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Synthesis of substituted 3-trifluoromethylbenzo[*b*]thiophenes

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Abstract—A straightforward method for the synthesis of 5/6-substituted 3-trifluoromethylbenzo[*b*]thiophenes and their precursor *o*-fluorinated trifluoro acetophenones is reported.

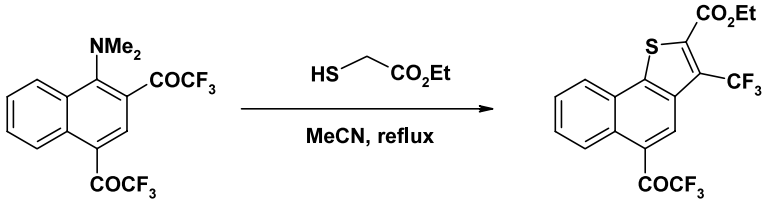
The trifluoromethyl group is a very valuable substituent to include in any organic series owing to the unique physical and biological properties it confers.[1] Access was recently required to 5- and 6-substituted-3-trifluoromethyl benzo[*b*]thiophenes. A review of the literature revealed a paucity of references to 3-trifluoromethylbenzothiophenes. 3-Trifluoromethylbenzo[*b*]thiophene itself has been noted[2] as a constituent of the product mixture arising from the reaction of benzothiophene with bis(trifluoroacetylperoxide) at 70°C in Freon 113. 7-Methyl-3-trifluoromethylbenzo[*b*]thiophene has been prepared[3] in 54% yield from 7-methyl-3-bromobenzo[*b*]thiophene by reaction with sodium trifluoroacetate and copper(I) iodide in *N*-methylpyrrolidine at 180°C. Neither of these methods were thought appropriate to the project needs. It was felt necessary therefore to devise a new, scaleable route to 3-trifluoromethylbenzo[*b*]thiophenes that could provide substituents in the 5 or 6 position capable of further elaboration.

There is one example in the literature[4] of the formation of a 2-carboxyethyl-3-trifluoromethyl-naphtho[1,2-*b*]thiophene by the displacement of dimethylamine from 1-*N*,*N*-dimethylamino-2,4-bis(trifluoroacetyl)naphthalene with ethyl thioglycolate in acetonitrile (Scheme 1).

Ethyl thioglycolate has also been reported[5] to displace fluoride from 2-fluorobenzonitriles and the products spontaneously cyclise to give high yields of ethyl 3-aminobenzothiophene-2-carboxylates in triethylamine/DMSO at 100°C.

These references prompted the consideration of the possibility of displacing fluorine from 2-fluoro-trifluoroacetophenones with thioglycolate, and subsequent ring closure and decarboxylation, as a route to the desired 3-trifluoromethyl benzo[*b*]thiophene-2-carboxylates (Scheme 2). As benzo[*b*]thiophene-2-carboxylic acids are known[6] to undergo decarboxylation to benzothiophenes, this four step sequence was considered a viable possibility for the synthesis of 3-trifluoromethyl benzo[*b*]thiophenes.

Thus 2-fluoro-2′,2′,2′-trifluoroacetophenone was reacted with methylthio- glycolate in the presence of triethylamine.[7] Work-up and chromatography gave the required methyl-3-trifluoromethylbenzo[*b*]thiophene-2-carboxylate in 66% yield.



Scheme 1.

Keywords: lithiation; trifluoromethylbenzothiophenes.
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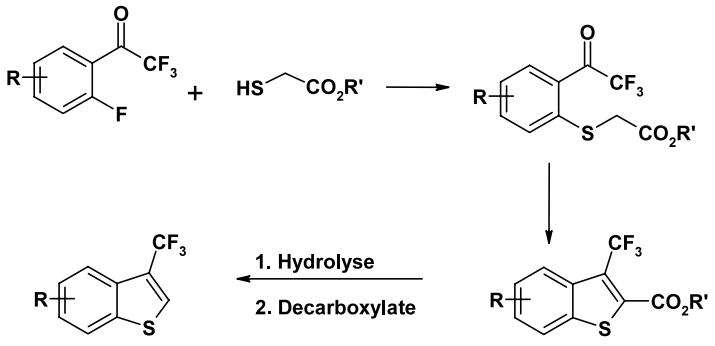
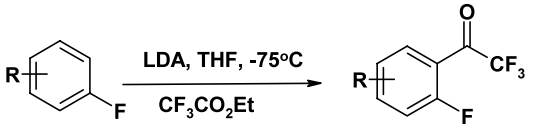


Scheme 2.

Table 1.



Starting material	Product	Yield[a]
R = 4-Br	R = 5-Br	65
4-Cl	5-Cl	40
4-CN	5-CN	63
3-Br	4-Br	41 (via trimethylsilyl)

[a] Reported yields (%) are for pure isolated products after chromatography.

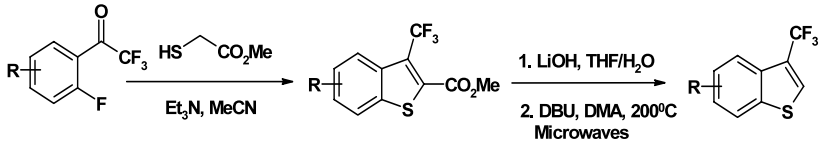
With the demonstration of the utility of this route, we set out to prepare a series of substituted 3-trifluoromethylbenzo[*b*]thiophenes. However, the required 4- or 5-substituted-2-fluoro-2′,2′,2′-trifluoroacetophenones are not commercially available or even reported; we therefore had to consider their synthesis.

