Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 7181–7183

A novel and facile synthesis of 7,8-diacylcoumarins

Antigoni Kotali,[a,*] Ioannis S. Lafazanis[a] and Philip A. Harris[b]

[a]*Laboratory of Organic Chemistry, Department of Chemical Engineering, University of Thessaloniki, Thessaloniki 54124, Greece*
[b]*GlaxoSmithKline, 1250 South Collegeville Road, PO Box 5089, Collegeville, PA 19426-0989, USA*

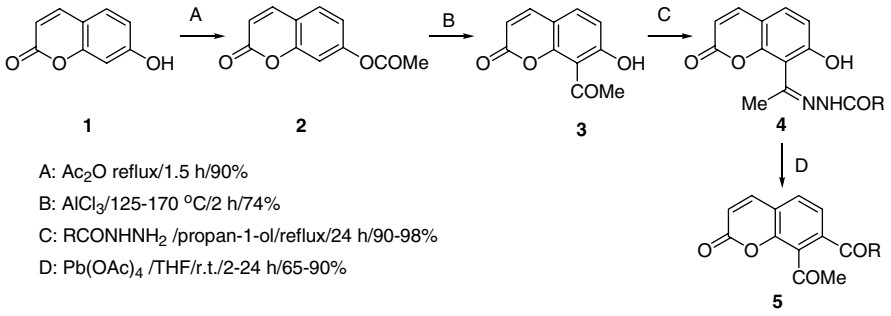
Received 25 May 2007; revised 27 July 2007; accepted 30 July 2007
Available online 2 August 2007

Abstract—Oxidation of *N*-carbonylhydrazones of 7-hydroxy-8-acetylcoumarin with lead tetraacetate results in the synthesis of 7,8-diacylcoumarins in good yields. The reaction proceeds via the transformation of a hydroxy into an acyl group reported for the first time in heterocyclic chemistry.

It is well-known that coumarin is a biologically active substance, with numerous metabolites, and is widespread in Nature.[1] Coumarin derivatives have been used widely for the treatment of a variety of diseases such as heart disease,[2–4] lymphoedema and other high-protein edemas.[5] They have also found pharmaceutical applications in the treatment of patients with chronic venous insufficiency,[6] skin cancer,[7] renal cell carcinoma,[8] prostate cancer[9] as well as in the treatment of thermal injuries.[10] They may also be useful in preventing oxidative stress and apoptosis in HIV infection.[11]

Having in mind the biological activity of the coumarin nucleus as well as the importance of the presence of acyl substituents at *ortho* positions in aromatic systems[12] we designed a synthesis of 7,8-diacylcoumarins (**5**) applying an earlier method found in our laboratory[13–15] (Scheme 1). The method involves treatment of the *N*-acylhydrazone of an *o*-hydroxyaryl ketone with lead tetraacetate (LTA) and results in the transformation of the hydroxy into an acyl group.[14]

Thus, 7-hydroxycoumarin (**1**) was initially reacted with acetic anhydride to give 7-acetoxycoumarin (**2**), which on treatment with aluminium chloride afforded[5] 7-hydroxy-8-acetylcoumarin (**3**). *N*-Carbonylhydrazones (**4**) of 7-hydroxy-8-acetylcoumarin were then prepared[16] and subsequently oxidized with LTA.[17] Compounds (**4**) and (**5**) are new and they were identified by MS, ^{1}H and ^{13}C NMR spectra and elemental analyses (Tables 1 and 2). Hydrazones **4a–d** were formed as mixtures of two isomers in ca. 1:1 ratio as shown by their



Scheme 1. Synthesis of 7,8-diacylcoumarins **5**.

