Stereoselective synthesis of 2,4,5-trisubstituted piperidines by carbonyl ene and Prins cyclisations

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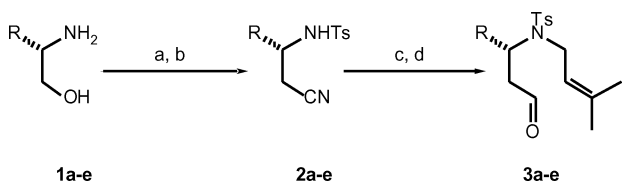
Cyclisation of aldehydes 3a–e catalysed by concentrated hydrochloric acid affords predominantly the all *cis* 2,4,5-trisubstituted piperidines 4a–e when the 2-substituent is small, while catalysis by $MeAlCl_2$ in refluxing chloroform gives the *trans* piperidines 5a–e with diastereomeric ratios of up to 99 : 1.

Piperidines are widely distributed throughout Nature[1] and are an important scaffold for drug discovery,[2] forming the core of many pharmaceuticals. Methods for their stereocontrolled synthesis are of continuing interest, driven by the wide variety of functionality and substitution patterns present in piperidine targets.[3]

Intramolecular carbonyl ene reactions present an attractive method for ring closure, leading to the formation of two contiguous stereocentres with an often high degree of stereocontrol.[4] We recently published a route to 3,4-disubstituted piperidines which had a carbonyl ene reaction as the key ring-closing step.[5] The Brønsted acid-catalysed reaction at low temperatures strongly favoured a *cis* relationship between the two new stereocentres, while the Lewis acid-catalysed reaction at elevated temperatures gave the corresponding *trans* product.

We now describe our efforts towards extending this approach to the synthesis of 2,4,5-trisubstituted piperidines, using cyclisation precursors derived from α-amino alcohols. Such trisubstituted piperidines are of particular interest as they form the core of a number of important natural products, including the pseudodistomin family of anti-tumour compounds. These were isolated by Kobayashi[6] from a marine tunicate, and have recently been the focus of synthetic attention.[7]

The cyclisation precursors were readily synthesised from commercially available α-amino alcohols *via* a procedure involving a one-carbon homologation by cyanide, Scheme 1. Bis tosylation of the α-amino alcohols **1a**–**e** followed by displacement of the *O*-tosyl group by sodium cyanide in DMF proceeded smoothly and in good yield to afford the *N*-tosyl-β-amino nitriles **2a**–**e**. These were alkylated with prenyl bromide before being reduced by Dibal-H to the β-amino aldehyde cyclisation precursors **3a**–**e** in excellent overall yield. The β-amino aldehydes could be readily chromatographed and were unchanged on storing for several weeks at −20 °C.



1a-e **2a-e** **3a-e**

Scheme 1 Synthesis of cyclisation precursors. (a) TsCl, pyridine, CH_2Cl_2, 25 °C, 68–85%; (b) NaCN, DMF, 25 °C, 70–90%; (c) $BrCH_2CH{=}C(CH_3)_2$, Cs_2CO_3, CH_3CN, 25 °C, 82–98%; (d) Dibal-H, CH_2Cl_2, −78 °C, 83–97%.

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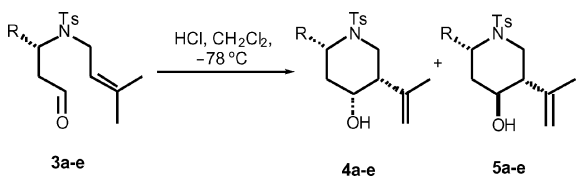
Cyclisation of **3a**–**e** was first studied using our optimised Brønsted acid conditions† of three equivalents of concentrated hydrochloric acid in CH_2Cl_2 at −78 °C.[5] In our earlier work, these conditions were found to favour formation of the kinetic product, in which there is a *cis* relationship between the hydroxyl and isopropenyl substituents. The results are summarised in Table 1.

