Pergamon

Tetrahedron Letters 43 (2002) 7781–7783

TETRAHEDRON LETTERS

Combined Claisen rearrangement and ring-closing metathesis as a route to oxepin- and oxocin-annulated coumarins

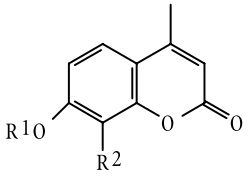
Shital K. Chattopadhyay,* Susama Maity and Srikanta Panja

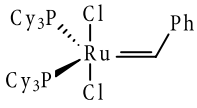
Department of Chemistry, University of Kalyani, Kalyani-741235, West Bengal, India

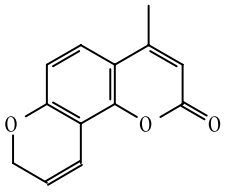
Received 20 June 2002; revised 9 August 2002; accepted 23 August 2002

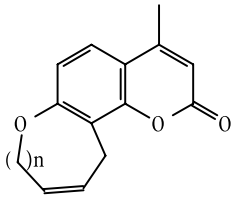
Abstract—A new route involving a tandem Claisen rearrangement and ring-closing metathesis reaction has been developed for the synthesis of some hitherto unknown oxepin- and oxocin-annulated coumarin derivatives.

Coumarins fused with other heterocycles are known to have interesting biological and photodynamic properties[1] which, in turn, has encouraged research with regard to procedures for the preparation of families of these compounds. Thus a number of methodologies have been reported[2] for the synthesis of various 3,4-, 6,7- and 7,8-fused furo- and pyranocoumarins as some members belonging to these two families have shown[3] useful levels of biological activities. On the other hand, very little information is known about medium ring oxacycle fused coumarins which may, in part, be due to lack of general methods[4] for the synthesis of such ring systems. In recent years, ring-closing metathesis (RCM) has emerged[5] as a valuable tool for the construction of various carbocyclic and heterocyclic ring systems especially for medium to large rings. Although numerous applications have already appeared,[6] including some benzannulated constructs,[7] the formation of medium sized rings by this method still poses considerable challenges.[6d] Claisen rearrangement[8] of allyl phenyl ethers to 2-allylphenols is a well studied reaction and its extension to the corresponding aza- and thia-analogues has rendered it more versatile for the synthesis of numerous five- and six-membered oxygen, nitrogen and sulphur heterocycles through synthetic ramification of the initial rearrangement products.[9] It appeared to us that a combination of a Claisen rearrangement and RCM could be useful to access various hitherto unknown medium sized heterocycle-annulated heterocyclic sys-









1, R^1 = -CH_2-CH = CH_2 ; R^2 = H

2, R^1 = H, R^2 = -CH_2-CH = CH_2

3, $R^1 = R^2$ = -CH_2-CH=CH_2,

4, R^1 = -CH_2-CH_2-CH = CH_2 ; R^2 = -CH_2-CH = CH_2

5

6

7, n=1

7b, n=2

Figure 1.

Keywords: ring-closing metathesis; Claisen rearrangement; oxepin; oxocin; coumarin.

* Corresponding author. Fax: (+) 91+33+582+8282; e-mail: skc@klyuniv.ernet.in

0040-4039/02/$ - see front matter
PII: S0040-4039(02)01806-3

tems of interest. In this communication, we wish to report some successful applications of this general approach towards the construction of oxepin and oxocin annulated coumarin derivatives.

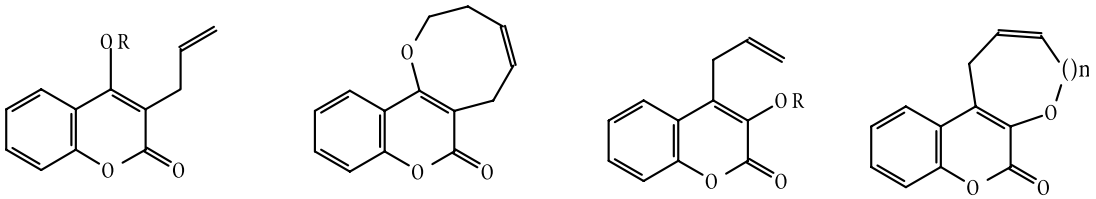
Thus, 7-allyloxy-4-methylcoumarin **1**, obtainable from allylation of the easily available 7-hydroxy-4-methylcoumarin, on thermal rearrangement provided the known[10] 8-allyl-7-hydroxy-4-methylcoumarin **2** (Fig. 1). We observed that the rearrangement of **1** proceeds better in refluxing diphenyl ether and also the isolation of the product from this solvent is easier than under the reported conditions.[10] The rearrangement is also regiospecific under the modified conditions. The rearrangement product **2** on further alkylation with allyl bromide in refluxing acetone in the presence of potassium carbonate gave the allyl ether **3** as a colourless crystalline solid, mp 94°C (91%). The butenyl ether **4**, mp 98°C was prepared analogously (89%) by alkylation of **2** with 4-bromo-1-butene.

