Convenient Synthesis of Optically Active 2*H*-Azirine-2-carboxylic esters by Swern Oxidation of Aziridine-2-carboxylic esters

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Abstract: The synthesis of optically active 2*H*-azirine-2-carboxylic esters was achieved by Swern oxidation of the corresponding aziridine-carboxylic esters. For both *trans* and *cis* aziridine esters this oxidation gives a regioselective introduction of the double bond which is not in conjugation with the ester function. The methyl ester of *ent*-Azirinomycin was prepared in this manner.

Recently we reported¹ a synthesis of 2*H*-azirine-2-carboxylic esters **4** from the corresponding aziridine-2-carboxylic esters **2** by a two step process involving N-chlorination of **2** with *tert*-butyl hypochlorite and a subsequent dehydrochlorination of **3** with base. The starting materials **2** were conveniently prepared from the corresponding oxirane-2-carboxylic esters **1** by successive treatment with sodium azide (in the presence of ammonium chloride) and triphenylphosphine, and subsequent heating either in acetonitrile or dimethylformamide².

Scheme 1

This sequence of events, which is depicted in Scheme 1, is attractive for the preparation of azirine esters **4** as it constitutes an entree to homochiral compounds. Previous syntheses of azirine esters by Harvey³, Hassner⁴, Shin⁵ and Wade⁶ are based on the photolysis or thermolysis of azido alkenoates and that by Nishiwaki⁷, Auricchio⁸ and Ueda⁹ on transformation of an isoxazole ring. None of these syntheses allows the preparation of optically active azirine esters **4**. However, the attractiveness of the conversion of aziridine esters **2** into azirine esters **4** described above (Scheme 1) is overshadowed by the moderate yields (9-39%) of the HCl elimination reaction of **3**. Therefore, we searched for alternative methods to accomplish the conversion of **2** into **4**. In essence, the overall reaction is an oxidation of a secondary amine to an imine. A series of oxidizing agents recommended¹⁰ for such oxidation was tried in the present case, but none of these attempts was successful. Gratifyingly however, we found that the Swern oxidation¹¹ is an excellent method for the desired

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conversion of **2** into **4**. At first sight, this method did not seem promising, because it was only mentioned a few times for the oxidation of amines^{12,13} and moreover, the reagent deemed incompatible with our three-membered ring substrate.

In a typical procedure dimethyl sulfoxide (4.8 equiv.) dissolved in dichloromethane was added to a stirred solution of 2.2 mole equivalents of oxalyl chloride in the same solvent at -70 °C. After 10 min. one equivalent of substrate **2** was added at this temperature in 5 min. Then an excess of triethylamine (5 equivalents) was added and the reaction mixture was allowed to attain room temperature slowly. After 4h the cloudy reaction mixture was concentrated at reduced pressure, diethyl ether was added and the precipitated salts were filtered off. Work-up then gave the azirine esters, which were purified by flash chromatography over silica gel (ethyl acetate/hexane 1/9). The structure of the products was deduced from IR and ¹H-NMR spectral data¹⁴. The results for the *trans* aziridine esters **2** are collected in Table 1.

Table 1

	R	config.	e.e. 2 , ¹⁷ (%)	conversion (%)		yield (%)	α_D^{20} in CHCl ₃
a	n-C ₃ H ₇	(-)-2R,3S	89	86	a	72	-76.0 c=0.7
b	n-C ₇ H ₁₅	(+)-2S,3R	nd	91	b	86	+55.5 c=1.1
c	n-C ₈ H ₁₇	(-)-2R,3S	95	85	c	83	-30.0 c=0.6
d	Ph	(+)-2S,3R	100	96	d	84	+274 c=0.6
e	Ph	(-)-2R,3S	100	96	e	86	-290 c=1.1

The Swern oxidation of the *trans* esters **2** exclusively leads to 2*H*-azirine-2-carboxylic esters **4**. No sign of any isomeric 2*H*-azirine-3-carboxylic ester with the imine function in conjugation with the ester group was observed. This result can be explained by adopting the mechanism of the Swern oxidation of alcohols which involves the intermediacy of chloro-dimethylsulfonium chloride (Me₂S⁺-Cl·Cl⁻)¹¹. This species reacts with the aziridine nitrogen atom to give a sulfonium salt **5**. (Scheme 2). Subsequent reaction with base then produces a sulfonium ylide **6** which undergoes a *syn* elimination through facile intramolecular proton transfer (Scheme 2) to give azirine **4**. To explain the exclusive formation of **4** and none of its isomer, it must be assumed that the invertomer of **5** with the Me₂S⁺ group *syn* to the ester function is (strongly) preferred (Scheme 2). Considering this proposed mechanism one would expect that for *cis* aziridine esters **7** the

intermediate sulfonium unit **8** has a preferred conformation in which the Me₂S⁺ group is positioned *anti* to both the R substituent and the ester function, and *syn* to both abstractable hydrogens (Scheme 3). Therefore, at

least some azirine ester with the imine function in conjugation with the ester group would be expected, given the higher acidity of the C₂ proton as compared with the C₃ proton.

Scheme 3

Surprisingly however, Swern oxidation of the *cis* substrate 7, in all cases studied, again gave exclusive formation of azirine ester 4 (Scheme 3, Table 2). It is clear that a more detailed mechanistic study is needed to satisfactorily explain the regiochemistry of the Swern oxidation of *trans* and *cis* aziridine esters. Experiments in this direction are currently ongoing.

Table 2

	R	config.	e.e. (%) ¹⁷	conversion (%)		yield (%)	α^{20}_{D} in CHCl_3
f	PhCH_2	2S,3S	nd	100	f	70	+58.3 $c=0.6$
g	$c\text{-C}_6\text{H}_{11}$	2R,3R	nd	77	g	63	-66.9 $c=0.2$
h	CH_3	(-)-2R,3R	100	100	h	54	-98.9 $c=0.5$
i	Ph	(-)-2R,3R	100	70	e	60	-281 $c=0.5$

Oxidation of enantiopure¹⁷ antipodal aziridine esters **2d** and **2e** strongly suggests that the integrity of the stereogenic center at the C₂ atom is retained, because the azirine esters **4d** and **4e** have opposite optical rotation of almost the same magnitude. Entry h in Table 2 is of interest, as it essentially represents the synthesis of naturally occurring azirinomycin which is the corresponding *ent* carboxylic acid¹⁵. In this case the homochiral aziridine ester (α^{20}_{D} -29.5, CHCl_3 $c=0.5$) **7h** was prepared from threonine. Azirine ester **4h** was obtained as an enantiopure compound¹⁶ (α^{20}_{D} -98.9, CHCl_3 $c=0.5$). When homochiral **7i**¹⁷ was used, compound **4e** was obtained in good yield, proving that indeed steric integrity is retained during the Swern oxidation process.

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