

Michael-Addition Reaction of Malononitrile with α,β -Unsaturated Cycloketones Catalyzed by $\text{KF}/\text{Al}_2\text{O}_3$

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A series of $\text{KF}/\text{Al}_2\text{O}_3$ catalyzed Michael-addition reactions between malononitrile and α,β -unsaturated cycloketones in DMF solution were studied. At room temperature, 2-cyano-3-aryl-3-(1,2,3,4-tetrahydronaphthalen-1-one-2-yl) propionitrile derivatives were synthesized by the reaction between 2-arylmethylidene-1,2,3,4-tetrahydronaphthalen-1-one and malononitrile. However, if the temperature was increased to 80 °C, 2-amino-3-cyano-4-aryl-4H-benzo[h]chromene derivatives were obtained in high yields. When the α,β -unsaturated ketones were replaced by 2,6-biarylmethylidenecyclohexanone or 2,5-biarylmethylidenecyclopentanone, another series of 2-amino-3-cyano-4H-pyran derivatives was isolated successfully. The structures of the products were confirmed by X-ray diffraction analysis.

Keywords 2-amino-3-cyano-4H-pyran derivative, α,β -unsaturated cycloketone, Michael-addition reaction, synthesis

The utility of fluoride salts as potential base in a variety of synthetic reactions has been recognized in recent years.¹ However, low solubility of fluoride salts in ordinary solvents hampers their wide applications in organic synthesis. On the other hand, there has been increasing use of inorganic solid supports as catalysts for many years² resulting in higher selectivity, milder reaction conditions and easier work-up. Especially potassium fluoride-coated alumina (KF -alumina) has been a versatile solid-supported reagent used for Knoevenagel reaction,³ Henry reaction,⁴ Darzens reaction,⁵ Wittig reaction,⁶ alkylation,⁷ elimination⁵ and many other reactions.⁸ In our previous paper,⁹ we reported the reaction of 1,3-diaryl-2-propen-1-one with malononitrile using $\text{KF}/\text{Al}_2\text{O}_3$ as catalyst. As an extension to the study, herein we would like to report the Michael-addition reaction between malononitrile and α,β -unsaturated cycloketones catalyzed by $\text{KF}/\text{Al}_2\text{O}_3$.

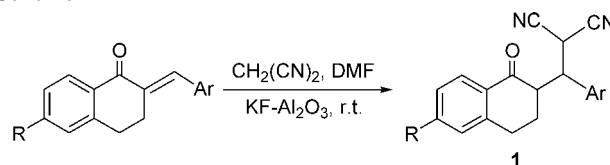
Results and discussion

When malononitrile and 2-arylmethylidene-1,2,3,4-tetrahydronaphthalene-1-one were treated with KF -alumina in DMF at room temperature (Scheme 1), the desired 2-cyano-3-aryl-3-(1,2,3,4-tetrahydronaphthalen-1-one-2-yl) propionitrile derivatives (**1**) were obtained in good yields (73%—93%).

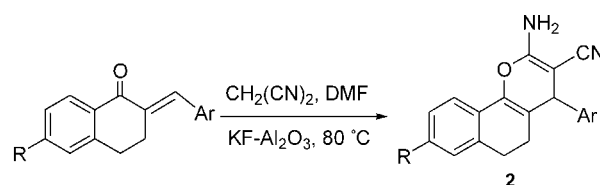
However it was interesting to note that when the reaction temperature was increased to 80 °C, the 2-amino-3-cyano-4-aryl-4H-benzo[h]chromene derivatives (**2**) were obtained in high yields (86%—94%)

(Scheme 2), which were not just the addition reaction products.

Scheme 1



Scheme 2



It should be noted that when α,β -unsaturated cycloketones, such as 2,6-biarylmethylidenecyclohexanone or 2,5-biarylmethylidenecyclopentanone were used in this reaction, the simple Michael addition products were not detected at all, instead 2-amino-3-cyano-4-aryl-8-arylmethylidene-1,4,5,6,7,8-hexahydrobenzo[b]pyran or 2-amino-3-cyano-4-aryl-7-arylmethylidenecyclopentano[b]pyran derivatives (**3**) were obtained (Scheme 3), although the reaction was controlled at room temperature. The results of **1**, **2** and **3** are summarized in Table 1.

