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Novel aziridine esters by the addition of aromatic nitrogen heterocycles to a 2*H*-azirine-3-carboxylic ester

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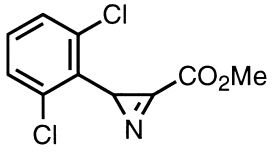
Abstract

Methyl 2-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate acts as an efficient alkylating agent for a variety of five-membered aromatic heterocycles. The aziridines derived from heterocycles that bear an α-carbonyl substituent react with TFA to give pyrroloimidazoles; 2,6-dichlorobenzaldehyde is also produced.

Keywords: 2*H*-azirines; aziridines; 5*H*-pyrrolo[1,2-*c*]imidazoles.

2*H*-Azirines are more susceptible to nucleophilic attack than other imines because of the strained nature of the C=N bond.[1] When this ring strain is combined with the presence of an activating group on the carbon atom nucleophilic addition reactions occur very easily, as we have previously shown for the azirine ester **1**.[2] This azirine reacts rapidly with alcohols, thiols and amines at room temperature. With simple primary or secondary amines as nucleophiles the intermediate aminoaziridine adducts cannot be isolated because the three-membered ring is easily cleaved.



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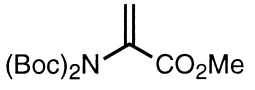

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It was reported earlier that five-membered heteroaromatic compounds undergo conjugate addition to *N*,*N*-bis(*tert*-butyloxycarbonyl)dehydroalanine methyl ester **2** in the presence of potassium carbonate to give β-substituted alanine derivatives.[3] We have now found that these

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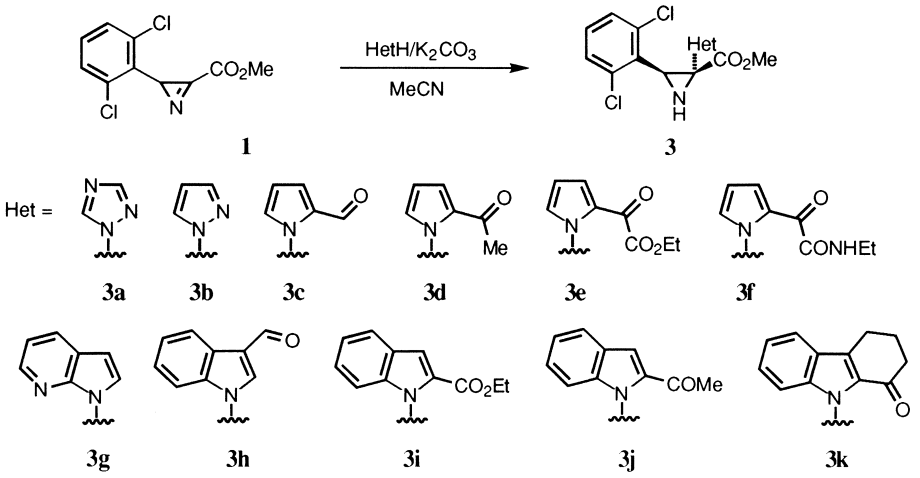
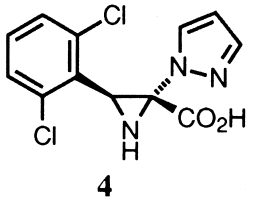
heterocycles react with the azirine ester **1** under similar conditions to give the novel aziridine esters **3** (Scheme 1 and Table 1).[4] The reactions are, in most cases, highly stereoselective. We have previously shown that oxygen and sulfur nucleophiles add to the C=N bond of this azirine from the less hindered face, leading to aziridines in which the aryl substituent and incoming nucleophile are *trans*;[2] the stereochemistry of the esters **3** has been assigned on the basis of these earlier results. Aziridines that are unsubstituted on nitrogen and that bear an amino substituent are uncommon because the lone pair on the exocyclic nitrogen tends to promote opening of the ring. The relatively greater stability of these aziridines is probably due to the delocalisation of the nitrogen lone pair into the heteroaromatic ring system. In a recent communication Barroso and Kascheres described the nucleophilic addition of imidazoles and pyrazoles to 3-phenyl-2*H*-azirines; in these reactions the intermediate aziridine adducts could be detected by NMR but were too unstable to allow their isolation.[5] Our aziridines are stable to chromatograhy but the aziridines **3g** and **3k** derived from 7-azaindole and from tetrahydrocarbazolone were found to regenerate the parent heterocycle in high yield when they were treated with TFA at room temperature. On the other hand the aziridine **3b** was hydrolysed in basic conditions without cleavage of the substituent to give the amino acid **4**.[6]



Scheme 1.



