A Simplified Route to a Key Intermediate in the Synthesis of the Chinese Nootropic Agent Huperzine A

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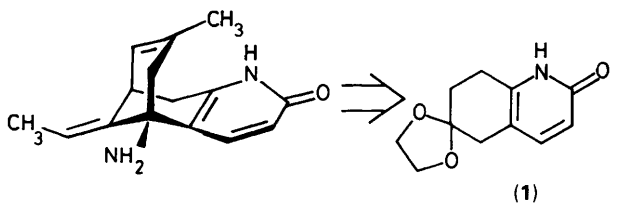
An efficient one-pot, three-component process for the preparation of 2-pyridones from a carbonyl compound, ammonia, and methyl propiolate has been found which provides ready access to a key intermediate in the synthesis of huperzine A.

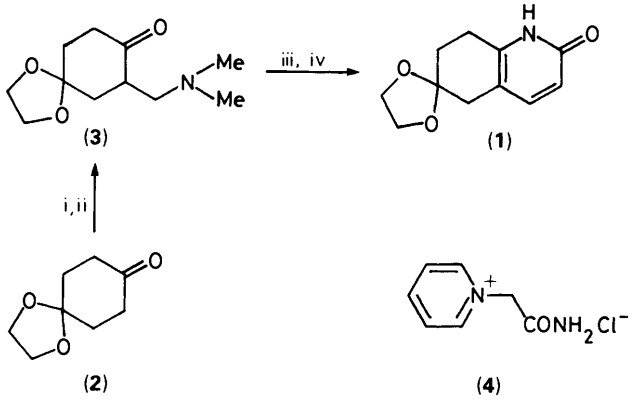
Recently we have reported on the total synthesis of the alkaloid natural product huperzine A. This compound is available in small quantities from the clubmoss *Huperzia serrata* (Thunb.) Trev. = *Lycopodium serratum* Thunb., a Chinese folk medicine. Huperzine A has been shown to improve memory in aged individuals suffering from various forms of memory impairment including Alzheimer's dementia.[1] Due to the difficulty of obtaining huperzine A from natural sources, an efficient

synthesis of this material is of considerable importance. While our reported synthesis is fairly efficient,[2] additional improvements are being sought in order to facilitate scale-up procedures. In particular, the route reported in the earlier publication for the preparation of the fused-ring pyridone intermediate (**1**) is somewhat lengthy and requires the use of several expensive reagents (phenylselenyl chloride and palladium hydroxide).



(**1**)

Accordingly, we have examined several alternate routes to the pyridone (**1**) which are detailed herein. The first of these was based upon an old procedure first reported in the German literature.[3] The Mannich base (**3**) of the monoethylene ketal of cyclohexane-1,4-dione (prepared from the enol silyl ether and *N*,*N*-dimethylmethyleneammonium chloride)[4] was refluxed with the pyridinium salt (**4**) generated from α-chloroacetamide and pyridine (Scheme 1). This simple protocol delivered the

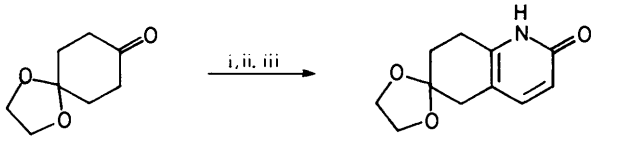


(**3**) (**1**) (**2**) (**4**)

Scheme 1. *Reagents and conditions:* i, TMSCl, Et_3N, DMF; ii, $Me_2\overset{+}{N}{=}CH_2$, Cl^-; iii, (**4**), MeOH, reflux, 2 h; iv, DMF, HOAc, heat, 2 h.

fused ring pyridone (**1**) in 9% yield (Scheme 1). This reaction, which represents an extension of a pyridone synthesis first described by Thesing and Müller in 1957, most likely proceeds by an initial Michael addition reaction of the anion formed from the pyridinium salt (**4**) on the unsaturated ketone derived from the Mannich base (**3**) by loss of dimethylamine. Heating in dimethyl formamide (DMF) with acetic acid then results in ring closure and loss of pyridine.

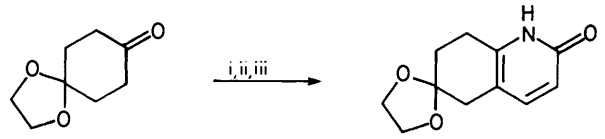
The next route tried consisted of refluxing the pyrrolidine enamine of (**2**) with α-chloroacrylamide in dioxane as solvent (Scheme 2). This process was studied rather extensively and many variations in reactions conditions were sampled. Unfortunately, a maximum yield of only 11% of (**1**) could be isolated.



(**2**) (**1**)

Scheme 2. *Reagents and conditions:* i, pyrrolidine, *p*-TsOH, PhH, reflux, 3h; ii, $CH_2{=}C(Cl)CONH_2$, dioxane, reflux, 12 h; iii, H_2O, reflux, 10 h.

A variation on this theme was tried next in which the anion of (**2**) was reacted first with methyl *cis*-3-chloroacrylate[5] (Scheme 3). The crude product of the addition–elimination step was then

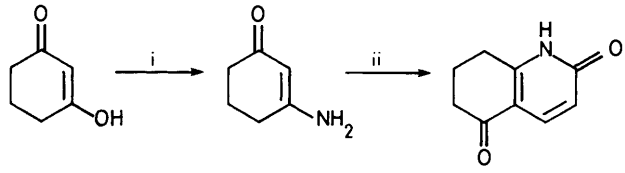


(**2**) (**1**)

Scheme 3. *Reagents and conditions:* i, LDA, THF, −78 °C; ii, $ClCH{=}CHCO_2Me$, 5 h at −78 °C then warm to room temp.; iii, NH_4OH, 48 h, room temp.

exposed to aqueous ammonium hydroxide to provide the desired pyridone (**1**) in 22% yield. While this process was clearly an improvement over the former two, it was still not adequate for our needs.

