Approaches to benzo[*b*]thiophenes by gas-phase pyrolysis of methyl 2-(alkylthio)cinnamates

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Abstract

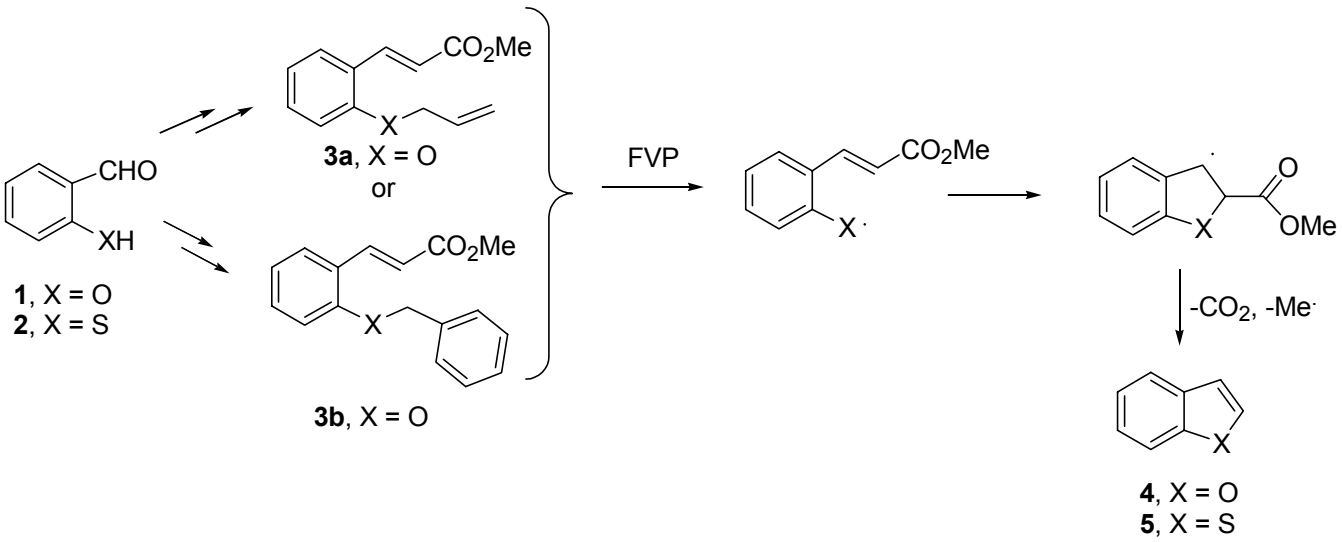
Flash vacuum pyrolysis (FVP) of 3-[2-(t-butylthio)phenyl]propenoate **7** at 700 °C (0.01 Torr) unexpectedly gave a mixture of benzo[*b*]thiophene derivatives **5** (15%) and **8** (21%), and thiocoumarin **9** (28%). Control experiments show that thiophenoxyls (*e.g.* **15**) cyclise efficiently to benzo[*b*]thiophene **5** under similar conditions. It follows that FVP of *S*-t-butyl derivatives of thiophenols, is not an efficient means of generating thiophenoxyl radicals owing to competing hydrogen capture processes.

Keywords: Flash vacuum pyrolysis, radicals, benzothiophenes, thiocoumarins

Introduction

We have shown that benzo[*b*]furans **4** can be generated by flash vacuum pyrolysis (FVP) of 2-(benzyloxy)- or 2-(allyloxy)-cinnamate esters **3** (X = O); these precursors act as sources of the corresponding phenoxyl radical by homolysis of the weak *O*-benzyl and *O*-allyl bonds respectively (Scheme 1).[1,2] Often, phenoxyls and thiophenoxyls show very different properties in the gas-phase[3,4] and so it was of interest to explore whether the strategy could be extended to benzo[*b*]thiophene **5** synthesis. The methods we previously used to prepare benzo[*b*]furan precursors, from salicylaldehyde **1**, are inapplicable in this case because of the poor stability of 2-mercaptobenzaldehyde[5] **2** and so, in the first part of this paper, we discuss whether the *S*-*t*-butyl group can act as a thiophenoxyl radical generator in the gas-phase. Because this aspect of the work was only partially successful, we also present the results of a short feasibility study exploring the use of 2-(benzylthio)cinnamates in this application.

