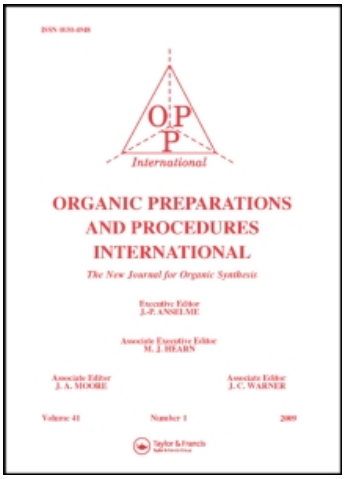

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A CONVENIENT DIRECT PREPARATION OF 2-CYANOPYRIMIDINE

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A CONVENIENT DIRECT PREPARATION OF 2-CYANOPYRIMIDINE

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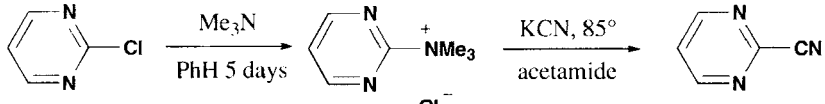
Despite its simple structure and its importance as a key starting material in a variety of complex heterocyclic syntheses, no direct preparation of 2-cyanopyrimidine (**1**) from 2-halopyrimidines or pyrimidine itself has been reported. To date, preparations of 2-cyanopyrimidine involve multistep conversions of the 2-halo-pyrimidines into sulfur or nitrogen derivatives which are then converted to the title compound.[1-4] The most convenient procedure, involved conversion of 2-chloropyrimidine to 2-pyrimidyltrimethylammonium chloride by reaction with excess trimethylamine over 5 days. Treatment of this salt with potassium cyanide in *molten* acetamide was reported to afford the desired 2-cyanopyrimidine (**1**).[3]



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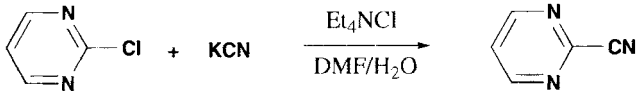
We required multi-gram quantities of **1** as a starting material for the preparation of a variety of pyrimidine derivatives with carbon substituents at the 2-position. While the first step of the published reaction sequence worked well, in our hands the displacement with cyanide proceeded quite unsatisfactorily affording only traces (<1%) of the nitrile. Attempts to modify this procedure using DMF, DMA or DMSO as solvents and varying reaction temperatures and times were also unsuccessful. Direct cyanide displacement on 2-chloropyrimidine using a variety of reaction conditions including palladium catalysis[6] similarly failed. This is not unexpected since nucleophilic addition to such electron-deficient heterocyclic systems (rather than substitution) is quite common.[6]

A number of other attempted routes to pyrimidines with oxidized carbon functions at the 2-position were also unsuccessful. These included attempted direct metallation of pyrimidine (which fails due to nucleophilic addition of base to the heterocycle),[6] attempted Grignard formation from 2-chloropyrimidine, and Sandmeyer type reactions of 2-aminopyrimidine. These synthetic difficulties made a convenient route to **1** even more important.



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Remarkably, the direct cyanide displacement reaction could be successfully carried out on the 2-chloropyrimidine in the presence of aqueous tetraethylammonium chloride. 2-Chloropyrimidine was treated with a slight excess of potassium cyanide in aqueous DMF in the presence of 0.25 molar

equivalents of tetraethylammonium chloride. Heating at 90° for 48 hrs followed by aqueous workup and ether extraction afforded crystalline 2-cyanopyrimidine (**1**) in modest yields of 21-27%. No starting material or ether-soluble by-products were observed under these conditions.[7] The crude nitrile was sufficiently pure for direct conversion to the 2-acetylpyrimidine and other C-2 substituted derivatives. It should be noted that under identical conditions, the 2-trimethylammonium chloride salt did not afford significant amounts of **1**.

Despite the relatively low yield of product, the ease of preparation starting directly from inexpensive, commercially available 2-chloropyrimidine and the absence of contaminants makes this route the method of choice for the preparation of **1**.

EXPERIMENTAL SECTION

Melting points obtained on a Fisher Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 1600 series FTIR. 200 MHz ^{1}H NMR were recorded with Varian XL 200 spectrometer. Microanalysis were performed by Desert Analytics, Tucson, Arizona. All reagents were commercially available and were used without further purification.

