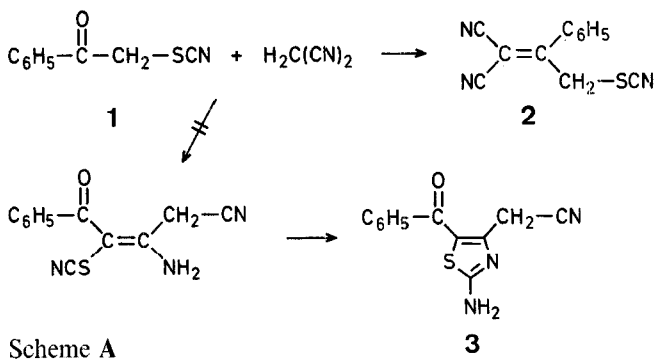
Activated Nitriles in Heterocyclic Synthesis: A New Approach for the Synthesis of Pyridine and Pyridinopyrimidine Derivatives

Fathy Mohamed ABDELRAZEK*, Nadia Sobhy IBRAHIM, Zaghloul El-Shahat KANDEEL, Mohamed Hilmy ELNAGDI

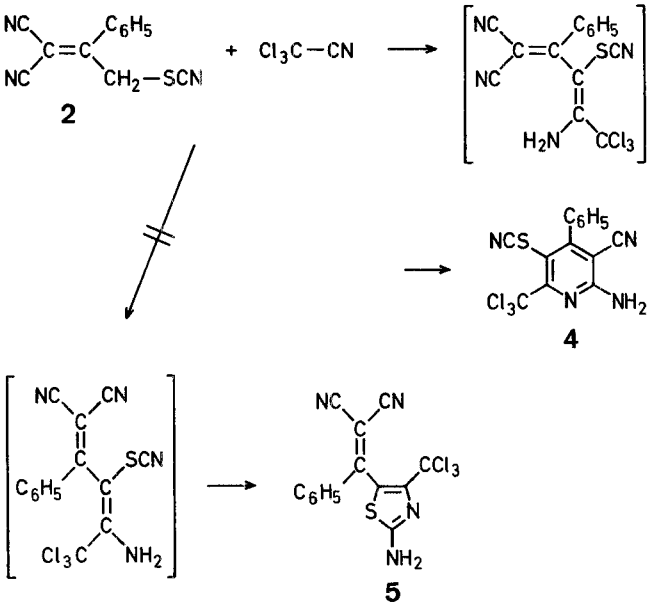
Department of Chemistry, Faculty of Science, Cairo University, Giza, A.R. Egypt

Polyfunctional nitriles are highly reactive reagents that have been extensively used in heterocyclic synthesis[1-4]. In continuation of our program directed towards the development of new procedures for the synthesis of azoles, azines, and their condensed derivatives utilizing the readily obtainable polyfunctional nitriles[5,6], we report here a new synthesis of substituted pyridines and pyridinopyrimidines from polyfunctional nitriles. Reaction of phenacyl thiocyanate (**1**) with malononitrile affords a 1:1 condensation product. Two theoretically possible structures **2** or **3** can be considered (Scheme **A**), however, the structure of the Knovenagel condensation product **2** was assigned, based on the presence of two strong absorption bands in the I.R. spectrum at ν = 2180 cm^{-1} corresponding to SCN and at ν = 2205 cm^{-1} corresponding to the CN groups of the malononitrile moiety and the absence of the carbonyl absorption. The ^{1}H-N.M.R.-spectrum shows the methylene protons as a singlet at δ = 3.32 ppm.



Scheme **A**

Although trichloroacetonitrile has an extremely reactive cyanofunction, with exception of our previous reports[7-10], its utility in heterocyclic synthesis has received very little attention[11]. In continuation of our previous work, we report here the reactivity of this reagent toward the active methylene compound **2**. Reaction of trichloroacetonitrile with **2** in refluxing toluene in the presence of a catalytic amount of piperidine yields a 1:1 adduct. Again two theoretically possible structures **4** and **5** can be considered (Scheme **B**).



