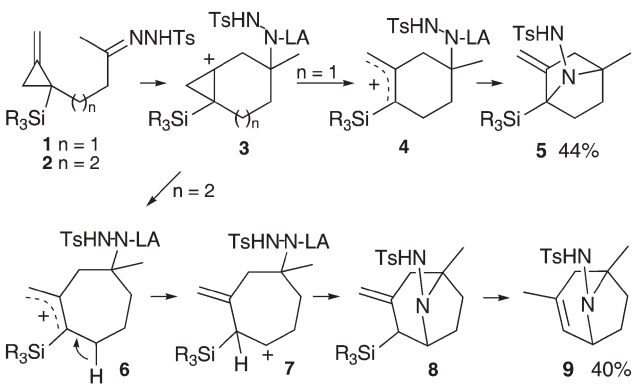
Lewis acid mediated *endo*-cyclisation of trimethylsilylmethylenecyclopropyl imines—a stereoselective route to indolizidines

Suvi Rajamaki and Jeremy D. Kilburn*

Received (in Cambridge, UK) 10th December 2004, Accepted 20th January 2005
First published as an Advance Article on the web 2nd February 2005
DOI: 10.1039/b418476a

Lewis acid mediated *endo*-cyclisation of trimethylsilylmethylenecyclopropyl imines provides a stereoselective route to indolizidines *via* a novel cascade sequence.

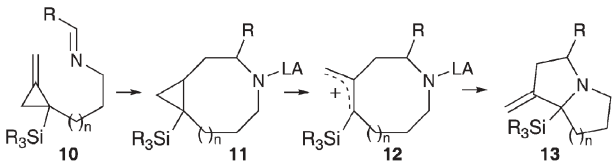
Methylenecyclopropane derivatives continue to be widely utilized in new synthetic methodology due to their considerable reactivity.[1] In recent years Lewis acid mediated reactions of methylenecyclopropanes have been extensively investigated.[2–6] We have reported that trialkylsilylmethylenecyclopropanes (which can be viewed as strained allylsilanes) react with aldehydes and ketones, mediated by Lewis acids, to give a range of tetrahydrofuran products.[3,5–8] In order to extend this chemistry to the synthesis of N-heterocycles we recently described studies of *exo*-cyclisations onto the C=N double bond of a hydrazone.[4] Cyclisation of hydrazone **1** gave the anticipated product **5**, following the general mechanistic pathway identified for analogous reactions with aldehydes and ketones,[3] involving cationic intermediates **3** and **4**. However, with the longer chain analogue **2** the major product **9** results from a 1,2 hydride transfer followed by intramolecular trapping of the resulting cation **7** by the hydrazinyl anion and protodesilylation of **8** (Scheme 1).



Scheme 1

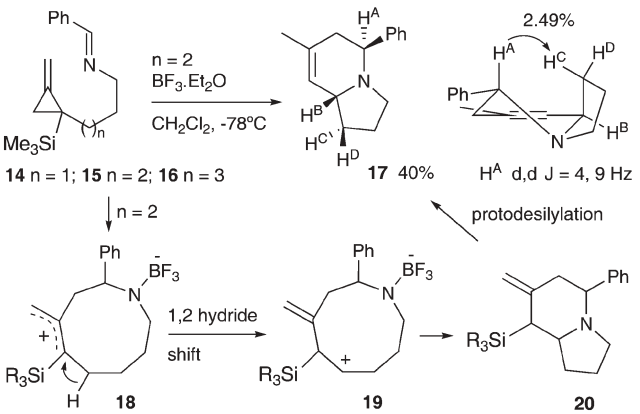
An alternative mode of cyclisation would involve *endo*-cyclisation of a methylenecyclopropyl imine, *e.g.* **10**, and subsequent trapping of the allyl cation **12** by the *endo*-cyclic nitrogen, leading to bicyclic amines **13**, with natural product-like structures (Scheme 2).

To investigate this possibility we have studied the Lewis acid mediated cyclisations of a range of trimethylsilylmethylenecyclopropyl imines.† Unfortunately neither imine **14** or **16** gave any



Scheme 2

cyclised products when treated with a range of Lewis acids.[9] Imine **15**, however, did react cleanly when treated with $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at −78 °C, to give indolizidine **17** as a single diastereoisomer in 40% yield[10] (Scheme 3).

