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Thallium in Organic Synthesis. XXXIX. A Convenient Synthesis of Nitroaryl Iodides[1,2]

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A method is described for the conversion of aromatic substrates to nitroaryl iodides by (1) thallation with thallium(III) trifluoroacetate (TTFA) in trifluoroacetic acid (TFA), (2) nitration of the isolated arylthallium ditrifluoroacetate with acetyl nitrate, and (3) treatment of the resulting nitroarylthallium intermediate with iodine in chloroform. Nitration occurs meta to the thallium substituent, and iodine enters the ring at the position formerly occupied by thallium.

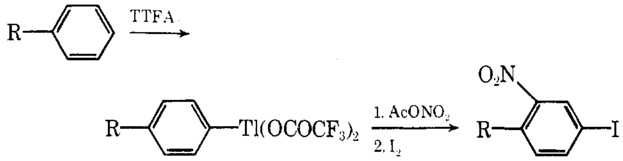
The classic route to nitroaryl iodides from aromatic substrates comprises a sequence of reactions involving nitration or dinitration, selective reduction of one of the nitro groups to an amine, diazotization, and subsequent replacement of the diazonium group with iodine utilizing potassium iodide.[3] Alternatively, nitroarenes can be iodinated with molecular iodine in various media.[4–6] The drawbacks of the former approach are the multiple reaction steps required and the frequently observed iodine atom migration which occurs under acidic conditions;[7] a disadvantage of the latter synthesis is the occasional occurrence of polyiodination when 20% oleum–iodine is employed.[4]

We describe a facile conversion of aromatic substrates to nitroaryl iodides via arylthallium ditrifluoroacetates. The appropriate arene is first thallated with thallium(III) trifluoroacetate (TTFA) in trifluoroacetic acid (TFA).[8] The *isolated* arylthallium ditrifluoroacetate is then nitrated with acetyl nitrate[9] (conveniently generated in situ by adding 70% nitric acid to an excess of acetic anhydride) in the presence of concentrated sulfuric acid, and the intermediate nitroarylthallium derivative is then refluxed with molecular iodine in chloroform. In the resulting nitroaryl iodide, the iodine atom enters the ring at the position formerly occupied by thallium; i.e., the position which is generally most reactive to electrophilic substitution. The nitro substituent is almost invariably meta to the iodine atom. Since nitration and iodination of the arylthallium ditrifluoroacetate can be achieved without isolation of the intermediate nitroarylthallium species, this overall procedure constitutes a two-step synthesis of nitroaryl iodides from arenes. Furthermore, the requisite arylthallium ditrifluoroacetate intermediates are readily prepared from the precursor arenes utilizing TTFA in TFA,[8] and are stable, crystalline solids which can be kept indefinitely.

Representative yields of nitroaryl iodides prepared by this technique are listed in Table I.

Varying amounts of sulfuric acid were employed to promote the nitration of the above arylthallium ditrifluoroacetates, the amount of sulfuric acid being determined by the reactivity of the latter intermediates to electrophilic substitution.[9] Arylthallium ditrifluoroacetates substituted with electron-withdrawing groups are not nitrated satisfactorily under the above conditions. For example, 4-chlorophenylthallium ditrifluoroacetate gives only very small amounts of ring nitration with acetyl nitrate, even in the presence of a large excess of concentrated sulfuric acid.[15]

Table I
Synthesis of Nitroaryl Iodides



Starting material	Product	Yield, %[a,b]
Benzene	3-Nitroiodobenzene	87[c]
Toluene	2-Nitro-4-iodotoluene	90[d]
Ethylbenzene	2-Nitro-4-iodoethylbenzene	92
Mesitylene	Nitroiodomesitylene	94[e]
Anisole	2-Nitro-4-iodoanisole	98[f]
m-Xylene	4-Nitro-6-iodo-*m*-xylene	99[g]
Biphenyl	4-Nitro-4′-iodobiphenyl	55[h]
	2-Nitro-4′-iodobiphenyl	45

[a] Yields were determined by GLC analysis of the crude product and are based on the weight of isolated arylthallium ditrifluoroacetate. [b] In some cases, it was possible to isolate the major isomer by simple crystallization of the crude product from ethanol. [c] Contains 14% 2-nitroiodobenzene and 5% nitrobenzene. [d] Contains 5% 2-iodo-4-nitrotoluene, 3% 2-nitro-6-iodotoluene, 1% 2-nitrotoluene, 1% 4-nitrotoluene, and 2% of an unidentified material. [e] Contains 5% dinitromesitylene. [f] Contains 8% 2-iodo-4-nitroanisole. [g] Contains 27% 2-nitro-4-iodo-*m*-xylene. [h] Contains 3% 4-nitrobiphenyl.

