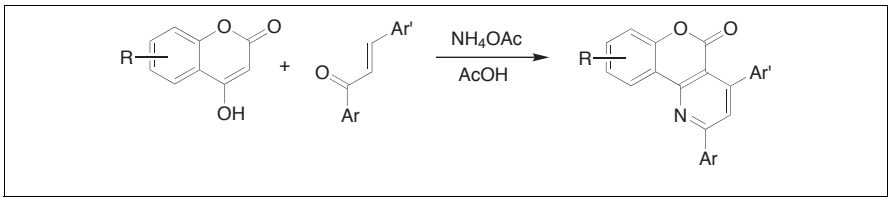
Shashi U. Pandya, Urvish R. Pandya, Bhanu R. Hirani and Dinker I. Brahmbhatt*

Department of Chemistry, Sardar Patel University, Vallabh Vidyanagar - 388 120 India
Tel.: +91-2692-226855/56/57, Fax: +91-2692-236475
Email: dib.chem@spu.ernet.in
Received March 23, 2005



Various diarylpyrido[3,2-*c*]coumarins **3a-l** have been synthesized in one step by reacting 4-hydroxy coumarins **1a-d** with α,β-unsaturated ketones **2a-c** in the presence of ammonium acetate and acetic acid under Kroehnke's reaction conditions.

J. Heterocyclic Chem., **43**, 795 (2006).

Introduction.

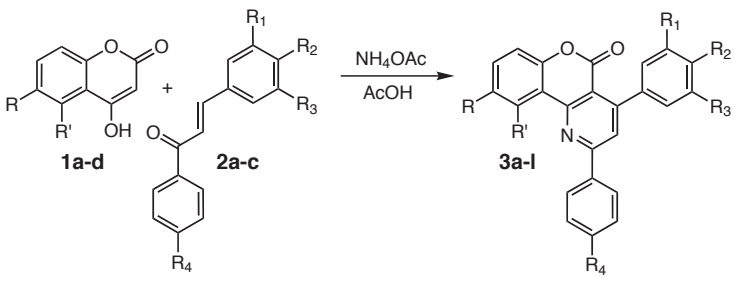
Coumarins (2*H*-1-benzopyran-2-ones) are well known aromatic lactones isolated from variety of plant sources [1]. Owing to their diverse bioactivities *viz.* anticoagulant [2], antibacterial, and antifungal [3] *etc.* many natural, semi synthetic and synthetic coumarins have become an important class of molecules in drug research. In this direction, several biological activities have been claimed for compounds comprising both coumarins and coumarins fused to a pyridine ring. For instance, coumarin nucleus is present in promising drug candidates as nonpeptidic HIV protease inhibitors [4], topoisomerase II [5] and tyrosine kinase [6] inhibitors. Coumarins fused with pyridines have also been reported to possess antiallergic [7], anticoagulant [8], antidiabetic [9] activities, and even analgesic [10] properties, being characterized by a phenanthrene-like structure as found in tetrahydrocannabinol. Pyrido[2,3-*c*]coumarin constitutes the backbone of naturally occurring alkaloids, Santiagonamine [11] isolated from Berberis Darwinii (Berberidacea). This alkaloid has shown interesting wound healing properties [12]. Owing to such interesting properties, synthesis of pyridocoumarins has remained an active subject of interest [13]. However, a survey of these literature quotes reveals that most of the methods are multistep or require difficult starting materials. Hence, it was thought worthwhile to envisage a simple synthesis of pyrido fused coumarins.

As quoted by Kroehnke [14], reaction of an α,β-unsaturated ketone with the active methylene function of phenacyl bromide pyridinium salt in presence ammonium acetate and acetic acid yields pyridine. This methodology has been successfully utilized, by us for the synthesis of a variety of pyridyl substituted coumarins [15]. In the present work this strategy has been extended to synthesize pyrido fused coumarins.

