Electrophilic aromatic thallation of phenol ethers: an improved experimental procedure

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Abstract

In this report we present a simple modification of the classical electrophilic aromatic thallation reaction, in which iodination of several phenol ethers can be achieved in high yields under very mild reaction conditions with the mixture $TTFA/BF_3 \cdot Et_2O/ClCH_2CH_2Cl$, whereby both oxidative dimerizations and hydrolysis have been successfully suppressed.

1. Introduction

Electrophilic thallation represents a versatile methodology in electrophilic aromatic substitution reactions, not only because the arylthallium compounds can be converted into several kinds of product [1–6], but also because of its applications to orientation control in the synthesis of substituted aromatic nuclei [7,8].

A relatively common method of thallation of arenes involves the treatment of these compounds with thallium(III) trifluoroacetate (TTFA) in trifluoroacetic acid (TFA) [9]. A practical difficulty of this reaction arises from the instability of sensitive substrates in the strongly acidic TTFA/TFA mixture. Although excellent results have been reported for simple arenes, electron-rich arenes normally undergo oxidative couplings, and acid-sensitive substrates usually cannot be employed. Also, purification of the final products requires a rather harsh work-up.

Our efforts to prepare substituted aromatic iodo compounds from **3** and **4** have led us to search for an

alternative method. A preliminary investigation revealed that use of the combined reagents thallium(III) trifluoroacetate–boron trifluoride etherate (catalytic quantity) in 1,2-dichloroethane, followed by treatment with aqueous potassium iodide, resulted in formation of the desired products. Moreover, no intermolecular oxidative coupling was observed.
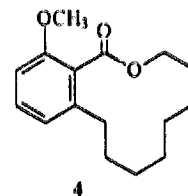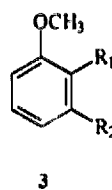
3	R₁	R₂
a	H	$n\text{-}C_{15}H_{31}$
b	CO_2Me	$n\text{-}C_{15}H_{31}$
c	CO_2Me	$n\text{-}C_7H_{14}CO_2Me$

We therefore suggest an improved experimental procedure for aromatic thallation of phenol ethers that

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appears to be superior to that using TTFA/TFA. The clear advantages of this modification are: shortened reaction times, no organic by-products, and high yields.
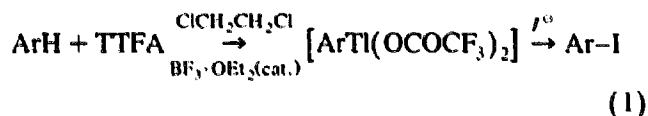
2. Results and discussion

Several reports in the literature show that the treatment of a variety of activated aromatic substrates with thallium(III) trifluoroacetate in trifluoroacetic acid or carbon tetrachloride or acetonitrile containing boron trifluoride etherate results in smooth, rapid, and direct regiospecific oxidative dehydrodimerization to give symmetrical biaryls in good to excellent yield [10–12].

In the last few years it was reported that the treatment of electron-rich arenes with thallium(III) trifluoroacetate and boron trifluoride etherate in dichloromethane resulted in intramolecular non-phenolic coupling to give the respective bridged biaryl systems [13–15]. In a recent communication, Cambie et al. [15] confirmed that the inclusion of boron trifluoride etherate in a thallium(III) trifluoroacetate medium induced intramolecular non-phenolic oxidative aryl–aryl couplings.

Taylor et al. [16], according to the model observed by Fukuzume and Kochi [17], suggested that the electrophilic thallation reaction proceeds by rate-limiting formation of a radical ion pair which collapses to the arylthallium bis(trifluoroacetate). Thus, they envisioned that the effective solvation of this ion pair by TFA would facilitate its separation from the thallium(II) species, leading to biaryl formation. Taking into consideration this hypothesis, Taylor et al. [16] demonstrated that the addition of ether apparently prevents such solvation, and the ion pair remains intact until its collapse to the electrophilic thallation product.

Our initial attempts to apply the methodology of the combined reagents TTFA/TFA/Et$_2$O to our substrates failed, resulting in the recovery of the starting materials. We therefore searched for inspiration in the model of Taylor et al. [16], according to which we decided to omit the TFA from the reaction medium. In striking contrast to the hypothesis of Cambie et al. [15], our exploratory experiments to determine the optimal conditions of thallation of the phenol ethers 3 and 4 showed that the best results could be achieved by thallium(III) trifluoroacetate in 1,2-dichloroethane using boron trifluoride in only catalytic quantities (about 10% v/v). Treatment of these mixtures with iodide ions led to high yields of very pure iodinated products, Eq. (1).

