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The Knoevenagel Reaction of Malononitrile with Acetylacetone: New Route of Pyrazole, Pyrazolo[2,3-C]pyridine, Benzene, Pyridazine and Benzo[C]pyridazine Derivatives

Rafat Milad Mohareb*
Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt
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Abstract □ The Knoevenagal reaction of malononitrile and acetylacetone **gave** the acyclic product 3 which **was** separated in a good yield and identified. The reactivity of 3 towards some chemical reagents is studied. Thus, the reaction of 3 with aromatic aldehydes, hydrazines and cyanomethylene derivatives **gave** products 6-12. Reaction of 3 with benzenediazonium chloride **gave** the primidine derivative 14.

keywords □ Malononitrile, acetylacetone, pyrazole, pyridazine

Pyrazoles and their anellated ring systems are versatile heterocycles of considerable biological potency, used as bactericidal[1], fungicidal[2] and antipyretic[3] agents. Aditionally, many pyridazines and their benzo analogues have been used as drugs[4], insecticides[5] and fungicides[6].

The biological activities and medicinal uses of such heterocyclic ring system noted above stimulate us to search the literature to find an easy, and direct preparative route for these derivatives.

Study of the literature reveals that the reaction of malononitrile with 1,3-diketones has been extensively investigated[7-9]. Thus, the reaction of malononitrile with acetylacetone in the presence of a catalytic amount of diethylamine in ice bath afforded the pyridin-2-one derivative[10]. On the other hand, when the same reaction was carried out in refluxing ethanol in the presence of a catalytic amount of piperidine, the pyridine derivative 2 was isolated[11].

RESULTS AND DISCUSSION

In the present work our trial to conduct the knoevenagel condensation reaction between equimolecular amounts of malononitrile and acetylacetone in benzene containing a catalytic amount of acetic acid and ammonium acetate gave only one product of molecular formula $C_8H_8N_2O$ (Ms, M^+ = 148). Four, theoretically possible, alternative structures **1**, **3**, **4**, **5** were considered for the reaction product (cf. Chart 1). The possibility of structures **1**,**4** and **5** was ruled out based on IR spectrum of the reaction product which revealed the presence of OH stretching frequence at 3600-3450 cm^{-1}, two CN groups stretching at 2220, 2210 cm^{-1} and one C=O stretching at 1690 cm^{-1}. ^{1}H-NMR spectrum of the reaction product revealed the presence of two singlets at δ=2.25 and δ=2.53 ppm for two CH_3 groups, a singlet at δ=6.19 ppm for CH group and a broad singlet at δ=8.81 ppm for OH group. However, the above spectral data agree with structure **3** as the reaction product which exists in both the keto and enol forms. Further confirmation of this structure was obtained through studying the reactivity of the reaction product with chemical reagents to form heterocyclic and fused heterocyclic ring systems.

Reaction of **3** with aromatic aldehydes in refluxing ethanol containing a catalytic amount of piperidine afforded arylidene derivatives. Thus, with benzaldehyde and salicylaldehyde it yielded the benzal derivatives **6a** and **6b** respectively. The structures of the products were confirmed based on the obtained analytical and spectral data (cf. Table I and II).

Treatment of **3** with hydrazine hydrate in refluxing ethanol solution afforded the 3,5-diaminopy-

