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Regioselective Synthesis of Thieno[3,2-*c*][1]benzopyran-4-ones by Thio-*Claisen* Rearrangement

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Summary. A number of thieno[3,2-*c*][1]benzopyran-4-ones, potential antiinflamatory, antipyretic, and antiallergic drugs, are synthesized in 65–80% yield by thermal thio-*Claisen* rearrangement of 4-allylthio[1]benzopyran-2-ones in refluxing quinoline for 0.5–8.0 h. The 4-allylthio[1]benzopyran-2-ones are in turn prepared in 75–85% yield from 4-mercaptocoumarin and different allylic halides by phase-transfer-catalysed alkylation with *TBAB* or *BTEAC* catalyst in chloroform-aq. NaOH at room temperature.

Keywords. Allylic halides; 4-Mercaptocoumarin; Phase-transfer-catalysed alkylation; [3,3]-Sigmatropic rearrangement; Thio-*Claisen* rearrangement.

Introduction

Coumarin [1] and its derivatives [2] are important for their physiological activities. In continuation of our work on the synthesis of potential bioactive heterocycles [3] containing a coumarin nucleus by means of [3,3]-sigmatropic rearrangement [4] we ended up in the study of the related thio-*Claisen* rearrangement [5]. As compared to oxygen [6] and aza-*Claisen* rearrangements [7] not much work has been carried out on the corresponding thio-*Claisen* rearrangement [8]. Our recent finding [9] on the regioselective synthesis of 2*H*-thiopyrano[3,2-*c*]coumarins by thermal [3,3]-sigmatropic rearrangement prompted us to undertake a study on the thio-*Claisen* rearrangement of 4-allylmercaptocoumarin. Here we report the results.

Results and Discussion

4-Mercaptocoumarin (**1**) was reacted with different allylic halides (**2a**–**2f**) under phase-transfer-catalysis condition [10] using tetrabutylammoniumbromide (*TBAB*) or benzyltriethylammoniumchloride (*BTEAC*) in chloroform-aqueous sodium

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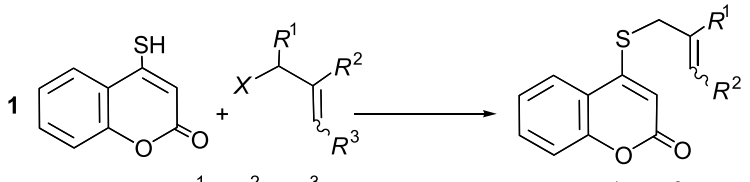


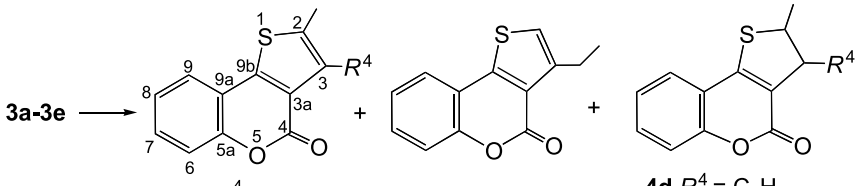
	R^1	R^2	R^3	X
2a	H	H	H	Br
2b	H	H	CH_3	Br
2c	H	H	CH_2Cl	Cl
2d	H	H	C_6H_5	Br
2e	H	Cl	H	Cl
2f	CH_3	H	H	Br

	R^1	R^2
3a	H	H
3b	H	CH_3
3c	H	CH_2Cl
3d	H	C_6H_5
3e	Cl	H

Scheme 1

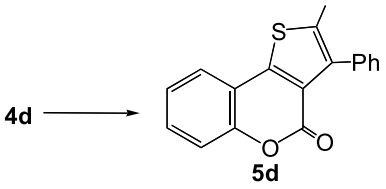
hydroxide (1%) at room temperature for 4 h to give a number of 4-allylthiocoumarin derivatives (**3a**–**3e**) in 75–85% yield, which served as the starting materials (Scheme 1). Halides **2b** and **2f** gave the same sulfide **3b** because of a $S_{N_{2'}}$ displacement in case of **2f**. Compounds **3a**–**3e** were characterised from elemental analyses and spectroscopic data.

