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Thiophenol-catalyzed Claisen rearrangement and radical cyclization: formation of furo- and pyrano-coumarin derivatives

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Abstract—Regioselective synthesis of dihydrofurocoumarins and dihydropyranocoumarins in excellent yields from 4-prop-2-ynyloxy coumarin via a thiol mediated radical reaction is described. Alkenyl radicals are generated from easily available terminal alkynes and thiophenol. Thiophenol catalyzed the Claisen rearrangement of the 4-prop-2-ynyloxycoumarin ethers.
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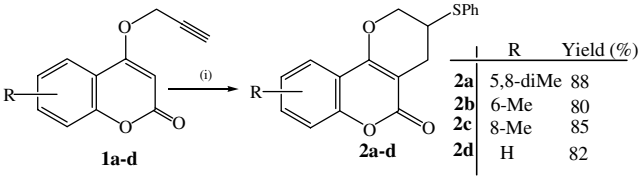
Coumarin and its derivatives are important heterocyclic compounds, which are found in many natural products.[1] Coumarins fused with other heterocycles have interesting biological and photodynamic properties:[2] for example, dihydrofurocoumarins show significant cytotoxicity against KB cells[3] and the ability to inhibit c-AMP[4] synthetase, as well as acetylcholinesterase.[5] Recently, we demonstrated the synthesis of coumarin-annulated heterocycles by the application of the Claisen rearrangement, radical cyclization and ring closing metathesis.[6] The traditional methods for accomplishing the Claisen rearrangement are based on thermally controlled procedures. However, thermal rearrangements require a high temperature and long reaction times. In recent years, several attempts have been made to develop new methods using catalysts for the Claisen rearrangement.[7] On the other hand, free radical cyclization is regarded as a versatile route for the construction of carbocycles as well as heterocycles.[8] In particular, the formation of C–S bonds by the intermolecular addition of S-centred radicals to π-systems is a major challenge in organic synthesis. Intermolecular addition of radicals to terminal alkynes offers an attractive strategy for the generation of alkenyl radicals,[9] and thiophenol[10] is a very efficient reagent for this purpose. Moreover, during the cyclization process a phenylthio moiety is incorporated into the final cyclized products, which is particularly attractive for further transformation/functionalization.[10b,c] All previous efforts on thiophenol mediated methodologies were directed towards radical cyclizations.[10] Here, we report the thiophenol catalyzed Claisen rearrangement as well as thiophenol mediated radical cyclization.

The requisite starting materials for our study, coumarin-4-yl-prop-2-ynyl ethers **1a–d** were synthesized by refluxing various substituted 4-hydroxycoumarins and propargyl bromide in dry acetone for 10–12 h. The thiophenol mediated cyclization was performed with **1a** under standard conditions [PhSH (2 equiv), AIBN (1.5 equiv)] in dry *t*-butanol as a solvent for 1 h to afford **2a** as a solid, mp 148–149 °C in 88% yield (Scheme 1). The product was characterized as the dihydropyranocoumarin derivative on the basis of its spectral and analytical data. Encouraged by this result, substrates **1b–d** were similarly treated to give **2b–d** in 80–85% yields.



	R	Yield (%)
2a	5,8-diMe	88
2b	6-Me	80
2c	8-Me	85
2d	H	82

Scheme 1. Reagents and conditions: (i) PhSH, AIBN, *t*-butanol, reflux, 1 h.

Keywords: Thiophenol; AIBN; [3,3] Sigmatropic rearrangement; Radical cyclization; Dihydrofurocoumarin; Dihydropyranocoumarin.
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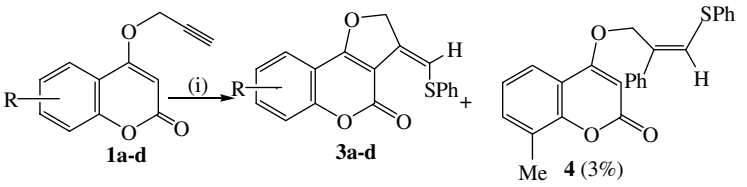
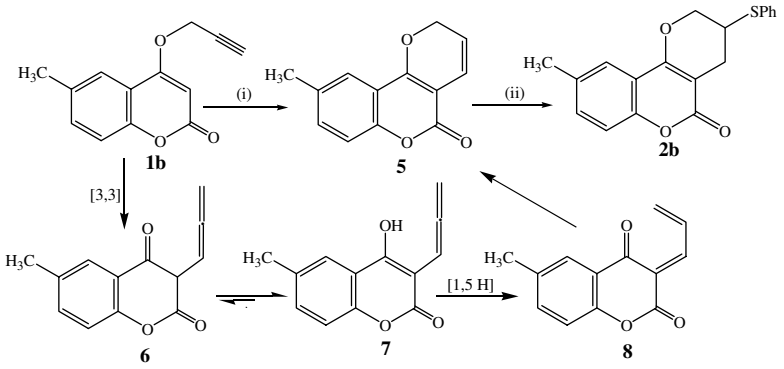