The aziridine **3c** derived from pyrrole-2-carboxaldehyde was found to undergo a further unusual transformation when treated with TFA at room temperature, giving the 5*H*-pyrrolo[1,2-*c*]imidazole **5a** in good yield.[7] 2,6-Dichlorobenzaldehyde was also formed in high yield. The acylpyrroles **3d–f** were similarly converted into the pyrroloimidazoles **5b–d**, respectively. The structures of the products were established by elemental analysis and by ^{1}H NMR spectroscopy; in particular, by the presence of a 2H singlet for H-5 close to δ 4.8 in each spectrum. The course

Table 1
Aziridines **3**

No.	Yield (%)	M.p./ °C	^{1}H NMR ($CDCl_3$)			
			NH (δ)[a]	3-H (δ)[a]	*J* (Hz)	Me (δ)
3a	90[b]	125.5–126.5[c]	3.34	3.87	9.6	3.65
3b	76[b]	101.5–102.5[d]	3.23	3.91	10.2	3.64
3c	97[e]	114–115.5[f]	3.36	3.94	10.5	3.58
3d	99[b]	132.5–133.5[d]	3.32	3.91	10.5	3.58
3e	94[b]	105–107[e]	3.35	3.92	10.2	3.59
3f	94[b]	147–148[c]	3.29	3.93	10.2	3.59
3g	92[b]	125–126.5[d]	3.54	4.00	10.5	3.54
3h	89[g]	141.5–142.5[d]	3.33	3.93	10.2	3.60
3i	93[b]	131–132[d]	2.91	4.15	10.5	3.70
3j	51[h]	138.4–139.5[f]	2.87	4.11	10.8	3.67
3k	39[i]	109–110.5[d]	2.94	4.15	10.5	3.66

[a] All signals are doublets.

[b] Based on sample pure by NMR but before recrystallisation.

[c] From ether.

[d] From ethyl acetate–hexane.

[e] NMR shows the presence of a minor isomer; δ 3.81 (3 H, s, Me) and 4.31 (1 H, d, *J* 10.2 Hz, aziridine 3-H).

[f] From ether–hexane.

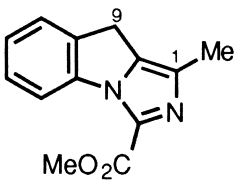
[g] NMR shows presence of a minor isomer; δ 3.83 (3 H, s, Me) and 4.30 (1 H, d, *J* 10.2 Hz, aziridine 3-H).

[h] After recrystallisation.

[i] After purification by column chromatography.

of the reaction can be rationalised as shown in Scheme 2, the cyclisation being initiated by protonation of the carbonyl group. Overall the azirine **1** is acting as a synthetic equivalent of the (unknown) imine of methyl glyoxylate. There are few literature examples of the 5*H*-pyrrolo[1,2-*c*]imidazole ring system and all are derived from imidazoles.[8]

The annulation reaction was also carried out with the aziridine **3j** derived from 2-acetylindole. This gave the 9*H*-imidazo[1,5-*a*]indole **6**[9] in 78% yield. An attempt to extend the reaction sequence to 2-formylimidazole was unsuccessful; a complex mixture was obtained from the reaction of this compound with the azirine **1**.



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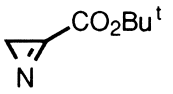

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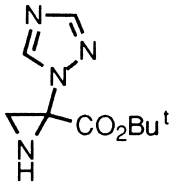

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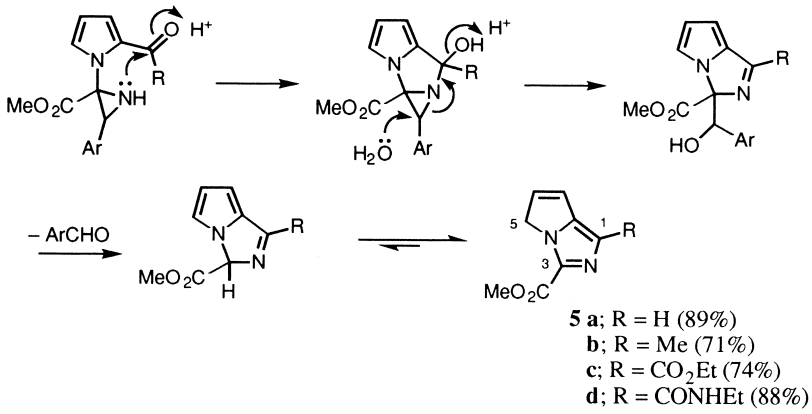

Scheme 2.