No change was observed when **3a** was subjected to heating in chlorobenzene. This was then heated in 1,2-dichlorobenzene. The reaction was monitored by TLC. No change was recorded. Although the α-pyrone ring of coumarin does not involve a π-sextet and was thus expected to undergo thio-*Claisen* rearrangement at lower temperature [11], substrate **3a** did not show any conversion in TLCs when heated in chlorobenzene, 1,2-dichlorobenzene, and even in *N,N*-diethylaniline (216°C). However, when refluxed in quinoline (238°C) for 8 h, **3a** gave **5a**, a white crystalline solid (yield 80%). The ^{1}H NMR spectrum of **5a** exhibited a singlet at $\delta = 2.59$ ppm due to $-CH_3$ and a multiplet at $\delta = 7.28$–7.63 ppm due to four ArH and one =CH. The ^{13}C spectrum of **5a** also strongly supported its structure. The ^{13}C chemical shifts and multiplicity of compound **5a** were assigned by a DEPT experiment. The mass spectrum of **5a** showed a moleculer ion peak at $m/z = 216$ (M^+). It was also characterized from its elemental analysis and spectral data. Substrates **3b** and **3c** were similarly heated in quinoline to afford products **5b** and **5c** in 76 and 70% yield. However, **3d** on similar treatment in quinoline for 2.5 h gave unlike **3a**–**3c**, the dihydro compound **4d** (65%) (Scheme 2).



