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

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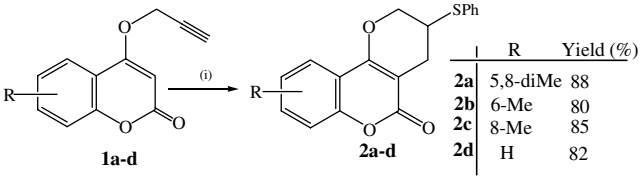
Abstract—Regioselective synthesis of dihydrofurocoumarins and dihydropyranocoumarins in excellent yields from 4-prop-2-ynyloxy coumarin via a thiol mediated radical reaction is described. Alkenyl radicals are generated from easily available terminal alkynes and thiophenol. Thiophenol catalyzed the Claisen rearrangement of the 4-prop-2-ynyloxycoumarin ethers.

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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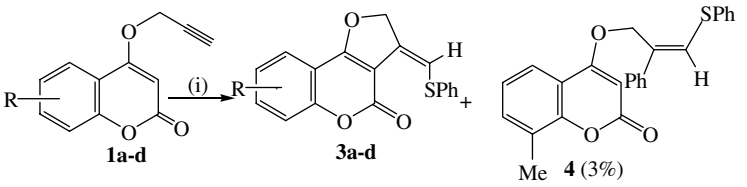
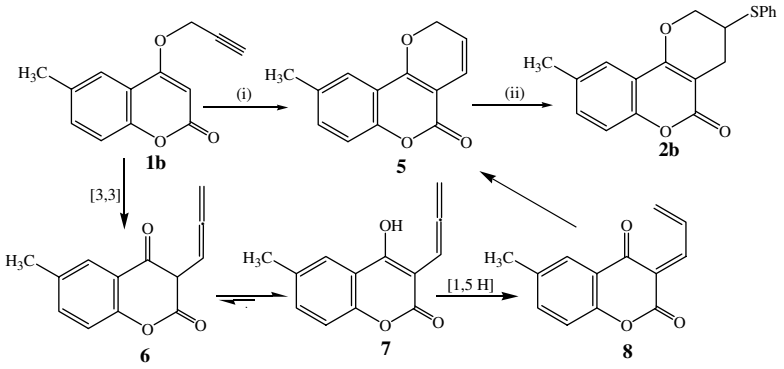


	R	Yield (%)
3a	5,8-diMe	80
3b	6-Me	88
3c	8-Me	86
3d	H	78

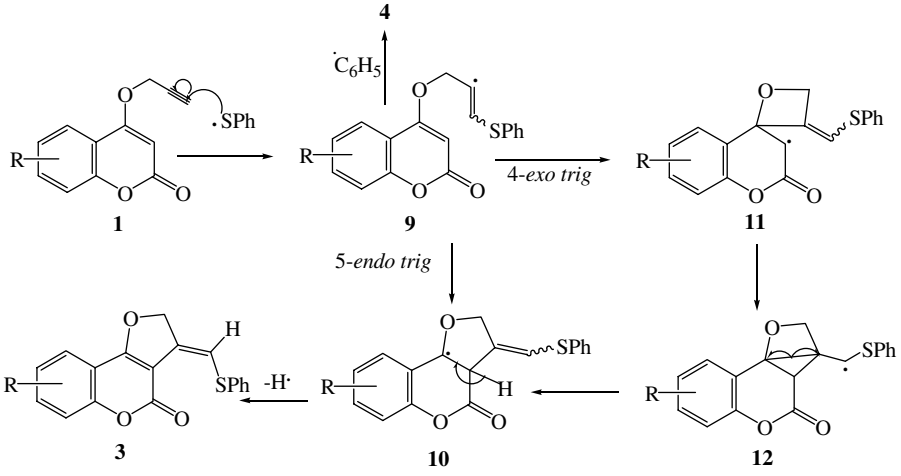
Scheme 2. Reagents and conditions: (i) PhSH, AIBN, dry benzene, reflux, 40–50 min.

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.