N-Phthalimidoaziridines by Diastereoselective Addition to α,β-Unsaturated Amides: a Route to Chiral β-Substituted α-Hydrazino Acid Derivatives

James T. Kapron, Bernard D. Santarsiero and John C. Vederas*

Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2

Lead tetraacetate oxidation of *N*-aminophthalimide **1** in the presence of *N*-enoylbornane[10,2]sultams (Oppolzer auxiliary) generates corresponding *N*-phthalimidoaziridine adducts (12–94% yield) with 33% to ≥95% diastereofacial selectivity (*syn* attack at the *re* face of the α-carbon for **4a**); these chiral *N*-aminoaziridine derivatives readily undergo ring opening by sulfur nucleophiles to give α-hydrazino acid derivatives.

Interest in stereospecific synthesis of α-hydrazino acids[1–9] is spurred by their action as inhibitors of enzymes which metabolise the corresponding α-amino acids,[10] their natural occurrence in peptide antibiotics[11] and their use in metabolically-stable peptide mimetics with potential for treatment of viral infections.[12] The formation and ring opening of chiral *N*-aminoaziridine derivatives could provide a new route to such compounds. Extensive studies have demonstrated that oxidation of *N*-aminophthalimide **1** with lead tetraacetate in the presence of olefins results in stereospecific *syn* addition to afford racemic *N*-phthalimidoaziridines **2** (Scheme 1).[13,14] Initially this was believed to occur *via* the aminonitrene **A**, but recent investigations by Atkinson and coworkers indicate that the actual intermediate may be the *N*-acetoxyaminophthalimide **B**.[14,15] Surprisingly, only a few chiral versions of this reaction have been explored.[16,17] Condensations of the intermediate derived by oxidation of **1** with chiral α,β-unsaturated esters having an alkoxy substituent at a γ stereocentre proceed at −40 °C with high (>30 : 1) facial selectivities for (*E*)-olefins.[16] It thus seemed likely that an α,β-unsaturated acid derivative bearing an appropriate chiral auxiliary at the carbonyl could also induce diastereoface selection by the intermediate generated from **1**.

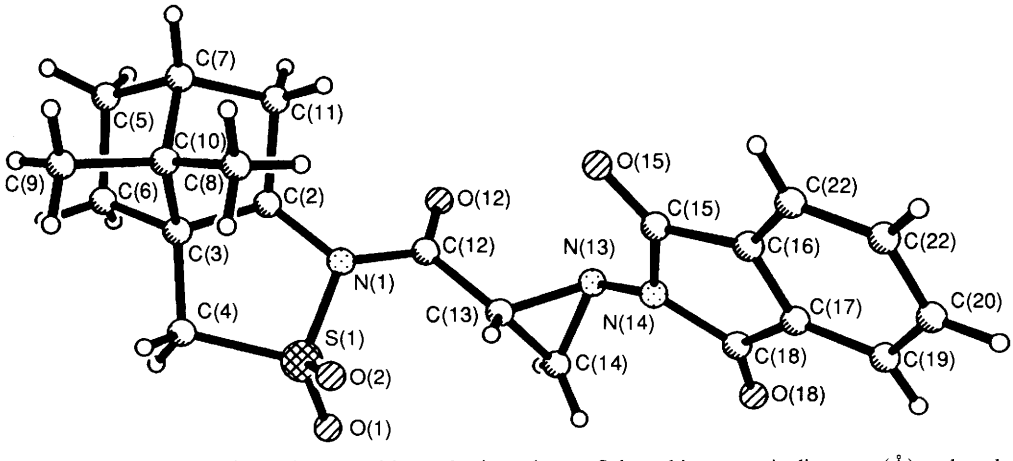
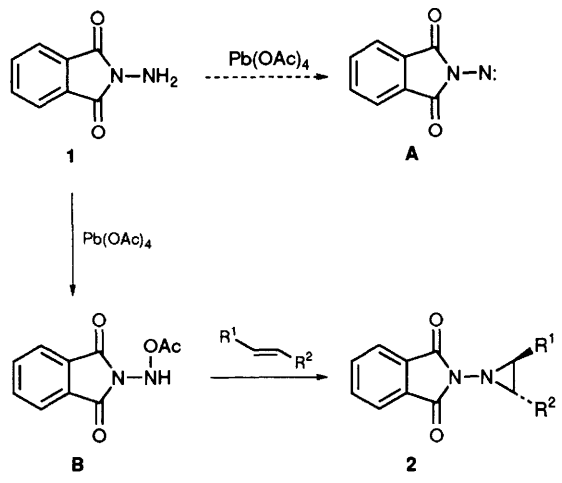


