Michael-Addition of Malononitrile to 1,3-Diaryl-2-propen-1-ones

Mohammad M. Al-Arab,*[1] Hani D. Tabba,[a] Bader S. Ghanem,[a] Marilyn M. Olmstead[b]

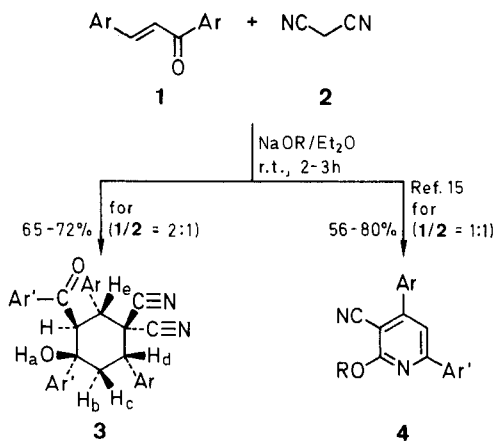
[a] Department of Chemistry, Yarmouk University, Irbid, Jordan
[b] Department of Chemistry, University of California, Davis, CA 95616, USA

2,4,6-Triaryl-3-aroyl-4-hydroxy-1,1-cyclohexanedicarbonitriles have been prepared by the base-catalyzed reaction of variously substituted α,β-unsaturated ketones with malononitrile in anhydrous ether at room temperature. Their structures have been established on the basis of their elemental analyses, IR, ^{1}H- and ^{13}C-NMR spectral data and X-ray crystallography.

There has been a large volume of work published on the condensation of α,β-unsaturated Michael acceptors with active methylene compounds.[2-9] For example, α,β-unsaturated ketones react with malononitrile and ethyl cyanoacetate in presence of ammonium acetate to give cyanopyridines in very low yield.[10-12] α,β-Unsaturated ketones also undergo Michael reaction[13] with malononitrile in refluxing sodium ethoxide/ethanol to give dehydropiperidinone, which subsequently hydrolyze in hydrochloric acid solution to furnish the corresponding glutarimides. Additionally 6-alkoxy-2(1*H*)-pyridones were obtained by reaction of α-cyanocinnamates with malononitrile.[14]

Recently, we reported the base catalyzed reaction of 1,3-diaryl-2-propen-1-ones with malononitrile using sodium ethoxide in ethanol at room temperature to afford 2,4-diaryl-5-cyano-6-ethoxypyridine **4** (R = Et).[15] Similarly, 2,4-diaryl-5-cyano-6-methoxypyridines **4** (R = Me) were prepared using sodium methoxide in methanol as catalyst.

As a continuation of our work[16-21] on the condensation of α,β-unsaturated Michael acceptors with active methylene compounds, we describe herein the base-catalyzed cyclocondensation reaction of 1,3-diaryl-2-propen-1-ones with malononitrile in anhydrous diethyl ether at room temperature to afford the highly substituted cyclohexanol derivatives **3**. This convenient and facile reaction is performed by stirring a mixture of the ketone **1** and malononitrile **2** in 2:1 molar ratio with diethyl ether as the solvent, using a suspension of sodium ethoxide in anhydrous diethyl ether as the base, for 2–3 hours at room temperature. A yellow precipitate is formed which upon workup and crystallization furnishes cyclohexanol derivatives **3**. Although we have not undertaken a mechanistic investigation of the reaction, it is proposed that the cyclohexanols **3** arise from a double Michael addition of malononitrile **2** to two molecules of 1,2-diaryl-2-propen-1-ones **1** to give a bis-adduct, which then undergoes an intramolecular aldol cyclization to give the hydroxycyclohexanedicarbonitriles **3**.



3	Ar	Ar'
a	4-$CH_3C_6H_4$	4-ClC_6H_4
b	2,4-$Cl_2C_6H_3$	4-$CH_3C_6H_4$
c	4-ClC_6H_4	4-ClC_6H_4
d	2,4-$Cl_2C_6H_3$	4-ClC_6H_4
e	4-$CH_3C_6H_4$	Ph

The structure of the cyclohexanol derivatives **3** was established on the basis of their elemental analyses, NMR, IR data and X-ray crystallography. The IR spectra of compounds **3a–e** showed a peak at ν = 2200–2250 cm^{-1} due to the cyano groups. An intense band at ν = 1670 cm^{-1} characteristic of the benzoyl group stretching frequency was also observed. As a representative example, the ^{1}H-NMR spectrum of **3a** showed a doublet at δ = 5.23 for OH_a, which was exchangeable with deuterium oxide. The doublet is due to long range coupling with H_c ($J_{a,c}$ = 2.6 Hz) in a rigid W geometry, which makes this coupling possible. The long range W coupling also indicates the presence of a nearly perfect chair configuration (Table 1).

The ^{13}C-NMR data showed a signal at δ = 204 characteristic of an aroyl carbonyl carbon and another two signals at δ = 113.8 and 113.9 due to the cyano groups, in addition to the cyclohexane carbons (Table 2).

