Synthesis of Thiocoumarins from Acrylic and Propiolic Ortho Esters and Benzenethiols

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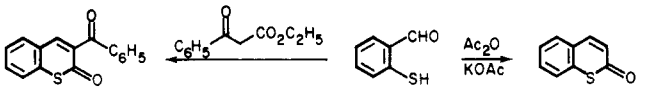
A new, versatile thiocoumarin synthesis has been developed that is based on the Claisen rearrangement of allylic or propargylic aryl ethers, which are at the same time monothio ortho esters. It proceeds by first exchange between a benzenethiol and an orthoacrylate or orthopropiolate. The resulting arylthio ortho ester then thermally rearranges to the *o*-mercaptodihydrocinnamic or *o*-mercaptocinnamic acid. Ring closure leads to the thiocoumarins, after dehydrogenation in the case of the acrylates and directly in the case of the propiolates.

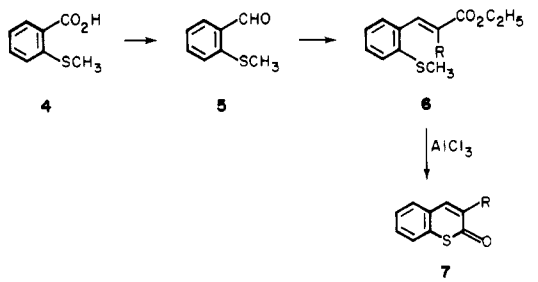
Thiocoumarins have recently been extensively reviewed.[1] Their numerous applications as pharmaceuticals, in plant and animal treatment, and as photoactive agents have been comprehensively noted. Many synthetic routes have been followed to the thiocoumarins; however, the methods are generally of low yield and require many steps and are limited in scope.

This synthetic difficulty derives primarily from the fact that the Pechmann reaction, the most widely applied route to coumarins, has very limited utility for thiocoumarins. Therefore, ortho-substituted benzenethiols, themselves prepared through many steps, have been required. For example, the unstable intermediate 2-mercaptobenzaldehyde (1) has been used to prepare thiocoumarin (2) in low yield under Perkin conditions.[2] If aldehyde 1 is condensed with an active methylene derivative followed by acid-catalyzed cyclization, 3-substituted thiocoumarins can be obtained in fair yield. Thus 3-benzoylthiocoumarin (3) was synthesized from 1 and ethyl benzoylacetate.[1]



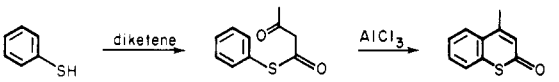
3 1 2

However, since 2-mercaptobenzaldehyde (1) is not readily available and is prone to resinification on storage, the S-protected 2-(methylthio)benzaldehyde (5), prepared from 2-mercaptobenzoic acid (4), has been used.[3] Reformatsky reaction with 5 yielded upon dehydration the corresponding cinnamic ester 6. Thioether cleavage and cyclization could be effected with aluminum chloride or phosphoryl chloride to give the corresponding thiocoumarin 7. Similarly, aluminum chloride cyclization of thioester 8, prepared from thiophenol (9) and diketene, gave 4-methylthiocoumarin (2c) in 38% yield.[4]



4 5 6 7

Since the methods for synthesizing thiocoumarins are seriously limited, we have explored new routes to this ring system. The method we have developed is based on a new application of the Claisen rearrangement that we used to synthesize coumarins.[5] It utilizes acrylic and propiolic



9 8 2c

ortho esters, which on exchange with phenols yield allyl or propargyl aryl ethers in which the allylic or propargylic α-carbon is fully oxygenated. Substitution of benzenethiols for phenols leads to completely parallel reactions. This general route to thiocoumarins is illustrated in Scheme I. To demonstrate its utility we have prepared thiocoumarin (2), 4-methylthiocoumarin (2c), 6-methylthiocoumarin (2b), and 7-methoxythiocoumarin (2a).