4-Hydroxy coumarins, due to their tautomeric existence, act as cyclic β-keto esters. The active methylene group of such cyclic β-keto ester has been used by us for the synthesis of a variety of heterocyclic fused coumarins [16] *viz.* pyrimido, thiopyrimido and furo fused coumarins. Hence, it was thought that such tautomeric forms of 4-hydroxy coumarin would also react with α,β-unsaturated ketone systems under Kroehnke's reaction conditions and can result in the pyrido[3,2-*c*]coumarin ring system (Scheme - I).

The formation of the products **3a-l** follows the Kroehnke's mechanism. The mechanism involves

Scheme - I



Michael addition of the active methylene function of **1a-d** onto α,β-unsaturated ketones **2a-c** (we believe the addition is probably *via* the enamine) giving rise to intermediate **4** (not isolated) which in the presence of acetic acid dehydrates *in situ* and aromatizes to afford the 2,4-diarylpyrido[3,2-*c*]coumarins **3a-l** (Scheme - II).

Scheme - II

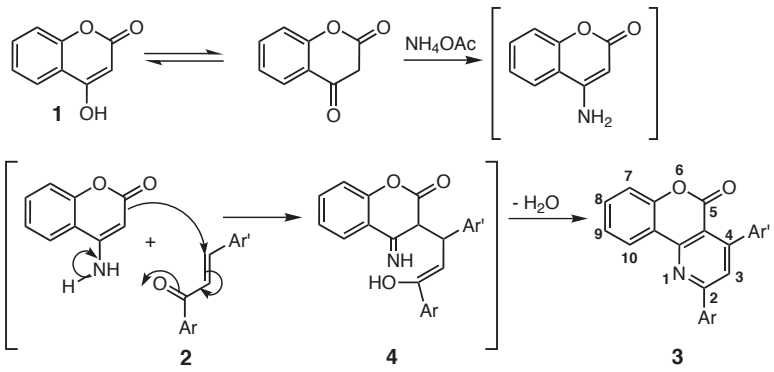


Table 1

Yield and melting points of 2,4-Diarylpyrido[3,2-*c*]coumarins **3a-l**

Entry	R	R'	R_1	R_2	R_3	R_4	Yield (%)	mp
a	H	H	H	H	H	H	65	205-07
b	H	H	H	H	H	OCH_3	62	208-10
c	H	H	OCH_3	OCH_3	OCH_3	H	60	230-32
d	CH_3	H	H	H	H	H	67	217-20
e	CH_3	H	H	H	H	OCH_3	30	191-93
f	CH_3	H	OCH_3	OCH_3	OCH_3	H	32	194-96
g	Cl	H	H	H	H	H	55	207-09
h	Cl	H	H	H	H	OCH_3	42	203-05
i	Cl	H	OCH_3	OCH_3	OCH_3	H	59	251-53
j	-Benzo-		H	H	H	H	41	125-27
k	-Benzo-		H	H	H	OCH_3	50	168-70
l	-Benzo-		OCH_3	OCH_3	OCH_3	H	35	175-77

In conclusion, the present synthesis is a simple, straight forward, one pot method with general applicability and affords diarylpyrido[3,2-*c*]coumarins in moderate to good yields (Table 1). The required starting materials, 4-hydroxy coumarins **1a-d** [17] andα,β-unsaturated ketones **2a-c** [18] were prepared according literature procedures.

EXPERIMENTAL

All the melting points reported are in degree centigrade and are uncorrected. All the ir spectra were recorded on Niclolett Impact 400 spectrometer. ^{1}H nmr spectra of all the compounds were recorded on Hitachi R-1500 spectrometer at 60 MHz in $CDCl_3$/DMSO-d_6 (with TMS as internal standard). ^{13}C and ^{1}H nmr spectra of some selected compounds were scanned on Bruker Avance 500 MHz and Varian Gemini 200 MHz spectrometers. Elemental analyses were carried out with a Hareaus CHNO analyser.

