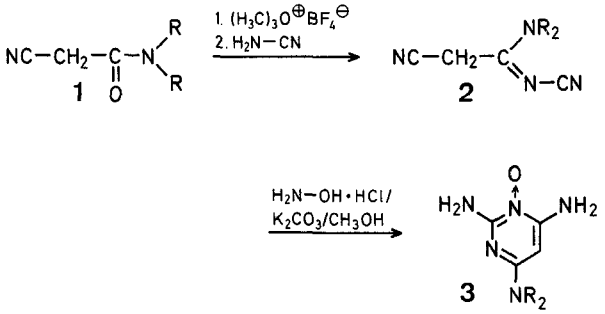
3-Amino-3-cyaniminopropanenitriles; Useful Precursors for 2-Chloro-4,6-diamino- and 2,4,6-Triaminopyrimidine *N*-Oxides

John M. McCall*, Ruth E. TenBrink

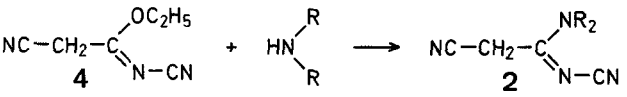
Research Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001, U.S.A.

Triaminopyrimidine *N*-oxides **3** have shown useful hypotensive activity in man[1]. We have reported a synthesis of such compounds in which 3-amino-3-cyaniminopropanenitriles were condensed with hydroxylamine to produce triaminopyrimidine *N*-oxides (Scheme **A**)[2]. In the route of Scheme **A**, a 3-amino-3-cyaniminopropanenitrile **2** was prepared from the enol ether of the cyanoacetamide **1**. We now report a superior synthesis of 3-amino-3-cyaniminopropanenitriles **2** and the application of these intermediates to the synthesis of triaminopyrimidine *N*-oxides and 2-chloro-4,6-diaminopyrimidines.



Scheme **A**

Ethyl *N*-cyano-cyanoacetimidate (**4**) was prepared from malononitrile by literature methods[3] in 90% yield. This acetimidate reacts quickly and cleanly in methanol or tetrahydrofuran solvent with a variety of secondary amines to give 3-cyanimino-3-aminopropanenitriles **2** in good yields (Scheme **B**). Normally, these compounds are converted directly to the desired pyrimidines (see below). However, in order to characterize this reaction, 3-cyanimino-3-aminopropanenitriles **2a–d** were isolated and characterized (Table 1).

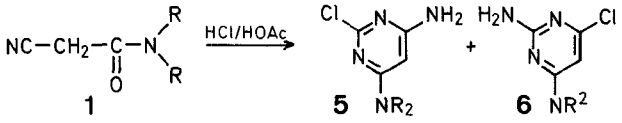


Scheme **B**

Compounds of structure **2** are excellent precursors of triaminopyrimidine *N*-oxides. 3-Cyanimino-3-diethylaminopropanenitrile which was prepared in 62% yield by the method of Scheme **B** was reacted with hydroxylamine (Scheme **A**) to produce 2,4-diamino-6-diethylaminopyrimidine 3-oxide (**3**, $R=C_2H_5$) in 57% yield. This method of pyrimidine *N*-oxide synthesis has several advantages. The overall yield from malononitrile, the precursor of ethyl *N*-cyano-cyanoacetimidate (**4**) was high. The chemistry is very practical. The process avoids the alkylation step of Scheme **A**. The product pyrimidine 3-oxide was isolated in analytical purity by crystallization from methanol and water. No chromatography was necessary. Intermediates **4** and **2** were isolated by simple filtration or extraction techniques. Finally, from a strategic viewpoint, this is an excellent route because the position of the *N*-oxide in the product is definite.

