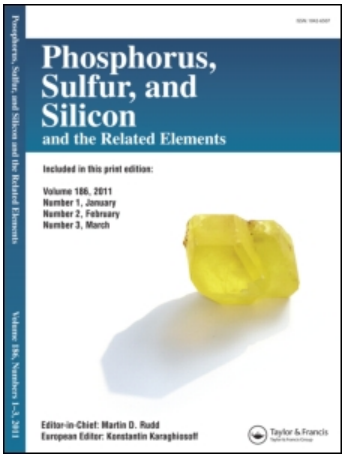


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESIS OF 3-(1,2,3-THIADIAZOL-4-YL) AND 3-(6-HYDROXYTHIAZOLO [3,2-a] BENZIMIDAZOL-3-YL) COUMARINS

V. Ravi Kumar[a]; V. Rajeshwar Rao[a]
[a] Department of Chemistry, Regional Engineering College, Warangal, A.P, India

To cite this Article Kumar, V. Ravi and Rao, V. Rajeshwar(1997) 'SYNTHESIS OF 3-(1,2,3-THIADIAZOL-4-YL) AND 3-(6-HYDROXYTHIAZOLO [3,2-a] BENZIMIDAZOL-3-YL) COUMARINS', Phosphorus, Sulfur, and Silicon and the Related Elements, 130: 1, 185 — 191
To link to this Article: DOI: 10.1080/10426509708033708
URL: http://dx.doi.org/10.1080/10426509708033708

Phosphorus, Sulphur, and Silicon, 1997, Vol. 130, pp. 185–191
Reprints available directly from the publisher
Photocopying permitted by license only

SYNTHESIS OF 3-(1,2,3-THIADIAZOL-4-YL) AND 3-(6-HYDROXYTHIAZOLO [3,2-a] BENZIMIDAZOL-3-YL) COUMARINS

V. RAVI KUMAR and V. RAJESHWAR RAO*

Department of Chemistry, Regional Engineering College, Warangal (A.P.) 506 004, India

(Received 1 May 1997; Revised 27 August 1997; In final form 27 August 1997)

Some 3-(1,2,3-thiadiazol-4-yl) coumarins (III) have been prepared from 3-acetyl coumarin semicarbazones (II) by treating the latter with thionyl chloride. Compounds II are obtained by interaction of 3-acetyl coumarins (I) with semicarbazide hydrochloride in pyridine. Certain condensed heterocycles such as 3-(6-hydroxythiazolo[3,2-a] benzimidazol-3-yl) coumarins (V) have also been prepared from condensation of 3-(2-amino-4-thiazolyl) coumarins with p-benzoquinone. The structures of these compounds have been established by elemental analysis and spectral data.