General Procedure for the Synthesis of 2,4-Diarylpyrido[3,2-*c*]-coumarins (**3a-l**).

To a mixture of appropriate 4-hydroxycoumarin **1a-d** (0.006 mole) in acetic acid (15 mL) were added ammonium acetate (6.0 g) and a solution of appropriate chalcone (α,β-unsaturated ketone) **2a-c** (0.006 mole) in acetic acid (15 mL) at room temperature. The reaction mixture was stirred at room temperature for 1 hr and then refluxed for 6 hrs in an oil-bath at 130 °C. The reaction mixture was allowed to reach room temperature and was poured into ice cold water (100 mL). The resultant sticky material was extracted with chloroform (3 × 50 mL). The chloroform extract was successively washed with saturated $NaHCO_3$ solution (2 × 50mL), water (3 × 50mL), brine (3 x 50mL) and dried over anhydrous Na_2SO_4. Distillation of chloroform resulted in gummy residues which upon column chromatography over silica gel with ethyl acetate-pet. ether (10:1) as an eluent afforded the title compounds **3a-l** in 30 to 67% yield. The compounds were recrystallised from chloroform-hexane. All the compounds gave satisfactory analytical and spectroscopic data (Table-2).

Selected Spectroscopic Data (**3h**).

Crystalline solid; ^{1}H NMR ($CDCl_3$, 500MHz): 3.89 (3H, s, -OCH_3), 7.03 (2H, d, J = 8.7 Hz, H_2 & H_6 of Ar at C-2), 7.29 (1H, d, J = 8.7 Hz, H_7), 7.38 (2H, d, J = 8.7 Hz, H_3 & H_5 of Ar at C-2), 7.52 (1H, dd, J =8.7Hz and 2.6Hz, H_8), 7.57 (3H, m, H_3,

Table 2
Analytical and Spectroscopic Data of Compounds **3a-l**

Compd*	Molecular formula	% Found (Cal.) C	H	N	^{1}H-NMR (™, ppm)
3a[13a]	$C_{24}H_{15}NO_2$	82.4 (82.5	4.3 4.3	4.1 4.0)	7.2 – 8.9 (15H, m, Ar-H)
3b	$C_{25}H_{17}NO_3$	79.3 (79.1	4.4 4.5	3.9 3.7)	3.9 (3H, s, -OCH_3), 7.25 – 9.00 (14H, m, Ar-H)
3c	$C_{27}H_{21}NO_5$	73.7 (73.8	4.9 4.8	3.1 3.2)	3.95 and 4.00 (9H, 2 x s, 3 x -OCH_3), 6.7 – 9.0 (12H, m, Ar-H)
3d	$C_{25}H_{17}NO_2$	82.8 (82.6	4.6 4.7	3.8 3.9)	2.42 (3H, s, -CH_3), 7.32 – 7.59 (14H, m, Ar-H)
3e	$C_{26}H_{19}NO_3$	79.3 (79.4	4.6 4.8	3.3 3.6)	2.41 (3H, s, -CH_3), 4.0 (3H, s, -OCH_3), 7.3 – 7.59 (13H, m, Ar-H)
3f	$C_{28}H_{23}NO_5$	74.1 (74.2	5.4 5.1	3.0 3.1)	2.54 (3H, s, -CH_3), 3.91 and 3.96 (9H, 2 x s, 3 x -OCH_3), 6.64 – 8.65 (13H, m, Ar-H)
3g	$C_{24}H_{14}NO_2Cl$	75.3 (75.1	3.5 3.6	3.8 3.6)	7.27 – 8.31 (14H, m, Ar-H)
3h**	$C_{25}H_{16}NO_3Cl$	72.5 (72.6	4.1 3.9	3.1 3.4)	3.91 (3H, s, -OCH_3), 6.96 – 8.75 (13H, m, Ar-H)
3i**	$C_{27}H_{20}NO_5Cl$	68.4 (68.4	4.4 4.2	2.9 3.0)	3.89 and 3.96 (9H, 2 x s, 3 x -OCH_3), 6.8 – 8.8 (11H, m, Ar-H)
3j	$C_{28}H_{17}NO_2$	84.6 (84.2	4.3 4.3	3.7 3.5)	7.18 – 8.28 (17H, m, Ar-H)
3k	$C_{29}H_{19}NO_3$	81.5 (81.1	4.1 4.4	3.6 3.3)	3.88 (3H, s, -OCH_3), 6.97 – 8.24 (16H, m, Ar-H)
3l	$C_{31}H_{23}NO_5$	75.8 (76.1	4.3 4.7	3.2 2.9)	3.94 (9H, s, 3 x -OCH_3), 6.91 – 8.22 (14H, m, Ar-H)

