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The synthesis of enantiomerically pure disubstituted aziridines and *N*-alkoxy aziridines

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Abstract

The addition of a chloroallyl phosphonamide anion to oximes has allowed the preparation of a variety of *cis*-disubstituted *N*-alkoxy aziridines in enantiomerically pure form. Oxidative cleavage of the chiral auxiliary followed by derivatization of the products has allowed the preparation of enantiopure *N*-alkoxy aziridines.

The synthesis of enantiomerically pure aziridines has been of interest in synthetic organic and medicinal chemistry,[1] because of their biological properties,[2] their utilization as precursors to non-natural amino acids,[1,3] and as intermediates in the total synthesis of natural products.[4] Especially interesting are aziridines bearing a carboxylic acid functionality because of their structural similarity to α-amino acids, and for the products obtained from nucleophilic ring opening reactions.[5] On the other hand, *N*-hydroxy and *N*-alkoxy aziridines have received little attention despite early reports of their preparation,[6] and their possible uses as *N*-hydroxy amino acids. The usual method for the preparation of *N*-alkoxy aziridines involves the dipolar cycloaddition of diazomethane to activated oximes to yield mixtures of isomers,[7] or the electrophilic addition of *O*-methylhydroxylamine to olefins,[8] although other classical methods have also been reported.[9] Enantiomerically pure *N*-hydroxy aziridines have been prepared by the resolution of racemic mixtures[10] and by the use of chiral non-racemic oximes,[11] in connection with studies of the effects of substituents on the inversion barrier of the nitrogen atom.[12] *N*-Alkoxy aziridines are reported to stimulate the production of leukocytes.[9]

We report herein on the formation of enantiopure *N*-alkoxy aziridines from the reaction of the anion of chloroallyl phosphonamide **1**[13] with different oximes. Our initial attempts led to mixtures of diastereoisomers or to the recovery of starting material. However, the reaction of the anion of **1**, generated from NaHMDS, with an *iso*-propyl glyoxylate *O*-benzyl oxime **2** led to aziridine **3** in 46% yield (recovery of 15% of **1**) as a single isomer (Scheme 1).

Since variation of the reaction conditions did not improve the yield, we varied the ester group in **2**. However, the reaction of the anion of **1** with **2** (R_1=Me, Bn) afforded only traces of the corresponding

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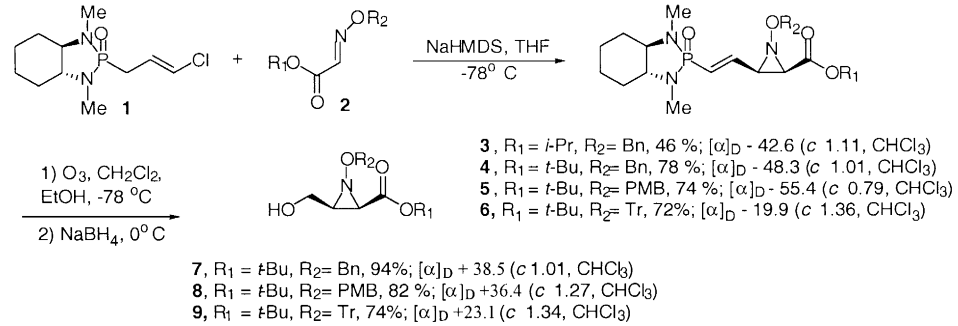
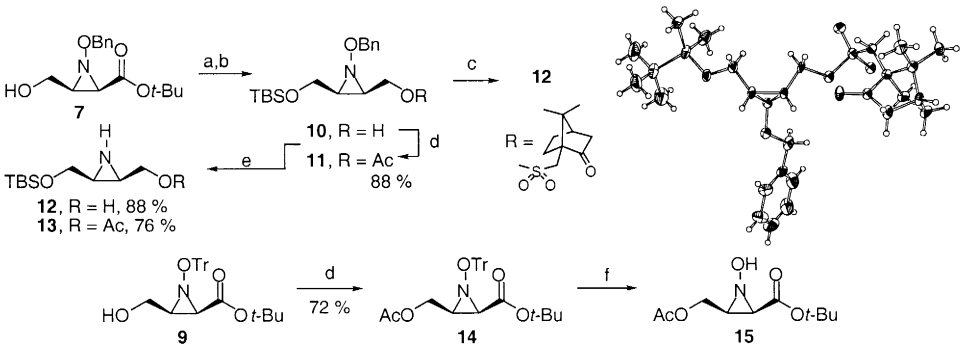


