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SYNTHESIS OF NOVEL BICYCLIC 2-AMINO-4(1H)-PYRIDONES. REACTION OF LACTIM ETHERS WITH α-CYANOACETONE DIANION.

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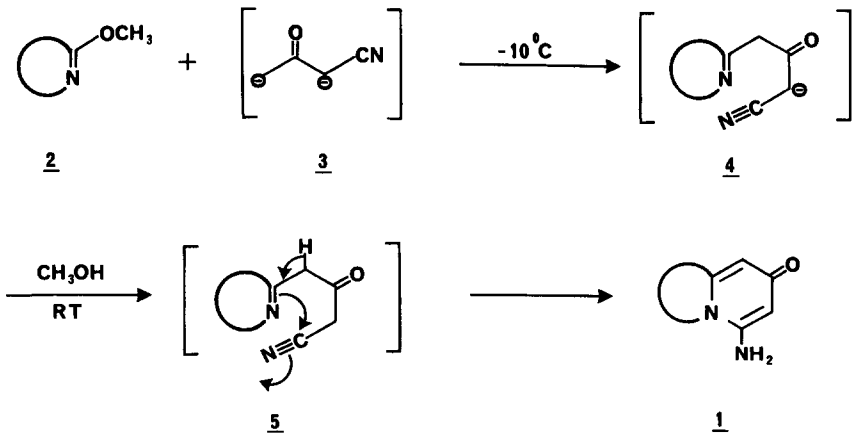
Summary: Reactions of lactim ethers with α-cyanoacetone dianion gave bicyclic 2-amino-4(1H)-pyridones.

Nitrogen-bridged polycyclic systems comprise a major portion of naturally occuring as well as synthetic medicinal agents and, accordingly, there has been a great deal of synthetic effort directed toward synthesis of compounds in this class. [1,2] New methodologies for constructing such structures continue to be needed, particularly those methods leading to products generally useful as building blocks in heterocyclic syntheses. We now describe a convenient synthesis of a versatile nitrogen-bridged heterocyclic system 1 containing several potentially reactive sites [3] for further structural elaboration.

When a lactim ether of general structure 2 [4] (0.1 M) was added with mechanical stirring at -10 °C to a solution of the dianion 3 [5] (0.1 M) preformed from LDA (0.2 M) and 5-methylisoxazole (0.1 M) in dry THF (100 mL) at -10 °C, a light orange suspension was obtained. This suspension was brought to RT for 12 hr and slowly quenched with dry CH_3OH (50 mL). The resultant reddish solution was further stirred at RT for 2 - 5 hr before evaporation of the solvents in vacuo. The thick oil thus obtained was flash column chromatographed (30 % CH_3OH in CH_2Cl_2 on silica gel 60) to afford after recrystallization (CH_3OH/acetone) white crystalline products represented by 1 (Table I).

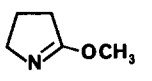
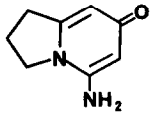
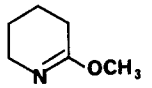
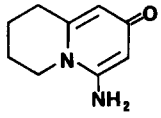
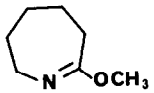
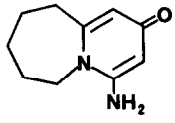
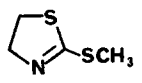
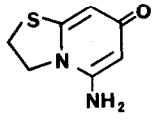
Scheme I



2 3 4 5 1

The course of this reaction is outlined in Scheme I. The initial nucleophilic attack of dianion 3 on lactim ether 2 [6] results in the formation of anion 4 which undergoes cyclization in CH_3OH to afford the bicyclic product 1. In the absence of CH_3OH, the ring closure was not observed, indicating that the proton exchange taking place in the anion-quenching step (4 → 5) is necessary for the subsequent nucleophilic addition of the imino nitrogen to the nitrile group. Replacing CH_3OH with H_2O did not bring about the desired cyclization but led, instead, to a mixture of several unknown products. It is possible that intermediate 5 decomposes very rapidly in aqueous basic media before it can undergo cyclization.

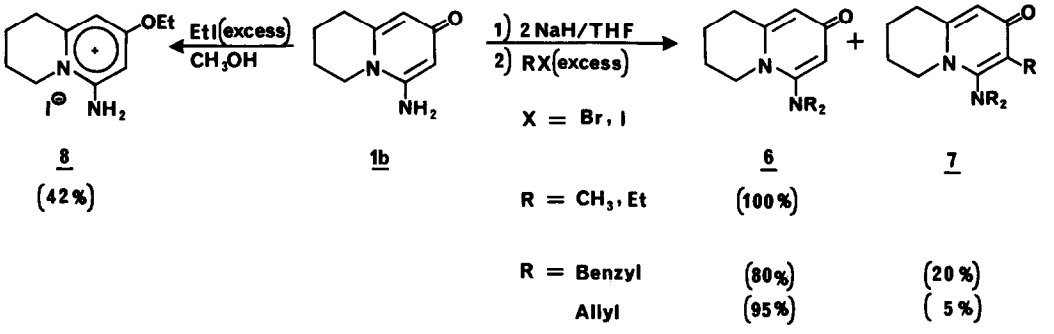
Table I [7]

