Acylnitrilium ion initiated spiroannulations in heterocycle synthesis: an application directed toward the total synthesis of the *Lycopodium* alkaloid (±)-serratine

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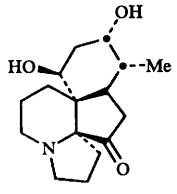
A concise synthesis of a prospective tricyclic intermediate *en route* to the *Lycopodium* alkaloid (±)-serratine is described which involves the consecutive utilization of an acylnitrilium ion initiated spiroannulation and intramolecular Michael addition.

Alkaloids belonging to the *Lycopodium* family have remained an enduring challenge for efficient chemical synthesis. Although a number of these alkaloids possess intriguing pharmacology,[1] the ongoing interest in total synthesis would appear to be stimulated at least as much by the structural complexity of these substances and the attendant strategic imperatives for skeletal construction. Despite the continuing activity in this area, relatively little progress has been reported with regard to the synthesis of the irregular alkaloids belonging to the serratinane subgroup. With the exception of (±)-serratinine **1**[2] and the corresponding 8-deoxy derivative,[3] each of which have been synthesized once previously, no completed syntheses of alkaloids in this category have appeared.



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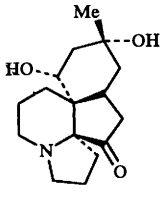

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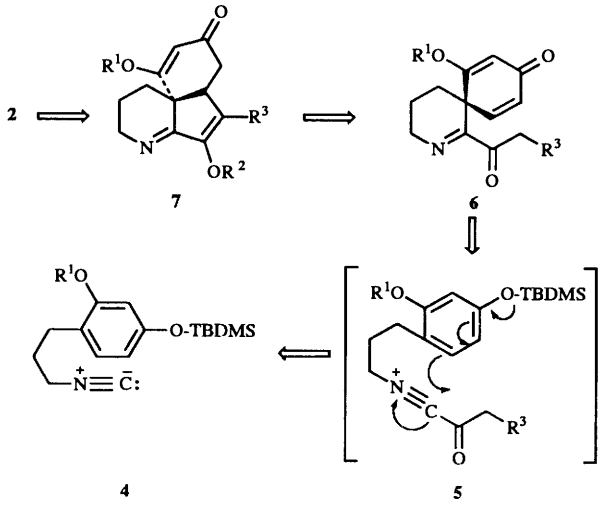
We have previously shown that cyclizations initiated by acylnitrilium ions can provide access to a wide variety of heterocyclic systems.[4] In addition, we have demonstrated that this heteroannulation method can facilitate unusually efficient syntheses of the erythrinane skeleton[5] as well as the *Orchidaceae* alkaloid dendrobine.[6] Our interest in (±)-serratine **2**[7] was stimulated by the possibility that the essential tricyclic core of this *Lycopodium* alkaloid could be derived from a simple arene nucleus *via* sequential utilization of an acylnitrilium ion initiated spiroannulation and intramolecular 1,4-addition (Scheme 1). In this communication we report the successful implementation of this strategy.

The key isonitrile **4a** that was employed in this investigation was prepared by sequential formylation/dehydration (i, EtOCHO; ii, $POCl_3$–Et_3N, THF, 0 °C) of 3-[4-(*tert*-butyldimethylsiloxy)-2-methoxyphenyl]propanamine **3**. Acylation of **3** with the acyl chlorides **8a–f** (CH_2Cl_2, room temp.) was found to proceed in close analogy with previous examples[4–6] to provide the intermediate α-ketoimidoyl chlorides **9a–f** in *ca.* quantitative yield (NMR). Exposure of **9a–f** to $AgBF_4$ (1.5 equiv.) in $ClCH_2CH_2Cl$–CH_2Cl_2 (1:1) at −70 °C resulted, without exception, in the *immediate* precipitation of AgCl signalling the generation of the corresponding transient



