Tetrahedron Letters, Vol. 33. No. 49. pp. 7499-7502, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Fluorine as an ortho-Directing Group in Aromatic Metalation: A Two Step Preparation of Substituted Benzo[b]thiophene-2-carboxylates

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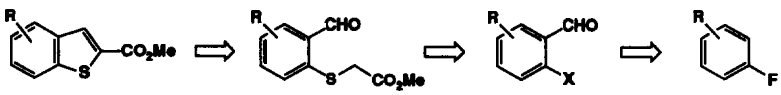
Abstract: A simple 2-step synthesis of B-ring substituted benzo[b]thiophene-2-carboxylates from aryl fluorides has been developed. The route involves a selective lithiation ortho to fluorine, followed by formylation, and subsequently, displacement of fluorine with thioglycollate and base-induced ring closure in a single operation.

In connection with a pharmaceutical project we required a series of B-ring substituted benzo[b]thiophene-2-carboxylates **1.** From a practical point of view, a process was needed which fused the constant part of the molecule. the thiophene ring, onto a readily available benzene derivative to ensure a wide array of B-ring substituents. Such a strategy has been recently employed by Buchwald[1] in an elegant zirconocene mediated preparation, and by Johnson2 who used a directed-metalation based approach. The ester functionality of **1** allows the economical use of an intramolecular aldol reaction of 2 to construct the thienyl ring. Several routes can be envisioned to 2, but nucleophilic displacement by thloglycollate on a suitably 2-substituted benzaldehyde 3 appeared attractive, as many benzaldehydes are commercially available. However, the regioselective introduction of a leaving group ortho to an aryl aldehyde is not a straightforward problem. One of the best leaving groups in activated aromatic systems is fluorine? and this has been heavily exploited, especially in the synthesis of the extremely potent quinolone antibiotics.[4] Another useful property of fluorine is the strong acidification of the ortho protons.5 This allows one to consider using the fluorine atom both as a leaving group for nucleophilic substitution, and as a template to introduce an electron withdrawing carbonyl substituent via directed-metalation. Both of these properties of fluorine have been exploited.6 Such a strategy leads to the retrosynthetic analysis of Figure 1, where an aryl fluoride 4, of which a large number are commercially available, is the precursor for benzothiophene **1.**



1 2 3 (X=F) 4

Figure 1. Retrosynthetic Analysis for Benzo[b]thiophene Synthesis from Aryl Fluorides.

In the preceding communication.7 we have demonstrated that lithiation ortho to fluorine in aryl fluorides is a very general and synthetically useful process, with very predictable regiocontrol by fluorine. In this communication we wish to report that formylation of lithiated aryl fluorides, followed by a base induced nucleophilic displacement of fluoride by thioglycollate and subsequent intramolecular aldol condensation, is a very simple and general two pot preparation of a wide variety of B-ring substituted benzo[b]thiophene-2-carboxylate esters **1.**

Metalations of aryl fluorides 4 were carried out with: lithium diisopropylamide (LDA, Method A) if possible, n-butyllithium with or without *N,N,N',N'*-tetramethylethylenediamine (TMEDA, Method B) as the second choice, *sec*-butyllithium with or without TMEDA (Method C), or lithium 2,2,6,6-tetramethylpiperidide

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(LiTMP, Method D). We found that a -78°C quench of the aryllithium with slightly more than 1 equivalent of DMF. followed 10 minutes later by excess acetic acid and a rapid aqueous workup, gave the benzaldehydes 3 in generally good yields (Table 1).[8] The major impurity was most often unreacted starting material, and in practice, we found that no purification was usually needed prior to the next step.

After some experimentation, a simple procedure (Method 1) was devised for *small scale* (≤10 mmol) thiophene annulations. Methyl thioglycollate (1.1 equiv) was added dropwise at 20°C to a slurry of hexane-washed NaH (1.5-2 equiv) in DMSO. The aldehyde 3 was then added rapidly to the mixture *with no external cooling* and a vigorous exotherm, darkening to red-orange colors, and gas evolution occurred unchecked. If these changes were not seen, the reaction was not successful. After 2-5 minutes the reaction mixture was poured onto rapidly stirred ice-water, and the product 1 was collected by suction filtration, usually in >90% purity regardless of the purity of the starting aldehyde.8 Occasionally, nothing precipitated (Entry 5), and organic extractions and further purification were carried out.

