COMMUNICATION

ChemComm
www.rsc.org/chemcomm

Aziridinyl anions from a chiral, nonracemic 2-isopropylidineaziridine: surprisingly diastereoselective alkylation reactions

J. F. Hayes,[a] N. Prévost,[b] I. Prokeš,[b] M. Shipman,*[b] A. M. Z. Slawin[c] and H. Twin[b]

[a] *GlaxoSmithKline, Old Powder Mills, Tonbridge, Kent, UK TN11 9AN*

[b] *School of Chemistry, University of Exeter, Stocker Road, Exeter, Devon, UK EX4 4QD. E-mail: m.shipman@exeter.ac.uk; Fax: +44 1392 263434; Tel: +44 1392 263469*

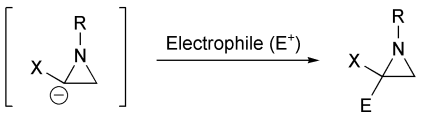
[c] *School of Chemistry, University of St. Andrews, Purdie Building, St. Andrews, Fife, UK KY16 9ST*

Received (in Cambridge, UK) 26th March 2003, Accepted 28th April 2003
First published as an Advance Article on the web 20th April 2003

Lithiation and alkylation of a 2-isopropylidineaziridine bearing an (*S*)-α-methylbenzyl group on nitrogen proceeds with high levels of diastereocontrol (80–90% de).

The chemistry of aziridines is dominated by reactions which involve rupture of the strained heterocyclic ring by nucleophiles.[1] Less commonly encountered are reactions wherein one of the carbon atoms of the three-membered ring serves as a nucleophile by way of the corresponding aziridinyl anion.[2] In principle, this latter chemistry offers an attractive way to make functionalised aziridines by further trapping with electrophiles (Scheme 1). Most studies in this area have focused on systems where the anion bearing carbon has been substituted (X ≠ H).[2,3] Few examples of aziridinyl anions devoid of an adjacent substituent (X = H) are known.[4] In the context of stereoselective synthesis, such unsubstituted aziridinyl anions (X = H) are especially interesting as the process of anion generation and alkylation produces a new asymmetric centre.

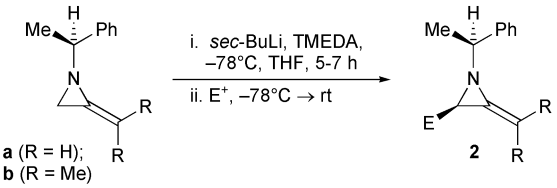
In pioneering work on unsubstituted aziridinyl anions, Quast and Vélez demonstrated that 1-*tert*-butyl-2-methyleneaziridine can be deprotonated with *sec*-butyllithium at −78 °C and alkylated with a limited range of electrophiles (MeOD, MeI or Me_3SiCl).[4a] These workers went on to show that asymmetry can be induced in the lithiation/alkylation reactions of 1-methyl-2-methyleneaziridine by using an external chiral ligand [(*S*,*S*)-(+)-1,4-bis(dimethylamino)-2,3-dimethoxybutane] as cosolvent. Unfortunately, the levels of enantioselectivity achieved were very modest (12.4% ee) and the reaction was far from practical.[4b] We reasoned that much better levels of asymmetric induction might be achieved by incorporating a chiral, nonracemic element within the nitrogen substituent of the aziridine such that it might exert influence and control on the lithiation/alkylation process. In this communication, we demonstrate that this approach has some merit and show that the alkylation of enantiopure 2-isopropylidineaziridinyl anions proceeds in a highly diastereoselective manner.



Scheme 1 Aziridine functionalisation *via* aziridinyl anions.

Two enantiomerically enriched 2-alkylidineaziridines (*S*)-**1a** and (*S*)-**1b** were used. The α-methylbenzyl group was chosen as the chiral control element because of its simplicity, low cost and widespread use in asymmetric synthesis.[5] Methyleneaziridine (*S*)-**1a** was prepared by the literature method.[6] (*S*)-**1b** was made in 62% overall yield from 1,1-dibromo-2,2-dimethylcyclopropane and (*S*)-α-methylbenzylamine using a two-step method similar to that described for the synthesis of racemic material.[7] The enantiomeric purity of (*S*)-**1b** was determined to be ≥97% ee by chiral HPLC analysis.†

