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CYANOTHIOACETAMIDE IN HETEROCYCLIC SYNTHESIS

A NOVEL SYNTHESIS OF 2-PYRIDOTHIONE DERIVATIVES

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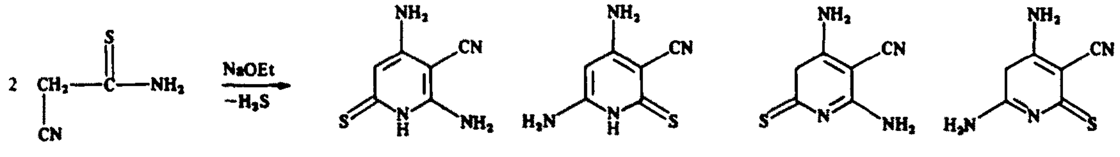
Abstract—Cyanothioacetamide (1) shows intermolecular cyclocondensation via refluxing in ethanolic sodium ethoxide solution to give a pyridothione derivative 5. Establishment of its structure as well as some of its chemical behaviour is discussed briefly.

2-Pyridothiones are versatile reagents and their chemistry has received considerable attention recently.[1,2] Several methods are reported for their synthesis. These include the use of 2-halopyridine[3] and 2-hydroxy pyridine[4] as starting compounds or via cycloaddition of isothiocyanates with unsaturated aldehydes[5] and 1,3-diketones.[6] Recently Soto and coworkers[7] reported a preparation via the reaction of cyanothioacetamide with cinnamonitrile derivatives.

This paper deals with the use of cyanothioacetamide (1)[8] as starting material undergoing self condensation in order to obtain 2-pyridothione derivatives. When cyanothioacetamide (1) was treated with alcoholic sodium ethoxide solution under reflux a single product was isolated with molecular formula $C_6H_6N_4S$. Four possible isomeric structures 2–5 are possible for the reaction product. The IR spectrum of the product reveals two NH_2 stretching bands at 3450–3300 cm^{-1}, CH_2 stretching at 2980 cm^{-1}, one CN stretching band at 2220 cm^{-1} and C═S at 1190–1200 cm^{-1}. The ^{1}H-NMR spectrum revealed a singlet at δ 3.55 ppm for CH_2 protons and two singlets at δ 5.45 and δ 6.23 ppm for the two NH_2 groups. Thus, structures 2 and 3 were eliminated based on the absence of the characteristic broad signal for an NH group in the ^{1}H-NMR spectrum of the product obtained. It seems difficult to differentiate between the other two structures by the spectral date available. The only way to check the identity of the reaction product is to synthesize it by an unambiguous route or to identify its derivatives with authentic compounds synthesised in the same way.



1 2 3 4 5

When benzylidinemalononitrile (6) was reacted with cyanothioacetamide (1) in ethanolic sodium ethoxide solution the benzylidine of the 2-pyridothione derivative 9 was obtained which was found to be identical with that produced via reacting equimolecular amounts of the condensation product 4 (or 5) with benzaldehyde. On the contrary, reacting the benzylidine derivative 7 with malononitrile (8) under the same conditions did not yield 9. This result established structure 5 for the product of self condensation of cyanothioacetamide.

