COMMUNICATION

Diastereoselectivity in the addition and cycloaddition reactions of a chiral ester of 2*H*-azirine-3-carboxylic acid

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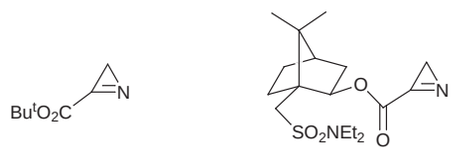
The azirine ester 2 bearing Oppolzer's *N*,*N*-diethyl-(1*R*)-isobornyl-10-sulfonamide chiral auxiliary shows moderate diastereoselectivity in its Diels–Alder reaction with cyclopentadiene whereas the addition of thiophenol is highly diastereoselective; X-ray crystal structures of the aziridine esters 6 and 7 are reported.

We recently described the generation in solution and Diels–Alder reactions of *tert*-butyl 2*H*-azirine-3-carboxylate **1**.[1] The



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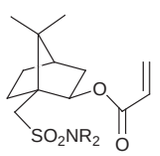

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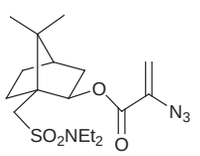

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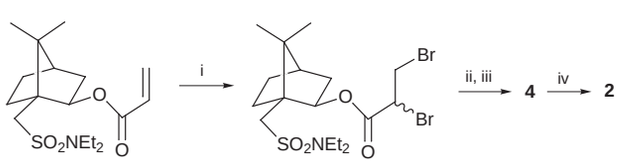
ester reacts with dienes in a highly selective manner, all the reactions involving *endo* cycloaddition with respect to the three-membered ring. We now report on the generation of the corresponding chiral ester **2** which has been studied in order to assess the potential of such azirines in asymmetric synthesis.

Oppolzer and co-workers have described the synthesis of acrylic esters **3** by the reaction of acrylic acid with *N*,*N*-dialkyl-(1*R*)-isoborneol-10-sulfonamides.[2,3] The ester **3** (R = Et) proved to be a suitable starting material for the preparation of the corresponding 2-azido ester **4**, the route being the same as that we described for *tert*-butyl 2-azidoacrylate.[1] The azirine ester **2** was then generated from the azide by thermolysis of a dilute solution in boiling toluene. The route is illustrated in Scheme 1.



Scheme 1 *Reagents*: (i) Br_2, DCM; (ii) NaN_3 (3 equiv.), DMF; (iii) DBU; (iv) toluene, 110 °C, 1.5 h.

Since the *tert*-butyl ester **1** had proved to be unstable the azirine **2** was not isolated, but used in solution.

Reaction of the ester **2** with cyclopentadiene proceeded smoothly at room temperature and was complete within 19 h. Two diastereoisomeric cycloadducts were formed in a 2:1 ratio and in a combined yield of 73%; samples of both were separated by flash chromatography and each isomer was fully characterised. Their structures were established by means of an X-ray crystal structure of the minor isomer (Fig. 1).[4] From this, the

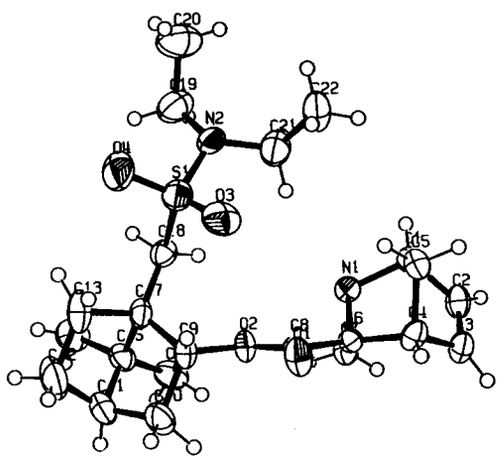


Fig. 1 An ORTEP drawing of **6** (crystallographic numbering).

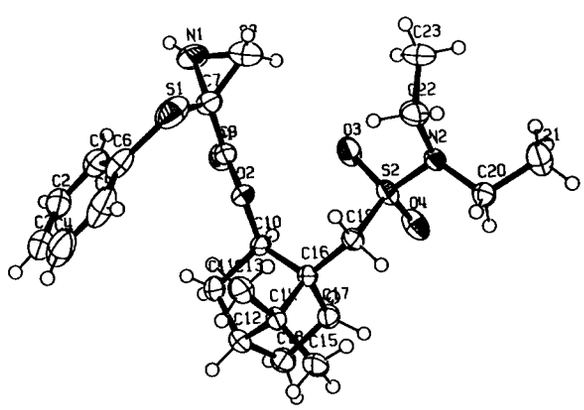
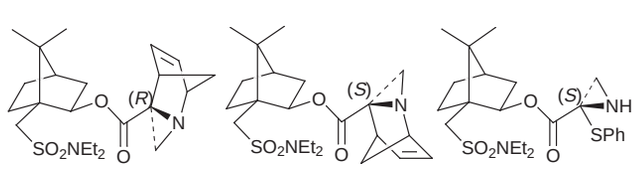


Fig. 2 An ORTEP drawing of **7** (crystallographic numbering).

structures of the major and minor isomers were assigned as **5** and **6**, respectively.