Treatment of 2-methyleneaziridine (*S*)-**1a** with *sec*-BuLi and tetramethylethylenediamine (TMEDA) in THF for 7 h then benzyl bromide provided **2a** in good yield but as an inseparable 53 : 47 mixture of diastereomers (14% de before purification) (Eqn. 1 and Table 1).‡ Under near identical reaction conditions, 2-isopropylidineaziridine (*S*)-**1b** gave alkylated product **2b** with a dramatically improved level of diastereocontrol (Table 1, entry 2 *cf.* entry 1).§ Using (*S*)-**1b**, reasonable efficiency (43–80%) and excellent diastereoselectivity (80–90% de) was observed with a broad range of electrophiles (Table 1, entries 2–7).¶ With the exception of **2a** and **2d**, the alkylated products were isolated as single diastereomers after silica gel chromatography. The use of TMEDA was not essential in these reactions although higher yields were normally obtained when it was added. The relative stereochemistry of **2g** has been unambiguously established by X-ray crystallography (Fig. 1).‖ All the other alkylated isopropylidineaziridines **2b–f** are tentatively assigned as having the same configuration at C-3.



(1)

The origin of the large differences in the levels of diastereoselectivity observed in the lithiation/alkylation of **1a** (14% de) and **1b** (88% de) with benzyl bromide, and indeed other electrophiles, remains unclear. As aziridinyl anions are normally configurationally stable, we suggest that the selectivity in these reactions most likely arises from diastereocontrol in the initial lithiation of the aziridine ring. At first glance, the

Table 1 Diastereoselective alkylations of 2-alkylidineaziridines

Entry	Substrate	Electrophile (E^+)	Product	Yield (%)[a]	Crude d.e. (%)[b]	Optical rotation, $[\alpha]_D$[c]
1	**1a**	BnBr	**2a** (R = H, E = Bn)	70[d]	14	n.d.
2	**1b**	BnBr	**2b** (R = Me, E = Bn)	68	88	−152 (*c* 1.0)
3	**1b**	MeI	**2c** (R = Me, E = Me)	47	80	−235 (*c* 1.0)
4	**1b**	n-BuI	**2d** (R = Me, E = Bu)	53[e]	n.d.	n.d.
5	**1b**	Me_3SiCl	**2e** (R = Me, E = $SiMe_3$)	80	90	−133 (*c* 1.1)
6	**1b**	AllylBr	**2f** (R = Me, E = $CH_2CH{=}CH_2$)	63	84	−210 (*c* 1.0)
7	**1b**	Ph_2CO	**2g** (R = Me, E = $C(OH)Ph_2$)	43[f]	88	−111 (*c* 1.0)

[a] Isolated yield of major diastereomer after purification by silica gel chromatography unless otherwise stated. [b] Ratio determined by ^1H NMR analysis prior to purification. [c] Recorded in $CHCl_3$ at 22 (entries 2, 6 & 7) or 21 °C (entries 3 & 5). [d] Isolated as a 53 : 47 mixture of diastereomers after bulb-to-bulb distillation. [e] Isolated as a 93 : 7 mixture of diastereomers. [f] To remove excess Ph_2CO, product treated with $NaBH_4$ in EtOH prior to purification.

DOI: 10.1039/b303252c

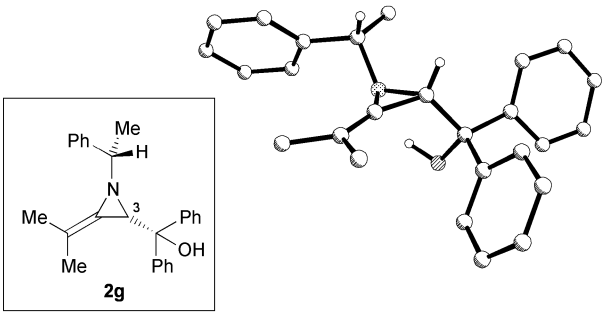


Fig. 1 X-Ray crystal structure of **2g**.

methyl groups on the alkene terminus of **1b** appear too remote to exert any increased bias in the stereoselectivity of this process compared with **1a**. However, the stereochemical analysis is complicated by the fact that enantiomerically pure **1a** and **1b** exist as mixtures of diastereomers as a result of N-inversion. Indeed, ^{1}H NMR spectra recorded in d_8-THF at 400 MHz confirm that both **1a** and **1b** exist as mixtures of N-invertomers at −80 °C. Interestingly, the coalescence temperature is appreciably higher for **1b** (*ca.* 0 °C) than **1a** (*ca.* −50 °C) indicating that the N-inversion is slower upon substitution of the exocyclic double bond. Small differences in the relative proportions of the N-invertomers at −80 °C were also measured (**1a**: 63 : 37; **1b**: 72 : 28). In contrast, the X-ray crystal structure of **2g**, and variable temperature NMR (–80 to +90 °C) and NOE experiments performed using **2b** reveal that C-3 substituted isopropylidineaziridines exist as single N-invertomers adopting an *anti*-disposition of the N-1 and C-3 substituents. Whether such observations account for the differences in stereoselectivity in the alkylation reactions of **1a** and **1b** awaits the outcome of further mechanistic studies.