5a R^4 = H
5b R^4 = CH_3
5c
4d R^4 = C_6H_5

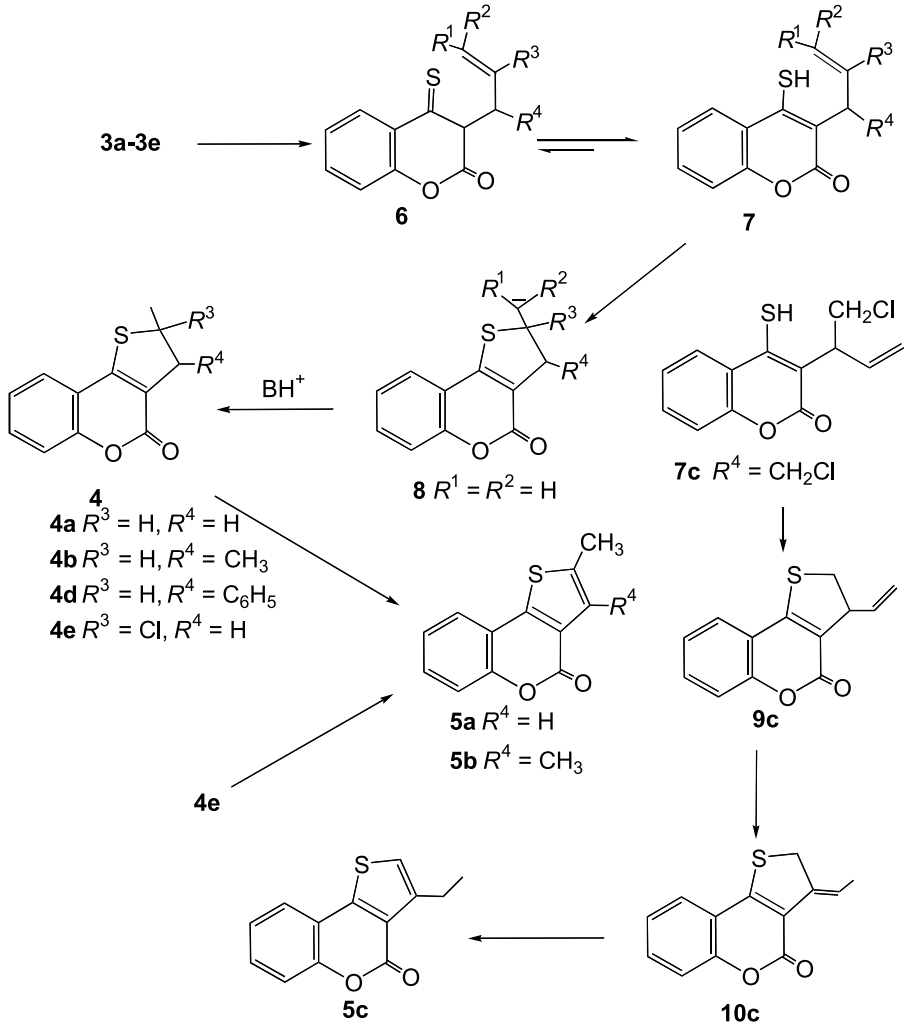
Scheme 2



Scheme 3

Substrates **3a** and **3e** afforded the same product **5a**. Compound **4d** was dehydrogenated to the corresponding aromatic product **5d** by reaction with palladised charcoal in refluxing diphenylether for 2 h (Scheme 3).

The formation of products **5a**–**5c** and **4d** from **3a**–**3e** may be explained by an initial [3,3]-sigmatropic rearrangement followed by enolization to give allylene-thiol **7**. Quinoline base may bring about the cyclization of allylene-thiols **7a**, **7b**, **7d**, and **7e** to **4a**, **4b**, **4d**, and **4e**. Intermediates **4a** and **4b** undergo oxidation to **5a**



Scheme 4

and **5b** under these reaction conditions. Intermediate **4e** eliminates one molecule of HCl to give **5a**. Allylene-thiol **7c** undergoes cyclization to **9c**, which after two 1,3-prototropic shifts furnishes **5c** (Scheme 4).

Thieno[3,2-*c*]coumarins reported earlier by *Makisumi et al.* have been shown to be antiinflamatory, antipyretic, and antiallergic drugs [12]. In conclusion it was seen that all the cases studied so far involve thio-*Claisen* rearrangement and no [1,3]-radical shift [13] was observed. Thus, this reaction provides a simple regioselective synthesis of thieno[3,2-*c*]coumarins.

Experimental

Melting points were measured on a sulfuric acid bath and are uncorrected. UV/Vis absorption spectra were recorded on a UV-VIS Spectrophotometer Shimadzu UV-2401PC (absolute ethanol). IR spectra were run on KBr discs on a Perkin-Elmer 1330 apparatus and FTIR spectrophotometer Perkin-Elmer L120-000A. ^{1}H NMR spectra were recorded in $CDCl_3$ with *TMS* as internal standard on Bruker DPX-300 (300 MHz) and Bruker DPX-500 (500 MHz) spectrometers. The ^{13}C NMR (125 MHz) spectra were recorded on a Bruker DPX-500 spectrometer. Elemental analyses results agreed favourably with the calculated values and mass spectra were recorded at RSIC (CDRI) Lacknow on a JEOL D-300 (EI) instrument. Silica gel (60–120) was obtained from Spectrochem. Extracts were dried over anhydrous Na_2SO_4. Compound **1** was prepared according to Ref. [14].

Alkylation of 4-Mercaptocoumarin

To a mixture of 4 mmol of 4-mercaptocoumarin and 6 mmol of allylic halide in 50 cm^3 of $CHCl_3$ was added a solution of 0.9 mmol of *BTEAC* (0.25 g) in 50 cm^3 1% aq. NaOH and the mixture was stirred for a period of 4 h. This was then diluted with 125 cm^3 of H_2O and extracted with 2×50 cm^3 of $CHCl_3$. The $CHCl_3$ extract was washed successively with 2×50 cm^3 of 2 *N* HCl, 2×50 cm^3 of brine, 50 cm^3 of H_2O, and dried (Na_2SO_4). Chloroform was removed and the residual mass was purified by column chromatography over silica gel. The product was obtained by eluting the column with benzene.

4-(Prop-2-enylthio)[1]benzopyran-2-one (**3a**, $C_{12}H_{10}O_2S$)

Yield 80% (0.7 g); white solid; mp 106°C; ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 3.70$ (d, $J = 6$ Hz, SC**H**$_2$), 5.32–5.47 (m, =C**H**$_2$), 5.89–5.97 (m, SCH$_2$C**H**), 6.18 (s, COC**H**), 7.28–7.76 (m, 4Ar**H**) ppm; IR (KBr): $\bar{\nu} = 1710$, 1590, 1180 cm^{-1}; UV/Vis (*Et*OH): λ_{max} ($\log \varepsilon$) = 213 (4.27), 274 (3.97), 298 (4.02) nm; MS: $m/z = 218$ (M$^+$).

