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# THE SYNTHESIS OF ANNELATED 3-CYANO-2-PYRIDONES

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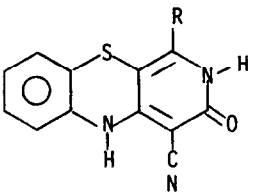
Annelated tricyclic 3-cyano-2-pyridones were synthesized from cyanoacetamide adducts using a thermal cyclization process which had previously been reported to afford an annelated pyrimidone product.

In previous work on the total synthesis of 2-azaestratrienes we had discovered a novel α-pyridone synthesis which we utilized for the preparation of the 7-aza-6-methoxy-1-tetralone precursor of these compounds.[1,2] We now wish to report on an extension of this reaction as it applies to the synthesis of the heretofore unknown 2,3-dihydro-3-oxo-5H-pyrido[3,4-b]-[1,4]benzothiazine-4-carbonitriles (1). These annelated heterocycles also result from the conversion of cyanoacetamide adducts into α-pyridones but are formed via a thermal cyclization which differs mechanistically from our earlier work. Moreover, the pyridone products contrast those of previous reports where thermal cyclization of analogous systems afforded an annelated pyrimidone.[3]



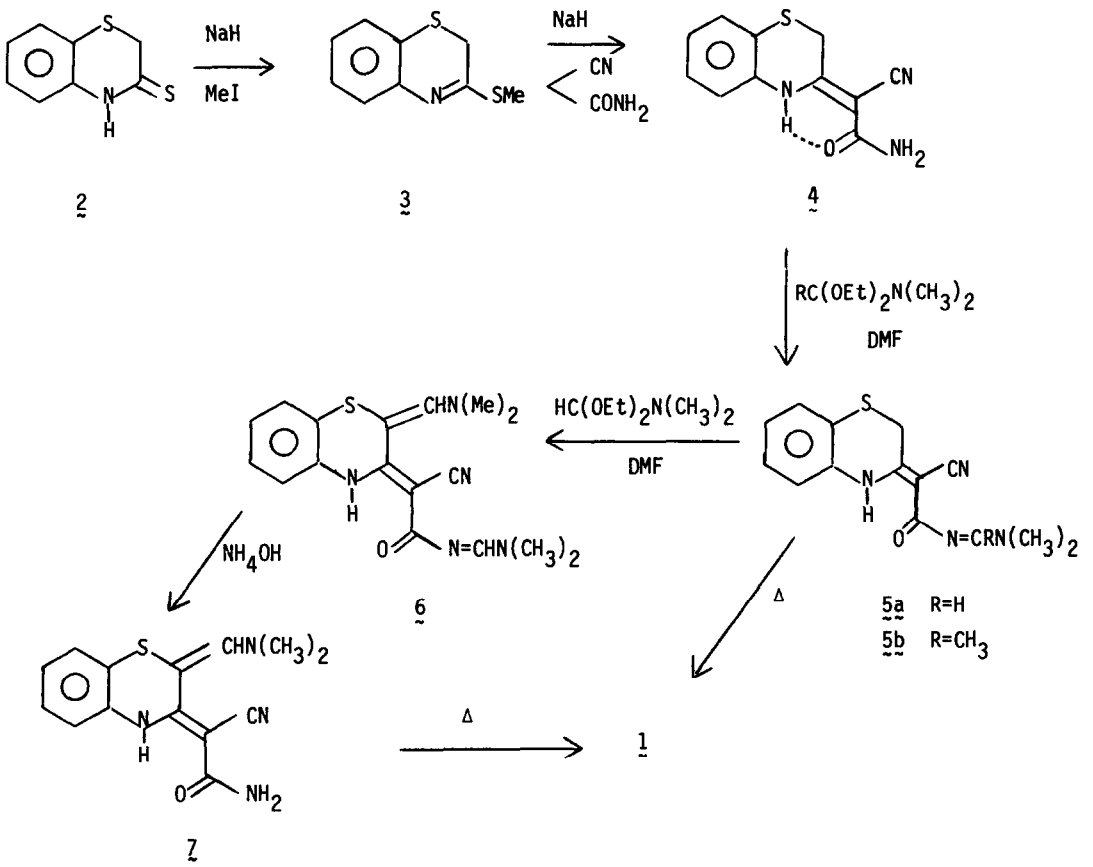
1a R=H
1b R=$CH_3$

When 2H-1,4-benzothiazine-3(4H)-thione[4] (2) was treated with sodium hydride in THF at room temperature and the resultant sodium salt alkylated with methyl iodide, the thioimino ether 3 was rapidly produced: NMR($CDCl_3$) 2.52 ppm (3H,s,S-$CH_3$), 3.20 (2H,s,-$CH_2$). The solution of 3 was then added to the sodium salt of 2-cyanoacetamide in DMF also generated from sodium hydride at room temperature. After heating the resultant reaction mixture at 70-75°C for 6 h, the cyanoacetamide adduct 4 was obtained in yields up to 87%: mp 267-268°C; UV(MeOH) 276 nm (ε 22,000). The