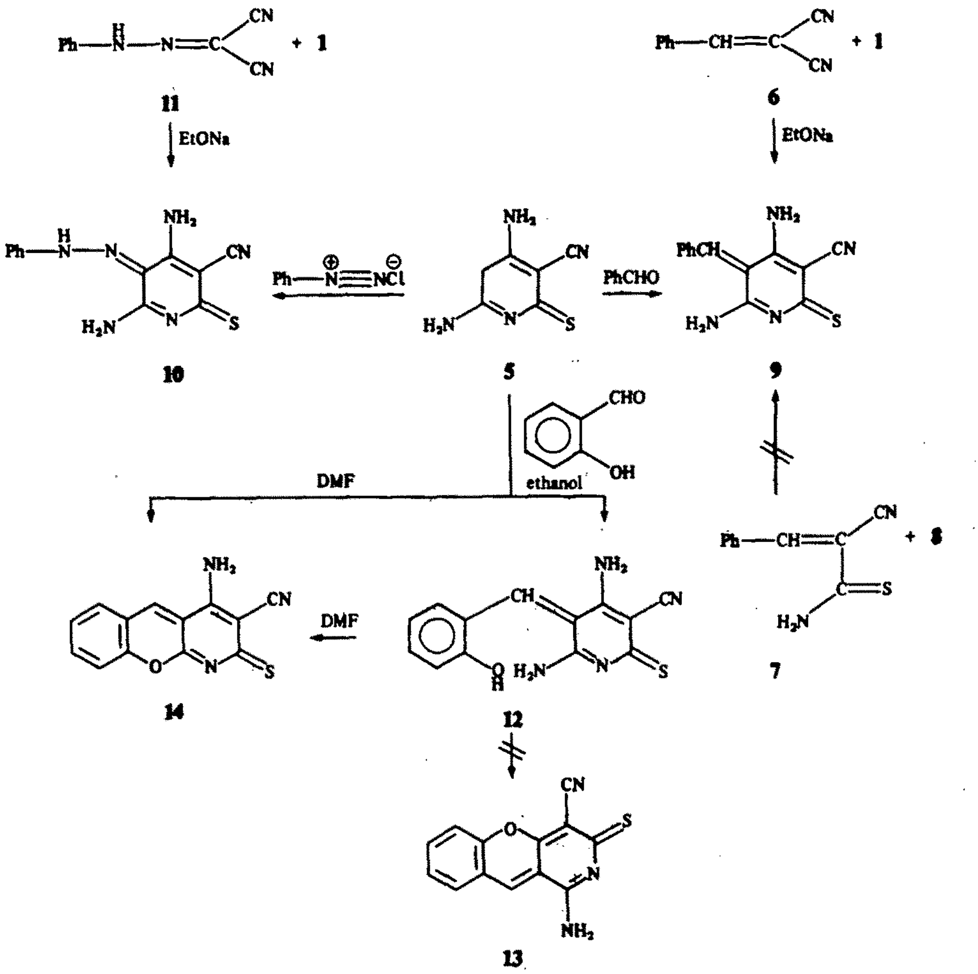
This enhances us to prepare 5 via another route. On reacting 1 with 8 in ethanolic triethylamine 5 is isolated again, despite the expected relative reactivities of the methylene groups of 1 and 8 which should give the pyridine derivative 4. This parallels the reported preparation of the codimer of malononitrile and ethylcyanoacetate by Junek *et al.*[9]