Triethyl orthoacrylate (14) and triethyl orthopropiolate (15) were both readily prepared from triethyl orthopropionate.[6] Both ortho esters have successfully undergone exchange and Claisen rearrangement with many phenols,[5] and similar behavior was anticipated with thiophenols. Thus triethyl orthopropiolate (15) and thiophenol (9) were heated in refluxing *p*-cymene containing pivalic acid. Chromatography of the reaction mixture and spectral analysis indicated that exchange had occurred. Indeed, under the same conditions, reaction proceeded through the intermediate *S*-phenyl *O,O*-diethyl orthothiopropiolate and Claisen rearrangement to give directly ethyl 2-mercaptocinnamate (11) in 75% yield. Hydrolysis of cinnamate 11 and ring closure to thiocoumarin (2) proceeded in 38% overall yield on the basis of thiophenol as shown in Scheme I.

We then applied our new route to thiocoumarins to triethyl orthopropiolate (15) and two additional thiophenols, 3-methoxythiophenol (9a) and 4-methylthiophenol (9b). The reactions proceeded in identical fashion through the corresponding intermediates of Scheme I. 7-Methoxythiocoumarin (2a) and 6-methylthiocoumarin (2b) were thus prepared from each thiophenol in 30% and 35% overall yield, respectively (Table I).

Another possibility offered by the orthopropiolate was its ready extension to the synthesis of 4-substituted thiocoumarins. Conversion of orthopropiolate 15 to a substituted acetylenic ortho ester can be realized by generating the anion of 15 followed by addition of an electrophile. Quenching of this anion with methyl iodide gave triethyl

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(4) Nakazumi, H.; Asada, A.; Kitao, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2046.
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(6) Stetter, H.; Uerdingen, W. *Synthesis* **1973**, 207.

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Scheme I. Preparation of Thiocoumarins from Ortho Esters and Benzenethiols

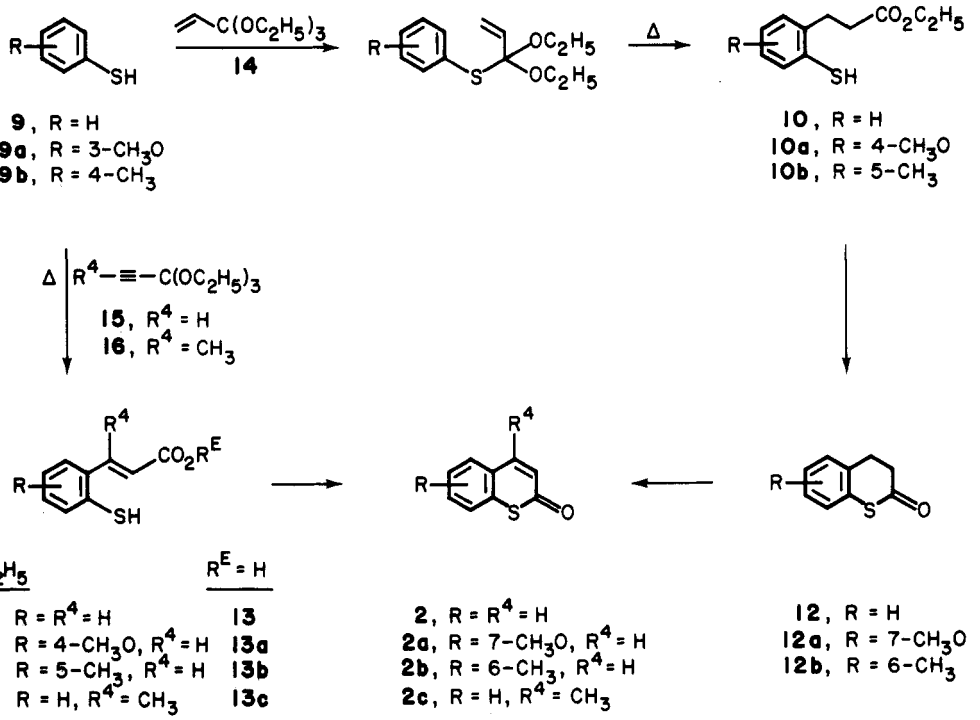

Table I. Preparation of Thiocoumarins 2 from Ortho Esters 14-16 and Benzenethiols 9

