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THE USE OF MALONONITRILE IN THE SYNTHESIS OF NOVEL α-AMINO NITRILES

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ABSTRACT

Continuing earlier studies designed to obtain compounds of pharmaceutical interest, we used acetyl acetone (**1**, $R = CH_3$) and ethyl acetoacetate (**1**, $R = OEt$) for the preparation of some novel α-amino nitriles (**3**, **6** and **7**). The structures of the new ring systems have been confirmed by IR, NMR and mass spectral data.

Key Words: Synthesis; Malononitrile; Amino nitriles

The ready availability of β-diketones and the enhanced reactivity of their electrophilic sites have made them the starting materials of choice for a great variety of synthesis. As a further extension on the reaction of acetyl acetone and ethyl acetoacetate with some reagents,[1–7] thiocarbamoylation followed by reaction of (**1**, $R = CH_3$) with malononitrile and the reaction of (**1**, $R = OEt$) with aniline and/or aryldiazonium salts and malononitrile were investigated.

Application of thiocarbamoylation to (**1**, $R = CH_3$), gave 2-acetyl-1-thioacetoacetanilide (**2**).[8] Heating **2** with malononitrile in ethanol and

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piperidine as a catalyst gave 2-acetyl-3-phenylamino-4-cyano-5-aminophenol (**3**) in a good yield. The structure of compound **3** was based on IR, ^{1}H-NMR and mass spectral data. The formation of compound **3** may be rationalized in terms of carbanion attack at the thiocarbonyl carbon atom of **2** to give the dicyanomethylidine intermediate (A). This intermediate undergoes a ring closur to give intermediate (B) which rearranges to the final product **3**.

The reaction of (**1**, R = OEt), with aniline gave acetoacetanilide (**4**).[9] Coupling of **4** with aryldiazonim salts resulted in the formation of the arylazo derivatives (**5**).[10] The reaction of **5** with malononitrile in ethanol-piperidine gave 3-arylazo-1-phenyl-4-methyl-5-cyano-6-amino-2-pyridones (**6a–c**) in a good yield.

An alternative approach to the pyridones (**6a–c**) was treating **4** with malononitrile in ethanol-piperidine to give the 2-pyridone **7**. Coupling of **7** with aryldiazonium salts gave pyridones **(6a–c)**. Structure **7** was established by ^{1}H-NMR and mass spectral data. In the presence of alcohol the formation of **6** and **7** proceeds through cyanocarbon acid (C) intermediate, which on subsequent cyclization gives intermediate (D) and finally **6** and **7**.

EXPERIMENTAL

All melting points are uncorrected. Elemental analyses were performed in the Microanalytical Unit, Mansoura and Cairo University. IR spectra (in cm^{-1}) were recorded by means of pressed KBr on a Perkin-Elmer 883 Infrared Spectrophotometer. ^{1}H-NMR spectra are obtained at 400 MHz using TMS as an internal standard. Mass spectra were obtained using Varian MAT 711 at 70 eV.

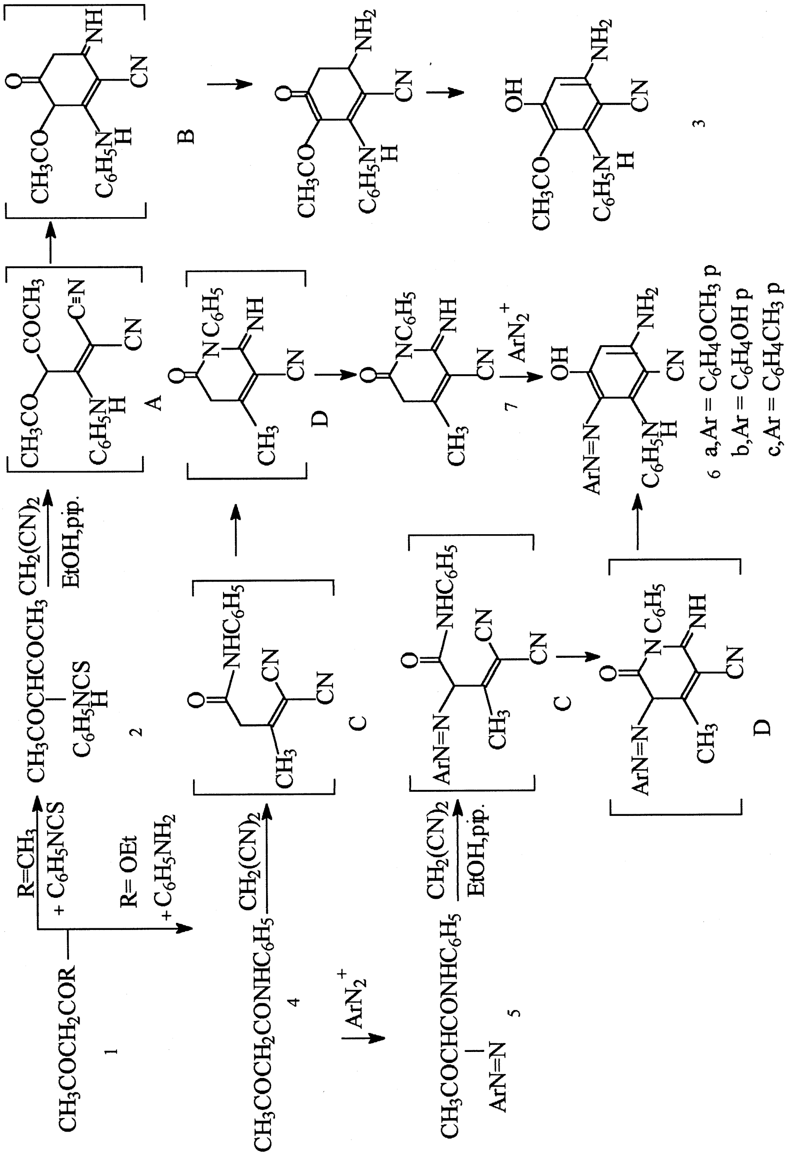
2-Acetyl-1-thioacetoacetanilide (2)

