A Simple and Efficient Synthesis of 3-Cyano-4-phenyl-2-pyridone

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A preparatively useful method for the synthesis of 3-cyano-4-phenyl-2-pyridone (I) is described. Reaction of 2-cyano-3-methylcinnamamide (VII) with *N,N*-dimethylformamide dimethyl acetal affords the corresponding dimethylaminomethylidene amide VIII which in turn, is thermally cyclized to I in DMF solvent. The advantages of this method include mild reaction conditions for short periods to give good yields of I on large scales without chromatographic purification.

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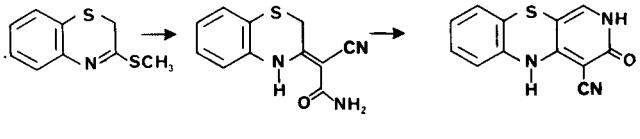
Considerable attention has been given to the synthesis of 3-cyano-4-phenyl-2-pyridone (I) which has been used as an intermediate in the synthesis of several more complex heterocycles and various natural products. Powers and Ponticello (1) obtained a 10% yield of (I) in three steps starting with 2-cyano-3-methylcinnamamide (VII) which is available from acetophenone and cyanoacetamide according to the procedure of Foucaud (2). Powers and Ponticello also reported a three step sequence ending with the condensation of 3-amino-1-phenylprop-2-en-1-one (II) with ethyl cyanoacetate to give I also in 10% overall yield (1).

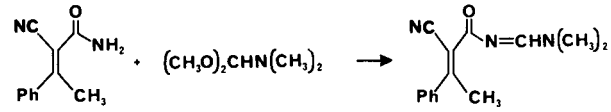
It is essential for the success of this reaction for amide formation to take place prior to alkylation, otherwise, a pyridone with the undesired substitution pattern is obtained. The unstable nature of enaminoketone II and the necessity to use the crude reagent are presumably additional causes for the low yield. Bowden, *et al.* (3) improved the yield of I to 19% by modification of the workup procedure.

These results were confirmed in our hands. Attempted purification of II by filtration through silica gel, neutral alumina, or florisil uniformly gave 15% yields of I. Similarly, the use of ethyl cyanoacetate, diethyl malonate, monoethyl malonate, or potassium ethyl malonate as the active methylene component as well as variation of the stoichiometry of the reaction did not improve the yield.

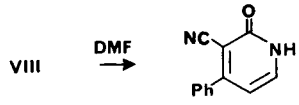
Junek and Stolz (4) suggested that the use of the unsaturated ketone was not necessary and that the desired pyridone condensation could be carried out by the reaction of 3-dimethylaminopropiophenone with "malononitrile dimer". When we attempted this reaction with 2-cyanoacetamide in place of the "malononitrile dimer" none of the desired pyridone was obtained. Junek, *et al.* (5) have also reported the conversion of 2-cyano-3-phenyl-5-dimethylaminopenta-2,4-dienamide (III) to pyridone I under acidic conditions, although the yield of I was not specified. When we attempted this route to I, using acidic, basic, or neutral conditions, we obtained a three component mixture which required chromatography for separation and purification.



V VI IV



VII VIII



VIII I

In devising a preparatively useful route to I we considered the use of *N,N*-dimethylformamide dimethyl acetal. This reagent has been used to generate masked acyl functions in the synthesis of hetercyclic (6) systems including certain bicyclic and tricyclic fused 3-cyano-2-pyridone derivatives (7). Thus, Chorvat and Radak (7c) have used dimethylformamide dimethyl acetal in the synthesis of 3-oxo-5*H*-pyrido[3,4-*b*][1,4]benzothiazine-4-carbonitriles IV from 2-methylthio-3,4-dihydro-[1,4]benzothiazine (V) *via* intermediate VI. It occurred to us that the use of this elegant method may provide an efficient, high yield approach to the synthesis of simple, monocyclic 3-cyano-2-pyridinones including the troublesome 3-cyano-4-phenyl-2-pyridone (I).

Amide VII represents an opportunity to take advantage of both modes of reactivity of the acetal. Formation of intermediate VIII would expose the electron deficient methine carbon to the relatively acidic methyl group and result in incorporation of the formyl carbon of the acetal as C-6 of I. Preparation of VII was accomplished by the method of Foucaud, *et al.* (2) When this material was stirred with a small excess of *N,N*-dimethylformamide dimethyl acetal the initially dry solid slowly became a

green slurry which, after 1 hour at room temperature became an opaque green solution. Although this material was not isolated it is presumably a solution of dimethylaminomethylidene amide VIII.

