A Synthesis of Isocryptolepine

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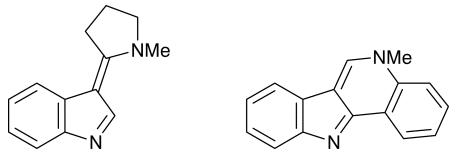
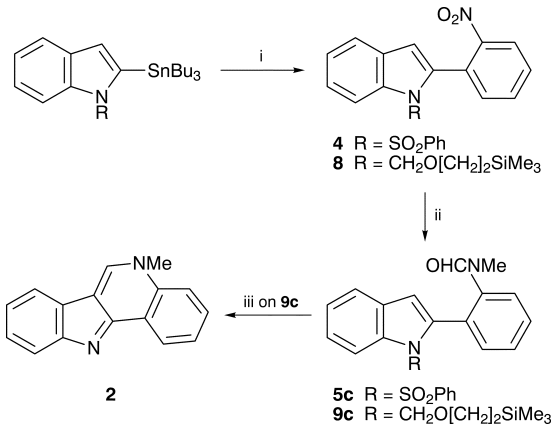
A synthesis of isocryptolepine **2** is described the key steps in which are (a) palladium(0) coupling to an indol-2-ylstannane and (b) an intramolecular Vilsmeier reaction to construct the 3-aminoalkylidene-3*H*-indole unit of the alkaloid.

More than ten alkaloids have been isolated and characterised[1] from *Cryptolepis sanguinolenta* (Lindl.) Schlechter (Asclepiadaceae), a West African plant to the extracts of which have been attributed a variety of medicinal properties.[2] The alkaloids are mainly tetracyclic substances containing two nitrogen atoms and an indole nucleus, and include examples of indolo[3,2-*b*]quinoline, indolo[2,3-*b*]-quinoline and indolo[3,2-*b*][1]benzazepine ring systems. Our previous work[3] on 3-aminoalkylidene-3*H*-indoles such as **1** attracted us to the indolo[3,2-*c*]quinoline structure of isocryptolepine[1d] **2**, which incorporates such a unit.



1 **2** Isocryptolepine

Compound **1** results from treatment of indole with 1-methylpyrrolidin-2-one and phosphorus oxychloride, in which the usual 3-aminoalkylidene-3*H*-indole Vilsmeier intermediate is not hydrolysed and thus is an isolable, stable compound. We describe here a short synthesis of isocryptolepine which utilises Vilsmeier methodology in an intramolecular sense to produce the 3-aminoalkylidene-3*H*-indole unit of the alkaloid. There have been two[5,6] previous syntheses of isocryptolepine, one predating its isolation from a natural source, both of which employ completely different strategies to that described here.



Scheme 1 *Reagents and conditions*: i, $PdCl_2(PPh_3)_2$, 2-$BrC_6H_4NO_2$, DMF, 110 °C (60% **4**), $Pd(PPh_3)_4$, 2-$IC_6H_4NO_2$, THF, reflux (98% **8**); ii, H_2, Pd–C, AcOH, $CHCl_3$, room temp. and pressure, (90%) then AFA, THF, −20 °C (95%) then NaH, THF, room temp. then MeI (72% **5c**); H_2, Pd–C, EtOH, room temp. and pressure (98%) then AFA, THF, −20 °C (95%) then NaH, THF, room temp. then MeI (95% **9c**); iii, EtOH, H_2SO_4 (10%), reflux (50% **2**)

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Palladium(0)-catalysed couplings of 2-tributylstannyl *N*-protected indoles with 2-halonitrobenzenes gave the 2-(*ortho*-nitrophenyl)indoles **4** and **8**. Each of these was converted by comparable sequences involving nitro group reduction, *N*-formylation and *N*-methylation into the formamides **5c** and **9c**, respectively, each now ready for intramolecular Vilsmeier closure (Scheme 1).

All efforts to achieve cyclisation with the *N*-phenylsulfonyl protected indole **5c** produced complex mixtures in which at best an ion for the desired product could be detected by mass spectrometry. Reasoning that an alternative indole-*N*-blocking group which would not deactivate the ring to electrophilic attack was required, we examined the SEM-protected formamide **9c**. Ring closure was effected by treating **9c** with sulfuric acid in ethanol, the polar product **2** being isolated after chromatography in 50% yield and having spectroscopic properties identical with those reported[1d,f] for isocryptolepine.

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Techniques used: IR, UV, ^1H and ^{13}C NMR, mass spectrometry

References: 16

Schemes: 2

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References cited in this synopsis

1 (*a*) E. Gellért, Raymond-Hamet and E. Schlittler, *Helv. Chim. Acta*, 1951, **34**, 643; (*b*) A. N. Tackie, M. H. M. Sharaf, P. L. Schiff, G. L. Boye, R. C. Crouch and G. E. Martin, *J. Heterocycl. Chem.*, 1991, **28**, 1429; (*c*) A. N. Tackie, G. L. Boye, M. H. M. Sharaf, P. L. Schiff, R. C. Crouch, T. D. Spitzer, R. L. Johnson, J. Dunn, D. Minick and G. E. Martin, *J. Nat. Prod.*, 1993, **56**, 653; (*d*) J.-L. Pousset, M.-T. Martin, A. Jossang and B. Bodo, *Phytochemistry*, 1995, **39**, 735; (*e*) A. Paulo, E. T. Gomes and P. J. Houghton, *J. Nat. Prod.*, 1995, **58**, 1485; (*f*) M. H. M. Sharaf, P. L. Schiff, A. N. Tackie, C. H. Phoebe and G. E. Martin, *J. Heterocycl. Chem.*, 1996, **33**, 239; (*g*) M. H. M. Sharaf, P. L. Schiff, A. N. Tackie, C. H. Phoebe, R. L. Johnson, D. Minick, C. W. Andrews, R. C. Crouch and G. E. Martin, *J. Heterocycl. Chem.*, 1996, **33**, 789; (*h*) K. Cimanga, T. De Bruyne, L. Pieters, M. Claeys and A. Vlietinck, *Tetrahedron Lett.*, 1996, **37**, 1703.
2 For a summary see refs 1*c* and 1*e*.
4 M. Harris and J. A. Joule, *J. Chem. Res.*, 1978, (*S*) 25; (*M*) 0470; D. I. Bishop, I. K. Al-Khawaja and J. A. Joule, *J. Chem. Res.*, 1981, (*S*) 361; (*M*) 4279; D. I. Bishop, I. K. Al-Khawaja, F. Heatley and J. A. Joule, *J. Chem. Res.*, 1982, (*S*) 159; (*M*) 1766; I. K. Al-Khawaja, R. L. Beddoes, D. I. Bishop, R. J. Cernik, J. A. Joule and O. S. Mills, *J. Chem. Res.*, 1984, (*S*) 296; (*M*) 2738; M. Salas, I. K. Al-Khawaja, M. J. Thomas and J. A. Joule, *J. Chem. Res.*, 1988; (*S*) 218; (*M*) 1666.
5 W. O. Kermack and N. E. Storey, *J. Chem. Soc.*, 1950, 607.
6 S. V. Dubovitskii, O. S. Radchenko and V. L. Novikov, *Russ. Chem. Bull.*, 1996, **45**, 2656.