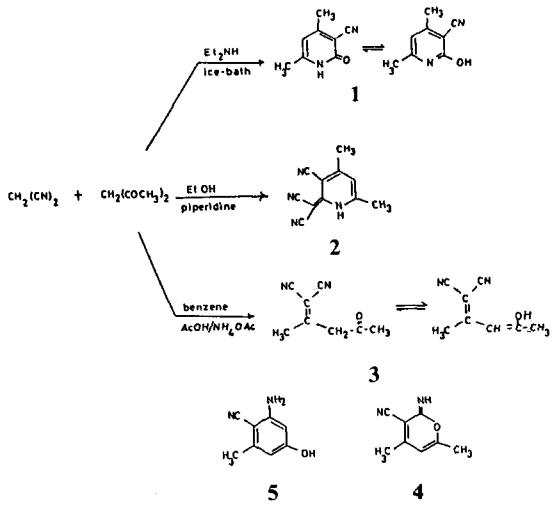

Chart 1

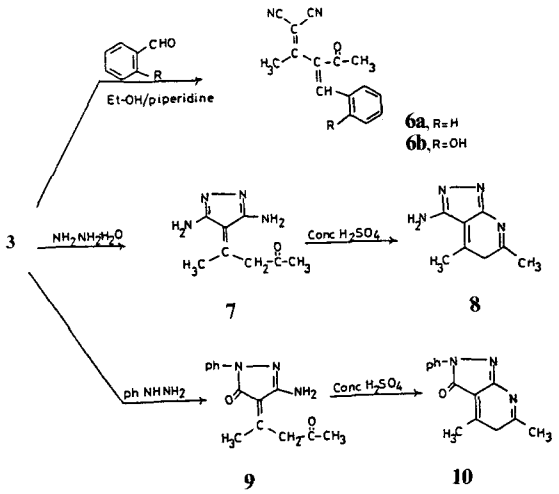

Chart 2

Table I. List of the newly synthesized compounds

Compd.	Yield %	mp.[a] ℃	Molecular formula	Anal. Calcd. (Found) C%	H%	N%
3	90	295 (A)	$C_8H_8N_2O$	64.85	5.43	18.90
			(148.15)	64.7	5.43	18.7
6a	79	300 (A)	$C_{15}H_{12}N_2O$	76.25	5.11	11.85
			(236.26)	76.2	5.0	11.8
6b	69	220 (B)	$C_{15}H_{12}N_2O_2$	71.42	4.79	11.10
			(252.26)	71.2	4.6	11.1
7	75	178 (B)	$C_8H_{12}N_4O$	53.32	6.70	31.09
			(180.20)	53.2	6.4	31.0
8	69	261 (A)	$C_8H_{10}N_4$	59.24	6.20	34.54
			(162.18)	59.2	6.0	34.1
9	82	159 (C)	$C_{14}H_{15}N_3O_2$	65.34	5.87	16.34
			(257.14)	65.4	5.8	16.3
10	78	205 (B)	$C_{14}H_{13}N_3O$	70.26	5.47	17.57
			(239.12)	70.2	5.4	17.4
11	65	99 (B)	$C_{11}H_{10}N_4O$	61.65	4.70	26.16
			(214.10)	61.6	4.7	26.0
12	72	213 (B)	$C_{11}H_9N_3O_2$	61.37	4.21	19.53
			(215.10)	61.0	4.4	19.1
13	79	179 (A)	$C_{14}H_{12}N_4O$	66.60	4.75	22.20
			(252.24)	67.0	4.3	22.4
14	68	169 (B)	$C_{14}H_{11}N_3O_2$	66.39	4.37	16.59
			(253.25)	66.1	4.1	16.2
15	60	80 (B)	$C_{14}H_{10}N_3O_2Br$	50.62	3.03	12.65
			(332.15)	50.3	3.2	12.3
16	75	183 (C)	$C_{15}H_{10}N_4O_2$	64.69	3.59	20.12
			(278.25)	64.8	3.0	19.8

