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Application of directed metalation in synthesis. Part 7: Synthesis of suitably functionalised benzo[*b*]thiophenes as key intermediates in the synthesis of benzothienopyranones☆

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Abstract—One-pot syntheses of (3-hydroxybenzo[*b*]thiophen-2-yl) aryl methanones from *ortho*-methylsulfanylaryl *N*,*N*-diethyl amides and of 1-(3-hydroxybenzo[*b*]thiophen-2-yl)ethanone and 1-(3-hydroxybenzo[*b*]thiophen-2-yl)propan-1-one via an anionic *ortho*-Fries rearrangement are described. The hydroxy ketones were used as key intermediates in the synthesis of benzothienopyranones.

Benzothienopyranones, sulfur analogs of furanochromanones and furanocoumarins[1] are interesting synthetic targets because of their potential to show biological activity.[2] In this class of compounds, examples in which the oxygenated ring is fused to the benzene ring of the benzo[*b*]thiophene, are known in greater number than those in which the pyranone ring is annulated to the thiophene moiety, despite the pronounced biological activities shown by some members of the latter group. For example 4-oxo-4*H*-benzo[*b*]thieno[3,2-*b*]pyran-3-carboxylic acid **1** has pronounced antiasthmatic activity[2] (Fig. 1). It may be presumed that suitably functionalised benzo[*b*]thiophenes, which could be intermediates in the synthesis of this class of benzothienopyranones, are less easily accessible. In this communication we present two expedient routes to benzo[*b*]thiophenes possessing ketone and hydroxy functions at the 2- and 3-positions, respectively, and utilisation of the functionalised molecules in the annulation of a pyranone ring. The syntheses also constitute a novel application of directed metalation.[3]

While examining the scope of the one-pot synthesis of thioaurones,[4] from *ortho*-methylsulfanyl *N*,*N*-diethyl carboxamides by treatment with LDA and an appropriate aryl aldehyde, earlier reported by us,[5] it was observed that the desired thioaurones were always accompanied by varying amounts of other compounds and by careful control of the experimental conditions it was possible to achieve the exclusive formation of either of the two types of product. In a typical experiment, the *ortho*-methylsulfanyl tertiary aryl amides were treated with LDA followed by addition of the aryl aldehydes at 0 °C. Acidic work up after 1 h at that temperature gave the thioaurones. On the other hand, if the reaction mixture was allowed to attain room temperature and stirred for 5–6 h before acidic work up, (3-hydroxybenzo[*b*]thiophen-2-yl) aryl methanones were obtained.

The IR spectrum of the latter showed peaks due to hydroxyl and carbonyl functions at 3440–3450 cm^{-1} and at 1590 cm^{-1}, respectively, suggesting intramolecular hydrogen bonding between the two functionalities. The existence of hydrogen bonding was further corroborated by the ^1H NMR spectra, which displayed signals due to a hydrogen bonded OH as a one proton singlet at around 13.5 ppm. From analytical and spectroscopic data these compounds were assigned the (3-hydroxy benzo[*b*]thiophen-2-yl) aryl ketone[6] structures **5a–f** (Table 1). A plausible reaction mechanism requires formation of the thioindoxyl **2** (Scheme 1) as the common intermediate for both the thioaurones and the hydroxyketones. Deprotonation at the 2-position of **2** and subsequent attack by the incipient carbanion on the carbonyl carbon of the aryl aldehyde affords the

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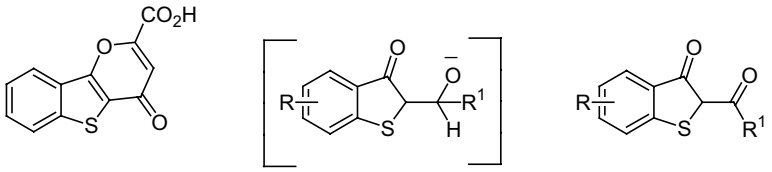


1 **2a** **2b**

Figure 1.