	R	Yield (%)
3a	5,8-diMe	80
3b	6-Me	88
3c	8-Me	86
3d	H	78

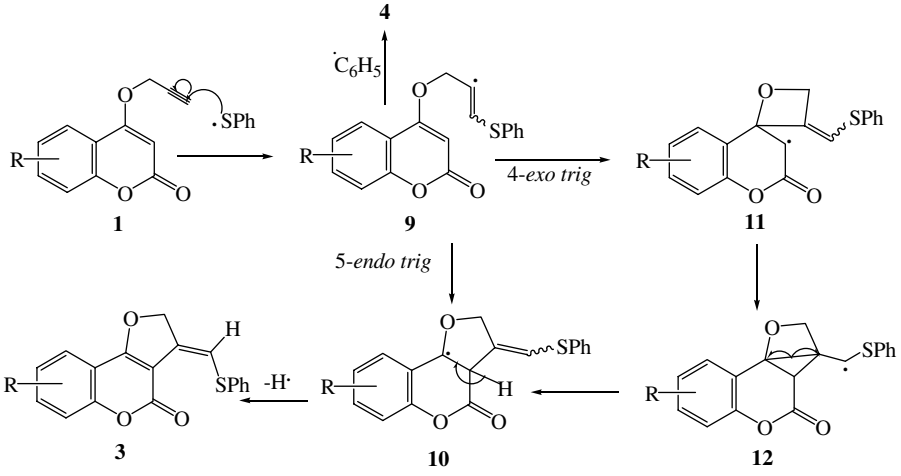
Scheme 2. Reagents and conditions: (i) PhSH, AIBN, dry benzene, reflux, 40–50 min.

The formation of products **2** during the thiophenol mediated cyclization of **1** is unusual. Thus, a second series of experiments was carried out in dry benzene instead of *t*-butanol as solvent with substrate **1a**. On this occasion a totally different product **3a**, mp: 163–165 °C was obtained in 80% yield (Scheme 2). Compound **3a** was characterized as a dihydrofurocoumarin from its elemental analysis and spectroscopic data. The stereochemistry of the exocyclic double bond in **3a** was found to be *Z* on the basis of an NOE correlation between the methylene (–OCH_2) resonance at $\delta = 5.39$ ppm and the exocyclic proton at $\delta = 5.89$ ppm. Substrates **1b–d** were similarly treated to give **3b–d** in 78–88% yields along with a by-product **4** (isolated in the case of **1c**, 3% yield) resulting from the addition of the vinyl radicals to benzene.[10d]

A clear trend related to the solvent polarity or ability to form hydrogen bonds accounts for the outcome of these experiments. In polar *t*-butanol, thiophenol catalyzed the Claisen rearrangement of **1** (Scheme 3). Thus Claisen rearrangement[6b] of ethers **1** occurs at a faster rate than the addition of thiophenol to the terminal alkyne to give the 2*H*-pyranobenzopyran ring system **5** to which addition of a thiyl radical occurs in the presence of AIBN, to afford **2**. The formation of products **2** through intermediates **5** has been confirmed by the following experiment. Substrate **1b** was refluxed in *t*-butanol under a nitrogen atmosphere for 10 h; however, no reaction occurred. When a catalytic amount of thiophenol (0.5 equiv) was added to the reaction mixture, the reaction was complete within 1 h. The product was isolated and treated with 2 equiv of PhSH and 1.5 equiv of



Scheme 3. Reagents and conditions: (i) *t*-Butanol, PhSH, reflux, 1 h. (ii) *t*-Butanol, AIBN, PhSH, reflux, 30 min.



Scheme 4.

