Nitriles in Heterocyclic Synthesis: New Approaches for Synthesis of Some Pyridine Derivatives

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A variety of pyridines was prepared from reaction of N-benzylidenecyanoethanoic hydrazide (**2**) with malononitrile, benzoylacetone, cyanoacetamide and cinnamonnitrile derivatives. The reactivity of **2** towards a variety of ketones was studied.

Polyfunctional nitriles are highly reactive reagents that have been extensively used in heterocyclic synthesis [1–3]. In continuation of our program directed to the development of new procedures for synthesis of azoles, azines, and their condensed derivatives from readily available materials [4, 5], we report here a new synthesis of substituted pyridines from polyfunctional nitriles. Reaction of cyanoethanoic hydrazide (**1**) with benzaldehyde affords a 1:1 condensation product. Structure **2** was established for the reaction product based on ¹H NMR spectrum which revealed a singlet at δ 4.0 ppm for the methylene protons. A signal of only one D₂O exchangeable proton at δ 5.5 ppm was observed. If this product was **3**, three D₂O exchangeable protons should have been observed.

Compound **2** reacted with malononitrile to yield a 1:1 adduct. Structure **5** was assigned for the reaction product based on IR, ¹H NMR and mass spectra. IR spectrum revealed only one CN stretching band at ν = 2220 cm⁻¹. The ¹H NMR spectrum revealed signals of four D₂O exchangeable protons at δ 5.6 and 8.3 ppm corresponding to the two amino functions. A multiplet for aromatic and arylidene protons appeared at δ 7.2–7.6 ppm. Structure **5** was assumed to be formed through the intermediate **4**.

Compound **2** reacted with cyanoacetamide affording the pyridine derivative **6**, through the cyclization of the non-isolable adduct **7**. Structure **6** was established based on the IR spectrum which revealed the absence of CN stretching band expected at $\sim$ 2200 cm⁻¹. Compound **2** condensed with benzoyl-

acetone to yield the N-aminopyridine **8**. Compound **2** reacted with cinnamonnitrile derivatives **9a, b** affording products of molecular formulae C₂₀H₁₃N₅O and C₂₆H₁₈N₄O₂ respectively. Pyridine structure **12** was assigned based on IR and ¹H NMR data. The formation of **12** in this reaction was assumed to proceed *via* addition of the methylene group in **2** to the activated double bond in **9** to yield the acyclic intermediate **10** which cyclizes into **11**. This is followed by aromatization *via* loss of hydrogen molecule to yield **12**. Ready autoxidation of dihydropyridines into pyridines under similar conditions has been reported [6]. Compound **2** condensed with acetophenone and ethyl acetoacetate yielding **13** and **14**. In case of acetylacetone, compound **2** underwent condensation reaction yielding the pyridine derivative **15** *via* loss of two water molecules.

Compound **14** coupled with benzenediazonium chloride to yield the hydrazone **17** which was converted into the pyridazin-6-imine (**18**) on refluxing in acetic-hydrochloric acid mixture. Structure **18** was established based on the IR spectrum which revealed the absence of CN stretching and expected at $\sim$ 2200 cm⁻¹.

Compound **14** reacted with trichloroacetone to yield the pyridine derivative **20** which is formed through cyclization of the non isolable intermediate **19** as reported [1].

Experimental

All melting point are uncorrected. IR spectra were recorded on a Pye-Unicam Spectrophotometer. ¹H NMR spectra on a Varian EM-90 MHz spectrometer. The Microanalytical data were performed by the Microanalytical Unit at Cairo University.

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***N*-Benzylidenecyanoethanoic hydrazide (2)**

Compound **1** (0.99 g, 0.01 mole) was refluxed with (1.06 g, 0.01 mole) of benzaldehyde in 20 ml of ethanol catalyzed with piperidine for 2 h. The solid product, so formed, was filtered off and crystallized from ethanol as colourless crystals; m.p. 165 °C, yield 1.77 g (95%). – IR (KBr, cm^{-1}): $\nu(\text{NH})$: 3300, $\nu(\text{CN})$: 2200, $\nu(\text{CO})$: 1700. – ^1H NMR (DMSO): δ = 4.0 ppm (s, CH_2); 5.5 (s, NH); 7.2–7.6 (m, C_6H_5 , CH).

$\text{C}_{10}\text{H}_9\text{N}_3\text{O}$ (187.22)

Calcd	C 64.14	H 4.85	N 22.44,
Found	C 64.20	H 4.80	N 22.30.

***1*-Benzalimino-4,6-diamino-2(2*H*)-pyridinone-3-carbonitrile (5)**

Compound **2** (1.87 g; 0.01 mole) was refluxed with (0.66 g, 0.01 mole) malononitrile in ethanol (20 ml) catalyzed with piperidine for 2 h. The resulting solid product was collected by filtration and crystallized from acetic acid as colourless crystals; m.p. 312 °C; yield 2.27 g (90%). – IR (KBr, cm^{-1}): $\nu(\text{NH}_2)$: 3410, 3390, 3240; $\nu(\text{CN})$: 2220 (CN); $\nu(\text{CO})$: 1690. – ^1H NMR (DMSO): δ = 5.6 ppm (s, NH_2); 7.2–7.6 (m, C_6H_5 , H-5, exocyclic CH); 8.3 (s, NH_2). – MS: m/z = 253 (M^+).

