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N-Cyanomethyl-β-chloroamines: a convenient source of aziridinium ions

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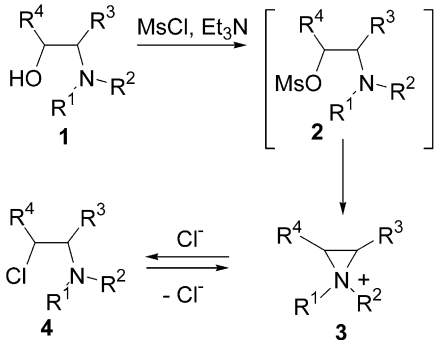
Abstract—*N*-Cyanomethyl-β-chloroamines smoothly react with a range of alcohols or amines to give regio- and stereoselectively 1,2-aminoethers or 1,2-diamines. The reaction proceeds through the formation of an intermediate aziridinium ion. The *N*-cyanomethyl group can then be cleaved easily.

Due to the discovery of efficient methods for the asymmetric synthesis of aziridines,[1] and systematic studies of their nucleophilic opening,[2] these compounds have emerged as useful electrophilic synthons within the past decades. In contrast, *N*,*N*-dialkyl aziridinium ions **3**, despite their stronger electrophilic character compared to neutral aziridines, have only scarcely been used as key intermediates in organic synthesis.[3] This can be explained by the lack of availability of a stable and easy to handle precursor to these highly electrophilic ammonium salts that would allow for a smooth and direct generation.

As a matter of fact, *N*,*N*-dialkyl aziridinium ions are most often produced by mesylation of the corresponding β-amino alcohol.[4] Beside the problem of regioselectivity in the course of the nucleophilic opening of the aziridinium, this activation affords various mixtures of aziridinium ion **3** and of β-chloro amine **4**, the sense of the equilibrium depicted in Scheme 1 depending of different factors such as the steric hindrance around the dialkyl amine and the electrophilic character (e.g., a benzylic position) of the chlorine bearing carbon.

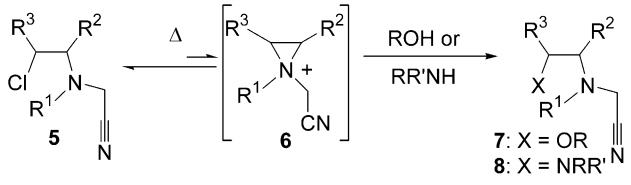
In addition to producing difficult to handle mixtures of neutral β-chloroamines and charged aziridinium ions, this method does not allow for the introduction of common and easy to cleave protecting groups (R^1 or R^2 in **1**) on the amine moiety of the starting β-amino alcohol. As



Scheme 1.

a matter of fact a carbamate would act as an internal nucleophile to produce oxazolidinones[5] and *N*-sulfonyl protecting groups, in addition to their difficult cleavage,[6] would deactivate the nucleophilic character of the nitrogen atom and prevent the formation of the aziridinium ion.

We wish to describe herein the use of *N*-cyanomethyl β-chloroamines **5** as stable precursors of aziridinium ions



Scheme 2.

Keywords: 1,2-Aminoethers; 1,2-Diamines.
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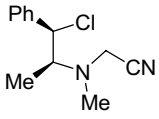
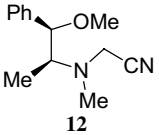
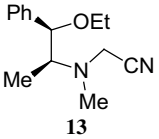
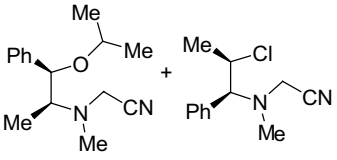
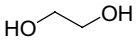
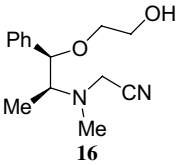
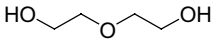
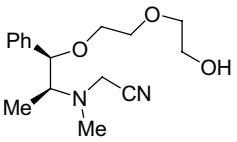
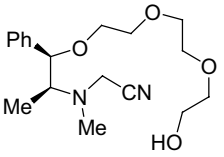
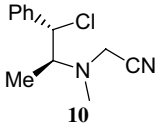
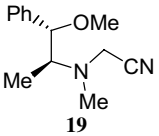
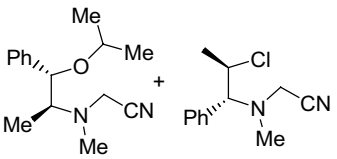
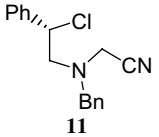
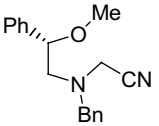
6, able to smoothly produce these electrophilic species and react further with alcohols or amines to give *N*-cyanomethyl protected β-aminoethers **7** or 1,2-diamines **8** (Scheme 2).