Keywords: p-benzoquinone; thiadiazole; thiazolyl coumarin

INTRODUCTION

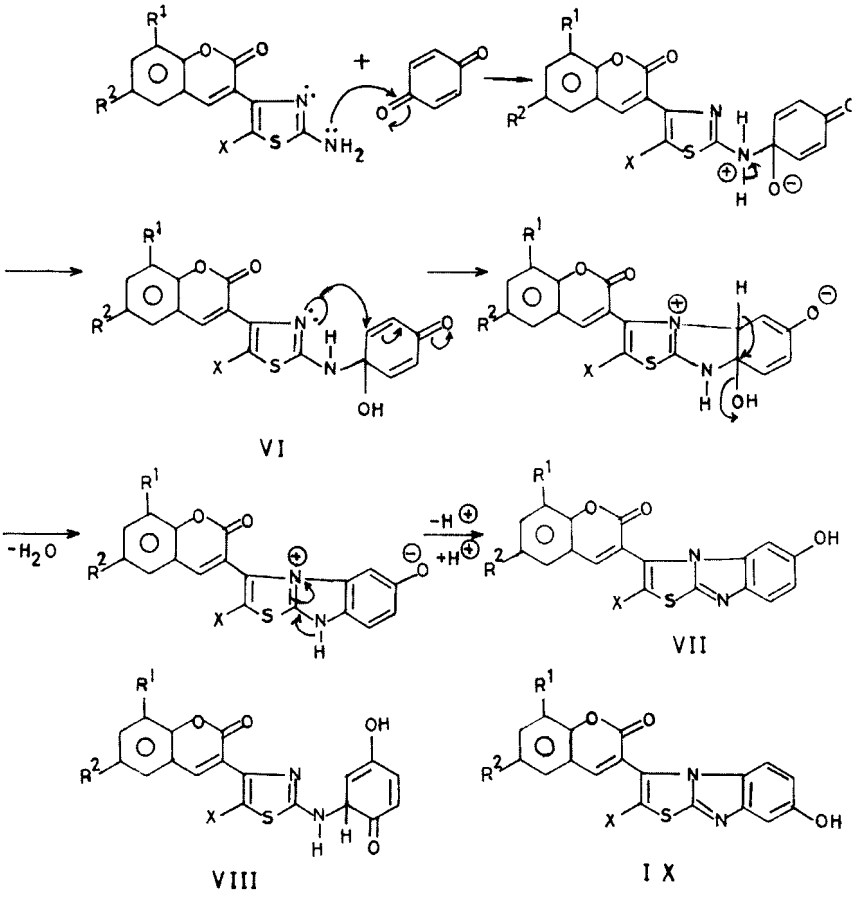
Coumarins bearing one or more phenolic groups and containing a pyridyl moiety at the 3-position are spasmolytic and uricosuric agents.[1] Further 1,2,3-thiadiazoles are reported to exhibit antibacterial[2] and platelet aggregation inhibiting activity[3] *in vivo* in humans. The chemotherapeutic importance of imidazole derivatives is well recognised.[4–6] The effectiveness of condensed heterocycles containing thiazole and imidazole ring as antiprotozoal agents,[7] anticonvulsants,[8] antidepressants,[9] antihelminthic agents,[9–12] antidiabetic,[13] and as inhibitors of dihydro folate[14] led us to synthesize two new series of title compounds.

*Corresponding author.

RESULTS AND DISCUSSION

In continuation of our earlier work on heterocyclic systems from coumarins,[15–19] we now report the preparation of 3-(1,2,3-thiadiazol-4-yl) coumarins (III) in a two step process starting from 3-acetyl coumarins. 3-Acetyl coumarins (I) were obtained by literature[20,21] method. The reaction of I in pyridine with semicarbazide hydrochloride afforded the expected semicarbazones (II) The IR spectra of II with bands in the region of 3387–3499 (NH), 1682 (-$CONH_2$), 1720 (lactone) and 1562 cm^{-1} (-C=N-) were compatible with the structures. Synthesis of 3-(1,2,3-thiadiazol-4-yl) coumarins (III) was accomplished by treating semicarbazones of 3-acetyl coumarins (II) with thionyl chloride.[22] Lack of absorption in the IR spectra of III in the region of 3387–3499 and 1682 showed the absence of amino and amide carbonyl groups respectively. Additional bands in the region of 3100 and 802 corresponding to C-H and C-S stretching respectively suggest cyclic structure for III. The structures of III were supported by their ^{1}H-NMR spectra. The ^{1}H-NMR spectrum of IIIa ($R^1=H$, $R^2=H$) exhibited a characteristic[2] singlet for the thiadiazole proton at δ 9.6. The remaining protons were observed in the expected region.[23] 3-(6-hydroxythiazolo[3,2-a] benzimidazol-3-yl) coumarins were prepared by the acid catalysed cyclodehydration of amino heterocycles (IV) with p-benzoquinone in acetic acid. The reaction involves an initial nucleophillic attack of the amino group at the carbonyl carbon to give the unstable intermediate VI which undergoes cyclodehydration to give VII by attack at the ortho carbon through imino nitrogen.

