Pergamon

Tetrahedron Letters 43 (2002) 2293–2295

TETRAHEDRON LETTERS

A facile three-component reaction involving [4+1] cycloaddition leading to furan annulated heterocycles†

Vijay Nair,* Rajeev S. Menon, A. U. Vinod and S. Viji

Organic Chemistry Division, Regional Research Laboratory, Trivandrum 695 019, India

Received 19 November 2001; revised 17 January 2002; accepted 30 January 2002

Abstract—The in situ generated quinone methides from 4-hydroxycoumarin and 4-hydroxy-6-methylpyrone with various aldehydes underwent facile reaction with cyclohexyl isocyanide to produce furocoumarins in good yields. Quinone methides from 4-hydroxy-1-methylquinolinone afforded furoquinolones. The reaction presumably occurs via a [4+1] cycloaddition followed by a [1,3] H shift. © 2002 Published by Elsevier Science Ltd.

Furocoumarins are an important class of compounds, presumably related to the natural defense of plants against fungal attack.[1] They are inherently photosensitive and found to have therapeutic uses. The photochemotherapeutic effect relies on their ability to intercalate with the pyrimidine bases of microorganism DNA.[2]

Recently we have reported Diels–Alder reactions of quinone methides generated from 4-hydroxycoumarin and 4-hydroxy-1-methylquinolinone to afford pyranocoumarins and quinolones.[3] In this context it appeared that a [4+1] cycloaddition could be effected in one pot with nucleophilic carbenes such as isocyanides.[4] Although the participation of isocyanides in [4+1] cycloaddition reactions is well precedented,[5] the reported reactions involve two or more steps, for example barbituryl benzylidenes prepared by Perkin condensation of aromatic aldehydes with dimethyl barbituric acid underwent cycloaddition with phenyl isocyanide.[6] Herein we wish to report a facile one-pot synthesis of furan annulated heterocycles involving a [4+1] cycloaddition with various in situ generated heterocyclic quinone methides and isocyanides, which offers a convenient alternative to the multistep synthesis of furocoumarins and quinolones reported previously.

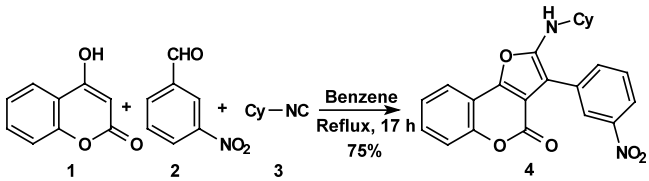
Our studies were initiated with 4-hydroxy coumarin, which upon treatment with a stoichiometric amount of 3-nitrobenzaldehyde and cyclohexyl isocyanide afforded the product **4** in 75% yield (Scheme 1).[7]

The product was characterized on the basis of spectroscopic data. The IR spectrum of the product showed a strong peak at 1724 cm^{-1}. This value is typical for the coumarin carbonyl group indicating that the product is the angular one. In the ^1H NMR spectrum the aromatic protons were seen between δ 7.31–8.35 and the amine hydrogen atom resonated at δ 4.36 as a doublet (exchangeable by D_2O).

Several examples of this addition reaction which attest to the synthetic utility of the process are compiled in Table 1.

Mechanistically the following scheme may be invoked to explain the formation of product **4**. It is conceivable that the initially generated quinone methide participates in a [4+1] cycloaddition reaction with the isocyanide to afford a dihydrofuran derivative **5**, which then undergoes a [1,3] H shift to yield the furocoumarin as the end product (Scheme 2).

To extend the scope of the reaction, we briefly investigated the reaction of quinone methides[8] generated from



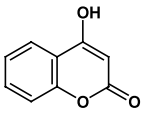
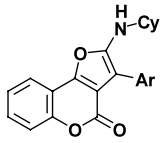
Scheme 1.

* Corresponding author. Tel.: 91-471-490324; fax: 91-471-491712; e-mail: gvn@csrrltrd.ren.nic.in

† This paper is dedicated with best wishes and regards to Professor Dr. Binne Zwannenburg.

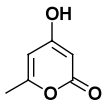
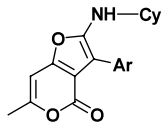
0040-4039/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4039(02)00226-5

