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Reactions with β-Cyanoethylhydrazine, III[1] A New Approach for the Synthesis of Substituted 3,5-Diaminopyrazole and 1,2,4-Triazoles

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The reactivity of β-cyanoethylhydrazine toward enaminonitrile and aroyl isothiocyanates is reported. A variety of 3,5-diaminopyrazole and Δ^3-1,2,4-triazolin-5-thione derivatives could be prepared.

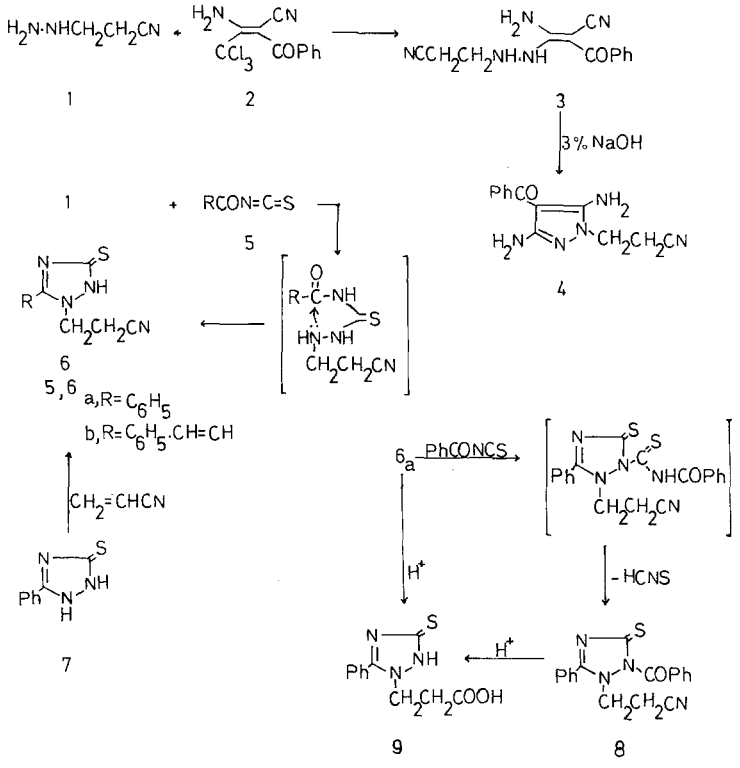
(Keywords: β-Cyanoethylhydrazine; Pyrazoles; Triazoles)

Reaktionen mit β-Canyethylhydrazin, 3. Mitt.: Ein neuer Weg zur Synthese von substituierten 3,5-Diaminopyrazolen und 1,2,4-Triazolen

Es wird über die Reaktivität von β-Cyanethylhydrazin gegenüber Enaminonitril und Aroylisothiocyanaten berichtet. Es konnte eine Reihe von 3,5-Diaminopyrazol- und Δ^3-1,2,4-Triazolin-Derivaten hergestellt werden.

In connection with a research program directed towards development of new, simple and efficient procedures for the synthesis of azoles of biological interest[2,3], the reactivity of β-cyanoethylhydrazine (**1**) towards enaminonitrile **2** and aroyl isothiocyanates **5 a, b** was investigated. Thus, it has been found that **1** reacted with **2** to afford a condensation product. Analytical data indicated that the reaction product was formed from the condensation of **2** with **1** via elimination of chloroform. ^{1}H-NMR of the product revealed, in addition to the multiplet at δ 7.5 for the aromatic protons, signals at 2.75 and 3.12 for two methylene groups and broad signals at 5.55 and 10.1 ppm, which rapidly fades out in deuterium oxide, for NH and NH_2 protons. These data can be only interpreted in terms of structure **3** which results from preferential attack by the less hindered nitrogen atom of the reagent.

Treatment of compound **3** with 3% sodium hydroxide solution resulted in the formation of 3,5-diaminopyrazole derivative **4** in an



excellent yield. The structure of the product was inferred from correct elemental and spectral data. Trials to effect cyclization of **4** into pyrazolo[1,5—*a*]pyrimidine derivative, following our previously reported[1] procedure for converting similar compounds into pyrazolo[1,5—*a*]pyrimidines, were unsuccessful. Compound **4** was decomposed and no simple product could be isolated.

In previous work from this laboratory we have reported[4—6] the reaction of isothiocyanates with a variety of cyclic amidines. In conjunction of this work we report, here, the reaction of benzoyl and 3-phenyl-2-propenoyl isothiocyanates (**5a, b**) with *β*-cyanoethylhydrazine (**1**). The work has resulted in development of new efficient one step synthesis of 5-thioxo-1,2,4-triazole derivatives. Thus, it has been found that benzoyl isothiocyanate (**5a**) reacts with **1** in dioxane at room temperature to yield a product of molecular formula $C_{11}H_{10}N_4S$. Structure **6** was assigned for the reaction product based on analogy to similar systems[7] and identity of an authentic speciment prepared via cyanoethylation of triazolinethione (**7**).

Similar to the behaviour of compound **5a** towards **1**, compound **5b** reacted with **1** to afford compound **6b** in excellent yield. Treatment of compound **6a** with benzoyl isothiocyanate resulted in the formation of the N 1-benzoyl derivative **8** via loss of HCNS. All trials made to cyclise compound **6a** were unsuccessful and in each case the carboxylic acid **9** was the only isolable reaction product. The same acid could be also obtained by refluxing compound **8** in ethanolic-hydrochloric acid mixture. Compound **9** was found to be identical (m. p., mixed m. p. and IR) with that previously reported[8].