In all cases, of the four possible stereoisomers, only two, piperidines **4** and **5**, were observed, in excellent combined yields. In the case of β-amino aldehydes with sterically undemanding 2-substituents, entries 1–3, the diastereoselectivity was moderate to good, although it decreased markedly in the case of **3d** and **3e** with very bulky 2-substituents. Traces (typically <5%) of chloride side-products were often isolated, arising from the addition of HCl across the double bond in **4** or **5**. These were generally separable by chromatography, but could also be converted back to the alkenes **4** and **5** by stirring with aqueous ammonia in THF.

The major diastereomer was confirmed as the all *cis* piperidine **4** by single crystal X-ray analysis of **4c**, Fig. 1.‡ Formation of this product can be rationalised by considering two factors. Firstly, there is a strong preference for the 2-substituent to adopt an axial disposition in the chair-like transition state, thus avoiding the pseudo A[1,3] strain with the sulfonamide; this stereochemical preference in *N*-acyl and *N*-sulfonamido piperidines has been shown to be pronounced in a number of cases.[9] The second factor

Table 1 Cyclisations of **3a**–**e** with HCl



3a-e **4a-e** **5a-e**

Entry	Aldehyde	R	**4** : **5**[a]	Yield (%)[b]
1	**3a**	Me	78 : 22	70 (22)
2	**3b**	Bn	94 : 6	70 (3)
3	**3c**	^{i}Pr	80 : 20	75 (19)
4	**3d**	^{t}Bu	47 : 53	42 (37)
5	**3e**	Ph	54 : 46	53 (40)

[a] Ratio determined by ^{1}H NMR of crude reaction mixtures. [b] Isolated yields of major (minor in parentheses) isomers following chromatography.

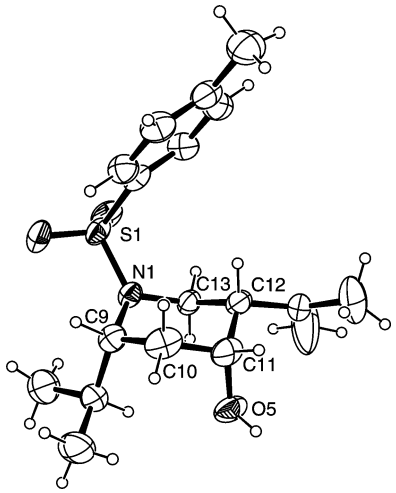


Fig. 1 ORTEP[8] representation of **4c**; ellipsoids drawn at the 30% probability level.

is the kinetic preference for the ene component and the aldehyde to adopt a *cis* relationship in the cyclisation transition state, as observed in our earlier work.[5] This *cis* relationship is achieved with the aldehyde lying in an axial position in the TS, and the more bulky ene component lying equatorial, Fig. 2. More bulky 2-substituents lead to a lowering of the diastereoselectivity as a result of increased 1,3-diaxial interactions with the aldehyde, forcing the aldehyde into an equatorial position to give **5**.

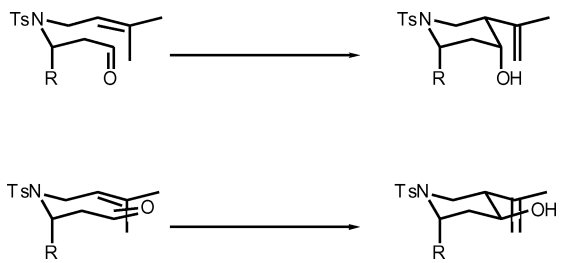


Fig. 2 Conformations leading to major and minor isomers in the Brønsted acid-catalysed reactions.

