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A FACILE SYNTHESIS OF AROMATIC TRIFLUOROMETHYL COMPOUNDS VIA ORTHOTHIO ESTERS

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Abstract: Aromatic trifluoromethyl compounds (2) are prepared by treatment of aromatic orthothio esters (1) with 1,3-dibromo-5,5-dimethylhydantoin (DBH) or N-bromosuccinimide (NBS) followed by HF/pyridine complex. The starting materials (1) were readily obtained by literature methodology.

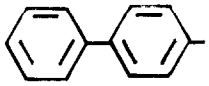
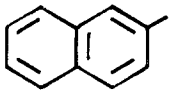
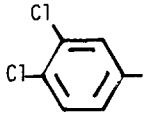
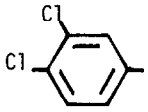
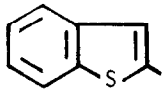
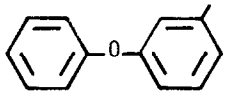
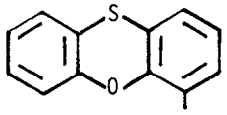
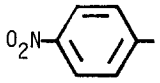
There has been considerable interest in trifluoromethyl-substituted aromatic compounds as pharmaceutical and agricultural agents.[1] The importance of developing useful methodology for the introduction of trifluoromethyl groups onto aromatic compounds is demonstrated by the number of methods recently reported for this transformation.[2] However, these methods require highly toxic or expensive reagents and/or vigorous reaction conditions. Very recently, Wiemers and Burton[2a] reported an elegant method for the preparation of benzotrifluorides *via* a metathesis reaction utilizing Freons to generate a stable CF_3Cu species.

We wish to report a convenient procedure for the preparation of trifluoromethyl aromatic compounds (2) that is readily carried out under normal laboratory reaction conditions on a multigram scale. Treatment of an aromatic orthothio ester (1)[3] with either DBH or NBS, followed by the addition of HF/pyridine provided 2 (see Table). This new reaction most likely proceeds by similar mechanism as the conversion of phenyl thioglycosides to glycosyl fluorides reported by Nicolaou and co-workers,[4] and the formation of geminal difluoro compounds from thioacetals reported by Pochapsky and Katzenellenbogen.[5]

The triethylorthothio esters (1, R=Et) were readily prepared from the corresponding acid chloride by treatment with ethanethiol and either zinc chloride[3a] or aluminum chloride.[3b] Alternatively, trimethylorthothio esters (1, R=Me) were obtained from the methyl ester by treatment with trimethylsilylmethylsulfide and aluminum chloride.[3b]

Table. Formation of Aryltrifluoromethyl Compounds (2) from Orthothio Esters 1[7]

$$ArC(SR)_3 \;(1) \xrightarrow[2)\ HF\text{-pyridine}]{1)\ DBH \text{ or } NBS} ArCF_3 \;(2)$$

Entry	Ar	R	% Yield[a]	mp/bp°C
a		Et	59	64-66[b]
b		Et	49	64.5-66.5[c]
c		Et	43	173-174 (760mm)[d,e]
d		Me	46	
e		Et	40	55-56 (MeOH/H_2O)
f		Et	67[f]	d,g
g		Et	37[f]	160-170 (0.7mm)[d]
h		Me	34	41[e,h]

[a]Based on isolated purified product. [b]Lit. (Ref. 8) does not report mp. [c]No Lit. mp availablle. [d]Isolated as a colorless oil. [e]Identical to an authentic sample. [f]Dehalogenated (EtOH, 10% Pd/C, KOAc, 50 psi hydrogen) to remove bromine. [g]Lit. (Ref. 9) bp 81°C (1mm). [h]mp of sample from Aldrich, 41-42°C.

An example of the experimental procedure for the preparation of 2 from 1 is as follows: To a dry 3-neck flask with stirring bar, thermometer, nitrogen inlet valve and septum was added 1,3-dibromo-5,5-dimethylhydantoin (11.4 g, 40 mmol) and dry CH_2Cl_2 (100 mL). The mixture was cooled to -20°C and a solution of 1a[3a] (3.5 g, 10 mmol) in CH_2Cl_2 (5 mL) was added via syringe. The reaction turned yellow-orange and was allowed to stir for 3 minutes at -20 to -30°C. HF/pyridine complex (Aldrich) (10 mL) was added via a disposable plastic syringe. The thermometer was removed and the reaction was stirred for one hour while warming to room temperature. The yellow-orange mixture was poured onto a large column containing basic alumina (300 mL) packed with CH_2Cl_2. A vigorous neutralization reaction occurs initially as the reaction mixture is allowed to slowly adsorb on the alumina. The desired product elutes near the solvent front with a small amount of ethyl disulfide. Evaporation of the appropriate fractions provided 2a[7] as a white crystalline solid after drying under high vacuum (1.3 g, 59%), mp 64-66°C; IR (CCl_4) 2959, 1328 (asym CF_3Ar), 1170 (sym CF_3Ar), 1133 cm^{-1} (sym CF_3Ar); ^1H NMR ($CDCl_3$) δ 7.3-7.7 (m): MS (CI/CH_4) m/z 223 (MH^+).

The conditions for the reaction are not critical. Both NBS and DBH gave similar yields of 2a. The reaction tolerates electron rich and electron poor aromatic rings and is compatible with thioethers. However, concomitant bromination of electron rich rings was observed for 2e and 2f. Compound 2e was isolated as the meta-(4-bromophenoxy)-benzotrifluoride and 2f as a mixture of monobromo and desired product. The brominated products were dehalogenated under standard conditions (EtOH, 10% Pd/C, KOAc, 50 psi H_2). Isolation of the volatile benzotrifluoride obtained in entry 2c required removal of ethyl disulfide by treatment of the CH_2Cl_2 elutant containing 3,4-dichlorobenzotrifluoride with excess meta-chloroperbenzoic acid followed by silica gel flash chromatography (pentane). Alternatively, 3,4-dichlorobenzotrifluoride was isolated free of disulfide by utilizing the trimethylorthothio ester (entry d) by simple distillation of methyl disulfide after filtration through alumina.

In conclusion, the new method for obtaining 2 provides a two step procedure from readily available acid chlorides or methyl esters that requires no special equipment and utilizes inexpensive reagents. The reaction conditions are mild and provide a convenient route to gram quantities of aromatic trifluoromethyl compounds including the novel analogues 2e and 2g.

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