Keywords: 7,8-Diacylcoumarins; Transformation; *N*-Acylhydrazones; Lead tetraacetate.
* Corresponding author. Tel.: +30 2310 996253; fax: +30 2310 996253; e-mail: kotali@eng.auth.gr

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.07.202

Table 1. Preparation[a] and MS data of compounds **4** and **5**

Compound	R	Yield (%)	Mp[b] (°C)	Molecular formula[c]	MS *m*/*z* (ES+)
4a	Me	96	248–250	$C_{13}H_{12}N_2O_4$	283 (M+23), 261 (M+1)
4b	*p*-MeC_6H_4	98	241.5–243.8	$C_{19}H_{16}N_2O_4$	359 (M+23), 337 (M+1), 202
4c	*p*-HOC_6H_4	96	275.5–276.3	$C_{18}H_{14}N_2O_5$	361 (M+23), 339 (M+1)
4d	*o*-$NO_2C_6H_4$	91	217.3–219.1	$C_{18}H_{13}N_3O_6$	368 (M+1)
4e	*p*-Pyridyl	93	287–288	$C_{17}H_{13}N_3O_4$	324 (M+1)
4f	2-Thienyl	92	258.4–260.6	$C_{16}H_{12}N_2O_4S$	329 (M+1), 271, 202
4g	OEt	90	193.7	$C_{14}H_{14}N_2O_5$	313 (M+23), 291 (M+1), 245, 202
5a	Me	90	174–175.8	$C_{13}H_{10}O_4$	231 (M+1)
5b	*p*-MeC_6H_4	92	169.5–170.7	$C_{19}H_{14}O_4$	329 (M+23), 307 (M+1)
5c	*p*-HOC_6H_4	73	191.5–193.5	$C_{18}H_{12}O_5$	331 (M+23), 309 (M+1), 291, 215
5d	*o*-$NO_2C_6H_4$	90	172.5–174.5	$C_{18}H_{11}NO_6$	360 (M+23), 338 (M+1)
5e	4-Pyridyl	75	152.5–154.5	$C_{17}H_{11}NO_4$	294 (M+1)
5f	2-Thienyl	78	153.2–154.2	$C_{16}H_{10}O_4S$	321 (M+23), 298 (M), 215
5g	OEt	65	130.4–132.4	$C_{14}H_{12}O_5$	283 (M+23), 261 (M+1), 217, 215, 187

[a] The molar ratio of hydrazone/LTA for the preparation of compounds **5** was 1:1.3 for **4a** and **4b**, 1:1.7 for **4c**, 1:1.5 for **4d** and **4g** and 1:2 for **4e** and **4f** whereas the reaction time was 3 h for **4a**, 2 h for **4b**, **4c**, **4d** and **4f** and 24 h for **4e** and **4g**.
[b] Melting points are uncorrected.
[c] Satisfactory microanalyses were obtained for all the compounds **4** and **5**.