Scheme 1

acylnitrilium ions. In contrast to most previously reported examples,[4–6] cation interception by the pendant carbon centred nucleophile did not occur rapidly at −78 °C. Optimally, preformed solutions of the reactive intermediates were subsequently warmed to −20 °C and maintained at this temperature for 20 h to induce spirocyclization. By way of this procedure the spiro[cyclohexa-2,5-diene-1,3′-(3′,4′,5′,6′-tetrahydropyridin)]-ones **6a–e** could be obtained on a preparative scale in 80–84% purified yield. It is of interest that cyclization of **9f** under an analogous set of reaction conditions resulted in only a modest yield (55%) of the desired spirocyclic intermediate **6f**. Presumably, the enhanced propensity of the β-ketosulfonyl moiety of **9f** to enolize was responsible for the degradation of spirocyclization efficiency in this instance. In this connection, the successful conversion of **9b–f** to **6b–f** constitutes the first reasonably comprehensive series of acylnitrilium ion cyclizations involving substrates that possess readily enolizable sites α- to the carbonyl function.

The predisposition of the spirocyclic intermediates **6b–e** to undergo intramolecular 1,4-addition was subsequently examined. Several attempts to convert **6c** into the corresponding tricycle **10a** *via* free-radical intermediates under reductive conditions (Bu_3SnH)[8] led only to the production of **6b** albeit in excellent (>90%) yield. By way of contrast, base-mediated cyclization of **6d** and **6e** gave more encouraging results. In an initial experiment, exposure of **6d** to NaH (1.1 equiv.) in DMF [0 °C (10 min)→25 °C (8 h)] followed by protonolysis (AcOH, 1.1 equiv.) afforded the unstable α-phenylthioketone **10b** in good yield. We suspected that the observed instability of **10b**

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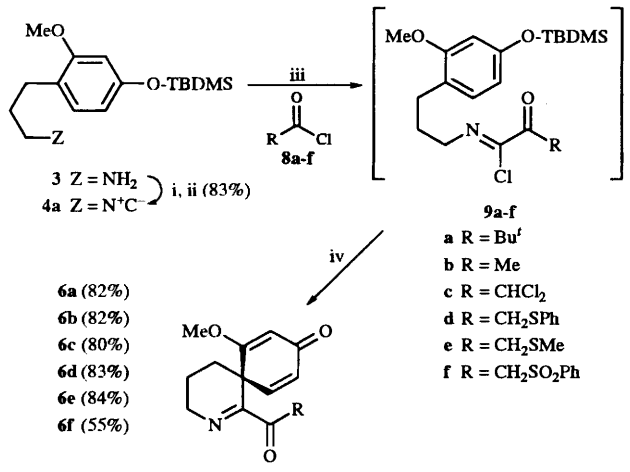
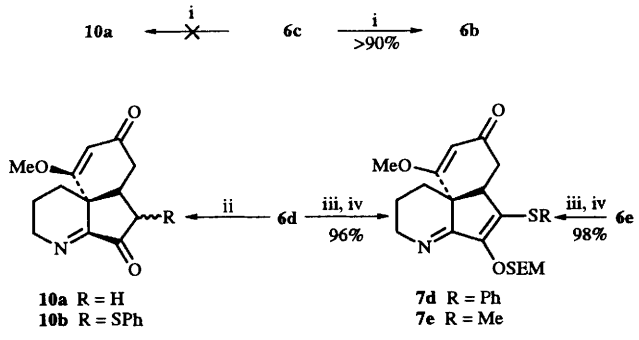


i, EtOCHO, 25 °C; ii, $POCl_3$–Et_3N, THF, 0 °C; iii, CH_2Cl_2 or $CDCl_3$, 25 °C; iv, $AgBF_4$ (1.5 equiv.), $ClCH_2CH_2Cl$–CH_2Cl_2, −78 °C→−20 °C

might be a consequence of initial tautomerization involving the sensitive α-keto imine moiety. Accordingly, this bifunctional array was derivatized by alkylative protection *in situ*. To this end, cyclization of **6d** (NaH–DMF, 0 °C→25 °C) followed by enolate interception [SEM-Cl (1.1 equiv.), −60 °C→25 °C] furnished the tricyclic imine **7d** in 96% purified yield. Cyclization of **6e** in a similar manner provided **7e** in 98% yield.‡ Although **6f** could be induced to undergo an analogous cyclization, **6b** proved resistant toward base-mediated intramolecular Michael addition.



