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Synthesis of coumarins by ring-closing metathesis using Grubbs' catalyst

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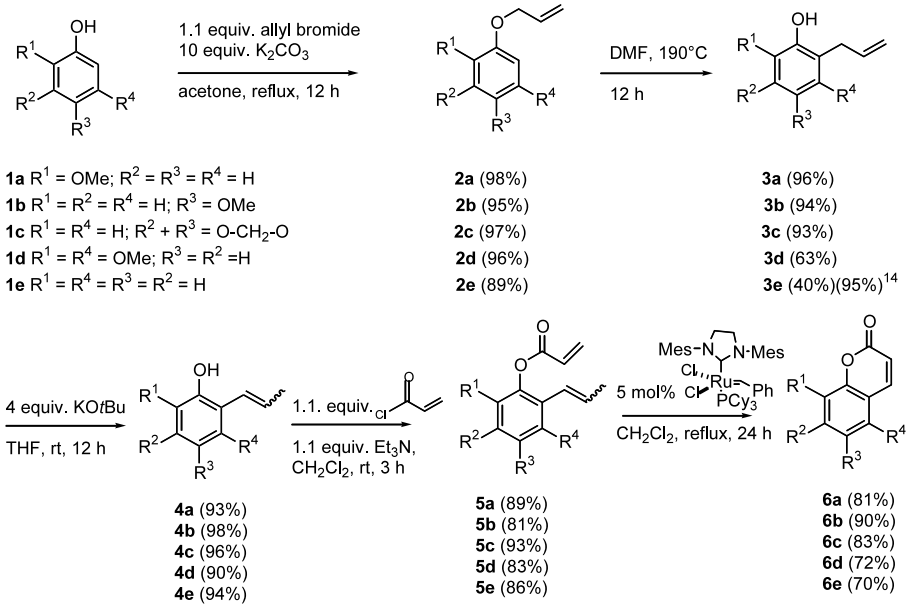
Abstract—A novel generally applicable synthesis of coumarins from phenolic substrates utilizing ring-closing metathesis is described. This sequence involves *O*-allylation of phenols followed by *ortho*-Claisen rearrangement, subsequent based-induced isomerization affording 2-(1-propenyl)phenols, acylation with acryloyl chloride, and finally ring-closing metathesis (RCM) with Grubbs' second generation catalyst. © 2003 Elsevier Science Ltd. All rights reserved.

Coumarins are widespread in nature as physiologically active constituents of plants.[1–3] In addition, coumarin derivatives have a broad range of applications in the pharmaceutical, perfume, and cosmetic industries. They have been used as additives to food and cosmetics, optical brightening agents and dispersed fluorescent and laser dyes. The diverse biological activities of coumarins is well known as anticoagulants, antithrombotics,[4] antimicrobial,[2c] antibacterial activities,[2] anticancer[3] and anti-HIV activity.[5] The interesting biological activity of these coumarins made these compounds attractive targets in organic synthesis. Several synthetic strategies for the synthesis of coumarins have already been developed. Coumarins can be synthesized by the Perkin reaction,[6a] Pechmann reaction[6b] or by Knoevenagel condensation of salicylaldehydes with



Scheme 1.

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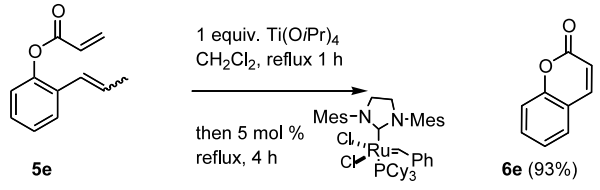
malonic acid,[7,8] malonic esters,[8,9] cyanoacetic esters[10a] or Meldrum's acid.[10b] Recently, the Wittig reaction in *N*,*N*-diethylaniline was also conveniently applied for the synthesis of coumarins.[11] However, all reported methods have disadvantages (harsh reaction condition, low yield, difficult purification), making the development of a new reliable high-yielding method for the synthesis of coumarins an important subject.

In continuation of our longstanding interest in coumarin chemistry, in which several new coumarins have been isolated from medicinal plants and some of them were synthesized,[12] a new method for the synthesis of coumarins by ring-closing metathesis using Grubbs' catalyst was developed.

The starting materials, phenols **1a**–**e**, were alkylated by treatment with allyl bromide in the presence of potassium carbonate in acetone at reflux for 12 h affording the corresponding allyl ethers **2a**–**e** in very good yield (Scheme 1).[13] *ortho*-Claisen rearrangement of compounds **2a**–**e** by heating in DMF (v/v 1/1) at 190°C gave the corresponding phenols **3a**–**e**.[13] In the case of compound **2d**, the reaction product was obtained as a result of *ortho*-Claisen rearrangement (63%) and *para*-Claisen rearrangement (30%). Allylaryl ether **2e** was heated in DMF at 190°C for 36 h. Only 40% conversion to 2-allylphenol **3e** was obtained under this condition, but the neat ether **2e** rearranged to 2-allylphenol **3d** at 290°C almost exclusively.[14] Isomerization of phenols **3a**–**e** was carried out by treatment with potassium *tert*-butoxide in THF[15] for 12 h at room temperature to give phenols **4a**–**e** in 90–98% yield as a mixture of *E*- and *Z*-isomer (about 4:1). In the case of 2-allylphenol derivative **3d**, compound **4d** was obtained in only 5% yield. In order to improve the yield of the reaction, the reaction mixture was refluxed in THF for 24 h yielding 2(1-propenyl)phenol **4d** in 90% yield as the *E*-isomer, exclusively. Acylation of phenols **4a**–**e** was carried out by treatment with acryloyl chloride in dichloromethane in the presence of triethylamine, affording unsaturated aryl esters **5a**–**e** in 81–93% yield.[16]

The past few years, there has been intense interest in the ring-closing metathesis (RCM) reaction of diolefins. This type of carbon–carbon bond formation has proven to be a very powerful method for the synthesis of cyclic systems.[17] However, RCM using Grubbs' catalysts on olefins with electron-withdrawing functionalities such as α,β-unsaturated (π-conjugated) aldehydes, ketones, and esters, remains difficult and is known with limited success.[18a] The complexation between the catalyst and the olefin decreases the activity dramatically.[17e]



Scheme 2.