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Received June 11, 2003; revised October 8, 2003; accepted November 28, 2003.

Project supported by the Foundation of the "Surpassing Project" of Jiangsu Province.

Scheme 3

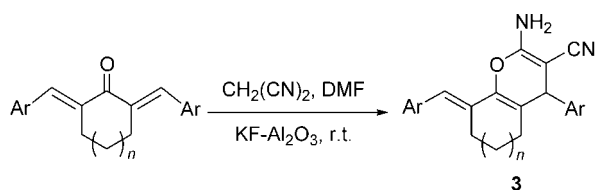


Table 1 Synthetic data of 1, 2 and 3

Entry	Ar	R or n	m.p./°C	Yield/%
1a	C ₆ H ₅	H	144—146	83
1b	C ₆ H ₅	CH ₃	140—142	93
1c	4-CH ₃ C ₆ H ₄	H	188—189	76
1d	4-CH ₃ C ₆ H ₄	CH ₃	142—144	91
1e	4-ClC ₆ H ₄	H	151—153	73
1f	2,4-Cl ₂ C ₆ H ₃	H	190—192	80
1g	2-ClC ₆ H ₄	H	182—184	90
2a	4-CH ₃ OC ₆ H ₄	H	183—184	92
2b	C ₆ H ₅	H	201—203	90
2c	4-CH ₃ C ₆ H ₄	H	166—168	87
2d	4-ClC ₆ H ₄	H	175—177	94
2e	3-NO ₂ C ₆ H ₄	H	176—177	90
2f	2,4-Cl ₂ C ₆ H ₃	H	211—212	89
2g	4-CH ₃ C ₆ H ₄	CH ₃	204—206	86
1h	4-ClC ₆ H ₄	CH ₃	200—202	92
3a	2-ClC ₆ H ₄	1	237—238	82
3b	C ₆ H ₅	1	232—233 (lit. ¹⁰ 228—230)	81
3c	3,4-OCH ₂ OC ₆ H ₃	1	236—238	86
3d	4-CH ₃ C ₆ H ₄	1	162—163	76
3e	2,4-Cl ₂ C ₆ H ₃	1	195—196	68
3f	2,4-Cl ₂ C ₆ H ₃	0	238—239	80
3g	C ₆ H ₅	0	228—230	90
3h	2-ClC ₆ H ₄	0	214—215	73

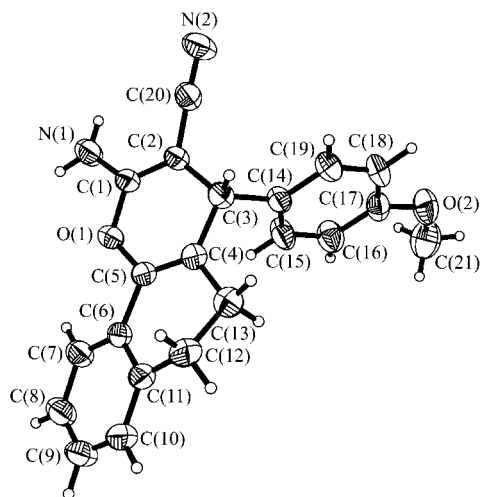


Figure 1 Structure of compound 2a.

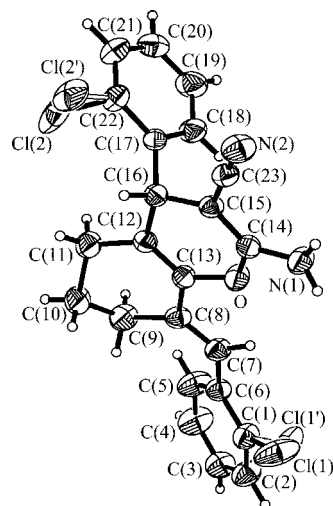


Figure 2 Structure of compound 3a.