The UV spectrum of VIIa ($R^1=R^2=H$) prepared from 3-(2-amino-4-thiazolyl) coumarin with p-benzoquinone in neutral methanol showed a band at 351 nm. The absorption band underwent bathochromic shift in 0.01 M NaOH (ν max at 356 nm) and 348.5 nm. in 0.1 M HCl solutions. The greater shift in alkaline medium may be due to quinonoid structure as one of the contributing forms. However, the slightly shift in acid solution is ascribable to salt formation. The possibility for the formation of 3-(7-hydroxy thiazolo [3,2-a]benzimidazolyl) coumarins (IX) through the initial attack of amino nucleophillic group at the electrophillic metacarbon VIIIb with respect to the carbonyl group and subsequent cyclodehydration was ruled out because IX cannot give rise to quinonoid structure and the spectral behaviour of the compound cannot be explained. This type of change in the structure at different pH values has been observed by other workers.[24] It indicates that the presence of hydroxyl group in these title compounds which being more acidic causes the molecule to attain greater dipolar character at different pH thereby facilitating absorption in the longer wavelengths.



All the hydroxy thiazolobenzimidazolyl coumarins (V) displayed strong absorption bands due to the -OH and lactone carbonyl frequencies at 3353 and 1720 cm^{-1}.

The ^{1}H-NMR spectrum of Va showed a characteristic down field proton at δ 12.2 for phenolic OH group. The remaining protons were observed in the usual region.

EXPERIMENTAL

All melting points were determined in open capillary tubes using a sulphuric acid bath and are uncorrected. IR spectra (ν max cm^{-1}) were recorded on Perkin-Elmer 282 instrument. The ^{1}H-NMR spectra ($CDCl_3$ and DMSO-d_6) were

TABLE I Analytical data of compounds II, III and V

Compd	R^1 R^2	*X*	*m.p.*[a] *(°C)*	*Formula (m.w.)*	*Recrystallization solvent*	*Calc. (Found) %*	
						N	*S*
IIa	H	–	232–234	$C_{12}H_{11}N_3O_3$	AcOH	17.14	–
	H			(245)		(17.12)	
IIb	OCH_3	–	208–210	$C_{13}H_{13}N_3O_4$	AcOH	15.27	–
	H			(275)		(15.18)	
IIc	H	–	233–235	$C_{12}H_{10}BrN_3O_3$	DMF	12.96	–
	Br			(324)		(12.92)	
IId	Br	–	218–220	$C_{12}H_9Br_2N_3O_3$	AcOH	10.42	–
	Br			(403)		(10.41)	
IIe	5,6-benzo	–	213–215	$C_{16}H_{13}N_3O_3$	Aq·AcOH	14.23	–
	H			(295)		(14.20)	
IIf	H	–	211–213	$C_{13}H_{13}N_3O_3$	Aq·DMF	16.21	–
	CH_3			(259)		(16.18)	
IIIa	H	–	127–129	$C_{11}H_6N_2O_2S$	MeOH/H_2O	12.17	13.91
	H			(230)		(12.14)	(13.89)
IIIb	OCH_3	–	172–174	$C_{12}H_8N_2O_3S$	MeOH/H_2O	10.76	12.30
	H					(10.73)	(12.16)
IIIc	H	–	227–229	$C_{11}H_5BrN_2O_2S$	MeOH/H_2O	9.06	10.35
	Br			(309)		(9.00)	(10.31)
IIId	Br	–	167–169	$C_{11}H_4Br_2N_2O_2S$	$MeCO_2H/H_2O$	7.21	8.21
	Br			(388)		(7.20)	(8.18)
IIIe	5.6-benzo	–	210–212	$C_{15}H_8N_2O_2S$	$MeCO_2H/H_2O$	10.00	11.42
	H			(380)		(10.00)	(11.39)
IIIf	H	–	144–146	$C_{12}H_8N_2O_2S$	$MeCO_2H/H_2O$	11.47	13.11
	CH_3			(244)		(11.45)	(13.10)
Va	H	–	240–242	$C_{18}H_{10}N_2O_3S$	MeOH/H_2O	8.38	9.58
	H			(334)		(8.34)	(9.56)
Vb	OCH_3	–	>300	$C_{19}H_{12}N_2O_4S$	MeOH/H_2O	7.69	8.79
	H			(364)		(7.65)	(8.76)
Vc	H	–	274–276	$C_{18}H_9BrN_2O_2S$	MeOH/H_2O	6.77	7.74
	Br			(413)		(6.73)	(7.71)
Vd	Br	–	261–263	$C_{18}H_8Br_2N_2O_3S$	MeOH/H_2O	5.69	6.50
	Br			(492)		(5.65)	(6.47)
Ve	5.6-benzo	–	266–268	$C_{12}H_{14}N_2O_3S$	MeOH/H_2O	7.29	8.33
	H			(384)		(7.23)	(8.30)
Vf	H	–	221–223	$C_{18}H_{12}N_2O_3S$	MeOH/H_2O	8.33	9.52
	CH_3			(336)		(8.31)	(9.49)
Vg	H	Br	212–214	$C_{18}H_9N_2O_3SBr$	$MeCO_2H/H_2O$	6.77	7.74
	H			(413)		(6.72)	(7.72)
Vh	H	Br	>300	$C_{18}H_8N_2O_3SBr_2$	$MeCO_2H/H_2O$	5.69	6.50
	Br			(492)		(5.66)	(6.48)
Vi	Br	Br	154–156	$C_{18}H_7N_2O_3Br_3$	$MeCO_2H/H_2O$	4.90	5.60
	Br			(571)		(4.87)	(5.57)
Vj	OCH_3	Br	>300	$C_{19}H_{11}N_2O_4SBr$	$MeCO_2H/H_2O$	6.32	7.22
	H			(443)		(6.31)	(7.20)