Table 2. ^{1}H NMR and ^{13}C NMR data of compounds **4** and **5**

Compound[a]	^{1}H NMR[b] δ, J (Hz)	^{13}C NMR[b] δ
4a	2.10 (s, 3H), 2.21 (s, 3H), 2.35 (s, 3H), 2.43 (s, 3H), 6.19–6.23 (m, 2H), 6.86–6.89 (m, 2H), 7.49–7.55 (m, 2H), 7.92–7.96 (m, 2H), 10.49 (s, 1H), 10.80 (s, 1H), 11.8 (br, 1H), 12.2 (br,1H)	18.0,18.3, 20.8, 21.3, 111.2, 111.3, 111.4, 111.5, 112.0, 113.0, 113.7, 115.2, 129.0, 129.7, 143.4, 144.7, 145.0, 149.6, 152.6, 153.2, 158.7, 159.8, 160.0, 160.2, 166.5, 172.7
4b	2.30 (s, 3H), 2.34 (s, 3H), 2.42 (s, 3H), 2.54 (s, 3H), 6.27–6.31 (m, 2H), 6.96–6.99 (m, 2H), 7.22–7.24 (m, 2H), 7.36–7.65 (m, 6H), 7.89–7.91 (m, 2H), 8.00–8.03 (m, 2H), 10.05 (br, 1H), 11.22 (br, 2H), 12.55 (s, 1H)	19.0, 20.9, 21.8, 23.7, 109.4, 111.3, 111.4, 111.5 111.8, 111.9, 112.8, 113.8, 127.8, 128.1, 128,7, 128.9, 129.9, 130.0, 130.9, 141.5, 142.0, 144.7,144.9, 145.0, 148.0, 152.4, 153.5, 154.0, 157.4,159.8, 159.9, 160.1, 163.8, 165.0
4c	2.21 (s, 3H), 2.46 (s, 3H), 6.20–6.23 (m, 2H), 6.71 (d, 1H, $J = 8.3$), 6.84–6.91 (m, 5H), 7.52–7.57 (m, 4H), 7.82 (d, 2H, $J = 8.3$), 7.93 (d, 2H, $J = 9.5$), 9.65 (s, 1H), 9.88 (s, 1H), 10.15 (s, 2H), 10.90 (s, 2H)	19.4, 24.3, 110.0, 111.9, 112.0, 112.2, 112.5, 113.5, 114.5, 115.5, 124.1, 124.2, 125.1, 130.6, 131.0, 131.1, 145.3, 145.6, 153.1, 154.0, 154.1, 158.0, 160.4, 160.5, 160.6, 160.7, 160.9, 161.0, 161.1, 161.2, 161.5, 165.0
4d	2.19 (s, 3H), 2.32 (s, 3H), 6.13–6.23 (m, 2H), 6.74–6.92 (m, 2H), 7.31 (d, 1H, $J = 8.4$), 7.53–7.98 (m, 10H), 8.16 (d, 1H, $J = 8.0$), 10.56 (s, 1H), 11.42 (s, 1H), 11.49 (s, 1H), 11.91 (s, 1H)	19.0, 19.6, 111.9, 112.1, 113.1, 113.4, 114.2, 115.1, 124.2, 124.3, 124.9, 129.8, 130.0, 130.3, 130.6, 130.7, 130.8, 131.8, 132.8, 134.4, 134.7, 145.2, 145.4, 145.5, 146.7, 146.8, 147.3, 153.1, 153.7, 153.8, 156.4, 159.3, 160.4, 160.5, 163.5, 169.4
4e	2.25 (s, 3H), 2.43 (s, 3H), 6.20–6.22 (m, 2H), 6.88–6.70 (m, 2H), 7.38–7.95 (m, 8H), 8.60–8.76 (m, 4H), 10.49 (s, 1H), 1.30 (br, 1H), 11.40 (br, 1H), 11.96 (s, 1H)	19.7, 24.4, 110.2, 112.0, 112.2, 112.5, 113.1, 113.6, 114.2, 114.3, 122.3, 122.6, 123.3, 130.7, 131.0, 141.2, 142.1, 145.4, 145.5, 150.5, 150.6, 150.7, 153.0, 153.8, 155.7, 158.7, 160.4, 160.7, 162.9, 163.6
4f	2.25 (s, 3H), 6.20 (d, 1H, $J = 9.6$), 6.86–7.12 (m, 2H), 7.51–7.99 (m, 4H), 10.10 (s, 1H), 11.06 (s, 1H)	24.0, 112.1, 112.2, 112.6, 113.5, 113.9, 127.3, 130.2, 131.0, 135.3, 145.4, 145.5, 153.0, 158.3, 160.6, 160.7
4g	1.25 (t, 3H, $J = 7.0$), 2.23 (s, 3H), 4.17 (q, 2H, $J = 7.0$), 6.22 (d, 1H, $J = 9.5$), 6.88 (d, 1H, $J = 8.5$), 7.53 (d, 1H, $J = 8.5$), 7 (d, 1H, $J = 9.5$), 10.47 (br, 1H), 11.58 (br, 1H)	15.3, 19.0, 34.9, 107.1, 112.0, 113.9, 114.0, 130.0, 137.9, 145.5, 153.6, 154.8, 160.1, 160.6
5a	2.44 (s, 3H), 2.59 (s, 3H), 6.61 (d, 1H, $J = 9.6$), 7.85 (d, 1H, $J = 8.1$), 7.93 (d, 1H, $J = 8.1$), 8 (d, 1H, $J = 9.6$)	28.2, 31.9, 119.4, 122.9, 126.2, 129.8, 130.8, 137.0, 149.7, 149.9, 159.3, 198.9, 201.0
5b	2.39 (s, 3H), 2.61 (s, 3H), 6.67 (d, 1H, $J = 9.6$), 7.34 (dd, 2H, $J = 7.8$), 7.43 (d, 1H, $J = 7.9$), 7.62 (dd, 2H, $J = 7.8$), 7.94 (d, 1H, $J = 7.9$), 8.19 (d, 1H, $J = 9.6$)	21.2, 31.8, 117.9, 129.9, 124.5, 129.1, 129.3, 129.7, 130.0, 133.5, 140.3, 143.5, 144.3, 150.4, 158.6, 194.6, 199.7
5c	2.56 (s, 3H), 6.62 (d, 1H, $J = 9.5$), 6.85 (dd, 2H, $J = 8.6$), 7.39 (d, 1H, $J = 7.8$), 7.59 (dd, 2H, $J = 8.6$), 7.86 (d, 1H, $J = 7.8$), 8.13 (d, 1H, $J = 9.5$), 10.57 (s, 1H)	32.6, 116.2, 118.4, 121.7, 125.1, 128.1, 130.0, 130.4, 133.2, 141.4, 144.2, 151.0, 159.3, 163.4, 193.9, 200.6

