Asymmetric Synthesis of 2*H*-Azirine Carboxylic Esters by an Alkaloid-Mediated Neber Reaction

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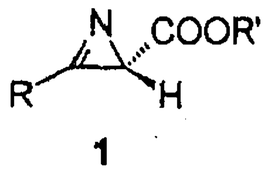
Received April 29, 1996

The highly strained and reactive 2*H*-azirines have been extensively studied for various synthetic purposes, such as ring expansion reactions,[1,2] cycloaddition reactions,[2,3] and preparation of functionalized amines[3] and substituted aziridines.[1−3] The applicability of these small-ring heterocycles is strongly determined by the nature of the substituents.[2,3] 2*H*-Azirine 2-carboxylic acids and esters are of particular interest as they form an entrée to *e.g.* nonprotein amino acids.[4] Moreover, azirinomycin[5] (**1**, R = Me, R′ = H), disydazirine[6,7] (**1**, R = *trans*-n-$C_{13}H_{27}CH{=}CH$, R′ = Me), and antazirine[7] (**1**, R = *trans*-$Br_2C{=}CH(CH_2)_9CH{=}CH$, R′ = Me) are naturally occurring antibiotics; the first mentioned was isolated from *Streptomyces aureus*, and the latter two were isolated from the marine sponge *Dysidea fragilis*.



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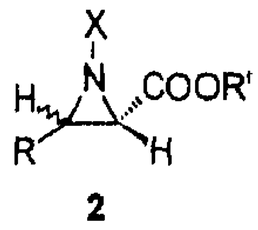

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This communication focuses on the asymmetric synthesis of azirine esters **1**. Previous synthesis of azirine esters are based on the photolysis or thermolysis of azido alkenoates[8] or on a transformation of an isoxazole ring:[9] These routes to azirines are not suited for the preparation of single enantiomers of the target compounds. Recently, elimination reactions of appropriately *N*-substituted aziridine 2-carboxylic esters **2** were successfully used for the preparation of azirine esters **1** of high enantiopurity, *viz.* dehydrochlorination from *N*-chloroaziridines[10] (*e.g. trans*-**2**, X = Cl, R = Ph, R′ = Me) and the elimination of sulfenic acid from *N*-sulfinylaziridines[11] (*e.g. cis*-**2**, X = *p*-TolS(O), R = Ph, R′ = Me). A remarkable synthesis of optically active azirine esters **1** is the Swern oxidation of aziridine esters[12] (*e.g. trans*-**2**, X = H, R = n-C_3H_7, R′ = Me) which in essence is a base-induced *syn* elimination reaction of *N*-dimethylsulfonium intermediates **2** (X = Me_2S^+). The three aforementioned methods start with aziridine esters of high enantiopurity, the preparation of which is rather lengthy.[13] The Neber reaction,[2,14] *i.e.* the formation of aminoketones by treatment of sulfonic esters of ketoximes with alkoxide, proceeds via an azirine intermediate,[2,15] and by proper modification this reaction can be used for the synthesis of azirines[2,16] but is lacking generality mainly due to the subsequent reaction of the azirine.[2,17] Only one example of the synthesis of optically active azirines *via* this route is known in the literature. Piskunova *et al.*[16d] reported a chiral auxiliary mediated asymmetric Neber reaction with a de of 92%.

For the target compounds **1** ketoxime *p*-toluenesulfonates of 3-oxocarboxylic esters **4** are the principal starting materials. The methylene protons in these substrates are doubly activated, thus allowing the use of a mild base during the Neber reaction to azirines **1**.

A series of β-keto esters **3** was readily converted into the ketoxime tosylates **4** in a simple two-step procedure in fair yields (Scheme 1). The intermediate ketoximes must be tosylated immediately after their preparation, as otherwise the competing formation of isoxazolones takes place.[18] The oxime tosylates **4** are obtained as a mixture of *syn* and *anti* isomers that are in equilibrium at ambient temperature. Treatment of tosylates **4** with triethylamine in dichloromethane at room temperature for 6 h gave a smooth conversion to the desired azirines **1** in good yields after purification by distillation[19,20] (Scheme 1). Spectral data of compounds **1b**[8c] and **1d**[8c,10] are in accordance with literature data.

