Experiments towards the Synthesis of the Ergot Alkaloids and Related Structures. Part 7.[1] Novel Syntheses of some 4-Acyl-2,3,4,4a,5,6-hexahydrobenzo[*f*]quinolin-2-ones

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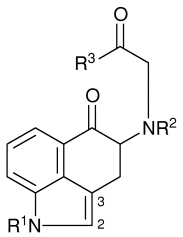
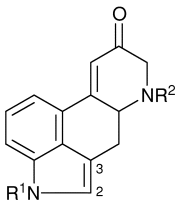
Reaction of the *N*-formyl enol-lactone **4** and the corresponding *N*-acetyl **10** and *N*-methoxycarbonyl **11** derivatives with bis(trimethylsilyl)potassiomalonate in THF at 60 °C followed by treatment with aqueous sodium hydrogen carbonate and cyclisation as above, yielded the 4-formyl-, 4-acetyl- and 4-methoxycarbonyl-tricyclic ketones **7**, **13** and **14** in yields of 31, 35 and 36%, respectively.

In Part 4,[2] one of us (R.E.B.) reported the synthesis of the *N*-methoxycarbonyl tricyclic diketone **1a** and the subsequent failure to achieve the base-catalysed cyclisation to give the potentially valuable tetracyclic ketone **2a** despite analogous ring-closures which had been shown to take place readily in the case of the corresponding *N*-methylindoline diketone **1b**[3] (to give **2b**) and the corresponding 6-desazaanalogue.[4] Similar situations have been reported in some model acyclic and bicyclic *N*-acyl-3-aza-1,5-diketones including the *N*-despyrrole analogue of **1a** and the corresponding *N*-methoxycarbonyl derivative.[5]



1a R^1 = Ts, R^2 = CO_2Me, R^3 = Me
1b (2,3-Dihydro) R^1 = PhCO, R^2 = R^3 = Me
1c R^1 = Ts, R^2 = CO_2Me, R^3 = CH_2CO_2H



2a R^1 = Ts, R^2 = CO_2Me
2b (2,3-Dihydro) R^1 = PhCO, R^2 = Me

These latter results supported our earlier conclusion that the presence of acyl groups on the exocyclic nitrogen atom brought about deactivation of either the ring ketone or the terminal methyl group. The first alternative seemed unlikely on account of earlier work[2] and it was concluded that deactivation of the terminal methyl group was the problem to be solved by attachment of an activating group as present in the β-keto acid **1c** which we expected would undergo cyclisation in mildly alkaline aqueous media to yield the target tetracyclic ketone **2a** with concomitant loss of carbon dioxide.

Our initial work focused on the synthesis of the model *N*-formyl tricyclic ketone **7** on account of the literature statement[6] that 'it (the *N*-formyl group) is surprisingly resistant to basic hydrolysis but readily solvolysed in dilute acid' thus permitting its ready removal when required at a latter stage in the synthesis and yet stable enough to survive the mild aqueous alkaline conditions for cyclisation.

The readily available starting *N*-formyl keto acid[1] **3** did not yield an acid chloride but was readily converted in high yield into the enol-lactone **4** by treatment with acetic anhydride in the presence of triethylamine at 90–95 °C (Scheme 1). Reaction of **4** with benzyl lithioacetate at −70 to 0 °C furnished a viscous oil containing the benzyl ester of the *N*-formyl-1-oxo-β-keto acid **5**. Removal of the benzyl group (Pd/C–H_2) and extraction with aqueous sodium hydrogen carbonate yielded a solution containing the sodium salt of the 1-oxo-β-keto-acid **6** which on heating at 60–65 °C deposited a gum from which the tricyclic 4-formyl-2,3,4-4a,5,6-hexahydrobenzo[*f*]quinolin-2-one **7** was obtained in low overall yield.

In another approach, reaction of the same lactone **4** and the corresponding *N*-acetyl **10** and *N*-methoxycarbonyl **11** derivatives with bis(trimethylsilyl) potassiomalonate in THF at 60 °C for 1.5 h followed by treatment with aqueous sodium hydrogen carbonate and cyclisation as before furnished the *N*-formyl tricyclic ketone **7** in 31% yield; the corresponding *N*-acetyl- and *N*-methoxycarbonyl ketones **13** and **14** were obtained similarly from the *N*-acylenol-lactones **10** and **11** in yields of 35 and 36%.