Reagents and conditions: i, Bu_3SnH, PhH, reflux; ii, NaH (1.1 equiv.), DMF, 0 °C→25 °C; iii, NaH (1.1 equiv.), DMF, 0 °C→25 °C; iv, SEM-Cl (1.1 equiv.), −60 °C→25 °C

At least three features of the preceding cyclizations are worthy of comment. These studies have shown that a variety of functionally varied α-keto imidoyl chlorides can serve as effective precursors to synthetically viable acylnitrilium ions; intramolecular capture of the enolates derived from **6d** and **6e** by the least substituted (and most electrophilic) cyclohexadienone β-carbon is completely selective; and the *in situ* enolate trapping protocol gives rise to the functionally well differentiated intermediates **7d** and **7e**. Studies directed toward the stereodefined annulation of the serratinane D ring and the completion of the synthesis of (±)-serratine **2** are underway. Progress in these areas will be disclosed in due course.

‡ The tricyclic imines **7d** and **7e** were found to undergo *slow* decomposition at room temperature but could be stored indefinitely in a benzene matrix under argon at −20 °C.

Experimental

2-Methoxy-2′-methylsulfanylacetylspiro[cyclohexa-2,5-diene-1,3′-(3′,4′,5′,6′-tetrahydropyridin)]-4-one 6e

An oven-dried NMR tube fitted with a rubber septum was purged with Ar and then charged with compound **4a** (0.305 g, 1.0 mmol), methylsulfanylacetyl chloride (137 mg, 1.1 mmol) and $CDCl_3$ (1.0 cm^3). The coupling reaction, monitored by NMR, was found to be complete after 3 h. After the volatile components had been removed under reduced pressure from the imidoyl chloride, the crude material was diluted with CH_2Cl_2 (4.5 cm^3), and 1,2-dichloroethane (4.5 cm^3) and cooled to −78 °C. The solution was then added dropwise *via* a cannula to a stirred solution of $AgBF_4$ (0.50 mol dm^{-3} in 1,2-dichloroethane; 3.0 cm^3, 1.5 mmol, 1.5 equiv.) and CH_2Cl_2 (3.0 cm^3) maintained at −70 °C. After the addition, the reaction mixture was stirred for 1 h at −70 °C and then maintained at −20 °C for 20 h whereupon it was quenched with 10% aqueous $KHCO_3$ (30 cm^3). The resulting white–grey slurry was subsequently filtered through a pad of Celite. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (4 × 20 cm^3). The combined organic layer and extracts were washed with brine (65 cm^3), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue on Florisil (50% ethyl acetate–CH_2Cl_2 for elution) provided **6e** as a viscous oil (0.235 g, 84%); $\delta_H(CDCl_3)$ 6.59 (d, *J* 9.9, 1 H, C*H*=CH), 6.23 (dd, *J* 9.9, 1.6, 1 H, C*H*=CH), 5.63 (d, *J* 1.2, 1 H, CH_3OC=C*H*), 4.15–4.07 (m, 1 H, *H*CHN=C), 3.95–3.84 (m, 1 H, HC*H*N=C), 3.67 (s, 3 H, OCH_3), 3.62 (d, *J* 13.2, 1 H, O=CC*H*HSCH$_3$), 3.47 (d, *J* 13.2, 1 H, O=CCH*H*–SCH$_3$), 2.14 (m, 1 H, *H*CH=CH_2), 1.97 (s, 3 H, SCH_3) and 1.86–1.73 (m, 3 H, HC*H*=CH_2); $\delta_C(CDCl_3)$ 191.7 (C), 187.3 (C), 177.8 (C), 161.7 (C), 144.6 (CH), 128.3 (CH), 101.7 (CH), 55.9 (CH_3), 50.0 (CH_2), 45.4 (C), 36.7 (CH_2), 33.7 (CH_2), 18.0 (CH_2) and 15.6 (CH_3); ν_{max}(film)/cm^{-1} 3365, 2958, 2930, 2857, 1693, 1658, 1637, 1592, 1539, 1504, 1464, 1392, 1362, 1324, 1286, 1260, 1224, 1179, 1105, 1017, 980, 945, 841 and 798; *m*/*z* (EI) 279, 191, 164, 137, 77 and 61 [Found (HRMS): M^+, 279.0929. Calc. for $C_{14}H_{17}NO_3S$: M^+, 279.0929].

