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# A NEW ROUTE TO PYRIDONES VIA IMINES OF PYRUVIC ESTERS

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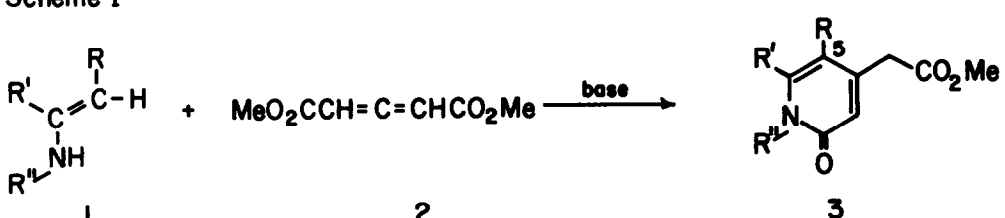
The nucleophilic addition of enamines to a dicarboxy allene has provided the basis for an extremely valuable method of preparing highly substituted 2-pyridones.[1] (See Scheme I). It was of interest to study the extension of this reaction to include the synthesis of pyridones where C-5 (3, R=H) was unsubstituted. Such products are not directly available from the previous synthesis. A motivation for this study may be found in the synthesis of the anti-tumor alkaloid camptothecin (5)[2] which is unsubstituted at C-14.

Each of the enamines utilized in the previous study was conjugated with a carboxyl or carbonyl group (1, R=$CO_2$Et or COMe). The synthesis of the unsubstituted pyridones by this method would require the use of enamines in which R is hydrogen.

The adducts of primary amines and carbonyl compounds generally exist as the imine tautomers.[3] However, the stability of the enamine tautomer is increased by conjugation with an electron withdrawing group. Thus, in those compounds utilized in the previous study the enamine tautomers 1 would be expected to predominate. However, the compounds required

Scheme I

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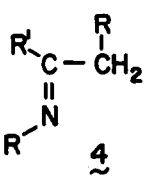


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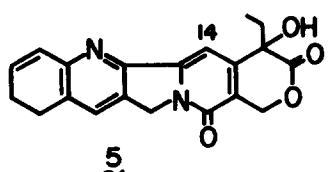


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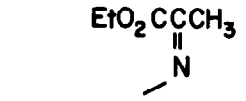

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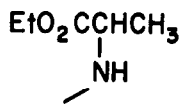

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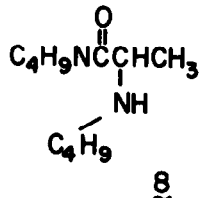

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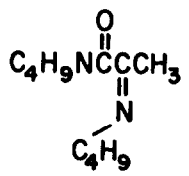

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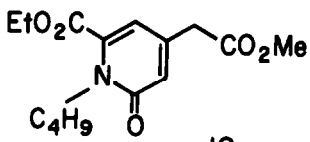

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for the synthesis of 5-unsubstituted pyridones would be expected to exist in the imine form 4.

Although we have found no examples of imines acting as carbon-nucleophiles without the mediation of a strong base or a Lewis acid, some oxidations and reductions of imines may be explained by invoking the action of small amounts of the tautomeric enamine.[4] It was our hope that 4 (R=H) might add as a nucleophile to the allene 2 via 1 (R=H).