4-(3-Methylprop-2-enylthio)[1]benzopyran-2-one (**3b**, $C_{13}H_{12}O_2S$)

Yield 85% (0.79 g); white solid; mp 92°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.74$ (d, $J = 6.6$ Hz, =CHC**H**$_3$), 3.65 (d, $J = 6$ Hz, SC**H**$_2$), 5.51–5.61 (m, SCH$_2$C**H**=), 5.83–5.94 (m, =C**H**CH$_3$), 6.18 (s, COC**H**), 7.24–7.75 (m, 4Ar**H**) ppm; IR (KBr): $\bar{\nu} = 1700$, 1590, 1170 cm^{-1}; UV/Vis (*Et*OH): λ_{max} ($\log \varepsilon$) = 212 (4.25), 274 (3.97), 299 (4.02) nm; MS: $m/z = 232$ (M$^+$).

4-(4-Chlorobut-2-enylthio)[1]benzopyran-2-one (**3c**, $C_{13}H_{11}ClO_2S$)

Yield 85% (0.91 g); white solid; mp 91°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 3.71$–4.19 (m, SC**H**$_2$ and C**H**$_2$Cl), 5.8–6.06 (m, C**H**=C**H**), 6.16 (s, COC**H**), 7.28–7.74 (m, 4Ar**H**) ppm; IR (KBr): $\bar{\nu} = 1700$, 1595, 1180 cm^{-1}; UV/Vis (*Et*OH): λ_{max} ($\log \varepsilon$) = 212 (4.3), 274 (3.98), 297 (4.01) nm; MS: $m/z = 266$, 268 (M$^+$).

4-(3-Phenylprop-2-enylthio)[1]benzopyran-2-one (**3d**, $C_{18}H_{14}O_2S$)

Yield 80% (0.94 g); white solid; mp 140°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 3.88$ (d, $J = 6$ Hz, SC**H**$_2$), 6.23–6.33 (m, SCH_2C**H** and COC**H**), 6.74 (d, $J = 15$ Hz, PhC**H**), 7.28–7.77 (m, 9Ar**H**) ppm; IR (KBr): $\bar{\nu} = 1717$, 1593, 1193 cm^{-1}; UV/Vis (*Et*OH): λ_{max} ($\log \varepsilon$) = 210 (4.47), 258 (4.22), 285 (4.03), 294 (4.03) nm; MS: $m/z = 294$ (M^+).

4-(2-Chloroprop-2-enylthio)[1]benzopyran-2-one (**3e**, $C_{12}H_9ClO_2S$)

Yield 75% (0.76 g); white solid; mp 112°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 3.95$ (s, SC**H**$_2$), 5.52 (s, CCl=C**H**), 5.65 (s, CCl=C**H**), 6.18 (s, COC**H**), 7.28–7.79 (m, 4Ar**H**) ppm; IR (KBr): $\bar{\nu} = 1700$, 1590, 1185 cm^{-1}; UV/Vis (*Et*OH): λ_{max} ($\log \varepsilon$) = 212 (4.34), 273 (4.02), 295 (4.03) nm; MS: $m/z = 252$, 254 (M^+).

Thermal Rearrangement of 4-Allylthio[1]benzopyran-2-ones

Compounds **3a**–**3e** (2 mmol) were refluxed in 3 cm^3 of quinoline for 0.5–8.0 h. The reaction mixture was cooled and poured into ice-cold HCl (6 *N*). This was then extracted with 3×25 cm^3 of $CHCl_3$. The $CHCl_3$ extract was washed with 3×25 cm^3 of 1:1 HCl, 3×25 cm^3 of H_2O, and dried (Na_2SO_4). The $CHCl_3$ was removed and the crude mass was purified by column chromatography over silica gel using benzene:petroleum ether (1:1) as the eluent.

