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An Unusual and Highly Efficient Access to Thieno[2,3-b]-benzothiopyran Structures

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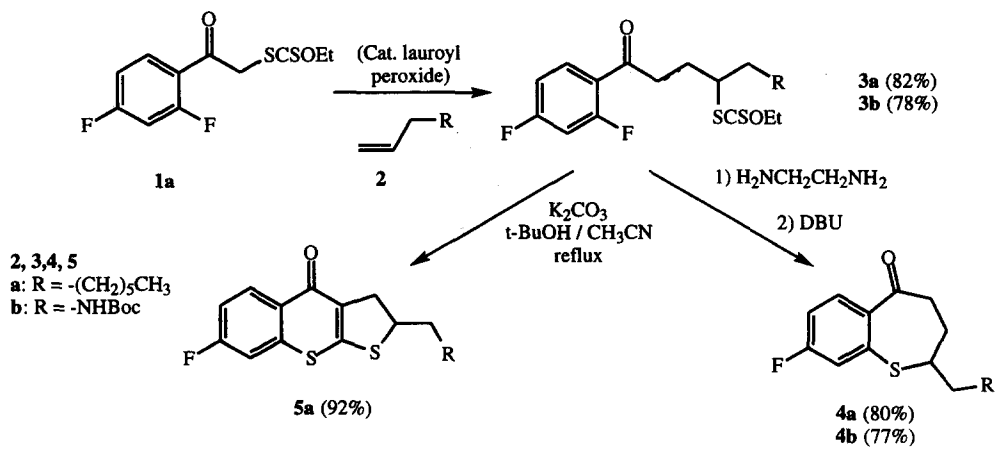
Abstract : Dihydrothieno[2,3-b]-benzothiopyran-4-ones are easily obtained by an intermolecular radical addition to an unactivated olefin using an *S-o*-fluorophenacyl xanthate followed by a novel, base induced domino cyclisation. © 1999 Elsevier Science Ltd. All rights reserved.

As part of our ongoing study of the radical and non radical chemistry of xanthates,[1] we considered the possibility of rapidly constructing the pharmacologically interesting[2] but hitherto not readily accessible[2,3] tetrahydro-1-benzothiepine system. Our three-step approach, outlined in Scheme 1, hinged on a) intermolecular radical addition from 2,4-difluorophenacyl xanthate **1** onto an olefin **2**; b) aminolysis of the xanthate group in the adduct, **3**; and, finally, base induced ring closure. In the event, this sequence could be implemented quite easily as shown by the efficient obtention of compounds **4a,b**. However, when we attempted to carry out the xanthate cleavage and ring closure directly by refluxing the radical adduct **3a** in a suspension of potassium carbonate in a 1:9 mixture of methanol (or t-butanol) / acetonitrile, the reaction took another course leading to the nicely crystalline tricyclic derivative **5a** in nearly quantitative yield.



Scheme 1

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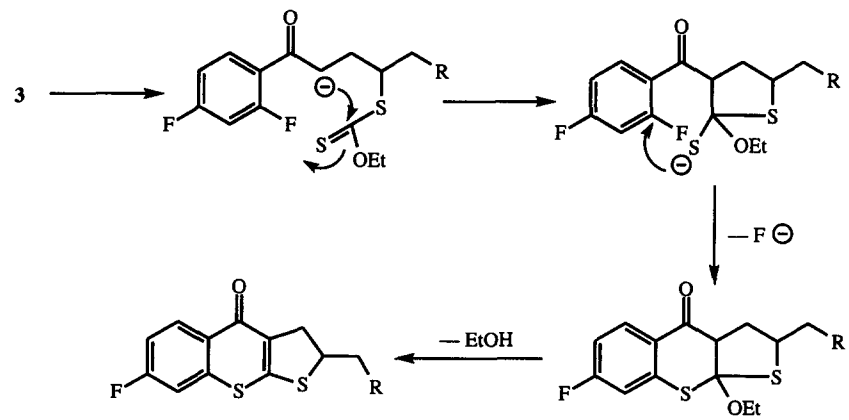
This initially surprising finding can be rationalised by the simplified mechanistic picture displayed in Scheme 2. Under the modified conditions, enolate formation is faster than cleavage of the xanthate group, and the Claisen-like shift of the thiocarbonyl moiety is then followed by nucleophilic aromatic substitution and loss of ethanol to provide the observed product.



