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Unprecedented Rearrangement Reaction of 2-Aziridinemethanols with "Lower Order" Lithium Methylcyanocuprate

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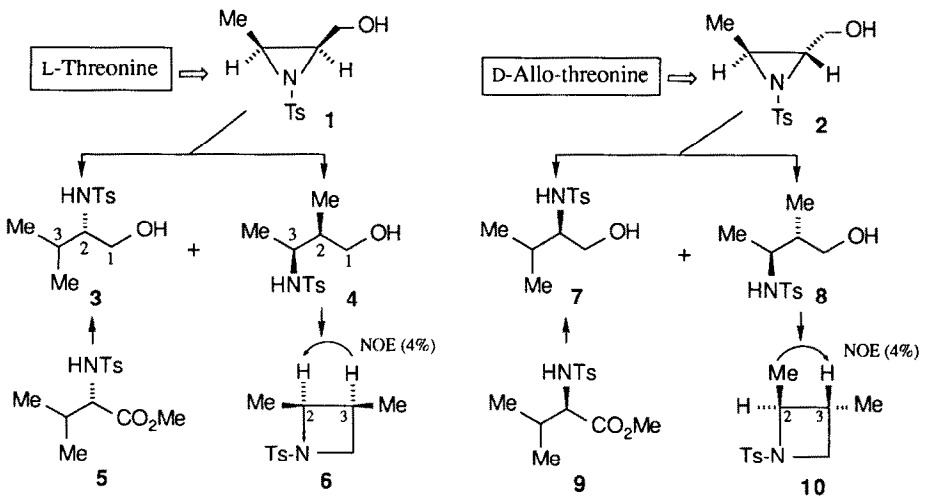
Abstract: Complementary selectivity can be achieved in ring opening reactions of 2-aziridinemethanols by using either the Gilman reagent or lower order cyanocuprate. In the former case, the usual attack of the Gilman reagent to the substrates **1** and **2** results in the formation of the expected ring opening products (**3** and **4**) and (**7** and **8**), respectively. In contrast, exposure of both **1** and **2** to the lower order cyanocuprate proceeds in an unprecedented fashion, presumably via epoxides **D** and **G**, to yield unexpected secondary alcohols (**11** and **12**) as the major products.

The ring-opening reaction of aziridines and subsequent manipulations have found widespread application in the synthesis of biologically important cyclic and acyclic compounds.[1] Notably, N-activated aziridines undergo ring-opening reactions with various kinds of nucleophiles such as organocopper reagents,[2] Grignard reagents,[3] heteroatomic nucleophiles,[4] cyanotrimethylsilane-lanthanide tricyanide,[5] acetone cyanohydrine-lanthanide alkoxide,[6] and trialkyl aluminum[7] to give protected primary or secondary amines in good to excellent chemical yields. We have been interested in the ring-opening reaction of N-activated aziridines in connection with studies of peptide isosteres in our laboratories. In addition, we have needed a series of amino alcohols with stereochemically well defined structure as synthetic intermediates for unusual amino acids.



We report herein the results of organocopper-mediated ring-opening reactions of two homochiral N-tosylated aziridinemethanols (**1** and **2**). The requisite substrates **1** and **2** were readily prepared from L-threonine and D-allo-threonine, respectively, in acceptable yields.[8]

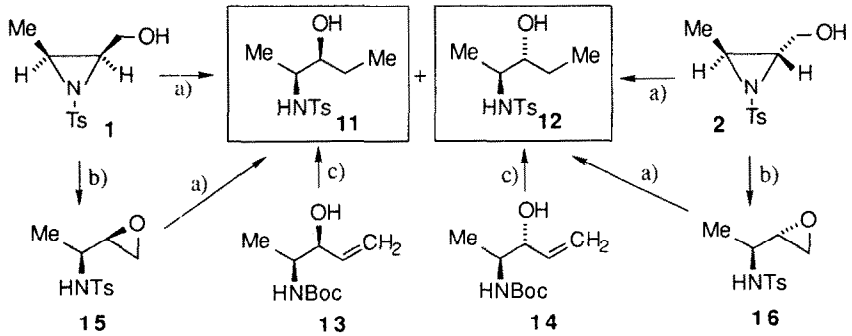
Exposure of the aziridine **1** to lithium dimethylcuprate, $Me_2CuLi.LiI$, at - 78 °C (initial reaction temperature) followed by reaction at room temperature for 18 h in ether yielded a mixture (51:49) of the two expected methylation products **3** and **4** in 94 % combined yield (Table I, Entry 1). A comparable result was obtained by treatment of **1** with the "higher order" (HO) cyanocuprate (Table I, Entry 2). It is apparent that the presence of a hydroxymethylene group on the aziridine ring has no significant directive effect on the regiochemical reaction course. All attempts to enhance the relative portion of either **3** or **4** in this mixture were to no avail. This low selectivity is reminisent of Katsuki's lithium dimethylcuprate-mediated non-selective ring-opening of a chiral 2,3-epoxy alcohol.[9] The absolute configuration at the chiral carbon center in **3** was substantiated by comparison of **3** with an authentic sample prepared by diisobutylaluminum hydride reduction of methyl L-*N*-(*p*-toluenesulfonyl)valinate **5**. The stereochemistry of **4** was established as follows. Treatment of **4** with diethyl azodicarboxylate-triphenylphosphine in THF gave the azacyclobutane derivative **6** in 99 % yield. The 2,3-*cis* stereochemistry of vicinal hydrogens in **6**, and hence the 2,3-*syn* stereochemistry of **4**, was assigned on the basis of the ^1H NMR data (^1H-^1H COSY and selective decoupling experiments).