TABLE II Spectral data of compounds II, III and V

Compd	*C-H*	*C-S*	*-C-NH_2*	*-C-O-*	*-NH- -OH*	*^{1}H-NMR (δ ppm)*	*Mass spectrum*
IIa	–	–	1682	1720	3387–3490	—-	—
IIIa	3100	802	–	–	–	7.5–7.8 (m, 4H, aromatic), 9.1 (s, 1H, coumarin C4), 9.6 (s, 1H, thiadiazole).	51(13.9), 62(11.6), 63(118.6), 69(13.41), 74(10.6), 75(12), 87(14.2), 102(60), 114(10.4), 130(21.6), 145(38.7), 146(42.3), 174(46.7), 202(100), 203(18.1), and 230 (31.4).
Va	3100	802	–	1720	3000–3500	7.3–7.6 (m, 7H, Ar-H), 7.97 (s, 1H, thiazole), 8.56 (s, 1H, C4 of coumarin) and 12.2 (s, 1H, phenolic OH).	102(25), 145(23.2), 211(24.3), 244(100), 245(29), 286(34.7), 287(5.9) and 334 (23).

recorded on a Varian 90 MHz and 300 MHz spectrometers using tetramethylsilane as internal standard. Chemical shifts are expressed in δ ppm mass spectra were scanned on JEOL-JMS 300 spectrometer using 70 eV.

Semicarbazones of 3-acetyl coumarins (IIa)

To a hot solution of 3-acetyl coumarin (0.05 mol) in pyridine was added a solution of semicarbazide hydrochloride (0.01 mol) in water (1.2 ml) during 15 minutes. The reaction mixture was left at room temperature for 48 hr. The precipitated yellow solid was filtered, washed with water and recrystallized from appropriate solvents viz. Table I.

3-(1,2,3-Thiadiazol-4-yl)coumarins (IIIa)

3-Acetyl semicarbazonocoumarin (0.004 mol) was added portion wise to cold solution of thionyl chloride (15 ml). The reaction mixture was refluxed for 4 hr, cooled and poured on crushed ice. The resulting mass was triturated with saturated sodium carbonate solution. The solid obtained was recrystallized from suitable solvents.

3-(6-Hydroxythiazolo[3,2-a]benzimidazol-3-yl)coumarins (Va)

A solution of p-benzoquinone (0.005 mol) in glacial acetic acid (10 ml) was added dropwise to a solution of 3-(2-amino-4-thiazolyl) coumarin (0.05 mol) with stirring. The reaction mixture was refluxed for 8 hr, cooled and poured over crushed ice. The solid separated was filtered and recrystallized from respective solvents. Data used to characterize these compounds are presented in the Table I.