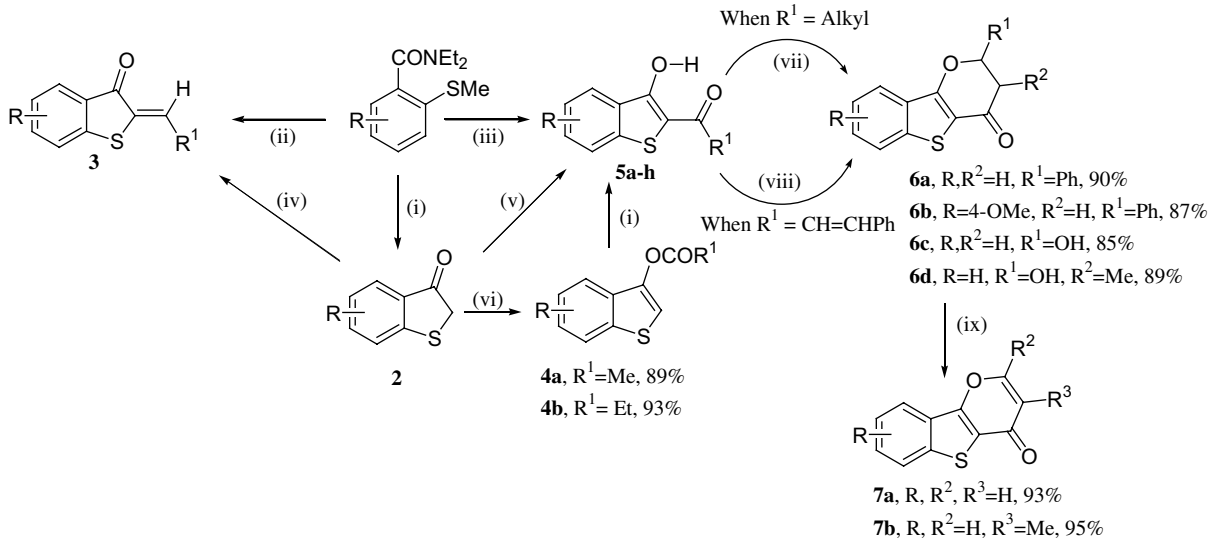
Table 1. (3-Hydroxybenzo[*b*]thiophen-2-yl) alkyl or aryl ketone

Entry	R	R^1	Mp (°C)	Yield (%)
5a	H	Ph	102	93
5b	H	PhCH=CH	139–141	89
5c	H	2-Thienyl	118	88
5d	4-OMe	Ph	138	91
5e	4-OMe	PhCH=CH	164–166	89
5f	4-OMe	2-Thienyl	174–176	90
5g	H	Me	53	67
5h	H	Et	69	73

ionic intermediate **2a** (Fig. 1). Acidic work up after 1 h results in dehydration leading to the thioaurones. When the reaction mixture was stirred at room temperature in the presence of an aryl aldehyde for 5–6 h it had sufficient time to undergo Cannizzaro type hydride transfer affording the 1,3-dicarbonyl product **2b** (Fig. 1) which enolises to the hydroxyketone. It was difficult to isolate the resulting reduced alcohol after work up. However, from GC analysis of the crude reaction product obtained from compound **2** (R = H) and benzaldehyde we observed the formation of benzyl alcohol confirming the occurrence of the Cannizzaro type reaction.[7] An interesting switch of chemoselectivity is thus observed between the elimination products **3** and the enolic 1,3-dicarbonyl derivatives **5a**–**f** depending upon the reaction conditions.

We also synthesised two (3-hydroxybenzo[*b*]thiophen-2-yl) alkyl ketones **5g**–**h** through a hitherto unreported anionic *ortho*-Fries rearrangement. The anionic *ortho*-Fries rearrangement[8] first reported by Snieckus consists of directed lithiation *ortho* to an *O*-carbamate and intramolecular rearrangement in the absence of an electrophile quench, leading to the salicylamide. We have shown for the first time that a similar rearrangement is possible with *ortho*-lithio derivatives of aryl acetates and propionates. Thus benzo[*b*]thiophen-3-yl acetate **4a** and benzo[*b*]thiophen-3-yl propionate **4b**,[9] which were prepared by treating the thioindoxyl with acetyl chloride and propionyl chloride, respectively, in the presence of sodium hydride or LDA in tetrahydrofuran, were lithiated at the 2-position with LDA. The deprotonated species upon stirring at room temperature for 8–10 h underwent intramolecular rearrangement to afford 1-(3-hydroxybenzo[*b*]thiophen-2-yl)ethanone **5g** and 1-(3-hydroxybenzo[*b*]thiophen-2-yl)propan-1-one **5h**, respectively.

With the suitably functionalised benzo[*b*]thiophenes in hand we proceeded with the annulation reactions, representative examples of which are given below. Thus **5c** and **5f** were cyclised in ethanol by bubbling in dry hydrogen chloride gas to afford **6a** and **6b** in 90% and 87% yields, respectively.[10] Compounds **5g** and **5h** were formylated with ethyl formate in the presence of sodium



Scheme 1. Reagents and conditions: (i) LDA (1.5 equiv)/THF/−78 °C to rt; (ii) LDA (2.5 equiv)/THF/R^1CHO/−10–0 °C; (iii) LDA (2.5 equiv)/THF/R^1CHO/−10 °C to rt; (iv) LDA (1.5 equiv)/THF/R^1CHO/−10–0 °C; (v) LDA (1.5 equiv)/THF/R^1CHO/−10 °C to rt; (vi) NaH/THF/R^1COCl/rt; (vii) NaH/THF/HCO_2Et; (viii) ethanol/dry HCl (gas); (ix) PTSA/benzene.

hydride and the formyl derivatives were cyclised in situ to afford **6c** in 85% and **6d** in 89% as mixtures of diastereomers. Dehydration of **6c** and **6d** with *p*-toluenesulfonic acid (PTSA) in dry benzene afforded **7a** and **7b**,[11] respectively, in almost quantitative yields. Pathways leading to the formation of compounds **3**–**7** are summarised in Scheme 1.