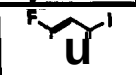
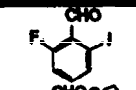
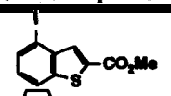
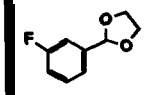
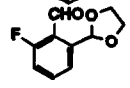
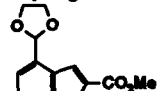
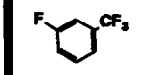
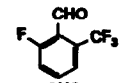
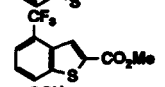
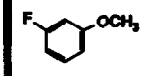
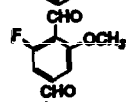
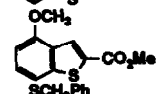
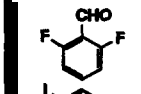
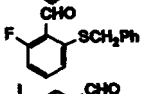
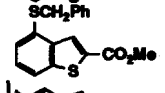
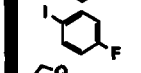
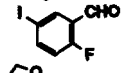
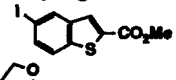
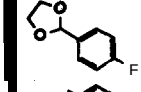
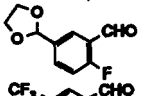
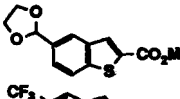
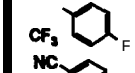
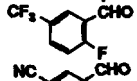
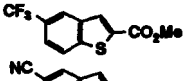
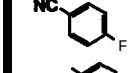
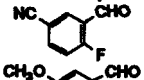
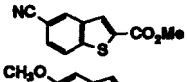
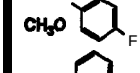
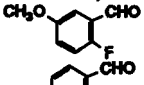
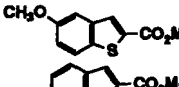
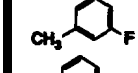
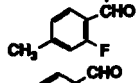
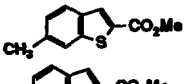
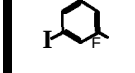
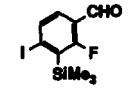
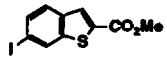
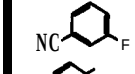
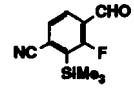
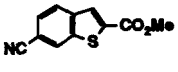
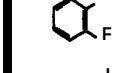
Although this procedure is marked by extreme rapidity and simplicity, it does not scale up well, giving lower yields and less pure products above the 10 mmol scale. *Larger scale use of this procedure would likely be hazardous, as an uncontrolled exotherm is required, whilst hydrogen* is *being evolved.* A less spectacular procedure (Method 2) was devised using Et_3N (2-2.5 equiv) as the base in DMSO, this time heating to 70-100°C for several hours. The displacement/cyclization could be readily followed by tlc, and when the reaction was complete, it was worked up by the same ice-water quench and filtration as before.

Table 1 illustrates the usefulness and generality of this synthesis. If the substiment on the B-ring is itself an ortho director for metalation, Csubstituents are very easy to incorporate, as shown in Entries 1-4, where 3-substituted fluorobenzenes are the starting materials. If the substituent does not ortho-direct metalation (eg methyl) this is not a synthetically useful procedure, (although a protection&protection strategy would presumably solve the problem, as in Entries 12 and 13.). A variant on the general process is shown in Entry 5, where mono-displacement on 2,6-difluorobenzaldehyde with sodium benzylthiolate was followed by thioglycollate annulation. Many pant-substituted fluorobenzenes can be metalated ortho to the fluorine atom7 (Entries 6-10), and then annulated to form the desired 2,5-disubstituted heterocycles. The very low yield obtained in the annulation step of the 5-methoxy derivative (Entry 10) presumably reflects the deactivating effect of a strong electron donor towards para nucleophilic attack on the ring. If the substituent is not ortho directing, obtaining 6-substituted compounds should be straightforward as the meta-substituted aromatic should lithiate preferentially on the less hindered side of the fluorine atom. The final product in Entry 11. however, was contaminated with 20% of the 4-methyl benzothiophene. (Purification at the aldehyde stage was possible by chromatography, but an extremely facile autooxidation of the fluorotolualdehydes cut the yield to below 10%). If the substituent is an ortho director (Entries 12 and 13), then the reactive 2-position of the original fluoroaromatic was blocked by the Snieckus strategy of silylation. followed by another metalation and formylation on the less acidic side of the fluorine atom.[9] Partially desilylated products were produced from the thiophene annulations, and Entry 12 was completely desilylated with TFA and Entry 13 with TBAF. Formation of 'I-substituted benzothiophenes (Entry 14) is straightforward and involves metalation of the appropriate ortho disubstituted fluorobenzene.7 More highly substituted compounds can be produced by starting with more highly substituted benzene derivatives as illustrated in Entry 15.