2-Cyanopyrimidine (1).- A mixture of potassium cyanide (1.5 g, 23 mmol) and tetraethylammonium chloride monohydrate (1.0 g, 0.54 mmol) in water (1.5 mL) was stirred at 60-70° for 15 min. 2-Chloropyrimidine (2.29 g, 20 mmol) and DMF (30 mL) were added. The mixture was heated at 90 (±5)° for 48 hrs. [Increasing the temperature to 110° significantly lowered the yield of **1**.] The mixture was cooled to room temperature, poured into water (150 mL) and extracted with ether (5 x 75 mL). The ethereal phase was washed with water until the aqueous phase remained colorless (3 X 50 mL). The ethereal layer was dried over sodium sulfate and concentrated affording 0.45-0.56 g (21-27%) of the product as pale yellow crystals, mp. 39-40°, satisfactory for further synthetic transformations. Recrystallization from petroleum ether (38-50°) afforded analytically pure 2-cyanopyrimidine (**1**), mp. 41-42°, lit.[3] mp. 41-42°, IR (KBr): 1981, 1634, 1565, 1399, 1270, 1090, 992, 820, 789, 549 cm^{-1}, NMR ($CDCl_3$): δ 8.90 (d, 2H), 7.60 (t, 1H).

Anal. Calcd. for $C_5H_3N_3$: C, 57.14; H, 2.88; N, 39.98. Found: C, 57.18; H, 2.74; N, 39.91

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REFERENCES

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1. *via* 2-Methylsulfonylpyrimidine: D. J. Brown and P. W. Ford, *J. Chem. Soc. (C)*, 568 (**1967**).

2. *via* 2-Sulfopyrimidine: E. Ochiai and H. Yamanaki, *Pharm. Bull. (Tokyo)*, **3**, 173 (1955); *Chem. Abs.*, **50**, 7810d (1956).

3. *via* the 2-Trimethylammonium chloride salt: F. H. Case and E. Koft, *J. Am. Chem. Soc.*, **81**, 905 (1959). The reported yields in this two step procedure were 97 % and 54 % respectively.

4. Other routes to (**1**) involve dehydrations of 2-carbon-substituted derivatives normally prepared from (**1**) e.g. via the 2-carboxamidopyrimidine with phosphoryl chloride, M. Robba, *Ann. Chim. (France)*, **5**, 351 (1960).

5. M. Uno, K. Seto and S. Takahashi, *Chem. Commun.*, 932 (**1984**).

6. G. Queguiner, F. Marsais, V. Sniekus and J. Epsztajn, *Advances in Heterocyclic Chemistry* **52**, p. 194 (1991).

7. It is likely that under these reaction conditions a competing pyrimidine ring-opening occurred affording water-soluble organic by-products.

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ANALOGS OF TRYPTOPHAN

Submitted by (05/09/94) Emil Pop*, Katalin Prókai-Tátrai, Marcus E. Brewster and Nicholas Bodor

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L-Tryptophan (L-Trp), an essential amino acid commonly used as nutrient has recently been tested as a potential antihypertensive agent.[1-3] Unfavorable properties (high polarity, low lipophilicity) and competition with other amino acids however limit the large neutral amino acid mediated transport of Trp to the central nervous system (CNS), the site of its primary action.[2-4] Since administration of high doses of Trp may have unwanted side-effects,[5] methods of enhancing CNS concentrations of Trp were investigated.[6] The synthesis of novel, analogues of Trp is described herein. Replacement of the amino group of Trp with a dihydropyridine ↔ pyridinium salt moiety (Scheme 1) confers a dual lipophilic ↔ hydrophilic character on the analogues, which could result in brain selective delivery and activity properties.[7]

Racemic D,L-tryptophan (**1a**) was used in these experiments. The carboxylic group of Trp was esterified to provide lipophilic character. Both methyl (**1b**) and ethyl (**1c**) esters were used. The synthesis of redox analogues utilized the Zincke procedure for forming pyridinium salts.[8-10] The amino group of **1b** and **1c** were reacted in dry methanol with 3-carbamoyl-1-(2,4-dinitrophenyl)pyridinium chloride (**2**), obtained from nicotinamide and 1-chloro-2,4-dinitrobenzene,[9] in the presence of sodium bicarbonate and catalytic amounts of pyridine. The pyridinium salts (**3b** and **3c**) were formed *via* a ANRORC mechanism[11] and were purified through several recrystallizations. The 1,4-dihydropy-