ortho ester	thiophenol	thiocoumarin	overall yield, %
$C(OC_2H_5)_3$ 14	9	2	41
$\equiv-C(OC_2H_5)_3$ 15	9	2	38
$CH_3-\equiv-C(OC_2H_5)_3$ 16	9	2c	37
15	9a	2a	30
15	9b	2b	35

orthobut-2-ynoate (16) in quantitative yield. Treating 16 with thiophenol (9) in refluxing *p*-cymene containing pivalic acid gave the β-methylcinnamate 11c in 72% yield. Then hydrolysis of 11c followed by ring closure gave 4-methylthiocoumarin (2c) in 37% overall yield. Although we have presented only one example of this extension to a 1-thiopyrone-substituted thiocoumarin, it appears that the method has considerable generality.

Thiophenol (9) was also treated with triethyl orthoacrylate (14) in refluxing *p*-cymene containing pivalic acid to give, after chromatography, a 94% yield of ethyl 2-mercaptodihydrocinnamate (10). Heating 10 in refluxing diphenyl ether with a catalytic amount of *p*-toluenesulfonic acid resulted in ring closure to dihydrothiocoumarin (12). 7-Methoxydihydrothiocoumarin (12a) and 6-methyldihydrothiocoumarin (12b) have also been prepared in this fashion. Dehydrogenation was effected with 10% Pd/C in refluxing diphenyl ether to afford the corresponding thiocoumarins.

In summary, new, versatile, high-yield processes have been developed for the synthesis of thiocoumarins. The methods proceed from readily available educts and afford thiocoumarins that can be variously substituted in the benzene or thiopyrone nuclei.

Experimental Section

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded in chloroform on a Perkin-Elmer 137 spectrophotometer. ^1H NMR (internal Me_4Si) spectra were taken in $CDCl_3$ on a Varian EM-390 instrument. UV spectra were taken in 95% ethanol on a Cary 118 spectrometer. Thin-layer chromatography was done on E. Merck silica gel 60F-254 plates (0.2 mm), and preparative thin-layer chromatography was done on Analtech silica gel GF plates (2 mm). Organic solutions were evaporated in a Berkeley rotary evaporator. High-resolution mass spectra were obtained on a modified Kratos/AEI HS902 mass spectrometer. Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, Unversity of California, Berkeley, CA.

Ethyl 2-Mercaptocinnamate (11). A solution of 2.0 g (18 mmol) of freshly distilled thiophenol (9), 3.27 g (19 mmol) of triethyl orthopropiolate (15),[6] and 1.60 g (15 mmol) of pivalic acid in 10 mL of *p*-cymene was heated at reflux for 26 h. The reaction mixture was cooled to room temperature and then column chromatographed (hexane/Et_2O, 9/1) on silica gel to give 2.79 g (75% yield) of 11 as a pale-yellow liquid: IR 3000, 1720, 1600, 1495, 1440 cm^{-1}; NMR δ 7.65 (d, 1 H), 7.1–7.45 (m, 4 H), 5.55 (d, 1 H), 4.05 (q, 2 H), 1.15 (t, 3 H); MS calcd for $C_{11}H_{12}O_2S$ *m/e* 208.0558 (M^+), found 208.0560.

The following cinnamates 11a–11c were prepared in identical fashion.