Table 1. Reaction of *N*-cyanomethyl β-chloroamines with alcohols

Entry	Substrate	Nucleophile	Conditions	Product	Yield[a] (%)
1	 **9**	MeOH	Neat, 0.5 h, 70 °C	 **12**	91
2	**9**	EtOH	Neat, 0.5 h, 70 °C	 **13**	71
3	**9**	*i*-PrOH	Neat, 1 h, 100 °C	 **14** + **15**	65 (for **14**)[b] **14**/**15**: 6.5/2.5
4	**9**		Neat, 0.5 h, 80 °C	 **16**	70
5	**9**		Neat, 1 h, 80 °C	 **17**	80
6	**9**		Neat, 1 h, 80 °C	 **18**	82
7	 **10**	MeOH	Neat, reflux, 3 h	 **19**	77
8	**10**	*i*-PrOH	Neat, reflux, 4 h	 **20** + **21**	16 (for **20**)[b] **20**/**21**: 1.6/4.4
9	 **11**	MeOH	Neat, reflux, 24 h	 **22**	90

[a] Yield of isolated products.
[b] Crude yield determined by NMR: see text.

In order to circumvent the formation of regioisomers in the above reaction, we focused our study on chlorides **5** in which R^3 is an aromatic, since it is well-established that in this case the benzylic position in the produced aziridinium ion is attacked regioselectively.[4] Therefore, reaction of chlorides **9**–**11**, easily prepared from (1*R*,2*S*)-ephedrine, (1*S*,2*S*)-*pseudo*-ephedrine and (*R*)-phenylglycinol, respectively,[7] with different alcohols was studied and the results are collected in Table 1.

Before commenting these results, the ease of preparation of the starting chlorides as well as their stability should be emphasized: these crystalline compounds can be stored for long periods without detectable degradation and they do not show any propensity to give aziridiniums ions at room temperature. This can be ascribed to the *N*-cyanomethyl protecting group, which deactivates the nucleophilic character of the amine moiety by anomeric effect.[10e,8]

In spite of this deactivation, chlorides **9**–**11** reversibly produce under moderate heating low concentrations of aziridinium ions able to smoothly react with alcohols or amines, as demonstrated by the results collected in Table 1. As shown in this Table, aminoethers are easily produced by simply heating the starting chlorides in the required alcohol for a few hours, and the new aminoethers are produced with high regio- and stereoselectivity. The stereospecificity observed for this reaction, together with our previously reported work demonstrating that chlorides **9**–**11** exclusively react with azide anions via aziridiniums ions secure here the occurrence of such mechanism. The kinetic of this reaction depends of two main factors: the ability of the substrate to form an aziridinium ion, and the rate of the subsequent irreversible reaction of the ion with the nucleophile, competing the attack of the chloride anion. Considering that the overall rate of this reaction depends essentially on the concentration of the produced aziridinium ion, the relative stabilities of these ions has to be considered in order to explain the differences of reactivity of the starting chlorides. By comparing the reaction times required for completion for the reaction of the different chlorides with methanol, it appears clearly that **9** is the most reactive, followed by **10** and **11**, since protracted times of reaction are needed to reach completion. This difference of reactivity can be attributed to the relative stabilities of aziridinium ions **23**, **24**, **25**, derived from **9**, **10**, **11**, respectively. Aziridinium ion **23** (from **9**) is probably more stable than **24** (from **10**), in which the *cis* relationship of the substituents brings a steric strain.[4a] Logically, aziridinium **25** derived from the less reactive chlorides **11** should be the less stable. The reason for this is less clear, but it can be attributed to the introduction of the large *N*-benzyl group on the amine, that brings a steric strain in the produced ion (Fig. 1).