The structures of **2a** and **3a** were confirmed by X-ray diffraction analysis, as shown in Figures 1 and 2, respectively. The selected crystallographic data are listed in Table 2. The X-ray diffraction analysis reveals that in the molecule **2a** the pyran ring is slightly distorted and adopts a half-chair conformation; the atoms C(1), C(2), C(4), C(5) and O(1) are coplanar, with C(3) deviating from the plane by $-0.0149(2)$ nm. The dihedral angle between the plane and phenyl ring [C(14)—C(19)] is 96.68° . In molecule **3a**, the pyran ring adopts boat conformation; the atoms O and C(16) deviate from the mean plane defined by C(12), C(13), C(14) and C(15) by -0.01226 nm and -0.01687 nm, respectively. The phenyl ring [C(17)—C(22)] is nearly perpendicular to the pyran ring with dihedral angle of 86.08° .

According to the structures of **2** and **3**, a sequential reaction of the Michael-addition followed by the intramolecular cyclization may take place during the formation of the product. The possible mechanism is shown in Scheme 4 (using the formation of compound **2** as example).

Scheme 4

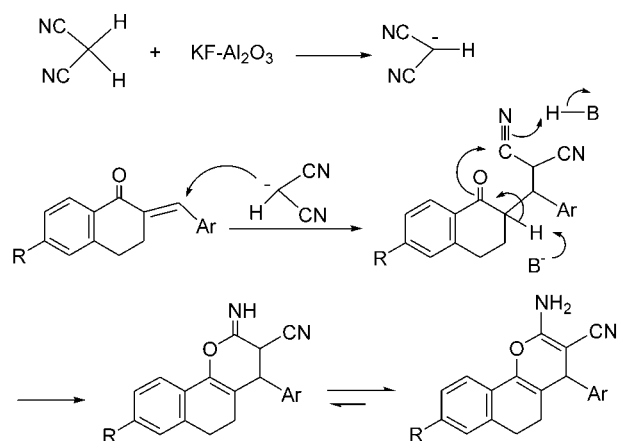


Table 2 Crystallographic data for **2a** and **3a**

Compound	2a	3a
Empirical formula	C ₂₁ H ₁₈ N ₂ O ₂	C ₂₃ H ₁₈ Cl ₂ N ₂ O
Color/shape	Yellow/Block	Pale yellow/Block
Formula weight	330.37	409.29
Temperature	296(2) K	296(2) K
Crystal system	Monoclinic	Monoclinic
Space group	<i>P</i> 2(1)/ <i>c</i>	<i>P</i> 2(1)/ <i>n</i>
Unit cell dimensions	<i>a</i> =0.6487(1) nm, <i>b</i> =2.5557(5) nm, β =96.75(2)°, <i>c</i> =1.0459(2) nm	<i>a</i> =1.3582(2) nm, <i>b</i> =0.8974(1) nm, β =103.34(1)°, <i>c</i> =1.6960(2) nm
Volume	1.7344(5) nm ³	2.011.4(4) nm ³
<i>Z</i>	4	4
Density (calculated)	1.265 Mg • m ⁻³	1.352 Mg • m ⁻³
Absorption coefficient/mm ⁻¹	0.082	0.339
Diffractometer/scan	Siemens P4/ ω	Siemens P4/ ω
<i>F</i> (000)	696	848
Crystal size	0.58 mm × 0.44 mm × 0.40 mm	0.50 mm × 0.44 mm × 0.32 mm
θ range for data collection	1.59° to 25.25°	1.74° to 25.00°
Limiting indices	0 ≤ <i>h</i> ≤ 7, 0 ≤ <i>k</i> ≤ 30, -12 ≤ <i>l</i> ≤ 12	0 ≤ <i>h</i> ≤ 8, 0 ≤ <i>k</i> ≤ 10, -20 ≤ <i>l</i> ≤ 19
Reflections collected	3360	4108
Independent reflections	3147 [<i>R</i> (int)=0.0103]	3550 [<i>R</i> (int)=0.0177]
Data/restraint/parameter	3147/2/236	3550/2/282
Goodness-of-fit on <i>F</i> ²	0.891	0.876
Final <i>R</i> indices [<i>I</i> > 2σ(<i>I</i>)]	<i>R</i> ₁ =0.0367, <i>wR</i> ₂ =0.0854	<i>R</i> ₁ =0.0361, <i>wR</i> ₂ =0.0790
<i>R</i> indices (all data)	<i>R</i> ₁ =0.0666, <i>wR</i> ₂ =0.0933	<i>R</i> ₁ =0.0707, <i>wR</i> ₂ =0.0887
Extinction coefficient	0.0165(14)	0.0118(10)
Largest diff. peak and hole	148 and -111 e • nm ⁻³	138 and -156 e • nm ⁻³