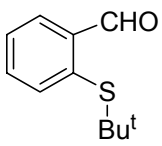
‡ John Cadogan was Chairman of the RSC Heterocyclic Group during the period 1975-1977
§ Hamish McNab was Secretary and Treasurer of the RSC Heterocyclic Group during the period 1989-1992



Scheme 1

Results and Discussion

In order to probe the effectiveness of *S*-t-butyl groups as gas-phase thiophenoxyl radical generators, the cinnamate **7** was readily made under standard Wittig conditions from the commercially available aldehyde **6**. The X-ray crystal structure of **7** has been reported.[6] The electron impact (EI) mass spectrum of **7** apparently provides benzothiophenium species as the base-peak cluster (in agreement with the anticipated thermal behaviour), though the mechanism of formation under EI conditions appears to involve a multi-step process (Scheme 2).



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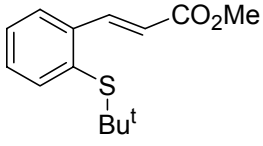

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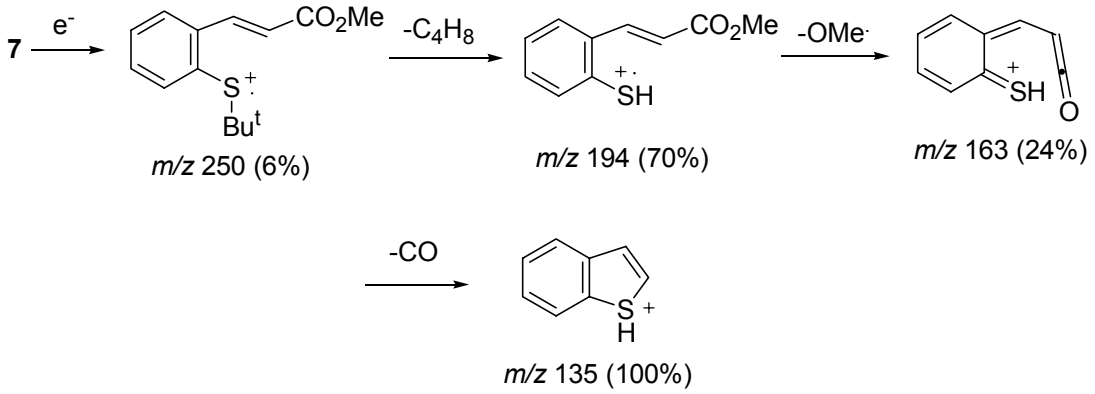
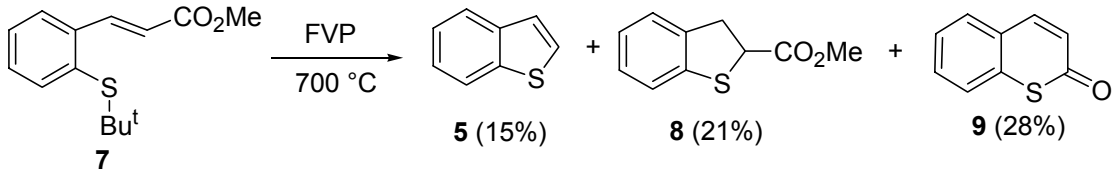


