Reaction of Amines on 3-Ureidomethylenecoumarins. A New Route to *N*-(Methylene-4-oxocoumarinyl)amines

Maâmar Hamdi

Laboratoire des Composés Organiques Hétérocycliques Institut de Chimie, Université des Sciences et de la Technologie H. Boumediène, BP 32, El-Alia, Bab Ezzouar, Alger, Algeria

Patrick Granier, Reine Sakellariou and Vincent Spéziale*

Laboratoire des Interactions Moléculaires et Réactivité Chimique et Photochimique, UA CNRS 470, Université Paul Sabatier, 118 route de Narbonne, 31062 Toulouse Cédex, France

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N-(Methylene-4-oxocoumarinyl)amines were prepared in good yield by reacting aliphatic and aromatic amines bearing functional groups with the relevant 3-ureidomethylenecoumarins.

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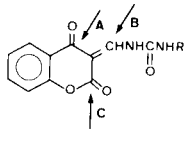
In previous studies, we examined the reaction of 4-hydroxycoumarin with various types of amines in the presence of ethyl orthoformate. We prepared the 3-ureidomethylenecoumarins [1], the *N*-(methylene-4-oxocoumarinyl)carbamates [2] and the *N*-(methylene-4-oxocoumarinyl)-amino acids [3] in good yield by reaction with the corresponding ureas, carbamates and α-amino acids respectively. We are currently studying the reactivity of these compounds and their potential biological activity.

We report here our preliminary results on the activity of 3-ureidomethylenecoumarins, especially towards amines. Inspection of the structure of the 3-ureidomethylenecoumarins suggests that they would be susceptible to attack by amines at various sites A, B or C leading to quite different products.



We selected the reaction with 3-ureidomethylenecoumarin (R = H) in view of the almost quantitative yield obtained in its preparation. The initial experiments were carried out with the aliphatic amine, *n*-butylamine. The reaction mixture was heated for 2 hours in a mixture of ethanol and DMF (2/1, v/v). The reaction was followed by thin layer chromatography (eluant, dichloromethane/methanol, 10/1, v/v), which showed the formation of a single product. After purification and recrystallization, analysis by ^{1}H nmr and mass spectrometry provided the following information. We observed in the ^{1}H nmr spectrum the disappearance of the NH_2 from 3-ureidomethylenecoumarin, the presence of a split doublet at δ = 8.46 ppm and two other doublets at δ = 10.18 and 10.93 ppm, comparable to those of 3-ureidomethylenecoumarin for the ethylene protons (δ = 8.8 ppm) and the NH group (δ = 11.25 and 12.25 ppm). The split doublet stems from the presence of two isomeric forms [4,5].

We also observed the presence of signals from the butyl protons, a triplet at δ = 0.97 ppm from the CH_3 group, multiplets due to CH_2 groups at δ = 1.46 and 3.53 ppm. The mass spectrum revealed the presence of the molecular peak (M^+, 245), and also signals corresponding to the butyl group and fragmentation of the coumarin ring [6,7]. The structure of the compound was thus attributed to that of *N*-(methylene-4-oxocoumarinyl)butylamine *via* the reaction of *n*-butylamine at the B site of 3-ureidomethylenecoumarin with elimination of urea. This was supported by the results of the elemental analysis.

To find out if this reaction could be generalized, we examined the reaction of the 3-ureidomethylenecoumarins with both aliphatic and aromatic amines bearing functional groups. In all cases tested, a single product was formed, which was identified by nmr and ms as the corresponding *N*-(methylene-4-oxocoumarinyl)amine, whose purity was verified by thin layer chromatography. The course of this reaction is illustrated in Scheme 1. The results are listed in Table 1.

Scheme 1

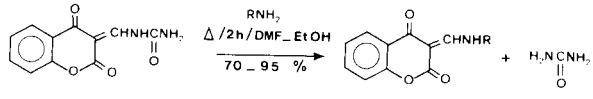


Table 1

N-(Methylene-4-oxocoumarinyl)amines Prepared from 3-Ureidomethylenecoumarin

Product	R	Yield %
1	$(CH_2)_3CH_3$	95
2	$(CH_2)_{11}CH_3$	80
3	C_6H_{11}	70
4	$CH_2CH(CH_3)C_2H_5$	75
5	$CH_2C_6H_5$	95
6	C_6H_5	90
7	CH_2CH_2OH	85
8	$(CH_2)_3COOH$	75

Yields were high for all amines tested. The presence of a substituent (methyl group) or a functional group (OH, COOH) on the hydrocarbon chain of the amine had very little effect on the reactivity of the amine towards the 3-ureidomethylenecoumarin. Furthermore, the basicity of the amine did not influence the reaction significantly as a high yield was obtained with aniline (90%).

The addition of the amine at site B of the unsaturated α,β-ketone system with elimination of urea indicates that the RNH moiety is a poor leaving group [8]. This reaction can also be carried out with substituted 3-ureidomethylenecoumarin with elimination of the substituted urea. The reaction with diamines is not reported here due to the increased complexity from reaction of the other NH_2 group in the molecule. This will form the subject of a future publication.