In a similar manner, the aziridinemethanol **2** was converted to protected amino alcohols **7** (64 % yield) and **8** (34 % yield) by treatment with lithium dimethylcuprate in ether (Table I, Entry 3). The stereochemistry of both products (**7** and **8**) was substantiated by a procedure identical with that for the stereochemical assignments for **3** and **4**.

Table I

Entry	Substr.	Reagent*1	Yield	(**3** : **4** : **7** : **8** : **11** : **12**)
1	**1**	$Me_2CuLi.2LiBr.LiI$ (4 eq.)	94 %	(**51** : **49** : - : - : - : -)*2
2	**1**	$Me_2Cu(CN)Li_2.2LiBr$ (5 eq.)	80 %	(**44** : **56** : - : - : - : -)*3
3	**2**	$Me_2CuLi.2LiBr.LiI$ (5 eq.)	98 %	(- : - : **65** : **35** : - : -)*2
4	**1**	MeCu(CN)Li.LiBr (4 eq.)	93 %	(trace : 8 : - : - : **36** : **55**)*4
5	**2**	MeCu(CN)Li.LiBr (5 eq.)	81 %	(- : - : 7 : trace : **39** : **53**)*4

*1 All reactions were carried out by treatment of the substrate (**1** or **2**) with the indicated reagents at -78 °C and then warming the reaction to ambient temperature with stirring for 18 h. *2 Reaction was performed in Et_2O. *3 Reaction was carried out in Et_2O. Reaction in THF-Et_2O (4:1) gave a comparable result. *4 Reaction was carried out in THF-Et_2O (3 ~ 4 : 1).

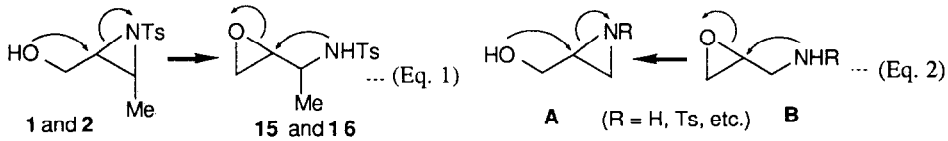


Reagents : a) McCu(CN)Li.LiBr; b) NaH in THF - HMPA (12 : 1);
c) i. H_2/PtO_2 in EtOH, ii. TFA - CH_2Cl_2, iii. TsCl-Et_3N

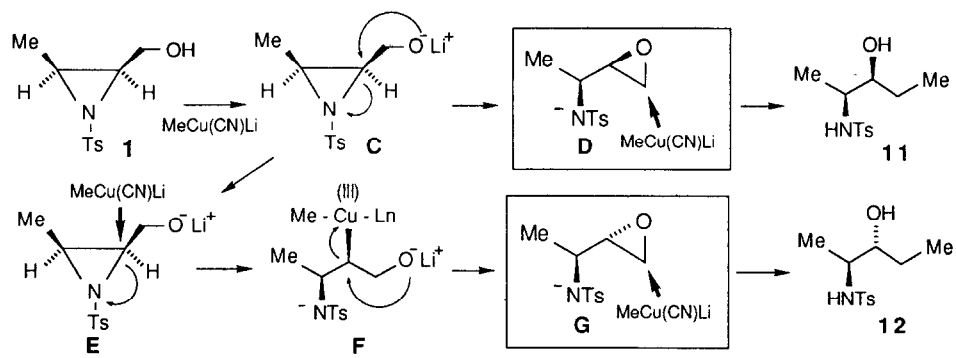
Of special interest is the new finding that the reaction of **1** with the "lower order" (LO) cyanocuprate, MeCu(CN)Li, was found to give an 84 % combined yield of unexpected amino alcohols (**11** and **12**) along with the "normal" ring-opening products (**3** and **4**) as the minor products (Table I, Entry 4). A comparable result was