10-Methoxy-6-methylsulfanyl-5-[(2′-trimethylsilylethoxy)-methoxy]-2,3,5,6,6a,7-hexahydro-1*H*-indeno[1,7a-*b*]pyridin-8-one 7e

To a slurry of NaH (12 mg, 0.5 mmol, 1.1 equiv.) in DMF (3.0 cm^3) at 0 °C was added dropwise over 10 min a solution of **6e** (127 mg, 0.45 mmol) in DMF (6.0 cm^3). The resulting mixture was allowed to warm to 25 °C over several hours. After 12 h the mixture was cooled to −60 °C and SEM-Cl (84 mg, 88 μl, 0.5 mmol, 1.1 equiv.) was added to it over 1 min. The reaction mixture was allowed to warm to 25 °C over 2 h whereupon it was poured into water (20 cm^3) and extracted with ethyl acetate (4 × 10 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure after which the residue was purified by chromatography on Florisil (50% ethyl acetate–CH_2Cl_2 for elution) to provide **7e** as a viscous oil (0.180 g, 98%). This compound was found to deteriorate over a short amount of time if not stored at −20 °C in a matrix of benzene. Silica gel and alumina were found to be incompatible with this compound: $\delta_H(CDCl_3)$ 5.45 (d, *J* 5.9, 1 H, OC*H*H–O), 5.33 (s, 1 H, CH_3OC=C*H*), 5.04 (d, *J* 5.9, 1 H, OCH*H*O), 3.78–3.67 (m, 3 H, OC*H*HCH$_2$), 3.63 (s, 3 H, OCH_3), 3.58 (m, 1 H, OCH*H*CH$_2$), 3.03 (d, *J* 5.5, 1 H, C*H*CH$_2$), 2.84 (d, *J* 17.7, 1 H, CHC*H*H), 2.58 (dd, *J* 17.7, 6.3 Hz, 1 H, CHCH*H*), 2.46 (s, 3 H, SCH_3), 2.13–1.86 (m, 3 H, *H*CH), 1.58–1.40 (m, 1 H, HC*H*), 0.92–0.79 [m, 2 H, C*H*$_2$Si(CH$_3$)$_3$] and −0.03 (s, 9 H, 3 CH_3); $\delta_C(CDCl_3)$ 195.1 (C), 178.7 (C), 166.8 (C), 150.9 (C), 131.6 (C), 101.5 (CH), 93.5 (CH_2), 47.4 (CH), 47.3 (C), 33.3 (CH_2), 28.1 (CH_2), 20.0 (CH_2), 18.2 (CH_2), 15.4 (CH_3) and −1.4 (CH_3);

ν_{max}(film)/cm^{-1} 2949, 1660, 1603, 1506, 1438, 1416, 1346, 1249, 1217, 1148, 1100, 1039, 1007, 948, 859, 836 and 758; *m*/*z* (EI) 409, 366, 336, 308, 231, 117, 73, 57 and 43 [Found (HRMS): M^+, 409.1743. Calc. for $C_{20}H_{31}NO_4SSi$: M^+, 409.1743].

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