Experimental

Typical experimental procedure

Melting points were determined in open capillaries and uncorrected. IR spectra were recorded on a TEN-SOR 27 spectrometer in KBr pellet. ¹H NMR spectra were obtained via an Inova-400 spectrometer, using DMSO-*d*₆ or CDCl₃ as solvents, and Me₄Si as internal standard. Elemental analyses were carried out using Carlo Erba 1110 analyzer. X-ray diffraction was measured on a Siemens P4 diffractometer.

A dry 50-mL flask was charged with malononitrile (3 mmol), α,β -unsaturated cycloketones (2 mmol), KF-alumina (500 mg) and DMF (15 mL). The mixture was stirred at room temperature for 8–10 h (at 80 °C for 4–5 h, then cooled down to room temperature for products **2**), and then poured into 200 mL of water. The yellow solid was filtered and washed with water. The crude product was purified by recrystallization from 95% EtOH to give **1** or **2** or **3**.

Selected spectral data

1a m.p. 144–146 °C; IR (KBr) ν : 2964, 2265, 1673, 1599, 1513, 1455, 1431, 1379, 1301, 1268, 1214, 1192, 1150, 1115, 942, 893, 812, 776, 738, 595, 538 cm⁻¹; ¹H NMR (CDCl₃) δ : 1.71–2.18 (m, 2H, CH₂), 2.91–3.16 (m, 2H, CH₂), 3.25–3.30 (m, 1H, CH), 3.47 (dd, *J*=10, 4.4 Hz, 1H, CH), 5.65 (d, *J*=10.0 Hz, 1H, CH), 7.20 (d, *J*=7 Hz, 1H, ArH), 7.30–7.32 (m, 6H, ArH), 7.48 (m, 1H, ArH), 8.03 (d, *J*=8 Hz, 1H, ArH). Anal. calcd for C₂₀H₁₆N₂O: C 79.98, H 5.37, N 9.33; found C 80.21, H 5.30, N 9.24.

2a m.p. 183–184 °C; IR (KBr) ν : 3427, 3325, 3066, 2933, 2898, 2192, 1698, 1639, 1588, 1470, 1420, 1274, 1090, 840, 765 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ : 1.83–2.18 (m, 2H, CH₂), 2.57–2.76 (m, 2H, CH₂), 3.74 (s, 3H, OCH₃), 4.02 (s, 1H, CH), 6.75 (s, 2H, ArH), 6.90 (d, *J*=8.8 Hz, 2H, ArH), 7.15 (b, 3H, NH₂+ArH), 7.22–7.29 (m, 2H, ArH), 7.51 (d, *J*=6.4 Hz, 1H, ArH). Anal. calcd for C₂₁H₁₈N₂O₂: C 76.34, H 5.49, N 8.48; found C 76.28, H 5.60, N 8.35.

3a m.p. 237—238 °C; IR (KBr) ν : 3464, 3344, 2920, 2191, 1671, 1637, 1594, 1468, 1414, 1254, 1130, 1030, 859, 822, 747, 693 cm^{-1} ; ^1H NMR (DMSO- d_6) δ : 1.46—1.54 (m, 2H, CH_2), 1.69—2.10 (m, 2H, CH_2), 2.33—2.45 (m, 2H, CH_2), 4.57 (s, 1H, CH), 6.91 (s, 2H, NH_2), 6.97 (s, 1H, CH=), 7.28—7.51 (m, 8H, ArH). Anal. calcd for $\text{C}_{23}\text{H}_{18}\text{Cl}_2\text{N}_2\text{O}$: C 67.49, H 4.43, N 6.84; found C 67.58, H 4.40, N 6.88.

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(E0306117 PAN, B. F.)