate arylthallium ditrifluoroacetate. A critical feature of this synthesis is that *the entering iodine substituent always replaces thallium at the same position on the aromatic ring.*[15a]

Three general procedures have been developed for the synthesis of aromatic iodides *via* thallation.

Method A. Thallation of the aromatic substrate is carried out in the usual manner (see above). An aqueous solution of potassium iodide is then added directly to the reaction mixture. Reaction is generally complete within a few minutes, and isolation of the aromatic iodide is effected merely by removal of the thallium(I) iodide by filtration, extraction of the aqueous filtrate with ether, and concentration of the dried extract.

Method B. The intermediate arylthallium ditrifluoroacetate may be isolated from the thallation mixture as described in the Experimental Section. A suspension of this compound in water is then treated as in method A with an aqueous solution of potassium iodide.

Method C. For acid-sensitive substrates it is advantageous to use a solution of solid TTFA in acetonitrile for the thallation step. Addition of an aqueous solution of potassium iodide to the reaction mixture then yields the aromatic iodide.

Methods A–C were successful with the majority of aromatic substrates studied. It has not yet proved possible, however, to apply the thallation–iodination sequence to a small number of highly reactive compounds. In particular, naphthalene and biphenyl gave intensely colored solutions on treatment with TTFA. While initial thallation may indeed have taken place in these cases, competitive oxidation reactions[22] resulted in extensive decomposition of the substrate and led only to intractable tars on addition of potassium iodide.

It was, however, possible to iodinate the above sensitive substrates by employing molecular iodine as the electrophilic reagent and utilizing TTFA as oxidant[22] for the hydrogen iodide produced in the reaction. Thus a fourth general procedure (method D) for the preparation of aromatic iodides consists of addition of a solution of iodine in carbon tetrachloride to a stirred suspension of TTFA in carbon tetrachloride containing the aromatic substrate. Formation of the aromatic iodide is rapid, and is easily monitored by the rate of discharge of the iodine color.

Representative examples of aromatic iodides prepared by methods A–D are given in Table II.

From the data in Table II it is evident that the main advantages of the thallation procedure for the synthesis of aromatic iodides are manipulative simplicity and high yields of products. Moreover, examination of the isomer distribution data for monosubstituted benzenoid compounds containing simple ortho–para directing substituent groups reveals a significant preference for para substitution. These data are not wholly unexpected in view of the steric bulk of the thallium electrophile. It should be noted, however, that the orientation of the incoming thallium electrophile can be dramatically influenced by the nature of aromatic nuclear substituents and by the temperature at which the thallation reaction is carried out. A striking example of the former effect is with benzoic acid, where initial complexation of the TTFA electrophile with the substituent leads to ortho thallation, and the subsequent formation of *o*-iodobenzoic acid. The effect of temperature on the orientation of thallation (and, as a consequence, of iodination as well) is vividly illustrated with cumene, which gives predominately (94%) para substitution when thallation is carried out at room temperature, but predominately (85%) meta substitution at 73°. A detailed discussion of these effects, and their application to orientation control in the synthesis of aromatic iodides, is given in the accompanying paper.[15b]

In contrast to the thallation reaction, we are unable at present to suggest a satisfactory mechanistic explanation for the reaction of arylthallium ditrifluoroacetates with potassium iodide. Organothallium compounds of the type ArTlI$_2$ are unknown except as complexes where Ar is C$_6$F$_5$,[23] while the instability of thallium(III) iodide itself is well documented.[24] The ease of cleavage of the carbon–thallium bond in ArTlX$_2$ compounds is apparently a function of X, with iodine lying at the most reactive end of the spectrum. Even compounds of the type ArTlXI are unstable and decompose to aryl iodides; thus, treatment of phenylthallium ditrifluoroacetate with only 1 equiv of potassium iodide still resulted in the formation of iodobenzene in almost quantitative yield; no thallium(I) iodide was formed. Further investigation of this particular problem is currently in progress.

Experimental Section[25]

Thallium(III) Trifluoroacetate. A vigorously stirred suspension of 50 g of thallium(III) oxide in 200 ml of TFA containing 25 ml of water was heated under reflux for 12 hr in a flask wrapped with

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[22] TTFA is an effective and highly selective oxidizing agent. The first of a number of papers dealing with these aspects of the chemistry of TTFA has recently appeared (A. McKillop, B. P. Swann, M. J. Zelesko, and E. C. Taylor, *Angew. Chem., Int. Ed. Engl.*, **9**, 74 (1970)).

[23] G. B. Deacon and J. C. Parrott, *J. Organometal. Chem.*, **15**, 11 (1968).

[24] F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," Interscience, New York, N. Y., 1966, p 440.

[25] Melting points were determined on a Kofler hot-stage melting point apparatus and are uncorrected. Microanalyses were performed by Mr. A. R. Saunders of the University of East Anglia and by the Baron Consulting Co., Orange, Conn. Glc traces were obtained using Perkin-Elmer Models F 11 and 452 flame ionization gas chromatographs, and employing a 50-m PPG capillary column for analytical work. Isomer ratios were calculated using a Vitatron UR 400 digital readout integrator. Purity and identity of the aromatic iodides were confirmed by comparison of glc retention times and ir and nmr spectra with authentic samples.