$\text{C}_{13}\text{H}_{11}\text{N}_5\text{O}$ (253.29)

Calcd	C 61.64	H 4.38	N 27.65,
Found	C 61.60	H 4.20	N 27.80.

***5*-Benzalhydrazido-4,6-diamino-2-hydroxypyridine (6)**

To a solution of compound **2** (1.87 g, 0.01 mole) in dimethylformamide (20 ml), cyanoacetamide (0.84 g, 0.01 mole) was added. The reaction mixture was refluxed for 3 h then poured into ice/water containing few drops of hydrochloric acid. The solid product, so formed, was collected by filtration and crystallized from acetic acid as orange crystals; m.p. 250 °C, yield 2.02 g (75%). – IR (KBr, cm^{-1}): $\nu(\text{OH})$: 3600; $\nu(\text{NH}_2, \text{NH})$: 3400, 3200; $\nu(\text{CO})$: 1710.

$\text{C}_{13}\text{H}_{12}\text{N}_5\text{O}_2$ (270.30)

Calcd	C 57.76	H 4.48	N 25.91,
Found	C 57.60	H 4.30	N 25.70.

***6*-Amino-1-benzalimino-4-phenyl-2(2*H*)-pyridinone-3-carbonitrile (8)**

Compound **2** (1.87 g, 0.01 mole) was refluxed with (1.45 g, 0.01 mole) benzoylacetone nitrile in pyridine (20 ml) for 2 h. The reaction mixture was poured into water. The resulting solid product was collected by filtration and crystallized from DMF as brown crystals; m.p. 206 °C; yield 2.04 g (65%). – IR

(KBr, cm^{-1}): $\nu(\text{NH}_2)$: 3400, 3300; $\nu(\text{CN})$: 2210; $\nu(\text{CO})$: 1690. – ^1H NMR (DMSO): δ = 3.0 ppm (s, NH_2); 7.4–7.9 (m, $2\times\text{C}_6\text{H}_5$, H-7, and exocyclic CH).

$\text{C}_{19}\text{H}_{14}\text{N}_4\text{O}$ (314.37)

Calcd	C 72.58	H 4.49	N 17.82,
Found	C 72.60	H 4.50	N 17.80.

Reaction of 2 with cinnamonitrile derivatives 9a, b

Equimolecular amounts (0.01 mole) of either **9a** (1.54 g) or **9b** (2.33 g) were refluxed with compound **2** (1.87 g, 0.01 mole) in ethanol (30 ml) catalyzed with piperidine for 5 h. The solid products so formed, were collected by filtration and crystallized from the proper solvent.

***6*-Amino-1-benzalimino-4-phenyl-2(2*H*)-pyridinone-3,5-dicarbonitrile (12a)**

M.p. 302 °C; yield 2.54 g (75%), buff crystals from DMF. – IR (KBr, cm^{-1}): $\nu(\text{NH}_2)$: 3400, 3300; $\nu(\text{CN})$: 2210, 2190; $\nu(\text{CO})$: 1700. – ^1H NMR (DMSO): δ = 3.3 ppm (s, NH_2); 7.3–7.7 (m, $2\times\text{C}_6\text{H}_5$, exocyclic CH).

$\text{C}_{20}\text{H}_{13}\text{N}_5\text{O}$ (339.38)

Calcd	C 70.77	H 3.86	N 20.64,
Found	C 70.80	H 3.80	N 20.50.

***6*-Amino-1-benzalimino-5-benzoyl-4-phenyl-2(2*H*)-pyridinone-3-carbonitrile (12b)**

M.p. 120 °C; yield 2.50 g (60%); yellow crystals from ethanol. – IR (KBr, cm^{-1}): $\nu(\text{NH}_2)$: 3400, 3350; $\nu(\text{CN})$: 2200; $\nu(\text{CO})$: 1710, 1690. – ^1H NMR (DMSO): δ = 3.5 ppm (s, NH_2); 7.3–7.9 (m, $3\times\text{C}_6\text{H}_5$, exocyclic CH).

$\text{C}_{26}\text{H}_{18}\text{N}_4\text{O}_2$ (418.48)

Calcd	C 74.61	H 4.34	N 13.39,
Found	C 74.60	H 4.10	N 13.50.

Reaction of 2 with acetophenone and ethyl acetoacetate to give 13 and 14 respectively

To a solution of compound **2** (1.87 g, 0.01 mole) in dimethylformamide (20 ml) catalyzed with few drops of piperidine; either acetophenone (1.2 g, 0.01 mole) or ethyl acetoacetate (1.3 g, 0.01 mole) was added. The reaction mixture was refluxed for 3 h and then poured into ice-water containing few drops of hydrochloric acid. The solid products, so formed, were collected by filtration and crystallized from the proper solvent.

