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Asymmetric synthesis of 2-substituted piperidines using a multi-component coupling reaction: rapid assembly of (*S*)-coniine from (*S*)-1-(1-phenylethyl)-2-methyleneaziridine

Jerome F. Hayes,[a] Michael Shipman*[b] and Heather Twin[b]

[a] *GlaxoSmithKline, Old Powder Mills, Tonbridge, Kent, UK TN11 9AN*
[b] *School of Chemistry, University of Exeter, Exeter, Devon, UK EX4 4QD. E-mail: m.shipman@exeter.ac.uk; Fax: +44 1392 263434; Tel: +44 1392 263469*

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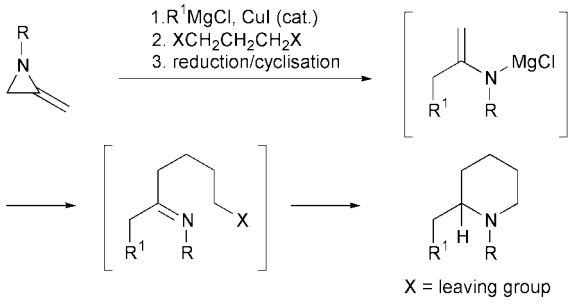
(*S*)-Coniine is made using a reaction which assembles the piperidine ring by the sequential formation of four new chemical bonds and installs the C-2 stereogenic centre with high levels of diastereocontrol (90% de).

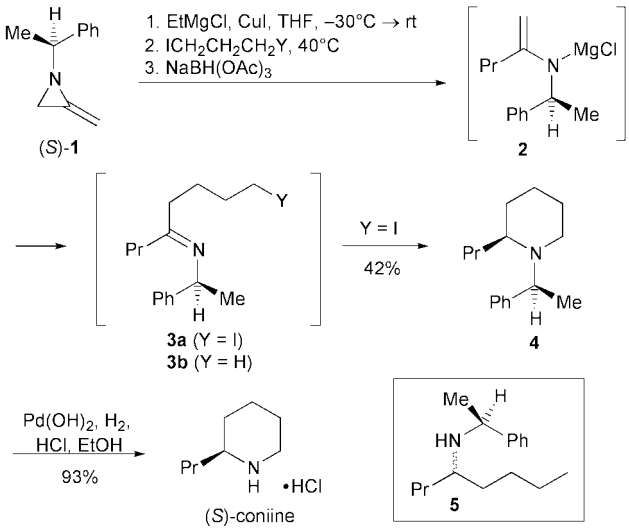
We recently devised a new type of multi-component coupling reaction using 2-methyleneaziridines.[1] Ring opening of this stable and readily accessible heterocyclic system with a Grignard reagent in the presence of copper(I) iodide furnishes a metalloenamine in a regiocontrolled fashion by formation of a carbon–carbon bond. This methodology was originally used to make simple ketones by further *in situ C*-alkylation of the metalloenamine followed by imine hydrolysis. We imagined that by suitable modification, this multi-component coupling reaction could be used to assemble 2-substituted piperidines, important structural motifs in organic chemistry.[2] Our basic approach to these piperidines is depicted in Scheme 1. Alkylation of the initially generated metalloenamine with a 1,3-difunctionalised electrophile ($XCH_2CH_2CH_2X$) followed by reduction of the resultant imine and *in situ* cyclisation was anticipated to lead directly to the piperidine ring system by the sequential formation of two carbon–carbon bonds, one carbon–nitrogen bond and a carbon–hydrogen bond in a single transformation. Furthermore, since 2-methyleneaziridines bearing chiral, nonracemic substituents on nitrogen are known,[3] we hoped that control of the absolute stereochemistry at C-2 of the piperidine ring may be possible by effecting a diastereocontrolled reduction of the intermediate imine using an enantiomerically pure 2-methyleneaziridine starting material.[4] In this communication, we report the successful realisation of these concepts as demonstrated by the enantiocontrolled synthesis of the hemlock alkaloid (*S*)-coniine in a very concise fashion.[5]

We chose to use (*S*)-1-(1-phenylethyl)-2-methyleneaziridine **1** for this study as it is readily accessible in two steps from (*S*)-1-phenylethylamine in good overall yield.[3b] In addition to bearing a group suitable for effecting stereocontrolled reduction of the imine double bond, it possesses the additional attribute that the PhCHMe group can ultimately be removed by cleavage of the benzylic C–N bond. Treatment of (*S*)-**1** with EtMgCl and copper(I) iodide, then 1,3-diiodopropane, and finally sodium triacetoxyborohydride results in the production of piperidine **4** in 42% yield as essentially a single diastereomer (97% de) after chromatography on neutral alumina (Scheme 2).†‡ Slightly larger amounts of the (2*R*)-diastereomer can be detected {(2*S*):(2*R*) = 95:5} by GC analysis prior to chromatography. Piperidine **4** (97% de) was obtained in identical yield using sodium borohydride as the reducing agent, however, the crude diastereomeric ratio was slightly lower {(2*S*):(2*R*) = 88:12}. Metalloenamine **2** must be added to a solution of excess 1,3-diiodopropane (5 equiv.) in THF (inverse addition) to obtain these chemical yields. In this way, additional intermolecular reactions of imine **3a** are suppressed. Using a normal addition mode, quantities of *N*-(1-phenylethyl)-4-decylamine (21%) were produced as a result of displacement of the second iodide by excess ethylmagnesium chloride present in the reaction mixture. Further hydrogenolysis of **4** provides (*S*)-(+)-coniine hydrochloride in 93% yield whose physical and spectroscopic data were in good agreement with those reported previously {mp 212 °C (lit. mp 217 °C[6]); $[\alpha]_D^{25}$ +8.1 (*c* 0.6, EtOH) [lit. $[\alpha]_D^{28}$ + 5.8 (*c* 0.43, EtOH)][6]}. The enantiomeric excess of the synthetic (*S*)-coniine was established to be ⩾95% ee by preparation of the corresponding Mosher amide using (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride.§

