3-(2,2-Dicyano-1-methylvinyl)coumarin in Heterocyclic Synthesis: Synthesis of Some New Coumarin Derivatives†

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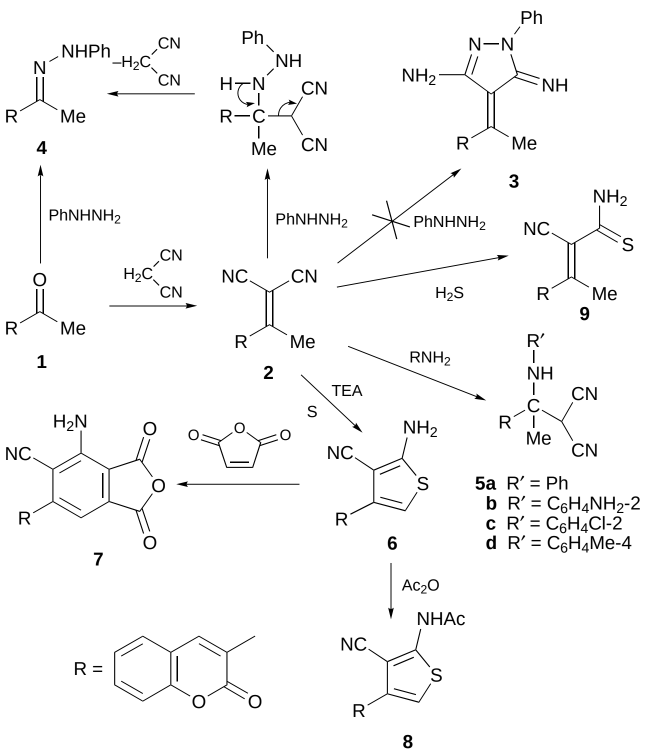
The reaction of 3-acetylcoumarin with activated nitriles provides a convenient route to a range of new coumarin derivatives.

Cyanocoumarins are of considerable interest as potential building blocks for nitrogen-containing heterocyclic systems. In addition to the study of the behaviour of a variety of aromatic or heterocyclic amino compounds with activated nitriles, interest has been shown in coumarin derivatives on account of their pharmacological activity.[1–3] In continuation of our work[4–7] on coumarins, we sought to synthesize new coumarin derivatives which might be biologically active. Thus condensation of 3-acetylcoumarin (**1**) with malononitrile in boiling benzene containing ammonium acetate and acetic acid using a Dean–Stark water separator afforded 3-(2,2-dicyano-1-methylvinyl)coumarin (**2**)[8] (Scheme 1).



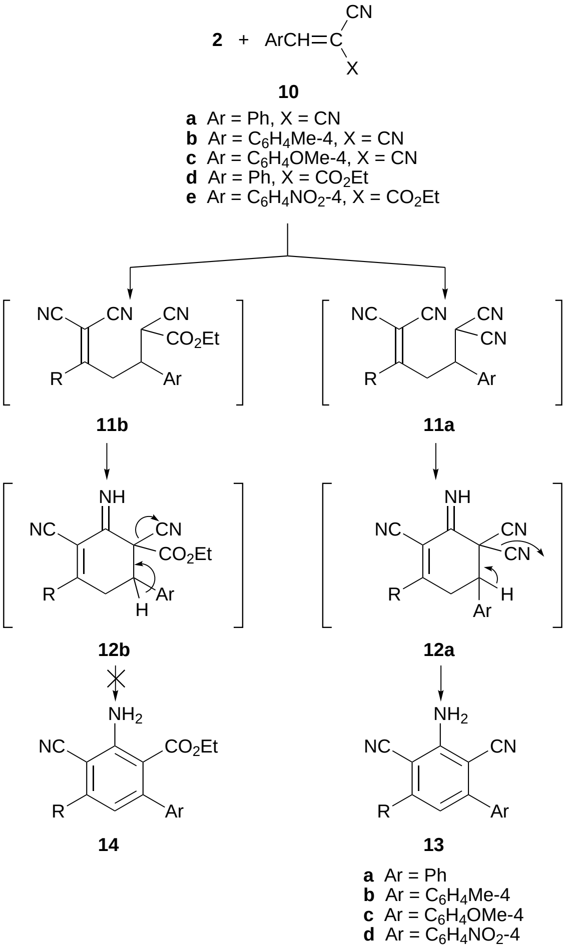
Scheme 1

In contrast to the anticipated formation of pyrazoline derivatives **3**,[9] the reaction of **2** with phenylhydrazine in boiling ethanol gave the imino compound **4**. This is assumed to proceed *via* elimination of malononitrile. The suggested structure for **4** was confirmed by its independent synthesis from **1** on refluxing with phenylhydrazine in boiling ethanol[10] (Scheme 1).