Ring-closing metathesis of **3** with Grubb's catalyst[11] bis(tricyclohexylphosphine)benzylidene–ruthenium(IV) dichloride (**5**) proved to be sluggish at room temperature under varied concentrations (ranging from 0.01 to 0.001 M) in dichloromethane or benzene. However, in refluxing dichloromethane (0.01 M, 10 mol% catalyst, 4 h), clean formation of two products was observed. The products were characterised as being the pyranocoumarin **6**, mp 184°C (24%) and the oxepin derivative **7a** (33%) on the basis of spectral data. The formation of the new pyran ring in **6** could be explained if it is assumed that a selective isomerisation of the *C*-allyl group in **3** takes place before RCM. Similar type of isomerisations have previously been noted in RCM reactions[12] and very recently,[13] a synthetic protocol for the deprotection of allyl ethers based on such an isomerisation has been developed. In the present instance, selective isomerisation of the *C*-allyl group in **3** is probably due to formation of the more stable olefin. On the other hand, the butenyl ether **4** underwent uncomplicated RCM under analogous conditions and the oxocin derivative **7b** was obtained as a colourless crystalline solid, mp 244°C (59%).

3-Allyl-4-hydroxycoumarin **8** (Fig. 2) has been prepared[14] previously by Claisen rearrangement of 4-allyloxycoumarin in refluxing acetic anhydride in the presence of sodium acetate followed by hydrolysis of the resulting acetate **9**. We observed that this two step protocol for the synthesis of **8** could be avoided if the Claisen rearrangement of 4-allyloxycoumarin is carried out in refluxing chlorobenzene. The product **8** was obtained directly (89%). Refluxing **8** with 4-bromo-1-butene in acetone in the presence of anhydrous potassium carbonate led to the formation of the butenyl ether **10** (89%). Ring-closing metathesis of **10** [Grubb's catalyst **5** (10 mol%), CH_2Cl_2 (0.01 M), rt, 16 h] was found to be clean and the oxocin derivative **11**, mp 92°C, was realised in a satisfactory 77% yield.

Similarly, 4-allyl-3-hydroxycoumarin **12** (Fig. 2) was obtained from the Claisen rearrangement of 3-allyloxycoumarin in refluxing chlorobenzene (12 h, 89%) and it was observed that this procedure was advantageous over the one reported previously.[15] The product **12** on alkylation with allyl bromide in refluxing acetone in the presence of potassium carbonate provided the allyl ether **13** in high yield (94%). The butenyl ether **14** was analogously prepared (91%). RCM of **13** under the same conditions as employed for **10** was much faster (3 h) and the oxepin derivative **15** was obtained in a pleasing 79% yield. The butenyl ether **14** also underwent smooth cyclisation under identical conditions to give the oxocin derivative **16** as a colourless crystalline solid, mp 110°C (81%). It is interesting to note that the oxocin derivatives **8**, **11** and **16** are formed with such ease since it is known[6d] that eight membered cycloalkenes are prone to the reverse process, i.e. ring-opening metathesis (ROM) or ring-opening metathesis polymerization (ROMP).

Thus, we have demonstrated that the combined Claisen rearrangement and ring-closing metathesis reactions is a viable strategy for the synthesis of some potentially bio-active oxepin- and oxocin-annulated coumarins.[16] Efforts are underway to extend this methodology to other heterocyclic systems of interest.



8, R = H **11** **12**, R = H **15,** n=1

9, R = $COCH_3$ **13**, R = CH_2-CH=CH_2 **16,** n=2

10, R = CH_2-CH_2-CH=CH_2 **14,** R = CH_2-CH_2-CH=CH_2

Figure 2.

Acknowledgements

Financial assistance from the CSIR (New Delhi) (Grant No.: 01/1676/00/EMR-II) is gratefully acknowledged. The authors also thank Prof. Goverdhan Mehta, I.I.Sc., Bangalore for some spectral data.