obtained in the reaction of aziridine **2** with the LO cyanocuprate to give the amino alcohols **11** and **12** as the major products (Table I, Entry 5). The formation of secondary alcohols (**11** and **12**) in the reaction of aziridines (**1** and **2**) possessing a hydroxymethylene group at the C-2 position is specific to the LO cyanocuprate reactions and is not observed in the reactions with the Gilman reagent.

Structural and stereochemical assignments for the amino alcohols **11** and **12** were made by comparison of spectral data (^{1}H NMR, IR, and $[\alpha]_D$) with those of authentic samples prepared from known homochiral amino alcohols **13**[10] and **14**[10] through a sequence of reactions (i. H_2/PtO_2; ii. TFA; iii. TsCl-Et_3N). Alternatively, both pure amino alcohols (**11** and **12**) could be prepared from **1** and **2**, respectively, by the following two reactions. Treatment of **1** and **2** with sodium hydride (4 ~ 5 eq.) in a mixed solvent of THF and HMPA (12 : 1) at - 78 °C ~ r. t. for 18 h yielded protected epoxy amines **15** (92 % yield) and **16** (87 % yield), respectively. The presence of HMPA in the aza-version of the Payne rearrangement was essential for the clean conversion. Reactions of **15** and **16** with MeCu(CN)Li afforded protected amino alcohols **11** and **12** in yields of 99 % and 85 %, respectively. Lithium methylcyanocuprate-mediated reactions occur exclusively at the less substituted position of the epoxides **15** and **16** to yield the amino alcohols **11** and **12**, respectively.



It should be clearly noted that the conversion of aziridinemethanols **1** and **2** to 2,3-epoxyamines **15** and **16** by exposure of **1** and **2** to NaH in a mixed solvent of THF and HMPA may proceed via an aza-version mechanism of the Payne rearrangement.[11] The equilibrium lies almost exclusively to the right as shown in Eq. 1. We were unable to detect any unreacted aziridinemethanols **1** and **2** by HPLC analysis of the crude reaction products. The above behavior runs counter to the general trend that the equilibrium lies to the left in the presence of sodium hydroxide,[12] boron trifluoride,[13] n-BuLi-Me_3Al,[14] and $Ti(OPr^i)_4$.[15] as shown in Eq. 2.



Because the organocopper-mediated ring opening of N-activated aziridines usually proceeds via an S_N2-type mechanism at the C-2 or C-3 carbon center,[16] there remains the important question why substrates **1** and **2** were transformed into the unusual secondary amino alcohols (**11** and **12**) as the major products by treatment with the LO cyanocuprate. Although all of the controlling factors in the reactions of **1** and **2** with the LO cyanocuprate are not clear, the following explanation concerning the formation of **11** and **12** from the substrate **1** could be drawn.

One equivalent of MeCu(CN)Li removes the proton of hydroxy group to generate an anion species **C**, from which formation of oxirane **D** via intramolecular attack of the anion to a proximate electrophilic carbon center could be expected. In fact, the oxirane **15**, which is a protonated form of an intermediate **D**, can be isolated in the

reaction of **1** with MeCu(CN)Li at 0 °C for 3 h. Subsequent nucleophilic attack of MeCu(CN)Li to the less substituted carbon of the oxirane **D** would provide the amino alcohol **11**. On the other hand, nucleophilic attack of the LO cyanocuprate at the C-2 position of **C** followed by oxirane formation via an intermediate **F** could lead to an oxirane **G**. Finally, attack of MeCu(CN)Li to the less substituted carbon of the oxirane **G** would provide the isomeric amino alcohol **12**. Needless to say, although the precise reaction mechanism for the formation of the unexpected amino alcohols **11** and **12** is not apparent, the picture we use is conveniently simple at this stage in the development of our understanding.

In summary, selection of either the Gilman, the HO- or the LO-cyanocuprate reagent is very important in the reaction of 2-aziridinemethanols. The formation of unexpected amino alcohols **11** and **12** is taken as an indication that the reaction proceeds by a mechanism involving oxirane intermediates. In addition, both the aziridinemethanols **1** and **2** yielded protected 2,3-epoxy amines **15** and **16**, respectively. These results run counter to the general trend seen in analogous compounds.

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