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An access to some functionalized azocine derivatives

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Abstract

The syntheses, from readily accessible 3-alkyl-4-methoxy-1,3,4,5-tetrahydropyridine **1**, of functionalized 1,6,7,8-tetrahydroazocine **7** and 1,2,7,8-tetrahydroazocine **9** are reported. © 2000 Published by Elsevier Science Ltd.

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Eight-membered nitrogen heterocycles constitute an important class of compounds, especially in view of their pharmacological properties.[1] These derivatives are generally difficult to obtain[2] and, accordingly, relatively few methods are available for their preparation. This is especially the case of highly functionalized derivatives or derivatives suitable for further chemoselective reactions.

We recently reported[3] that tetrahydropyridines **1** (Scheme 1, R^1 and R^2 = alkyl group) are good precursors of 3-alkyl 1,6-dihydropyridines **2** which were too unstable to be isolated, but could be trapped with common dienophiles to produce isoquinuclidine derivatives **3**. As a continuation of our studies concerning the reactivity of derivatives **1**, we now report that the reaction of these reactive intermediates with ethyl propiolate gave highly functionalized azocines heterocycles **4** in high yield.

Dihydropyridinium salt **5** (Scheme 2) was obtained from the corresponding pyridinium salt following well-established procedures.[4] The reaction of salt **5** with sodium methoxide in methanol gave adduct **1a** in good yield.[3] Adduct **1a**, when treated with ethyl propiolate in refluxing acetonitrile, gave the functionalized 1,6,7,8-tetrahydroazocine[5] **7** in 90% yield. It is believed that azocine formation involves an initial [2+2] cycloaddition[3,6] reaction between the enamine **1a** to give the cyclobutene intermediate **6**, followed by an electrocyclic ring opening to give the azocine system.

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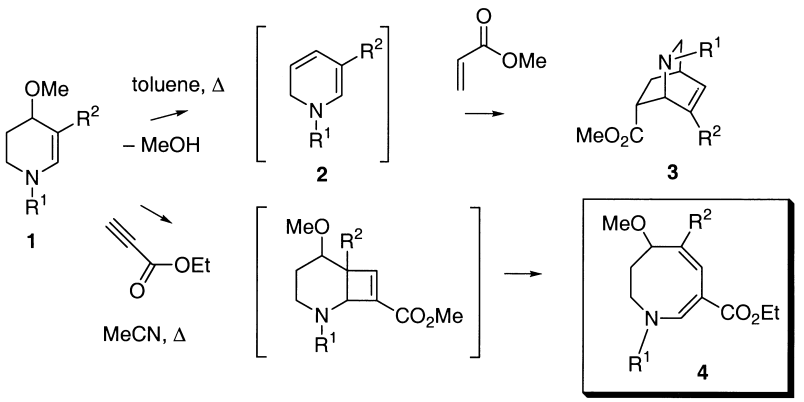
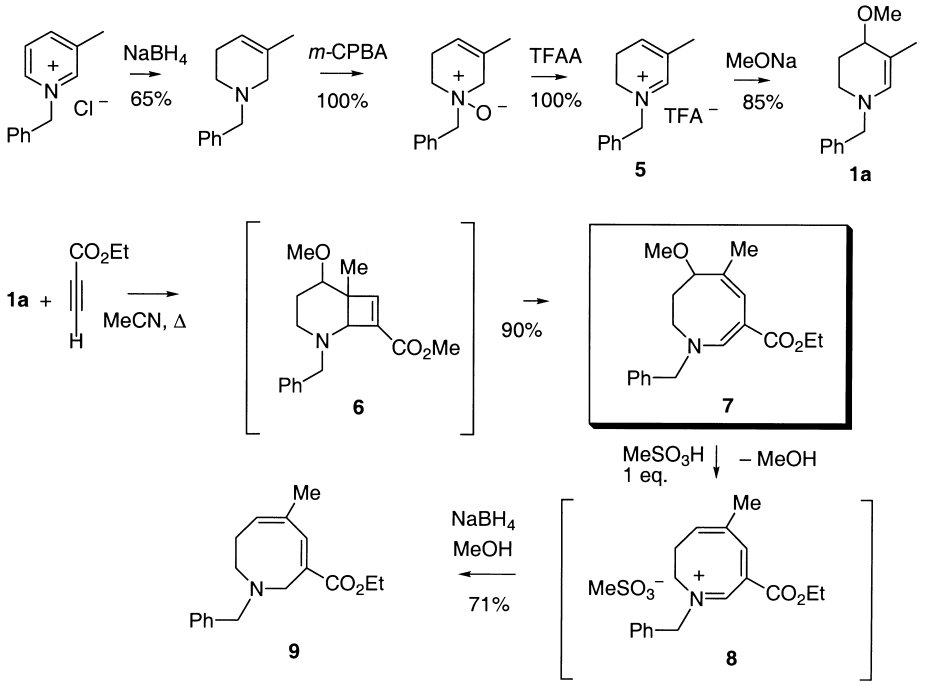


Scheme 1.



Scheme 2.

Azocine **7** was treated with 1 equivalent of methanesulfonic acid to give, presumably, an iminium salt (**8**, not isolated). Reduction of this salt with $NaBH_4$ in methanol finally gave 1,2,7,8-tetrahydroazocine **9**.

Further studies to extend this approach to other azocines are currently in progress.

Acknowledgements

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5. Selected data for **7**: mp 112°C (ether–heptane); IR (cm^{-1}) 2981, 2931, 1685, 1605, 1577, 1453, 1421, 1364, 1291, 1251, 1196; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.03 (1H, m), 1.29 (3H, t, $J = 7.1$ Hz), 1.57 (1H, tt, $J = 12.6$, 5 Hz), 1.64 (3H, d, $J = 1.6$, 1.8 Hz), 2.85 (1H, m), 3.24 (3H, s), 3.60 (1H, m), 4.00–4.40 (3H, m), 4.20 (2H, q, $J = 7.1$ Hz), 6.28 (1H, m), 7.23–7.40 (5H, m), 7.61 (1H, s); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 14.74, 16.82, 21.12, 44.98, 57.07, 59.82, 61.51, 79.21, 95.26, 122.39, 127.78, 128.18, 128.93, 131.33, 136.61, 148.99, 169.88; HRMS calcd for $C_{19}H_{25}NO_3$: 315.1835; found: 315.1842; anal. calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44; O, 15.22; found: C, 72.07; H, 8.24; N, 4.53; O, 15.03.
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