0039–7881/78/0932–0673 $ 03.00

3-Amino-3-cyaniminopropanenitriles of structure **2** can also be treated with anhydrous hydrogen chloride in acetic acid to produce predominantly and often exclusively 2-chloro-4-amino-6-substituted-aminopyrimidines **5**. Analogous conversions of *N*-cyano-cyanoacetimidates were described by Hirayama et al.[3b]. Hirayama and his co-workers found that in acetic acid/hydrogen chloride, *N*-cyano-cyanoacetimidates cyclized predominantly or exclusively to 2-chloro-4-amino-6-alkoxypyrimidines. In our case, hydrogen chloride also adds preferentially to the cyanamide. Thus, pyrimidines of structure **5** are formed in preference to the corresponding 4-chlorides of structure **6** (Scheme **C**). Typical reaction products are described in Table 2.



Scheme **C**

Ethyl *N*-Cyano-cyanoacetimidate:
Hydrogen chloride gas is bubbled vigorously through an ice-cold solution of malononitrile (33.0 g, 0.50 mol) and dry ethanol (23.0 g, 0.50 mol) in dry ether (400 ml) for 1.5 h. The resultant precipitate is filtered, washed with ether, and dried at room temperature in vacuo to yield of ethyl cyanoacetimidate hydrochloride (72 g, 97 %). A mixture of ethyl cyanoacetimidate hydrochloride (44.70 g, 0.302 mol) and cyanamide (13.29 g) in benzene (400 ml) is stirred under nitrogen for 15 h. The precipitated ammonium chloride is filtered. The residue is washed twice with benzene (2 × 50 ml). The combined organic phases are concentrated in vacuo to give a pale yellow crystalline material; yield: 41.36 g. The product is clean by T.L.C. and N.M.R. The crude crystalline material melts at 51–63°.

3-Cyanimino-3-piperidinopropanenitrile:
Piperidine (25.67 g, 0.302 mol) is added dropwise to a solution of ethyl *N*-cyano-cyanoacetimidate (41.36 g, 0.302 mol) in methanol (60 ml). A 25° reaction temperature is maintained. After 50 min, the reaction is partitioned between dichloromethane and aqueous saturated sodium hydrogen carbonate. The organic phase is dried over sodium sulfate and concentrated in vacuo to give a yellow oil, which by T.L.C. appeared to be pure product; yield: 43 g (81 %). The product can be purified by chromatography on silica gel (2 % methanol/dichloromethane) and crystallized from dichloromethane/cyclohexane.

3-Cyanimino-3-morpholinopropanenitrile:
Morpholine (2.54 g, 0.0292 mol) is added to an ice-cooled solution of ethyl *N*-cyano-cyanoacetimidate (4.00 g, 0.0292 mol) in dry tetrahydrofuran (80 ml). After 145 min at room temperature, the reaction mixture is concentrated and filtered through 75 ml of silica gel. The silica gel is washed with 4 % methanol in dichloromethane. The organic wash is concentrated. The resultant crude product is chromatographed on silica gel (2 % methanol in dichloromethane) and crystallized from dichloromethane/cyclohexane to give a 1st crop of white needles (4.00 g; m.p. 129–130°) and a 2nd crop (0.35 g, m.p. 128–130°); total yield: 84 %.

2,4-Diamino-6-diethylaminopyrimidine 3-Oxide:
Diethylamine (2.87 g, 0.039 mol) and ethyl *N*-cyanoacetimidate (4.90 g, 0.036 mol) are stirred in dichloromethane (75 ml) for 6 h. The mixture is partitioned with aqueous sodium hydrogen carbonate. The organic phase is dried over sodium sulfate and concentrated in vacuo to give a pale yellow oil which is clean by T.L.C.; yield: 3.68 g (62 %). This oil is stirred in methanol (120 ml) with hydroxylamine hydrochloride (2.50 g, 0.036 mol) and potassium carbonate (4.97 g, 0.036 mol) for 50 h. The precipitated salts are filtered and washed with hot methanol (20 ml). Water (10 ml) is added and the solution is treated with Nuchar®[4]. Water (10 ml) is added and the solution is concentrated until crystals begin to

Table 1. 3-Amino-3-cyaniminopropanenitriles (**2**)