[a]Solvent of cryst.: A, dimethylformamide, B, dioxane, C, ethanol

Table II. Specuroscopic data of products listed in Table I

Comd.	IR [cm^{-1}]	^{1}H-NMR [δ values]
3	3600-3450 (OH), 2950, 2880 (CH_3, CH_2), 2220, 2210 (2CN), 1690 (CO), 1630 (C=C).	2.25 (s, 3H,CH_3), 2.53 (s, 3H, $COCH_3$) 6.19 (s, 1H, CH), 8.81 (s, br, 1H, CH), 8.81 (s, br, 1H, OH).
6a	3050 (aromatic CH), 2890 (CH_3), 2220, 2210, (2CN), 1690 (CO), 1630 (C=C).	2.23 (s, 3H, CH_3), 2.51 (s, 3H, $COCH_3$) 6.21 (s, 1H, ylidene CH), 7.30-7.36 (m, 5H, C_6H_5).
6b	3620-3450 (OH), 3050 (aromatic CH), 2980, (CH_3), 2220, 2210 (2CN), 1680 (CO).	2.25 (s, 3H, CH_3), 2.53 (s, 3H, $COCH_3$) 6.33 (s, 1H, ylidene CH), 7.28-7.30 (m, 4H, C_6H_4), 10.34 (s, br, 1H, OH).
7	3440-3300 ($2NH_2$), 2940, 2890 (CH_3, CH_2), 1690 (CO), 1630 (C=C).	2.21 (s, 3H, CH_3), 2.52 (s, 3H, $COCH_3$) 4.49 (s, 2H, NH_2), 5.59 (s, 2H, CH2) 6.21 (s, 2H, NH_2).
8	3450-3350 (NH_2), 2980, 2890 (CH_3, CH_2), 1630 (C=C).	2.11, 2.23 (2s, 6H, $2CH_3$), 4.42 (s, 2H, NH_2), 6.02 (s, 2H, CH_2).
9	3445-3300 (NH_2), 3050 (aromatic CH), 2980, 2890 (CH_3, CH_2), 1690, 1680 (2CO), 1630 (C=C).	2.21 (s, 3H, CH_3), 2.49 (s, 3H, $COCH_3$) 4.39 (s, 2H, NH_2), 5.51 (s, 2H, CH_2) 7.35 (s, 5H, C_6H_5).
10	3050 (aromatic CH), 2985, 2890 (CH_3, CH_2), 1690 (CO), 1630 (C=C).	1.69, 1.88 (2s, 6H, $2CH_3$), 6.26 (s, 2H, CH_2), 7.35 (s, 5H, C_6H_5).
11	3650-3450 (OH), 3440-3300 ($2NH_2$), 3050 (aromatic CH), 2978 (CH_3), 2220, 2210 (2CN), 1690 (CO).	1.68 (s, 3H, CH_3), 4.25 (s, 2H, NH_2), 5.37 (s, 2H, NH_2), 7.33, 7.36 (2s, 2H benzene H-2, H-4), 9.87 (s, br, 1H, OH).
12	3640-3440 (2OH), 3420-3300 (NH_2), 3050 (aromatic CH), 2970 (CH_3), 2220, 2210 (2CN), 1630 (C=C).	1.69 (s, 3H, CH_3), 4.35 (s, 2H, NH_2), 7.34, 7.37 (2s, 2H, benzene H-2, H-4) 9.33, 10.12 (2s, br, 2H, 2OH).
13	3450-3300 (NH), 3050 (CH aromatic), 2975 (CH_3), 2220, 2210 (2CN), 1690 (CO), 1630 (C=C).	2.13 (s, 3H, CH_3), 2.17 (s, 3H, $COCH_3$), 7.32-7.35 (m, 5H, C_6H_5), 8.89 (s, 1H, NH).
14	3050 (aromatic CH), 2940 (CH_3), 2220 (CN), 1690, 1680 (2CO).	2.13 (s, 3H, CH_3), 2.23 (s, 3H, $COCH_3$), 7.35-7.37 (m, 5H, C_6H_5).
15	3050 (aromatic CH), 2960, 2890 (CH_3, CH_2), 2210 (CN) 1690, 1680 (2CO).	1.66 (s, 3H, CH_3), 5.21 (s, 2H, CH_2), 7.33-7.36 (m, 5H, C_6H_5).
17	3600-3450 (OH), 3440-3300 (NH_2), 3040 (aromatic CH), 2880 (CH_2), 2220 (CN), 1690 (CO).	4.33 (s, 2H, NH_2), 7.0, 7.21 (2s, 2H, benzene H-2, H-4), 7.34-7.37 (m, 5H, C_6H_5), 10.21 (s, br, 1H, OH).

razole derivative **7**. Formation of such diamino-pyrazole derivative from dicyanomethine derivatives was reported earlier in the literature[12]. Fusion of **7** with concentrated sulphuric acid in a boiling water bath for 2 h eliminated one molecule of water to give the expected pyrazolo[3,4-b]pyridine derivative **8**. The proposed structures of **7** and **8** was corroborated by their correct analystical and spectral data (cf. Table I and II). Similarly, **3** reacted with phenylhydrazine under the same experimental conditions to afford the pyrazol-3-one derivative **9** which in analogy was cyclized in the presence of cencentrated sulphuric acid to the corresponding pyrazolo[3,4-b]pyridine derivative **10** (Chart 2).