Experimental

All melting points are uncorrected. IR spectra were recorded (KBr) on a Pye Unicam SP-1100 spectrophotometer. ^{1}H-NMR spectra were measured on a Varian EM-360-60 MHz NMR spectrometer and chemical shifts are expressed as δ/ppm. Microanalytical data (C, H, N) were obtained from the Microanalytical Centre at Cairo University.

Reaction of the Enaminonitrile **2** *with β-Cyanoethylhydrazine*

To a suspension of **2** (0.01 mol) in ethanol (30 ml), β-cyanoethylhydrazine (1 ml) was added drop by drop with continuous stirring. The reaction mixture was left at room temperature for 1 h, triturated with ethanol and the solid product, so formed, was collected by filtration and crystallised from ethanol. Compound **3** formed grey crystals; m. p. 177 °C; yield 78%.

IR: 3 420 (OH); 3 280, 3 260, 3 100 (NH_2 and NH); 2 180 (conjugated CN) and 1 620 cm^{-1} (C=C).

^{1}H-NMR (*DMSO-d_6*): 2.75 (t, 3 H, CH_2), 3.12 (t, 3 H, CH_2), 3.55 (br, 2 H, NH_2), 5.55 (br, 1 H, NH), 7.5–7.9 (m, 5 H, C_6H_5), 10.1 (br, 1 H, NH).

$C_{13}H_{13}N_5O$ (255). Found. C 61.3 H 5.2 N 27.4.
Calcd. C 61.2 H 5.2 N 27.5.

1-β-Cyanoethyl-4-benzoyl-3,5-diaminopyrazole (**4**)

A suspension of **3** (0.01 mol) in ethanol (20 ml) was treated with sodium hydroxide solution (3%; 100 ml). The reaction mixture was refluxed for 2 h, left to cool and then acidified with concentrated hydrochloric acid. The solid product, so formed, was collected by filtration and crystallised from acetic acid. Compound **4** formed red crystals; m. p. 230 °C; yield 71%.

IR: 3 500, 3 380, 3 220, 3 180 (NH_2); 2 225 (CN); 1 665 (benzoyl CO); 1 650 (NH_2) and 1 610 cm^{-1} (C=N).

$C_{13}H_{13}N_5O$ (255). Found. C 61.1 H 5.1 N 27.2.
Calcd. C 61.2 H 5.2 N 27.5.

2-β-Cyanoethyl-3-substituted-Δ^3-1,2,4-triazoline-5-thione (**6a, b**)

To a suspension of **1** (0.01 mol) in dioxane (50 ml) was added the appropriate isothiocyanate solution (prepared as has been previously described[6]). The reaction mixture was refluxed for 3 h and then evaporated under reduced pressure. The remaining product was triturated with water, collected by filtration, washed several times with water and crystalllised from ethanol.

Compound **6a** could be also obtained via another route, by refluxing compound **7** and acrylonitrile in pyridine for 2 h following the procedure

previously described[8]. Compound **6a** formed colourless crystals; m.p. 189 °C; yield 88%.

IR: 3200 (NH); 2250 (unconjugated CN), and 1610 cm^{-1} (C=N).

$C_{11}H_{10}N_4S$ (230). Found. C 57.2 H 4.5 N 24.1.
Calcd. C 57.4 H 4.4 N 24.3.

Compound **6b** formed colourless crystals; m.p. 129 °C; yield 85%.

IR: 3200 (NH); 2225 (CN); 1650 (C=C), and 1610 cm^{-1} (C=N).

^{1}H-NMR ($CDCl_3$): 2.85 (t, 2H, CH_2), 4.20 (t, 2H, CH_2), 4.75 (br. s, 1H, NH), 7.35–7.80 (m, 7H, olefinic and aromatic protons).

1-Benzoyl-2-β-cyanoethyl-3-phenyl-Δ^3-1,2,4-triazolin-5-thione (**8**)

A solution of compound **6a** (10 mmol) in acetone (20 ml) was treated with benzoyl isothiocyanate (12 mmol) and the experimental procedure described above for the preparation of **6** was adopted. Compound **8** formed colourless crystals from ethanol, m.p. 135 °C; yield 65%.

IR: 2250 (CN) and 1675 cm^{-1} (benzoyl CO).

$C_{18}H_{14}N_4OS$ (334). Found. C 64.4 H 4.1 N 16.6 S 9.5.
Calcd. C 64.6 H 4.2 N 16.7 S 9.6.

2-β-Carboxyethyl-3-phenyl-Δ^3-1,2,4-triazolin-5-thione (**9**)

To a solution of each of **6a** and **8** (2.0 g) in ethanol (30 ml) was added hydrochloric acid (3.0 ml; 37%). The reaction mixture was refluxed for 20 min, then diluted with water. The formed product was collected by filtration and crystallised from ethanol. Compound **9** formed colourless crystals, m.p. 194 °C; yield 86%.

IR: 3050 (NH); 2500–2900 (OH dimer); and 1700–1705 cm^{-1} (carboxyl CO).

$C_{11}H_{11}N_3O_2S$ (249). Found. C 52.9 H 4.5 N 16.5 S 12.9.
Calcd. C 53.0 H 4.4 N 16.8 S 12.8.

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