Scheme **B**

Structure **4** was suggested for this product based on the presence of two absorption bands in the I.R.-spectrum at ν = 2160 and 2185 cm^{-1} corresponding to SCN and CN groups, respectively, and a broad band at ν = 3460–3360 cm^{-1} corresponding to the chelated amino group. The trichloromethyl moiety in compound **4** proved highly unstable, being substituted by a hydroxy group when reacted with water or even left in the air for a time, giving compound **6a**. This gives a rationalization to the presence of chelated OH broad band in the I.R.-spectrum at ν = 3270–3210 cm^{-1} and a band at ν = 1220 cm^{-1} characteristic of phenolic C—O stretching.

The trichloromethyl moiety is also easily substituted by the ethoxy group, when compound **4** was boiled in absolute ethanol with the aim of recrystallization, giving compound **6b**. The presence of ethoxy group in **6b** was confirmed by spectral and analytical data. The ready replacement of the trichloromethyl moiety with ethanol and water via loss of chloroform under mild conditions has been recently observed by us[12].

Enaminonitriles are known to react with a variety of reagents to afford different heterocyclic compounds[13,14]. In the present work, we have explored the potentialities of the enaminonitrile moiety towards trichloroacetonitrile essentially to obtain pyridinopyrimidine derivatives. Thus, compounds **6a** and **6b** were allowed to react with trichloroacetonitrile in dry refluxing toluene. The products formed, **7a** and **7b**, have low melting points and are assumed to be unstable like the trichloromethyl compounds **4**.

Actually, when compounds **7a** and **7b** were treated with water or ethanol, they afforded the high melting products **8–11** (Scheme **C**, Table). This type of compounds is now the subject of further investigations to explore their potential utility for the synthesis of other heterocyclic systems of biological interest.

I.R.-spectra were recorded as KBr discs using a PYE-Unicam Sp-1100 spectrophotometer. ^{1}H-N.M.R.-spectra were recorded on a Varian A-60 spectrometer using TMS as internal standard. Analytical data were obtained from the microanalytical centre at Cairo university. All melting points are uncorrected.

α-Cyano-β-thiocyanatomethylcinnamonitrile (2):

To a solution of phenacyl thiocyanate (**1**; 17.7 g, 0.1 mol) in absolute ethanol (100 ml) is added malononitrile (6.6 g, 0.1 mol) followed by piperidine (1 ml). The mixture is refluxed for 1 h, when the colour darkens to green, the reaction mixture is allowed to cool to room temperature, poured onto ice-cold water (100 ml), and acidified with cold concentrated hydrochloric acid till neutral. The solid precipitated is collected by filtration, washed with water, and recrystallized from dimethylformamide; yield: 11.26 g (50%); m.p. 260°C.

$C_{12}H_7N_3S$ (225.3) calc. C 63.97 H 3.13 N 18.65
found 63.68 3.08 18.32

I.R. (KBr): ν = 2205 (CN), 2180 cm^{-1} (SCN).

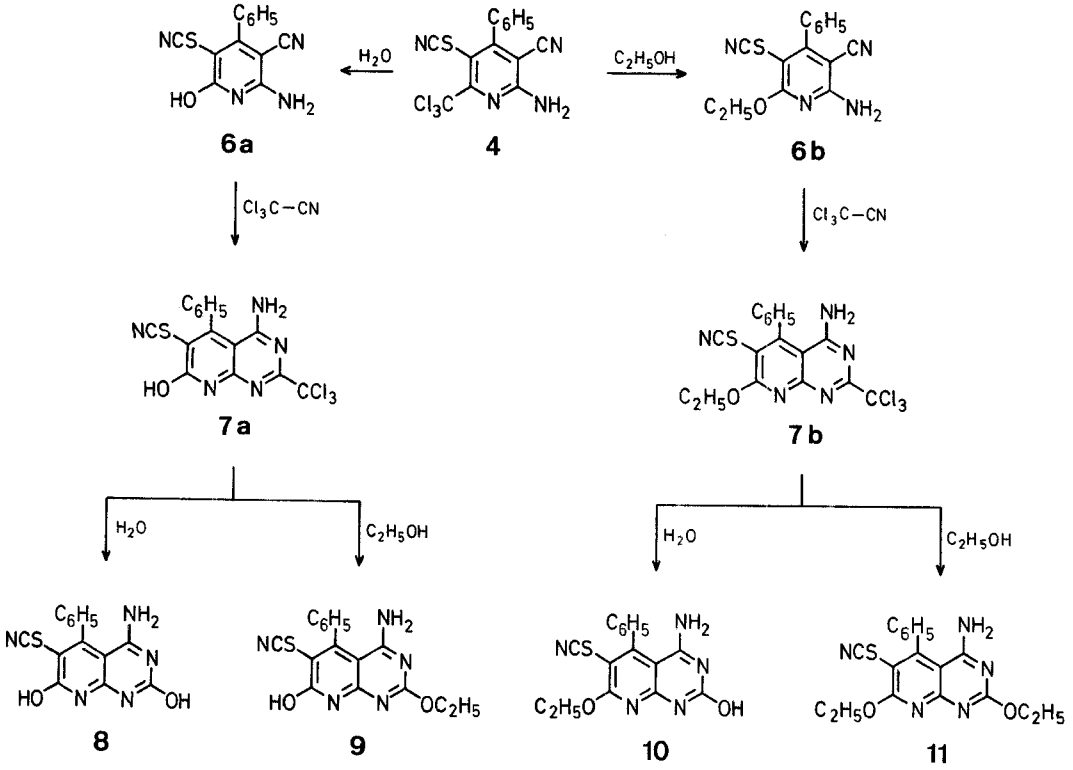
^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 3.3 (s, 2H, CH_2); 7.4–7.8 ppm (m, 5H$_{arom}$).