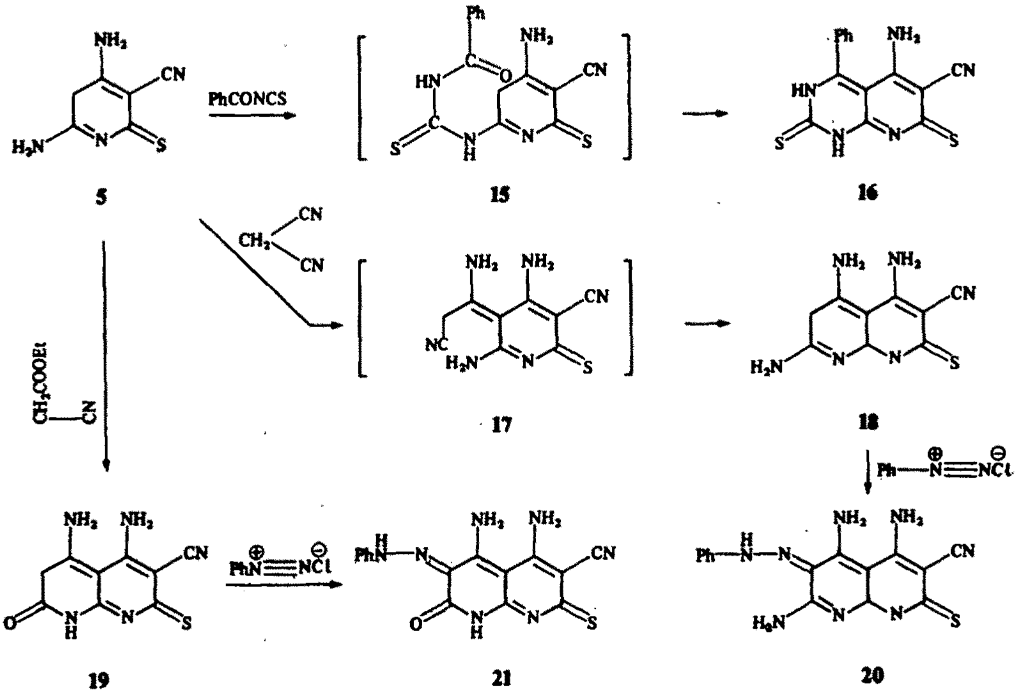
$$1+\underset{8}{CH_2(CN)_2}\xrightarrow[Et_3N]{EtOH}5$$

Compound 5 reacted with salicylaldehyde to give the benzylidine derivative 12 which is readily cyclized on refluxing in dimethylformamide via loss of ammonia to give the benzo(2′,3′)-pyrano[2,3-b]pyridine derivative 14. Compound 14 can also be obtained in one step by conducting the reaction of 1 with salicylaldehyde in dimethylformamide instead of alcohol. The cyclization via the 6-amino group of pyridine to give 14 seems more logical than via the 4-amino pyridine which yields 13, since it is reported that the amino group of a pseudoaromatic enaminonitrile is inactive.[10]

Compound 5 reacted with benzoylisothiocyanate to form a pyrido[2,3-b]pyrimidine derivative 16 through intermediate formation of adduct 15. The structure of 16 was established based on analytical and spectral data.

Compound 5 reacts with active methylene reagents to give fused heterocyclic products. Thus, it reacts with malononitrile to give a pyrido[2,3-b]pyridine derivative 18. The reaction is assumed to take place through intermediate formation of the Michael adduct 17. The structure of 18 was confirmed by IR and ^{1}H-NMR spectra. The IR spectrum revealed the presence of only one CN stretching band at 2220 cm^{-1}. The ^{1}H-NMR spectrum revealed the presence of six D_2O exchangeable protons, four of which appear at δ 5.45–5.89 ppm and the other two appear at δ 6.23 ppm. These were assigned to the three amino functions. In a similar manner 5 reacts with ethylcyanoacetate to give a pyrido[2,3-b]pyridine derivative 19. The structure of


+ 1
11
EtONa
+ 1
6
EtONa
10
Ph—N≡NCl
5
PhCHO
9
ethanol
DMF
DMF
+ 8
7
14
12
13


5
PhCONCS
15
16
CH₂(CN)₂
17
18
CH₂COOEt / CN
Ph—N≡NCl
19
PhN≡NCl
21
20

19 is established based on analytical and spectral data. Compounds **18** and **19** were found to couple with benzenediazonium chloride to give the corresponding phenylhydrazone derivatives **20** and **21**, respectively.

Further study of the chemistry of **5** is now undertaken.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were recorded on a Pye–Unicam spectrophotometer and ^{1}H-NMR spectra on a Varian EM-90 MHZ spectrometer. Microanalytical data were performed by the Microanalytical Data Unit at Cairo University.