The behaviour of **3** towards some methylenonitrile reagents was also undertaken. Thus, treatment of **3** with malononitrile in refluxing ethanol containing a catalytic amount of triethylamine afforded the phenolic compound **11**, the structure of which was confirmed based on the analytical and spectral data (cf. Tables I and II). Analogously, **3** reacted with ethyl cyanoacetate to furnish the resorcinol deriva-

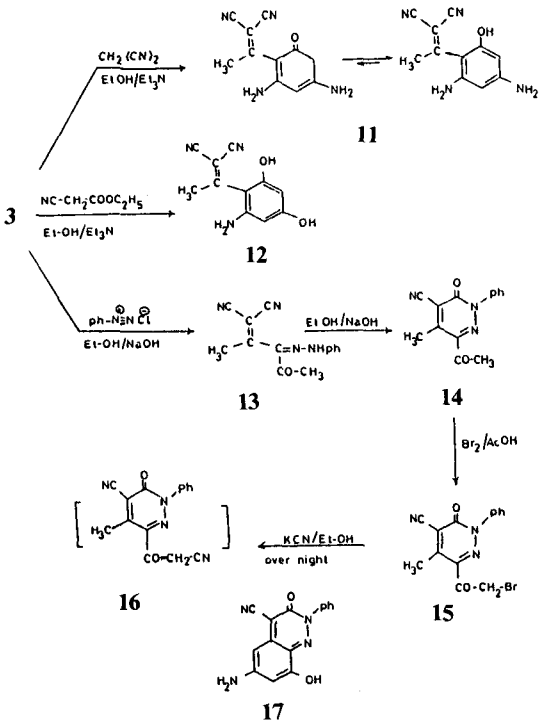

Chart 3

tive **12** in a good yield (Chart 3).

Coupling of **3** with benzenediazonium chloride in alkaline medium (pH=8) at 0℃ gave the hydrazone derivative **13**. The structure of compound **13** was established based on its IR spectrum which revealed the presence of NH stretching at 3450-3000 cm^{-1}, two CN groups streching at 2220-2210 cm^{-1} and ^{1}H-NMR spectrum which revealed the presence of a multiplet at δ=7.32-7.35 ppm corresponding to the phenyl protons and a singlet at δ=8.89 ppm corresponding to NH proton. Compound **13** underwent ready cyclization to give the corresponding pyridazone derivative **14** which has been achieved in refluxing ethanol containing sodium hydroxide. Such cyclization of phenzyl hydrazone of dicyanomethylino derivatives into the corresponding pyridazinone derivatives was reported in the literature[13].

The reactivity of the acetyl moiety of compound **14** was studied thus: treatment of **14** with bromine in the presence of hot acetic acid afforded the bromo derivative **15**. The latter derivative underwent nucleophilic attack with CN^-ion. Thus, the ethanolic solution of **15** reacted with potassium cyanide to afford the benzo[c]pyridazine derivative **17**. Formation of **17** took place through the intermediate formation of the expected 3-cyanomethyleno pyridazine derivative **16**. Formation of **17** was based on analytical and spectral data. The IR spectrum of the reaction product revealed the presence of a hydroxyl group stretching at 3600-3450 cm^{-1}, one amino group stretching at 3440-3300 cm^{-1}, one cyano group stretching at 2220 cm^{-1} and one carbonyl group at 1690 cm^{-1}. The ^{1}H-NMR spectrum revealed the presence of a D_2O exchangeable proton signal at δ=4.33 ppm for NH_2 group and two singlets at δ=7.0 and δ=7.21 ppm corresponding for benzene H-2 and H-4, a multiplet at δ=7.34-7.37 corresponding for C_6H_5 protons and a signal at δ=10.21 ppm for OH group.

Preliminary screening of the biological activities of the newly synthesized products showed some interesting reults which are currently under research.

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EXPERIMENTAL

All melting points are not corrected. The IR spectra in KBr disks were recorded on a Pye-Unicam SP_3-300 Spectrophotometer. The ^{1}H-NMR spectra were recorded in $CDCl_3$ or $(CD_3)_2SO$ on a Varian EM-360 spectrometer (90 MHz), with TMS as an internal reference. The elemental analyses ware carried out by the Microanalytical data Unit at Cairo University, A.R. Egypt.

2-Dicyanomethino-4-pentanone 3

To a solution of acetylacetone (10g, 0.1 mole) in benzene (50 m*l*) containing ammonium acetate (2g) and glacial acetic acid (4 m*l*), malononitrile (6.6g, 0.01 mole) is added. The whole mixture is heated under reflex for 15 min. in the presence of azeotropic water separator. The solid product formed is collected by filtration and crystallized from the suitable solvent (Table I).