Fluorine has been reported[8] to be an effective *ortho*-directing group in aromatic metalation in the presence of a number of other aromatic substituents. Quenching of a lithio species generated by such *o*-directed metalation with ethyl trifluoroacetate[9] should give entry to the required 4- or 5-substituted 2-fluoro trifluoroacetophenones; this proved to be the case[10] (Table 1). In the case of 3-bromofluorobenzene, a survey of the literature[8] shows that the first lithiation occurs in the 2-position; to access the required 4-bromo-2-fluorotrifluoroacetophenone it was necessary to block the 2 position with a trimethylsilyl group and lithiate again using lithium 2,2,6,6-tetramethylpiperidide, before quenching with ethyl trifluoroacetate and desilylating with Bu_4NF (1N in THF, rt for 12 h).

With these materials in hand we proceeded with the reaction with methyl thioglycolate. In the case of 5-cyano-2-fluoro-2′,2′,2′-trifluoroacetophenone it was found that reaction with methyl thioglycolate and triethylamine at room temperature in acetonitrile was sufficient to produce the methyl 3-trifluoromethyl-5-cyano benzo[*b*]thiophene-2-carboxylate (Table 2). Hydrolysis of the methyl esters was accomplished in near quantitative yield with lithium hydroxide in THF/water (19:1) at room temperature. Decarboxylation was accomplished in good yield with DBU in dimethylacetamide at 200°C for one hour in a CEM MARS microwave reactor.[11,12] All new materials were characterised by ^1H NMR and accurate mass measurement.[13]

In conclusion the chemistry described provides a straightforward route via *o*-fluorinated trifluoroacetophenones to previously inaccessible 3-trifluoromethyl benz[*b*]thiophenes ring substituted with substituents capable of further synthetic elaboration.

Table 2.



Starting material	Benzo[*b*]thiophene ester[a]	Benzo[*b*]thiophene[a]
R = H	66	75
5-Br	70	65
5-Cl	54	62
5-CN	49	78
4-Br	76	78

[a] Reported yields (%) are for pure isolated products after chromatography.

Acknowledgements

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4. Okada, E.; Masuda, R.; Hojo, M.; Imazaki, N.; Miya, H. *Heterocycles* **1992**, *43*, 103.
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6. Zambias, R. A.; Hammond, M. L. *Synth. Commun.* **1991**, *21*, 959.
7. Methylthioglycolate (1.1 equiv.) and triethylamine (1.3 equiv.) were dissolved in acetonitrile and stirred under nitrogen at room temperature. 2-Fluoro-2′,2′,2′-trifluoro acetophenone (Rieke chemicals) (1 equiv.) was added and the reaction mixture was heated under reflux for 18 h. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and dilute aqueous NaOH. The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The oily residue was passed through a pad of silica (eluent: hexane/ethyl acetate 5:1) to give methyl-3-trifl-uoromethylbenzo-thiophene-2-carboxylate as a yellow oil (66% yield).
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9. Morita, C.; Hashimoto, K.; Okuno, T.; Shirahama, H. *Heterocycles* **2000**, *52*, 1163.
10. Experimental conditions (as Ref. 5): lithium diisopropyl-amide (1.1 equiv.) in dry THF was stirred under nitrogen and cooled to −75°C. 4-Bromofluorobenzene (1 equiv.) in dry THF was added slowly, keeping the temperature below −70°C. The reaction mixture was stirred for 1 h and ethyl trifluoroacetate (1.1 equiv.) was added over 5 min keeping the temperature below −70°C. The reaction was allowed to warm to room temperature overnight and was quenched by addition of saturated aqueous NH_4Cl soln. Ethyl acetate was added and the organic phase was collected, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was passed through a pad of silica (eluent: hexane/ethyl acetate, 4:1) to give 2-fluoro-5-chloro-2′2′2′-trifluoroacetophenone in 40% yield.
11. A mixture of 3-trifluoromethylbenzothiophene-2-carboxylic acid (3.12 g, 12.7 mmol) and diazobicycloundecane (8 g, 52.5 mmol) in dimethylacetamide (20 ml) was heated in a sealed vessel in a microwave reactor (300 W, 100%) for 1 h. After cooling to room temperature the mixture was poured into 1N $HCl_{(aq)}$ and extracted into ethyl acetate. The organic phase was collected, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was passed through a pad of silica (eluent: hexane/ethyl acetate, 19:1) to give 3-trifluoromethylbenzo-thiophene (1.92 g, 9.5 mmol) in 75% yield.
12. CEM (Microwave Technology) Ltd, website: http://www.cemsynthesis.com
13. e.g. 3-Trifluoromethyl-6-bromobenzo[*b*]thiophene. ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.0 (1H, d, $J=1.5$ Hz), 7.88 (1H, s), 7.79 (1H, d, $J=8.3$ Hz), 7.58 (1H, dd, $J=8.7$, 1.9 Hz). MS: $C_9H_4F_3BrS$ requires 279.9169, found 279.9160.