Scheme 2

Thieno[2,3-b]-benzothiopyran-4-ones have hardly been described in the literature. Two early patent applications,[4] mentioning their synthesis and use in the preparartion of drugs for treating psychotic disturbances, were followed by a brief study by Majumdar and his co-workers[5] and by a report on the benzo-fused series.[6] In contrast to these previous approaches which lack scope and flexibility, our serendipitous route to this class of heterocyclic system is short, efficient, and fairly general. This is demonstrated by the examples collected in Figure 1 below.

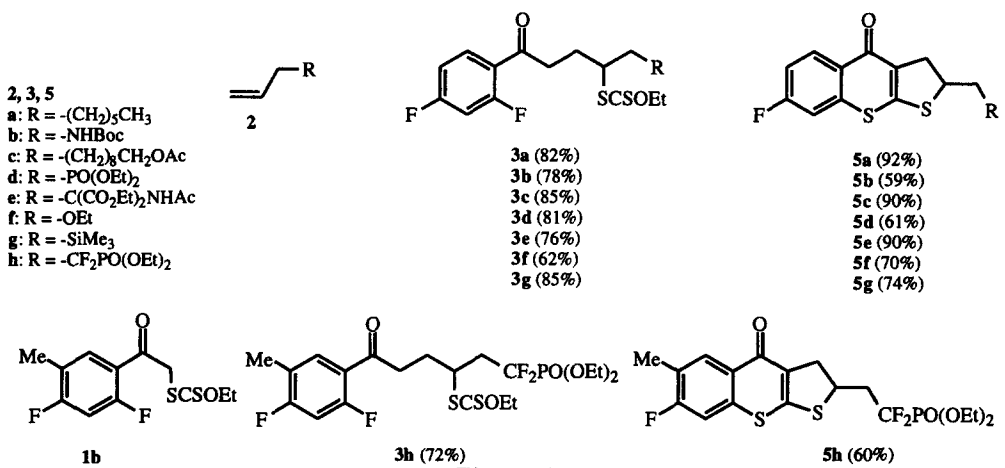
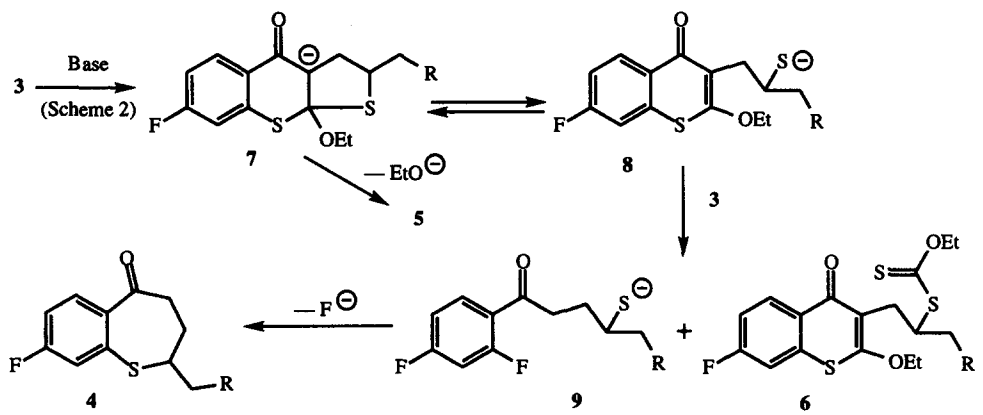


Figure 1

The large variety of substituents that can be introduced in the side-chain results from the power of the first radical addition step which tolerates many functional groups. Adduct **3h** was previously used in a synthesis of a thionucleoside analogue[7] but, under the present conditions, it leads to the corresponding benzothiopyran **5h** in 60% yield. A typical experimental procedure and spectroscopic data for compounds **3a**, **4a**, and **5a** are given in reference 8.