It seems probable that the actual substrate undergoing nitration may, at least in some instances, be the corresponding diarylthallium trifluoroacetate, formed in situ by "disproportionation" of the initial arylthallium ditrifluoroacetate.[16] For example, treatment of phenylthallium ditrifluoroacetate with acetyl nitrate in the absence of concentrated sulfuric acid led to the formation of small amounts of diphenylthallium trifluoroacetate. In a subsequent experiment, it could be shown that this latter compound was readily converted with acetyl nitrate and sulfuric acid (followed by iodine) to the same mixture of nitroaryl iodides obtained from phenylthallium ditrifluoroacetate itself. Furthermore, di-2-tolylthallium trifluoroacetate under the same conditions gave (in 99% yield) a mixture of nitroiodotoluenes consisting of 2-iodo-4-nitrotoluene (61%) and 2-nitro-6-iodotoluene (39%). Since, however, we have been able to show in an independent study that diarylthallium trifluoroacetates appear to undergo all of the thallium displacement reactions exhibited by arylthallium ditrifluoroacetates[17] (again with the new substituent entering the ring at the position previously occupied by thallium), such in situ disproportionation under the above nitration conditions is of no practical concern.

The formation of 2-nitroiodobenzene (see footnote *c*, Table I) from phenylthallium ditrifluoroacetate or diphenylthallium trifluoroacetate under the above conditions is unexpected, but consistent with the well-documented ability of the electron-deficient thallium(III) atom to complex with Lewis bases.[18,19] Thus complexation of thallium (and mercury)[20] electrophiles by electron-rich substituents on aromatic rings, which is followed by intramolecular delivery of the electrophile to the ortho position, is thoroughly documented. It would thus appear that the above ortho nitration probably arises by complexation of thallium with acetyl nitrate. It is interesting to note that attempted thallation of nitrobenzene with TTFA in refluxing TFA, although only 15% complete after 7 days, resulted in significant thallation ortho to the nitro group (41% of the total thallation which occurred; see Experimental Section). Once again, this high percentage of ortho thallation is undoubtedly due to complexation of TTFA by the substituent nitro group, followed by intramolecular delivery of the thallium electrophile. It is significant that no para thallation was observed.

Experimental Section[21]

General Procedure for Nitration–Iodination of Arylthallium Ditrifluoroacetates. The general procedure is illustrated below with 2,4-dimethylphenylthallium ditrifluoroacetate.

Acetic anhydride (25 ml) was placed in a 100-ml round-bottomed flask immersed in an ice bath, and stirred until the temperature had fallen to 15°. Nitric acid (70%) was then added cautiously until the temperature of the stirred solution rose to approximately 20°.[22] During the nitric acid addition, the temperature must be maintained between 15 and 20°. After the requisite amount (3.60 g, 0.04 mol) had been added, the temperature of the reaction mixture was allowed to fall to 2°, and 0.50 g of concentrated sulfuric acid was carefully added while maintaining the temperature below 10°. When the temperature had again fallen to 2°, 5.35 g (0.01 mol) of 2,4-dimethylphenylthallium ditrifluoroacetate was added rapidly, and the stirred reaction mixture was allowed to warm to room temperature. After 2.5 hr, the reaction mixture was cooled, and ice was added to destroy any unreacted acetyl nitrate. Distilled water (25 ml) was then added cautiously, and the reaction mixture was then transferred to a 500-ml round-bottomed flask. The pH was adjusted to 6 with 6 *M* aqueous sodium hydroxide while maintaining the temperature below 35°, and 4.00 g (0.0157 mol) of iodine in 80 ml of chloroform was added. The two-phase reaction mixture was then stirred under reflux for 12 hr, cooled, and 10.0 g (0.052 mol) of sodium metabisulfite added. Thallium(I) iodide was then removed by filtration through Celite, and the chloroform layer in the filtrate was separated, extracted with distilled water, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residual oil (2.81 g) consisted of 2.75 g (99%) of two isomeric nitroiodo-*m*-xylenes (GLC analysis), each of which was isolated by preparative gas chromatography. 4-Iodo-6-nitro-*m*-xylene (73%): mp 84–86° (lit.[23] mp 87°); NMR δ 2.43 (3, s), 2.52 (3, s), 7.23 (1, $J \simeq 0$ Hz), and 8.43 (1, $J \simeq 0$ Hz). 2-Nitro-4-iodo-*m*-xylene (27%): mp 68–70°; NMR δ 2.24 (3, s), 2.39 (3, s), 6.87 (1, d, $J = 8$ Hz), and 7.85 (1, d, $J = 8$ Hz).

Anal. Calcd for $C_8H_8INO_2$: C, 34.68; H, 2.91; N, 5.06. Found: C, 34.92; H, 3.02; N, 4.74.