We searched the literature for other routes to the *N*-(methylene-4-oxocoumarinyl)amines. To our knowledge the only publications on this subject are those of Wolfbeis and Ziegler [4]. These authors heated an aromatic amine, aniline or 4-chloroaniline, with 4-hydroxycoumarin in solution in 2-propanol or acetic acid in the presence of ethyl orthoformate. The condensation reaction afforded the corresponding aromatic *N*-substituted amines. Since no systematic study of this reaction has been reported, we decided to prepare the substituted amines from the relevant 3-ureidomethylenecoumarins using the method of Wolfbeis and Ziegler, to compare it with our method and provide additional confirmation for our structural determination. Starting from 2-propanol, we obtained a solid product whose spectroscopic characteristics and elemental analysis were in agreement with those of the compound prepared using our method (Scheme 2). The results are listd in Table 2.

Scheme 2

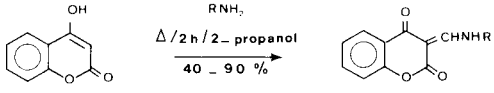


Table 2

N-(Methylene-4-oxocoumarinyl)amines Prepared from 4-Hydroxy-coumarin.

Product	R	Yield %
1	$(CH_2)_3CH_3$	40
2	$(CH_2)_{11}CH_3$	45
3	C_6H_{11}	50
4	$CH_2CH(CH_3)C_2H_5$	50
5	$CH_2C_6H_5$	90
6	C_6H_5	90
7	CH_2CH_2OH	80
8	$(CH_2)_3COOH$	60

The yields were lower than those obtained by our method except those of the reactions with aniline and benzylamine. Although not observed here, the competitive intermolecular condensation of 4-hydroxycoumarin could take place with certain amines *via* interaction with ethyl orthoformate [9]. Our route to the *N*-(methylene-4-oxocoumarinyl)amines from 3-ureidomethylenecoumarin is thus a valuable method which can be employed with all types of amine. The requirement for a two stage reaction is not a drawback as 3-ureidomethylenecoumarin can be prepared in almost quantitative yield from commercially available compounds. The urea formed during the reaction is readily eliminated and this synthetic method can thus be considered as an amination reaction of the 3-ureidomethylenecoumarin with loss of urea.

EXPERIMENTAL

Melting points were determinated on an Electrothermal apparatus. The ^1H nmr spectra were recorded on a Bruker AC 80 spectrometer, and the mass spectra were recorded on a Nermag R 1010 instrument. Elemental analyses were carried out at the Inter-University microanalysis center in Toulouse, France. 4-Hydroxycoumarin, ureas, ethyl orthoformate and the amines were obtained from Aldrich or Janssen Chemical Co.

N-(Methylene-4-oxocoumarinyl)amines.

General Procedure.

1) From 3-Ureidomethylenecoumarin.

A solution of 3-ureidomethylenecoumarin (0.58 g, 0.0025 mole) and the amine (0.0025 mole) was refluxed while stirring in a mixture of DMF (15 ml) and absolute ethanol (30 ml) for 2 hours. The precipitate was obtained either from hot or cold solutions or after evaporation of the solvents and was dissolved in a minimum volume of chloroform to eliminate urea. The solution was filtered and evaporated and the product recrystallized.

2) From 4-Hydroxycoumarin.

A solution of the amine (0.01 mole), 4-hydroxycoumarin (1.62 g, 0.01 mole), ethyl orthoformate (2.25 g, 50% excess) was refluxed while stirring for 2 hours. The precipitate formed either while hot or on cooling to room temperature and was recrystallized.

N-(Methylene-4-oxocoumarinyl)butylamine (**1**).

This compound was crystallized from chloroform-hexane, mp 131-132°; pmr (deuteriochloroform): δ 0.97 (t, 3H, CH_3), 1.46 (m, 4H, CH_2), 3.53 (m, 2H, CH_2), 7.14-8.07 (m, 4H, Ar), 8.46 (dd, 1H, CH, *Z* and *E*), 10.18 and 10.93 (dd, 1H, NH, *Z* and *E*); ms: (m/z %) 245 (M^+, 87), 216 (100), 203 (30), 202 (18), 188 (13), 175 (26), 121 (59), 92 (46), 85 (54), 65 (29).

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.57; H, 6.12; N, 5.71. Found: C, 68.36; H, 5.92; N, 5.54.

N-(Methylene-4-oxocoumarinyl)dodecylamine (**2**).

This compound was crystallized from dichloromethane-methanol, mp 132-133°; pmr (deuteriochloroform): δ 0.90 (t, 3H, CH_3), 1.00-1.81 (m, 20H, CH_2), 3.50 (m, 2H, CH_2), 7.12-8.12 (m, 4H, Ar), 8.43 (dd, 1H, CH, *Z* and *E*), 10.21 and 11.85 (dd, 1H, NH, *Z* and *E*); ms: (m/z %) 357 (M^+, 69), 258 (34), 244 (65), 216 (87), 203 (73),

202 (18), 188 (14), 175 (35), 121 (100), 120 (15), 93 (16), 92 (33), 70 (45), 65 (13), 43 (68).