Table 1. Reaction of 4-hydroxycoumarin and aldehydes with cyclohexyl isocyanide

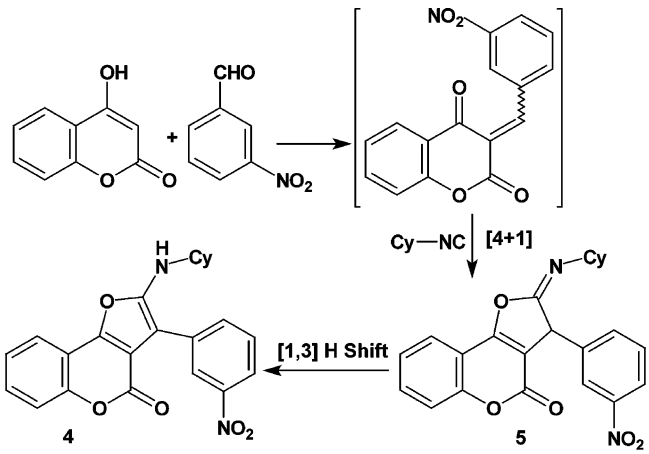
Coumarin		Ar-CHO	t/h	Yield (%)[a]	Product
	Ar =	1. 2-NO_2-Ph	24	69	
		2. 4-NO_2-Ph	16	93	
		3. 4-Cl -Ph	24	61	
		4. Ph	24	77	
		5. 4-MeO-Ph	16	62	
		6. 4-Me-Ph	24	72	

[a] = isolated yield, Cy = cyclohexyl

Table 2. Reaction of 4-hydroxy-6-methylpyrone and aldehydes with cyclohexyl isocyanide

Pyrone		Ar-CHO	t/h	Yield (%)[a]	Product
	Ar =	1. 4-NO_2-Ph	16	85	
		2. 4-Cl -Ph	16	51	
		3. Ph	16	62	
		4. 4-MeO-Ph	14	34	

[a] = isolated yield, Cy = cyclohexyl



Scheme 2.

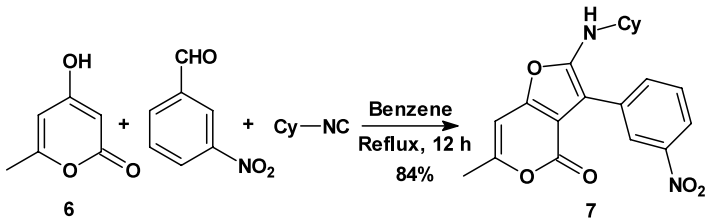
4-hydroxy-6-methylpyrone. In a prototype experiment, the pyrone was treated with 3-nitrobenzaldehyde and a stoichiometric amount of cyclohexyl isocyanide to afford the product in 84% yield (Scheme 3).[9] The reaction proceeds well with other aromatic aldehydes also. The results are presented in Table 2.

A similar cycloaddition reaction of quinone methides generated from quinolinone[10] appeared attractive from the standpoint of potential synthesis of novel furoquinolone compounds. In the event experiments involving 4-hydroxy-1-methylquinolinone, stoichiometric amounts of 4-nitrobenzaldehyde and cyclohexyl isocyanide in refluxing benzene afforded the product in 84% yield (Scheme 4).[11] 3-Nitrobenzaldehyde similarly gave **9b**.

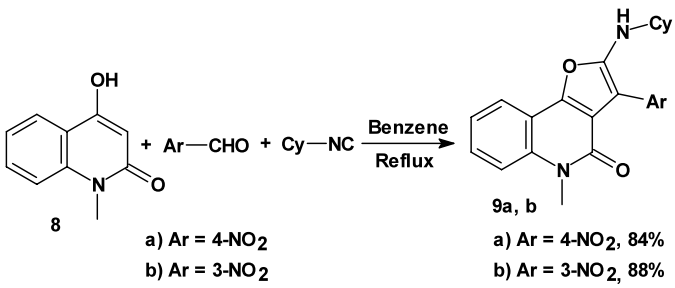
In conclusion, we have devised an easy and facile one-pot synthesis of furocoumarins and quinolones by the reaction of in situ generated quinone methides with isocyanides. It is conceivable that these compounds may have important applications in medicinal and synthetic organic chemistry.

Acknowledgements

R.S.M. and A.U.V. thank CSIR, New Delhi, for research fellowships. The authors also thank Ms. Saumini Mathew for high resolution NMR spectra.



Scheme 3.



Scheme 4.