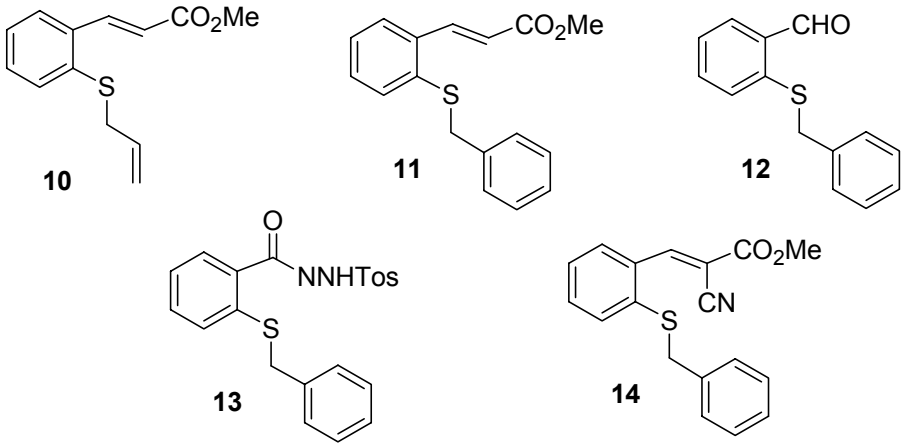
Scheme 2

Under FVP conditions, cleavage of the *S*-t-butyl group of **7** required a marginally higher furnace temperature (700 °C in our apparatus) than *S*-allyl- or *S*-benzyl-derivatives (650 °C), but the product mixture was more complex than expected. Benzo[*b*]thiophene **5** was indeed formed, though only in 15% yield and the major products were the dihydrobenzothiophene **8** (21%) and the thiocoumarin (benzothiopyran-2-one) **9** (28%) (Scheme 3). Compounds **5**, **8** and **9** are known and were identified by their spectra (see Experimental section). The possibility of a rearrangement leading to the isomeric thiochromone (benzothiopyran-4-one) system was readily excluded, since the ^{1}H NMR spectra of thiocoumarins and thiochromones are characteristic.[7] Thus, signals of simple thiocoumarins generally occur at δ_H <8.0 p.p.m whereas thiochromones show a peak at δ_H *ca.* 8.5 p.p.m., due to H(5), deshielded by the neighbouring carbonyl group.[8]

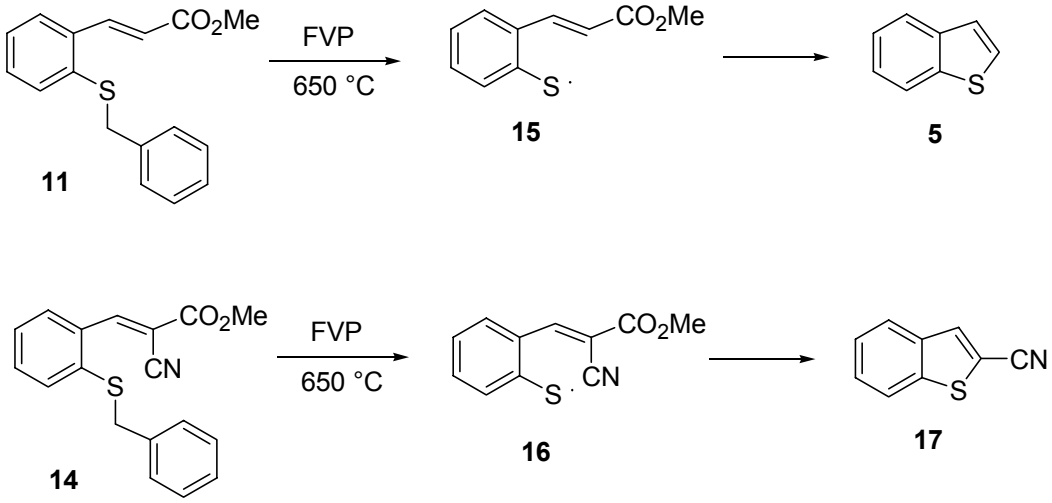


Scheme 3

At this stage in the study it was not clear whether the anomalous thermal behaviour of **7** was due to the t-butyl group acting as an inefficient radical generator, or whether the thiophenoxyl, once generated, behaves differently from the corresponding phenoxyl and is inefficient at cyclising onto propenoate groups. It was therefore important to establish this point by the synthesis and FVP of the allyl- or benzyl-compounds **10** or **11** respectively. At the time this work was carried out, the aldehyde precursor to the allylthio compound **10** was unknown, but 2-benzylthiobenzaldehyde **12** could be made by 5-step synthesis, the key step of which was the McFadyen-Stevens degradation of the hydrazide **13** (see Experimental section).[13] With the aldehyde **12** in hand, Wittig reaction provided the cinnamate **11** (82%) and Knoevenagel condensation gave the cyano-derivative **14** (23%).