2-*Cyano-4,6-diamino-2-pyridothione* (5)

Method (a). To a soln of 0.5 mol NaOEt (prepared by dissolving 11.5 g Na metal in 154 ml abs EtOH), 100 g (1 mol) of cyanothioacetamide is added. The mixture is heated under reflux in a boiling water bath for 3 hr, then left to cool. The resultant Na salt is dissolved in the least amount of water then neutralized with dil HCl till pH 6–7. The solid product, so formed on standing, is collected by filtration.

Method (b). To a soln of cyanothioacetamide 2.0 g (0.02 mol) in EtOH 30 ml containing 0.5 ml of Et_3N, malononitrile 1.2 g (0.02 mol) is added. The mixture is heated under reflux for 4 hr then evaporated *in vacuo*. The solid product so formed on adding ice/water, is collected by filtration (50% yield).

Compound **5** formed red crystals from DMF, yield 65%, m.p. >300°. IR (KBr): 3450–3300 cm^{-1} (NH_2), 2980 cm^{-1} (CH_2), 2220 cm^{-1} (CN), and 1190–1200 cm^{-1} (C=S). ^{1}H-NMR: 3.55 (s, 2H, CH_2), 5.45 (s, 2H, NH_2), and 6.23 (s, 2H, NH_2). (Found: C, 43.22; H, 3.41; N, 33.34; S, 19.43. Calc for $C_6H_6N_4S$: C, 43.37; H, 3.61; N, 33.73; S, 19.43%.)

3-*Cyano-4,6-diamino-5-benzylidine-2-pyridothione* (9)

Method (a). To a soln of **5** (1.6 g, 0.01 mol) in EtOH (30 ml) containing 0.25 ml of piperidine, benzaldehyde (1.08 ml) is added and the whole mixture is heated under reflux for 4 hr, then evaporated *in vacuo*. The solid product, so formed on adding ice/water is collected by filtration.

Method (b). To a suspension of **6** (1.5 g, 0.01 mol) in NaOEt soln (prepared from 0.23 g Na metal and 40 ml abs EtOH) cyanothioacetamide (1 g, 0.01 mol) is added. The mixture is refluxed in a boiling water bath for 4 hr then evaporated *in vacuo*. The solid product, so formed on adding dil HCl, is collected by filtration.

Compound **9** formed yellow crystals from dioxan, m.p. 220–222°, yield 70%. IR (KBr): 3450–3300 cm^{-1} (two NH_2), 3050 cm^{-1} (CH aromatic), 2985 cm^{-1} (CH), 2220 cm^{-1} (CN), 1635 cm^{-1} (NH_2 deformation), and 1200–1190 cm^{-1} (C=S). ^{1}H-NMR: 5.65 (s, 2H, NH_2), 6.78 (s, 2H, NH_2), 7.01 (s, 1H, CH), and 7.36 (s, 5H, C_6H_5). (Found: C, 61.21; H, 3.78; N, 22.18; S, 12.79. Calc for $C_{13}H_{10}N_4S$: C, 61.41; H, 3.93; N, 22.04; S, 12.59%.)

3-*Cyano-4,6-diamino-5-phenylhydrazono-2-pyridothione* (10)

Method (a). To a soln of **5** (1.6 g, 0.01 mol) in EtOH (50 ml) containing NaOH (5 ml, 5%), benzenediazonium chloride (0.01 mol) [prepared by adding $NaNO_2$ (0.01 mol) to the appropriate quantity of aniline in HCl] is added with stirring. The mixture is left at room temp for 30 min and the ppt is collected by filtration.

Method (b). To a soln of **11** (1.3 g, 0.01 mol) in NaOEt (prepared as above) cyanothioacetamide (1 g, 0.01 mol) is added. The mixture is refluxed for 4 hr in a boiling water bath then evaporated *in vacuo*. The solid product, so formed on adding dil HCl, is collected by filtration.