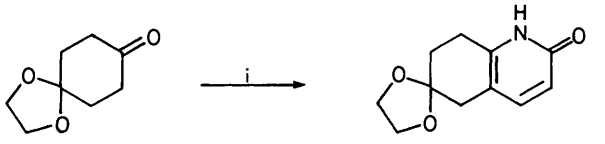
While 2-pyridones have been assembled from enamino ketones by reaction with methyl propiolate (Scheme 4),[6] this



Scheme 4. *Reagents and conditions:* i, NH_3, H_2; ii, $HC{\equiv}CCO_2Me$, heat.

reaction would appear to be somewhat special in view of the resonance stabilization of the enamino group. No examples of the application of this process to simple carbonyl compounds as opposed to 1,3-diketones had to our knowledge ever been described.

Nonetheless, barring these concerns the ketone (**2**), an ammonia saturated solution of methanol, and methyl propiolate were placed in a Parr reactor and heated with stirring at 100 °C (internal pressure reached 200 psi) for 10 h (Scheme 5). After cooling, the solvent was removed and the residue

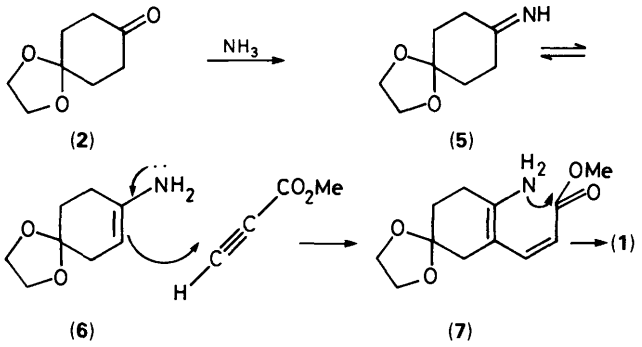


(**2**) (**1**)

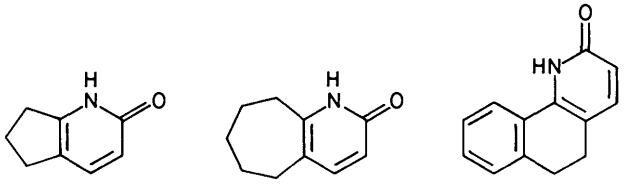
Scheme 5. *Reagents and conditions:* i, $HC{\equiv}CCO_2Me$, NH_3, MeOH, 100 °C, 10 h.

flash chromatographed on silica gel to deliver the crystalline pyridone (**1**) in 70% yield! This good yielding, one-step process is clearly superior to the five-step protocol published earlier which proceeds in at best 45% overall yield.[2]

The pyridone yielding process of Scheme 5 is to be further contrasted with Speckamp's enamino ketone based approach in that prior formation and isolation of the enamine derivative is not required. Presumably, the reaction course involves initial condensation of the ammonia with the ketone (**2**) to provide an imine (**5**) which reacts *via* its tautomeric enamine form (**6**) in a Michael fashion with the methyl propiolate. Subsequent attack of nitrogen on the ester carbonyl group then completes pyridone ring formation (Scheme 6).[7] Extension of the method to cyclopentanone,[8] cycloheptanone, and α-tetralone provided 2-pyridones (**8**), (**9**), and (**10**), respectively in good yield.



Scheme 6.



Given the relatively common occurrence of the pyridone moiety in nature,[9] and in view of the utility of this heterocycle as a diene component in the Diels–Alder reaction,[10] we believe the present three component, one-pot process should find ready applicability in organic synthesis. A representative procedure follows.

Experimental

Pyridone (**1**).—To a solution of cyclohexane-1,4-dione monoethylene ketal (3 g, 0.019 mol) in 60 ml of ammonia saturated methanol contained in a Parr reaction vessel was added 3.2 g (0.038 mol) of methyl propiolate. The reaction mixture was heated with stirring at 100 °C for 10 h. During this time the internal pressure reached a maximum of 200 psi. After cooling, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography with 15% MeOH–ethyl acetate as the eluant to afford 2.78 g (70%) of the pyridone (**1**) as a light-yellow solid: m.p. (dec.) above 250 °C; ν_{max} 2 930, 1 639, 1 620, 1 554, 1 506, 1 464, 1 446, 1 379, 1 269, 1 130, 1 097, 1 061, 1 014, 949, 837, and 696 cm^{-1}; δ_H ($CDCl_3$) 12.56 (1 H, br, s), 7.14 (1 H, d, *J* 9.3 Hz), 6.40 (1 H, d, *J* 9.3 Hz), 4.02 (4 H, s), 2.89 (2 H, t, *J* 6.6 Hz), 2.71 (2 H, s), and 1.93 (2 H, t, *J* 6.6 Hz); δ_C ($CDCl_3$) 165.0, 143.4, 141.8, 117.3, 111.9, 107.3, 64.6, 36.2, 30.1, and 25.7; *m/z* 207 (M^+), 164, 134, 86, 69, and 57; HRMS (Found: 207.0896. Calc. for $C_{11}H_{13}NO_3$: 207.0895).

Acknowledgements

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