* All compounds exhibited the characteristic IR bands at 3060 – 3000 (C-H stretching of pyridine ring), 1735 – 1682 cm-1 (™ - lactone of coumarin), **High resolution NMR (^{1}H & ^{13}C) data of these compounds is given below

H_4, H_5 of Ar at C-4), 7.79 (1H, s, H_3), 8.23 (2H, dd, J = 7.6Hz and 1.9 Hz, H_2 & H_6 of Ar at C-4), 8.74 (1H, d, J = 2.5 Hz, H_{10}); ^{13}C NMR ($CDCl_3$, on 125.75MHz): 55.05 (OCH_3), 112.94 (C), 113.34 (C_2 & C_6 of Ar at C_2), 117.98 (C_7), 120.79 (C), 123.37 (C_3), 124.81 (C_{10}), 127.47 (C_2 & C_6 of Ar at C-4), 128.76 (2xCH of Ar at C_4), 129.45 (C_3 & C_5 of Ar at C-2), 129.70 (C), 130.64 (CH of Ar at C-4), 131.72 (C_8), 130.87 (C), 137.03 (C), 150.91 (C), 151.71 (C), 154.90 (C), 158.67 (C), 159.80 (C_9), 160.69 (C=O).

Selected spectroscopic data: **3i**,

Crystalline solid; ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 200MHz): 3.89 (6H, s, 2xOCH_3), 3.96 (3H, s, OCH_3), 6.65 (1H, s, H_3), 7.38 & 7.91 (2H, s, H_2 & H_6 of Ar at C-4), 7.51-7.61 (5H, m, ArH at C-2), 8.28-8.38 (2H, dd, J = 6.7Hz and 2.9Hz H_7 & H_8), 8.75 (1H, d, J = 2.5 Hz, H_{10}); ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 50.4MHz): 55.23 (2xOCH_3), 59.69 (OCH_3), 102.95 (C), 104.82 (2xCH), 106.88 (C), 117.32 (CH), 119.98 (C), 122.50 (CH), 123.88 (CH), 126.81 (2xCH), 128.05 (2xCH), 130.02 (CH), 130.25 (C), 131.08 (CH), 133.56 (C), 135.02 (C), 136.11 (C), 151.82 (2xC), 154.09 (C), 159.10 (C), 167.89 (C=O).

Acknowledgements.

The authors are grateful to Head Department of chemistry for providing research facilities. The authors SP and BH are also grateful to University Grants Commission, India and Gujarat Government respectively for research fellowships. The authors also wish to thank Department of Organic Chemistry, University of Debrecen, Hungary, for high field spectroscopic analysis.

REFERENCES

[1a] T. A. Geissman, The Chemistry of Flavonoid Compounds, Pergamon Press: Oxford, 1962; [b] J. B. Harborne, The Flavonoids: The Advances in Research since 1980, Chapman & Hall: London, 1988; [c] J. B. Harborne, The Flavonoids: The Advances in Research since 1986; Chapman & Hall: London, 1994.

