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Base promoted isomerization of aziridinyl ethers: a new access to α- and β-amino acids†

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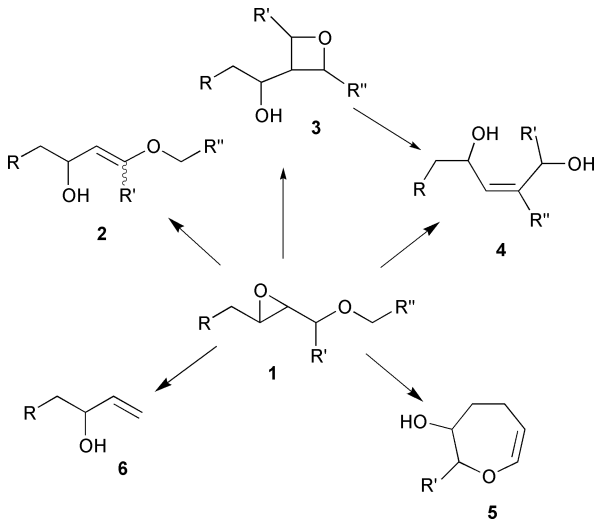
Aziridinyl ethers are selectively and easily converted to either amino vinyl ethers or alkoxy allylamines by treatment with mixed metal bases (superbases).

In the last few years we have extensively studied the base-promoted isomerization of oxiranyl ethers showing that they can be stereoselectively converted into a number of synthetically useful products by treatment with mixed metal reagents (superbases).[1–3] We have indeed found that depending on the substrate and the base used, oxiranyl ethers **1** can be transformed into hydroxy enethers **2** (R′ = H) *via* a *syn*-periplanar β-elimination process,[4,5] di- and tri-substituted oxetanes **3** *via* a 4-*endo* ring-closure (R′= H or alkyl),[6–8] 1,4-diols **4** probably through a carbene rearrangement,[9,10] tetrahydrooxepines **5** (R″ = CH=CH$_2$)[11] by means of a 7-*endo* process and terminal allylic alcohols **6** (R″ = SPh) *via* a fragmentation reaction when radical anions are used (Scheme 1). The use of superbasic mixtures has found to be essential in most cases in order to have highly regio- and stereoselective reactions and high yields of converted products.

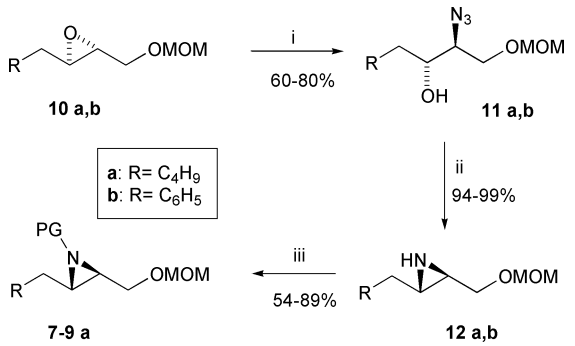


Scheme 1

In order to further extend the scope of our studies, we have recently undertaken an investigation of the reactivity of the nitrogen analogues, the aziridinyl ethers, with superbasic reagents, aiming at the synthesis of hydroxy amines and α- or β-amino acids. Even if aziridines are known[12] to be transformed into allylic amines by treatment with Vitamin B$_{12}$, their base-promoted isomerization is practically unknown except for a recent single report in which treatment of the *N*-tosyl aziridine of cyclohexene with *sec*-butyllithium in the presence of (−)-sparteine has been shown to afford the expected allylic amine albeit in low yield and selectivity.[13]

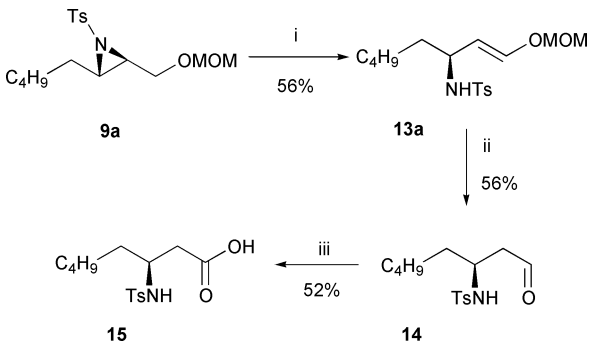
† Electronic supplementary information (ESI) available: experimental procedures and NMR data. See http://www.rsc.org/suppdata/cc/b2/b200708h/.

