Chemistry of Heterocyclic Compounds, Vol. 40, No. 8, 2004

SYNTHESIS OF 3,3-DIALKYL-1-(3-COUMARINYL)-3,4-DIHYDROISOQUINOLINES

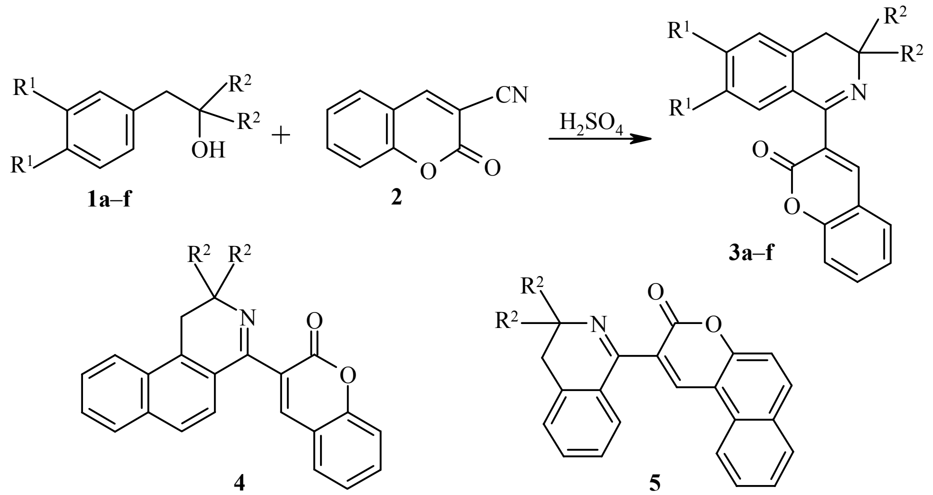
A. G. Mikhailovskii[1] and M. I. Vahrin[2]

The reaction of dialkylbenzylcarbinols with 3-cyanocoumarin in the presence of sulfuric acid gave 3,3-dialkyl-1-(3-coumarinyl)- 3,4-dihydroisoquinoline.

Keywords: dialkylbenzylcarbinols, 3,3-dialkyl-1-(3-coumarinyl)isoquinolines, Ritter cyclocondensation.

The role and importance of isoquinolines [1-3] and coumarin [4-7] derivatives in organic synthesis, nature and medicine are well known. However substances which have both isoquinoline and coumarins in their structures have not been described in the literature until now. Coupling of these two heterocylic units in one molecule is of undoubted interest since new potential synthons would be formed in this way. Moreover the presence of a nitrogen-containing heterocycle opens the possibility of preparing salts suitable for pharmacological study.

We have previously shown the possibility of using the Ritter reaction for the synthesis of the isoquinoline ring [8-10]. In a continuation of studies in this field we have observed that the carbinols **1a-f** reacted with 3-cyanocoumarin (**2**) in the presence of sulfuric acid to form the 3,3-dialkyl-1-(3-coumarinyl)-3,4-dihydroisoquinolines **3a-f**. Use of 2-methyl-3-(1-naphthyl)propanol-2 as the carbinol gave compound **4.** Carbinol **1a** reacted with 3-cyanobenzo[*f*]coumarin in benzene and sulfuric acid to give compound **5**. The characteristics of compounds **3-5** are cited in Table 1. The small yield of compound **5** may probably be explained by the steric effect of the nitrile which contains an additional annelated phenyl ring in its structure.



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[1] Institute of Technical Chemistry, Ural Division, Russian Academy of Sciences, Perm 61460, Russia; e-mail: cheminst@mpm.ru. [2] Perm State Pharmaceutical Academy, Perm 614990, Russia; e-mail: pfa@degacom.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, 1198-1200, August, 2004. Original article submitted September 20, 2002.