We then investigated a series of chiral tertiary bases for the reaction of **4b** to achieve an asymmetric synthesis. In all cases studied the azirine was obtained (Table 1); however, asymmetric conversion was only observed for the three pairs of cinchona alkaloids.[21] With sparteine, brucine, and strychnine virtually no optically active heterocycle was formed. The best results were obtained with dihydroquinidine, and therefore the reaction conditions were optimized using this base. The solvent of choice turned out to be toluene (Table 1), the optimum concentration 2 mg/mL, and the best reaction temperature 0 °C. Quinidine gave essentially the same results under these conditions and was used in subsequent reactions. It should be noted that in a hydroxylic solvent such as ethanol no asymmetric conversion was observed. The results for the substrates **4a**−**e**

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(19) The purity of the compounds is >95% (^{1}H-NMR and GLC analyses).

(20) The ketoxime tosylate from ethyl 2-methyl-3-oxobutanoate did not react with Et_3N, but needed the stronger base *t*BuOK for its conversion in the corresponding azirine.

(21) The enantiopurity of the azirine esters **1** was determined by ^{1}H-NMR measurements in $CHCl_3$ using Yb(tfc)$_3$ as chiral shift reagent by the shift difference of the C_2-protons and (except for **1d**) the C_4-protons.

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Scheme 1

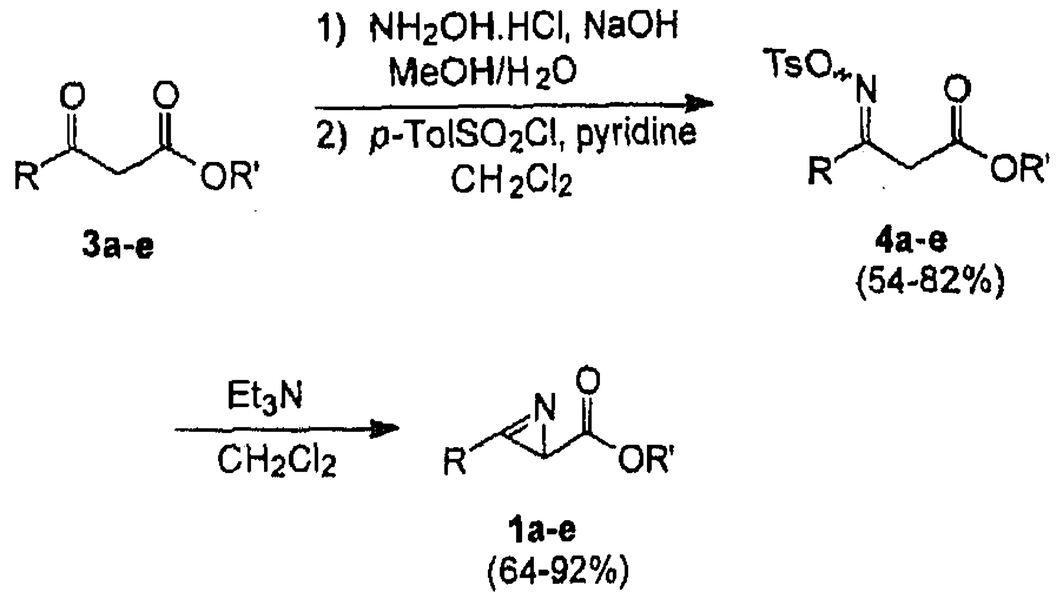


Table 1. Influence of Base and Solvent in the Enantioselective Synthesis of **1b** *via* the Neber Reaction (at Ambient Temperature)

base	solvent	yield[a] (%)	ee[21] (%)
sparteine	CH_2Cl_2	53	0
brucine		38	5 (+)
strychnine		37	4 (+)
cinchonine		52	32 (−)
cinchonidine		43	24 (+)
quinine		34	24 (+)
quinidine		37	45 (−)
dihydroquinine		41	22 (+)
dihydroquinidine		47	47 (−)
dihydroquinidine	ethanol	75	0
	acetonitrile	47	8 (−)
	ether	48	45 (−)
	hexane	59	47 (−)
	CS_2	77	63 (−)
	toluene	74	70 (−)

[a] Not optimized.