Fig. 1 Perspective view of one of two conformations **5a** with numbering scheme. Selected interatomic distances (Å) and angles (°): N(1)–C(12) 1.375(10), C(12)–O(12) 1.190(10), C(12)–C(13) 1.542(13), C(13)–N(13) 1.484(11), C(13)–C(14) 1.462(16), N(13)–N(14) 1.425(8), C(14)–N(13) 1.460(13); S(1)–N(1)–C(12) 123.0(6), N(1)–C(12)–O(12) 122.6(8), N(1)–C(12)–C(13) 113.1(7), C(12)–C(13)–N(13) 112.4(7), C(12)–C(13)–C(14) 121.0(8), C(13)–C(14)–N(13) 61.0(6), C(13)–N(13)–C(14) 59.5(7), C(14)–C(13)–N(13) 59.4(7), C(14)–N(13)–N(14) 113.2(7), N(13)–N(14)–C(15) 119.0(7). The other conformation shows slight displacement of the aziridine and phthalimido ring systems due in part to rotation around the N(1)–C(12) bond: N(1)–C(12)–C(13) 116.8(7).



Scheme 1

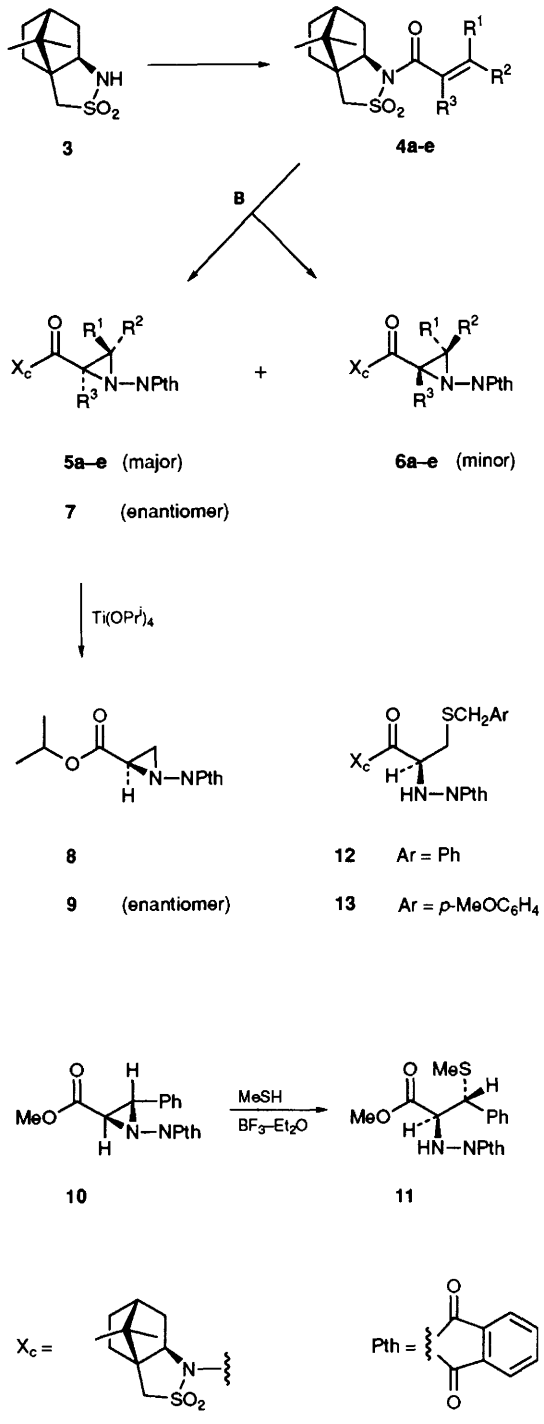
Table 1 Aziridination of chiral *N*-enoyl sultams **4**[a]

Alkene **4**	R^1	R^2	R^3	% Yield (**5** and **6**)[b]	% D.e. (**5**)[c]
a	H	H	H	94	78
b	H	Me	H	61	33
c	H	Ph	H	90	80
d	Me	Me	H	67	>95[d]
e	H	H	Me	12	70

[a] All compounds were characterized by IR, ^{1}H NMR, MS and elemental analysis. [b] Isolated yield of mixture of **5** and **6** after chromatography. [c] Determined by ^{1}H NMR spectroscopy of crude reaction products. [d] Isomer **6d** could not be detected.