3-Benzal-2-dicyanomethino-4-pentanone 6a: 2-Dicyanomethino-3-(2'-hydroxybenzal)-4-pentanone 6b

General procedure: To a solution of 3 (0.01 mole) in ethanol (40 m*l*) containing 1/2 m*l* of piperidine the appropriate aldehyde (0.01 mole) was added. The whole mixture is boiled under reflux for 3 h, evaporated *in vacuo* and left to cool, then triturated with water. The solid product, so precipitated in each case, is collected by filtration and crystallized from the proper solvent (cf. Tables I and II).

2-(3',5'-Diamino-pyrazol-4'-yl)-4-pentanone 7

To a suspension of **3** (0.01 mole) in ethanol (40 m*l*), hydrazine hydrate (0.01 mole) is added. The reaction mixture is boiled under reflux for 6 h then poured onto ice/water containing few drops of hydrochloric acid. The solid product, so formed, is collected by filtration washed with water and crystallized from the proper solvent (cf. Tables I and II).

5-Amino-2,4-dimethyl-pyrido[2,3-c]pyrazole 8

A mixture of **7** (0.01 mole) and sulphuric acid (70%, 15 m*l*) is heated under reflux in a boil water bath for 2 h, then poured onto ice/water mixture. The solid product, so precipitated upon addition of sodium hydroxide (25%, till pH=10), is collected by filtration and crystallized from the suitable solvent (cf. Table I and II).

2-(3'-Amino-5'-oxo-1'-phenyl-4-yl)-4-pentanone 9

The same experimental procedure described before for synthesis of **7** is carried out except for the use of phenylhydrazine instead of hydrazine hydrate (cf. Table I and II).

2,4-Dimethyl-5-oxo-6-phenyl-pyrido[2,3-c]pyrazole 10

The same experimental procedure described for synthesis of **8** is carried out except for the use of **9** instead of **7** (cf Table I and II).

2-Cyano-3-(4,5-diamino-6-hydroxy-phenyl)-crotononitrile 11

A mixture of **3** (0.01 mole) and malononitrile (0.01 mole) in ethanol (30 m*l*) containing a catalytic amount of triethyl amine (3 drops) is heated under reflux for 3 h. The mixture is evaporated *in vacuo* and the solid product remained is triturated with benzene, collected by filtration and crystallized from the proper solvent (cf Table I and II).

3-(2'-Amino-4,6-dihydroxy)-2-cyano-crotononitrile 12

The same experimental procedure described before for synthesis of **11** is carried out except for the use of ethyl cyanoacetate instead of malononitrile (cf Table I and II).

2-(dicyanomethino)-3-phenylhydrazo-4-pentanone 13

To a solution of **3** (0.01 mole) in ethanol (40 m*l*) containing sodium hydroxide (10 m*l*, 5%), benzenediazonium chloride (0.01 mole) [prepared by adding sodium nitrite solution (0.01 mole) to a cold solution of aniline (0.01 mole) containing the appropriate quantity of hydrochloric acid with continuous stirring] is added with continuous stirring. The reaction mixture is kept at 0℃ with stirring and the solid product, so formed, is collected by filtration (cf Table I and II).

3-Acetyl-5-cyano-4-methyl-6-oxo-1-phenyl-pyridazine 14

A solution of **3** (0.01 mole) in ethanol (40 m*l*) containing sodium hydroxide (0.1 g) is refluxed for 2 h. The reaction mixture is left to cool then neutralized with acetic acid. The solid product, so formed, is collected by filtration and crystallized from the suitable solvent (cf Table I and II).

3-Bromoacetyl-5-cyano-4-methyl-6-oxo-1-phenylpyridazine 15

To a hot solution of **14** (0.01 mole) in glacial acetic acid (30 m), bromine (0.01 mole) is added dropwise with continuous shaking. The reaction mixture is left at room temperature overnight and the solid product, so formed, is collected by filtration and crystallized from the proper solvent (cf Table I and II).

5-Amino-7-cyano-3-hydroxy-8-oxo-1-phenylbenzo[c]pyridazine 17

To a solution of **15** (0.01 mole) in ethanol at 70℃, potassium cyanide (0.01 mole) solution is added. The whole mixture is kept at 70℃ for 4 h. The solid product formed upon dilution with water containing few drops of hydrochloric acid (till pH=6) is collected by filtration (cf Table I and II).

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