Interaction of **2** with primary aromatic amines in boiling ethanol afforded 3-(2,2-dicyano-1-arylamino-1-methylethyl)coumarins (**5a–d**) resulting from initial attack of the nucleophile at C-β of the olefinic bond of the dicyano derivatives (Scheme 1).

Reaction of **2** with sulfur in a Gewald reaction[11] produced 3-(5-amino-4-cyano-3-thienyl)coumarin (**6**). Interaction of **6** with maleic anhydride in a Diels–Alder reaction furnished **7**, while its acetylation produced the corresponding acylated compound **8** (Scheme 1). Passing hydrogen sulfide gas into a solution of **2** in ethanol containing a few drops of triethylamine afforded 3-(2-cyano-1-methyl-2-thiocarboxamidovinyl)coumarin (**9**) (Scheme 1).

Condensation of **2** with various substituted α-cyanocinnamonitriles **10a–c** in boiling ethanol containing a few drops of piperidine produced 3-(3-amino-2,4-dicyano-5-arylphenyl)coumarins **13a–c** (Scheme 2). These are assumed to be formed *via* Michael addition of the methyl function in **2** to the activated double bond in **10**, yielding the adduct **11** which then cyclizes into **12**, the latter readily losing hydrogen cyanide to yield the stable compound **13**. In contrast to the anticipated formation of the ester **14**, the reaction of **2**



Scheme 2 R as in Scheme 1

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with **10d,e** afforded **13a,d**, presumably *via* elimination of ethyl formate from the intermediate **12b** (Scheme 2).

Experimental

Mps are uncorrected. Elemental analyses were carried out in the microanalytical laboratories of the Faculty of Science, Cairo University. IR spectra (KBr) were measured on a Shimadzu IR 440 spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL FX 90Q (90 MHz) spectrometer and mass spectra on a Shimadzu GC-MS-QPm 1000 EX spectrometer using the direct-inlet system.

3-(2,2-*Dicyano-1-methylvinyl*)*coumarin* (**2**).—To a solution of 3-acetylcoumarin **1** (0.1 mol) in dry benzene (10 ml) was added malononitrile (0.1 mol), ammonium acetate (2 g) and acetic acid (2 ml). The reaction mixture was heated under reflux using a Dean–Stark water separator until water ceased to be collected. The product obtained was crystallized from ethanol to give the title *compound* **2**, (85%), mp 155 °C, ν_{max}/cm^{-1} 2200 (CN), 1720 (C=O), 1620 (C=C); δ_H ([^{2}H$_6$]DMSO) 2.7 (3 H, s, CH$_3$), 7.7–8.3 (4 H, m, ArH), 8.9 (1 H, s, H-4) (Found: C, 71.30; H, 3.40 $C_{14}H_8N_2O_2$ requires C, 71.18, H 3.38%).

3-[1-(*Phenylhydrazonoethyl*]*coumarin* (**4**).—A mixture of **1** or **2** (0.01 mol) and phenylhydrazine (0.01 mol) in ethanol (30 ml) was heated under reflux for 2 h. The reaction mixture was cooled to give a solid which was filtered off and crystallized from ethanol to give the title *compound* **4** (80%), mp 180 °C, ν_{max}/cm^{-1} 3484, 3298 (NH), 1720 (C=O), 1601 (C=); δ_H (CDCl$_3$) 2.50 (3 H, s, CH$_3$), 7.5–8.8 (9 H, m, ArH), 8.9 (1 H, s, H-4) and 9.3 (1 H, br, NH exchangeable with D$_2$O) (Found: C, 73.20; H, 4.90 $C_{17}H_{14}N_2O_2$ requires C, 73.38, H, 5.03%).

Reaction of 3-(2,2-*Dicyano*-1-*methylvinyl*)*coumarin* (**2**) *with Aromatic Amines*.—To a solution of **2** (0.01 mol) in ethanol (30 ml) was added the amine (0.01 mol) in ethanol (30 ml) in portions. The mixture was heated under reflux for 2 h and then left to cool. The precipitated product was filtered off, dried and crystallized from ethanol to give 3-(2,2-dicyano-1-arylamino-1-methylethyl) coumarins **5a–d**.

