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Solvent Effect and Product Selectivity in the Reaction of 4-Alkylaminocoumarins and Dibenzoylacetylene

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The reaction of dibenzoylacetylene with 4-alkylaminocoumarins in THF/H_2O (50:50) leads to the formation of 4-(alkylamino)-3-(1,4-dioxo-1,4-diphenylbut-2-en-2-yl)-2*H*-chromen-2-one derivatives in good yields. The cyclized products 2-hydroxy-1-alkyl-3-(2-oxo-2-phenylethylidene)-2-phenyl-2,3-dihydrochromeno [4,3-*b*] pyrrol-4(1*H*)-ones were formed in good yields, when the reaction was carried-out in DMSO.

Keywords: *β*-Enaminones, Dibenzoylacetylene, Aminocoumarins

INTRODUCTION

Coumarins comprise an interesting group of heterocycles. They are found in a large variety of natural and synthetic biologically active compounds [1-3]. One of the most important groups of coumarin derivatives are aminocoumarins. Some of aminocoumarins display antimicrobial activities [4]. In addition, some of the aminocoumarins pose interesting photochemical behaviour [5] and many of them can be used as fluorescent markers [6].

An interesting method for the synthesis of organic compounds is the addition reaction of nucleophiles to the activated alkynes. This addition results in zwitterionic species that can be trapped with a variety of electrophiles or proton donors. These conversions can either be a two-component or multicomponent reactions [7-12]. In continuation of our interest in using enaminones in organic synthesis [13-17], here, we report the reaction of dibenzoylacetylene and 4-alkylaminocoumarins in THF/H_2O (50:50) and DMSO to produce 4-(alkylamino)-3-(1,4-dioxo-1,4-diphenylbut-2-en-2-yl)-2*H*-chromen-2-ones and 2-hydroxy-1-alkyl-3-(2-oxo-2-phenylethylidene)-2-phenyl-2,3-dihydrochromeno [4,3-*b*] pyrrol-4(1*H*)-ones respectively in good yields.

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EXPERIMENTAL PLAN/METHODS

Dibenzoylacetylene [22,23] and enaminones were prepared by known methods [24]. Other starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Melting points were measured with an Electrothermal 9100 apparatus. IR spectra were measured with a Shimadzu IR-460 spectrometer. NMR spectra were recorded with a Bruker DRX-300 or 250 AVANCE instrument (300.1 and 250.1 MHz for ^{1}H and 75.5 and 62.9 MHz for ^{13}C) with $CDCl_3$ or DMSO as solvent. Mass spectra were recorded with an Agilent-5975 C inert XL MSD mass spectrometer operating at an ionization potential of 70 eV.

General Procedure for Synthesis of Compounds 3a-3c

To a stirred solution of enaminone 2 (2 mmol) in 5 ml THF/H_2O (1:1) was added dibenzoylacetylene 1 (2 mmol) at

room temperature. The reaction mixture was allowed to stir for 8 h. After completion, the solvent was removed under reduced pressure and the obtained precipitate was washed with a mixture of *n*-Hexane and EtOAC to give compounds 3.

2-[4-(Isopropylamino)-2-oxo-2*H*-chromene-3-yl]-1,4-diphenyl-2-butene-1,4-dione (3a). Yellow powder, m.p.: 190-191 °C, yield: 75%. IR (KBr) (υ_{max}/cm^{-1}): 3280 (NH), 1641, 1600 (C=O). ^{1}H NMR (250.1 MHz, $CDCl_3$): δ_H 0.67 (3H, d, $^3J_{HH}$ = 6.2 Hz, CH_3), 1.35 (3H, d, $^3J_{HH}$ = 6.0 Hz, CH_3), 4.25 (1H, m, C*H*(CH_3)$_2$), 6.31 (1H, brs, C=C*H*), 6.86-8.06 (14H, m, Ar), 10.93 (1H, d, $^3J_{HH}$ = 9.2 Hz, NH), ^{13}C NMR (62.9 MHz, $CDCl_3$): δ_C 22.6 and 24.4 (2CH_3), 47.9 (*C*HMe_2), 85.6 (N-C=*C*), 107.0 (C=*C*H), 124.5 and 126.9 (2CH-Ar), 127.4, 127.5, 128.0, and 128.2 (8CH-Ar), 128.3 and 128.9 (2CH-Ar), 129.8 (C), 131.6 and 133.1 (2CH-Ar), 136.7, 139.0, 139.3, and 140.7 (4C), 153.9 (N-*C*=C), 176.4 (C=O), 192.3, 194.0 (2COPh). EI-MS (70 eV): MS: *m*/*z* (%) = 394 (M^+-43, 1), 293 (40), 146 (100), 105 (70), 77 (54),