We have presented above a convenient method for the synthesis of the benzo[4,5]thieno[3,2-*b*]pyranone system. The synthesis of other members of this series, in order to examine the scope of the reaction, is underway and will be reported latter in due course.

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6. Representative example: (*3-hydroxybenzo*[*b*]*thiophen-2-yl*) *phenyl methanone* **5a**. To a well stirred solution of LDA (2.2 mmol) in anhydrous THF (7 mL) *ortho*-methylsulfanyl benzamide (0.223 g, 1 mmol) in anhydrous THF (4 mL) was added at −10 °C using a syringe. After stirring for 1 h at that temperature, benzaldehyde (0.1 g, 1 mmol) in THF (2 mL) was added, the mixture was warmed to room temperature and kept for 6 h at that temperature. Next, water (25 mL) was added to the reaction mixture and the pH was maintained at 4–5 by dropwise addition of 2 N HCl. The reaction mixture was extracted with chloroform (3 × 20 mL) and the organic layer was washed with water (3 × 25 mL) and dried over Na_2SO_4. Removal of solvent left the crude material, which was purified by column chromatography [eluant: ethyl acetate–petroleum ether (1:19)]. Crystallisation from ethyl acetate–petroleum ether gave a bright yellow solid (0.23 g, 93%). Mp 102 °C. IR ν_{max} (KBr) 3445, 1595 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 13.44 (1H, s, O*H*), 8.04–7.89 (3H, m), 7.72–7.62 (1H, m), 7.57–7.42 (4H, m), 7.36–7.23 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 191.7, 165.3, 140.7, 138.1, 132.5, 130.1, 130.0, 128.6, 128.6, 128.3, 124.6, 123.8, 112.8, 109.4. MS (EI) (*m*/*z*) 254.6, (M^+); Anal. Calcd for $C_{15}H_{10}O_2S$: M (254.30) C, 70.84; H, 3.96. Found: C, 70.93; H, 3.85.
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9. Representative example: *benzo*[*b*]*thiophen-3-yl propionate* **4b**. Liquid compound (0.57 g, 93%). IR ν_{max} (neat) 1764 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.85–7.79 (1H, m), 7.75–7.69 (1H, m), 7.47–7.36 (3H, m), 2.74 (2H, q, *J* 7.5 Hz, C*H*$_2$), 1.37 (3H, t, *J* 7.5 Hz, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.7, 140.7, 136.8, 132.2, 125.1, 124.3, 122.9, 120.4, 111.7, 27.7, 9.2. Anal. Calcd for $C_{11}H_{10}O_2S$: C, 64.05; H, 4.89. Found: C, 64.23; H, 4.73.
10. Representative example: *2-phenyl-2,3-dihydrobenzo*[*4,5*]*thieno*[3,2-*b*]*pyran-4-one* **6a**. Solid, Mp 146 °C (0.25 g, 90%); IR ν_{max} (KBr) 1668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.92 (1H, d, *J* 7.7 Hz), 7.82 (1H, d, *J* 8.1 Hz), 7.56–7.36 (7H, m), 5.80 (1H, dd, *J* 3.3, 13.6 Hz, OC*H*CH$_2$), 3.24–2.90 (2H, m, COC*H*$_2$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 186.6, 161.1, 141.3, 138.3, 130.4, 129.8, 129.4, 129.2, 126.6, 125.1, 124.1, 123.6, 115.5, 83.2, 44.3. Anal. Calcd for $C_{17}H_{12}O_2S$: C, 72.83; H, 4.31. Found: C, 72.74; H, 4.43.
11. Representative example: *3-methylbenzo*[*4,5*]*thieno*[3,2-*b*]*pyran-4-one* **7b**. Solid, Mp 186 °C (0.20 g, 95%); IR ν_{max} (KBr) 1635, 1620 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.03 (1H, d, *J* 7.7 Hz), 7.89–7.86 (2H, m), 7.58–7.46 (2H, m), 2.1 (3H, s, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 190.3, 150.4, 140.3, 137.3, 129.7, 128.8 125.1, 123.8, 122.3, 121.8, 109.3, 11.0. Anal. Calcd $C_{12}H_8O_2S$: C, 66.65; H, 3.73. Found: C, 66.53; H, 3.61.
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