5 **6** **7**

We had earlier found that methyl 2-aryl-2*H*-azirine-3-carboxylates react rapidly with thiols to give the corresponding aziridines resulting from simple addition of the thiol to the C=N bond.[5] In a similar way, thiophenol reacted with the azirine ester **2**. Only one adduct could be detected in the ^{1}H NMR spectrum of the crude reaction mixture. This compound was easily isolated by chromatography followed by crystallisation and its structure was established as **7** by X-ray crystallography (Fig. 2).[6]

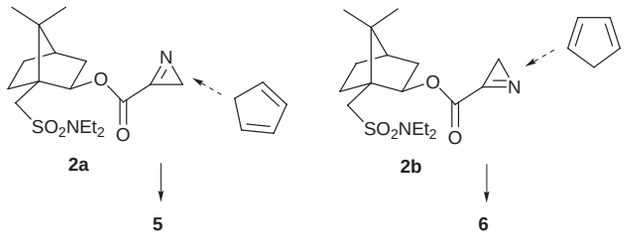
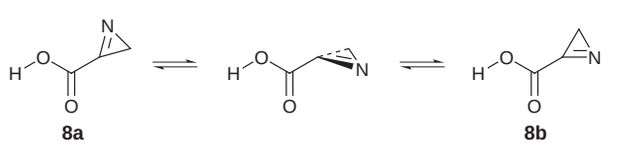


Fig. 3 Approach of cyclopentadiene to the less hindered face of two rotamers of the azirine **2**.

In their studies of Diels–Alder reactions of acrylates bearing this type of chiral auxiliary Oppolzer and co-workers found that the acrylate function adopted a strictly antiperiplanar disposition of the carbonyl group and the carbon–carbon double bond, resulting in shielding of the *re* face and preferential cycloaddition to the *si* face.[3] Molecular orbital calculations on the conformations of 2*H*-azirine-3-carboxylic acid[7] indicate that the two minimum energy conformations **8a** and **8b** are almost identical in energy and that there is a very low energy barrier to rotation of 8 kJ mol^{-1} (Scheme 2). The relatively low diastereoselectivity in the Diels–Alder reaction of the azirine **2** may therefore be due to *endo* cycloaddition to the less hindered face in each of two possible conformations, **2a** and **2b** (Fig. 3). These do not differ greatly in steric interactions and it is unlikely that the ratio would be altered significantly by using a more bulky sulfonamide side chain.[8] On the other hand, the approach of a nucleophile along the axis of the C=N bond of the azirine in conformation **2b** is apparently more favourable than the corresponding approach in conformation **2a**. This may be due either to an unfavourable interaction with the carbonyl group, or steric hindrance by a methylene group of the norbornyl unit, in conformation **2a**.[9]



Scheme 2

Because the adducts can be obtained pure by chromatography and crystallisation the reactions offer a route to new types of aziridinecarboxylic acids in optically pure form. Chiral aziridines have found a range of applications in synthetic chemistry.[10]

Experimental

(1*R*)-10-(*N*,*N*-Diethylsulfamoyl)isobornyl acrylate 3 (R = Et)

This ester was prepared by the general method described by Oppolzer and co-workers,[3] mp 91–92.5 °C; ν_{max}(Nujol)/cm^{-1} 1715; δ_H (300 MHz) (vinyl H) 5.92 (1 H, dd, *J* 10.4 and 1.8 Hz), 6.19 (1 H, dd, *J* 17.2 and 10.4 Hz) and 6.38 (1 H, dd, *J* 17.2 and 1.8 Hz).

(1*R*)-10-(*N*,*N*-Diethylsulfamoyl)isobornyl 2-azidoacrylate 4

(i) Bromine (0.47 g, 2.9 mmol) was added dropwise to a solution of the acrylate **3** (R = Et) (1.0 g, 2.9 mmol) in DCM. The dibromo ester was isolated as an oil (1:1 mixture of diastereoisomers).

(ii) Sodium azide (0.56 g, 8.6 mmol) was added to a solution of the dibromo ester (1.46 g, 2.9 mmol) in DMF (7 ml). The suspension was stirred at room temp. for 48 h. It was then diluted with DCM (50 ml) and extracted with water (8 × 50 ml). The organic layer was dried and DBU (0.44 g, 2.9 mmol) was added. After 20 min the solution was washed with aq. citric acid (10%) and water. The azido ester **4** was obtained from the organic layer as an oil (1.00 g, 90%); ν_{max}(film)/cm^{-1} 2111 and 1726; δ_H (300 MHz) 5.75 (1 H, d, *J* 1.4 Hz) and 5.31 (1 H, d, *J* 1.4 Hz) (C=CH_2).