2-[4-(Benzylamino)-2-oxo-2*H*-chromene-3-yl]-1,4-diphenyl-2-butene-1,4-dione (3b). Yellow powder, m.p.: 145-146 °C, yield: 60%. IR (KBr) (υ_{max}/cm^{-1}): 3300 (NH), 1646, 1608 (C=O), ^{1}H NMR (250.1 MHz, $CDCl_3$): δ_H 4.53 and 4.83 (2H, ABX system, δ_A = 4.53 ppm, δ_B = 4.83 ppm, J_{AB} = 15.0 Hz, J_{AX} = 7.0 Hz, J_{BX} = 5.7 Hz, CH_2), 6.33 (1H, s, C=C*H*), 6.61-8.09 (19H, m, Ar), 11.02 (1H, brs, NH), ^{13}C NMR (62.9 MHz, $CDCl_3$): δ_C 49.1 (CH_2), 85.8 (N-C=*C*), 108.0 (C=*C*H), 124.6 and 126.9 (2CH-Ar), 127.5, 127.6, 127.9, and 128.1 (8CH-Ar), 128.2 (CH-Ar), 128.4 and 128.8 (4CH-Ar), 129.1 and 130.0 (2CH-Ar), 130.3 (C), 131.8 and 133.2 (2CH-Ar), 135.7, 136.7, 138.6, 138.9, and 140.5 (5C), 153.6 (N-*C*=C), 176.8 (C=O), 192.4, 194.7 (2COPh). MS: *m*/*z* (%) = 390 (M^+-95, 2), 279 (20), 167 (40), 149 (100), 105 (15).

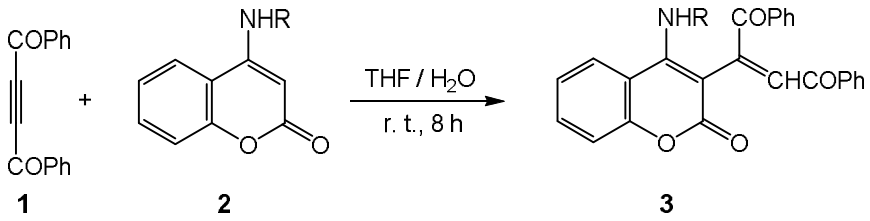
2-[2-Oxo-4-(phenethylamino)-2*H*-chromen-3-yl]-1,4-diphenyl-2-butene-1,4-dione (3c). Yellow powder, m.p.: 199-200 °C, yield: 68%. IR (KBr) (υ_{max}/cm^{-1}): 3320 (NH), 1645, 1616 (C=O). ^{1}H NMR (250.1 MHz, $CDCl_3$): δ_H 2.44-2.70 (2H, m, CH_2Ph), 3.60-3.90 (2H, m, NCH_2), 6.28 (1H, s, C=C*H*), 6.81-7.69 (19H, m, Ar), 10.98 (1H, brs, NH), ^{13}C NMR (62.9 MHz, $CDCl_3$): δ_C 36.5 (*C*H_2Ph), 46.4 (NCH_2), 85.7 (N-C=*C*), 107.9 (C=*C*H), 120.0 (C), 124.6 and 126.7 (2CH-Ar), 127.5 and 127.6 (4CH-Ar), 128.1 and 128.2 (2CH-Ar), 128.3, 128.6, 128.7, 129.1 (8CH-Ar), 129.9 (C), 131.8, 133.2, and 136.7 (3CH-Ar), 137.3, 138.8, 138.9, and 140.6 (4C), 153.7 (N-*C*=C), 177.3 (C=O), 192.4, 194.7 (2 COPh). MS: *m*/*z* (%) = 408 (M^+-91, 1), 167 (40), 146 (100), 105 (30).

General Procedure for Synthesis of Compounds 6a, 6b

To a stirred solution of enaminone 2 (2 mmol) in 0.5 ml DMSO was added dibenzoylacetylene 1 (2 mmol) at room temperature. The reaction mixture was allowed to stir for 8 h. After completion, the solvent was extracted by a mixture of H_2O and CH_2Cl_2. The organic solvent was removed under reduced pressure and the obtained precipitate was washed by a mixture of *n*-Hexane and EtOAC to produce compounds 6.