Ethyl 2-mercapto-4-methoxycinnamate (11a): 69% yield; IR 3000, 1705, 1640, 1600, 1500, 1360 cm^{-1}; NMR δ 7.75 (d, 1 H), 6.8–7.3 (m, 3 H), 5.65 (d, 1 H), 4.1 (q, 2 H), 3.75 (s, 3 H), 1.2 (t, 3 H); MS calcd for $C_{12}H_{14}O_3S$ *m/e* 238.0664 (M^+), found 238.0669.

Ethyl 2-mercapto-5-methylcinnamate (11b): 73% yield; IR 3000, 1715, 1590, 1500 cm^{-1}; NMR δ 7.75 (d, 1 H), 6.9–7.4 (m, 3 H), 5.5 (d, 1 H), 4.05 (q, 2 H), 2.3 (s, 3 H), 1.15 (t, 3 H); MS calcd for $C_{12}H_{14}O_2S$ *m/e* 222.0714 (M^+), found 222.0709.

Ethyl 2-mercapto-β-methylcinnamate (11c): 72% yield from thiophenol (**9**) and triethyl orthobut-2-ynoate (**16**);[5] IR 3200, 3000, 1710, 1600, 1470, 1430 cm^{-1}; NMR δ 7.33 (m, 4 H), 5.2 (s, 1 H), 3.95 (q, 2 H), 2.33 (s, 3 H), 1.1 (t, 3 H); MS calcd for $C_{12}H_{16}O_2S$ *m/e* 224.0871 (M^+), found 224.0860.

2-Mercaptocinnamic Acid (13). To ethyl 2-mercaptocinnamate (**11**; 1.00 g, 5.4 mmol) dissolved in 10 mL of 95% EtOH was added 0.75 g (13.4 mmol) of KOH. The reaction mixture was heated at reflux for 2 h, then cooled to 25 °C, and acidified with 5% aqueous HCl. The aqueous phase was extracted with ether (3 × 20 mL), and the combined organic fractions were washed with H_2O (20 mL) and brine (20 mL), dried (Na_2SO_4), and evaporated. An 87% yield (0.85 g) of crystalline **13** was obtained: mp 128–129 °C; UV λ_{max} 250 nm (ε 7350), 275 (9700); NMR δ 7.8 (d, 1 H), 7.15–7.45 (m, 4 H), 5.5 (d, 1 H). Anal. Calcd for $C_9H_8O_2S$: C, 60.0; H, 4.5. Found: C, 60.2; H, 4.6.

The following cinnamic acids **13a–13c** were prepared in identical fashion.

2-Mercapto-4-methoxycinnamic Acid (13a): 78% yield; mp 98–99 °C from hexane; UV λ_{max} 215 nm (ε 13 670), 260 (9940), 278 (13 770); NMR δ 7.85 (d, 1 H), 6.9–7.3 (m, 3 H), 5.6 (d, 1 H), 3.8 (s, 3 H). Anal. Calcd for $C_{10}H_{10}O_3S$: C, 57.1; H, 4.8. Found: C, 57.1; H, 4.8.

2-Mercapto-5-methylcinnamic Acid (13b): 90% yield; mp 137–138 °C from hexane; UV λ_{max} 217 nm (ε 14 240), 254 (12 950), 278 (16 180); NMR δ 7.85 (d, 1 H), 7.25 (m, 3 H), 5.5 (d, 1 H), 2.35 (s, 3 H). Anal. Calcd for $C_{10}H_{10}O_2S$: C, 61.8; H, 5.2. Found: C, 62.0; H, 5.2.

2-Mercapto-β-methylcinnamic Acid (13c): 100% yield; mp 182–183 °C from hexane; UV λ_{max} 215 nm (ε 11 470), 237 (9880), 276 (9575); NMR δ 7.4 (s, 4 H), 5.2 (s, 1 H), 2.4 (s, 3 H). Anal. Calcd for $C_{10}H_{10}O_2S$: C, 61.8; H, 5.2. Found: C, 61.8; H, 5.3.