Small-scale FVP of **11** and **14** both gave pyrolysates consisting of bibenzyl and a single cyclised product, *viz* the benzothiophenes **5** and **17** respectively. The thiophenoxyls **15** and **16** therefore behave in the same manner as the corresponding phenoxyl to provide the 5-membered ring heterocycles (Scheme 4). The results are therefore clear; the anomalous thermal behaviour of **7** is due to the poor generation of thiophenoxyls from such *S*-t-butyl derivatives.



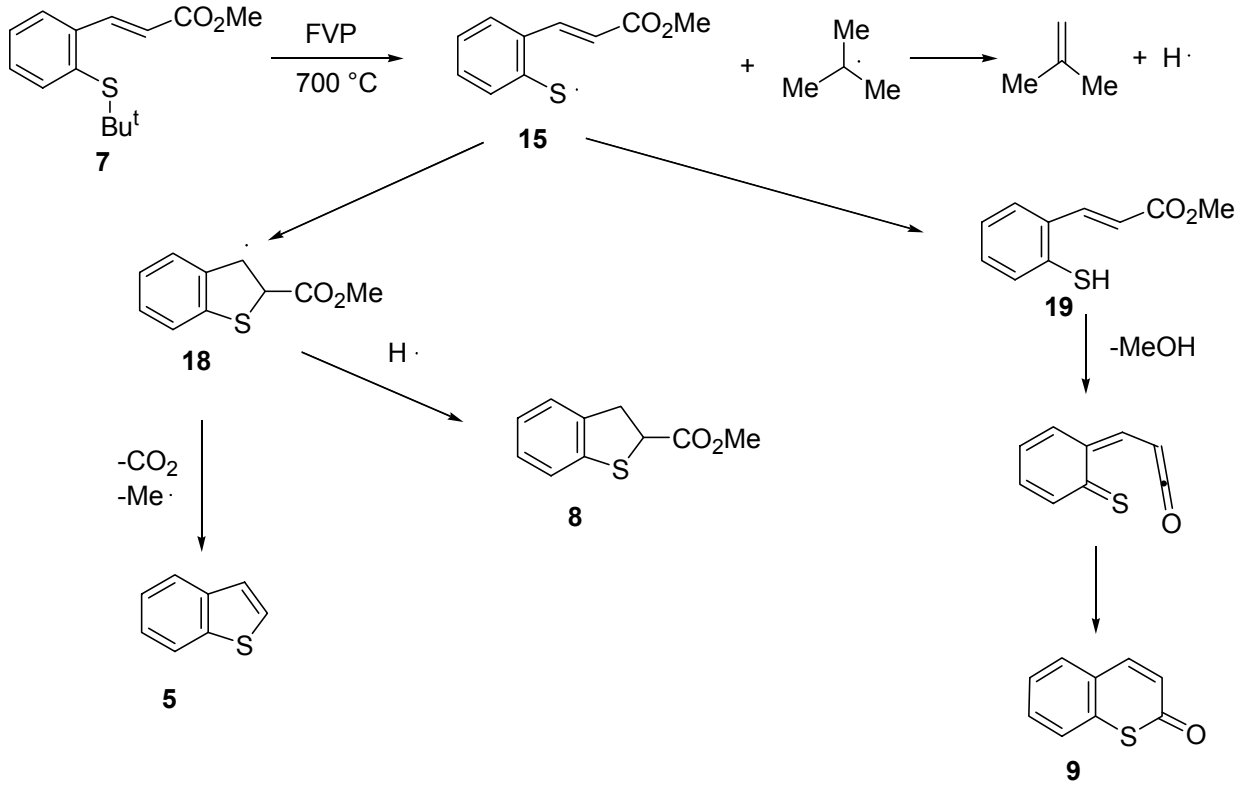
Scheme 4

We rationalise the formation of products **5**, **8** and **9** from FVP of the t-butyl derivative **7**, as shown in Scheme 5. After initial homolysis of the *S*-t-butyl bond, some thiophenoxyl **15** is able to undergo standard cyclisation to provide the benzothiophene **5** obtained in this experiment.