References

1. Murray, R. D. H. *The Natural Coumarins, Occurrence, Chemistry and Biochemistry*; Wiley-Interscience: New York, 1982.
2. Edelson, R. L. *J. Photochem. Photobiol. B.* **1991**, *10*, 165.
3. (a) Nair, V.; Jayan, C. N.; Radhakrishnan, K. V.; Anilkumar, G.; Rath, N. P. *Tetrahedron* **2001**, *57*, 5807; (b) Nair, V.; Treesa, P. M.; Jayan, C. N.; Rath, N. P.; Vairamani, M.; Prabhakar, S. *Tetrahedron* **2001**, *57*, 7711.
4. *Isonitrile Chemistry*; Ugi, I., Ed.; Academic Press: New York, 1971.
5. (a) Obata, N.; Takizawa, T. *Tetrahedron Lett.* **1969**, *10*, 3403; (b) Ito, Y.; Kato, H.; Saegusa, T. *J. Org. Chem.* **1982**, *47*, 741; (c) Gambarayan, N. P.; Rokhlin, E. M.; Zeifmann, Yu. V.; Simonyan, L. A.; Knunyans, I. L. *Dokl. Akad. Nauk SSR* **1966**, *166*, 864; (d) Rigby, J. H.; Qabar, M. N. *J. Am. Chem. Soc.* **1991**, *113*, 8975; (e) Kollenz, G.; Ott, W.; Ziegler, E.; Peters, K.; v. Schnering, H. G.; Quast, H. *Liebigs Ann. Chem.* **1980**, 1801; (f) Ott, W.; Kratky, Chr.; Seiler, P. *Liebigs Ann. Chem.* **1980**, 1711; (g) Ott, W.; Kollenz, G.; Peters, K.; Peters, E.-M.; v. Schnering, H. G.; Quast, H. *Liebigs Ann. Chem.* **1983**, 635.
6. Figueroa-Villar, J. D.; Carneiro, C. L.; Cruz, E. R. *Heterocycles* **1992**, *34*, 91.
7. Representative experimental procedure and spectroscopic data for compound **4**: To a mixture of the hydroxycoumarin (163 mg, 1 mmol) and 3-nitrobenzaldehyde (167 mg, 1.1 mmol) in benzene (15 mL), cyclohexyl isocyanide (120 mg, 1.1 mmol) was added and the reaction mixture refluxed for 17 h. The residue obtained after the removal of the solvent was dissolved in CH_2Cl_2–hexane mixture for recrystallization. The crystallized product was separated and washed with hexane (4×5 mL) to give **4** as a red crystalline solid (315 mg, 75%). Mp 155–156°C. IR (KBr) ν_{max}: 3323, 2934, 2855, 1724, 1608, 1529, 1450, 1347, 1091 cm^{-1}. ^1H NMR: δ 1.21–2.10 (m, 10H), 3.60 (m, 1H), 4.36 (d, 1H, $J=7.82$, D_2O exchangeable), 7.28–7.45 (m, 3H), 7.56 (t, 1H, $J=7.98$), 7.75 (d, 1H, $J=7.27$), 7.90 (d, 1H, $J=7.71$), 8.06 (d, 1H, $J=8.16$), 8.35 (s, 1H). ^{13}C NMR: δ 24.77, 25.40, 34.00, 53.57, 95.21, 96.23, 110.38, 112.47, 116.92, 119.52, 121.19, 123.15, 124.26, 129.01, 129.31, 135.55, 148.31, 150.04, 151.35, 155.12, 157.50. Anal. calcd for $C_{23}H_{20}N_2O_5$: C, 68.30; H, 4.98; N, 6.92. Found: C, 68.52; H, 4.81; N, 7.10.
8. Hua, D. H.; Chen, Y.; Sin, H.-S.; Maroto, M. J.; Robinson, P. D.; Newell, S. W.; Perchellet, E. M.; Ladesich, J. B.; Freeman, J. A.; Perchellet, J. P.; Chiang, P. K. *J. Org. Chem.* **1997**, *62*, 6888.
9. Spectroscopic data for compound **7**: IR (KBr) ν_{max}: 3312, 2935, 2861, 1715, 1613, 1566, 1512, 1445, 1344, 1263 cm^{-1}. ^1H NMR: δ 1.22–2.02 (m, 10H), 2.32 (s, 3H), 3.44 (m, 1H), 4.30 (br s, 1H), 6.33 (s, 1H), 7.49 (t, 1H, $J=7.98$), 7.86 (d, 1H, $J=7.71$), 7.98 (d, 1H, $J=8.19$), 8.31 (s, 1H). ^{13}C NMR: δ 20.02, 24.84, 25.47, 34.04, 53.52, 95.15, 96.16, 108.01, 120.73, 122.96, 129.19, 132.93, 135.30, 148.23, 153.96, 155.22, 157.26, 159.31.
10. Desimoni, G.; Tacconi, G. *Chem. Rev.* **1975**, *75*, 651.
11. Spectroscopic data for quinolone **9a**: IR (KBr) ν_{max}: 3243, 2928, 2853, 1648, 1593, 1506, 1333, 1247, 1111 cm^{-1}. ^1H NMR: δ 1.28–2.12 (m, 10H), 3.68 (m, 1H), 3.76 (s, 3H), 4.48 (d, 1H, $J=7.98$), 7.29–7.50 (m, 3H), 7.73 (d, 2H, $J=8.74$), 7.89 (d, 1H, $J=7.78$), 8.23 (d, 2H, $J=8.75$). ^{13}C NMR: δ 24.87, 25.51, 29.29, 34.05, 53.30, 96.13, 112.48, 114.53, 114.71, 119.88, 122.20, 123.41, 128.03, 129.72, 136.58, 139.32, 145.30, 148.07, 155.25, 158.73.