2-Amino-3-cyano-4-phenyl-5-thiocyanato-6-trichloromethylpyridine (4):

To a solution of **2** (11.27 g, 0.05 mol) in dry toluene (150 ml) is added trichloroacetonitrile (7.22 g, 0.05 mol) and a catalytic amount of piperidine. The reaction mixture is then refluxed for 1 h at which time it becomes dark green. The reaction flask is cooled in crushed ice till the oily product has solidified, collected by filtration as soon as possible, and kept in a dessicator; yield: 12.9 g (70%).

I.R. (KBr): ν = 3460–3360 (chelated NH_2), 2185 (CN), 2160 cm^{-1} (SCN).

As the compound is highly unstable it is immediately used for the preparation of **6a** and **6b**.



Scheme **C**

Table. Compounds **8**–**11** prepared

Product No.	Yield [%]	m.p. [°C]	Molecular formula[a]	I.R. (KBr) ν[cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ[ppm]
8	65	110°	$C_{14}H_9N_5O_2S$ (311.3)	3460–3330 (NH_2); 3280 (OH); 2160 (SCN)	6.7 (s, 2H, NH_2); 7.3–7.8 (m, 5H$_{arom}$); 8.0 (br. s, 2H, OH)
9	65	> 300°	$C_{16}H_{13}N_5O_2S$ (339.4)	3455–3370 (NH_2); 3295 (OH); 2155 (SCN)	1.5–1.7 (t, 3H, CH_3); 3.1–3.4 (q, 2H, CH_2); 6.8 (s, 2H, NH_2); 7.9 (br. s, 1H, OH); 7.35–7.8 (m, 5H$_{arom}$)
10	65	65°	$C_{16}H_{13}N_5O_2S$ (339.4)	3460–3375 (NH_2); 3275 (OH); 2165 (SCN)	1.5–1.7 (t, 3H, CH_3); 3.15–3.45 (q, 2H, CH_2); 6.8 (s, 2H, NH_2); 8.2 (br. s, 1H, OH); 7.35–7.85 (m, 5H$_{arom}$)
11	80	> 300°	$C_{18}H_{17}N_5O_2S$	3450, 3392 (NH_2); 2150 (SCN)	1.5–1.7 (t, 6H, CH_3); 3.2–3.5 (q, 4H, CH_2); 6.75 (t, 2H, NH_2); 7.3–7.8 (m, 5H$_{arom}$)

[a] Satisfactory microanalyses obtained: C ± 0.23, H ± 0.34, N ± 0.45, S ± 0.35.

2-Amino-3-cyano-4-phenyl-5-thiocyanato-6-hydroxypyridine (6a): Compound **4** (3.7 g, 0.01 mol) is boiled with water (30 ml) for 5 min, allowed to cool, filtered, and recrystallized from ethanol; yield: 1.9 g (70%); m.p. 95°C.