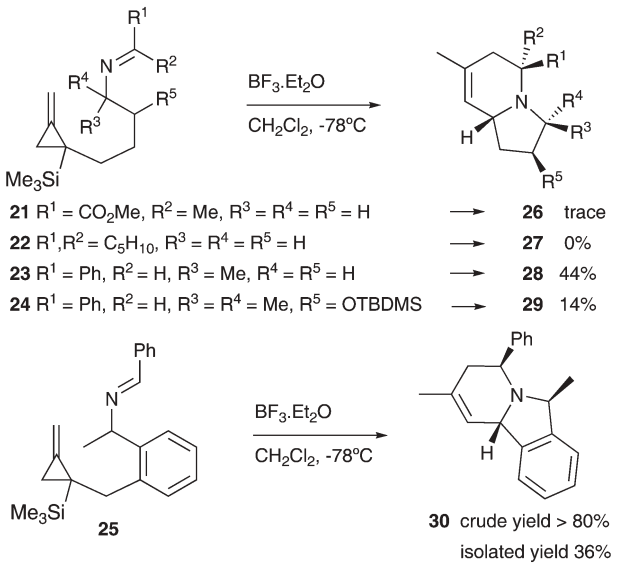


Scheme 3

The rather low yield of isolated product can in part be attributed to the partial hydrolysis of the imine under the reaction conditions, giving the starting amine as the only other isolable product from the reaction. $BF_3{\cdot}Et_2O$ proved to be the best Lewis acid of those investigated ($In(OTf)_3$ gave comparable yields to $BF_3{\cdot}Et_2O$, but $TiCl_4$ and $SnCl_4$ led only to decomposition) and use of $EtNO_2$ as solvent did not improve the yield. The structure of **17** was established by NMR studies and the stereochemistry was confirmed by consideration of coupling constants and NOE experiments, with a strong NOE from H^A to H^C, but no enhancement between H^A and H^B.

The formation of **17** was unexpected but can be rationalized by the mechanism depicted in Scheme 3. Thus initial *endo*-cyclisation onto the imine gives the cyclopropyl cation which rearranges to the allylic cation **18** as expected. A 1,2 hydride shift leads to a β-silyl cation **19**, which is then trapped by the aminyl anion. Finally, *in situ* protodesilylation of **20** gives the observed product.

*jdk1@soton.ac.uk



Scheme 4

This pathway is in fact identical to that previously described for the cyclisation of hydrazone **2** (Scheme 1), and in both cases presumably direct trapping of the allyl cation (**6** or **18**) is impeded by the rigidity of this intermediate and consequential poor orbital overlap, whereas the β-silyl cations (**7** or **19**) can more readily adopt a conformation allowing trapping by the aminyl anion.

With the successful cyclisation of **15** established, the cyclisations of a range of other imines **21**–**25** were investigated (Scheme 4). Not surprisingly neither of the imines **21** nor **22**, which are prone to tautomerisation, cyclised effectively. Imine **23** gave bicycle **28** in a slightly improved 44% yield (compared with **17**), but imine **24** featuring a *gem*-dimethyl group only gave the corresponding bicycle **29** in 14% yield. In both cases, however, the products were isolated as single diastereoisomers with complete control of the additional chiral centre. Gratifyingly the most constrained of the imines, **25**, gave a very clean reaction and inspection of the ^{1}H NMR spectrum of the crude reaction mixture revealed that the product **30** was formed in >80% yield. The product, however, proved to be rather unstable on silica, and consequently gave a reduced yield after chromatography. In all cases the structures of the products were unequivocally established by NMR studies,[10] with consideration of coupling constants and NOE experiments used to assign the stereochemistry.

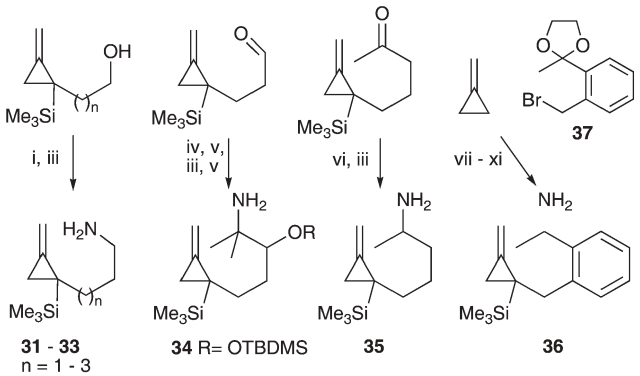
In conclusion the *exo*-cyclisations of a number of trimethylsilylmethylenecyclopropyl imines have been investigated. Although the yields are not high for several of the substrates, the reaction is highly stereoselective and provides a simple route to structurally complex indolizidine products. There is clearly scope for improvement using more reactive imine equivalents such as acyl iminiums and such studies are currently underway in our laboratory.

We thank the EPSRC for supporting this work (GR/N23424/01) with a studentship for SR.