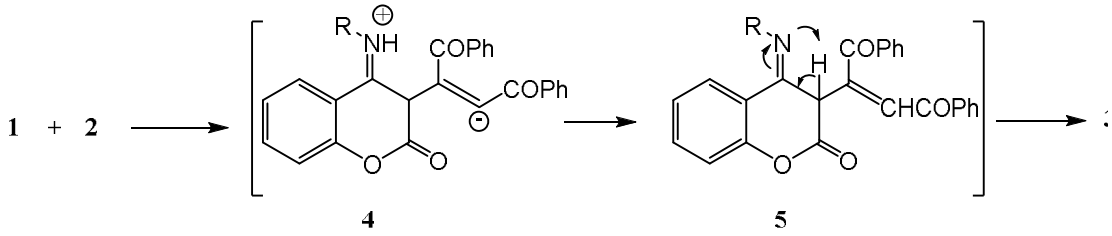
2-Hydroxy-1-isopropyl-3-[(*Z*)-2-oxo-2-phenylethylidene]-2-phenyl-1,2-dihydrochromeno[4,3-*b*]pyrrol-4-one (6a). Yellow powder, m.p.: 188-189 °C, yield: 60%. IR (KBr) (υ_{max}/cm^{-1}): 3450 (OH), 1652, 1600 (C=O). ^{1}H NMR (300.1 MHz, DMSO-d_6): δ_H 1.16 (6H, d, $^3J_{HH}$ = 6.5 Hz, 2CH_3), 3.25 (1H, m, *CH*Me_2), 7.11-7.79 (15H, m, Ar), 7.54 (brs, 1H, OH), 8.75 (1H, s, C=CH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ_C 20.7 (2CH_3), 43.4 (*C*HMe_2), 98.9 (HO-C), 113.4 (N-C=*C*), 116.1 (C=*C*H), 122.2, 123.0, and 125.9 (3CH-Ar), 127.4, 127.9, 128.1, 128.9 (8CH-Ar), 130.7 and 132.0 (2C), 132.2 (CH), 139.3 (C), 139.9 (CH), 153.6, 157.4, 162.9, 175.1, and 188.0 (5C), 197.2 (COPh). MS: *m*/*z* (%) = 437 (M^+, 68), 394 (10), 291 (82), 105 (100), 77 (30).

2-Hydroxy-3-[(*Z*)-2-oxo-2-phenylethylidene]-1-phenethyl-2-phenyl-1,2-dihydrochromeno[4,3-*b*]pyrrol-4-one (6b). Yellow powder, m.p.: 191-192 °C, yield: 66%. IR (KBr) (υ_{max}/cm^{-1}): 3350 (OH), 1649, 1600 (C=O). ^{1}H NMR (300.1 MHz, DMSO-d_6): δ_H 2.81-2.86 (2H, m, CH_2Ph), 3.01-3.06 (2H, m, NCH_2), 7.11-7.79 (19 H, m, Ar), 7.70 (1H, brs, OH), 8.75 (1H, s, C=CH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ_C 33.1 (CH_2Ph), 39.0 (NCH_2), 99.0 (HO-C), 114.3 (N-C=*C*), 116.2 (C=*C*H), 122.0, 123.3, and 125.9 (3CH-Ar), 127.3, 127.4, 128.0, 128.2, 129.0, and 129.2 (12 CH-Ar), 131.1 and 132.4 (2C), 132.6, 137.3, 139.0, and 139.6 (4CH), 142.2, 153.4, 156.9, 163.4, 175.5, and 188.6 (6C), 197.9 (COPh). MS: *m*/*z* (%) = 499 (M^+, 35), 408 (52), 339 (74), 248 (100), 105 (35), 91 (33), 77 (22).