The formation of reduced derivatives such as **8** is unusual under FVP conditions, which normally favour products at high oxidation level. It seems likely that the key intermediate **18** can be diverted, prior to elimination, by hydrogen atom capture to provide **8**. The hydrogen atom flux is provided by the decomposition of the t-butyl radicals to 2-methylpropene. It is also known that FVP of 2-hydroxycinnamates is a good synthetic route to coumarins[14] so we propose that the

thiocoumarin **9** is formed from the thiophenol **19** by an analogous mechanism (Scheme 5). The thiophenol **19** itself may be obtained directly by intramolecular decomposition of the precursor **7**, or by hydrogen capture by the thiophenoxyl **15** prior to cyclisation.

In conclusion, we have shown that pyrolysis of *S*-t-butyl derivatives is a poor route to thiophenoxyl radicals under FVP conditions, probably because an increased hydrogen atom flux compared with allyl and (especially) benzyl precursors allows a number of other pathways to compete with cyclisation. We have also shown that thiophenoxyl radicals, once formed, can in appropriate circumstances cyclise efficiently to benzothiophenes, though realistically a much better route to 2-benzylthiobenzaldehyde **12** (or its *S*-allyl analogue) will be required before the route is synthetically viable. We have therefore addressed this problem[15] and application of the nucleophilic substitution method[15] to benzothiophene precursors, and their subsequent cyclisation reactions, will be reported in a later paper.



Scheme 5

Experimental Section

General Procedures. ^{1}H and ^{13}C NMR spectra are recorded at 250 (or 200) and 63 (or 50) MHz respectively for solutions in [^{2}H]chloroform unless otherwise stated. Coupling constants are quoted in Hz; ^{13}C NMR signals refer to one CH resonance unless otherwise stated.

Methyl 3-[2-(*t*-butylthio)phenyl]propenoate (7). 2-(*t*-Butylthio)benzaldehyde **6** (1.94 g, 0.01 mol) was dissolved in dry dichloromethane (25 cm^3). With stirring, methyl (triphenylphosphoranylidene)acetate (3.34 g, 0.01 mol) was added. Stirring was continued for 48 h. T.l.c. showed a mixture of the product and a trace of starting aldehyde. The mixture was then pre-adsorbed on to silica (5 × weight of mixture), and separated by dry flash chromatography. This gave methyl 3-[2-(*t*-butylthio)phenyl]propenoate **7** (2.37 g, 95%), m.p. 59-60 °C (from hexane) (Found: M^+ 250.1028. $C_{14}H_{18}O_2S$ requires *M* 250.1027) δ_H 8.56 (1H, d, ^3J 16.2), 7.71-7.25 (4H, m), 6.37 (1H, d, ^3J 16.2), 3.80 (3H, s) and 1.26 (9H, s); δ_C 167.16 (quat), 144.34, 139.81 (quat), 139.62, 134.03 (quat), 129.56, 129.27, 126.54, 118.76, 51.54 (CH_3), 47.76 (quat) and 30.91 ($3CH_3$); *m/z* 250 (M^+, 6%), 195 (14), 194 (70), 193 (25), 163 (24), 161 (17), 149 (22), 136 (13), 135 (100), 134 (72), 91 (13), 59 (13), 57 (61) and 41 (23).