Cyclization of VIII to the pyridone I could conceivably take place under acidic or basic conditions. When freshly prepared VIII was stirred with aqueous hydrochloric acid at room temperature or on a steam bath only the starting amide VII was recovered. However, when VIII was stirred with a solution of sodium hydride in DMF, tlc showed the presence of I as well as three minor impurities. The cyclization was next attempted by thermal means. Dilution of a small aliquot of VIII with an equal volume of DMF and heating the resulting solution to approximately 140° resulted in a brown solution from which a solid was obtained on admixture with water. This solid displayed physical and spectral properties of I. Thin layer chromatography of the crude product revealed the presence of the desired pyridone as the only major component. A faint component migrating with the solvent front was also observed, however, this material does not interfere with further purification or use of the pyridone. This reaction has been done using up to 75 g of VII and 65% recrystallized yields of I are regularly obtained.

This novel route to pyridone I has several advantages over existing methods. Starting from amide VII it is a two step process which does not require the isolation or purification of the intermediate VIII and both reactions may be accomplished in the same vessel. The reaction times are short and large quantities of I may be generated in good yield without the need for chromatographic purification.

EXPERIMENTAL

3-Cyano-4-phenyl-2-pyridone (I).

A mixture of 55.8 g (0.3 mole) of (*E*)-2-cyano-3-methylcinnamamide (2) and 43 g (0.36 mole) of *N,N*-dimethylformamide dimethyl acetal was stirred at room temperature for one hour then diluted with 100 ml of dry DMF. The green solution was stirred in a 150° oil bath (the vessel remained open to allow volatile components to escape) for 65 minutes, then poured into 3 liters of water. The mixture was adjusted to *p*H 2 with 10% hydrochloric acid solution, filtered, the solid was washed successively with water, ethyl acetate (350 ml), and ether (250 ml) and air dried to give 48.1 g (82% crude) of I which was recrystallized from methanol to give 38.5 g (65%) of analytically pure I as beige needles, mp 228-231° [lit (1) mp 228.5-231.5°]; ir (KBr) 2210, 1655, 1605 cm^{-1}; nmr (DMSO-d_6): δ 7.79 (d, 1H, J = 7 Hz), 7.55 (s, 5H), 6.42 (d, 1H, J = 7 Hz).

Anal. Calcd. for $C_{12}H_8N_2O$: C, 73.45; H, 4.11; N, 14.28. Found: C, 73.39; H, 3.83; N, 14.26.

REFERENCES AND NOTES

(1) J. C. Powers and I. Ponticello, *J. Am. Chem. Soc.*, **90**, 7102 (1968).

(2) A. Foucaud, H. Person, and A. Robert, *Bull. Soc. Chim. France*, 1873 (1964).

(3) B. F. Bowden, K. Picker, E. Ritchie and W. C. Taylor, *Aust. J. Chem.*, **28**, 2681 (1975).

(4) H. Junek and G. Stolz, *Monatsh. Chem.*, **101**, 1234 (1970).

(5) H. Junek, G. Stolz, and A. R. O. Schmidt, *ibid.*, **102**, 154 (1971).

(6a) Y-i. Lin, S. A. Lang, Jr., M. F. Lovell, and N. A. Perkinson, *J. Org. Chem.*, **44**, 4160 (1979); (b) Y-i. Lin and S. A. Lang, Jr., *J. Heterocyclic Chem.*, **14**, 345 (1977); (c) Y-i. Lin, S. A. Lang, Jr., and S. R. Petty, *J. Org. Chem.*, **45**, 3750 (1980);(d) Y-i. Lin and S. A. Lang, Jr., *ibid.*, **45**, 4857 (1980).

(7a) R. J. Chorvat and R. Pappo, *Tetrahedron Letters*, 623 (1975); (b) R. J. Chorvat, J. R. Palmer and R. Pappo, *J. Org. Chem.*, **43**, 966 (1978); (c) R. J. Chorvat and S. E. Radak, *Tetrahedron Letters*, **21**, 421 (1980).