A General Synthesis of Alkyl-pyrrolones and Dihydro-pyridones

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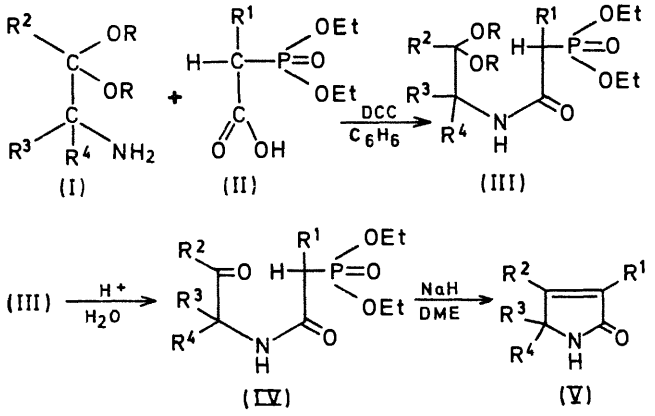
Summary A general synthesis of alkyl-pyrrolones and dihydro-pyridones is described.

In connection with some synthetic work we required various simple alkyl substituted pyrrolones of the type (V;R^4 = H). The existing methods[1] for the synthesis of these compounds did not provide an easy access to the desired substitution at the 3, 4, and 5 positions of the pyrrolone ring.

The simplest route to alkyl-pyrrolones has been described by Johnson[2] in which the corresponding alkyl-pyrrole is oxidised with hydrogen peroxide. The drawback of this method is the lack of selectivity shown in the oxidation of asymmetric pyrroles. The oxidation of 3-ethyl-4-methyl-pyrrole yields both possible pyrrolone isomers. Other more involved syntheses which avoid this possibility do not give substitution at all available ring positions.

We now report the success of a new method (see Scheme 1) which provides complete flexibility with respect to location of substituents and which uses as its key step an internal Emmons[3] reaction.



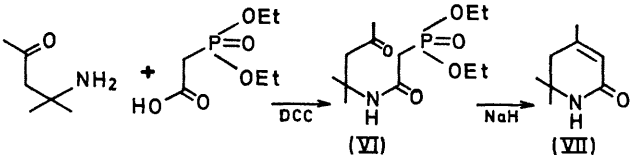
SCHEME 1

The appropriate phosphonoacetic acid derivative was obtained by catalytic debenzylation of the corresponding benzyl ester which was prepared in the usual way.†[4] These acids are unstable and readily lose CO_2 on heating.

A typical case involved the condensation of 2,2-diethoxybutylamine[5] with α-diethylphosphonopropionic acid (II; R^1 = Me) in the presence of dicyclohexylcarbodi-imide in benzene which led, upon acidic work-up, to 66% yield of the amido-ketone (IV; R^1 = Me, R^2 = Et, R^3 = R^4 = H) [i.r. (film) 5·82, 6·0, 8·05, 9·5, 10·3 μm; n.m.r. ($CDCl_3$) δ 1·0 (m, 12H), 2·2 (*q*, 2H), 4·0 (6H)]. This could be cyclized without further purification in 77% yield through the action of sodium hydride in dimethoxyethane (DME) under reflux to the desired pyrrolone (V; R^1 = Me, R^2 = Et, R^3 = R^4 = H). This compound is identical in all respects to the compound described by Plieninger and Dekker.[6] The overall yield of this sequence is approximately 50%.

As a test of the generality of the reaction, we prepared a pyrrolone substituted at the 3, 4, and 5 positions (V; R^1 = R^2 = R^3 = Me, R^4 = H). The required amino-acetal was prepared from the known 3-acetamidobutan-2-one[7] by acetalization with ethylene glycol in benzene followed by hydrolysis of the acetamido-group with refluxing 40% aqueous KOH–methanol. The resulting amino-acetal was treated with (II; R = Me) in the presence of DCC to give on acidic work-up a 55% yield of the required amido-ketone (IV; R^1 = R^2 = R^3 = Me, R^4 = H) [i.r. (film) 3·1, 5·8, 5·99 μm; n.m.r. ($CDCl_3$) δ 1·0 (m, 12H), 2·1 (s, 3H), 2·9 (d, 1H), 4·0 (m, 5H)]. This was cyclized in the manner described above to pyrrolone (V; R^1 = R^2 = R^3 = Me, R^4 = H) in 74% yield identical to that produced[2] by the oxidation of 3,4,5-trimethylpyrrole.

In an effort to extend the scope of this reaction, a study was made of the feasibility of its use for the construction of 6-membered unsaturated lactams. The ready availability of diacetoneamine[8] coupled with the fact that lactam (VII) had been previously described,[9] led us to attempt the synthesis of this compound as shown in Scheme 2. A



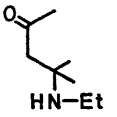
SCHEME 2

complicating factor in the synthesis of the 6-membered ring by this approach is that the nitrogen is now β to the carbonyl group and under the basic conditions of the cyclization, there exists the possibility that β-elimination could supervene. Should this process take place faster than the cyclization, the desired product would not be formed. If the elimination took place after the cyclization, however, the possibility of re-addition of the nitrogen to the resulting dienone would still remain.

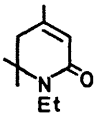
The condensation of diacetoneamine and diethylphosphonoacetic acid in the presence of DCC took place smoothly to yield the unstable (VI), i.r. (film) 5·85, 5·96, 8·0, 10·3 μm; n.m.r. ($CDCl_3$) δ 1·0 (m, 12 H), 2·4 (s, 2H), 2·8 (d, 2H), 3·0 (s, 3H), 3·9 (m, 4H) which was then submitted to the cyclization conditions which had been successful in the 5-membered case. However, from this reaction, no definable product could be isolated. Repetition of the cyclization at room temperature for 24 hr., however, produced a 43% yield of the unsaturated lactam (VII) which had properties (m.p. 120°) identical to those published for this compound.[10] In an effort to extend the

† All fully characterized compounds had correct analytical and spectral properties.

range of the synthesis one step further, an attempt was made to prepare (IX) from (VIII) by the same route. Although (VIII) itself could be prepared without difficulty, through the addition of ethylamine to mesityl oxide, efforts to condense it with diethylphosphonoacetic acid using DCC were completely fruitless and synthetic efforts along this line were not continued.



(VIII)



(IX)

We have shown that the synthetic sequence here described is a practical method for the production of pyrrolones and 5,6-dihydropyridones of varying substitution patterns. The only limitation that has been found so far, is that extensive crowding in the vicinity of the nitrogen makes the coupling reaction more difficult. This need not prevent the use of this synthesis if other methods for creating the amide linkage are available.

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