2-(Benzylthio)benzoic acid. Thiosalicyclic acid (10.41 g, 0.067 mol) was added to dimethylformamide (30 cm^3) containing anhydrous potassium carbonate (2.01 g, 0.014 mol). Benzyl bromide (22.45 g, 0.13 mol) was added dropwise to the mixture which was then stirred at room temperature for 24 h. After dilution with water (100 cm^3) the product was filtered, washed with ether (3 × 10 cm^3) and recrystallised from ethanol to provide 2-(benzylthio)benzoic acid (11.61 g, 71%) m.p. 190-191 °C (lit.,[13] 188-189 °C); δ_H 10.70 (1H, s, OH), 8.05-7.30 (9H, m) and 4.23 (2H, s).

Ethyl 2-(benzylthio)benzoate[13] 2-(Benzylthio)benzoic acid (11.70 g, 0.048 mol) was heated for 30 min with thionyl chloride (17.10 g, 0.14 mol). Excess thionyl chloride was removed on a water pump with gentle heating. Ethanol (100 cm^3) was added to the acid chloride and heated under reflux for 15 min. The solvent was removed under reduced pressure to give ethyl 2-(benzylthio)benzoate (10.05 g, 77%) m.p. 67-68 °C (lit.,[13] 68-69 °C) δ_H 7.98-7.28 (9H, m), 4.35 (2H, q), 4.14 (2H, s) and 1.36 (3H, t).

2-(Benzylthio)benzhydrazide[13]. Ethyl 2-(benzylthio)benzoate (8.11 g, 0.029 mol) was heated under reflux with hydrazine hydrate (7.80 g, 0.06 mol) with constant stirring for 24 h. After dilution with water (150 cm^3) the solution was extracted with dichloromethane (4 × 50 cm^3). The combined organic extracts were washed with water (3 × 50 cm^3), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give 2-(benzylthio)benzhydrazide (6.14 g, 82%) m.p.161-163 °C (lit.,[13] 163-164 °C) δ_H 10.52 (1H, t, NH), 10.04 (2H, d, NH), 7.55-7.14 (9H, m) and 4.06 (2H, s).

1-[2-(Benzylthio)benzoyl]-(4-tolylsulfonyl)hydrazide (13)[13]. 2-(Benzylthio)benzhydrazide (6.02 g, 0.023 mol) was added to dry pyridine (100 cm^3) and with constant stirring *p*-toluenesulfonyl chloride (5.20 g, 0.027 mol) was slowly added dropwise while the temperature was maintained below 10 °C. The solution was allowed to warm to room temperature and stirred for 3 h, then heated at 75 °C for a further 1 h. The hot solution was poured into a mixture of hydrochloric acid (175 cm^3) and ice (300 g). The precipitate was collected by filtration and washed with ether (3 × 10 cm^3). The remaining solution was extracted with dichloromethane (4 × 50 cm^3). The combined organic extracts were washed with water (3 × 50 cm^3), dried ($MgSO_4$) and the solvent was removed under reduced pressure leaving **13** (5.69 g, 60%) m.p. 144-145 °C

(lit.,[13] 145-146 °C) δ_H 10.48 (1H, d, NH), 10.00 (1H, d, NH), 7.76-7.21 (13H, m), 4.13 (2H, s) and 3.41 (3H, s).

2-(Benzylthio)benzaldehyde (12)[13]. A solution of 1-[2-(benzylthio)benzoyl]-4-tolylsulfonylhydrazide **13** (4.68 g, 0.01 mol) in freshly distilled ethylene glycol (38 cm^3) was heated to 160 °C, then anhydrous sodium carbonate (2.40 g, 0.028 mol) was added. The mixture was heated until evolution of gas had ceased (2-3 min). The solution was cooled and diluted with water (60 cm^3) and extracted with ether (4 × 60 cm^3). The combined organic extracts were washed with water (3 × 50 cm^3), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to provide **12** (2.07 g, 91%) m.p. 68-69 °C (lit.,[13] 75-76 °C) δ_H 10.24 (1H, s), 7.82-7.25 (9H, m) and 4.12 (2H, s).