Compound 13

M.p. 170 °C; yield 2.31 g (80%); yellow crystals from ethanol. – IR (KBr, cm^{-1}): $\nu(\text{NH})$: 3300, 3100;

$\nu(\text{CN})$: 2200; $\nu(\text{CO})$: 1690. — ^1H NMR (DMSO): δ = 1.3 ppm (s, CH_3); 7.2–7.9 (m, $2 \times \text{C}_6\text{H}_5$, CH); 8.3 (br, NH).

$\text{C}_{18}\text{H}_{15}\text{N}_3\text{O}$ (289.36)

Calcd C 74.71 H 5.23 N 14.52,
Found C 74.90 H 5.20 N 14.60.

Compound 14

M.p. 250 °C; yield 2.24 g (75%); orange crystals from acetic acid. — IR (KBr, cm^{-1}): $\nu(\text{NH})$: 3400, 3350; $\nu(\text{CN})$: 2220; $\nu(\text{CO})$: 1710. — ^1H NMR (DMSO): δ = 1.2 ppm (m, $2 \times \text{CH}_3$); 4.2 (m, $2 \times \text{CH}_2$); 7.2–7.7 (m, C_6H_5 , CH, NH).

$\text{C}_{16}\text{H}_{17}\text{N}_3\text{O}_3$ (299.36)

Calcd C 64.19 H 5.73 N 14.03,
Found C 64.30 H 5.50 N 14.10.

1-Benzalimino-4,6-diamino-2(2H)-pyridinone-3-carbonitrile (15)

Equimolecular amounts (0.01 mole) of **2** (1.87 g) and acetylacetone (1 g) were refluxed in dimethylformamide (20 ml) for 2 h. The reaction mixture was poured into ice/water acidified with few drops of hydrochloric acid. The solid product, so formed, was filtered off and crystallized from ethanol as buff crystals; m.p. 270 °C; yield 1.88 g (75%). — IR (KBr, cm^{-1}): $\nu(\text{CN})$: 2220; $\nu(\text{CO})$: 1690.

$\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}$ (251.31)

Calcd C 71.68 H 5.22 N 16.72,
Found C 71.70 H 5.30 N 16.90.

Coupling of compound 14

A solution of **14** (2.99 g, 0.01 mole) in ethanol (30 ml) containing sodium acetate (3.0 g) was coupled with an ice-cold solution of benzenediazonium chloride [prepared by adding sodium nitrite (0.69 g,

0.01 mole) to the appropriate quantity of aniline (0.93 g, 0.01 mole) in hydrochloric acid (26 ml)]. The solid product, so formed, was collected by filtration and crystallized from ethanol as red crystals; m.p. 195 °C; yield 3.62 g (90%). — IR (KBr, cm^{-1}): $\nu(\text{NH})$: 3400, 3300; $\nu(\text{CN})$: 2200; $\nu(\text{CO})$: 1710, 1690.

$\text{C}_{22}\text{H}_{21}\text{N}_5\text{O}_3$ (403.48)

Calcd C 65.48 H 5.25 N 17.36,
Found C 65.60 H 5.30 N 17.10.

Ethyl-(4-benzalhydrazido-5-methyl-2-phenyl-3(2H)-pyridazinimine)-6-carboxylate (18)

Compound **17** (4.03 g, 0.01 mole) was refluxed in a solution of acetic (30 ml) — hydrochloric (2 ml) acids mixture for 2 h. The reaction product was poured into water. The solid obtained was collected by filtration and crystallized from acetic acid as brown crystals; m.p. 230 °C; yield 3.02 g (75%). — IR (KBr, cm^{-1}): $\nu(\text{NH})$: 3350, 3200; $\nu(\text{CO})$: 1720, 1690.

$\text{C}_{22}\text{H}_{21}\text{N}_5\text{O}_3$ (403.48)

Calcd C 65.48 H 5.25 N 17.36,
Found C 65.40 H 5.40 N 17.40.

Ethyl-(2-amino-4-methyl-3-benzalhydrazido-6-trichloromethylpyridine)-5-carboxylate (20)

Trichloroacetonitrile (1.44 g, 0.01 mole) was added to a solution of **14** (2.99 g; 0.01 mole) in refluxing dioxane (30 ml) with a few drops of piperidine for 3 h. The solid product obtained was collected by filtration and crystallized from ethanol as buff crystals; m.p. 220 °C; yield 3.76 g (85%). — IR (KBr, cm^{-1}): $\nu(\text{NH}_2, \text{NH})$: 3450, 3330; $\nu(\text{CO})$: 1710, 1680.

$\text{C}_{18}\text{H}_{17}\text{N}_4\text{O}_3\text{Cl}_3$ (443.74)

Calcd C 48.71 H 3.86 N 12.62,
Found C 48.60 H 3.80 N 12.60.

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