The *anilino compound* **5a** (60%) had mp 142 °C, ν_{max}/cm^{-1} 3440 (NH), 3050, 2965, 2220 (CN), 1715 (C=O); δ_H (CDCl$_3$) 2.7 (3 H, s, CH$_3$), 2.8 (1 H, s, CH), 7.5–8.6 (9 H, m, ArH), 8.9 (1 H, s, H-4) and 9.2 (1 H, br, NH exchangeable with D$_2$O) (Found: C, 72.54; H, 4.60. $C_{20}H_{15}N_3O_2$ requires C, 72.94; H, 4.55%).

The 2-*aminophenylamino compound* **5b** (55%) had mp 130 °C, ν_{max}/cm^{-1} 3430, 3350 (NH$_2$, NH), 2930, 2230 (CN), 1725 (C=O); δ_H (CDCl$_3$) 2.6 (3 H, s, CH$_3$), 2.9 (1 H, s, CH), 5.3 (2 H, br, NH$_2$), 7.4–8.7 (8 H, m, ArH), 8.9 (1 H, s, H-4) and 9.3 (1 H, br, NH, exchangeable with D$_2$O) (Found: C, 69.30; H, 4.30. $C_{20}H_{16}N_4O_2$ requires C, 69.76; H, 4.65).

The 2-*chlorophenylamino compound* **5c** (58%) had mp 135 °C, ν_{max}/cm^{-1} 3440 (NH), 3040, 2960, 2210 (CN), 1700 (C=O); δ_H (CDCl$_3$) 2.7 (3 H, S, CH$_3$), 2.8 (1 H, s, CH), 7.6–8.8 (8 H, m, ArH), 8.8 (1 H, s, H-4), 9.4 (1 H, br, NH, exchangeable with D$_2$O) (Found: C, 65.20, H, 3.50. $C_{20}H_{14}ClN_3O_2$ requires C, 66.02; H, 3.85%).

The p-*tolylamino compound* **5d** (50%) had mp 140 °C, ν_{max}/cm^{-1} 3430 (NH), 2900, 2220 (CN), 1720 (C=O); δ_H (CDCl$_3$) 2.6 (3 H, s, CH$_3$), 2.7 (3 H, s, CH$_3$), 2.8 (1 H, s, CH), 7.6–8.8 (8 H, m, ArH), 8.9 (1 H, s, H-4), 9.3 (1 H, br, NH exchangeable with D$_2$O) (Found: C, 73.80; H, 4.80. $C_{21}H_{14}N_3O_2$ requires C, 73.46, H, 4.95%).

3-(5-*Amino*-4-*cyano*-3-*thienyl*)*coumarin* **6**.—Equimolar amounts (0.01 mol) of **2** and elemental sulfur in ethanol (30 ml) were treated with a few drops of triethylamine (TEA). The reaction mixture was heated under reflux for 2 h and then left to cool down to give a solid which was filtered off and crystallized from ethanol to give the *title compound* **6** (85%), mp 245 °C, ν_{max}/cm^{-1} 3472, 3332 (NH$_2$), 3056, 2211 (CN) and 1722 (C=O) (Found: C, 62.50; H, 2.80. $C_{14}H_8N_2O_2S$ requires C, 62.68; H, 2.98%).

3-*Amino*-4-*cyano*-5-(2-*oxo*-2H-*chromen*-3-*yl*) *phathalic Anhydride* **7**.—A mixture of **6** (0.01 mol), maleic anhydride (0.01 mol) and 1,4-dioxane (30 ml) was heated under reflux for 3 h. On cooling, a solid formed which was filtered off and crystallized from ethanol to give the *title compound* **7** (70%), mp 212 °C; ν_{max}/cm^{-1} 3430, 3350 (NH$_2$), 3050, 2200 (CN), 1725 (C=O), 1650 (CO); δ_H (CDCl$_3$) 5.6 (2 H, br, NH$_2$ exchangeable with D$_2$O), 7.6–8.6 (5 H, m, ArH), 8.95 (1 H, s, H-4) (Found: C, 65.10; H, 2.50. $C_{18}H_8N_2O_5$ requires C, 65.06; H, 2.40%).