AIBN in dry *t*-butanol under a nitrogen atmosphere for 30 min to afford a white solid mp 136–138 °C. This product was found to be identical to **2b** prepared earlier (Scheme 3).

The formation of products **3** from **1** may be explained by the generation of alkenyl radical **9** by radical addition of thiophenol to the terminal alkyne **1**. The alkenyl radical **9** may undergo either a 4-*exo trig* or a 5-*endo trig* cyclization at the double bond of the pyrone ring of the coumarin moiety. A 5-*endo trig* cyclization of radical **9** may produce the intermediate radical **10**, whilst 4-*exo trig* cyclization may give the spiroheterocyclic radical **11**, followed by neophyl rearrangement[11] to radical intermediate **12**. Oxidative elimination of hydrogen from **10** may afford **3**. On the other hand, addition of a phenyl radical to the vinyl radical **9** may afford product **4** (Scheme 4).

In conclusion, we have demonstrated the hitherto unreported thiophenol catalyzed Claisen rearrangement. We have also described the thiophenol mediated radical cyclization. The protocol presented here involves the generation of alkenyl radicals from easily available terminal alkynes and thiophenol. The methodology described here is simple and straightforward for the preparation of furo [3,2-*c*][1]benzopyran-4(2*H*)-one and 3,4-dihydropyrano[3,2-*c*][1]benzopyran-5(2*H*)-one derivatives.

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Compound **2a**: Yield: 88%; white solid; mp: 148–149 °C; IR (KBr): $\upsilon = 2977, 1692, 1092\ cm^{-1}$; ^1H NMR ($CDCl_3$, 500 MHz): $\delta_H = 2.39$ (s, 3H, ArCH_3), 2.51 (dd, 1H, $J = 9.21, 17.2$ Hz, CH_2), 2.59 (s, 3H, ArCH_3), 3.03 (ddd, 1H, $J = 1.9, 5.4, 17.2$ Hz, OCH_2), 3.52–3.58 (m, 1H, SC*H*), 4.00 (t, 1H, $J = 10.85$ Hz, CH_2), 4.40 (ddd, 1H, $J = 1.4, 3.4, 10.9$ Hz, OCH_2), 6.90 (d, 1H, $J = 7.6$ Hz, Ar*H*), 7.19 (d, 1H, $J = 7.6$ Hz, Ar*H*), 7.31–7.37 (m, 3H, Ar*H*), 7.50–7.52 (m, 2H, Ar*H*) ppm ^{13}C NMR (125 MHz): 16.2, 23.5, 26.3, 39.2, 69.8, 99.9, 114.2, 124.3, 127.3, 128.6, 129.6, 132.4, 132.5, 133.8, 134.1, 152.1, 162.8, 163.1 ppm; HRMS: *m*/*z* Calcd for $C_{20}H_{18}O_3S$ $[M+Na]^+$: 361.0859;

found, 361.0844. Anal. Calcd for $C_{20}H_{18}O_3S$: C, 70.98, H, 5.36%. Found: C, 71.17, H, 5.46%; Compound **3a**: Yield: 80%; white solid; mp:163–165 °C; IR (KBr): $\upsilon = 2926$, 1716, 1145 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta_H = 2.41$ (s, 3H, ArCH_3), 2.44 (s, 3H, ArCH_3), 5.39 (s, 2H, OCH_2), 5.89 (s, 1H, =C*H*), 6.87 (d, 1 H, $J = 7.6$ Hz, Ar*H*), 7.23 (d, 1H, $J = 7.6$ Hz, Ar*H*), 7.41–7.43 (m, 2H, Ar*H*), 7.60 (m, 1H, Ar*H*), 7.79–7.81 (m, 1H, Ar*H*), 7.91–7.93 (m, 1H, Ar*H*) ppm; ^{13}C NMR (125 MHz): 16.3, 23.8, 65.9, 91.2, 114.4, 122.0, 123.4, 124.6, 125.0, 125.3, 127.4, 127.6, 129.5, 133.3, 134.8, 137.9, 140.9, 153.4, 163.0, 168.9 ppm; HRMS: m/z Calcd for $C_{20}H_{16}O_3S$ $[M+Na]^+$: 359.0703; found, 359.0717. Anal. Calcd for $C_{20}H_{16}O_3S$: C, 71.41, H, 4.79%. Found: C, 71.64, H, 4.91%.