Recently, the improved highly reactive ruthenium-based olefin metathesis catalyst (Grubb's second generation catalyst) was found to catalyze the reaction more efficiently.[18c,d] Several practical methods for the intermolecular cross-metathesis and intramolecular ring-closing metathesis using ruthenium alkylidenes have been reported yet.[16,18b,18d] These results could be applied for the intramolecular ring-closing metathesis of α,β-unsaturated esters **5a**–**e** affording coumarins.

Accordingly (Scheme 1), 2-(1-propenyl)aryl acrylates **5a**–**d** were treated with 5 mol% of Grubbs' second generation catalyst in dichloromethane at reflux for 24 h giving rise to coumarins **6a**–**d** in 70–90% yield.[19] Via this synthesis of coumarins by RCM, the natural product ayapin **6c**, isolated from *Pterocaulon polystachium*,[12c] *P. virgatum*,[12e] *P. serrulatum*,[20a] *Dendrobium densiflorum*,[20b] and the natural 5,8-dimethoxycoumarin **6d** from *Artemisia carvifolia*,[20c] were synthesized in 83 and 72% yield, respectively. However, compound **5e**, when treated with the same catalyst in dichloromethane under reflux for 44 h, afforded coumarin **6e** only in 70% yield. In order to improve the yield of coumarin **6e**, the reaction conditions were modified (Scheme 2). In a first step, aryl acrylate **5e** was treated with 1 equiv. of $Ti(OiPr)_4$ in dichloromethane under reflux for 1 h, then 5 mol% of Grubbs' second generation catalyst was added and reflux was continued for 4 h, to give coumarin **6e**[21] in very good yield (93%). Probably, the use of $Ti(OiPr)_4$ could diminish the complexation between the carboxylic oxygen and the ruthenium catalyst.

In conclusion, ring-closing metathesis using second generation Grubbs' ruthenium catalyst as a new method for the synthesis of coumarins was developed.[23]

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19. General procedure for the ring-closing metathesis of 2-(1-propenyl)phenyl acrylates **5a–e** with Grubbs' second generation catalyst. To a solution of Grubbs' second generation catalyst (0.012 mmol) in CH_2Cl_2 (10 mL) was added a solution of 2-(1-propenyl)phenyl acrylates **5a–e** (0.24 mmol) in CH_2Cl_2 (5 mL). The resulting solution was stirred at reflux for 24 h. The solvent was evaporated in vacuo and the residue was purified by flash chromatography on silica gel (eluent hexane/EtOAc 4/1) to afford coumarins **6a–e** as a white powder. As an example, the spectroscopic data of ayapin **6c** are given here. (6,7-Methylenedioxy)coumarin (Ayapin) **6c**: ^{1}H NMR ($CDCl_3$) δ 6.07 (2H, s, O-CH_2-O), 6.27 (1H, d, $J=9.6$ Hz, H-3), 6.82 (1H, s, =CH), 6.83 (1H, s, =CH), 7.58 (1H, d, $J=9.6$ Hz, H-4). ^{13}C NMR ($CDCl_3$) δ 161.2 (C=O), 151.3 (C-6, C-7), 144.9 (C-9), 143.5 (C-4), 113.4 (C-5), 112.7 (C-10), 105.0 (C-3), 102.3 (O-CH_2-O), 98.4 (C-8). IR (KBr): 1707 (C=O), 1679, 1632, 1580 cm^{-1}. MS m/z (%): 190 (M^+, 100), 163 (8), 162 (60), 161 (37). Mp: 229–230°C (lit.[22a] 227–228°C).
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21. **Coumarin 6e**: A solution of Ti(O*i*Pr)$_4$ (0.24 mmol) and 2-(1-propenyl)phenyl acrylate **5e** (0.24 mmol) in CH_2Cl_2 (10 mL) was heated under reflux for 1 h. Then, Grubbs' second generation catalyst (0.012 mmol) was added to the solution, and resulting mixture was stirred at reflux for 4 h. The solvent was evaporated in vacuo and the residue was purified by flash chromatography on silica gel to afford coumarin **6e** as a white powder (93%). ^{1}H NMR ($CDCl_3$). Mp: 69–70°C (lit.[22b] 68–70°C).
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23. It came to our knowledge at the Flohet conference (Gainesville, USA, March 10–12, 2003) that the Grubbs group had independently developed a similar method for the synthesis of coumarins using RCM. In a personal communication, Professor R. Grubbs informed us that their paper was in a status of being in press for publication in Pure and Applied Chemistry (2003). The latter paper focussed on coumarins which were not substituted in the aromatic ring (only substituted at the α,β-unsaturated bond). In that respect, our present results are complimentary to the results of Grubbs group.