Table II

Substrate	Thallation condn[a]		Method[a]	Yield, %	Aromatic iodide product distn, %[b]		
	Temp, °C	Time, hr			Ortho	Meta	Para
Benzene	22	16	A	96	Iodobenzene		
			B	90			
Fluorobenzene	22	16	A	70	11		89
			D	75	7		93
Chlorobenzene	73	0.5	A	80	23		77
Bromobenzene	73	1.3	A	60	26	3	61
Toluene	22	1	A	69	9	4	87
			B	99	9		91
			D	98	5		95
n-Propylbenzene	22	0.8	A	86	3	6	91
tert-Butylbenzene	22	4.5	A	93	4-*tert*-Butyliodobenzene		
Biphenyl			D	70[c]	4-Iodobiphenyl		
o-Xylene	22	0.8	A	72	4-Iodo-*o*-xylene		
			B	98			
m-Xylene	22	0.8	A	100	4-Iodo-*m*-xylene		
			B	98			
p-Xylene	22	1.2	A	91	2-Iodo-*p*-xylene		
4-Bromo-*o*-xylene	22	22	C	67[c]	4-Bromo-5-iodo-*o*-xylene		
Mesitylene	22	1	A	94	Iodomesitylene		
			B	67			
Iodomesitylene	22	1.5	A	45	2,4-Diiodomesitylene		
Naphthalene			D	60[c]	1-Iodonaphthalene		
Thiophene	22	0.3	C	82	2-Iodothiophene[d]		
2-Chlorothiophene	22	0.3	A	73	2-Chloro-5-iodothiopene		
	22	1	C	98			
2-Bromothiophene	22	0.3	A	81	2-Bromo-5-iodothiophene		
	22	1	C	100			
2-Methylthiophene	22	0.3	C	98	2-Methyl-5-iodothiophene		
Anisole	22	0.25	A	75	7		93[e]
o-Nitroanisole	73	19	A	94[c]	4-Iodo-2-nitroanisole		
p-Nitroanisole	73	22	A	90[c]	2-Iodo-4-nitroanisole		
Benzoic acid	73	21	A	76	95	5[f]	
α,α,α-Trifluorotoluene	73	98	A	54	3	81	16

[a] Full details of each method are given in the Experimental Section. [b] Determined by comparison of glc retention times and/or infrared spectra with authentic samples. [c] Based on pure recrystallized material. [d] An unidentified, high boiling compound constituted ~9% of the crude product. [e] Thallation was carried out at −25°. When thallation was carried out at room temperature, the observed isomer distribution changed to 17% ortho, 83% para. The ratio of isomers in both cases was determined by integration of the methyl region of the 100-MHz nmr spectrum (expanded to 100 Hz). [f] Determined by methylation of the crude product with diazomethane and analysis of the resulting methyl esters by glc and 100-MHz nmr spectroscopy.

aluminum foil. Filtration of the cooled reaction mixture to remove a small amount of residual solid then gave an approximately 0.88 *M* solution of TTFA in TFA. Evaporation of the TFA from the colorless solution under reduced pressure gave solid TTFA as a granular solid which decomposed slowly when heated above 100°. The yield of TTFA is 90–100%.

General Procedure for the Preparation of Arylthallium Ditrifluoroacetates. The aromatic substrate was treated with an equimolar quantity of a standard solution of TTFA in TFA (normally prepared by dissolving the calculated amount of solid TTFA in the appropriate amount of TFA) for the required period of time (see Table II). In cases where the arylthallium ditrifluoroacetate crystallized from the reaction mixture it was isolated by simple filtration, washed with a little 1,2-dichloroethane, and dried. Otherwise, TFA was removed by evaporation under reduced pressure, the temperature being kept below 50° to avoid isomerization[15b] or symmetrization of the product to the corresponding diarylthallium trifluoroacetate.[15a] The solid arylthallium ditrifluoroacetate obtained in this way was thoroughly washed with 1,2-dichloroethane and dried. Analytical data for representative arylthallium ditrifluoroacetates are listed in Table I.

Synthesis of Aromatic Iodides. Method A. The aromatic compound was thallated as described above; details for individual compounds are summarized in Table II. An aqueous solution of potassium iodide (~2.3 mol equiv) was then added all at once to the stirred reaction mixture. Stirring was continued for 15 min at room temperature, sodium metabisulfite was added to destroy free iodine, and the mixture was stirred for a further 10–15 min. The reaction mixture was then made basic with 4 *N* sodium hydroxide solution and diluted with ether, and the precipitated thallium(I) iodide was removed by filtration. The ethereal layer was separated, the aqueous layer was extracted with ether, and the combined extracts were dried over anhydrous sodium sulfate. Concentration of the filtered solution gave the crude aromatic iodide, which was purified by standard techniques.

Method B. An identical procedure with that described above was used for the thallation step. The solid arylthallium ditrifluoroacetate was isolated and suspended in water, and an excess of potassium iodide was added. The aromatic iodide was isolated as described in method A.

Method C. The procedure here was identical with that described in method A, except that solid TTFA was employed for thallation, and all reactions were conducted in acetonitrile as solvent.

Method D. A suspension of TTFA (8.8 g, 20% excess) in 35 ml of anhydrous carbon tetrachloride containing 12 mmol of the aromatic substrate was heated to reflux. Iodine (1.5 g, 5.9 mmol) was added portionwise to the stirred mixture as fast as the iodine color was discharged. After addition of the iodine was completed, the mixture was heated under reflux for a further hour to ensure completion of the reaction. The mixture was cooled, filtered, and washed successively with 30 ml of saturated sodium bicarbonate solution. The carbon tetrachloride solution was then dried over anhydrous sodium sulfate and the solvent was removed by evaporation under reduced pressure. The residual solid was chromatographed on a short column of alumina or silica (*ca.* 6 × 1 in.) using methylene chloride as eluent. The crude product obtained by concentration of the eluent was then purified by standard procedures.