Turning to the Lewis acid-catalysed reaction, aldehydes **3a**–**e** were treated with one equivalent of methyl aluminium dichloride, which had been found to be the optimal Lewis acid in our earlier studies.[5] As in the Brønsted acid-catalysed reactions, only two of the four possible diastereomers were observed (Table 2). The

Table 2 Cyclisations with methyl aluminium dichloride[a]

Entry	Aldehyde	R	Temperature	**4** : **5**[b]	Yield (%)[c]
1	**3a**	Me	23	12 : 88	76 (5)
2	**3a**	Me	40	7 : 93	60 (4)
3	**3a**	Me	60	4 : 96	71 (4)
4	**3b**	Bn	23	10 : 90	61 (10)
5	**3b**	Bn	40	5 : 95	64 (5)
6	**3c**	^{i}Pr	40	2 : 98	82 (2)
7	**3d**	^{t}Bu	60	1 : 99	88 (1)
8	**3e**	Ph	60	2 : 98	80 (2)

[a] All reactions were performed using 1 equivalent of $MeAlCl_2$. [b] Ratio determined by ^{1}H NMR or HPLC of crude reaction mixtures. [c] Isolated yields of major (minor) isomers following chromatography.

stereoselectivities ranged from good to excellent, with the major diastereomer identified as **5** from a combination of NOE data and ^{1}H NMR coupling constants. Further confirmation came from single crystal X-ray analysis of **5a**, Fig. 3.§

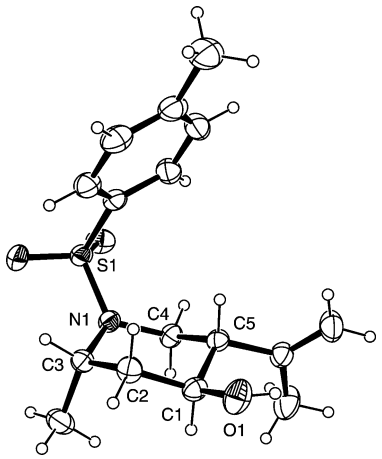


Fig. 3 ORTEP representation of **5a**; ellipsoids drawn at 30% probability level.

Under the equilibrating Lewis acidic conditions the thermodynamic product is favoured, in which the 4- and 5-substituents are equatorial, and the 2-substituent is axial to avoid the pseudo A^{1,3} strain with the sulfonamide. The increased 1,3-diaxial interactions present in the TS leading to **4** results in the equilibration to the thermodynamic product (Fig. 4) being facile even at room temperature, but improved ratios were obtained on heating at 40 or 60 °C (see, for example, entries 1–3).

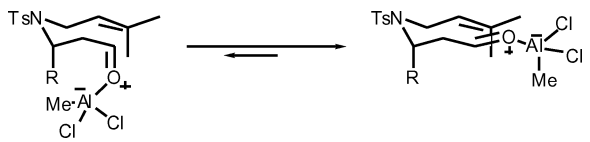
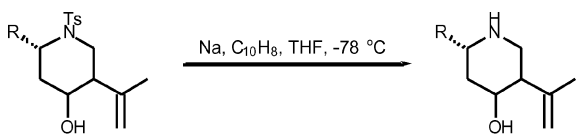


Fig. 4 Increased 1,3-diaxial interactions in Lewis acid-catalysed reaction favours the equatorial aldehyde.

Removal of the tosyl protecting group from a representative range piperidines was readily effected by stirring with sodium naphthalenide[10] for 5 min at −78 °C, Table 3. The crude yields of

Table 3 Tosyl removal



4 or **5** **6** or **7**

Entry	Tosyl piperidine	R	Product	Yield (%)
1	**4a**	Me	**6a**	54
2	**5a**	Me	**7a**	52
3	**4b**	Bn	**6b**	61
4	**5b**	Bn	**7b**	87
5	**5c**	^{i}Pr	**7c**	90
6	**5d**	^{t}Bu	**7d**	99
7	**5e**	Ph	**7e**	67

essentially pure piperidines were near quantitative in most cases, although compounds **4a** and **5a** in particular were difficult to handle and chromatograph due to their significant polarity and water solubility.

In summary, we have discovered a highly diastereoselective synthesis of 2,4,5-trisubstituted piperidines from simple acyclic precursors, which should have application to the synthesis of more complex molecules.

We thank the Engineering and Physical Sciences Research Council for the award of a studentship to C. A. M. C.