[2a] M. S. Y. Khan and P. Sharma, *Ind. J. Chem.*, **32B**, 374 (1993); [b] M. S. Y. Khan and P. Sharma, *Ind. J. Chem.*, **34B**, 237 (1995).

[3] J. A. A. Miky and A. A. Farrag, *Ind. J. Chem.*, **36B**, 357 (1997).

[4] Thaisrivongs, M. N. Janakiraman, K. T. Chong, P. K. Tomich, L. A. Dolack, S. R. Turner, J. W. Strohbach, J. C. Lynn, M. M. Horng, R. R. Hinshaw, K. D. Watenpaugh, *J. Med. Chem.*, **39**, 2400 (1996).

[5] G. Rappa, K. Shyam, A. Lorico, O. Fodstad, A. C. Sartorelli, *Oncology Res.*, **12**, 113 (2000).

[6] E. D. Yang, Y. N. Zhao, K. Zhang, P. Mack, *Biochem. Biophys. Res. Commun.*, **260**, 682-685 (1999).

[7] K. Ukawa, Ishiguro, Y. Wada, A. Nohara, *Heterocycles*, **24**, 1931 (1986).

[8] H. Brauninger, R. Plagemann, H. D. Schalicke, K. Peseke, *Naturwissenschaftliche Reihe*, **35**, 34-39 (1986).

[9] D. Heber, *Arch. Pharm.*, **320**, 402-406 (1987).

[10] D. Heber, T. Berghaus, *J. Heterocyclic Chem.*, **31**, 1353 (1994).

[11] E. Valencia, A. Patra, A. J. Freyer, M. Shamma, V. Fajardo, *Tetrahedron Lett.*, **25**, 3163 (1984).

[12] W. H. Lewis, R. J. Stonard, B. Porras-Reyes, T. A. Mustoe, A. Thomas, *US Patent 5156847* (1992); *Chem. Abstr.,* **117**, 245630t (1992).

[13a] J. N. Chatterjee, S. C. Shaw, J. N. Singh, S. N. Singh, *Ind. J. Chem.*, **15B**, 430 (1977); [b] F. Eiden, E. Baumann, H. Lotter, *Liebigs Ann. Chem.*, **2**, 165 (1983); [c] C. N. O'Callaghan, *Synthesis*, **5**, 499 (1987); [d] D. Heber, I. C. Ivanov, S. K. Karagiosov, *J. Heterocyclic Chem.*, **32**, 505 (1995); [e] G. Pave, P. Chalard, M-C. Viaud-Massuard, Y. Troin, G. Guillaumet, *Synlett*, **7**, 987 (2003); [f] E. M. Beccalli, A. Contini, P. Trimarco, *Tetrahedron Lett.*, **45**, 3447 (2004).

[14] F. Kroehnke, *Synthesis*. **1**, 1 (1976).

[15a] D. I. Brahmbhatt, B. R. Hirani, *Ind. J. Chem.*, **33B**, 1072 (1994); [b] D. I. Brahmbhatt, G. B. Raolji, S. U. Pandya, U. R. Pandya, *Ind. J. Chem.*, **38B**, 212 (1999); [c] D. I. Brahmbhatt, C. N. Patel, V. P. Pandya, M. A. Patel, *Ind. J. Chem.*, **43B**, 2228 (2004).

[16a] D. I. Brahmbhatt, G. B. Raolji, S. U. Pandya, U. R. Pandya, *Ind. J. Chem.*, **38B**, 839 (1999); [b] D. I. Brahmbhatt, B. R. Hirani, S. U. Pandya, U. R. Pandya, *Ind. J. Chem.*, **39B**, 233 (2000).

[17a] J. R. Giegy A. G., *Brit.* 755,162 (1956); *Chem. Abstr.,* **51**, 8146e (1957); [b] V. R. Shah, J. L. Bose, R. C. Shah, *J. Org. Chem.*, **25**, 677 (1960).

[18] W. Davey, D. Tivey, *J. Chem. Soc.*, 1230 (1958).