Thiocoumarin (2). 2-Mercaptocinnamic acid (**13**; 50 mg, 0.27 mmol) was stirred with 7 mL of polyphosphoric acid at 100–105 °C for 35 min. The reaction mixture was poured on ice, the aqueous phase was extracted with ether (4 × 25 mL), and the combined, dried (Na_2SO_4) organic phase was evaporated. Preparative thin-layer chromatography ($CHCl_3/CH_3OH$, 98/2) of the residue afforded 25 mg (57% yield) of crystalline **2**: mp 77–78 °C (lit.[2] mp 78–81 °C); UV λ_{max} 220 nm (ε 18 210), 247 (17 730), 274 (5530), 287 (4575), 335 (10 200); NMR δ 8.5 (m, 1 H), 7.8 (d, 1 H), 7.45–7.55 (m, 3 H), 6.95 (d, 1 H); MS calcd for C_9H_6OS *m/e* 162.0139 (M^+), found 162.0142.

The following coumarins **2a–2c** were prepared in identical fashion.

7-Methoxythiocoumarin (2a): 54% yield from 2-mercapto-5-methoxycinnamic acid (**13a**); mp 102–103 °C (lit.[7] mp 106–107 °C); UV λ_{max} 229 nm (ε 17 400), 260 (16 040), 267 (16 270), 287 (5875), 333 (7120); NMR δ 8.45 (d, 1 H), 7.65 (d, 1 H), 6.8–7.1 (m, 3 H), 3.85 (s, 3 H); MS calcd for $C_{10}H_8OS$ *m/e* 192.0245 (M^+), found 192.0248.

6-Methylthiocoumarin (2b): 52% yield from 2-mercapto-5-methylcinnamic acid (**13b**); mp 84–85 °C (lit.[7] mp 86–88 °C); UV λ_{max} 224 nm (ε 6250), 246 (7050), 277 (1765), 298 (1440), 340 (3125); NMR δ 8.4 (br s, 1 H), 7.75 (d, 1 H), 7.45 (br s, 2 H), 6.95 (d, 1 H), 2.4 (s, 3 H); MS calcd for $C_{10}H_8OS$ *m/e* 176.0296 (M^+), found 176.0299.

4-Methylthiocoumarin (2c): 49% yield from 2-mercapto-β-methylcinnamic acid (**13c**); mp 121–122 °C (lit.[4] mp 124–127 °C); UV λ_{max} 223 nm (ε 1150), 245 (1680), 274 (305), 286 (200), 335 (845); NMR δ 8.45 (m, 1 H), 7.5 (m, 3 H), 6.8 (br s, 1 H), 2.4 (s, 3 H); MS calcd for $C_{10}H_8OS$ *m/e* 176.0296 (M^+), found 176.0297.

Ethyl 2-Mercaptodihydrocinnamate (10). A solution of 0.1 g (0.9 mmol) of freshly distilled thiophenol (**9**), 0.23 g (1.8 mmol) of triethyl orthoacrylate (**14**),[6] and 0.046 g (0.45 mmol) of pivalic acid in 2 mL of *p*-cymene was heated at reflux for 20 h. The reaction mixture was cooled to 25 °C, 5 mL of ether was added, and the organic phase was washed with H_2O (2 × 5 mL) and brine (5 mL) and evaporated after drying (K_2CO_3) to afford 0.195 g of crude product. Preparative thin-layer chromatography (hexane/Et_2O, 4/1) on silica gel gave 0.18 g (94%) of **10** as a yellow oil: IR 3020, 1730, 1600 cm^{-1}; NMR δ 6.9–7.3 (m, 4 H), 3.95 (q, 2 H), 3.0 (t, 2 H), 1.15 (t, 3 H).

The following dihydrocinnamates **10a** and **10b** were prepared in identical fashion.