TABLE 1. Characteristics of the Compounds Synthesized

Com-pound	R^1 or R^1+R^1	R^2+R^2	Empirical formula	Found, % / Calculated, % C	H	N	mp, °C	Yield, %
3a	H	Me + Me	$C_{20}H_{17}NO_2$	79.1 79.2	5.6 5.7	4.7 4.6	154-155	77
3b	H	Me + Et	$C_{21}H_{19}NO_2$	79.4 79.5	6.0 6.0	4.4 4.4	148-150	71
3c	MeO	Me + Me	$C_{22}H_{21}NO_4$	72.7 72.7	5.7 5.8	4.0 3.9	140-142	83
3d	H	$(CH_2)_4$	$C_{22}H_{19}NO_2$	80.1 80.2	5.7 5.8	4.4 4.3	131-132	43
3e	H	$(CH_2)_5$	$C_{23}H_{21}NO_2$	80.3 80.4	6.1 6.2	4.2 4.1	162-163	41
3f	$O(CH_2)O$	$(CH_2)_5$	$C_{24}H_{21}NO_4$	74.3 74.4	5.4 5.5	3.6 3.6	233-234	82
4	—	Me + Me	$C_{24}H_{19}NO_2$	81.5 81.6	5.3 5.4	3.9 4.0	189-191	67
5	—	Me + Me	$C_{24}H_{19}NO_2$	81.4 81.6	5.3 5.4	4.0 4.0	225-227	12

TABLE 2. ^{1}H NMR Spectra of the Compounds Synthesized

Com-pound	Chemical shifts, δ, ppm			
	R^2	3(1)-CH_2, s	arom. protons and R^1	HC=, s
3a	1.27, s (2CH_3)	2.78	6.90-7.63, m (8H)	7.93
3b	1.18, s (CH_3); 1.08, t ($\underline{CH_3}CH_2$); 1.35, q ($CH_3\underline{CH_2}$)	2.74	6.92-7.58, m (8H)	7.86
3c	1.23, s (2CH_3)	2.90	6.66, s (H-5), 6.68, s (H-8), 3.70, s and 3.83, s (2CH_3O), 7.17-7.67, m (4H)	7.94
3d	1.41-1.88, m (4CH_2)	2.87	7.08-7.73, m (4H)	8.03
3e	1.40-1.90, m (5CH_2)	2.83	7.12-7.75, m (4H)	8.02
3f	1.35-1.63, m (5CH_2)	2.70	6.85, s (H-5), 6.86, s (H-8), 6.88-7.45, m (4H), 5.97, s (OCH_2O)	8.10
4	1.35, s (2CH_3)	3.25	7.55-8.20, m (6H)	8.05
5	1.30, s (2CH_3)	2.85	7.72-8.50, m (6H)	8.07

All the ^{1}H NMR spectra of compounds **3-5** (Table 2) contain signals of the protons of the substituents R^1 and R^2, the 4-CH_2 groups of the dihydroisoquinoline ring, the aromatic protons and the characteristic singlets of the coumarin proton CH= (7.93-8.10 ppm), which completely confirms their structures.

The IR spectra of compounds **3-5** contain stretching bands at 1725 (C=O) and 1620 cm^{-1} (C=N).

Compounds **3-5** have azadiene structures [11] so that cycloaddition reactions are possible for them.

EXPERIMENTAL

^{1}H NMR spectra in $CDCl_3$ solutions with HMDS as internal standard were recorded with a Bruker AM-300 (300 MHz) instrument. IR spectra of nujol mulls were recorded on a UR-20 spectrometer.

The starting carbinols are known compounds [8-10]. The corresponding nitriles were prepared by a known method [12].

1-(3-Coumarinyl)-6,7-(R^1)$_2$-3,3-(R^2)$_2$-isoquinolines (3a-e), 4-(3-Coumarinyl)-2,2-dimethylbenzo-[*f*]isoquinoline (4), and 1-(3-Benzo[*f*]coumarinyl)-3,3-dimethylisoquinoline (5). The corresponding carbinol (10 mmol) and 3-cyanocoumarin (1.88 g, 11 mmol) (compounds **2-4**) or 3-cyanobenzo[*f*]coumarin (2.21 g, 10 mmol) (compound **5**) were mixed. Glacial acetic acid (2ml) was added in the case of compounds **3c,f**. Concentrated sulfuric acid (5 ml) was added dropwise to the stirred mixture at 0°C. The reaction mixture was stirred for 10 min, cooled to room temperature and poured into cold (~5°C) water (100 ml). The benzene layer was separated. Any small amount of precipitate was filtered off. The aqueous phase was neutralized with sodium hydrogen carbonate solution. The precipitate formed was filtered off, dried, and recrystallized from isopropanol.

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