Table 2. Synthesis of Azirine Carboxylic Esters **1** with a Stoichiometric Amount of Base Under Optimal Conditions

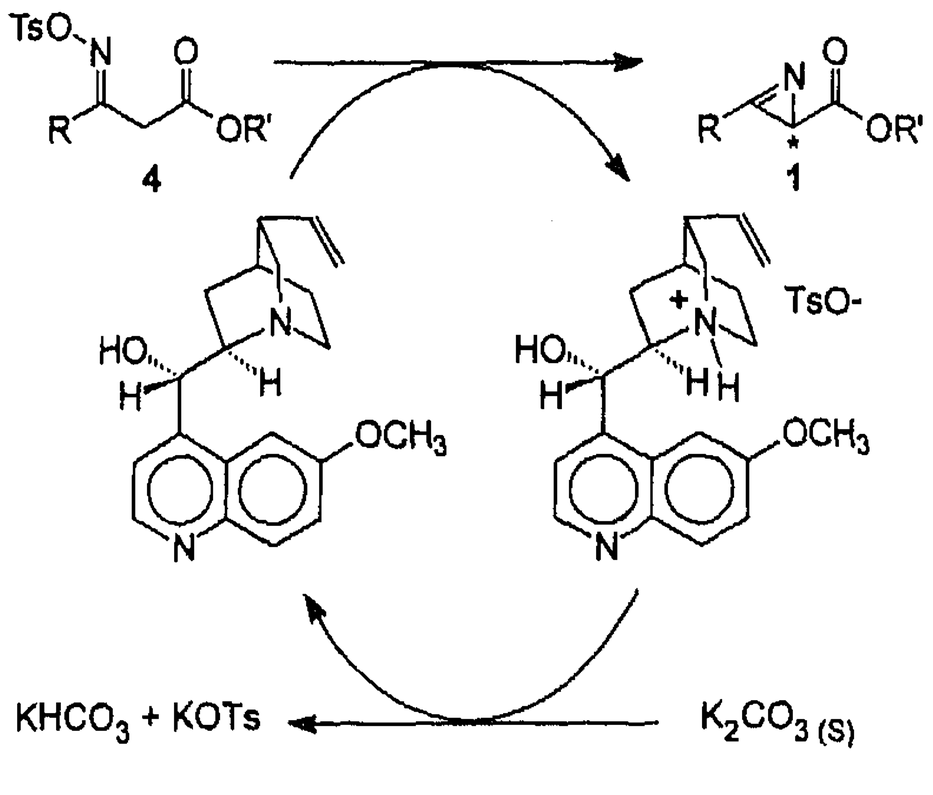
	R	R′	base	yield **4** (%)	yield **1** (%)	ee[21] (%)
a	Me	Me	quinidine	79	40	81 (R)
b	Me	Et	quinidine	72	43	82 (R)
			quinine		38	55 (S)
c	Me	*t*Bu	quinidine	92	29	44 (R)
d	*n*Pr	Et	quinidine	60	72	80 (R)
e	Bz	Et	quinidine	54	85	80 (R)
			quinine		58	57 (S)

are collected in Table 2. It is of importance to note that the pseudoenantiomers of the alkaloid bases gave opposite antipodes of the products **1**. The absolute configuration of the azirines was established by correlation with the optical rotation of compound **1a**[12] ($\alpha^{20}_D = -77.2°$, $CHCl_3$, $c = 0.5$), indicating that the use of quinidine as the base leads predominantly to the (*R*)-enantiomer.