It should be noted that the products **3a–e** possess their larger substituents in equatorial sites, hence in this cyclocondensation it is the thermodynamically more stable isomers that are obtained.

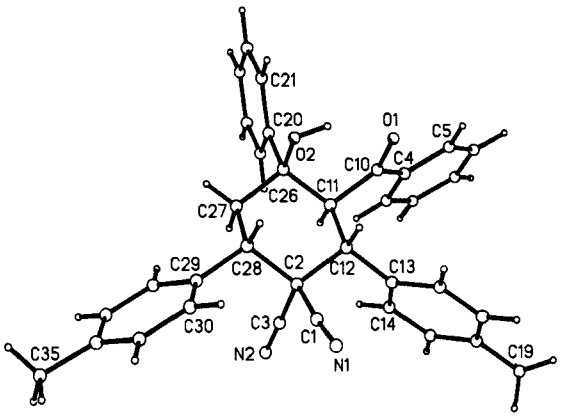


Figure. Molecular Plot of **3e**

Table 1. Compounds **3a–e** Prepared

Product	Yield (%)	mp (°C)	Molecular Formula	IR (KBr) ν(cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)
3a	67	183–185	$C_{35}H_{28}Cl_2N_2O_2$ (579.5)	2240, 2200 (C≡N), 1675 (C=O)	2.20 (s, 3H, $ArCH_3$), 2.24 (dd, 1H, J = 13.2, 3.6, H_b), 2.35 (s, 3H, $ArCH_3$), 3.02 (dt, 1H, J = 14.5, 2.6, 13.2, H_c), 4.24 (dd, 2H, J = 14.5, 2,6, 13.2, H_d, H_e), 4.93 (d, 1H, J = 12.5, H_f), 5.23 (d, 1H, J = 2.6, H_a), 6.95–8.10 (m, 16H_{arom})
3b	72	216–218	$C_{35}H_{26}Cl_4N_2O_2$ (648.4)	2235, 2200 (C≡N), 1670 (C=O)	2.22 (dd, 1H, J = 13.0, 3.5, H_b), 2.25 (s, 3H, $ArCH_3$), 2.30 (s, 3H, $ArCH_3$), 2.95 (dt, 1H, J = 14.6, 2.5, 13.1, H_c), 4.27 (dd, 2H, J = 14.5, 13.2, 2.6, H_d, H_e), 4.97 (d, 1H, J = 12.5, H_f), 5.20 (d, 1H, J = 2.6, H_a), 6.97–8.05 (m, 14H_{arom})
3c	65	170–172	$C_{33}H_{22}Cl_4N_2O_2$ (620.4)	2250, 2225 (C≡N), 1680 (C=O)	2.26 (dd, 1H, J = 13.3, 3.6, H_b), 3.05 (dt, 1H, J = 14.5, 2.5, 13.0, H_c), 4.27 (dd, 2H, J = 14.6, 13.0, 2.7, H_d, H_e), 5.05 (d, 1H, J = 12.6, H_f), 5.29 (d, 1H, J = 2.5, H_a), 7.01–7.95 (m, 16H_{arom})
3d	69	221–222	$C_{33}H_{20}Cl_6N_2O_2$ (689.3)	2235, 2225 (C≡N), 1675 (C=O)	2.25 (dd, 1H, J = 13.1, 3.5, H_b), 2.95 (dt, 1H, J = 14.5, 2.7, 13.1, H_c), 4.20 (dd, 2H, J = 14.5, 13.2, 2.5, H_d, H_e), 4.95 (d, 1H, J = 12.7, H_f), 5.32 (d, 1H, J = 2.6, H_a), 7.04–8.30 (m, 14H_{arom})
3e	68	192–193	$C_{35}H_{30}N_2O_2$ (510.6)	2250, 2230 (C≡N), 1680 (C=O)	2.13 (s, 3H, $ArCH_3$), 2.29 (dd, 1H, J = 13.2, 3.6, H_b), 2.34 (s, 3H, $ArCH_3$), 2.92 (dt, 1H, J = 14.5, 2.6, 13.1, H_c), 4.15 (dd, 1H, J = 14.6, 13.2, 2.6, H_d, H_e), 4.83 (d, 1H, J = 12.6, H_f), 5.13 (d, 1H, J = 2.7, H_a), 6.84–7.58 (m, 18H_{arom})

[a] Satisfactory microanalyses obtained: C ±0.34, H ±0.14, N ±0.14, Cl ±0.23.