Notes and references

† Brønsted acid-catalysed cyclisation procedure. Preparation of (2*S**, 4*R**, 5*S**)-2-methyl-5-*iso*-propenyl-1-(*p*-toluenesulfonyl)piperidin-4-ol **4a**. Concentrated HCl (37%, 85 μL) was added to a solution of aldehyde **3a** (0.102 g, 0.33 mmol) in dichloromethane (10 mL) at −78 °C. The solution was stirred at −78 °C overnight, after which it was quenched by addition of water (10 mL). The aqueous phase was then extracted with dichloromethane (4 × 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to leave a colourless oil, which was purified by flash column chromatography (silica; ethyl acetate–hexane, 2 : 3, $R_f = 0.41$) to afford the piperidine **4a** (0.07 g, 70%) as a colourless thick oil. $[a]_D^{27}$ −3.6 (*c* 0.5 in $CHCl_3$); ($\nu_{max}(CHCl_3)/cm^{-1}$ 3525 (O–H), 2923 (C–H), 1644 (C=C aliphatic), 1598 (C=C aromatic), 1494 (C=C aromatic), 1451 (C=C aromatic), 1383 (C–H), 1336 (SO_2), 1305 (C–H), 1153 (SO_2), 1088 (C–O); δ_H(300 MHz, $CDCl_3$) 1.21 (3H, d, *J* 7.0), 1.63–1.67 (2H, envelope), 1.73 (3H, s), 1.80–1.82 (1H, m), 2.12 (1H, broad d, *J* 11.8), 2.40 (3H, s), 3.30 (1H, t, *J* 12.7), 3.62 (1H, dd, *J* 4.1, *J* 13.2), 3.99 (1H, d, *J* 2.6), 4.17–4.22 (1H, m), 4.69 (1H, s), 5.00 (1H, s), 7.27 (2H, d, *J* 8.1), 7.69 (2H, d, *J* 8.1); δ_C(75 MHz, $CDCl_3$) 18.9, 21.5, 22.8, 35.7, 37.6, 46.5, 47.4, 64.6, 112.3, 127.0, 129.7, 138.4, 143.0, 144.1; *m*/*z* (ES^+) 332 (100%, $[M + Na]^+$) [HRMS Found: $(M + Na)^+$ 332.1297. $C_{16}H_{23}NNaO_3S$ requires M, 332.1296]. Lewis acid-catalysed cyclisation procedure. Preparation of (2*R*, 4*S*, 5*S*)-2-*tert*-butyl-5-*iso*-propenyl-1-(*p*-toluenesulfonyl)piperidin-4-ol **5d**. Methyl aluminium dichloride (1 M solution in hexane, 480 μL, 0.48 mmol) was added to a solution of the aldehyde **3d** (0.168 g, 0.48 mmol) in chloroform (20 mL). The solution was stirred overnight at 60 °C, after which it was quenched by addition of water (20 mL). The aqueous phase was then extracted with dichloromethane (4 × 20 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to leave a colourless oil, that was purified by flash column chromatography (silica; ethyl acetate–petroleum ether, 1 : 2, $R_f = 0.22$) to afford piperidine **5d** as a colourless oil (0.147 g, 88%). $[a]_D^{19}$ −6.0 (*c* 0.3 in $CHCl_3$); (Found: C, 64.8; H, 8.1; N, 3.8. $C_{19}H_{29}NO_3S$ requires C, 64.9; H, 8.3; N, 4.0%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3498 (O–H), 2964 (C–H), 1646 (C=C aliphatic), 1598 (C=C aromatic), 1401, 1367 (C–H), 1336 (SO_2), 1084 (C–O); δ_H(300 MHz, $CDCl_3$) 1.05 (9H, s), 1.16–1.27 (1H, m), 1.30–1.38 (1H, m), 1.60 (3H, s), 1.71 (1H, s), 2.13 (1H, dd, *J* 4.4, *J* 14.0), 2.42 (3H, s), 3.04 (1H, dd, *J* 12.3, *J* 15.4), 3.79 (1H, dd, *J* 3.7, *J* 15.4), 3.91 (1H, dt, *J* 4.7, *J* 11.0), 