Evidence for Disproportionation of Phenylthallium Ditrifluoroacetate in Acetic Anhydride–70% Nitric Acid. Acetyl nitrate was prepared from 3.60 g (0.04 mol) of 70% nitric acid and 25 ml of acetic anhydride as described above. Phenylthallium ditrifluoroacetate (5.07 g, 0.01 mol) was then rapidly added, and the stirred solution was maintained for 12 hr at room temperature. After destruction of unreacted acetyl nitrate and adjustment of the pH to 8 with 6 *M* aqueous sodium hydroxide, the ivory-colored solid which had separated was collected by filtration, washed with distilled water, and dried, yield, 2.88 g. A suspension of 0.5 g of this material was suspended in 5 ml of distilled water and 5 ml of TFA, stirred for 15 min at room temperature, diluted with 10 ml of distilled water, and filtered to give 0.15 g of diphenylthallium trifluoroacetate, mp 265–270°. This material was identical with an authentic sample of diphenylthallium trifluoroacetate.[16]

Nitration–Iodination of Di-2-tolylthallium Trifluoroacetate. Preparation of 2-Iodo-4-nitrotoluene and 2-Nitro-6-iodotoluene. The general procedure detailed above for nitration–iodination was employed for di-2-tolylthallium trifluoroacetate (1.25 g, 0.0025 mol), the amounts of the various reagents (acetic anhydride, iodine, etc.) being proportionally reduced. The weight of concentrated sulfuric acid employed was 0.38 g, and the stirred nitration mixture was kept at room temperature for 2.5 hr before proceeding with the iodination step (vide supra). Upon completion of the iodination, an oil (1.37 g) was obtained which was shown by GLC to contain two nitroiodotoluenes (1.31 g, 99%). These were isolated from the GLC column to give 2-iodo-4-nitrotoluene (61%), mp 50–52° (lit.[24] mp 54°), and 2-nitro-6-iodotoluene (39%), mp 34–35° (lit.[25] mp 34–36°).

Thallation of Nitrobenzene. A solution of 4.07 g (0.033 mol) of nitrobenzene in 25 ml of a 0.88 *M* TTFA–TFA solution (0.022 mol) was heated under reflux for 7 days. TFA was then removed by distillation under reduced pressure, and a solution of 7.80 g (0.03 mol) of iodine in 30 ml of chloroform was added to the residual red syrup. The resulting mixture was heated under reflux for 4 hr and cooled, and a solution of 10.0 g (0.052 mol) of sodium metabisulfite in 20 ml of distilled water was added. After 15 min of vigorous stirring, the precipitated thallium(I) iodide was removed by filtration through Celite and the chloroform layer in the filtrate was extracted with distilled water, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to give 4.18 g of an orange liquid. GLC analysis indicated the formation (15%) of a mixture of nitroiodobenzenes, consisting of 41% of 2-nitroiodobenzene and 59% of 3-nitroiodobenzene (GLC and ir analysis, and comparison with authentic samples). No 4-nitroiodobenzene could be detected.

4-Biphenylthallium Ditrifluoroacetate. A solution of 3.73 g (0.024 mol) of biphenyl in 25 ml of an 0.88 *M* TTFA–TFA solution (0.022 mol) was stirred at room temperature for 13 hr, the TFA was removed by evaporation under reduced pressure, and the residual gray solid was dissolved in a minimal amount of diethyl ether–1,2-dichloroethane (1:1). These solvents were then evaporated under reduced pressure, and the procedure was repeated once again. The residual gray solid was then suspended in 50 ml of 1,2-dichloroethane, cooled to 0°, and filtered to give 4.90 g (38%) of 4-biphenylthallium ditrifluoroacetate, mp 210–220° dec. Treatment of this intermediate with aqueous potassium iodide as previously described[8] gave 0.48 g (99%) of 4-iodobiphenyl, mp 109–112° (lit. mp 113°),[26] pure by GLC analysis. Thus, thallation had occurred only in the para position of biphenyl.

4-Biphenylthallium ditrifluoroacetate could be obtained as a white solid, mp 228–231° dec, by recrystallization from 1,2-dichloroethane.

Anal. Calcd for $C_{16}H_9F_6O_4Tl$: C, 32.93; H, 1.55. Found: C, 32.90, H, 1.90.

Registry No.—Benzene, 71-43-2; toluene, 108-88-3; ethylbenzene, 100-41-4; mesitylene, 108-67-8; anisole, 100-66-3; *m*-xylene, 108-38-3; biphenyl, 92-52-4; TTFA, 23586-53-0; $AcONO_2$, 591-09-3; I_2, 7553-56-2; 2,4-dimethylphenylthallium ditrifluoroacetate, 34202-98-7; 4-iodo-6-nitro-*m*-xylene, 4102-38-9; 2-nitro-4-iodo-*m*-xylene, 56404-21-8; phenylthallium ditrifluoroacetate, 23586-54-1; di-2-tolylthallium, trifluoroacetate, 27675-18-9; nitrobenzene, 98-95-3; 4-biphenylthallium ditrifluoroacetate, 55341-42-9.

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