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

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Z. Naturforsch. 43b, 1351–1354 (1988); received March 31, 1987/June 16, 1988

Cyanoethanolic Hydrazide, Heterocyclic Synthesis, Pyridine Derivatives

A variety of nitriles was prepared from reaction of N-benzylideneacyanoethanolic hydrazide (2) with malononitrile, benzyloacetonitrile, cyanoacetonamide and cinnamonicitrile derivatives. The reactivity of 2 towards a variety of ketones was studied.

Polynitrofunctional 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 polynitrofunctional nitriles. Reaction of cyanoethanolic 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 cyanacetonamide 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 ~2200 cm-1. Compound 2 condensed with benzoxy-

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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Verlag der Zeitschrift für Naturforschung, D-7400 Tübingen 0932–0776/88/1000–1351/$ 01.00/0

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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): ν(NH): 3300, 3100; ν(CN): 2200; ν(CO): 1700. - ¹H NMR (DMSO): δ = 4.0 ppm (s, CH₃); 5.5 (s, NH); 7.2-7.6 (m, C₆H₅, CH₃).

C₁₀H₁₂N₂O (187.22)
Calcd C 61.60 H 4.20 N 27.80.
Found C 61.64 H 4.38 N 27.80.

1-Benzalimino-4,6-diamino-2(2H)-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): ν(NH): 3410, 3390, 3240; ν(CN): 2220 (CN); ν(CO): 1690. - ¹H NMR (DMSO): δ = 3.5 ppm (s, NH); 7.3-7.7 (m, C₆H₅, H-5, exocyclic CH); 8.3 (s, CH₃). - MS: m/z = 253 (M⁺).

C₁₃H₁₁N₃O (253.29)
Calcd C 64.20 H 4.80 N 22.30.
Found C 64.14 H 4.85 N 22.44.

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): ν(OH): 3600; ν(NH₂, NH): 3400, 3200; ν(CO): 1710.

C₁₃H₁₂N₂O₂ (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(2H)-pyridinone-3-carbonitrile (8)

Compound 2 (1.87 g, 0.01 mole) was refluxed with (1.45 g, 0.01 mole) benzoylecyanonitrile 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): ν(NH): 3400, 3300; ν(CN): 2210; ν(CO): 1690. - ¹H NMR (DMSO): δ = 3.0 ppm (s, NH₂); 7.4-7.9 (m, 2×C₆H₅, H-7, and exocyclic CH).

C₁₅H₁₅N₃O (314.37)
Calcd C 74.61 H 4.34 N 13.39.
Found C 74.60 H 4.10 N 13.50.

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(2H)pyridinone-3,5-dicarbonitrile (12a)

M.p. 302 °C; yield 2.54 g (75%); buff crystals from DMF. - IR (KBr, cm⁻¹): ν(NH₂): 3400, 3300; ν(CN): 2210, 2190; ν(CO): 1700. - ¹H NMR (DMSO): δ = 3.3 ppm (s, NH₂); 7.3-7.7 (m, 2×C₆H₅, exocyclic CH).

C₂₅H₁₈N₄O₂ (393.48)
Calcd C 72.60 H 4.50 N 17.80.
Found C 72.80 H 4.30 N 17.80.

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

M.p. 120 °C; yield 2.50 g (60%); yellow crystals from ethanol. - IR (KBr, cm⁻¹): ν(NH₂): 3400, 3350; ν(CN): 2200; ν(CO): 1710, 1690. - ¹H NMR (DMSO): δ = 3.5 ppm (s, NH₂); 7.3-7.9 (m, 3×C₆H₅, exocyclic CH).

C₂₅H₁₈N₄O₂ (418.48)
Calcd C 74.61 H 4.34 N 13.43.
Found C 74.60 H 4.10 N 13.50.

Reaction of 2 with acetoephone 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 acetoephone (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): ν(NH): 3300, 3100;
\[ \nu(\text{CN}): 2200; \nu(\text{CO}): 1690. \]

- \[ \text{H NMR (DMSO)}: \delta = 1.3 \text{ ppm (s, CH\text{\textsubscript{3}})}; 7.2-7.9 \text{ ppm (m, } 2\times\text{C}_6\text{H}_5, \text{CH)}; 8.3 \text{ ppm (br, NH)}. \]

\[ \text{C}_{16}\text{H}_{15}\text{N}_3\text{O} \quad (289.36) \]

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\textsuperscript{-1}): \nu(\text{NH}): 3400, 3350; \nu(\text{CN}): 2220; \nu(\text{CO}): 1710, 1690.

- \[ \text{H NMR (DMSO)}: \delta = 1.2 \text{ ppm (m, } 2\times\text{CH\text{\textsubscript{2}}})\); 4.2 \text{ ppm (m, } 2\times\text{CH\text{\textsubscript{2}}}); 7.2-7.7 \text{ ppm (m, C}_6\text{H}_5, \text{CH, NH)}. \]

\[ \text{C}_{16}\text{H}_{17}\text{N}_3\text{O} \quad (299.36) \]

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

I-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\textsuperscript{-1}): \nu(\text{CN}): 2220; \nu(\text{CO}): 1690.

\[ \text{C}_{15}\text{H}_{13}\text{N}_3\text{O} \quad (251.31) \]

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\textsuperscript{-1}): \nu(\text{NH}): 3400, 3300; \nu(\text{CN}): 2200; \nu(\text{CO}): 1710, 1690.

\[ \text{C}_{12}\text{H}_{21}\text{N}_3\text{O}_3 \quad (403.48) \]

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\textsuperscript{-1}): \nu(\text{NH}): 3350, 3200; \nu(\text{CO}): 1720, 1690.

\[ \text{C}_{22}\text{H}_{21}\text{N}_3\text{O}_3 \quad (403.48) \]

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\textsuperscript{-1}): \nu(\text{NH}^2, \text{NH}): 3450, 3330; \nu(\text{CN}): 2220; \nu(\text{CO}): 1690.

\[ \text{C}_{18}\text{H}_{17}\text{N}_4\text{O}_3\text{C}_3 \quad (443.74) \]


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