Interestingly, when 1-iodopropane was used as the electrophile in this multi-component coupling reaction, amine **5** was isolated in 49% yield as a 58:42 mixture of diastereomers after reduction with $NaBH_4$, indicating that the presence of the remote iodine atom has a significant influence on the diastereoselectivity of the imine reduction. To account for these differences, we suggest that imine **3a** cyclises to iminium ion **6** prior to reduction (Scheme 3). The high level of stereochemical control seen in favour of the (2*S*)-diastereomer can be



Scheme 1 Planned one-pot piperidine synthesis.



Scheme 2 Asymmetric synthesis of (*S*)-coniine.

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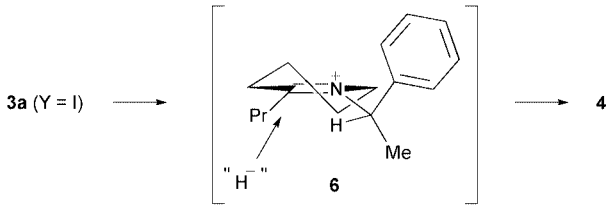

Scheme 3 Rationalisation of diastereoselectivity.

rationalised by assuming this iminium cation adopts a conformation in which allylic 1,3-strain is minimised by projecting the hydrogen atom of the benzylic carbon towards the propyl group, with subsequent hydride addition from the least hindered *Re*-face. In contrast, acyclic imine **3b** has much greater conformation freedom and is reduced in a non-selective fashion to **5**.

In conclusion, we have devised a very short and stereoselective synthesis of the piperidine alkaloid (*S*)-coniine by way of a multi-component coupling reaction. The key step forms four new chemical bonds (>80% efficiency for each) and is highly stereoselective (90% de). Since we have demonstrated that a variety of Grignard reagents (alkyl, aryl, benzyl) ring open 2-methyleneaziridines to metalloenamines,[1] this method should provide a rapid entry to a wide variety of enantiomerically enriched 2-substituted piperidines.

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Notes and references

† All new compounds have been fully characterised using standard spectroscopic and analytical methods.

‡ *Experimental procedure*: To CuI (72 mg, 0.378 mmol) in THF (6 ml) at −30 °C was added EtMgCl (2.0 M in THF, 2.36 ml, 4.72 mmol) dropwise. After stirring for 10 min, (*S*)-**1** (300 mg, 1.88 mmol) in THF (3 ml) was added. The reaction mixture was allowed to warm up to room temperature and stirred for 24 h. This mixture was then added to diiodopropane (1.09 mL, 9.49 mmol) in THF (2 ml) at 0 °C. A reflux condenser was fitted and the mixture was heated to 40 °C for 18 h. On cooling, the resultant dark green mixture was added to a solution of sodium borohydride (214 mg, 5.66 mmol) in glacial acetic acid (4 ml) at 10 °C. After 2 hours, water (6 ml) was slowly added, then 2 M NaOH (4 ml) and EtOAc (4 ml). After 10 min, the mixture was extracted with EtOAc then washed with aq. NH_4Cl (2 × 20 ml), aq. $NaHCO_3$ (2 × 20 ml) and brine (2 × 20 ml). The organic layer was dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Column chromatography on alumina (0.1% MeOH in CH_2Cl_2) gave **4** (183 mg, 42%, 97% de) as a pale yellow oil. $[\alpha]_D^{26}$ +14.0 (*c* 0.86, $CHCl_3$); ν_{max} (neat) 2929, 2797, 1445 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.45–7.19 (5H, m), 4.02 (1H, q, *J* 6.7 Hz), 2.75–2.73 (1H, m), 2.41–2.36 (1H, m), 2.25–2.17 (1H, m), 1.75–1.25 (10H, m, 5 × CH_2), 1.26 (3H, d, *J* 6.7 Hz), 0.94 (3H, t, *J* 7.2 Hz); δ_C (100.9 MHz, $CDCl_3$) 146.4 (s), 128.0 (d), 127.5 (d), 126.2 (d), 56.8 (d), 55.7 (d), 45.1 (t), 31.0 (t), 29.6 (t), 25.8 (t), 22.7 (t), 18.9 (t), 14.7 (q), 14.6 (q); Observed: 231.1995 (M^+); $C_{16}H_{25}N$ requires 231.1987; Anal. calc. for $C_{16}H_{25}N$: C, 83.06; H, 10.89; N, 6.05%. Found: C, 83.15; H, 11.17; N, 5.89%.

§ *rac*-Coniine was made and used for comparison purposes.

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