Application of Directed Metallation in Synthesis, Part 2[1]: An Expedient Synthesis of Methoxybenzo[*b*]thiophenes

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Received 28 November 2001

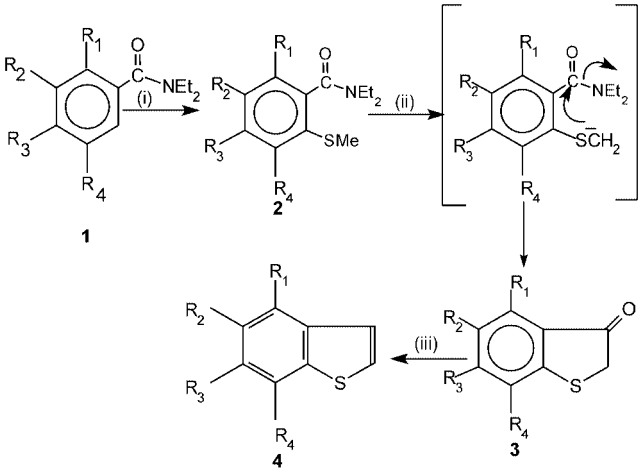
This paper is dedicated to Professor N. B. Chapman on the occasion of his 85th birthday.

Abstract: A short, simple and expedient synthesis of substituted benzo[*b*]thiophenes involving directed *ortho* lithiation-side-chain deprotonation-cyclisation-reduction is described. This method is a valuable improvement over earlier syntheses of the same class of compounds, both with respect to the number of steps and overall yields.

Key words: benzo[*b*]thiophene, thioindoxyl, directed metallation

There is continuous interest in benzo[*b*]thiophene derivatives because of their many varied uses. The chemistry[2] and biological activities[3] of benzo[*b*]thiophene derivatives have been reviewed. Besides the manifold uses of this class of compounds reported therein, benzo[*b*]thiophene derivatives carrying "one arm mustard" side-chains have shown anticancer activities.[4] Uses of benzo[*b*]thiophene derivatives as excitatory amino acid antagonists, in the treatment of myocardial eschemia, hypertension, fungal infection, as oral contraceptives and as hypoglycemic agents are known.[5] More recently there have been reports[6] on the anti-inflammatory, antiexudative, analgesic and antipsychotic activities of benzo[*b*]thiophene derivatives as well as on their inhibitory action on protein tyrosin phosphatase and 5-lypoxygenese.[7] The usefulness of suitably substituted benzo[*b*]thiophenes as synthetic intermediates is demonstrated in the synthesis of numerous polycondensed systems incorporating a fused thiophene ring, through annelation reactions carried out on a preformed benzo[*b*]thiophene or partially hydrogenated benzo[*b*]thiophene core.[2,8] We have recently prepared[1,9] sulfur analogues of the naturally occurring antifungal compound, semivioxanthin through annelation of dihydropyran ring on 4- and 5-methoxy benzo[*b*]thiophene.

Expedient access to substituted benzo[*b*]thiophenes is thus an important goal and we report a simple, short and efficient synthesis of benzo[*b*]thiophenes carrying single or multiple substituents on the benzene ring via a directed metallation-annelation (Scheme). Although the present communication is limited to the synthesis of different methoxybenzo[*b*]thiophenes, the general applicability of the method makes it suitable for the efficient synthesis of



Scheme *Reagents:* (i) *sec*-BuLi/ TMEDA/ THF/ –78 °C/ Me-S-S-Me (ii) LDA/ THF/ –78 °C (iii) $NaBH_4$/ MeOH/ 10% NaOH/ Δ

benzo[*b*]thiophene carrying a wide range of substituents.[10–13]

Under standard directed metallation condition[14,15] *N*,*N*-diethyl benzamide or diethyl benzamides of methoxybenzoic acids obtained from commercially available hydroxybenzoic acids, were lithiated in the position *ortho* to the amide function. Quenching the lithioderivative with dimethyl disulfide resulted in the introduction of the SMe[16] functionality in good yield. While using 1.1 molar eqivalent of *sec*-BuLi resulted in the introduction of single methyl sulfanyl group, use of 2.5 molar equivalent of the alkyl lithium afforded a mixture consisting mainly of the product in which both the free *ortho* positions of the amide function were substituted. In the former case quenching with dimethyl disulfide was followed by stirring the reaction mixture at room temperature for 5 h while, in the latter case the reaction mixture was stirred at room temperature for 10 h. It was not possible to separate the mono and dimethyl sulfanyl derivatives completely by column chromatography. In a few instances compound **2** could be purified by column chromatography over silica gel (eluent ethyl acetate–light petrol, l5:85). However in most cases separation of **2** from its unreacted precursor was frustrating because of the close R_f values. Nevertheless, even with partially pure **2** we could proceed to the next step. Side chain deprotonation of **2** with 2.5 molar equivalent of LDA[14,17] and instantaneous intramolecular

Synlett 2002, No. 2, 01 02 2002. Article Identifier:
1437-2096,E;2002,0,02,0325,0327,ftx,en;D24301ST.pdf.

