Tetrahedron Letters,Vol.30,No.36,pp 4881-4884,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

A CONVENIENT SYNTHESIS OF OPTICALLY ACTIVE 1H-AZIRIDINE-2-CARBOXYLIC ACIDS (ESTERS).

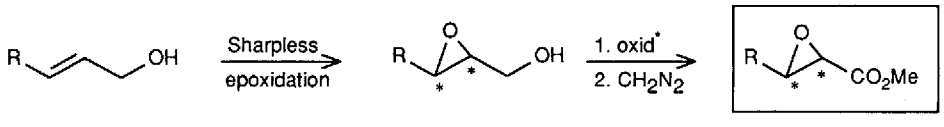
J. Legters, L. Thijs, B. Zwanenburg*

Department of Organic Chemistry, University of Nijmegen,
Toernooiveld, 6525 ED NIJMEGEN, The Netherlands.

Summary: Optically active glycidic esters, prepared from allylic alcohols employing the Sharpless epoxidation, were treated with sodium azide. In a subsequent reaction with PPh_3 the azido alcohols thus obtained were converted into aziridine-2-carboxylic esters of high optical purity in good yields.

Aziridine-2-carboxylic acids represent an interesting class of compounds since they may be considered simultaneously as α- or β-amino acid derivatives. Little attention has been devoted so far to these carboxylic acids, although a considerable amount of information is available about the chemistry of aziridines in general.[1-3] The syntheses of aziridinecarboxylic acids reported thusfar[4-9] are non-stereospecific and in most cases are not applicable to N-unsubstituted derivatives. We are particularly interested in N-unsubstituted representatives because they can be incorporated into a peptide chain and then serve therein as an electrophilic moiety.[10]

In this letter we report a convenient method for the synthesis of optically active 1H-aziridine-2-carboxylic acids (esters) **1** from the corresponding glycidic esters **4**. These epoxy esters **4** are readily accessible in optically active form, employing the Sharpless epoxidation of allylic alcohols,[11,12] as is outlined in scheme 1.

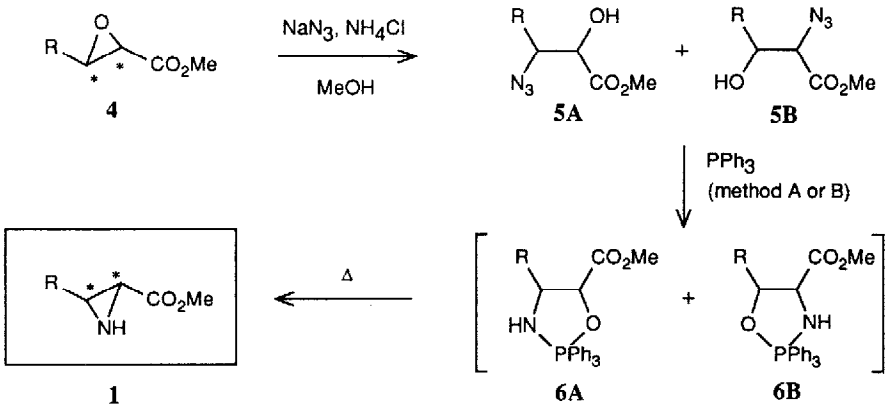


2 **3** **4**

*I: $RuCl_3$, $NaIO_4$; or II: a. $(COCl)_2$, DMSO, b. $NaClO_2$, NaH_2PO_4. *Scheme 1*

The glycidic esters **4** thus obtained were treated with sodium azide. In the case of alkyl substituted glycidic esters this S_N2-type reaction[13] invariably led to a mixture of the isomeric azido alcohols **5A** and **5B**. For substrate **4g**, with a 3-phenyl substituent, only one regioisomer, arising from attack at C-3, was obtained (scheme 2). The yields of these reactions are collected in the Table.