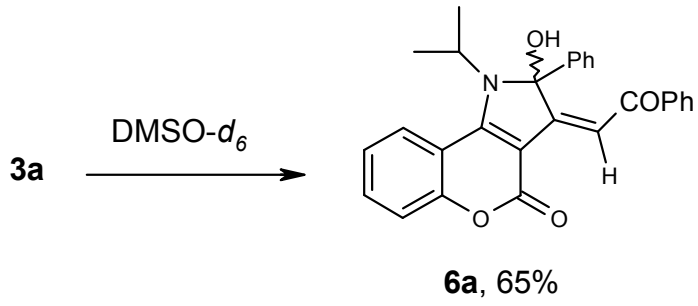


2, 3	R	Yield (%)
a	Me_2CH	75
b	$PhCH_2$	60
c	$PhCH_2CH_2$	68

Scheme 1. Synthesis of compounds 3 in THF/H_2O



Scheme 2. Proposed mechanism for the formation of 3



Scheme 3. Cyclization of 3a in DMSO

2-Hydroxy-1-methyl-3-[(*Z*)-2-oxo-2-phenyl-ethylidene]-2-phenyl-1,2-dihydrochromeno[4,3-*b*] pyrrol-4-one (6c). Yellow powder, m.p.: 180-181 °C, yield: 63%. IR (KBr): υ (cm^{-1}) = 3430 (OH), 1682, 1604 (C=O). ^1H NMR (300.1 MHz, DMSO-d_6): δ_H 2.36 (3H, s, CH_3), 7.11-7.80 (15H, m, Ar and OH), 8.76 (1H, s, C=CH),

^{13}C NMR (75.5 MHz, DMSO-d_6): δ_C 24.6 (CH_3), 98.5 (HO-C), 112.8 (N-C=*C*), 115.7 (C=*C*H), 121.9 (C), 122.5 and 125.5 (2CH-Ar), 127.0, 127.5, 127.6, and 128.5 (8CH-Ar), 130.2, 131.6, 131.7, 139.0, and 139.6 (5CH), 153.3, 157.1, 162.5, 174.7, and 187.5 (5C), 196.7 (COPh). MS: *m/z* (%) = 409 ($M^{+\cdot}$, 8), 291 (15), 122 (45), 105 (100), 77 (90).

RESULTS AND DISCUSSION

The reaction of dibenzoylacetylene 1 with enaminocarbonyl compounds 2 in THF/H_2O (50:50) was completed within a few hours at ambient temperature. The progress of the reaction was monitored by TLC. The reaction was completed after 8 h. IR, ^{1}H NMR, ^{13}C NMR, and CHN data of the isolated products clearly support the formation of 4-(alkylamino)-3-(1,4-dioxo-1,4-diphenylbut-2-en-2-yl)-2*H*-chromen-2-one derivatives 3 in good yields (Scheme 1).

The structures of compounds 3a–3c were deduced from their ^{1}H and ^{13}C NMR and IR and mass spectroscopic data. Two methyl groups of isopropyl residue in 3a are diastereotopic and in the ^{1}H NMR spectrum resonated as two doublets (δ = 0.67, $^3J_{HH}$ = 6.2 Hz and δ = 1.35 ppm, $^3J_{HH}$ = 6.0 Hz). Diatereotopicity of the methyl groups is interpreted in terms of a restricted rotation around the N-C_{sp2} bond caused by *Peri* interaction [18]. The vinylic proton appeared at δ = 6.31 ppm and the methine and aromatic protons resonate as two multiplets at δ = 4.25 and δ = 6.86-8.06 ppm, respectively. The NH proton appeared as a doublet at δ = 10.93 ppm ($^3J_{HH}$ = 9.2 Hz). The ^{13}C NMR spectrum of 3a exhibited 24 distinct resonances in agreement with the proposed structure.

Although the mechanism of the above reaction is unknown, a possible mechanism for this reaction is proposed in Scheme 2. On the basis of the well-established chemistry of enaminones, it is conceivable to assume that the reaction is initiated by addition of enaminone 2 to acetylenic ketone 1 [19,20] to produce zwitterionic intermediate 4 which converts to intermediate 5. Finally, this intermediate undergoes immine-enamine rearrangement to generate compound 3.

An interesting aspect of the aforementioned reaction is that when the ^{1}H NMR spectra of the compound 3a is measured in deuterated dimethylsolfoxide (DMSO-d_6) as solvent, the cyclization of 3a is observed and the ^{1}H NMR spectra consist of a mixture of open-chain and cyclized product 6a. More surprisingly, compounds 3b and 3c did not show this behavior (Scheme 3).