As 2-alkylidineaziridines participate in a variety of useful transformations including radical rearrangements,[8] multicomponent reactions,[7,9] and oxidative cleavage processes to α-lactams,[10] it is anticipated that the methodology described herein will find a number of useful applications in asymmetric synthesis. The use of a chiral, nonracemic element on nitrogen to control the diastereoselectivity of the alkylation of unsubstituted aziridinyl anions (Scheme 1, X = H) is novel. In future work, we will test the generality of this approach.

We are indebted to EPSRC and GlaxoSmithKline for their generous financial support of this work. We thank the EPSRC National Mass Spectrometry Centre for performing some of the mass spectral measurements and the EPSRC Chemical Database Service at Daresbury.[11]

Notes and references

† HPLC performed using a Diacel OD column (0.5% IPA in hexanes, 0.7 mL min^{-1}; λ = 252 nm) established (*S*)-**1b** to be ≥97% ee [retention times: (*S*)-**1b** = 5.51 min, (*R*)-**1b** = 6.25 min]. (±)-**1b** used for comparison purposes.

‡ Modest improvements in diastereoselectivity were observed reacting (*S*)-**1a** with other electrophiles, *e.g.* Me_3SiCl (*ca.* 60% de).

§ For the best results, **1a** and **1b** require slightly different lithiation times (**1a**: 7 h; **1b**: 5 h). No improvement in the diastereomeric excess of **2a** is observed when **1a** is lithiated for 5 h prior to treatment with BnBr.

¶ *Representative procedure*: To a stirred solution of (*S*)-**1b** (200 mg, 1.07 mmol) in THF (8 mL) at −78°C was added TMEDA (193 μL, 1.28 mmol) then *sec*-BuLi (1.0 M in cyclohexane, 1.39 mL, 1.39 mmol). After 5 h at −78 °C, benzyl bromide (190 μL, 1.60 mmol) was added and the mixture allowed to warm slowly to room temperature overnight. After addition of water (10 mL), the mixture extracted with diethyl ether (2 × 10 mL). The combined organic layers were washed with saturated sodium chloride solution (10 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. Column chromatography (0.5% Et_3N in petroleum ether) gave **2b** (201 mg, 68%) as a colourless oil. $[\alpha]_D^{22}$ −152 (*c* 1.0, $CHCl_3$); ν_{max} 3027, 2960, 2919, 2847, 1787, 1598, 1495, 1444 cm^{-1}; δ_H (400 MHz, C_6D_6) 7.54–7.51 (2H, m, Ar*H*), 7.35–7.15 (8H, m, Ar*H*), 3.00–2.90 (2H, m, CH_2Ph), 2.86 (1H, q, *J* 6.5 Hz, MeC*H*Ph), 2.15 (1H, m, C*H*CH$_2$Ph), 1.72 (3H, s, =CCH_3), 1.30 (3H, s, =CCH_3), 1.25 (3H, d, *J* 6.5 Hz, CHMe); δ_C (100 MHz, C_6D_6) 145.9 (s), 140.0 (s), 130.2 (s), 129.3 (d), 128.36 (d), 128.32 (d), 127.5 (d), 127.1 (d), 126.3 (d), 103.0 (s), 68.2 (d), 44.1 (d), 39.8 (t), 24.1 (q), 21.1 (q), 19.1 (q); HRMS calcd for $C_{20}H_{23}N$ (M^+) 277.1830; found *m*/*z* 277.1843.