Lactim Ethers 2		Products 1 (% Yield)		Nmr δ
	a		(30)	HCl salt in D_2O: 6.37 (m, 1 H), 6.07 (d, J = 2 Hz, 1 H), 4.10 (t, J = 7 Hz, 2 H), 3.17 (m, 2 H), 2.33 (m, 2 H).
	b		(40)	HCl salt in D_2O: 6.27 (m, 1 H), 6.10 (d, J = 3 Hz, 1 H), 3.83 (t, J = 6 Hz, 2 H), 2.95 (t, J = 6 Hz, 2 H), 1.97 (m, 4 H).
	c		(40)	Free base in CD_3OD: 5.92 (d, J = 2 Hz, 1 H), 5.67 (d, J = 2 Hz, 1 H), 4.05 (m, 2 H), 2.80 (m, 2 H), 1.77 (m, 6 H).
	d		(45)	Free base in CD_3OD: 5.92 (d, J = 2 Hz, 1 H), 5.48 (d, J = 2 Hz, 1 H), 4.28 (t, J = 7 Hz, 2 H), 3.47 (t, J = 7 Hz, 2 H).

In the course of this work we have examined the alkylation reactions of 1b [8] and our preliminary results are summarized in Scheme II. Exclusive N-alkylation to 6 was easily achieved (100 %) by treating 1b at RT with 2 equiv. of NaH followed by adding the appropriate alkyl halide (excess). However, with more reactive halides (e.g. allyl and benzyl) the trialkylated product 7 (5 - 20 %) resulting from further alkylation at the enaminone carbon was also isolated in addition to product 6 (80 - 95 %). Interestingly, at elevated temperatures in the absence of base, O-alkylation predominated giving rise to the quaternary salt 8 (42 %) as the sole product.

The chemistry and potential synthetic application of this novel bicyclic 2-amino-4(1H)-pyridone system (1) is currently under investigation. Results of these studies will be reported in due course.

Scheme II [7a,9]



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References and Notes

1. For a review of the syntheses of such compounds and their biological properties, see: (a) T. Uchida and K. Matsumoto, Synthesis, 209 (1976), and references cited therein; (b) V. Snieckus, "Survey of Progress in Chemistry", 9, 121 (1980).

2. For a recent example, see: T. Shono, Y. Matsumura, K. Uchida, K. Tsubata, and A. Makino, J. Org. Chem., 49, 300 (1984), and references cited therein.

3. The heterocyclic system 1 contains a bis-enaminone functionality. For reviews on enaminone chemistry, see: (a) T. Nishino, C. Kajima, Y. Omote, J. Syn. Org. Chem. Jpn., 34, 526 (1976); (b) J. V. Greenhill, Chem. Soc. Rev., 16, 277 (1977).

4. (a) A. E. Wick, P. A. Bartlett and D. Dolphin, Helv. Chim. Acta., 54, 513 (1971). (b) B. M. Trost and R. A. Kunz, J. Am. Chem. Soc., 97, 7152 (1975).

5. (a) F. J. Vinick, Y. Paff, and H. W. Gschwend, Tet. Lett., 4221 (1978). (b) For a recent review on 3-oxoalkanenitriles, see: M. H. Elnagdi, M. R. H. Elmoghayar, G. E. H. Elgemeie, Synthesis, 1 (1984).

6. For a review of lactim ether chemistry, see: R. G. Glushkov and V. G. Granik, "Advances in Heterocyclic Chemistry", 12, 185 (1970).

7. (a) All new compounds gave satisfactory elemental (C, H, and N) analyses. (b) Compounds 1a-d melted at temperatures higher than 250 °C.

8. Alkylation reactions of enaminones have been explored by several groups. For a recent report, see: J. V. Greenhill and M. A. Moten, Tetrahedron, 39, 3405 (1983).

9. 6, R = CH_3: nmr ($CDCl_3$) δ 6.05 (d, J = 2 Hz, 1 H), 5.95 (d, J = 2 Hz, 1 H), 3.92 (m, 2H), 2.8 - 2.5 (m, 2 H), 2.63 (s, 6 H), 1.83 (m, 4 H); R = Et: nmr (HBr salt in D_2O) δ 6.73 (d, J = 2 Hz, 1 H), 6.68 (d, J = 2 Hz, 1 H), 4.25 (m, 2 H), 3.27 (q, J = 8 Hz, 4 H), 2.98 (m, 2 H), 1.92 (m, 4 H), 1.13 (t, J = 8 Hz, 6 H).
7, R = allyl: nmr (HCl salt in D_2O) δ 7.05 (s, 1 H), 6.17 - 5.63 (m, 3 H), 5.38 - 5.08 (m, 6 H), 4.63 (m, 2 H), 3.83 (d, J = 6 Hz, 4 H), 3.47 (m, 2 H), 3.13 (m, 2 H), 1.87 (m, 6 H); R = benzyl: nmr (HCl salt in CD_3OD) δ 7.27 (m, 16 H), 4.43 (m, 2 H), 4.17 (s, 4 H), 3.80 (s, 2 H), 3.12 (m, 2 H), 1.77 - 1.47 (m, 6 H).
8: nmr (CD_3OD) δ 6.40 (s, 2 H), 4.10 (q, J = 7 Hz, 2 H), 3.90 (t, J = 6 Hz, 2 H), 3.03 (t, J = 6 Hz, 2 H), 2.00 (m, 4 H), 1.42 (t, J = 7 Hz, 3 H).

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