$$\mathrm{ArH + TTFA \xrightarrow[\mathrm{BF_3 \cdot OEt_2(cat.)}]{\mathrm{ClCH_2CH_2Cl}} [ArTl(OCOCF_3)_2] \xrightarrow{I^\ominus} Ar{-}I}$$

$$(1)$$

In order to examine the validity of this new procedure and its potential synthetic applications, several

Table 1
Iodo compounds synthesized by TTFA-KI procedure and analytical data

No.	Starting material	Product	Yield (%) [a] by method			M.p.
			A [b]	B [c]	C [d]	(°C) [f]
1	Anisole	1a	75 [e] (o) 7 (p) 93	(p) 90 [e] thallated product	90	47–48
2	3-Methylanisole	2a 2b 2c	— — —	(6-Tl) 89 [e] thallated product	90 product mixture	— — —
3a	3-Pentadecylanisole	3a-1 3a-2	not detected	93 isomer mixture	95 product mixture	— —
3b	1-Carbomethoxy-2-methoxy-6-pentadecylbenzene	3b-1	85	no reaction	97	56–57
3c	1-Carbomethoxy-2-methoxy-6-(8-methylheptanoate)-benzene	3c-1 3c-2	partial hydrolysis 50(3c-1) 25(3c-2)	no reaction	80	—
4	2-Methoxy-6-(8-hydroxy-octanyl)benzoic acid lactone	4a	81	no reaction	92	118–119

[a] Overall yield from ArH to ArI; all yields refer to isolated product. No attempt was made to optimize yields.
[b] Thallation was carried out in TFA at room temperature.
[c] Thallation was carried out in TFA/Et$_2$O at room temperature.
[d] Thallation was carried out in ClCH$_2$CH$_2$Cl/BF$_3$ · Et$_2$O.
[e] Data from the literature (Refs. [3] and [16]).
[f] Melting points are not corrected and refer to iodo compounds obtained by method C.

iodinated aromatic compounds were synthesized by this thallation–iodination procedure. The results are summarized in Table 1.

Table 2
^{1}H and ^{13}C NMR data of the iodo compounds

Compound	^{1}H NMR (δ_H, J (Hz))	^{13}C NMR (δ_C)
1a	7.47 (d, J = 9.0, 2H-3,5), 6.60 (d, J = 9.0, 2H-2,6), 3.69 (s, MeO-1)	159.38 (s, C-1), 138.13 (d, 2C-3,5), 116.30 (d, 2C-2,6), 82.50 (s, C-4), 55.27 (q, MeO-1)
2a	7.61 (d, J = 7.9, H-3), 6.65 (br s, H-6), 6.55 (br d, J = 7.9, H-4), 3.86 (s, MeO-1), 2.33 (br s, Me-5)	157.81 (s, C-1), 139.52 (s, C-5), 138.93 (d, C-3), 123.34 (d, C-4), 112.04 (d, C-6), 81.76 (s, C-2), 56.17 (q, MeO-1), 21.41 (q, Me-5)
2b	7.67 (d, J = 8.5, H-5), 6.83 (d, J = 2.9, H-2), 6.49 (dd, J = 8.5 and 2.9, H-6), 3.79 (s, MeO-1), 2.41 (s, Me-3)	159.72 (s, C-1), 142.67 (s, C-3), 139.16 (d, C-5), 115.72 (d, C-2), 113.23 (d, C-6), 89.55 (s, C-4), 55.17 (q, MeO-1), 28.12 (q, Me-3)
2c	8.12 (s, H-3), 6.72 (s, H-6), 3.86 (s, MeO-1), 2.41 (br, s, Me-5)	158.26 (s, C-1), 147.17 (d, C-3), 142.92 (s, C-5), 112.26 (d, C-6), 90.25 (s, C-4), 83.09 (s, C-2), 56.08 (q, MeO-1), 28.12 (q, Me-5)
3a-1	7.63 (d, J = 7.9, H-3), 6.65 (br s, H-6), 6.55 (br d, J = 7.9, H-4), 3.87 (s, MeO-1), 2.57 (t, J = 7.3, 2H-7), 1.60 (m, 2H-8), 1.26 (br s, 2H-9 to 2H-20), 0.89 (t, J = 7.0, 3H-21)	157.85 (s, C-1), 145.01 (s, C-5), 138.93 (d, C-3), 122.67 (d, C-4), 111.35 (d, C-6), 82.06 (s, C-2), 56.16 (q, MeO-1), 35.88 (t, C-7), 31.37 (t, C-8), 31.91 (t, C-19), 29.65–29.24 (all t, C-9 to C-18), 22.68 (t, C-20), 14.12 (q, C-21)
3a-2	8.09 (s, H-3), 6.66 (s, H-6), 3.84 (s, MeO-1), 2.64 (t, J = 6.3, 2H-7), 1.56 (m, 2H-8), 1.25 (br s, 2H-9 to 2H-20), 0.87 (t, J = 6.7, 3H-21)	158.50 (s, C-1), 147.66 (d, C-3), 146.97 (s, C-5), 111.72 (d, C-6), 89.73 (s, C-4), 83.45 (s, C-2), 56.32 (q, MeO-1), 40.87 (t, C-7), 30.23 (t, C-8), 31.90 (t, C-19), 29.66–29.33 (all t, C-9 to C-18), 22.67 (t, C-20), 14.12 (q, C-21)
3b-1	7.76 (d, J = 8.8, H-4), 6.52 (d, J = 8.8, H-3), 3.90 (s, MeO-22), 3.79 (s, MeO-2), 2.60 (m, 2H-7), 1.56 (m, 2H-8), 1.26 (br s, 2H-9 to 2H-20), 0.88 (t, J = 6.5, 3H-21)	168.03 (s, C-22), 156.47 (s, C-2), 142.84 (s, C-6), 140.90 (d, C-4), 124.58 (s, C-1), 110.69 (d, C-3), 89.73 (s, C-5), 55.99 (q, MeO-2), 52.35 (q, MeO-22), 38.64 (t, C-7), 31.91 (t, C-19), 29.78 (t, C-8), 29.78–29.18 (all t, C-9 to C-18), 22.68 (t, C-20), 14.12 (q, C-21)