‖ *Crystal data* for **2g**: X-ray diffraction studies on a colourless crystal grown from propanone/water were performed at 125 K using a Bruker SMART diffractometer with graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). The structure was solved by direct methods. $C_{26}H_{27}N_1O_1$, *M* = 369.49, orthorhombic, space group $P2_12_12$, *a* = 16.847(3), *b* = 22.696(4), *c* = 5.6162(10) Å, *U* = 2147.3(7) Å^3, *Z* = 4, D_c = 1.143 Mg m^{-3}, μ = 0.069 mm^{-1}, *F*(000) = 792, crystal size = 0.15 × 0.05 × 0.05 mm, Flack parameter 1(2). Of 9253 measured data, 3044 were unique (R_{int} = 0.1101) and 1485 observed [$I > 2\sigma(I)$]) to give R_1 = 0.0429 and wR_2 = 0.0526. All non-hydrogen atoms were refined with anisotropic displacement parameters; the OH proton was located from a Δ*F* map and allowed to refine isotropically subject to a distance constraint (O–H = 0.98 Å). All remaining hydrogen atoms bound to carbon were idealised. Structural refinements were by the full-matrix least-squares method on F^2. CCDC reference number 207055. See http://www.rsc.org/suppdata/cc/b3/b303252c/ for crystallographic data in CIF or other electronic format.

1 D. Tanner, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 599; W. McCoull and F. A. Davis, *Synthesis*, 2000, 1347; J. B. Sweeney, *Chem. Soc. Rev.*, 2002, **31**, 247.
2 For a review, see T. Satoh, *Chem. Rev.*, 1996, **96**, 3303.
3 For recent examples, see T. Satoh, M. Ozawa, K. Takano and M. Kudo, *Tetrahedron Lett.*, 1998, **39**, 2345; S. Florio, L. Troisi, V. Capriati and G. Ingrosso, *Tetrahedron Lett.*, 1999, **40**, 6101; A. R. Katritzky, J. Yao, W. Bao, M. Qi and P. J. Steel, *J. Org. Chem.*, 1999, **64**, 346; V. Alezra, M. Bonin, L. Micouin and H.-P. Husson, *Tetrahedron Lett.*, 2000, **41**, 651; T. Satoh, R. Matsue, T. Fujii and S. Morikawa, *Tetrahedron Lett.*, 2000, **41**, 6495; T. Satoh, M. Ozawa, K. Takano, T. Chyouma and A. Okawa, *Tetrahedron*, 2000, **56**, 4415; T. Satoh, R. Matsue, T. Fujii and S. Morikawa, *Tetrahedron*, 2001, **57**, 3891; V. Alezra, M. Bonin, L. Micouin, C. Policar and H.-P. Husson, *Eur. J. Org, Chem.*, 2001, 2589.
4 (*a*) H. Quast and C. A. Weise Vélez, *Angew. Chem., Int. Ed. Engl.*, 1974, **13**, 342; (*b*) H. Quast and C. A. Weise Vélez, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 213; (*c*) R. S. Atkinson and B. J. Kelly, *Tetrahedron Lett.*, 1989, **30**, 2703; (*d*) E. Vedejs and W. O. Moss, *J. Am. Chem. Soc.*, 1993, **115**, 1607; (*e*) P. Beak, S. Wu, E. K. Yum and Y. M. Jun, *J. Org. Chem.*, 1994, **59**, 276; (*f*) E. Vedejs and J. T. Kendall, *J. Am. Chem. Soc.*, 1997, **119**, 6941; (*g*) P. Bisseret, C. Bouix-Peter, O. Jacques, S. Henriot and J. Eustache, *Org. Lett.*, 1999, **1**, 1181; (*h*) V. K. Aggarwal, E. Alonso, M. Ferrara and S. E. Spey, *J. Org. Chem.*, 2002, **67**, 2335.
5 E. Juaristi, J. L. León-Romo, A. Reyes and J. Escalante, *Tetrahedron: Asymmetry*, 1999, **10**, 2441.
6 J. Ince, T. M. Ross, M. Shipman, A. M. Z. Slawin and D. S. Ennis, *Tetrahedron*, 1996, **52**, 7037.
7 J. F. Hayes, M. Shipman and H. Twin, *J. Org. Chem.*, 2002, **67**, 935.
8 N. Prévost and M. Shipman, *Tetrahedron*, 2002, **58**, 7165.
9 J. F. Hayes, M. Shipman, A. M. Z. Slawin and H. Twin, *Heterocycles*, 2002, **58**, 243.
10 T. Akasaka, Y. Nomura and W. Ando, *J. Org. Chem.*, 1988, **53**, 1670.
11 D. A. Fletcher, R. F. McMeeking and D. Parkin, *J. Chem. Inf. Comp. Sci.*, 1996, **36**, 746.