Entries 1, 6, 12, 14 and 15 produce iodldes, which we have shown to undergo the usual palladium-catalyzed coupling reactions of aryl iodides[10] in excellent yields, allowing for the ready elaboration of B-ring side chains. Entries 2 and 7 can be hydrolyzed to the corresponding aldehydes, and these too can act as excellent platforms for new carbon-carbon bond formation. By the use of o-fluorobenzoates, o-fluorobenzonitriles or *o*-fluoroacylphenones, one can also put hydroxy, amino, or alkyl substituents at the 3-position of the heterocycle, although these cyclizations never worked as well as the aldehyde cyclizations.

In summary, this paper describes a very flexible and rapid two step synthesis of 2,n (m)-polysubstituted

Table 1. Preparation of Benzo[b]thiophenes from Fluorobenzene Precursors.

Entry	Aryl Fluoride	Li[a]	Aldehyde 3	Yield	Method[b]	Benzothiophene 1	Yield
1		A		92%	2		81%
2		B+		91%	1		56%
3		A		80%	1		56%
4		B		89%	1		55%
5		--		90%	1		39%[c]
6		A		87%	1		40%
7		B+		49%	1		62%
8		A		77%	1		63%
9		A		77%	1		64%
10		B+		48%	1		7%
11		C+		82%[e]	1		61%[e]
12		A then D		63%	1 then TFA		29%
13		A then D		75%	1 then TBAF		26%
14		A		50%	1		64%
15		A		97%	1		74%

[a] Lithiation Method, see text, "+" means with TMEDA. [b] Annulation Method, see text. [c] Did not solidify; purified by prep tlc. [d] Contains 20% of the regioisomeric 6- tolualdehyde or 4-methylbenzothienyl products.

benzo[b]thiophenes. The strategy relies on the ability of a fluorine atom to acidify the neighboring aromatic proton(s), allowing for an activating group (formyl) to be introduced via lithiation. The sequence then dies on the ability of the fluorine atom on the activated aromatic systan to be subsequently displaced by mercaptide.

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8. A sample experimental for Entry 3 is described: n-Butyllithium (2.3 M in hexanes, 4.35 **mL,** 10 mmol) was added **dropwise** over 5 min to a solution of diisopropylamine (1.113 g, 11 mmol) in THF (20 **mL)** stirred under N_2 at **0°C.** After 10 **min,** the reaction mixture was cooled to **-78°C,** and **3-fluoro-1-(trifluoromethyl)benzene** (1.643 g, 10.0 mmol) was added **dropwise** over 5 min. After 1 h at **-78°C,** DMF (0.80 **mL,** 11 mmol) was added **dropwise** over 5 min. After a further 10 min at **-78°C,** the reaction mixture was quenched by the rapid addition of acetic acid (2 **mL),** followed quickly by **water** (50 **mL).** The cold solution was quickly extracted with ether (3 x 25 **mL),** and the combined organic extracts **were** washed with dilute **HCl** (0.2 M. 25 **mL),** water (25 **mL),** saturated brine (25 **mL),** and dried **($MgSO_4$).** The solvent was removed under reduced pressure to give crude **2-fluoro-6-(trifluoromethyl)benzaldehyde (1.85 g, 18%** by weight solvent, 80%) as a light yellow oil: ^1H NMR (CDC13) 10.43 **(1H,** sl br s), 7.69 **(1H,** sl br dt, J = 5.2, 8.0 Hz), 7.62 **(1H,** br d, J = 7.6 Hz), 7.42 **(1H, sl** br dd. J = 8.4, 10.2 Hz).

   Methyl thioglycollate (0.72 **mL,** 8 **mmol)** was added **dropwise** over 10 min to a **stirred** suspension of hexanewashed **NaH** (60% oil suspension, 0.50 g, 12.5 mmol) in DMSO (10 **mL)** stirred under N_2 on a **20°C** water bath. When gas evolution died down the bath was removed and the light yellow solution was **stirred** for 15 min. Crude **2-fluoro-6-(trifluoromethyl)benzaldehyde** (1.85 g, 18% by weight solvent, 8 mmol) in DMSO (2 **mL)** was added rapidly, and an exotherm, gas evolution and considerable darkening of the reaction mixture were observed. After 3 min the mixture was poured onto rapidly stirred ice-water (100 **mL),** and the precipitate was collected by suction filtration, rinsed with water (2 x 25 **mL),** and air dried to give **methyl 4-(trifluoromethyl)benzo[b]thiophene-2-carboxylate (1.17 g, 56%) as** a pale beige powder: ^1H NMR (CDC13) 8.27 **(1H,** sl br s). 8.06 **(1H,** d, J = 8.2 Hz), 7.73 **(1H,** dq. J = 7.5, 0.7 Hz), 7.54 **(1H,** sl br dd, J **= 8.2, 7.5** Hz), 3.98 **(3H,** s).
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(Received in USA 14 May 1992; accepted 2 September 1992)