References

1. (a) Murakami, A.; Gao, G.; Omura, M.; Yano, M.; Ito, C.; Furukawa, H.; Takahasi, D.; Koshimizu, K.; Ohigashi, H. *Biorg. Med. Chem. Lett.* **2000**, *10*, 59; (b) Rajski, S. R.; Williams, R. M. *Chem. Rev.* **1998**, *98*, 2723; (c) Ali, J. P.; Jackson, A. P.; Howells, A. J.; Maxwell, A. *Biochemistry* **1993**, *32*, 2717.
2. (a) Risitano, F.; Grassi, G.; Foti, F.; Billardo, C. *Tetrahedron Lett.* **2001**, *42*, 3503; (b) Nemeto, T.; Oshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2000**, *41*, 9569; (c) Santana, L.; Uriarte, E.; Dalla Via, L.; Gia, O. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 135; (d) Jia, C.; Piao, D.; Kitamura, T.; Fujiwara, Y. *J. Org. Chem.* **2000**, *65*, 7516; (e) Appendino, G.; Cravotto, G.; Toina, L.; Annunziata, R.; Palmisano, G. *J. Org. Chem.* **1994**, *59*, 5556; (f) Majumdar, K. C.; De, R. N.; Khan, A. T.; Chattopadhyay, S. K.; Dey, K.; Patra, A. *J. Chem. Soc., Chem. Commun.* **1988**, 777.
3. For an extensive bibliography, see: Wu, J.; Liao, Y.; Yang, Z. *J. Org. Chem.* **2001**, *66*, 3642.
4. For reviews, see: (a) Yet, L. *Chem Rev.* **2000**, *100*, 2963; (b) Hoberg, J. O. *Tetrahedron* **1998**, *54*, 12631.
5. For recent reviews, see: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18; (b) Schrock, R. R. *Tetrahedron* **1999**, *55*, 8141; (c) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371.
6. For recent examples, see: (a) Clark, J. S.; Trevitt, G. P.; Boyall, D.; Stammen, B. *J. Chem. Soc., Chem. Commun.* **1998**, 2629; (b) Frustner, A.; Radkowski, K. *J. Chem. Soc., Chem. Commun.* **2001**, 671; (c) Kariuki, B. M.; Owton, W. M.; Percy, J. M.; Pintat, S.; Smith, C. A.; Spencer, N. S.; Thomas, A. C.; Watson, M. *J. Chem. Soc., Chem. Commun.* **2002**, 228; (d) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073.
7. (a) Arisawa, M.; Theeraladanon, C.; Nishida, A.; Nakagawa, M. *Tetrahedron Lett.* **2001**, *42*, 8029; (b) Stefinovic, M.; Snieckus, V. *J. Org. Chem.* **1998**, *63*, 2808; (c) Lane, C.; Snieckus, V. *Synlett* **2000**, 1294; (d) Chang, S.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 864.
8. Claisen, L. *Chem. Ber.* **1912**, *45*, 3157.
9. For reviews, see: (a) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227; (b) Bennett, G. B. *Synthesis* **1977**, 589.
10. Kaufman, K. D. *J. Org. Chem.* **1961**, *26*, 117.
11. Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039.
12. (a) Alcaide, B.; Almendros, P.; Alonso, J. M.; Aly, F. M. *Org. Lett.* **2001**, *3*, 3781; (b) Kinderman, S. S.; van Maarseveen, J.-H.; Shoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Org. Lett.* **2001**, *3*, 2045.
13. Cadot, C.; Dalko, P. I.; Cossy, J. *Tetrahedron Lett.* **2002**, *43*, 1839.
14. Ahluwalia, V. K.; Singh, R. P.; Bala, S. *Tetrahedron Lett.* **1982**, *23*, 2049.
15. Mitra, A. K.; Mukhopadhyay, A. K.; Mishra, S. K.; Patra, A. *Ind. J. Chem.* **1982**, *21B*, 834.
16. All new compounds reported gave satisfactory spectroscopic and analytical data. Experimental procedure for the preparation of **11**: To a solution of the substrate **10** (52 mg, 0.2 mmol) in dry, degassed dichloromethane (20 ml) was added Grubb's catalyst (15 mg) under argon atmosphere and the resulting solution was stirred at ambient temperature for sixteen hours. The solvent was evaporated in vacuo and the residue was loaded on a pad of silica gel. Elution with 5% EtOAc–hexane afforded **11** as colourless solid (35 mg). Reaction of **14** (52 mg) with Grubb's catalyst under identical conditions led to **16** after three hours. Chromatography on silica gel using 5% EtOAc–hexane as eluent provided pure **16** as colourless solid (36 mg). Spectral data for **11**: IR (neat): 1678, 1609 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.79 (1H, d, $J=7.93$), 7.48 (1H, m), 7.27 (2H, m), 5.91 (1H, m), 5.71 (1H, m), 4.69 (2H, t, $J=5.71$), 3.58 (2H, d, $J=7.74$), 2.72 (2H, q, $J=5.14$): ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.3 (s), 162.9 (s), 151.7 (s), 131.3 (d), 128.1 (d), 128.0 (d), 123.8 (d), 123.3 (d), 117.8 (s), 116.2 (d), 109.4 (s), 70.8 (t), 31.3 (t), 23.1 (t). Elemental analyses: C, 74.10%; H, 5.47%; $C_{14}H_{12}O_3$ requires C, 73.67%; H, 5.30%. **16**: IR (neat): 1690, 1618 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.66 (1H, d, $J=8.1$), 7.48 (1H, m), 7.35 (2H, m), 6.05 (1H, m), 5.76 (1H, m), 4.12 (2H, t, $J=4.84$), 3.48 (2H, d, $J=7.59$), 2.65 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.4 (s), 151.2 (s), 145.9 (s), 140.7 (s), 130.9 (d), 130.5 (d), 130.3 (d), 124.5 (d), 124.2 (d), 119.3 (s), 117.0 (d), 72.3 (t), 29.9 (t), 25.2 (t). Mass (EI, 70 eV): m/z 229 (M^++1).