Table 2 (*continued*)

Compound[a]	^{1}H NMR[b] δ, J (Hz)	^{13}C NMR[b] δ
5d	2.68 (s, 3H), 6.50 (d, 1H, $J = 9.7$), 7.10 (d, 1H, $J = 8.0$), 7.46–7.50 (m, 2H), 7.78–7.83 (m, 3H), 8.20 (d, 1H, $J = 8.0$)	31.5, 119.9, 123.0, 124.9, 126.0, 128.6, 129.2, 129.3, 131.8, 132.2, 134.8, 135.6, 142.2, 146.8, 150.3, 158.7, 192.2, 200.5
5e	2.71 (s, 3H), 6.52 (d, 1H, $J = 9.5$), 7.28 (d, 1H, $J = 9.5$), 7.48 (dd, 2H, $J = 5.4$), 7.64 (d, 1H, $J = 7.8$), 7.77 (d, 1H, $J = 9.5$), 8.74 (dd, 2H, $J = 5.4$)	32.1, 118.9, 121.5, 122.3, 124.6, 130.0, 130.3, 140.9, 142.4, 142.9, 150.9, 151.7, 158.3, 194.6, 198.8
5f	2.74 (s, 3H), 6.51 (d, 1H, $J = 9.7$), 7.12 (d, 1H, $J = 8.7$), 7.48–7.52 (m, 2H), 7.61 (d, 1H, $J = 7.9$), 7.73–7.78 (m, 2H)	32.4, 118.7, 121.1, 124.6, 126.4, 129.0, 131.0, 135.4, 135.6, 141.1, 142.5, 143.3, 151.1, 158.6, 187.0, 199.7
5g	1.39 (t, 3H, $J = 7.2$), 2.70 (s, 3H), 4.38 (q, 2H, $J = 7.2$), 6.53 (d, 1H, $J = 9.8$), 7.54 (d, 1H, $J = 8.2$), 7.73 (d, 1H, $J = 9.8$), 7.88 (d, 1H, $J = 8.2$)	14.2, 32.2, 62.6, 119.3, 122.3, 125.9, 128.3, 130.3, 133.1, 142.6, 143.9, 159.0, 165.0, 200.7

[a] Data for compounds **4a**–**4e** are for isomeric mixtures whereas for **4f** and **4g** are for a single isomer.
[b] ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in DMSO-d_6.

NMR spectra whereas, hydrazones **4f** and **4g** were formed as single isomers. Both hydrazones (**4**) as well as diacyl derivatives (**5**) show prominent peaks corresponding to the ion [M+1] in their mass spectra (Table 1). The carbonyl carbons in 7,8-diacylcoumarins **5** appeared at 200.7 to 187.0 ppm in the ^{13}C NMR spectra whereas, in hydrazones **4** the peaks appearing at 172.7 to 159.9 ppm were assigned to amide carbonyl (Table 2).