(1*R*)-[10-(*N*,*N*-Diethylsulfamoyl)isobornyl] 2-azatricyclo-[3.2.1.$0^{2,4}$]oct-6-ene-4-carboxylates 5 and 6

A solution of the azide **4** (0.51 g, 1.33 mmol) in dry toluene (30 ml) was heated under reflux for 1.5 h. The solution was cooled to room temp. and cyclopentadiene (0.90 g, 13.3 mmol) was added. After 19 h the solvent was removed and the residue subjected to dry flash column chromatography (hexane–ether). The mixture of esters was partially separated, giving (i) the ester **6** (0.08 g), (ii) a mixture of **5** and **6** (0.20 g, **5**:**6** = 72:28) and (iii) the ester **5** (0.13 g); total yield (from azide **4**) 0.41 g (73%).

The ester **5** had mp 133–135 °C (from ether–hexane); $[\alpha]_D^{25}$ −150.3; ν_{max}(Nujol)/cm^{-1} 1711; δ_H (300 MHz) (selected signals) 0.89 and 1.04 (each 3 H, s, bridgehead Me), 3.47 (1 H, s) and 4.23 (1 H, s).

The ester **6** had mp 132–155 °C (from ether–hexane); $[\alpha]_D^{25}$ +19.8; ν_{max}(Nujol)/cm^{-1} 1726; δ_H (300 MHz) (selected signals) 0.89 and 0.98 (each 3 H, s, bridgehead Me), 3.52 (1 H, s) and 3.99 (1 H, s).

(1*R*)-[10-(*N*,*N*-Diethylsulfamoyl)isobornyl] 2-phenylthio-aziridine-2-carboxylate 7

A solution of the azide **4** (1.0 g, 2.6 mmol) in dry toluene (40 ml) was heated under reflux for 1.5 h. The solution was cooled in an ice–water bath and thiophenol (0.29 g, 2.6 mmol) was added. After 19 h the solvent was removed and the residue subjected to dry flash column chromatography (hexane–ether). This gave the ester **7** (0.71 g, 58%), mp 89–89.5 °C (from ether–hexane); $[\alpha]_D^{25}$ −48.7; ν_{max}(Nujol)/cm^{-1} 3274 and 1719; δ_C (75 MHz) (selected signals) 34.2 (C-3 of aziridine) and 43.4 (C-2 of aziridine).

Acknowledgements

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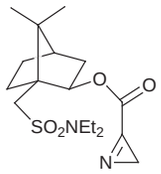
Notes and references

1 M. J. Alves and T. L. Gilchrist, *Tetrahedron Lett.*, 1998, **39**, 7579.
2 W. Oppolzer, C. Chapuis and M. J. Kelly, *Helv. Chim. Acta*, 1983, **66**, 2358; W. Oppolzer, *Tetrahedron*, 1987, **43**, 1969.
3 W. Oppolzer, C. Chapuis and G. Bernardinelli, *Tetrahedron Lett.*, 1984, **25**, 5885.
4 **Crystal data for 6**. $C_{22}H_{34}N_2O_4S$, *M* = 422.64, *a* = 7.4889(12), *b* = 8.9188(12), *c* = 16.948(2) Å, *U* = 1107.4(3) $Å^3$, *T* = 293(2) K, *Z* = 2, μ(Mo-Kα) = 0.135 mm^{-1}; 5572 reflections measured, 2891 unique (R_{int} = 0.0861). The final wR_2 was 0.1289 (all data). CCDC reference number 207/327. See http://www.rsc.org/suppdata/p1/1999/1399 for crystallographic files in .cif format.
5 M. J. Alves, T. L. Gilchrist and J. H. Sousa, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1305.
6 **Crystal data for 7**. $C_{23}H_{34}N_2O_4S_2$, *M* = 466.71, *a* = 10.5115(12), *b* = 11.468(3), *c* = 20.141(3) Å, *U* = 2427.9(7) $Å^3$, *T* = 213(2) K, *Z* = 4, μ(Mo-Kα) = 0.206 mm^{-1}; 13051 reflections measured, 3150 unique (R_{int} = 0. 0643). The final wR_2 was 0.0812 (all data).
7 Calculations were performed by Dr D. L. Cooper (University of Liverpool). RHF calculations with a standard 6-31G** basis were carried out in which the carbonyl carbon was forced coplanar with the heavy atoms of the ring and all other parameters were fully optimised for a given dihedral angle. The difference in energy of conformations with dihedral angle 0° and 180° is 3 kJ mol^{-1} and for conformations with dihedral angle 0° and 90° is 8 kJ mol^{-1}.
8 Preliminary results indicate that both diastereoisomers are also formed with the corresponding azirine bearing a more bulky *N*,*N*-dicyclohexylsulfonamidomethyl side chain.
9 A referee has questioned this explanation and has suggested that reaction might occur more selectively through a higher energy s-*cis* conformation of the ester, in which the rotamer **2c** would be preferred since it avoids interactions between the methylene group of the



2c

azirine and the methine of the auxiliary. This is feasible, although the proportion of the s-*cis* conformer of an ester is usually small at room temp. (K. B. Wiberg and K. E. Laidig, *J. Am. Chem. Soc.*, 1987, **109**, 5935). We thank the referee for this suggestion.

10 D. Tanner, *Angew. Chem.*, *Int. Ed. Engl.*, 1994, **33**, 599; H. M. I. Osborn and J. Sweeney, *Tetrahedron*: *Asymmetry*, 1997, **8**, 1693.

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