NMR spectrum (DMSO-$d_6$) of 4 showed a single resonance for the methylene protons adjacent to sulfur at 3.89 ppm and the absence of a methine proton, indicating the presence of an exo double bond. Further elucidation of this structure came from $^{13}$C-NMR which showed the presence of two olefinic carbon atoms at 73.1 and 121.1 ppm in addition to

the methylene carbon atom adjacent to sulfur at 26.8 ppm. The fact that each of the carbon resonances of the proton-decoupled spectra was a clean singlet suggested that either the compound was a single geometrical isomer about the exo double bond[5] or that the rotation rate about the double bond was out of the NMR time scale.[6] Previous work by Shvo and Belsky on conjugated ketene mercaptinal systems had shown that cyclic structures containing substituents on the double bond capable of hydrogen bonding as shown in 4 may have energy barriers to inversion which favor this isomer at room temperature.[7] Infrared studies by Singh and Gandhi also support this result.[8] We thus favor the Z-isomer of 4 as the exclusive form of this compound rather than a rapidly rotating mixture.

Initially 4 was treated with greater than two equivalents of N,N-dimethylformamide diethyl acetal in DMF at 95-100°C which resulted in the formation of the bis-dimethylaminomethylene adduct 6. The carboxamide could readily be liberated through hydrolysis with ammonium hydroxide solution in DMF to afford the mono-dimethylaminomethylene amide 7. Continued heating of the aqueous solution then caused cyclization to the tricyclic pyridone 1a

Scheme




2 3 4

6

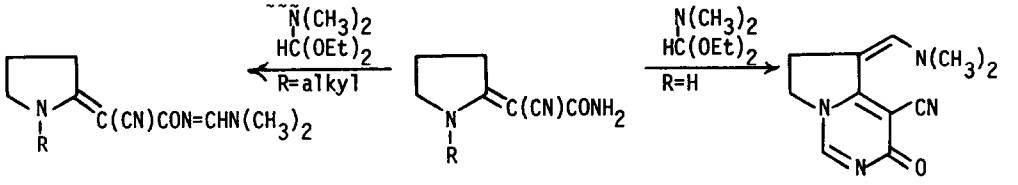
5a R=H
5b R=CH3

7

1

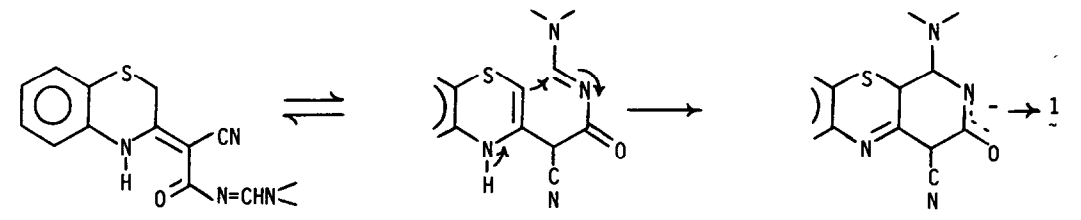
(70-80% yield from 4) via prototropic isomerization and subsequent cyclization.