We noticed with some examples (**5b, 5d, 5f-h**) that, under the standard conditions, the yield was lower than usual due to the formation of variable amounts (6-11%) of two other side-products which, in most cases, could not be separated from each other by chromatography. NMR and GC-MS indicated in each instance an equimolar amount of the corresponding benzothiepine **4** derivative and an unexpected xanthate of structure **6**. These structures were eventually confirmed in the case of **3g** where these two minor side products (respectively **4g** and **6g**) could be obtained reasonably pure by flash chromatography.

The origin of these two derivatives may be explained by the reaction manifold in Scheme 3. Intermediate **7**, en route to **5**, can apparently also open to the thiolate **8** which undergoes an intermolecular transfer of an ethoxythiocarbonyl group from the starting material to give **6** and another thiolate **9**. The latter can now only evolve into the benzothiepine structure **4**. Thus, each time a molecule of **6** is produced, it causes the formation of a molecule of **4**; whence an equimolar mixture of the **4** and **6** observed in each case. The importance of these unwanted side reactions can be reduced by simply decreasing the concentration of the starting xanthate **3** in the medium. Indeed, portion-wise addition (one third added every 30 min.) of a solution of **3b** in a acetonitrile / t-butanol to the refluxing suspension of potassium carbonate in the same solvent mixture resulted in a significant improvement in the yield (from 59% to 75%) and a decrease in the amount of side products **4b** and **6b** (from 11% to 5%).



Scheme 3

In summary, we have uncovered an unusual route to a little known class of heterocyclic compounds. This accidental finding also highlights the versatility of the radical xanthate transfer which not only allows the intermolecular formation of a new carbon-carbon bonds but also leads to adducts which, in this case, can be used to prepare either benzothiazepines or dihydrothieno[2,3-b]-benzothiopyran-4-ones, depending on the experimental conditions. Moreover, in the examples we have studied, the presence of the *p*-fluorine opens the way to the introduction of a large variety of substituents (amines, aryloxy, sulfides, etc..) by implementing a second, *intermolecular* nucleophilic aromatic substitution.[9] Finally, the possibility of replacing the fluorine by other leaving groups is being examined, as this will also increase the scope of the process.

References:

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8. *Typical experimental procedures : Synthesis of adducts* **3**:To a degassed, refluxing solution of xanthate **1a** (1 mmol) and olefin **2a** (2 mmol) in cyclohexane (1 ml) was added lauroyl peroxide, first a 5 mole% portion followed by 2 mole% portions every two hours until consumption of the xanthate (7-21 mole% are usually needed). Upon completion of the reaction as judged by TLC, the solvent was removed under partial vacuum and the residue purified by chromatography. Compound **3a** (pale yellow oil): IR (film) 1688, 1610, 1428, 1267, 1213, 1141, 1112, 1098, 1052 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.93 (ddd, J = 8.5, J_{HF} = 8.5, 6.7 Hz, 1H), 6.99-6.81 (m, 2H), 4.62 (q, J = 7.1 Hz, 2H), 3.81 (m, 1H), 3.11 (m, 2H), 2.25 (m, 1H), 2.02 (m, 1H), 1.77-1.65 (m, 2H), 1.52-1.35 (m, 2H), 1.40 (t, J = 7.1 Hz, 3H), 1.28 (bs, 6H), 0.88 (m, 3H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 214.3, 195.6 (d, J_{CF} = 4.0 Hz), 165.6 (dd, J_{CF} = -257.0, 12.0 Hz), 162.7 (dd, J_{CF} = -257.0, 12.5 Hz), 132.6 (m), 122.1 (d, J_{CF} = 13.0 Hz), 112.0 (d, J_{CF} = 21.5 Hz), 104.6 (t, J_{CF} = 26.5 Hz), 69.6, 50.9, 40.5 (d, J_{CF} = 7.0 Hz), 34.6, 31.6, 29.0, 28.4, 26.8, 22.5, 13.9, 13.6; MS (CI, NH_3) *m/z* 406 (M+NH_4^+), 389 (M+H^+), 267 (M-SC(S)OEt). *Synthesis of benzothiepine* **4a** (almost colouless oil): To a degassed solution of 1:1 ethanol/diethyl ether (1 ml) of xanthate **3a** (1 mmol) was added ethylenediamine (0.30 mL, 4 mmol). The reaction mixture was stirred under argon for 20-30 min at room temperature. Water was added, and the mixture was extracted with diethyl ether. The combined organic layers were washed with aqueous ammonium chloride, brine, dried over sodium sulfate, and evaporated. The crude product was taken up in 10 ml of THF and DBU (0.17 ml, 1.1 mmol) was added; the resulting solution was heated to reflux under argon for 4 hours. Aqueous ammonium chloride was added, and the mixture was extracted with diethyl ether. The organic layers were washed with brine, dried over sodium sulfate, and evaporated. The residue was purified by chromatography. Compound **4a** : IR (film) 1681, 1597, 1565, 1473, 1385, 1247, 1209 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84 (dd, J = 8.7, J_{HF} = 6.1 Hz, 1H), 7.16 (dd, J = 2.5, J_{HF} = 9.0 Hz, 1H), 6.94 (ddd, J = 8.7, 2.5, J_{HF} = 8.0 Hz, 1H), 3.35 (ddd, J = 11.5, 11.5, 6.7 Hz, 1H), 2.95 (dddd, J = 12.5, 6.8, 6.8, 5.3 Hz, 1H), 2.68 (ddd, J = 11.5, 5.3, 3.2 Hz, 1H), 2.35 (dddd, J = 12.8, 11.5, 5.3, 5.3 Hz, 1H), 1.94 (dddd, J = 12.8, 12.5, 6.7, 3.2 Hz, 1H), 1.64 (m, 2H), 1.48 (m, 1H), 1.38 (m, 1H), 1.26 (bs, 6H), 0.87 (m, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 201.6, 163.5 (d, J_{CF} = -255.0 Hz), 143.9 (d, J_{CF} = 9.0 Hz), 134.9, 132.4 (d, J_{CF} = 9.5 Hz), 117.1 (d, J_{CF} = 23.0 Hz), 113.6 (d, J_{CF} = 22.0 Hz), 51.3, 40.3, 35.8, 35.3, 31.6, 29.0, 27.4, 22.5, 14.0; MS (CI, NH_3) *m/z* 298 (M+NH_4^+), 281 (M+H^+); Anal. Calcd for $C_{16}H_{21}FOS$; C, 68.53; H, 7.55. Found: C, 68.35; H, 7.48. *Synthesis of benzothiopyran* **5a** (white crystals): Xanthate **3a** (1 mmol) was refluxed in a suspension of potassium carbonate (690 mg, 5 mmol) in a mixture 1:9 of t-butanol / acetonitrile (10 ml) for 2 hours. Water was added, and the mixture was extracted with diethyl ether. The organic layers were washed with brine, dried over sodium sulfate, and evaporated. The residue was essentially pure **5a**; it was simply filtered over silica gel to remove the small amount of coloured impurities before crystallisation. Compound **5a** : mp 84-85 °C (diethyl ether); IR (nujol) 1613, 1583, 1515, 1221, 1174, 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.51 (dd, J = 9.6, J_{HF} = 6.0 Hz, 1H), 7.26-7.15 (m, 2H), 4.05 (m, 1H), 3.52 (dd, J = 16.0, 8.6 Hz, 1H), 3.17 (dd, J = 16.0, 6.5 Hz, 1H), 1.85-1.71 (m, 2H), 1.45-1.21 (m, 8H), 0.89 (m, 3H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 174.2, 163.6 (d, J_{CF} = -255.0 Hz), 152.5, 138.3 (d, J_{CF} = 9.5 Hz), 131.5 (d, J_{CF} = 9.5 Hz), 130.5, 127.3, 115.7 (d, J_{CF} = 22.5 Hz), 111.8 (d, J_{CF} = 24.5 Hz), 52.1, 40.5, 36.5, 31.6, 28.9, 27.9, 22.5, 14.0; MS (CI, NH_3) *m/z* 323 (M+H^+); Anal. Calcd for $C_{17}H_{19}FOS_2$; C, 63.32; H, 5.94. Found: C, 62.91; H, 5.91.
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