Table 2 (continued)

Compound	^{1}H NMR (δ_H, J (Hz))	^{13}C NMR (δ_C)
3c-1	7.72 (d, J = 8.8, H-4), 6.49 (d, J = 8.8, H-3), 3.87 (s, MeO-15), 3.80 (s, MeO-2), 3.63 (s, MeO-14), 2.54 (m, 2H-7), 2.27 (t, J = 7.4, 2H-13), 1.6–1.2 (m, 2H-8 to CH$_2$-12)	167.96 (s, C-15), 174.21 (s, C-14), 156.36 (s, C-2), 142.59 (s, C-6), 140.88 (d, C-4), 124.48 (s, C-1), 110.66 (d, C-3), 89.61 (s, C-5), 55.96 (q, MeO-2), 52.37 (q, MeO-15), 51.41 (q, MeO-14), 38.49 (t, C-7), 34.00 (t, C-13), 29.60 (t, C-8), 29.50 (t, C-9), 28.94 (t, C-10), 28.75 (t, C-11), 24.82 (t, C-12)
4a	7.74 (d, J = 8.7, H-4), 6.52 (d, J = 8.7, H-3), 4.43 (m, 2H-14), 3.78 (s, MeO-2), 2.85 (m, 2H-7), 1.89 (m, 2H-13), 1.73 (m, 2H-8), 1.7–1.4 (m, 2H-9 to 2H-12)	168.00 (s, C-16), 156.41 (s, C-2), 142.62 (s, C-6), 140.77 (d, C-4), 125.33 (s, C-1), 110.66 (d, C-3), 89.49 (s, C-5), 67.72 (t, C-14), 55.99 (q, MeO-1), 35.31 (t, C-7), 26.64 (t, C-8), 26.30 (t, C-9), 26.24 (t, C-13), 25.76 (t, C-10), 25.60 (t, C-11), 23.21 (t, C-12)

^{a} The chemical shifts are given in δ (ppm) in CDCl$_3$; all ^{1}H and ^{13}C NMR are consistent with the assigned structures.
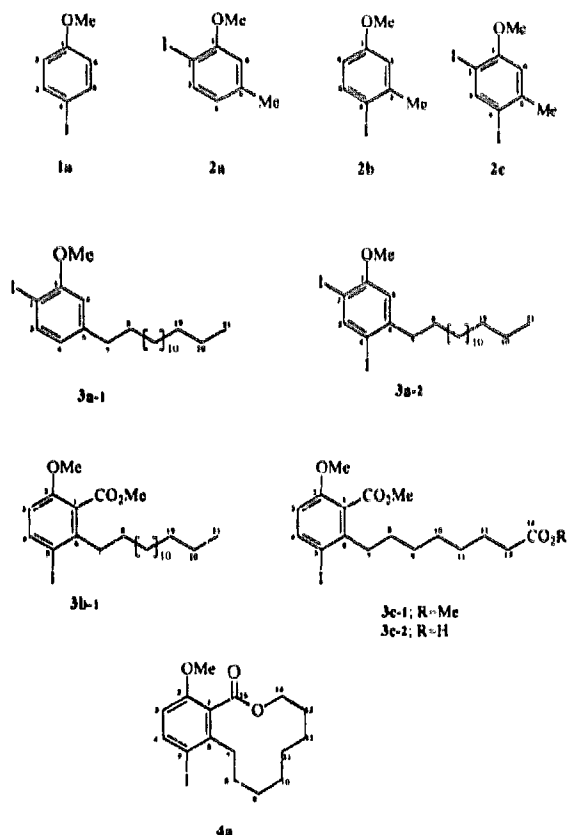^{b} The multiplicity of the signals was deduced by comparative analysis of proton-noise decoupled and DEPT spectra.

