New Method of Synthesis of *N*-Substituted Carbamates from 4-Hydroxycoumarin

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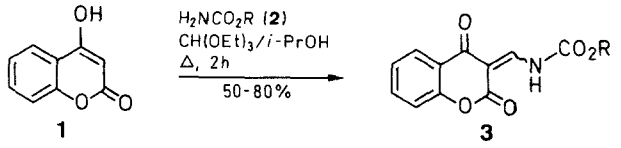
The synthesis of a new series of compounds, the *N*-(methylene-4-oxocoumarinyl)carbamates **3** by condensation of carbamates **2** with 4-hydroxycoumarin (**1**) in the presence of ethyl orthoformate in good yields is reported.

In the course of our research on pyrone and pyridone derivatives,[1] we recently investigated the condensation reactions of amine derivatives with coumarins as a route to compounds with interesting reactivity and of potential biological activity. The coumarin ring is found in many natural products and is also used as a synthetic intermediate for the preparation of numerous heterocyclic compounds with biological and pharmacological activity.[2]

Recently, we reported the preparation of 3-ureidomethylenecoumarins by the action of 4-hydroxycoumarin on substituted ureas in good yield.[3] Their reactivity is currently under investigation, and encouraging results have been obtained.[4]

We report here the reaction of carbamates **2**, some of which are widely used in other applications,[5] with 4-hydroxycoumarin (**1**) in 2-propanol in the presence of ethyl orthoformate. Refluxing the reaction mixture led to a new series of compounds, the *N*-(methylene-4-oxocoumarinyl)carbamates **3** (Table).

The carbamates used, apart from glycol carbamate which was prepared by action of a solution of ammonia on 1,3-dioxolon-2-one,[5] were commercially available. All compounds were synthesized in good yield as crystalline products. The presence of a functional group (alcohol) on the hydrocarbon chain of the carbamate did not affect its reaction with the coumarin and did not reduce the yield. The purities were checked by TLC (eluent: chloroform) and by elemental analyses. Their structures were determined by ^{1}H NMR and mass spectrometry.



2, 3	a	b	c	d	e	f	g
R	Me	Et	Bu	*t*-Bu	CH_2Ph	Ph	CH_2CH_2OH

The ^{1}H NMR spectra of carbamates **3** displayed two doublets between δ = 8.5 and 9.5 and between 10.5 and 13 attributed to the olefinic proton and the NH group, respectively. This is due to the existence of *Z*- and *E*-isomers in **3**, which we had previously observed with the 3-ureidomethylenecoumarins.[3]

Mass spectrometry showed, apart from the molecular ion peak, fragments of the coumarin ring[6] and fragments due to loss of $[OR]^{+\cdot}$ and CO.

This method of preparation is noteworthy from the synthetic point of view as it affords access to a new series of substituted carbamates in a simple and quick reaction. Studies are in progress on their chemical reactivity and potential biological activity.

Table. *N*-(Methylene-4-oxocoumarinyl)carbamates **3** Prepared

Product	Yield (%)	mp (°C)	Molecular Formula[a]	^{1}H NMR[b] δ, *J* (Hz)	MS (70 eV) *m/z* (%)
3a	80	193–194	$C_{12}H_9NO_5$ (247.2)	3.90 (s, 3H), 7.35–7.91 (m, 4H), 8.66 (2d, 1H, *J* = 12,5), 11.0 and 12.06 (2d, 1H, *J* = 12,5)	247 (M^+, 100), 217 (7), 188 (84), 121 (64), 120 (36), 93 (16), 92 (64), 65 (17)
3b	50	180–181	$C_{13}H_{11}NO_5$ (261.2)	1.38 (t, 3H), 4.39 (q, 2H), 7.15–7.54 (m, 4H), 8.94 (2d, 1H, *J* = 12,5), 10.95–12.20 (2d, 1H, *J* = 12,5)	261 (M^+, 100), 216 (9), 189 (18), 188 (32), 121 (67), 120 (44), 93 (15), 92 (49), 65 (17)
3c	75	133–134	$C_{15}H_{15}NO_5$ (289.2)	0.95 (t, 3H, *J* = 7,5), 1.49 (m, 4H), 4.33 (t, 2H, *J* = 7,5), 7.15–8.07 (m, 4H), 8.94 (2d, 1H), 10.95 and 12.20 (2d, 1H)	289 (M^+, 59), 261 (24), 216 (17), 189 (42), 188 (27), 121 (68), 120 (35), 93 (17), 92 (46), 65 (18)
3d	60	184–185	$C_{15}H_{15}NO_5$ (289.2)	1.56 (s, 9H), 7.15–8.14 (m, 4H), 8.92 (2d, 1H, *J* = 12,5), 10.81 and 12.06 (2d, 1H, *J* = 12,5)	289 (M^+, 10), 216 (12), 189 (13), 121 (9), 120 (5), 92 (9), 65 (3), 57 (100)
3e	75	182–183	$C_{18}H_{13}NO_5$ (323.3)	5.32 (s, 2H), 7.14–8.05 (m, 9H), 8.95 (2d, 1H, *J* = 12,5), 11.0 and 12.30 (2d, 1H, *J* = 12,5)	323 (M^+, 2), 279 (4), 217 (2), 188 (1), 121 (3), 120 (1), 92 (11), 91 (100), 65 (8)
3f	55	199–200	$C_{17}H_{11}NO_5$ (309.2)	7.15–8.12 (m, 9H), 9.02 (2d, 1H, *J* = 12,5), 11.18 and 12.50 (2d, 1H, *J* = 12,5)	309 (M^+, 3), 216 (79), 121 (46), 120 (16), 94 (100), 93 (19), 92 (37), 77 (34), 65 (47)
3g	60	155–156	$C_{13}H_{11}O_6$ (277.2)	3.70 (m, 2H), 4.32 (m, 2H), 7.25–7.98 (m, 4H), 8.66 (2d, 1H, *J* = 12,5), 10.91 and 12.02 (2d, 1H, *J* = 12,5)	277 (M^+, 100), 216 (17), 189 (30), 188 (28), 121 (31), 120 (19)

[a] Satisfactory microanalyses obtained: C ±0.35, H ±0.13, N ±0.39. [b] Solvents: DMSO-d_6 for **1** and **7**, $CDCl_3$ for **2–6**.

Melting points were determined in an Electrothermal apparatus. ^1H NMR spectra were recorded on a Bruker AC80 instrument, and mass spectra on a Nermag 1010 spectrometer. Elemental analyses were carried out at the Inter-University microanalysis center in Toulouse. The carbamates **2** and 4-hydroxycoumarin **(1)** were obtained from Aldrich and Janssen Chemical Co.

***N*-(Methylene-4-oxocoumarinyl)carbamates 3; General Procedure:** 4-Hydroxycoumarin (**1**; 1.62 g, 0.01 mol) and ethyl orthoformate (2.25 g, 0.015 mole) were added to a stirred solution of carbamate **2** (0.01 mol) in 2-propanol (30 mL). The mixture was refluxed for 2 h. The precipitate formed while hot or on cooling to r.t. was washed with 2-propanol, and then recrystallized ($CHCl_3$/hexane) (Table).

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