Methyl 3-[2-(benzylthio)phenyl]propenoate (11). 2-(Benzylthio)benzaldehyde (0.68 g, 3 mmol) was added to dry dichloromethane (50 cm^3), with stirring, methyl (triphenylphosphoranylidene)acetate (1.00 g, 3 mmol) was added and the solution stirred at room temperature for 21 h. The solvent was evaporated under reduced pressure and the mixture was separated using dry flash column chromatography on silica. A 5% ethyl acetate/ hexane solution was used to elute the column. Fractions showing a single spot were combined and the solvent evaporated under reduced pressure to provide methyl 3-[2-(benzylthio)phenyl]propenoate **11** (0.70 g, 82%)[16] m.p. 104-106 °C (Found: C, 71.95; H, 5.75. $C_{17}H_{16}O_2S$ requires C, 71.85; H, 5.65%) δ_H 8.21 (1H, d, ^3J 15.9), 7.56-7.21 (9H, m), 6.32 (1H, d, ^3J 15.9), 4.03 (2H, s), and 3.81 (3H, s); δ_C 166.99 (quat), 142.15, 136.75 (quat), 136.57 (quat), 135.92 (quat), 132.21, 130.05, 128.79 (2CH), 128.32 (2CH), 127.28, 127.14, 126.88, 119.43, 51.58 (CH_3) and 39.82 (CH_2); *m/z* 284 (M^+, 7%), 193 (27), 149 (36), 134 (56) and 91 (100).

Methyl 2-cyano-3-[2-(benzylthio)phenyl]propenoate (14). 2-(Benzylthio)benzaldehyde (0.68 g, 3 mmol) and methyl cyanoacetate (0.29 g, 3 mmol) were added to toluene (15 cm^3). Piperidine (5 drops) and acetic acid (5 drops) were then added and the solution was stirred at room temperature for 21 h. The solution was diluted with water (20 cm^3) and extracted with dichloromethane (3 × 10 cm^3). The combined organic extracts were washed with water (3 × 10 cm^3), dried ($MgSO_4$) and the solvent was removed under reduced pressure. Methyl 2-cyano-3-[2-(benzylthio)phenyl]propenoate **14** (0.61 g, 65%) was obtained and could be recrystallised from methanol m.p. 61-63 °C (Found: C, 69.6; H, 4.95; N, 4.25. M^+ 309.0823. $C_{18}H_{15}NO_2S$ requires C, 69.9; H, 4.85; N, 4.55%. *M* 309.0823) δ_H 8.65 (1H, s), 8.08 (1H, m), 7.58-7.10 (8H, m), 4.02 (2H, s) and 3.92 (3H, s); δ_C 162.48 (quat), 153.17, 138.63 (quat), 136.44 (quat), 133.54 (quat), 133.14, 132.66, 129.11, 128.80 (2CH), 128.55 (2CH), 127.84, 127.43, 104.14 (quat), 53.19 (CH_3) and 40.59 (CH_2) (one quaternary overlapping); *m/z* 309 (M^+, 15%), 248 (13), 192 (25), 159 (9) and 91 (100).

Pyrolysis experiments

FVP experiments were carried out by distillation of the substrate *in vacuo* through an electrically heated silica furnace tube (35 × 2.5 cm) and products were trapped in a U-tube, cooled by liquid nitrogen at the exit point of the furnace. Results are quoted as follows: substrate, quantity, furnace temperature (T_f), inlet temperature (T_i), pressure (P), pyrolysis time (t) and products. Small scale pyrolyses were analysed by NMR spectroscopy.

