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

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Received April 29, 1996

The highly strained and reactive 2H-azirines have been extensively studied for various synthetic purposes, such as ring expansion reactions,1,2 cycloadDITION reactions,3,4 and preparation of functionalized amines5 and substituted aziridines.1-3 The applicability of these small-ring heterocycles is strongly determined by the nature of the substituents.2,3 2H-Azirine 2-carboxylic acids and esters are of particular interest as they form an entrée to e.g. nonprotein amino acids.4 Moreover, azirino-5,6 (1, R = Me, R' = H), disydazirine6,7 (1, R = trans-C6H3=CH=CH, R' = Me), and antazirin8 (1, R = trans-C6H3=CH(CH2)2=CH=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.

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 alkanoates6 or on a transformation of an isoxazoline ring.8 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, sic, dehydrochlorination from N-chloroaziridines9 (e.g. trans-2, X = Cl, R = Ph, R' = Me) and the elimination of sulfonic acid from N-sulfinylaziridines10 (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 esters12 (e.g. trans-2, X = H, R = n-C3H7, R' = Me) which in essence is a base-induced syn elimination reaction of N-dimethylsulfoxonium intermediates 2 (X = Me2S+). The three aforementioned methods start with aziridine esters of high enantiopurity, the preparation of which is rather lengthy.13 The Neber reaction,9,14 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 azirines16 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.18 reported a chiral auxiliary mediated asymmetric Neber reaction with a de of 92%.

For the target compounds 1 ketoamine 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 ketoamine 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.19 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 distillation19,20 (Scheme 1). Spectral data of compounds 1 and d4,10 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 toluen (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 hydroxyl solvent such as ethanol no asymmetric conversion was observed. The results for the substrates 4a-e were...
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. 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 NaBH₄ leads exclusively to the formation of cis-aziridine carboxylic esters 2 (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 could be observed by NMR; therefore, the cis:trans ratio must be over 95:5. Furthermore, no loss of chirality is observed. 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.

JA9614140

(23) General procedure for the catalytic asymmetric synthesis of azirine esters 1: A solution of ketoxime tosylate 4 (200 mg) in dry tolune (10 mL) was added gradually to a vigorously stirred solution of quinidine (0.1–0.25 equiv) and a large excess of K₂CO₃ (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 MgSO₄, and concentrated in vacuo to give the azirine ester 1. The crude product was purified by bulb-to-bulb distillation.


(25) The enantiopurity of the aziridine ester 2b was determined by GLC analysis of the camphanoyl derivative.