Ethyl 2-mercapto-4-methoxydihydrocinnamate (10a): 86% yield; IR 3000, 1740, 1590, 1460 cm^{-1}; NMR δ 6.5–7.2 (m, 3 H), 3.9 (q, 2 H), 3.6 (s, 3 H), 3.0 (t, 2 H), 2.45 (t, 2 H), 1.1 (t, 3 H); MS calcd for $C_{12}H_{16}O_3S$ *m/e* 240.0820 (M^+), found 240.0822.

Ethyl 2-mercapto-5-methyldihydrocinnamate (10b): 93% yield; IR 3000, 1740, 1495, 1360 cm^{-1}; NMR δ 7.2 (m, 3 H), 4.0 (q, 2 H), 3.0 (t, 2 H), 2.5 (t, 2 H), 2.25 (s, 3 H), 1.2 (t, 2 H); MS calcd for $C_{12}H_{16}O_2S$ *m/e* 224.0871 (M^+), found 224.0869.

Dihydrothiocoumarin (12). Ethyl 2-mercaptodihydrocinnamate (**10**; 0.203 g, 0.95 mmol) was dissolved in 3 mL of diphenyl ether, the solution was heated at reflux for 24 h, and then 10 mg (0.05 mmol) of toluenesulfonic acid was added to the reaction mixture. After 18 h of reflux, the solution was cooled to 25 °C and washed with 1% aqueous NaOH. The aqueous phase was extracted with ether (3 × 20 mL), and the combined organic fractions were washed with H_2O (20 mL) and brine (20 mL), dried (Na_2SO_4), and evaporated. Preparative thin-layer chromatography (hexane) on silica gel gave 0.114 g (73%) of **12** as a yellow oil: NMR δ 8.05 (d, 1 H), 7.05–7.35 (m, 3 H), 3.1 (m, 2 H), 2.8 (m, 2 H); MS calcd for C_9H_8OS *m/e* 164.0296 (M^+), found 164.0295.

The following dihydrothiocoumarins **12a** and **12b** were prepared in identical fashion.

7-Methoxydihydrothiocoumarin (12a): 65% yield from **10a**; NMR δ 8.0–8.1 (m, 1 H), 7.2–7.4 (m, 1 H), 6.75 (s, 1 H), 3.8 (s, 3 H), 3.1–3.3 (m, 2 H), 2.7–3.0 (m, 2 H); MS calcd for $C_{10}H_{10}O_2S$ *m/e* 194.0378 (M^+), found 194.0402.

6-Methyldihydrothiocoumarin (12b): 70% yield from **10b**; NMR δ 7.85 (s, 1 H), 7.0–7.15 (m, 2 H), 2.7–3.2 (m, 4 H), 2.2 (s, 3 H); MS calcd for $C_{10}H_{10}OS$ *m/e* 178.0430 (M^+), found 178.0453.

Thiocoumarin (2) from Dihydrocoumarin (12). To 53 mg (0.32 mmol) of **12** was added 2 mL of diphenyl ether and 6 mg of 10% Pd/C. The mixture was heated at reflux for 26 h. Preparative thin-layer chromatography (hexane/Et_2O, 1/1) on silica gel gave 0.023 g, 44% yield, of **2** and recovered **12** in 30% yield.

Acknowledgment. This research was supported in part by the National Institute of General Medical Sciences, NIH.

Registry No. 2, 1075-14-5; **2a**, 20076-72-6; **2b**, 1199-06-0; **2c**, 21553-94-6; **9**, 108-98-5; **9a**, 15570-12-4; **9b**, 106-45-6; **10**, 81536-21-2; **10a**, 81536-22-3; **10b**, 81536-23-4; **11**, 81536-24-5; **11a**, 81536-25-6; **11b**, 81536-26-7; **11c**, 81536-27-8; **12**, 5962-02-7; **12a**, 81536-28-9; **12b**, 81553-86-8; **13**, 81536-29-0; **13a**, 81536-30-3; **13b**, 81536-31-4; **13c**, 81536-32-5; **14**, 42216-96-6; **15**, 42217-00-5; **16**, 919-27-7.

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