Compound **10** formed red–orange crystals from EtOH, m.p. 154°, yield 80%. IR (KBr): 3450–3330 cm^{-1} (two NH_2 and NH), 3045 cm^{-1} (CH aromatic), 2220 cm^{-1} (CN), 3160 cm^{-1} (NH_2 deformation), and 1200–1190 cm^{-1} (C=S). ^{1}H-NMR: 5.41 (s, 2H, NH_2), 6.11 (s, 2H, NH_2), 7.39 (s, 5H, C_6H_5), and 10.25 (s, br, 1H, NH). (Found: C, 52.99; H, 4.10; N, 31.35; S, 12.28. Calc for $C_{12}H_{10}N_6S$: C, 53.33; H, 3.70; N, 31.11; S, 11.85%.)

3-*Cyano-4,6-diamino-5-(o-hydroxy)benzylidine-2-pyridothione* (12)

To a soln of **5** (1.6 g, 0.01 mol) in EtOH (30 ml) containing 0.25 ml of piperidine, salicylaldehyde (1.3 ml) is added and the whole mixture is heated under reflux for 2 hr then evaporated *in vacuo*. The solid product, so formed on adding ice/water together with a few drops of dil HCl, is collected by filtration.

Compound **12** formed yellow crystals from EtOH, m.p. 150–152°, yield 65%. IR 3560 cm^{-1} (OH), 3450–3300 cm^{-1} (two NH_2), 3050 cm^{-1} (CH aromatic), 2220 cm^{-1} (CN), 1635–1625 cm^{-1} (NH_2 deformation), and 1210–1190 cm^{-1} (C=S). ^{1}H-NMR: 4.68 (s, 2H, NH_2), 6.10 (s, 2H, NH_2), and 7.45–8.12 (m, 6H, CH, OH, C_6H_4). (Found: C, 57.41; H, 3.85; S, 11.67; N, 20.83. Calc for $C_{13}H_{10}N_4OS$: C, 57.77; H, 3.70; N, 20.74; S, 11.85%.)

3-*Cyano-4-amino-2-thiono-benzo*(2′,3′)-*pyrano*[2,3-b]-*pyridine* (14)

Method (a). A soln of **12** (0.01 mol) in DMF (30 ml) is heated under reflux till evolution of ammonia ceases then evaporated *in vacuo*. The remaining product is triturated with water and the solid product, so formed, is collected by filtration (overall yield 72%).

Method (b). To a soln of **5** (1.6 g, 0.01 mol) in DMF (30 ml) containing 0.25 ml of piperidine, salicylaldehyde (1.2 ml, 0.01 mol) is added. The whole mixture is heated under reflux for 5 hr then evaporated *in vacuo*. The solid product, so formed on adding ice/water, is collected by filtration.

Compound **14** formed orange crystals from EtOH, m.p. 180°, yield 68%. IR (KBr): 3400–3350 cm^{-1} (NH_2), 3050 cm^{-1} (CH aromatic), 2220 cm^{-1} (CN), and 1205–1195 cm^{-1} (C=S). ^{1}H-NMR: 4.57 (s, 2H, NH_2), and 7.37–8.01 (m, 5H, C_6H_4 and pyrane-CH). (Found: C, 61.31; H, 3.10; N, 16.89; S, 12.60. Calc for $C_{13}H_7N_3OS$: C, 61.66; H, 2.76; N, 16.60; S, 12.64%.)

3-*Cyano-4-amino-2,7-dithiono-5-phenyl-pyrido*[2,3-b]-*pyrimidine* (16)

A soln of benzoylisothiocyanate [prepared by mixing 0.01 mol of benzoyl chloride in 30 ml dry acetone and ammonium thiocyanate (0.01 mol) and heating in a boiling water bath for 30 min] is added to 1.6 g (0.01 mol) of **5**. The mixture is refluxed in a boiling water bath for 4 hr then evaporated *in vacuo*. The solid product, so formed, is washed with alcohol and collected by suction.