Suvi Rajamaki and Jeremy D. Kilburn*
School of Chemistry, University of Southampton, Southampton, UK SO17 1BJ. E-mail: jdk1@soton.ac.uk; Fax: +44 023 80596805; Tel: +44 023 80593596

Notes and references

† Amines **31**–**36** were prepared from known methylenecyclopropane derivatives[3,4] (Scheme 5) and stirred with the appropriate carbonyl compound in the presence of molecular sieves, to give the corresponding imines **14**–**16** and **21**–**25**.



Scheme 5 *Reagents and conditions:* i) MsCl, Et_3N; ii) NaCN, DMSO, 60 °C; iii) $LiAlH_4$, Et_2O; iv) 2-nitropropane, DBU; v) TBDMSOTf, 2,6-lutidine; vi) NH_2OH; vii) BuLi, -78 °C, then TMSCl; viii) BuLi, -78 °C, **37**; ix) HCl, acetone–H_2O; x) $PhCH_2ONH_2$, pyridine; xi) Zn, AcOH.

1 (*a*) P. Binger and T. Schmidt, in *Houben-Weyl*, ed. A. de Meijere, Thieme, Stuttgart, 1997, **E17c**, 2217–2294; (*b*) A. Brandi and A. Goti, *Chem. Rev.*, 1998, **98**, 589–635; (*c*) I. Nakamura and Y. Yamamoto, *Adv. Synth. Catal.*, 2002, **344**, 111; (*d*) A. Brandi, S. Cicchi, F. M. Cordero and A. Goti, *Chem. Rev.*, 2003, **103**, 1213.
2 K. Miura, M. Takasumi, T. Hondo, H. Saito and A. Hosomi, *Tetrahedron Lett.*, 1997, **38**, 4587.
3 (*a*) G. L. N. Peron, J. Kitteringham and J. D. Kilburn, *Tetrahedron Lett.*, 1999, **40**, 3045; (*b*) G. L. N. Peron, J. Kitteringham and J. D. Kilburn, *Tetrahedron Lett.*, 2000, **41**, 1615; (*c*) G. L. N. Peron, D. Norton, J. Kitteringham and J. D. Kilburn, *Tetrahedron Lett.*, 2001, **42**, 347; (*d*) L. Patient, M. Berry and J. D. Kilburn, *Tetrahedron Lett.*, 2003, **44**, 1015.
4 L. Patient, M. Berry, S. J. Coles, M. B. Hursthouse and J. D. Kilburn, *Chem. Commun.*, 2003, 2552.
5 (*a*) M. Shi and B. Xu, *Org. Lett.*, 2002, **4**, 2145; (*b*) M. Shi, Y. Chen, B. Xu and J. Tang, *Tetrahedron Lett.*, 2002, **43**, 8019; (*c*) M. Shi, L.-X. Shao and B. Xu, *Org. Lett.*, 2003, **5**, 579; (*d*) M. Shi and B. Xu, *Org. Lett.*, 2003, **5**, 1415; (*e*) M. Shi and B. Xu, *Tetrahedron Lett.*, 2003, **44**, 3839; (*f*) M. Shi, B. Xu and J.-W. Huang, *Org. Lett.*, 2004, **6**, 1175.
6 (*a*) M. Lautens and W. Han, *J. Am. Chem. Soc.*, 2002, **124**, 6312; (*b*) M. Lautens, W. Han and J. H.-C. Liu, *J. Am. Chem. Soc.*, 2003, **125**, 4028.
7 For thermally promoted cycloadditions of dialkoxy substituted methylenecyclopropanes with aldehydes and imines, see: S. Yamago and E. Nakamura, *J. Org. Chem.*, 1990, **55**, 5553.
8 For transition metal promoted cycloadditions of methylenecyclopropanes with aldehydes and imines, see: (*a*) I. Nakamura, B. H. Oh, S. Saito and Y. Yamamoto, *Angew. Chem. Int. Ed.*, 2001, **40**, 1298; (*b*) B. H. Oh, I. Nakamura, S. Saito and Y. Yamamoto, *Tetrahedron Lett.*, 2001, **42**, 6203.
9 For review of allyl metal addition to imines see: R. Bloch, *Chem. Rev.*, 1998, **98**, 1407.
10 Selected data for **17**: δ_H (400 MHz; $CDCl_3$) 1.83 (3H, s, CH_3), 1.90 (1H, m, CH_AH_B), 2.07 (2H, m, CH_2), 2.31–2.42 (2H, m, CH_AH_B, CH_CH_D), 2.77 (1H, dd, J = 14, 8 Hz, CH_CH_D), 3.04 (1H, dt, J = 12, 8 Hz, CH_EH_F), 3.47 (1H, dt, J = 12, 8 Hz, CH_EH_F), 4.02 (1H, dd, J = 9, 4 Hz, CH), 4.27 (1H, br s, CH), 5.57 (1H, s, CH), 7.40–7.50 (5H, m, Ar); δ_C (100 MHz, $CDCl_3$) 21.8(2), 22.7 (3), 29.8 (2), 36.0 (2), 52.7 (2), 61.7 (1), 62.7 (1), 117.6 (1), 127.8 (1), 129.7 (1), 129.8 (1), 133.6 (0), 135.0 (0); HRMS (ES) $C_{15}H_{19}N$ $[M + H]^+$ requires 213.1517, found 213.1513; selected data for **28**: δ_H (300 MHz, $CDCl_3$) 1.11 (3H, d, J = 7 Hz, CH_3), 1.73 (1H, m, CH_AH_B), 1.82 (3H, s, CH_3), 1.92 (1H, dq, J = 12, 7 Hz, CH_CH_D), 2.21–2.28 (2H, m, CH_AH_B, CH_EH_F), 2.34 (1H, dq, J = 12,