In a subsequent step the azido alcohols were treated with triphenylphosphine to give the corresponding 1,3,2-oxazaphospholidines **6A** and **6B**. When this so-called Staudinger reaction[14] was carried out in ether as



Scheme 2

*Table : Conversion of optically active glycidic esters **4** into optically active aziridine-2-carboxylic esters **1**.*

entry	R	glycidic ester **4**			azido alcohols **5**	aziridine **1**			
		config	$[\alpha]_D^{20a}$	e.e.(%)[b]	yield (%)	yield (%)	method	$[\alpha]_D^{20a}$	e.e.(%)[c]
a	nC_3H_7	(2R,3S)	-24.0°	84	85	56	A	+72.5°	82
b		(2S,3R)	+26.1°	87	92	78	B	-85.5°	89
c	nC_6H_{13}	(2R,3S)	-26.0°	87	93	83	B	+78.0°	88
d		(2S,3R)	+25.5°	87	95	78	B	-77.1°	90
e	nC_8H_{17}	(2R,3S)	-24.9°	73	88	50	A	+66.7°	88
f		(2S,3R)	+24.5°		84	76	B	-70.8°	95
g	Ph	(2R,3S)	-173.3°	>96	96	66	B	+262.3°	>92

[a] *Measured in $CHCl_3$ solutions.*
[b] *E.e. of epoxy alcohol, determined from known optical rotations (entries a, e, g) or by 400 MHz ^{1}H-NMR analysis of the Mosher derivative (entries b, c, d).*
[c] *Determined from known optical rotation (entry g) or by 400 MHz ^{1}H-NMR analysis of the Mosher derivative (entries a, b, c, d, e, f).*

reaction medium, the oxazaphospholidines could be isolated. The compounds **6** were then subjected to a bulb-to-bulb distillation using a Kugelrohr apparatus, yielding the aziridinecarboxylic esters in moderate yields (method A) (entries a, e). When, however, the Staudinger reaction was performed in DMF or acetonitrile as the solvent, stirring at room temperature for 0.5 h followed by heating at about 80°C for a few hours afforded the aziridines in good yields without isolation of the intermediate oxazaphospholidines

(method B) (entries b, c, d, f, g). The progress of the aziridine formation was monitored by TLC and infrared spectroscopy. Mixtures of isomeric azido alcohols were used for the Staudinger reaction. Method A permits only the use of rather small amounts of substrate and the distillation procedure is experimentally rather difficult. Method B is much preferred, since the reaction can be carried out on at least a 10 g scale without decomposition problems.

The intermediate oxazaphospholidine derived from azido alcohol **5Ag** was characterized by means of an X-ray diffraction analysis (figure 1).[15] This reveals that the epoxide opening with azide occurs with inversion of configuration. Thus after the Staudinger reaction we obtained a *cis*-oxazaphospholidine from a *trans*-glycidic ester. All the oxazaphospholidines **6** showed a characteristic IR absorption near 3450 cm^{-1} (NH).

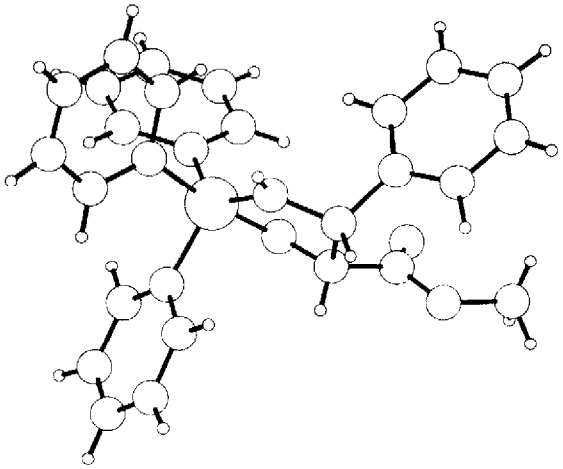
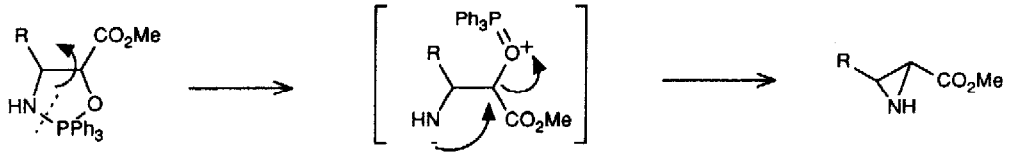
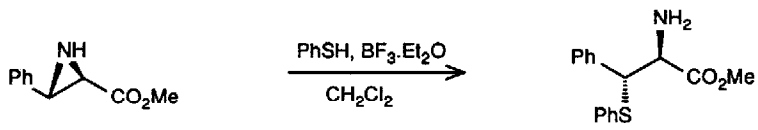