We later found that treatment of 4 with one equivalent of the acetal reagent in DMF at room temperature gave the mono-adduct 5a: NMR($CDCl_3$) 3.18 ppm (6H,s,-$N(CH_3)_2$), 3.83 (2H,s, -$CH_2$), 9.33 (1H,brds,=CHN<). Isolation of this compound was not necessary; when 5a was heated in DMF at 145°C for 6 h 1a was produced (56% from 4): mp>300°C; UV(MeOH) 252 nm (ε 42,600); NMR (DMSO-$d_6$) 6.9-7.6 ppm (4H, aromatic H's), 7.35 (1H,s,pyridone-H). This thermal cyclization product was surprising in view of earlier work on analogous cyanoacetamide adducts by Glushkov and coworkers.[3] The Russian group reported that in the pyrrolidine system i, the contrasting mode of thermal cyclization occurred when the ring nitrogen was unsubstituted, resulting in pyrimidone ii. While this system contains additional dimethylaminomethylene functionality at the site where pyridone formation would occur, this must have happened subsequent to pyrimidone formation. For when i (R=$CH_3$) was treated under similar conditions with excess ketal reagent only the monoadduct iii was reported without accompanying ring alkenylation.[9] To obtain the desired pyridone product, they then thermally cyclized the N-alkylated product iii at higher temperature.




iii i ii

The fact that the tricyclic α-pyridones 1 were the only isolated products from our cyclizations indicated that intermediates 5 and 7 must undergo double bond isomerization upon heating prior to cyclization. We feel the enhanced nucleophilicity of the carbon adjacent to sulfur in 5' directs cyclization via an enamine intermediate leading, after elimination of dimethylamine, to the pyridone 1.




5 5' 5''

The use of N,N-dimethylacetamide dimethyl acetal in forming the mono-adduct 5b also led, upon heating as described above, to the methylpyridone 1b: mp>300°C; NMR(DMSO-$d_6$) 2.10 ppm (-$CH_3$).[10]

The versatility of this reaction sequence for the preparation of tricyclics related to 1 using other malonate derivatives will appear in subsequent reports.

Acknowledgment: We thank Professor A. I. Meyers for helpful discussions and Dr. R. H. Bible, Jr. and associates for obtaining the $^{13}$C-NMR data.

## References and Notes

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2. R.J. Chorvat, J.R. Palmer and R. Pappo, J. Org. Chem., 43, 966 (1978).
3. V.A. Azimov, V.G. Granik, R.G. Glushkov and L.N. Yakhontov, Khim. Geterosikl. Soedin., 355 (1978).
4. R.N. Prasad, J. Med. Chem., 12, 290 (1969).
5. If not a single isomer, the distribution must be greater than that detectable by $^{13}$C-NMR spectroscopy (>95:5).
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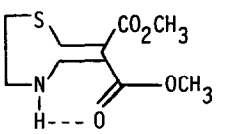
7. Y. Shvo and I. Belsky, Tetrahedron, 25, 4649 (1969). The compounds studied by these investigators which exhibited hydrogen bonding were:

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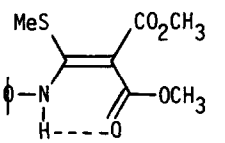


8. H. Singh and C.S. Gandhi, J. Chem. Res.,(S), 407 (1978).
9. V.G. Granik, N.B. Marchenko, T.F. Vlasova and R.G. Glushkov, Khim. Geterosikl. Soedin., 1509 (1976).
10. The mono-adduct 5b was the exclusive product when 4 was heated (95-100°) in excess of two equivalents of the acetamide ketal reagent. This differs from the formamide ketal reagent where the bis-adduct 6 was obtained. Apparently, steric requirements prohibit formation of the animal precursor of the dimethylaminoethylene grouping at this temperature.

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