Finally, careful acidification of the initial reaction mixture at 3 °C yielded the crystalline β-keto acid which would appear from its IR and ^{1}H NMR spectra to exist in the cyclic lactol structure **15** rather than in the open diketo form **6**. This acid **15** was stable at room temperature but on heating it decomposed at its melting point (115 °C) with vigorous evolution of gas, later resolidified and finally remelted sharply at 134 °C, the melting point of the *N*-formyl diketone **16** which was obtained by aqueous hydrolysis of **15** at 90 °C.

Techniques used: IR and ^{1}H NMR spectroscopy

Schemes: 2

References: 10

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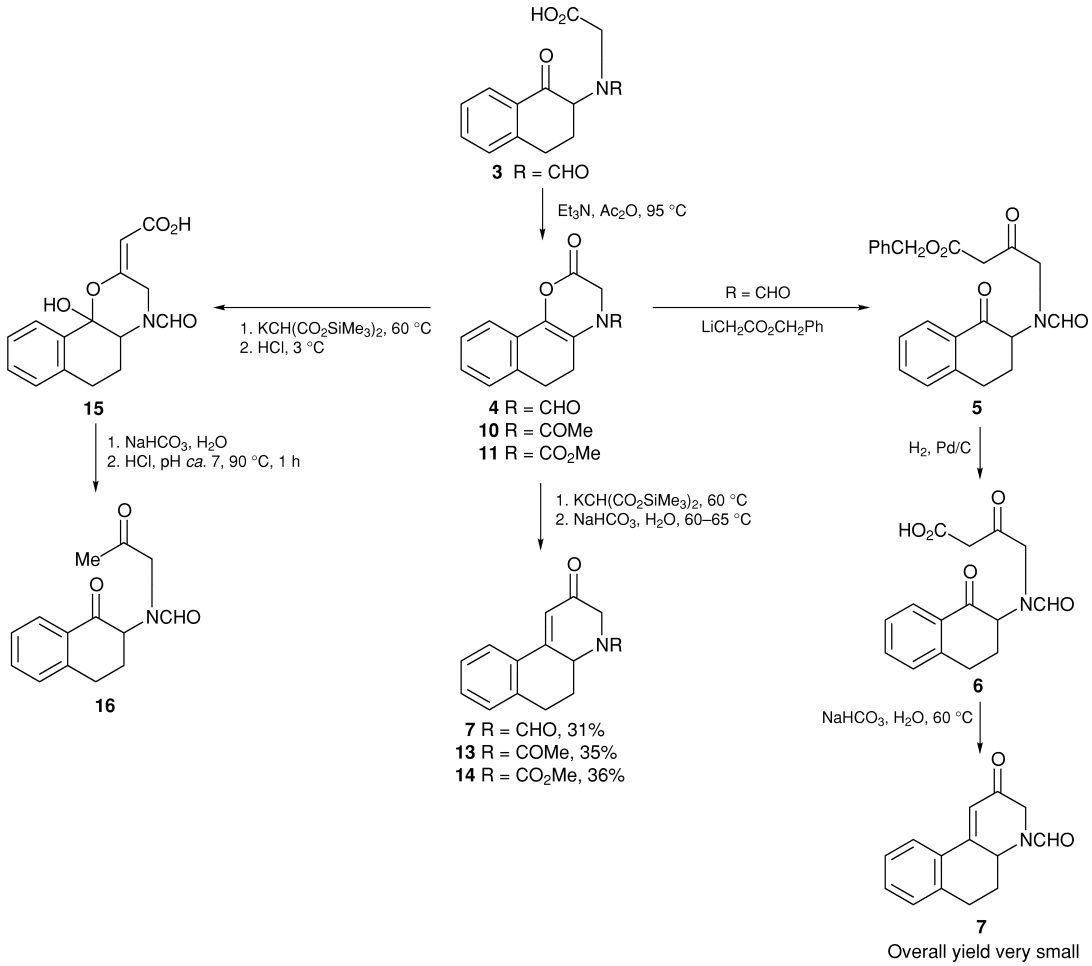

Scheme 1

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