Figure 1: X-ray minimum overlap view of oxazaphospholidine 6Ag.[15]

NMR analysis of aziridine **1g** showed the formation of a *trans* product. For the formation of this *trans* substituted aziridine ring a second inversion of configuration is necessary. We consider that the N-P bond in the oxazaphospholidine is cleaved initially and an intramolecular S_N2 displacement of $O{=}PPh_3$ then yields the aziridine **1**, with inversion at the substitution center (scheme 3). Overall, both chiral centers are inverted, one in the epoxide opening and the other in the aziridine ring closure.



Scheme 3



1g (2S, 3R) **7**

Scheme 4

Further applications of these optically active aziridinecarboxylic acid derivatives, e.g. peptide synthesis or nucleophilic ring opening, are currently under investigation. Ring opening of 3-aryl aziridine ester **1g** for example with thiophenol in the presence of one equivalent of boron trifluoride etherate affords the 3-phenylthio amino ester **7** in 67% yield as a single diastereoisomer ($[\alpha]_D^{20}$ = +192.3° (c = 1.2, $CHCl_3$)(scheme 4). Nucleophilic ring opening of 3-alkyl aziridine-2-carboxylic esters requires the use of an activating electron withdrawing group at nitrogen.

References and notes:

1. P.E. Fanta, in *"Heterocyclic Compounds with Three- and Four-membered Rings"*, Part 1, A. Weissberger (ed.), Wiley Interscience, New York (1964), p. 528.
2. J.A. Deyrup, in *"Small Ring Heterocycles"*, Part 1, A. Hassner (ed.), Wiley Interscience, New York (1983), p. 11.
3. O.C. Dermer, G.E. Ham, *"Ethylenimine and Other Aziridines"*, Academic Press, Inc., New York (1969), p. 1.
4. Y. Nakagawa, T. Tsuno, K. Nakajima, M. Iwai, H. Kawai, K. Okawa, *Bull. Chem. Soc. Jap.* **1972**, *45*, 1162.
5. K. Nakajima, F. Takai, T. Tanaka, K. Okawa, *Bull. Chem. Soc. Jap.* **1978**, *51*, 1577.
6. I. Nakamura, K. Harada, F. Gaymard, R. Guedj, *Chem. Lett.* **1979**, 313.
7. P. Scheiner, *J. Am. Chem. Soc.* **1968**, *90*, 988.
8. R.S. McDaniel, A.C. Oehlschlager, *Tetrahedron* **1969**, *25*, 1381.
9. R.S. Atkinson, G. Tughan, *J. Chem. Soc. Perkin Trans I* **1987**, 2803.
10. A Japanese group has published some work in this area,[5] but they used only two aziridinecarboxylic acids, derived from natural serine and threonine.
11. T. Katsuki, K.B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 5974.
12. Y. Gao, R.M. Hanson, J.M. Klunder, S.Y. Ko, H. Masamune, K.B. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765.
13. M. Bartók. K.L. Láng, in *"Small Ring Heterocycles"*, Part 3, A. Hassner (ed.), Wiley Interscience, New York (1985), p. 115.
14. Y.G. Gololobov, I.N. Zhmurova, L.F. Kasukhin, *Tetrahedron* **1981**, *37*, 437.
15. J.M.M. Smits, P.T. Beurskens, L. Thijs, A.A.W.M. van Loon, B. Zwanenburg, *J. Cryst. Spectr. Res.* **1988**, *18*, 625.

Acknowledgement:

This investigation was supported by the Netherlands Foundation of Chemical Research (SON) with financial aid from the Netherlands Organization for the Advancement of Research (NWO).

(Received in UK 12 July 1989)