FVP of methyl 3-[2-(*t*-butylthio)phenyl]propenoate (7). Methyl 3-[2-(*t*-butylthio)phenyl]propenoate **7** (0.560 g, 2.2 mmol), (T_f 700 °C, T_i 80-100 °C, P 0.01 Torr, t 15 min) gave three products which were separated by dry-flash chromatography: benzo[*b*]thiophene **5** (0.043 g, 15%) b.p. 90-94 °C (15 Torr) [lit.,[17] b.p. 86-88 °C (11 Torr)] δ_H 8.05-7.91 (2H, m) and 7.57-7.41 (4H, m); δ_C 139.54 (quat), 139.41 (quat), 126.08, 124.01, 123.97, 123.64, 123.42 and 122.29; *m/z* 134 (M^+, 100%) and 43 (48): 2-(carbomethoxy)-2,3-dihydrobenzothiophene **8** (0.090 g, 21%), b.p. 125-130 °C (0.1 Torr) (Found: M^+ 194.0409. $C_{10}H_{10}O_2S$ requires *M* 194.0401) δ_H 7.22-7.01 (4H, m), 4.46 (1H, dd, ^2J 8.8, ^3J 5.8), 3.76 (3H, s), 3.67 (1H, dd, ^3J 5.8 and 0.9), 3.51 (1H, dd, ^2J 8.8, ^3J 0.9) (*c.f.* ref 18); δ_C 172.04 (quat), 138.90 (quat), 138.11 (quat), 127.46, 124.56, 124.40, 121.43, 52.55 (CH_3), 48.30 and 37.98 (CH_2); *m/z* 194 (M^+, 33%), 136 (12), 135 (100), 134 (29) and 91 (21): *2H*-1-benzothiopyran-2-one **9** (0.102 g, 28%) m.p. 63-67 °C (from ethyl acetate) (lit.,[19] 79-80 °C) (Found: M^+ 162.0137. C_9H_6OS requires *M* 162.0139) δ_H 7.69 (1H, d, ^3J 10.6), 7.61-7.32 (4H, m) and 6.52 (1H, d, ^3J 10.6); δ_C 185.23 (quat), 143.62, 137.30 (quat), 131.40, 129.74, 126.28, 125.87 (quat), 125.67 and 123.89; *m/z* 162 (M^+, 74%), 135 (28), 134 (100) and 67 (11).

FVP of methyl 3-[2-(benzylthio)phenyl]propenoate (11). FVP of methyl 3-[2-(benzylthio)phenyl]propenoate (0.016 g, 0.056 mmol), (T_f 650 °C, T_i 150 °C, P 1×10^{-3} Torr, t 20 min) gave a pyrolysate which was washed into the trap with $CDCl_3$. The ^1H NMR spectrum showed that benzo[*b*]thiophene **5** was the only significant product δ_H 7.91-7.71 (2H, m) and 7.45-7.18 (4H, m, but including overlapping bibenzyl signals) (data consistent with literature values[20]). Bibenzyl was identified in the crude pyrolysate by its characteristic singlet at δ_H 2.93 (4H, s).[21]

FVP of methyl 2-cyano-3[2-(benzylthio)phenyl]propenoate (14). The products from FVP of methyl 2-cyano-3[2-(benzylthio)phenyl]propenoate (0.018 g, 0.058 mmol), (T_f 650 °C, T_i 150 °C, P 1×10^{-3} Torr, t 25 min) were washed into the trap with $CDCl_3$ and the presence of benzo[*b*]thiophene-2-carbonitrile **17** was confirmed by its ^1H NMR spectrum δ_H 7.91-7.84 (3H, m) and 7.58-7.43 (2H, m) (consistent with literature values[22]). Bibenzyl [δ_H 2.92 (4H, s)[21]] was also present.

Acknowledgements

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References and Footnotes

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8. During the course of this work, it was discovered that the NMR spectra reported by Panetta and Rapoport[9] from products obtained by reacting thiophenol with propiolic orthoesters and subsequent cyclisation, are those of thiochromones, not thiocoumarins as claimed. It follows that the reactions of thiophenols with propiolic orthoesters must take a different course from those of phenols,[10] probably owing the much harder nature of the nucleophile in the latter case. Finally, the structures of the intermediate 2-mercaptocinnamates[9] must be revised to corresponding β-(arylthio)acrylates – and available NMR data for the parent compound are also consistent with this interpretation.[11] In the light of these structural revisions, it now becomes clear why the cyclisation step in the phenol case takes place in the presence of base,[10] whereas the 'analogous' cyclisation of the thiophenol-derived intermediate is acid-catalysed,[9] – standard conditions for the formation of benzothiopyran-4-ones from β-(arylthio)acrylates.[12]
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