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Preliminary communication

THALLIUM IN ORGANIC SYNTHESIS

XLIV*. ELECTROPHILIC THALLATION OF ELECTRON—RICH ARENES

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Summary

Electron-rich arenes, which normally undergo oxidative coupling to biaryls with TTFA/TFA, can be smoothly thallated in high yield with TTFA in a 1/1 mixture of TTFA and ether.

The dual processes of electrophilic aromatic thallation, followed by replacement of the resulting thallium substituent by anions, olefins, arenes, or cations, represents a versatile methodology for controlled aromatic substitution [2]. A notable limitation to date, however, is the susceptibility of electron-rich arenes to oxidative dimerization under normal thallation conditions; i.e., thallium tris(trifluoroacetate) (TTFA) in trifluoroacetic acid (TFA) [3,4]. We describe in this paper a simple modification of these normal reaction conditions for electrophilic aromatic thallation whereby oxidative dimerization of electron-rich arenes with TTFA can be avoided, and the corresponding thallated arenes obtained in high yield.

Addition of electron-rich arenes to a solution of TTFA and TFA characteristically produces deep green to deep blue solutions, from which symmetrical biaryls are normally isolated; these deep colors have been associated with the formation of intermediate radical cations. We recently made the adventitious observation that colorless reaction mixtures were obtained when the TFA solvent was diluted with ether, thus suggesting suppression of radical cation formation. We initially explored this observation with 2,5-dimethylanisole,

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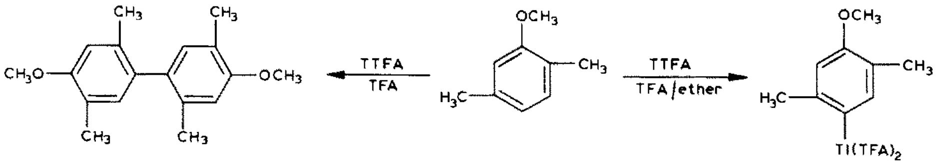
*Part XLIII see ref. 1.

which gives only the symmetrical biaryl I upon treatment with TTFA/TFA [5]. Dissolution of TTFA in ether produces a deep brown color. No apparent reaction takes place upon addition of one equivalent of 2,5-dimethylanisole to this solution. TFA is then added slowly (to avoid heat of mixing); when the volume of TFA added is approximately half of that of the ether solvent, the brown color of the reaction mixture vanishes, and a heavy white precipitate rapidly separates from the resulting colorless solution. This precipitate proved to be the arylthallium bis(trifluoroacetate) (II), formed analytically pure in 95% yield.

This procedure has been applied to a number of electron-rich arenes which normally undergo oxidative dimerization (or give deeply colored solutions from which no homogeneous product could previously be isolated) under normal thallation conditions. Our results are summarized in Table 1. Only moderate yields of thallated derivatives of 1-methyl- and 1-methoxy-naphthalene could be obtained; these substrates were previously shown to undergo instantaneous biaryl coupling under normal thallation conditions [3], and even under the present modified conditions coupling competes with thallation if TTFA is added too rapidly, or in excess. Application of the above procedure to 1,2- or 1,4-dimethoxybenzene resulted only in the formation of deeply



(I) (II)

TABLE 1

AROMATIC THALLATION OF ELECTRON-RICH ARENES WITH TTFA/TFA/ETHER

$$\text{ArH} + \text{TTFA} \xrightarrow[\text{TFA}]{\text{Et}_2\text{O}} \text{ArTl(TFA)}_2$$

Substrate	Thallated product		
	Yield (%)	m.p. (°C)	Position of thallation [a]
Anisole	78	174—176	4
2-Methylanisole	85	154—156	4
3-Methylanisole	89	179—181	6
4-Methylanisole	81	151—152	2
2,5-Dimethylanisole	95	160—161	4
1,2-Dimethoxybenzene	71	126—128	4
1,3-Dimethoxybenzene	61	151—152	4
1,4-Dimethoxybenzene	39	150—151	2
1-Methylnaphthalene	52	170—171	4
1-Methoxynaphthalene	41	106—107	4
3-(3,4-Dimethoxyphenyl)-propionic acid [b]	62	168—169	2

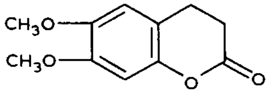
[a] We have developed a reliable method for determining the position of aromatic thallation by an analysis of the effects of individual substituents on thallium-proton coupling constants; this work will be published independently. [b] One of the thallium ligands is the side-chain carboxyl group; cf. structure V.

colored solutions from which no thallated products could be obtained. However, addition of these latter arenes to a mixture of TTFA in ether/TFA (2/1) gave colorless solutions from which the thallated arenes could then be isolated. It thus appears that radical cation formation (hence coupling) is extremely sensitive to the concentration of TFA in the reaction mixture.

Kochi has observed [6] that donor—acceptor complexes which form upon mixing an electrophile with an arene give charge-transfer absorption spectra which decay at a rate linearly related to the formation of electrophilic substitution products and has suggested that the rate of electrophilic substitution is directly related to the stability of this charge transfer species, which for any given electrophile is directly related to the ionization potential of the arene. According to this model, electrophilic thallation proceeds by rate-limiting formation of a radical ion pair which collapses to the arylthallium bis(trifluoroacetate). It appears that effective solvation of this ion pair by TFA facilitates its separation from the thallium(II) species, leading to reactions characteristic of radical cations; i.e., biaryl formation. The addition of ether apparently prevents such solvation, and the ion pair remains intact until its collapse to the electrophilic thallation product.

It is interesting to note that these electron-rich arylthallium bis(trifluoroacetates) dissolve in TFA to produce dark colors characteristic of intermediate radical cations; addition of an equivalent of the starting arene then leads to formation of the symmetrical biaryl. This result presumably is a consequence of protodethallation of the electron-rich arylthallium bis(trifluoroacetate) by TFA, followed by normal biaryl coupling (i.e., oxidation by TTFA).

We have reported previously that 3-(3,4-dimethoxyphenyl)propionic acid is converted into a mixture of the dihydrocoumarin III and the spirocyclohexadienone IV upon treatment with TTFA/TFA [7]. By contrast, however, *ortho*-thallation of this substrate by the procedure described above, followed by treatment of the isolated *ortho*-thallated 3-(3,4-dimethoxyphenyl)propionic acid (V) with TFA/CH_2Cl_2/$BF_3 \cdot Et_2O$, leads exclusively to formation of the dihydrocoumarin III; no spirocyclohexadienone IV could be detected in the reaction mixture. This two-step process for effecting oxidative cyclization thus offers interesting potential selectivity advantages and merits further investigation.



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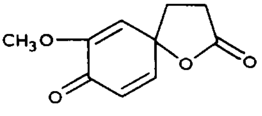

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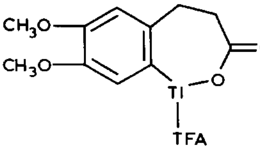

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