The ^{1}H NMR spectra of 3a in DMSO-d_6 exhibited two dublets at δ = 0.48 and δ = 1.26 ppm that were present (δ = 0.67 and δ = 1.35 ppm) in the ^{1}H NMR spectra measured in $CDCl_3$ implying to open-chain form. On the other hand, a doublet appeared at δ = 1.16 ppm corresponds to the methyl groups in the cyclic form. The ^{13}C NMR spectrum of 3a measured in DMSO-d_6 also verifies the presence of two forms, the signal appeared at 98.9 ppm is related to C-OH carbon [14-16].

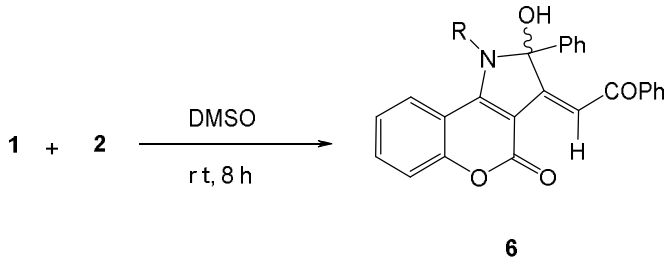
To investigate the role of DMSO in the structure of the products, we carried out the reaction of enaminones 2 with dibenzoylacetylene in DMSO instead of THF/H_2O (Scheme 4). The ^{1}H- and ^{13}C NMR spectra of the isolated product clearly showed that only cyclized compound (6) has been formed.

The structures of compounds 6a-6c were deduced from their ^{1}H, ^{13}C NMR, IR, and mass spectroscopic data. The ^{1}H NMR spectrum of 6b exhibited two multiplets (δ = 2.81-2.86 and δ = 3.01-3.06 ppm) identified as two methylene protons along with multiplets (δ = 7.11-7.79 ppm) for aromatic protons. The OH proton resonance at δ = 7.70 ppm disappeared after addition of D_2O to the DMSO-d_6 solution of 6b. The vinylic proton in 6b resonated at a lower field (δ = 8.75 ppm) since it lies in the nodal region of the carbonyl group [21]. The ^{13}C NMR spectrum of 6b exhibited 27 distinct resonances in agreement with the proposed structure. The mass spectra of 6b displayed the molecular ion peak at an appropriate *m/z* value.

Although the mechanism of the above reaction is unknown, possible path for this reaction is outlined in Scheme 5. It is reasonable to assume that 6 results from initial addition of enaminone 2 to acetylenic ketone [19,20] and subsequent cyclization of the intermediate 5 to yield 6 [14-16].

CONCLUSIONS

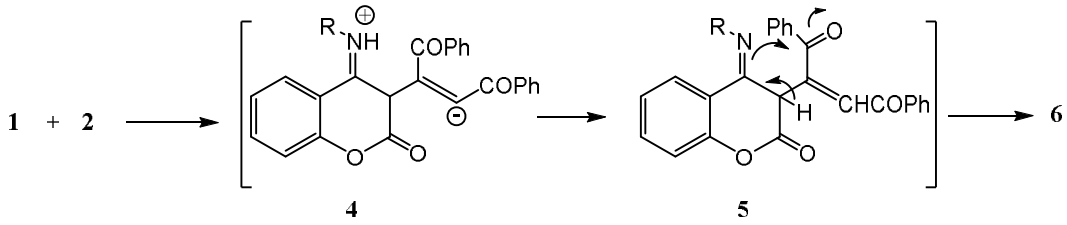
We have described the reaction between 4-alkylaminocoumarins and dibenzoylacetylene in THF/H_2O and DMSO. The reaction of dibenzoylacetylene with 4-



6

2: 2a, 2c, (2d: R = Me)	6	R	Yield (%)
	a	Me_2CH	66
	b	$PhCH_2CH_2$	60
	c	Me	63

Scheme 4. Synthesis of compounds 6



Scheme 5. Proposed mechanism for the formation of 6

alkylaminocoumarins in THF/H_2O (50:50) leads to the formation of 4-(alkylamino)-3-(1,4-dioxo-1,4-diphenylbut-2-en-2-yl)-2*H*-chromen-2-one derivatives in good yields. The cyclized products 2-hydroxy-1-alkyl-3-(2-oxo-2-phenylethylidene)-2-phenyl-2,3-dihydrochromeno [4,3-*b*] pyrrol-4(1*H*)-ones were formed in good yields, when the reaction was carried-out in DMSO.

SUPPLEMENTARY MATERIAL

Supplementary data (^{1}H NMR and ^{13}C NMR spectra for compounds 3a-3c and 6a-6c) associated with this article can be found in the online version.

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