Product	R	R	Yield[a] [%]	m.p. (solvent)	Molecular formula[b]
2a	—$(CH_2)_5$—		81	73–74.5° (CH_2Cl_2/C_6H_{12})	$C_9H_{12}N_4$ (176.2)
2b	—$(CH_2)_2$—O—$(CH_2)_2$—		84	129–130° (CH_2Cl_2/C_6H_{12})	$C_8H_{10}N_4O$ (178.2)
2c	—$(CH_2)_4$—		84	45–46° (ether)	$C_8H_{10}N_4$ (162.2)
2d	CH_3	CH_3	78	61–62° (ether)	$C_6H_8N_4$ (136.2)

[a] Yield of product isolated by chromatography on silica gel with 2 % methanol/dichloromethane and recrystallized.
[b] All products gave satisfactory microanalyses (C ±0.32 %, H ±0.27 %, N ±0.42 %) except **2c** (C ±0.73 %).

Table 2. 2-Chloro-4,6-diaminopyrimidines (**5**)

Product	R	R	Yield[a] [%]	m.p. (solvent)	Molecular formula[b]
5a	—$(CH_2)_5$—		91	223–225° (C_2H_5OH/C_2H_5OAc)	$C_9H_{13}ClN_4$ (212.7)
5b	—$(CH_2)_4$—		95	210–213°[c]	$C_8H_{11}ClN_4 \cdot \frac{1}{3}HCl$ (211.4)
5c	$H_2C{=}CH{-}CH_2$—	$H_2C{=}CH{-}CH_2$—	83	119.5–120.5° (C_2H_5OAc/C_6H_6)	$C_{10}H_{13}ClN_4$ (224.7)

[a] Yield of crystallized product.
[b] All products gave satisfactory microanalyses (C ±0.36 %, H ±0.29 %, N ±0.39 %, Cl ±0.57 %).
[c] Triturated with ether.

form. On standing, a first crop of 1.85 g, m.p. 255° decomp., and a second crop of 0.65 g are collected; total yield: 57 %.

$C_8H_{15}N_5O$	calc.	C 48.71	H 7.67	N 35.51
(197.2)	found	48.49	7.78	35.46

4-Amino-2-chloro-6-(*N*,*N*-diallylamino)-pyrimidine:
A solution of 3-cyanimino-3-diallylaminopropanenitrile (2.06 g, 0.0109 mol) in glacial acetic acid (25 ml) is treated with hydrogen chloride gas for 20 min. The flask is stoppered and stirred for 1.75 h. The reaction is concentrated and the residue partitioned between dichloromethane and aqueous 10 % potassium carbonate. The organic phase is dried and concentrated; yield: 2.89 g. The product is chromatographed on silica gel (3 % methanol/dichloromethane) and crystallized from ethyl acetate/cyclohexane to give the product; yield: 2.03 g (83 %).

Received: May 4, 1978

[1] (a) E. Gilmore, J. Weil, C. Chidsey III, *N. Engl. J. Med.* **282**, 521 (1970).
(b) T. B. Gottlieb, F. H. Katz, C. Chidsey III, *Circulation* **45**, 571 (1972).
(c) C. J. Limas, E. D. Freis, *Am. J. Cardiol.* **31**, 355 (1973).
(d) W. A. Pettinger, H. C. Mitchell, *N. Engl. J. Med.* **289**, 167 (1973).
(e) W. A. Pettinger, H. C. Mitchell, *Clin. Pharmacol. Ther.* **14**, 143 (1973).
[2] (a) J. M. McCall, R. E. TenBrink, J. J. Ursprung, *J. Org. Chem.* **40**, 3304 (1975).
(b) J. M. McCall, J. J. Ursprung, *U. S. Patent* 3910928 (1975), The Upjohn Company; *C. A.* **84**, 59536 (1976).
[3] (a) J. M. McCall, J. J. Ursprung, *U. S. Patent* 4032559 (1977), The Upjohn Company; *C. A.* **87**, 84564 (1977).
(b) T. Hirayama, M. Kamada, M. Mimura, H. Tsurumi, *Heterocycles* **2**, 461 (1974).
[4] From West Vaco Chemical Division.

0039–7881/78/0932–0675 $ 03.00