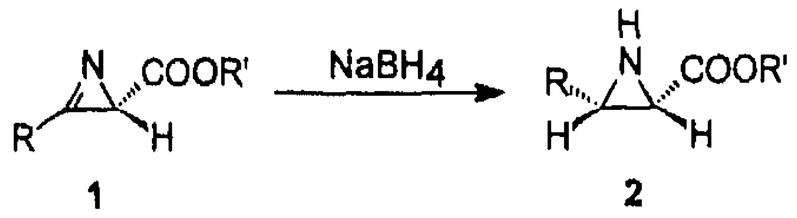
To explain this asymmetric Neber reaction, it is suggested that the alkaloid bases form a tightly bound complex with the ketoxime tosylate. Since the presence of an alcohol function in the alkaloid base seems to be a prerequisite, it is suggested that hydrogen bonding of the base and the substrate through this hydroxyl group is a governing factor in the enantiodifferentiation during the abstraction of the methylene protons. This proposal is supported by the observation that in a hydroxylic solvent no asymmetric induction takes place and that additives such as LiCl and especially H_2O lower the optical yield considerably. Furthermore, calculations at the semiempirical level[22] have shown that a hydrogen bond between the dihydroquinidine OH and one of the S=O moieties of the ketoxime tosylate leads to a stable complex in which the aromatic parts of the two molecules are placed in a favorable edge-on position.

(22) Mopac 93 @ Fujitsu. Calculations performed with the AM1 Hamiltonian.

Scheme 2



Scheme 3



In the above enantioselective azirine synthesis a stoichiometric amount of alkaloid base was used. This drawback could be overcome by regenerating the alkaloid base in situ (Scheme 2). This regeneration process should not interfere with the abstraction of the methylene protons, as this would lead to a decrease or even a complete loss of enantioselectivity. Excellent results were obtained when 10−20 equiv of potassium carbonate were added to the reaction mixture at room temperature using only 10 mol % of quinidine.[23] It was necessary to perform this reaction at ambient temperature as this reaction hardly proceeded at 0 °C. However, as in the case of the stoichiometric process, this resulted in a somewhat lower ee (~70%).

Reduction of the azirine esters **1** with $NaBH_4$[4] leads exclusively to the formation of *cis*-aziridine carboxylic esters **2**[24] (Scheme 3), which are difficult to obtain by other methods. When the reduction is performed with optically active azirine **1b**, no trace of the *trans*-aziridine[24b] could be observed by NMR; therefore, the *cis*/*trans* ratio must be over 95:5. Furthermore no loss of chirality is observed.[25] Thus, the Neber reaction provides an alternative route to optically active aziridine carboxylic esters **2** (X = H), which are important for the synthesis of various anomalous amino acids.

In conclusion, we accomplished a convenient novel catalytic asymmetric synthesis of azirine carboxylic esters by the Neber reaction of ketoxime tosylates derived from 3-oxocarboxylic esters.

Acknowledgment. This communication is dedicated to Professor Nelson J. Leonard on the occasion of his 80th birthday.

Supporting Information Available: Experimental procedures and analytical data for compounds **1**, **2b**, and **4** (7 pages). See any current masthead page for ordering and Internet access instructions.

JA961414O

(23) General procedure for the catalytic asymmetric synthesis of azirine esters **1**: A solution of ketoxime tosylate **4** (200 mg) in dry toluene (10 mL) was added gradually to a vigorously stirred solution of quinidine (0.1−0.25 equiv) and a large excess of K_2CO_3(s) (10 equiv) in dry toluene (90 mL) at room temperature. After 24 h the mixture was filtered, and dilute aqueous HCl (50 mL, 0.05 M) was added. The resulting mixture was extracted three times with diethyl ether (50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give the azirine ester **1**. The crude product was purified by bulb-to-bulb distillation.

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