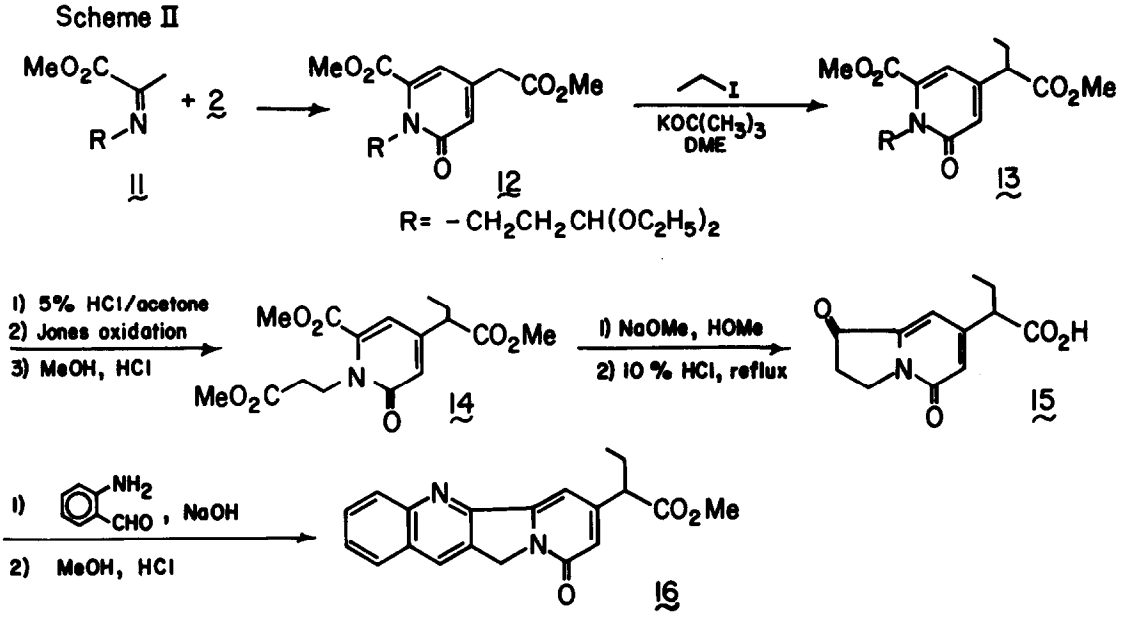
We chose to test this possibility with an imine of ethyl pyruvate. The only imines of pyruvates which were known previously were those derived from benzylic amines.[5] We were able to prepare imine 6 from butyl amine and ethyl pyruvate by allowing an equimolar solution of each component in benzene to stir at 0° for 1 hr followed by treatment with anhydrous sodium sulfate. The imine is unstable at room temperature. It slowly decomposes to an unidentified black oil. The NMR of the crude imine product was generally that which would be expected for 6.[6]

In order to further establish the nature of the product from the condensation it was treated with $NaBH_4$ in tetrahydrofuran. The resulting mixture contained principally ethyl α-butylaminopropionate (7) as well as smaller amounts of N-butyl α-butylaminopropionamide (8) and ethyl lactate. These were identified by comparison of the glc of the mixture with the glc of the authentic compounds.[7] Presumably the crude product before reduction contained 6 along with small amounts of the amido-imine 8 and ethyl pyruvate.

When a solution of the crude imine in dimethoxyethane (DME) was treated with 2 and triethylamine at -78° and allowed to warm slowly to room temperature, a 35% yield of pyridone 10[8] was obtained after chromatography. The lack of substitution at C-5 was confirmed by the presence of a two proton AB quartet at δ6.67 in the NMR.

We next sought to apply this technique to the synthesis of camptothecin. Thus, imine

Scheme II




11, prepared from the corresponding amine and methyl pyruvate, was condensed with the allene in the manner described above. The pyridone 12[8] (mp 57-8°, NMR δ6.64 AB quartet) was obtained in 37% yield. A 63% yield of the ethylated pyridone 13[8] was obtained from 12 (Scheme II). Hydrolysis of the side chain acetal afforded the aldehyde which was immediately oxidized to the acid which gave, after esterification, the triester, 14[8], in 65% yield. Dieckmann cyclization of 14 followed by hydrolysis and decarboylation of the β-keto-ester gave 15. The bicyclic ketone was subjected to a Friedlander condensation with o-aminobenzaldehyde to yield the tetracyclic intermediate 16[9] in 9% overall yield from methyl pyruvate. Since 16 has previously been converted to camptothecin,[10,11] this represents a formal total synthesis of camptothecin.

Although the yields in the pyridone forming step are not as high as one would hope for, this method is much better than the former procedure of obtaining these 5-unsubstituted pyridones which required a decarboxylation.[10,12] We are currently studying the reactions of imines from other α-keto-esters with allene 2 and with other Michael acceptors. This procedure should also simplify the preparation of analogs of camptothecin.

Acknowledgements

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References and Notes

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6. The pertinent signals were δ2.04 (s, $-N=\overset{t}{C}-CH_3$) and δ3.4 (broad t, $-CH_2-N=C\overset{t}{<}$).
7. Authentic samples of $7^8$ and $8^8$ were prepared by the action of butylamine on ethyl α-bromopropionate.
8. NMR and IR spectra and elemental analysis of this compound are consistent with the assigned structure.
9. This material was found to be identical in all respects with that previously prepared.[10]
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