Bornane[10,2]sultams, originally devised by Oppolzer and coworkers,[18] are excellent chiral auxiliaries for stereoselective reactions on attached acyl groups (including cyclopropanation of *N*-enoyl substituents).[19] Hence, the *N*-enoyl sultams **4a–e** (Scheme 2) were prepared from commercially available sultam **3** and the corresponding acid chlorides.[18,19] Treatment of a mixture of **4a** (1.19 g, 4.29 mmol) and **1** (1.07 g, 6.60 mmol) in dichloromethane (20 cm^3) with lead tetraacetate (95%, 3.12 g, 6.69 mmol) over 15 min at 20 °C gave an 8 : 1 mixture of **5a** and **6a** (94% total yield). The major isomer **5a** crystallized from toluene–hexane {m.p. 201–203 °C; $[\alpha]_D^{20}$ −7 (*c* 0.27 g per 100 cm^3 $CHCl_3$)} and its structure was confirmed by X-ray crystallographic analysis (Fig. 1).† As with most reactions of such *N*-enoyl sultams, this major isomer is formed by *syn* attack on the double bond from the *re* face at the α-carbon[18,19] of the unsaturated amide **4a**. The analogous process was explored with a variety of alkene substitution patterns (Table 1). In each case (**b–e**) the stereochemistry of the major isomer was tentatively assigned as **5**, based on the directing effect of the *N*-enoyl sultam auxiliary, but studies are in progress to confirm these assignments. The yield drops drastically if an α-substituent is present (*e.g.* **4e**), presumably

† *Crystal data* for **5a** ($C_{21}H_{23}N_3O_5S$ crystallised with 0.25 molecules of toluene): $C_{22.75}H_{25}N_3O_5S$, pale-yellow prisms, monoclinic, *C*2, *a* = 43.149(11), *b* = 7.582(2), *c* = 14.278(4) Å, β = 102.58(2)°, *V* = 4559.320(0) Å^3, *Z* = 8, *T* = 295 K, D_c = 1.318 g cm^{-3}, μ = 15.92 cm^{-1}. Of 7599 reflections collected (3.0° ≤ 2θ ≤ 115.0°), 6061 were independent and 4266 were observed ($6\sigma F_o$). A semi-empirical absorption correction was applied to the data; the maximum and minimum corrections applied to F_o were 0.9157 and 0.7773. Final R = 6.66%, R_w = 8.07%. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.



Scheme 2

because of steric crowding. It is presently unclear why the diastereoisomeric excess (d.e.) for aziridination of **4b** is low. The possible occurrence of invertomers at the aziridine ring nitrogen was examined by variable temperature (−50 to +50 °C) NMR spectroscopy, since it was known that equilibration between *cis* and *trans* forms is slow at −30 °C but very rapid at ambient temperature.[14,16] Crystalline **5a** exists as the *trans* invertomer, and no detectable levels of the *cis* isomer are formed either in the solid or in solution. Compound **6a** also appears to be a single invertomer (nitrogen stereochemistry uncertain) within NMR detection limits. Detailed stereochemical information on the preferred invertomers of **5b–e** and of **6** will be accessible through additional X-ray analyses.

Of the methods devised for removal of the sultam auxiliary, titanium-mediated alcoholysis proceeds under relatively mild conditions, and affords ready access to the parent carboxylic acids, especially if allyl alcohol is used.[20] Titanium isopropoxide cleavage[20] of **5a** or its antipode **7a** (generated analogously from the enantiomeric sultam) produces the isopropyl ester **8** or **9**, respectively (27% yield, not optimised). Comparison of pure **8** and **9** and mixtures of them by proton NMR spectroscopy using the chiral shift reagent, Eu(hfc)$_3$ {tris[3-heptafluoropropyl hydroxymethylene-(+)-camphorato] europium(III)}, confirms that no epimerisation occurs during the cleavage process.

To examine whether the nucleophilic ring opening of *N*-phthalimidoaziridines proceeds analogously to *N*-acyl aziridines,[21] a solution of racemic **10** (0.10 g, 0.31 mmol, prepared by aziridination of methyl cinnamate with **1**) and methanethiol (0.27 g, 5.6 mmol) in dichloromethane (2 cm^3) at −78 °C was exposed to BF_3–Et_2O (0.20 g, 1.4 mmol) for 1 h. Aqueous workup and crystallisation from methanol gave **11** in 87% yield. Analogous treatment of **5a** (54 mg, 0.126 mmol) and benzylthiol (1.0 cm^3) in dichloromethane (5 cm^3) with BF_3–Et_2O (0.86 g) at 20 °C for 1.5 h, followed by purification using flash chromatography (hexane–ethyl acetate, 3:2) produces the ring-opened product **12** in 78% yield (m.p. 93–95 °C). Similarly, *p*-methoxybenzylthiol generates **13** from **5a** in 56% yield. Clearly, the behaviour of *N*-phthalimidoaziridines with sulfur nucleophiles parallels that of the *N*-acylaziridines and affords access to α-hydrazino acid derivatives. Additional studies on the scope and utility of such transformations will be reported later.

We thank Dr Robert McDonald for helpful assistance and discussions. Financial support by Merck Frosst Ltd. and the Natural Sciences and Engineering Research Council of Canada is gratefully acknowledged.

Received, 3rd March 1993; Com. 3/01261A

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