$C_{13}H_8N_4OS$	calc.	C 58.20	H 3.01	N 20.88
(268.3)	found	57.9	3.2	20.5

I.R. (KBr): ν = 3460–3360 (chelated NH_2), 3270–3210 (chelated OH), 2185 (CN), 2160 cm^{-1} (SCN).

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 6.9 (s, 2H, NH_2); 7.3–7.9 (m, 5H_{arom}); 8.2 ppm (br.s, 1H, OH).

2-Amino-3-cyano-4-phenyl-5-thiocyanato-6-ethoxypyridine (6b): Compound **4** (3.7 g, 0.01 mol) is refluxed with absolute ethyl alcohol (30 ml) for 15 min and filtered hot. The solid precipitated on cooling is collected by suction; yield: 2.4 g (80%); m.p. 205°C (ethanol).

$C_{15}H_{12}N_4OS$	calc.	C 60.78	H 4.08	N 18.98
(296.4)	found	60.7	3.9	18.7

I.R. (KBr): ν = 3460–3360 (chelated NH_2), ~3040 (C—H_{arom}), ~2950 (C—$H_{aliphat}$), 2200 (CN), 2150 cm^{-1} (SCN).

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.5–1.7 (t, 3H, CH_3); 3.15–3.45 (q, 2H, CH_2); 6.95 (s, 2H, NH_2); 7.35–7.85 ppm (m, 5H_{arom}).

Pyridinopyrimidine Derivatives 8–11; General Procedure: Compound **6a** or **6b** (0.01 mol) and trichloroacetonitrile (0.01 mol) are refluxed in dry toluene (30 ml) with a catalytic amount of piperidine for 0.5 h. For obtaining compounds **8** and **10**, the resulting mixture is boiled with water (20 ml) for 5 min, cooled, filtered, and recrystallized from ethanol. Compounds **9** and **11** are prepared from the mixture by decanting the solvent, drying by evaporation, and refluxing the residue with absolute ethanol (20 ml) for 10 min. After cooling, the precipitated solid is filtered and recrystallized from ethanol (Table).

Received: March 28, 1984

[1] S. Abdou, S.M. Fahmy, K.U. Sadek, M.H. Elnagdi, *Heterocycles* **16**, 2177 (1981).

[2] S.M. Fahmy, N.M. Abed, R.M. Mohareb, M.H. Elnagdi, *Synthesis* **1982**, 490.

[3] H. Daboun, S. Abdou, M. Mustafa, M.H. Elnagdi, *Synthesis* **1982**, 502.

[4] H.A. Elfaham, K.U. Sadek, G.E.H. Elgomeie, M.H. Elangdi, *J. Chem. Soc. Perkin Trans 1* **1982**, 2663.

[5] M.H. Elnagdi, H. Wamhoff, *Chem. Lett.* **1981**, 419.

[6] B.Y. Riad, F.A. Khalifa, F.M. Abdel Gallil, M.H. Elnagdi, *Heterocycles* **19**, 1637 (1982).

[7] F.M. Abdelrazek, Z.E. Kandeel, K.M.H. Hilmy, M.H. Elnagdi, *Chem. Ind. (London)* **1983**, 439.

[8] M.H. Elnagdi, H.A. Elfaham, S.A.S. Ghoslan, G.E.H. Elgomeie, *J. Chem. Soc. Perkin Trans 1* **1982**, 2667.

[9] M.H. Elnagdi, S.M. Fahmy, E.A.A. Hafez, M.R.H. Elmoghayar, S.A.R. Amer, *J. Heterocyclic Chem.* **16** 1109 (1979).

[10] K.U. Sadek, S.M. Fahmy, R.M. Mohareb, M.H. Elnagdi, *Chem. Eng. Data Ser.*, in press.

[11] B.B. Gavarilenko, S.I. Miller, *J. Org. Chem.* **40**, 2720 (1975).

[12] N.S. Ibrahim, F.M. Abdelrazek, S.I. Aziz, M.H. Elnagdi, *Monatsh. Chem.*, in press.

[13] E.C. Taylor, A. McKillop, *The Chemistry of Cyclic Enaminonitriles and O-Aminonitriles*, John Wiley & Sons, New York, 1970, p. 306.

[14] M.H. Elnagdi, H. Wamhoff, *J. Heterocyclic Chem.* **18**, 1287 (1981).