Scheme 1.

aziridine. Reaction of the anion of **1** with *t*-butyl glyoxylate *O*-benzyl oxime, *O*-*p*-methoxybenzyl and *O*-trityl oximes proved much more rewarding. In each case, we isolated the corresponding aziridine derivatives **4**, **5**, and **6**, respectively, in good yields. Cleavage of the vinyl phosphonamide moiety in compounds **4**–**6** by ozonolysis,[13] and reduction of the resulting ozonide, afforded the corresponding aziridines **7**–**9** in good to excellent yields (Scheme 1). A single crystal X-ray analysis of the camphorsulfonate derivative **12**, obtained from **7**, allowed a definitive structural and stereochemical assignment (Scheme 2).

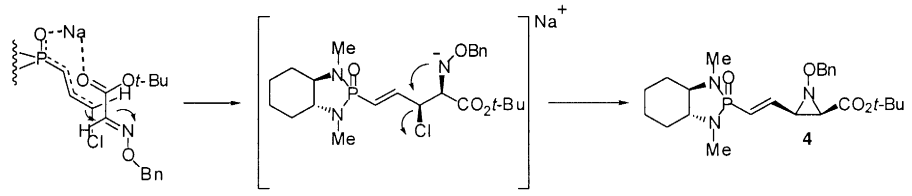


Scheme 2. Reagents: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 95%; (b) DIBAL-H, CH_2Cl_2, −78 to 0°C, 84%; (c) (+)-(1*S*)-camphorsulfonyl chloride, CH_2Cl_2, Et_3N, 0°C, 83%; (d) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0°C, 15 min; (e) 5% Pd/$BaSO_4$, H_2 (1 atm.), EtOH; (f) TFA, CH_2Cl_2, H_2O, 45–55%

With a reliable method to generate enantiomerically pure *N*-alkoxy aziridines, we turned our attention to the deprotection of the nitrogen to afford the corresponding *N*-hydroxy and *N*-H aziridines. Using catalytic hydrogenation conditions with the *O*-benzyl aziridines bearing an α-carboxyl substituent resulted only in the recovery of the starting material. On the other hand, reduction proceeded smoothly with **10** and **11** to give the 2,3-disubstituted aziridines **12** and **13**, respectively (Scheme 2). Oxidative cleavage of the *N*-OPMB derivative with DDQ or CAN, gave a product that decomposed under the reaction conditions. Access to the *N*-hydroxy aziridine derivative **15** was possible via deprotection of the *N*-trityloxy group by treatment of **14** with TFA in CH_2Cl_2 (Scheme 2). Compound **15** slowly decomposed above −20°C.

The stereochemistry of the aziridination product can be explained by an approach of the oxime from the less hindered left cleft of the phosphonamide anion **1**[13] in a Darzens-like reaction[14] (Scheme 3). The requirement of a bulky ester moiety such as *t*-butyl, may reflect a preferred reactive conformation, that results in an irreversible C–C bond formation.

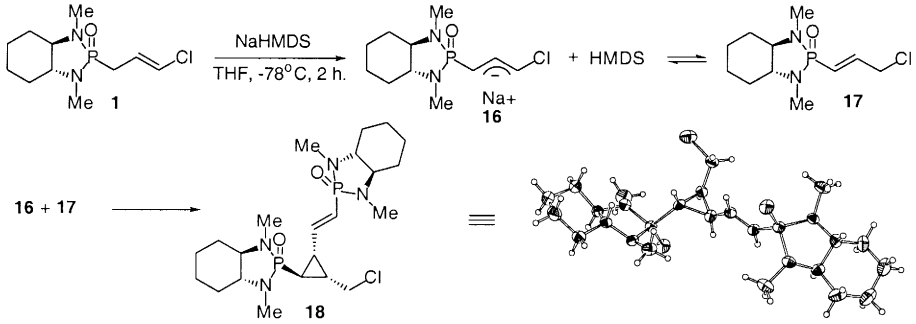
The fact that the *iso*-propyl ester of **2** gave a modest yield, and the methyl ester was recovered



Scheme 3.