Acknowledgements

The authors express their sincere thanks to the Principal, Regional Engineering College, Warangal for providing, a research grant under centre of excellence.

References

[1] W. Baker and C. S. Howese, *J. Chem. Soc.*, 119 (1953).
[2] B. M. Patil, B. V. Badami and G. S. Puranik, *Ind. J. Het. Chem.*, Vol. 3, Jan.–Mar. 193 (1994).
[3] Edward W. Thomas, Edward E. Nishizawa, Dawid C. Zimmermann and Davey J. Willams, *J. Med. Chem.*, **28**, 442 (1985).

[4] P. K. Smith and A. C. Hollinhead, *J. Pharmacol. Exp. Ther.*, **54**, 123 (1958).
[5] A. F. Wagner, P. E. Wihereich, A. Luisi and K. Folkers, *J. Org. Chem.*, **27**, 3236 (1962).
[6] E. W. Bernadt, H. D. Esser and B. G. Held, *J. Med. Chem.*, **12**, 371 (1969).
[7] J. M. Singh, *J. Med. Chem.*, **13**, 1019 (1970).
[8] C. J. Sharpe, R. S. Shadbolt, A. Ashferd and J. W. Ross, *J. Med. Chem.*, **14**, 977 (1972).
[9] I. F. Miller and R. E. Bambory, *J. Med. Chem.*, **15**, 415 (1972).
[10] R. K. Robins and G. H. Hitchings, *J. Am. Chem. Soc.*, **80**, 3449 (1958).
[11] A. H. M. Raeymakers, F. T. N. Alleuigin, J. Vandenherk, P. J. A. Domoen, T. T. T. V. Ottenwert and P. A. J. Janssen, *J. Med. Chem.*, **9**, 545 (1966).
[12] M. H. Fischer and A. Lusi, *J. Med. Chem.*, **15**, 983 (1972).
[13] K. Okamato, T. Tail, H. Koso, N. Takenaka, T. Hayakawa and T. Ibaraki, *J. Exptl. Med.*, **61**, 31 (1955).
[14] B. S. Hurbert, R. Perone, T. A. Hermann and G. H. Hitchings, *J. Med. Chem.*, **11**, 711 (1968).
[15] V. Rajeshwar Rao, M. S. Rao, and T. V. Padmanabha Rao, *Coll. Czech. Chem. Commun.*, **51**, 2214 (1986).
[16] V. Rajeshwar Rao and T. V. Padmanabha Rao, *Ind. J. Chem.*, **25B**, 413 (1986).
[17] V. Rajeshwar Rao and T. V. Padmanabha Rao, *Ibid.*, **25B**, 332 (1986).
[18] U. Veerabhadraiah, V. Rajeshwar Rao and T. V. Padmanabha Rao, *Coll. Czech. Chem. Commun.*, **55**, 535 (1990).
[19] V. Rajeshwar Rao and T. V. Padmanabha Rao, *Ind. J. Chem.*, **33B**, 470 (1994).
[20] Bull-Hoi Loc and Xuong, *Bull Soc. Chem.* (France), **3**, 561 (1957).
[21] N. V. Subba Rao and V. Sundaramurthy, *Proc. Ind. Acad. Sci.*, **54A**, 321 (1961), *Chem. Abstr.*, **57**, 1285e (1957).
[22] C. O. Hurd and R. I. Mori, *J. Am. Chem. Soc.*, **77**, 5359 (1955).
[23] V. Rajeshwar Rao, S. Ramanna and T. V. Padmanabha Rao, *Nat. Acad. Sci. Letters*, Vol. **17**, 11 & 12 (1994).
[24] a) D. W. Wolley, *J. Biol. Chem.*, **152**, 225 (1944). b) R. P. Soni, *J. Prakt. Chem.*, **323**, 853 (1981).