6 Hz, CH_CH_D), 2.93 (1H, dd, J = 18, 12 Hz, CH_EH_F), 3.53 (1H, dquintet, J = 8, 7 Hz, CH), 3.98 (1H, dd, J = 4, 12 Hz, CH), 4.43 (1H, br s with fine coupling, CH), 5.54 (1H, br s, CH), 7.43–7.50 (3H, m, Ar), 7.55–7.58 (2H, m, Ar); δ_C (75 MHz, $CDCl_3$) 19.0 (3), 22.6 (3), 30.7 (2), 31.6 (2), 35.8 (2), 62.9 (1), 63.2 (1), 64.8 (1), 117.1 (1), 128.4 (1), 129,7 (1), 130.0 (1), 133.8 (0), 134.0 (0); HRMS (ES) $C_{16}H_{22}N$ $[M + H]^+$ requires 228.1747, found 228.1741; selected data for **29**: δ_H (300 MHz, $CDCl_3$) 0.05 (3H, s, Me), 0.07 (3H, s, Me), 0.09 (9H, s, Me), 1.00 (3H, s, Me), 1.15 (3H, s, Me), 1.45 (1H, ddd, J = 9, 10, 12 Hz, CH_AH_B), 1.73 (3H, s, Me), 2.19 (1H, ddd, J = 8, 9, 12 Hz, CH_AH_B), 2.23 (1H, d, J = 18 Hz, CH_CH_D), 2.41 (1H, dd, J = 18, 7 Hz, CH_CH_D), 3.53 (1H, t with fine coupling, J = 9 Hz, CH), 3.87 (1H, dd, J = 10, 8 Hz, CH), 4.24 (1H, d, J = 7 Hz, CH), 5.43 (1H, br s, CH), 7.17 (1H, m, Ar), 7.25–7.35 (4H, m, Ar); δ_C (75 MHz, $CDCl_3$) −4.6 (3), −4.0 (3), 18.3 (3), 19.2 (0), 24.7 (3), 26.2 (3), 27.1 (3), 32.5 (2), 38.5 (2), 50.4 (1), 51.8 (1), 62.8 (0), 79.1 (1), 126.3 (1), 126.9 (1), 127.5 (1), 128.4 (1), 129.5 (0), 145.5 (0); HRMS (ES) $C_{23}H_{37}NOSi$ $[M + H]^+$ requires 372.2717, found 372.2722; selected data for **30**: δ_H (400 MHz, $CDCl_3$) 1.36 (3H, d, J = 7 Hz, CH_3), 1.70 (3H, s, CH_3), 2.18 (1H, dd, J = 17, 5 Hz, CH_AH_B), 2.58 (1H, dd, J = 17, 7 Hz, CH_AH_B), 3.81 (1H, dd, J = 7, 5 Hz, CH), 4.22 (1H, q, J = 7 Hz, CH), 5.07 (1H, br s, CH), 5.73 (1H, br s with fine coupling, CH), 7.15–7.38 (9H, m, Ar); δ_C (100 MHz, $CDCl_3$) 19.7 (3), 23.2 (3), 34.3 (2), 58.6 (1), 61.6 (1), 62.7 (1), 119.7 (0), 122.5 (1), 122.7 (1), 127.4 (1), 127.46 (1), 127.54 (1), 127.7 (1), 128.1 (1), 128.4 (0), 128.5 (0), 128.8 (1), 129.9 (1), 132.4 (1), 132.8 (0); HRMS (ES) $C_{20}H_{21}N$ $[M + H]^+$ requires 276.1747, found 276.1747.