We have thus found that the azirine **1** is a good alkylating agent for nitrogen heterocyles and that further useful transformations of the resulting aziridines are possible. In preliminary experiments we have also found that the simpler azirine-3-carboxylic ester **7**[10] lacking the aryl substituent can undergo an analogous reaction; it gave the aziridine **8**[11] with 1,2,4-triazole and potassium carbonate. The isolated yield of **8** was low, apparently because of its instability to silica gel chromatography. These addition reactions may nevertheless provide a more general entry into aziridine esters of this type.

References

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3. Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S. *Tetrahedron Lett.* **1999**, *40*, 4099–4102.
4. *General procedure for preparation of aziridines* **3**: The appropriate heterocycle (1 mmol) was added to a rapidly stirred solution of the azirine **1** (1 mmol) in acetonitrile (10 mL) at room temperature containing a suspension of K_2CO_3 (6 mmol). The reaction mixture was monitored by TLC until no azirine **1** was detectable. The reaction mixture was then filtered and the filtrate was evaporated to dryness. The residue contained the aziridine **3** by NMR, in some cases together with traces of a diastereoisomer (Table 1). Analytical samples were obtained by crystallisation of the residues; all new compounds gave correct elemental analyses.
5. Barroso, M. T.; Kascheres, A. *J. Org. Chem.* **1999**, *64*, 49–53.
6. The acid **4** was isolated (65%) from the hydrolysis of **3b** by NaOH in dioxane and had mp 111–112°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.29 (1H, s, aziridine 3-H), 3.6 (1H, br, NH), 6.46 (1H, t, $J=2.1$ Hz, pyrazole 4-H), 7.25–7.35 (3H, m, Ar-H), 7.34 (1H, dd, $J=2.0$ and 0.5 Hz, 5-H) and 7.92 (1H, dd, $J=2.0$ and 0.5 Hz, 3-H).
7. TFA (1 mmol) was added to a rapidly stirred solution of the aziridine **3c** (1 mmol) in acetonitrile (10 mL) at room temperature. The course of the reaction was followed by TLC and when no starting material remained the solution was evaporated to dryness under reduced pressure. The crude residue was dissolved in ethyl acetate and, after washing with aq. $NaHCO_3$ and silica gel chromatography, gave the ester **5a** (89%), mp 97.5–98.5°C (from ethyl acetate–ether); δ_H (300 MHz, $CDCl_3$): δ 3.97 (3H, s, Me), 4.78 (2H, t, $J_{56}=J_{57}=1.8$ Hz, 5-H), 6.57 (1H, dt, $J_{67}=6.1$ Hz, $J_{56}=1.8$ Hz, 6-H), 6.69 (1H, dt, $J_{67}=6.1$ Hz, $J_{57}=1.8$ Hz, 7-H) and 7.05 (1H, s, 1-H); δ_C (75 MHz, $CDCl_3$): 52.23, 53.38, 119.64, 120.80, 133.47, 133.68, 145.07 and 159.02. Compounds **5b**–**5d** have analogous spectra.
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9. Compound **6** was obtained from the aziridine **3j** and TFA (1.2 equiv.) in acetonitrile after heating under reflux for 3 h. Compound **6**: mp 150–151°C (from ether); δ (300 MHz, $CDCl_3$) 2.35 (3H, s, 1-Me), 3.87 (2H, s, 9-H), 4.02 (3H, s, ester Me), 7.30 (1H, td, $J=7.8$ and 0.9 Hz), 7.40 (1H, t, $J=7.8$ Hz), 7.48 (1H, d, $J=7.5$ Hz) and 8.66 (1H, d, $J=7.8$ Hz).
10. Alves, M. J.; Gilchrist, T. L. *Tetrahedron Lett*. **1998**, *39*, 7579–7582.
11. The aziridine **8** was isolated as a pale yellow oil (7.5%) by dry flash chromatography; δ (300 MHz, $CDCl_3$) 1.38 (9H, s), 2.26 (1H, br t, $J=10.5$ Hz (approx.), NH), 2.41 (1H, d, $J_{3,3'}0$, $J_{3,NH}=9.9$ Hz, 3-H), 2.70 (1H, d, $J_{3',NH}=11.1$ Hz, 3′-H), 7.92 (1H, s) and 8.26 (1H, s).