Compound **16** formed yellow crystals from DMF, yield 80%, m.p. 283–285°. IR 3450 cm^{-1} (NH_2), 3200 cm^{-1} (NH), 2220 cm^{-1} (CN), 1630 cm^{-1} (NH_2 deformation), and 1210–1195 cm^{-1} (two C=S). ^{1}H-NMR: 5.35 (s, 2H, NH_2), 7.35–7.48 (m, 5H, C_6H_5), and 9.59–10.0 (br, 2s, 2H, 2NH). (Found: C, 53.78; H, 2.42; N, 22.11; S, 20.81. Calc for $C_{14}H_9N_5S_2$: C, 54.02; H, 2.91; N, 22.52; S, 20.56%.)

Reaction of 5 *with malononitrile or ethylcyanoacetate*

To a soln of **5** (1.6 g, 0.01 mol) in 20 ml of DMF containing piperidine (0.5 ml) each malononitrile or ethylcyanoacetate (0.01 mol) is added. The mixture is boiled under reflux for 3 hr then evaporated *in vacuo*. The solid product, so formed, is triturated with water then collected by filtration.

Compound **18** formed yellow crystals from dioxan, yield 80%, m.p. 260°. IR: 3430–3300 cm^{-1} (three NH_2), 2220 cm^{-1} (CN), 1650 cm^{-1} (NH_2 deformation), and 1220–1190 cm^{-1} (C=S). ^{1}H-NMR: 3.50 (s, 2H, CH_2), 5.45–5.89 (m, 4H, 2NH_2), and 6.23 (s, 2H, NH_2). (Found: C, 46.55; H, 3.44; N, 36.0; S, 13.51. Calc for $C_9H_8N_6S$: C, 46.55; H, 3.44; N, 36.20; S, 13.79%.)

Compound **19** formed yellow crystals from an EtOH–dioxan mixture, yield 82%, m.p. 180°. IR: 3430–3300 cm^{-1} (two NH_2), 3200 cm^{-1} (NH), 2220 cm^{-1} (CN), 1700 cm^{-1} (C=O), 1650 cm^{-1} (NH_2 deformation), and 1190–1200 cm^{-1} (C=S). ^{1}H-

NMR: 3.52 (s, 2H, CH_2), 5.43–5.84 (m, 4H, $2NH_2$), and 8.91 (broad, 1H, NH). (Found: C, 46.55; H, 3.23; N, 30.17; S, 13.82. Calc for $C_9H_7ON_5S$: C, 46.35; H, 3.00; N, 13.73; S, 13.73%.)

Coupling of **18** *or* **19** *with benzenediazonium chloride*

A soln of benzenediazonium chloride prepared by adding $NaNO_2$ (0.01 mol) to aniline (0.01 mol) containing HCl is added to a stirred soln of **18** or **19** (0.01 mol) in EtOH (50 ml) containing NaOH (5 ml, 5%). The mixture is left at room temp for 15 min. The resultant solid, so formed, is collected by filtration.

Compound **20** formed red crystals from EtOH, yield 76%, m.p. >300°. IR 3450–3300 cm^{-1} (three NH_2), 2220 cm^{-1} (CN), 1650 cm^{-1} (NH_2 deformation), and 1190–1200 cm^{-1} (C=S). (Found: C, 53.44; H, 3.65; N, 33.33. Calc for $C_{15}H_{12}N_8S$: C, 53.57; H, 3.57; N, 33.33; S, 9.52%.)

Compound **21** formed red crystals from EtOH, yield 80%, m.p. 300°. IR: 3430–3300 cm^{-1} (two NH_2), 3200 cm^{-1} (NH), 2220 cm^{-1} (CN), 1700 cm^{-1} (C=O), 1650 cm^{-1} (NH_2 deformation), and 1190–1200 cm^{-1} (C=S). (Found: C, 53.21; H, 3.67; N, 29.57; S, 9.68. Calc for $C_{15}H_{11}N_7OS$: C, 53.43; H, 3.10; N, 29.08; S, 9.49%.)

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