3-(5-*Acetamido*-4-*cyano*-3-*thienyl*)*coumarin* (**8**).—A solution of **6** (0.01 mol) in acetic anhydride (30 ml) was heated under reflux for 3 h. The reaction mixture was cooled to give a solid which was filtered off and crystallized from ethanol to give the *title compound* **8** (85%), mp 266 °C; ν_{max}/cm^{-1} 3450 (NH), 3040, 2975, 2215 (CN), 1705 (C=O), 1680 (C=O); δ_H (CDCl$_3$) 3.5 (3 H, s, CH$_3$), 7.1 (1 H, s, CH), 7.5–8.7 (4 H, m, ArH), 9.1 (1 H, s, H-4), 9.4 (1 H, br, NH) (Found C, 62.10; H, 3.40. $C_{16}H_{10}N_2O_3S$ requires C, 61.93; H, 3.22%).

3-(2-*Cyano*-2-*methyl*-2-*thiocarboxamidovinyl*)*coumarin* (**9**).—A solution of **2** (0.01 mol) in ethanol (30 ml) and a few drops of triethylamine was treated with hydrogen sulfide gas for 2 h to give a solid, which was filtered off and crystallized from benzene to give the *title compound* **9** (75%), mp 183 °C; ν_{max}/cm^{-1} 3354, 3312 (NH$_2$), 3113, 2214 (CN), 1694 (C=O) (Found: C, 62.40; H, 3.80. $C_{14}H_{10}N_2O_2S$ requires C, 62.22; H, 3.70%).

Reaction of **2** *with Cinnamonitrile Derivatives* **10a–e**.—A suspension of **2** (0.01 mol) in ethanol (30 ml) was treated with **10a–e** (0.01 mol) and a catalytic amount of piperidine (0.1 ml). The reaction mixture was heated under reflux for 2 h. The precipitate was filtered off and crystallized to give 3-(3-amino-2,4-dicyano-5-arylphenyl)-coumarins **13a–d**.

The 5-phenyl compound **13a** (70%) had mp 257 °C (from EtOH); ν_{max}/cm^{-1} 3472, 3332 (NH$_2$), 3056, 2211 (CN), 1722 (C=O). δ_H (CDCl$_3$) 5.4 (2 H, br, NH$_2$ exchangeable with D$_2$O), 7.6–8.8 (10 H, m, ArH), 8.9 (1 H, s, H-4); *m/z* 363 (M$^+$, 100%), 336 (24), 335 (30), 306 (7), 279 (9), 182 (6), 139 (7), 126 (8), 113 (7), 77 (6) (Found: C, 76.10; H, 3.70. $C_{23}H_{13}N_3O_2$ requires C, 76.03; H, 3.58%).

The 5-p-*tolyl compound* **13b** (75%) had mp 268 °C (from EtOH); ν_{max}/cm^{-1} 3460, 3340 (NH$_2$), 3050, 2220 (CN), 1715 (C=O); δ_H (CDCl$_3$), 2.47 (3 H, s, CH$_3$), 5.6 (2 H, br, NH$_2$ exchangeable with D$_2$O), 7.6–8.1 (9 H, m, ArH), 8.8 (1 H, s, H-4) (Found: C, 75.20; H, 4.30. $C_{24}H_{15}N_3O_2$ requires C, 76.39; H, 3.97%).

The 5-(4-*methoxyphenyl*) *compound* **13c** (80%) had mp 320 °C (from benzene); ν_{max}/cm^{-1} 3440, 3340 (NH$_2$), 2950, 2210 (CN), 1715 (C=O); δ_H (CDCl$_3$) 4.2 (3 H, s, OCH$_3$), 5.4 (2 H, br, NH$_2$ exchangeable with D$_2$O), 7.3–8.5 (9 H, m, ArH), 8.9 (1 H, s, H-4) (Found: C, 73.20; H, 4.10. $C_{24}H_{15}N_3O_3$ requires C, 73.28; H, 3.81%).

The 5-(4-*nitrophenyl*) *compound* **13d** (78%) had mp 310 °C (from 1,4-dioxane), ν_{max}/cm^{-1} 3450, 3320 (NH$_2$), 3010, 2220 (CN), 1720 (C=O); δ_H (CDCl$_3$), 5.6 (2 H, br, NH$_2$ exchangeable with D$_2$O), 7.4–8.6 (9 H, m, ArH), 8.95 (1 H, s, H-4) (Found: C, 67.70; H, 3.20. $C_{23}H_{12}N_4O_4$ requires C, 67.64; H, 2.94%).

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