Anal. Calcd. for $C_{22}H_{31}NO_3$: C, 73.91; H, 8.74; N, 3.92. Found: C, 73.77; H, 8.89; N, 4.03.

N-(Methylene-4-oxocoumarinyl)cyclohexylamine (**3**).

This compound was crystallized from chloroform-hexane, mp 133-134°; pmr (DMSO-d_6): δ 0.82-2.18 (m, 10H, CH_2), 3.68 (m, 1H, CH), 7.12-8.12 (m, 4H, Ar), 8.56 (dd, 1H, CH, *Z* and *E*), 10.18 and 11.94 (dd, 1H, NH, *Z* and *E*); ms: (m/z %) 271 (M^+, 100), 203 (6), 188 (10), 175 (8), 121 (53), 120 (17), 97 (27), 93 (10), 92 (30), 65 (11), 55 (28).

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.84; H, 6.27; N, 5.16. Found: C, 70.78; H, 6.38; N, 5.24.

N-(Methylene-4-oxocoumarinyl)-2-methylbutylamine (**4**).

This compound was crystallized from DMF-water, mp 85-86°; pmr (deuteriochloroform): δ 0.75-1.75 (m, 9H, CH_3, CH_2, CH), 3.37 (m, 2H, CH_2), 7.12-8.18 (m, 4H, Ar), 8.25 (dd, 1H, CH, *Z* and *E*), 8.18 and 11.93 (dd, 1H, NH, *Z* and *E*); ms: (m/z %) 259 (M^+, 78), 230 (100), 203 (56), 202 (85), 188 (12), 175 (60), 121 (97), 120 (12), 93 (23), 92 (38), 85 (44), 83 (63), 65 (25), 44 (54).

Anal. Calcd. for $C_{15}H_{17}NO_3$: C, 69.49; H, 6.56; N, 5.40. Found: C, 69.41; H, 6.62; N, 5.35.

N-(Methylene-4-oxocoumarinyl)benzylamine (**5**).

This compound was crystallized from chloroform-hexane, mp 167-168°; pmr (deuteriochloroform): δ 4.62 (m, 2H, CH_2), 7.00-8.13 (m, 4H, Ar), 8.54 (dd, 1H, CH, *Z* and *E*), 10.50 and 12.12 (dd, 1H, NH, *Z* and *E*); ms: (m/z %) 279 (M^+, 43), 188 (9), 121 (13), 120 (4), 92 (22), 91 (100), 65 (28).

Anal. Calcd. for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.65; N, 5.01. Found: C, 72.81; H, 4.60; N, 5.11.

N-(Methylene-4-oxocoumarinyl)aniline (**6**).

This compound was crystallized from DMF, mp 209-210°, lit [4] 208°; pmr (deuteriochloroform): δ 7.06-8.18 (m, 9H, Ar), 8.90 (dd, 1H, CH, *Z* and *E*), 11.81 and 13.62 (dd, 1H, NH, *Z* and *E*); ms: (m/z %) 265 (M^+, 83), 188 (9), 121 (31), 120 (5), 93 (18), 92 (37), 85 (64), 83 (100), 65 (27).

Anal. Calcd. for $C_{16}H_{11}NO_3$: C, 72.45; H, 4.15; N, 5.28. Found: C, 72.10; H, 4.00; N, 5.20.

N-(Methylene-4-oxocoumarinyl)ethanolamine (**7**).

This compound was crystallized from dioxan-hexane, mp 197-198°; pmr (DMSO-d_6): δ 3.62 (m, 4H, CH_2), 5.00 (s, 1H, OH), 7.12-8.00 (m, 4H, Ar), 8.44 (dd, 1H, CH, *Z* and *E*), 10.18 and 11.62 (dd, 1H, NH, *Z* and *E*); ms: (m/z %) 233 (M^+, 100), 203 (15), 202 (64), 188 (18), 175 (59), 121 (83), 120 (15), 93 (18), 92 (37), 69 (38), 65 (23), 45 (82).

Anal. Calcd. for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.72; N, 6.00. Found: C, 61.46; H, 4.77; N, 6.15.

N-(Methylene-4-oxocoumarinyl)aminobutanoic Acid (**8**).

This compound was crystallized from DMF-water, mp 204-205°; pmr (DMSO-d_6): δ 1.68-2.37 (m, 4H, CH_2), 3.62 (m, 2H, CH_2), 7.12-8.00 (m, 4H, Ar), 8.5 (dd, 1H, CH, *Z* and *E*), 10.37 and 12.12 (dd, 1H, NH, *Z* and *E*), 11.62 (s, 1H, OH); ms: (m/z %) 275 (M^+, 16), 203 (3), 202 (2), 188 (2), 175 (5), 121 (24), 120 (7), 93 (12), 92 (11), 73 (67), 69 (89), 65 (5), 44 (100).

Anal. Calcd. for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.72; N, 5.09. Found: C, 60.76; H, 4.66; H, 5.20.

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