Table 2. ^{13}C-NMR Data of Compounds **3a–e**, δ ($CDCl_3$/TMS)

Product	C=O	C≡N	C≡N	Cyclohexane Carbons
3a	204.0	113.8	113.9	41.0, 45.9, 48.3, 50.1, 51.9, 74.6
3b	203.5	112.2	113.7	41.2, 45.8, 48.5, 50.6, 51.7, 74.5
3c	204.2	113.3	113.6	41.1, 45.2, 48.3, 51.0, 51.6, 74.5
3d	204.3	113.6	113.2	41.3, 45.3, 48.5, 50.9, 51.2, 74.5
3e	204.2	112.5	113.2	41.2, 45.7, 48.5, 50.3, 51.7, 74.6

Table 3. Selected Lengths and Bond Angles for **3e**

Bond Lengths in (Å)		Bond Angles in (°)	
O(1)–C(10)	1.230(4)	N(1)–C(1)–(C2)	175.7(3)
O(2)–C(26)	1.436(4)	C(12)–C(2)–C(28)	111.5(3)
N(2)–C(3)	1.141(5)	N(2)–C(3)–C(2)	177.3(3)
C(2)–C(3)	1.486(5)	C(2)–C(12)–C(11)	112.7(3)
C(2)–C(28)	1.574(6)	O(2)–C(26)–C(11)	110.5(3)
C(11)–C(12)	1.541(5)	O(2)–C(26)–C(20)	110.7(3)
C(12)–C(13)	1.514(6)	C(26)–C(27)–C(28)	113.0(3)
C(20)–C(26)	1.521(5)	C(1)–C(2)–C(3)	106.9(3)
C(26)–C(27)	1.528(3)	C(3)–C(2)–C(12)	113.0(3)
O(2)–HO(2)	0.87(2)	O(1)–C(10)–C(11)	117.8(3)
N(1)–C(1)	1.142(5)	C(12)–C(11)–C(26)	112.0(3)
C(1)–C(2)	1.484(5)	O(2)–C(26)–C(20)	110.5(3)
C(2)–C(12)	1.580(3)	C(11)–C(26)–C(27)	109.1(3)
C(10)–C(11)	1.530(3)	C(26)–O(2)–HO(2)	104.0(2)
C(11)–C(26)	1.557(6)		
C(16)–C(19)	1.508(7)		
C(27)–C(28)	1.532(5)		
C(28)–C(29)	1.519(3)		

All reagents were of commercial quality from freshly opened containers. Malononitrile was purchased from Aldrich Chemical Co. Reagent quality solvents were used without further purification. IR spectra were recorded as KBr disk using a Pye-Unicam SP3-100 instrument. ^{1}H- and ^{13}C-NMR spectra were run on a Bruker WP 80-SY instrument. Compounds were analyzed at M-H-W Laboratories, Phoenix, Arizona, USA. Melting points were determined on a electrothermal melting point apparatus and are uncorrected.

(2*R,3*S**,4*R**,6*S**)-(±)-2,4,6-Triaryl-3-aroyl-4-hydroxy-1,1-cyclohexanedicarbonitrile 3a–e; General Procedure:**

To a suspension of NaOEt (680 mg, 0.01 mol) in anhydrous Et_2O (150 mL) containing malononitrile (**2**; 660 mg, 0.01 mol) is added the α,β-unsaturated ketone **2** (0.02 mol). The mixture is stirred at r.t. for 2–3 h, the solid formed is filtered and recrystallized (Table).

The filtrate is poured into water (150 mL), the organic layer separated, dried (Na_2SO_4) and evaporated to give the crude unreacted starting materials.

X-ray analysis of **3e**:[22] The summary of crystal data, data collection and refinement for this compound are as follows: formula, $C_{35}H_{30}N_2O_2$; color and habit, colorless needles; crystal system, triclinic; space group P1; a (A°), 11.833(3); b (A°), 11.940 (3); c (A°), 12.194 (3); α (deg); 70.30 (2); β (deg), 62.91 (2); γ (deg), 89.46 (2); V (A^3), 1422.5 (7); T (deg), 130 K; Z, 2; crystal dimension (mm), 0.12 × 0.25 × 0.37; d_{calcd} (gcm^{-3}), 1.19; number of data collected, 5002; number of unique data, 5002; number of data used in refinement, 2952 [$I > 2\sigma(I)$]; number of parameters refined, 366; R[22], 0.060; R_w, 0.053 [$w = (\sigma^2 (F_0) + 0.000227\ F_0^2)^{-1}$].

Only random fluctuations of < 2% in the intensities of two standard reflections were observed during the course of data collection. The structure was solved by direct methods.[24,25] Hydrogen atoms bonded to the carbon atoms were included at calculated positions using a riding model, with C–H of 0.96 A° and $U_H = 1.2\ U_C$, except for the primary hydrogens, which were refined with free positional parameters. Table 3 shows selected bond lengths and bond angles of the same molecule.

The hydrogen atom bonded to oxygen was located in a difference map and allowed to freely refine. The largest feature on a final difference map was 0.33 eA^{-3} in height. There is intramolecular contact between O(1) and O(2) of 2.693(3) A° corresponding to a hydrogen bond. The H...O distance is 1.92(2) A° and the O–H...H angle is 147(2)°. The X-ray plot of **3e** is given in the Figure, which clearly shows the presence of the cyclohexane moiety.

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(1) On sabbatical leave at the Chemistry Department, Pennsylvania State University, University Park, PA 16802, USA.
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(23) $R = \Sigma||F_o|-|F_c||/|F_o|$ and $R_w = \Sigma||F_o|-|F_c||w^{1/2}/\Sigma|F_o w^{1/2}|$.
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