In conclusion, 7,8-diacylcoumarins have been prepared in good yields by a facile method that involves transformation of a hydroxy into an acyl group (step D, Scheme 1). This transformation is reported for the first time in heterocycles. This is considered to be significant with our previous findings on the transformation of a phenolic hydroxy into an acyl group in benzene derivatives.[14] By analogy, it is not unreasonable to assume that the presence of the hydroxy group in *N*-carbonylhydrazones (**4**) is crucial to the mechanism of the reaction.[15] The experimental simplicity, generality and low cost of the reagents add to the synthetic value of this method. Furthermore, 7,8-diacylcoumarins could serve as intermediates to various heterocycles with possible pharmaceutical properties.

Acknowledgement

The authors thank the Royal Society of Chemistry for financial support of this work.

References and notes

1. O'Kennedy, R.; Thornes, R. D. *Coumarins: Biology, Applications and Mode of Actions*; John Wiley: England, 1997, pp 333–336.
2. Ten Berg, J. M.; Kedler, J. C.; Plokker, T. H.; Van Hout, B. A. *Pharmacoeconomics* **2002**, *20*, 847–853.
3. Becker, R. C. N. *Engl. J. Med.* **2002**, *347*, 969–974.
4. Roma, G.; Braccio, M. D.; Carrieri, A.; Grossi, G.; Leoncini, G.; Grazia Signorello, M.; Carotti, A. *Bioorg. Med. Chem.* **2003**, *11*, 123–138.
5. Casley-Smith, J. R. *Coumarins: Biology, Applications and Mode of Actions*; John Wiley: England, 1997, pp 143–184.
6. Vanscheidt, W.; Rabe, E.; Naser-Hijazi, B.; Ramelet, A. A.; Partsch, H.; Diehm, C.; Schultz-Ehrenburg, U.; Spengel, F.; Wirsching, M.; Gotz, V.; Schnitkern, J.; Henneicke-von Zepelin, H. H. *Vasa* **2002**, *31*, 185–190.
7. Abramov, M. A.; Dehaen, W. *Synthesis* **2000**, 1529–1531.
8. Mohler, J. L.; Williams, B. D.; Freeman, J. A.; Marshall, M. E. *Coumarins: Biology, Applications and Mode of Actions*; John Wiley: England, 1997, pp 241–255.
9. Ebbinghaus, S. W.; Mohler, J. L.; Marshall, M. E. *Coumarins: Biology, Applications and Mode of Actions*; John Wiley: England, 1997, pp 209–221.
10. Piller, N. B. *Coumarins: Biology, Applications and Mode of Actions*; John Wiley: England, 1997, pp 185–208.
11. Greenspan, H. C. *Immunol. Today* **1994**, *14*, 209–213.
12. Kotali, A.; Harris, P. A. *Org. Prep. Proced. Int.* **2003**, 583–605.
13. Kotali, A.; Tsoungas, P. G. *Tetrahedron Lett.* **1987**, *28*, 4321–4322.
14. Kotali, A. *Curr. Org. Chem.* **2002**, *26*, 965–985, and references cited therein.
15. Katritzky, A. R.; Harris, P. A.; Kotali, A. *J. Org. Chem.* **1991**, *56*, 5049–5051.
16. *Preparation of 7-hydroxy-8-acetylcoumarin N-carbonylhydrazones* (**4**). A mixture of 7-hydroxy-8-acetylcoumarin **3** (5 mmol) and the corresponding hydrazide, in the molar ratio 1:1 were refluxed in propanol (20 ml), for 24 h. The mixture was allowed to cool and the resulting precipitate was filtered and subsequently dried to afford the pure products **4** as white solids (Tables 1 and 2).
17. *Preparation of 7,8-diacylcoumarins* **5**. Lead tetracetate was added to a stirred solution of hydrazone **4** (1 mmol) in THF (20 ml), in an ice bath. The molar ratios of hydrazone/LTA and the reaction times are presented in Table 1. The mixture was then stirred at rt with the exception of **4f**, which was stirred in an ice bath. The oily product obtained after filtration of lead diacetate and condensation of the filtrate was subjected to column chromatography (silica gel 70–230 mesh) eluting with a mixture of petroleum ether/ethyl acetate 1:1 to afford pure products **5** as white solids (Tables 1 and 2).