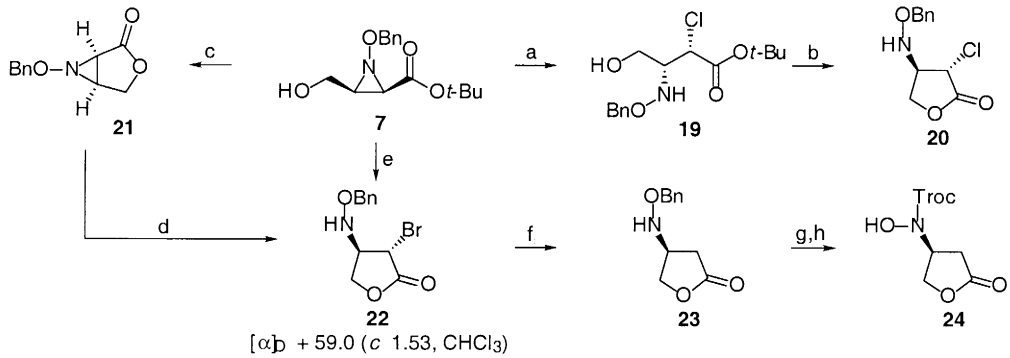
unchanged, may lend credence to this hypothesis. The necessity of using NaHMDS rather than the less effective Li or K bases is also of interest.

While trying to broaden the scope of the reaction to other C=N systems, the addition of the anion of **1** onto hydrazones gave a dimeric compound **18** whose structure was ascertained by single crystal X-ray analysis. The same compound could also be obtained in 70% yield by reacting **1** with NaHMDS at −78°C for 2 h (Scheme 4). A plausible mechanism involves the formation of the isomeric phosphonamide **17**, by internal quenching of **16** by HMDS.[15] Conjugate addition of an anion **16** onto **17**, followed by intramolecular elimination of chloride from the resulting intermediate, could explain the formation of **18**.



Scheme 4.

Unlike *N*-activated aziridine carboxylic esters,[5] treatment of derivatives of **7** with soft nucleophiles such as cuprates, thiolates and azide did not provide the desired ring opened products, even in the presence of Lewis acids. However, treatment of **7** with 4N HCl in dioxane[16] gave the α-chloro ester **19** which was subsequently lactonized to give **20** (Scheme 5).



Scheme 5. Reagents: (a) 4N, HCl/dioxane, dioxane, rt, 1 h, 89%; (b) TFA, CH_2Cl_2, rt, 46%; (c) NaH, THF, 0°C, 70%; (d) 30% HBr/AcOH, CH_2Cl_2, 89%; (e) 30% HBr/AcOH, CH_2Cl_2, 81%; (f) Bu_3SnH, VASO®, CH_2Cl_2, hν, −78°C, 30 min, 62%; (g) TrocCl, pyr., DMAP, CH_2Cl_2, 0°C, 73%; (h) H_2, 10% Pd/C, EtOAc, 86%

Similarly, treatment of **7** or **21** with HBr gave the bromo lactone **22** (NOESY NMR). Radical-mediated debromination of **22** gave the corresponding 3-amino lactone **23** which was in turn debenzylated to the *N*-hydroxy lactone **24** which was isolated as the *N*-Troc derivative. Hydroxylamines and their *N*-acylated derivatives are biologically interesting,[17] as exemplified by hadacidin (*N*-hydroxy-*N*-formyl glycine), which has herbicidal properties,[18] as well as related structures.[19]

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