ISSN 0936-5214

cyclisation of the deprotonated species afforded the thioindoxyls **3** (Table1) which were purified by column chromatography over silica gel (eluent ethyl acetate–light petrol, 1:9)

Table 1 Side Chain Deprotonation of **2** to Thioindoxyls **3**

Entry	R_1	R_2	R_3	R_4	mp (°C) (EtOH)	Yield (%)
a	H	H	H	H	60	67
b	H	H	OMe	H	112	78
c	OMe	OMe	H	H	63	70
d	OMe	H	OMe	H	97	65
e	OMe	H	H	H	101	65
f	H	H	H	OMe	99	69
g	SMe	H	H	H	121	66

Though the thioindoxyls were susceptible to slow decomposition upon prolonged exposure to air, they could be kept in the refrigerator for long periods with no visible sign of deterioration. Borohydride reduction[2] of thioindoxyls in 10% aqueous alkali afforded the substituted benzo[*b*]thiophenes **4** (Table 2) in good yield. Unfortunately we were unable to isolate pure 4-methylsulfanylbenzo[*b*]thiophene **4**, from the reduction of **3g** although it constituted a substantial part of the reaction product as evident from the ^{1}H NMR.

Table 2 Reduction of Thioindoxyls **3** to Benzo[*b*]thiophenes **4**

Entry	R_1	R_2	R_3	R_4	mp/bp (°C)	Yield (%)
a	H	H	H	H	32 (lit[2] 31–31.5)	67
b	H	H	OMe	H	(82/0.1 mm) (lit[2] 80/0.1 mm)	73
c	OMe	OMe	H	H	Oil	72
d	OMe	H	OMe	H	75 (cyclohexane)	85
e	OMe	H	H	H	(80/0.05 mm) (lit[20] 141/17 mm)	82
f	H	H	H	OMe	(87/0.1 mm) (lit[20] 85–90/0.1 mm)	71

The simple procedure described above constitutes a significant improvement over earlier methods of synthesis of methoxybenzo[*b*]thiophenes[2] because of the fewer steps involved and the avoidance of expensive thiols.[2,18] Synthesis of thioindoxyls, the key intermediates, is yet another demonstration of the power of directed metallation in the regiocontrolled introduction of substituents onto an aromatic ring and the subsequent utilisation of substituents for annelation purposes. Earlier syntheses[21] of thioindoxyls through intramolecular cyclisation used much more difficult to access intermediates.

This synthetic method has the potential to provide a general route to substituted benzo[*b*]thiophenes. Work is in progress for the synthesis of benzo[*b*]thiophenes carrying a wider variety of substituents.

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(10) All the compounds reported in this paper showed correct elemental analysis and the structures were corroborated by characteristic spectroscopic data.

(11) *Representative Procedure for Synthesis of Compound 2*: Compound **1** (R_1 = OMe, R_2 = H, R_3 = OMe, R_4 = H) was added to a stirred mixture of *sec*- BuLi (1.1 equiv) and TMEDA (1.1 equiv) in THF at -78 °C. After 40 minutes the *ortho* lithiated species was quenched with dimethyldisulfide (2 equiv) at -78 °C. The reaction mixture was allowed to attain room temperature and was kept at that temperature for 10 hours. Usual aqueous work up afforded compound **2d**. Yield: 84%; mp 80 °C (Ether–Petroleum ether); IR (KBr) = 1637.5 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 6.4 (d, 1 H, *J* = 2 Hz), 6.27 (d, 1 H, *J* = 2 Hz), 3.78 (s, 3 H), 3.76 (s, 3 H), 3.24 (q, 4 H), 2.42 (s, 3 H), 1.13 (t, 6 H); ^{13}C NMR (300MHz, $CDCl_3$) δ_c: (167.15, 161.18, 157.13, 137.76, 119.75, 104.39, 96.09, 56.04, 55.83, 43.03, 39.14, 16.75, 14.22, 13.01.

(12) *Representative Procedure for Synthesis of Compound 3*: Compound **2d** was treated with LDA (2 equiv) in THF at –78 °C for 50 min and the reaction mixture was stirred for 12 h at room temperature. Usual work up of the reaction

mixture afforded compound **3d**. IR (KBr) = 1679.9 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 6.37 (d, 1 H, *J* = 1.8 Hz), 6.07 (d, 1 H, *J* = 1.8 Hz), 3.83 (s, 3 H), 3.79 (s, 3 H), 3.68 (s, 2 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ_c: 196.47, 167.47, 161.85, 160.05, 113.91, 100.2, 96.05, 56.27, 40.12.

(13) *Representative Procedure for the Synthesis of Compound 4*: To a solution of compound **3d** in methanol and 10% NaOH (6:1), $NaBH_4$ (2 equiv) in methanol and 10% NaOH solution (10:3) were added. This mixture was refluxed for 1 h on steam bath and then allowed to stand just under boiling condition for 12 h. Methanol was removed and the reaction mixture was acidified with 10% H_2SO_4 and extracted with ether. Usual aqueous work up and removal of solvent afforded compound **4d**. ^1H NMR (300 MHz, $CDCl_3$) δ_H: 7.28 (d, 1 H, *J* = 5.49 Hz), 7.05 (d, 5.49), 6.82 (d, 1 H, *J* = 1.8 Hz), 6.31 (d, 1 H, *J* = 1.8), 3.81 (s, 3 H), 3.75 (s, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ_c: 159.23, 155.78, 142.5, 125.41, 122.25, 120.61, 96.62, 96.21, 56.06, 55.83.

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