This compound was prepared according to previously reported method.[8]

2-Acetyl-3-phenylamino-4-cyano-5-aminophenol (3), 3-Arylazo-1-phenyl-4-methyl-5-cyano-6-amino-2-pyridones (6a–c) and 1-Phenyl-4-methyl-5-cyano-6-amino-2-pyridone (7)

General Procedure

To (0.005 mol) of each of **2**,[8] **4**[9]or **5**[10] in ethanol (25 mL) and 2–3 drops of piperidine was added malononitrile (0.33 g, 0.005 mol). The reaction


CH3COCH2COR
1
R=CH3
+ C6H5NCS
R= OEt
+ C6H5NH2
CH3COCHCOCH3
C6H5NCS
H
2
CH2(CN)2
EtOH,pip.
CH3CO
COCH3
C≡N
C6H5N
H
CN
A
CH3CO
C6H5N
H
CN
NH
B
CH3CO
C6H5N
H
CN
NH2
CH3CO
C6H5N
H
OH
CN
NH2
3
CH3COCH2CONHC6H5
4
CH2(CN)2
NHC6H5
CH3
CN
CN
C
NC6H5
NH
CH3
CN
D
NC6H5
NH
CH3
CN
ArN2+
7
ArN2+
CH3COCHCONHC6H5
ArN=N
5
CH2(CN)2
EtOH,pip.
ArN=N
NHC6H5
CH3
CN
CN
C
ArN=N
N C6H5
NH
CH3
CN
D
ArN=N
OH
NH2
C6H5N
H
CN
6 a,Ar = C6H4OCH3 p
b,Ar = C6H4OH p
c,Ar = C6H4CH3 p

Structure.

mixture was refluxed for 4–6 hrs, left to cool and the solid product that separated in each case was filtered off, dried and recrystallized from ethanol.

Compound 3: obtained as colourless crystals, yield (70%), m.p. 110°C.

Analysis: $C_{14}H_{13}N_3O_2$ (267.27)
Calcd: C 67.40 H 4.90 N 15.72
Found: C 67.55 H 4.98 N 15.59
IR: $\nu = 1650$ (C = O bonded), 2200 (C ≡ N), 3200–3300 (br, NH and NH_2) and 3420 cm^{-1} (OH). ^{1}H-NMR: $\delta = 2.25$ (s, 3H, CH_3CO-), 5.09 (s, 2H, NH_2), 7.1 (s, 1H, H-6), 7.25 (s, 1H, -NH) and 7.55–7.7 (m, 5H, ArH). - M.S. m/z (rel. int.) 266 (M^+-1) (2), 241 (M^+-CN) (93), 241 (M^+-HCN) (100), 226 (19), 178 (19.5), 141 (17), 77 (20), 55 (21).

Compound 6a: obtained as orange crystals, yield (85%), m.p. 169°C.

Analysis: $C_{20}H_{17}N_5O_2$ (359.38)
Calcd: C 66.83 H 4.76 N 19.48
Found: C 66.95 H 4.91 N 19.26
IR: $\nu = 1665$ (C = O), 2270 (C ≡ N), 3050–3200 (br, NH_2).

Compound 6b: obtained as yellow crystals, yield (65%), m.p. 145°C.

Analysis: $C_{19}H_{15}N_5O_2$ (345.35)
Calcd: C 66.07 H 4.37 N 20.28
Found: C 66.11 H4.21 N 20.15
IR: $\nu = 1670$ (C = O), 2245 (C ≡ N), 3100–3250 (NH_2), 3420 (OH).

Compound 6c: obtained as brown crystals, yield (81%), m.p. 125°C.

Analysis: $C_{20}H_{17}N_5O$ (343.38)
Calcd: C 69.95 H 4.99 N 20.39
Found: C 70.09 H 4.91 N 20.43
IR: $\nu = 1665$ (C = O), 2235 (C ≡ N), 3120–3210 (NH_2).-M.S. m/z (rel. int.) 343 (M^+) (0,5), 295 (3), 225 (100), 197 (95), 182 (18), 93 (20), 77 (38).

Compound 7: obtained as colourless crystals, yield (71%), m.p. 295°C.

Analysis: $C_{13}H_{11}N_3O$ (225.24)
Calcd: C 69.31 H 4.92 N 18.65
Found: C 69.43 H 4.81 N 18.51
IR: $\nu = 1675$ (C = O), 2200 (C ≡ N), 3300, 3450 (NH_2).-^{1}H-NMR: $\delta = 2.26$ (s, 3H, CH_3), 5.15 (s, 2H, NH_2), 5.87 (s, 1H, H-3, olefinic proton), 7.25–7.7 (m, 5H, ArH).- M.S. (rel. int.): 225 (M^+) (100), 197 (92), 169 (18), 104 (16), 93 (20), 77 (39).

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