3.99 (1H, d, *J* 8.1), 4.64 (1H, s), 4.89 (1H, s), 7.30 (2H, d, *J* 8.1), 7.73 (2H, d, *J* 8.1); δ_C(75 MHz, $CDCl_3$) 20.3, 21.6, 29.5, 31.7, 36.9, 46.2, 49.9, 61.4, 66.5, 113.9, 127.2, 129.9, 138.4, 142.6, 143.4; *m*/*z* (ES^+) 374 (100%, $[M + Na]^+$) [HRMS Found: $(M + Na)^+$ 374.1768. $C_{19}H_{29}NNaO_3S$ requires M, 374.1766]. Tosyl group removal procedure. Preparation of (2*S*, 4*S*, 5*S*)-2-benzyl-5-*iso*-propenylpiperidin-4-ol **7b**. To a solution of **5b** (0.099 g, 0.26 mmol) in tetrahydrofuran (1.5 mL) under nitrogen was added at −78 °C a freshly prepared solution of sodium naphthalenide (1.2 mL of a 1 M solution in tetrahydrofuran, 4.6 eq). After 5 min the reaction was quenched with methanol (0.4 mL), warmed up to room temperature, diluted with water (5 mL) and acidified to pH 1 with aqueous HCl (2 M). The aqueous phase was washed with diethyl ether (3 × 10 mL), basified to pH 9 with aqueous NaOH (2 M) and extracted with ethyl acetate (4 × 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford piperidine **7b** (0.052 g, 87%) as colourless crystals. Mp 119 °C; $[a]_D^{23}$ −49 (*c* 0.98 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3306 (O–H, N–H), 2917 (C–H), 1641 (C=C aliphatic), 1602 (C=C aromatic), 1493 (C=C aromatic), 1455 (C=C aromatic); 1090 (C–O); δ_H(300 MHz, $CDCl_3$) 1.63 (1H, ddd, *J* 5.1, *J* 9.9, *J* 12.9), 1.79 (3H, s), 1.91 (1H, broad s), 1.97 (1H, dt, *J* 3.7, *J* 12.9), 2.07–2.15 (1H, m), 2.72 (1H, dd, *J* 6.4, *J* 13.4), 2.87–2.94 (3H, envelope), 3.33–3.40 (1H, m), 3.99 (1H, dt, *J* 4.1, *J* 9.4), 4.94 (1H, s), 4.98 (1H, s), 7.16–7.33 (5H, m); δ_C(75 MHz, $CDCl_3$) 21.2, 37.0, 38.8, 43.7, 53.4, 54.4, 66.4, 113.3, 126.4, 128.7, 129.1, 139.6, 144.4; *m*/*z* (ES^+) 232 (65%, $[M + H]^+$), 214.1 (100, $[M - OH]^+$) [HRMS Found: $(M + H)^+$ 232.1700. $C_{15}H_{22}NO$ requires *M*, 232.1701].

‡ Crystal data for **4c**. $C_{18}H_{27}NO_3S$, $M = 337.47$, monoclinic, $a = 8.4757(1)$, $b = 19.2080(3)$, $c = 11.8021(2)$ Å, $U = 1902.87(5)$ Å^3, $T = 296$ K, space group $P2_1$, $Z = 4$, μ(Cu Kα) = 1.617 mm^{-1}, 5917 reflections measured, 5423 unique ($R_{int} = 0.0374$) which were used in all calculations. The final $wR(F_2)$ was 0.1035 (all data). Crystal data for **4a**. $C_{16}H_{23}NO_3S$, $M = 309.41$, monoclinic, $a = 22.4722(3)$, $b = 7.8727(1)$, $c = 19.9610(2)$ Å, $U = 3270.17(7)$ Å^3, $T = 296$ K, space group $C2/c$, $Z = 8$, μ(Cu Kα) = 1.837 mm^{-1}, 2943 reflections measured, 2689 unique ($R_{int} = 0.0392$) which were used in all calculations. The final $wR(F_2)$ was 0.1150 (all data). CCDC reference number 288320. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b515547a

§ CCDC reference number 288321. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b515547a

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