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THALLIUM IN ORGANIC SYNTHESIS. 63. A CONVENIENT SYNTHESIS OF AROMATIC NITRILES[1,2]

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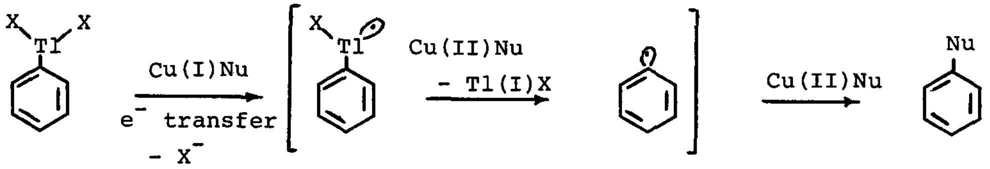
SUMMARY: Aromatic nitriles are readily formed by heating arylthallium bis(trifluoroacetates) with CuCN in acetonitrile.

Electrophilic thallation of arenes with thallium tris(trifluoroacetate) (TTFA), followed by replacement of the resulting thallium substituent by other groups, constitutes a flexible procedure for aromatic substitution, often with an unusual degree of orientation control.[3] Two methods, for example, have been described for the introduction of cyano groups by this general strategy. In the first, arylthallium bis(trifluoroacetates) are photolyzed in aqueous potassium cyanide.[4] However, this reaction is difficult to run on a preparative scale and is limited to arylthallium intermediates which are stable in aqueous solution (i.e., which do not protodethallate). In the second, arylthallium acetate perchlorate monohydrates are heated with CuCN (or "$Cu(CN)_2$" (?)) in pyridine.[5] In this case, the electrophilic thallium reagent used for the preparation of the above intermediates (thallium tris-(acetate)) thallates only a narrow range of activated aromatic substrates, and many of the resulting thallated arenes are susceptible to protodethallation, even by the water of hydration of the reagent. The reaction is also difficult to run preparatively (only GC yields were reported), since isolation of the products from pyridine is difficult.

It appeared to us that the mechanism of the latter transformation of arylthallium acetate perchlorate monohydrates to aromatic nitriles with CuCN was probably analogous to the Rosenmund-von Braun reaction[6] of arylhalides with CuCN, which is initiated by electron transfer from Cu(I).[7] Increasing the oxidation potential of Tl(III) in the $ArTlX_2$ intermediates should therefore facilitate this initial electron transfer process. This is most easily accomplished by replacing acetate by a more electronegative ligand such as trifluoroacetate. Of the $ArTlX_2$ compounds with the highest oxidation potentials, the bis(trifluoroacetates) are the best known and the most accessible,[3] and we have therefore explored the above concept with these intermediates. Indeed, reaction of a broad range of arylthallium bis(trifluoroacetates) with CuCN in acetonitrile as solvent led to the isolation of aromatic nitriles in excellent yield.

We suggest that this transformation proceeds as depicted in Scheme 1. Initial electron transfer from Cu(I) to the arylthallium bis(trifluoroacetate)



Scheme 1

produces an unstable Tl(II) species (analogous to an arylhalide radical anion). Homolysis of the C-Tl bond leads to Tl(I) and an aryl radical; i.e., the same intermediate proposed for the classical Rosenmund-von Braun reaction. The use of acetonitrile as solvent aids substantially in the subsequent regeneration of Cu(I) by stabilizing the latter through complexation.

Results are summarized in Table 1. It is important to note that both electron-poor (i.e., methyl benzoate) and electron-rich (i.e., methylnaphthalene, dimethylanisole) arenes can be converted to the corresponding nitriles in good yields by this two-step process. If the arene can be thallated in acetonitrile,[8] addition of CuCN then results in a one-pot conversion of the starting arene to the nitrile (i.e., thiophene → 2-cyanothiophene). In contrast to the reaction of Cu(I) salts with arylhalides, which is invariably run at high temperatures, and entails complicated work-up procedures,[7] the present synthesis of aromatic nitriles is conveniently carried out at the boiling point of acetonitrile (81° C), and the work-up procedure is trivial.

Other Cu(I) salts should react similarly with arylthallium bis(trifluoroacetates) in acetonitrile. Indeed, preliminary experiments have demonstrated that arylacetylenes, aryl benzoates, diaryl ethers, and α-arylmalonates can be readily formed by reaction of these $ArTlX_2$ intermediates with appropriate Cu(I) salts. These results will be reported in detail in forthcoming communications.

Formation of Aromatic Nitriles: General Procedure. The arylthallium bis(trifluoroacetate) (10 mmol) and CuCN (40 mmol) are mixed in dry acetonitrile (50 mL) and heated under reflux, under a steady stream of nitrogen, for the period of time specified in Table 1. The reaction mixture is then concentrated under reduced pressure and the resulting green sludge extracted with chloroform (4 x 50 mL). The combined extracts are then washed with water (2 x 25 mL), 1 N HCl (2 x 25 mL) and water (2 x 25 mL), dried over anhydrous magnesium sulfate, and the filtrate evaporated to give the aromatic nitrile.

Table 1. Formation of Aromatic Nitriles

$$ArTl(TFA)_2 + CuCN \xrightarrow{CH_3CN} ArCN$$

Product	Time (hr)	Yield (%)
Benzonitrile	17	72
4-Tolunitrile	17	64
4-Anisonitrile	17	66
2,5-Dimethyl-4-anisonitrile	17	84
2-Cyanobenzanilide	2	62
Methyl 2-Cyanobenzoate	5	73
4-Methyl-1-naphthonitrile	17	85
2-Cyanothiophene	15	53[a]

[a] Yield based upon thiophene; the $ArTl(TFA)_2$ intermediate was formed in acetonitrile and was not isolated.

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