Enantiomerically enriched aziridinyl ethers **7–9a**,**b** can be prepared in a number of ways,[14,15] among which we have selected the sequences starting from epoxy ethers **10a**,**b**, through ring opening with sodium azide and subsequent ring closure to aziridine either *via* mesylation followed by reduction with lithium aluminum hydride or in a single step with triphenyl phosphine (Scheme 2).[16] The hydrogen atom on nitrogen of aziridinyl ethers **12a**,**b** has then been replaced by some different protecting/activating groups. Thus benzyl- (**7**), *tert*-butoxy-carbonyl- (Boc, **8**) and *para*-toluenesulfonyl- (Ts, **9**) aziridines have been easily prepared following standard procedures.



Scheme 2 *Reagents and conditions*: i, NaN_3–NH_4Cl, $CH_3OCH_2CH_2OH$–H_2O 8 : 1 80 °C; ii, PPh_3, $PhCH_3$ reflux; iii, NaH, BnBr, THF or DMAP, Boc_2O, CH_2Cl_2 or pyridine, TsCl.

Compounds **7a**, **8a** and **9a** have then been submitted to treatment with various superbasic mixtures in order to first test the influence of the group on nitrogen on the isomerization process. We have found that only the tosyl aziridine **9a** can be isomerized with the superbase LIDAKOR (lithium diisopropylamide–potassium *tert*-butoxide)[17] to the corresponding amino vinyl ether **13a**, while the benzyl derivative **7a** doesn't react and the Boc-aziridine **8a** is surprisingly simply deprotected to the starting aziridine **12a** under the same reaction conditions. None of the tested substrates is isomerized by treatment with unactivated lithium diisopropylamide. The aziridine to amino vinyl ether conversion is highly regio- and stereoselective,



Scheme 3 *Reagents and conditions*: i, LIDAKOR, pentane, 25 °C; ii, Bu_4NI, Me_3SiCl, CH_2Cl_2, −20 °C; iii, H_5IO_6, cat. CrO_3, MeCN–H_2O 3 : 1, 0 °C.

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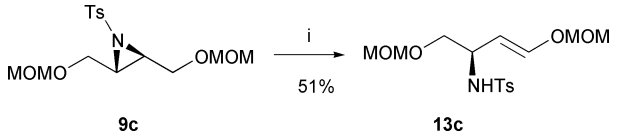
compound **13a** being the unique isomerized product detected. The amino vinyl ether **13a** is a very useful building block for further transformations: as an example it has been easily deprotected to the amino aldehyde **14** and the latter oxidized[18] to the β-amino acid **15** (Scheme 3). Both processes occur under mild reaction conditions and without epimerization thus leading to amino aldehydes and amino acids having the same optical purity as the starting oxirane.

As an additional example the symmetrical aziridine **9c**, obtained from diethyl tartrate in seven steps, has been also converted to the amino vinyl ether **13c** with good yield and high

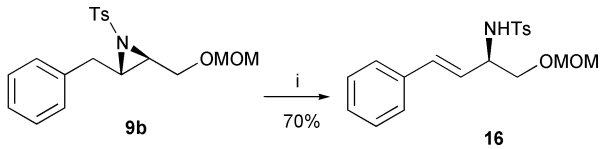


9c **13c**

Scheme 4 *Reagents and conditions*: i, LIDAKOR, pentane, 20% HMPA, 25 °C.

selectivity (Scheme 4). Compound **13c** is a very useful building block due to the large number of conveniently elaborable functional groups.

The formation of vinyl ethers **13a** and **13c** is obviously due to selective deprotonation of the methylene group adjacent to the OMOM group and the aziridinyl ring. When we have applied the same reaction conditions to the aziridine **9b**, having an additional acidic position (the benzylic methylene group), we have found a different reaction pathway, leading this time to the



9b **16**

Scheme 5 *Reagents and conditions*: i, LIDAKOR, pentane, 25 °C.

cinnamyl amino alcohol **16** in a very selective manner (Scheme 5). Compound **16** is the precursor of the β,γ-unsaturated α-amino acid, phenylglycine and the extension of this methodology to other similar substrates could lead to a new approach to a large variety of unsaturated α-amino acids.

Therefore, depending on the nature of the substituents on the aziridine ring, the base-promoted rearrangement may disclose new pathways to unnatural α- and β-amino acid precursors.

Investigation of the reactivity of a variety of aziridines with superbases is in progress in our laboratory.

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