2-Methylthieno[3,2-c]benzopyran-4-one (**5a**, $C_{12}H_8O_2S$)

Yield 80% (0.35 g); white solid; mp 140°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 2.59$ (s, C**H**$_3$), 7.28–7.63 (m, 5Ar**H**) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 16.08$ (CH_3), 117.79, 123.55, 124.52, 124.92, 130.21 (C-3, C-6, C-7, C-8, C-9), 117.62, 125.97, 141.61, 147.58, 151.48 (C-2, C-3a, C-5a, C-9a, C-9b), 157.54 (C-4) ppm; IR (KBr): $\bar{\nu} = 2910$, 1720, 1605, 1460, 1190 cm^{-1}; UV/Vis (*Et*OH): λ_{max} ($\log \varepsilon$) = 232 (4.3), 257 (3.62), 297 (3.73), 325 (4.07) nm; MS: $m/z = 216$ (M^+).

2,3-Dimethylthieno[3,2-c]benzopyran-4-one (**5b**, $C_{13}H_{10}O_2S$)

Yield 76% (0.35 g); white solid; mp 130°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 2.45$ (s, C**H**$_3$), 2.49 (s, C**H**$_3$), 7.22–7.62 (m, 4Ar**H**) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 13.57$, 13.71 ($2CH_3$), 117.44, 123.25, 124.69, 129.88 (C-6, C-7, C-8, C-9), 117.74, 124.52, 134.17, 134.44, 146.02, 151.09 (C-2, C-3, C-3a, C-5a, C-9a, C-9b), 157.54 (C-4) ppm; IR (KBr): $\bar{\nu} = 2910$, 1700, 1604, 1470, 1190 cm^{-1}; UV/Vis (*Et*OH): λ_{max} ($\log \varepsilon$) = 235 (4.25), 262 (3.73), 271 (3.61), 332 (4.09) nm; MS: $m/z = 230$ (M^+).

3-Ethylthieno[3,2-c]benzopyran-4-one (**5c**, $C_{13}H_{10}O_2S$)

Yield 70% (0.32 g); white solid; mp 87°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.30$ (t, $J = 7.3$ Hz, CH_2C**H**$_3$), 3.03 (q, $J = 7.3$ Hz, C**H**$_2$$CH_3$), 7.02 (s, SC**H**), 7.25–7.71 (m, 4Ar**H**) ppm; IR (KBr): $\bar{\nu} = 2922$, 1723, 1604, 1473, 1190 cm^{-1}; UV/Vis (*Et*OH): λ_{max} ($\log \varepsilon$) = 231 (4.24), 262 (3.72), 272 (3.7), 325 (4.08) nm; MS: $m/z = 230$ (M^+).

2,3-Dihydro-2-methyl-3-phenylthieno[3,2-c]benzopyran-4-one (**4d**, $C_{18}H_{14}O_2S$)

Yield 65% (0.38 g); white solid; mp 126°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.63$ (d, $J = 6.9$ Hz, C**H**$_3$), 3.88–3.96 (m, SC**H**), 4.39 (d, $J = 2.7$ Hz, PhC**H**), 7.07–7.73 (m, 9Ar**H**) ppm; IR (KBr):

$\bar{\nu} = 1713, 1605, 1485, 1190\,cm^{-1}$; UV/Vis (*Et*OH): λ_{max} ($\log \varepsilon$) = 232 (4.28), 268 (3.97), 312 (4.03), 329 (4.02), 343 (3.82) nm; MS: $m/z = 294$ (M^+).

*Dehydrogenation of Compound **4d***

Compound **4d** (0.147 g, 0.5 mmol) was refluxed with 10 mg 10% Pd-C in 2 cm^3 of diphenylether for 2 h. The product **5d** was obtained by column chromatography over silica gel using benzene:petroleum ether (1:3) as eluent.

2-Methyl-3-phenylthieno[3,2-c]benzopyran-4-one (**5d**, $C_{18}H_{12}O_2S$)

Yield 80% (0.12 g); white solid; mp 142°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 2.4$ (s, C**H**$_3$), 7.29–7.708 (m, 9Ar**H**) ppm; IR (KBr): $\bar{\nu} = 1737, 1605, 1477, 1220\,cm^{-1}$; UV/Vis (*Et*OH): λ_{max} ($\log \varepsilon$) = 206 (4.37), 232 (4.21), 331 (3.97) nm; MS: $m/z = 292$ (M^+).

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