1a   2a   2b   2c

3a-1   3a-2

3b-1

3c-1; R=Me
3c-2; R=H

4a

Table 3
IR and mass data of the iodo compounds

Compound	IR (cm⁻¹)	MS [m / z, relative intensity (%)]
1a	1581, 1480, 1243 and 1026	234(M⁺, 100), 219(30), 191(20), 127(10), 92(30), 77(10)
2(a–c)	1579, 1489, 1243 and 1045	2a,b: 248(M⁺, 100), 233(20), 127(8), 121(10), 106(25), 91(18), 78(10) 2c: 374(M⁺, 100), 359(25), 247(10), 232(60), 204(20), 127(25), 105(20), 89(20), 77(25)
3a-1	1465, 1575, 1258 and 1047	444(M⁺, 20), 247(65), 121(100), 91(20), 77(8)
3a-2	1580, 1460, 1244 and 1046	570(M⁺, 50), 373(90), 287(30), 247(100), 161(50), 147(30), 90(25), 57(25), 43(60)
3b-1	1733, 1574, 1464, 1264 and 1089	502(M⁺, 90), 471(75), 375(15), 343(90), 306(97), 287(90), 179(90), 161(80), 91(20), 55(25), 43(100)
3c-1	1734, 1573, 1461, 1260, 1207 and 1084	448(M⁺, 8), 416(20), 287(100), 257(40), 179(40), 161(55), 105(20), 91(25)
3c-2	3400–2400 (br), 1722, 1558, 1460, 1432, 1258 and 1083	434(M⁺, 20), 402(25), 287(100), 257(70), 91(10), 77(25), 60(45)
4a	1722, 1559,1460, 1259, 1140 and 1083	388(M⁺, 38), 301(25), 287(40), 231(20), 161(60), 149(55), 121(50), 115(70), 91(70), 89(90), 77(80), 55(100)

In contrast with the classical method, by which compound **3c** suffered partial hydrolysis to produce a mixture of **3c-1** and **3c-2**, our modified conditions led exclusively to the formation of the iodine substituted dimethyl ester (**3c-1**). Application of the above procedure to chlorobenzene resulted in the formation of 1-chloro-4-iodobenzene.

Interestingly, we have also established that compounds of the type **2** and **3a** led to mixtures of products under thallation–iodination conditions. In such cases, our method showed no improvement over the classical methods, probably owing to quite indistinguishable thallation sites in that class of compounds.

In summary, the new procedure offers an attractive alternative for electrophilic aromatic thallation of phenol ethers. As shown in Table 1, it represents a considerable improvement over previously described methods. Comparatively, this procedure is more general, since it can be used to promote substitutions in both electron-

deficient and electron-rich arenes, with comparable and very good yields. Its effectiveness, allied to its ease of implementation, should certainly recommend it.

3. Experimental details

All aryl compounds were thallated as described above. Replacement of thallium di(trifluoroacetate) with potassium iodide at room temperature followed by the usual work-up led to a cleaner solution. Determination of the position of the aromatic thallation–iodination could be achieved by employing mainly one- and two-dimensional ¹H and ¹³C NMR (Tables 2 and 3).

3.1. Typical procedure

The aryl compound (0.2–0.5 mmol) was dissolved in 1,2-dichloroethane (3–6 ml) and solid thallium(III) trifluoroacetate (1.3 equiv.) was added under stirring. A solution of boron trifluoride etherate (about 10% v/v) was added dropwise and the mixture was stirred at room temperature. After the thallation was complete (TLC), the mixture was treated with excess aqueous potassium iodide and the suspension produced was stirred for 1 h at room temperature. Solid potassium carbonate was then added, followed by solid sodium metabisulfite (to reduce iodine which had been formed during the reaction) and the stirring was continued for another 30 min. The precipitated thallium(I) iodide was then filtered off and the collected inorganic material was washed thoroughly with 1,2-dichloroethane. The filtrate was washed with brine, dried over anhydrous Na₂SO₄ and evaporated. Typical yields were 80–97%.

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