When comparing different alcohols, it appears that the steric hindrance of the nucleophilic alcohol strongly influences the rate of the second step: while primary alcohols react in a highly regio- and stereoselective manner with **9**–**11** at a reasonable rate (entries 1, 2, 4–7 and

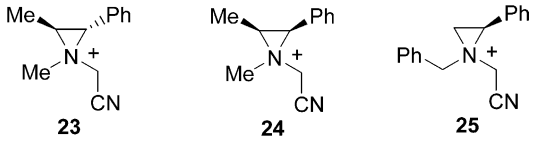
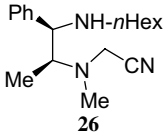
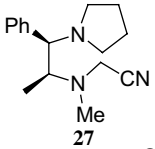
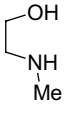
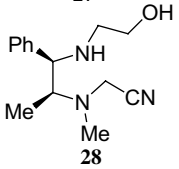
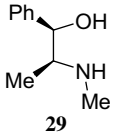
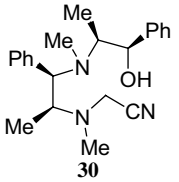


Figure 1.

Table 2. Reaction of *N*-cyanomethyl β-chloro amines with amines

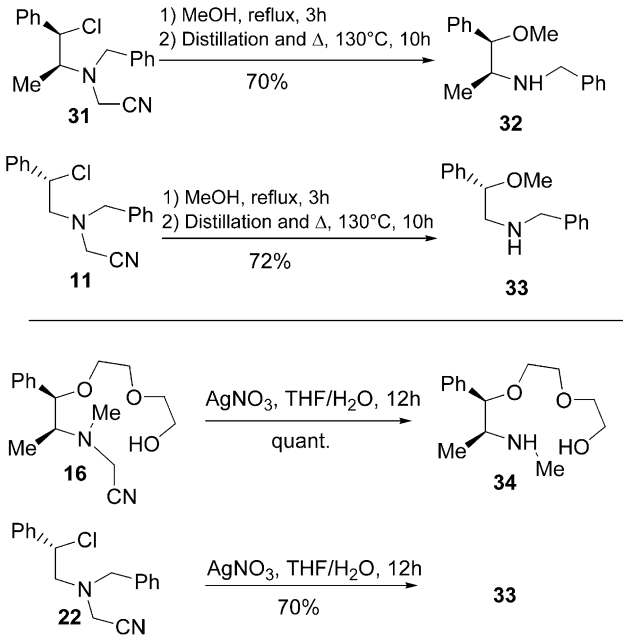
Entry	Substrate	Nucleophile	Conditions	Product	Yield[a] (%)
1	**9**	*n*-HexNH_2	Neat, 2 h, 70 °C	 **26**	90
2	**9**	Pyrrolidine	Neat, 1 h, 40 °C	 **27**	75
3	**9**		Neat, 0.5 h, 60 °C	 **28**	76
4	**9**	 **29**	1 equiv, DMF, 1.5 h, 110 °C	 **30**	20

[a] Yield of isolated pure products.

9), a secondary alcohol (*i*-PrOH) reacted in a much more sluggish manner (entries 3 and 8). Thus, upon heating in *i*-PrOH at 100 °C for 1 h, **9** gave a crude inseparable mixture of starting compound **9**, the expected product **14** and rearranged chloride **15** in a 1/6.5/2.5 respective ratio (entry 3). Similarly, when this reaction was conducted with less reactive **10** (entry 8), a 4/1.6/4.4 respective ratio of **10**, **20** and rearranged chloride **21** was obtained. Chlorides **15** and **21** result from an attack of the aziridinium by the chloride anion at the nonbenzylic position. It should be mentioned that in the case of **9**, addition of silver(I) nitrate (1 equiv) as an aziridinium ion promoter induced completion of the reaction with *i*-PrOH at 50–60 °C within 0.5 h and gave **14** in a 76% isolated yield, albeit with a slight erosion (de 84%) of the diastereoselectivity.

Next was studied the reactions with amines: results are collected in Table 2. In this case, both primary and secondary amines reacted efficiently (entries 1 and 2) and with high chemoselectivity (entry 3). The use of a crowded secondary amine ((1*R*,2*S*)-ephedrine **29**, entry 4) used in this case as an equimolecular mixture with **9** in DMF gave the substitution product **30** in modest yield, again accompanied by rearranged chloride **15**. In this case, nor solvent screening, nor addition of silver(I) nitrate allowed for an optimisation of the yield.

Finally, deprotection of the *N*-cyanomethyl group was studied. We found that it could be achieved either thermally, which allowed to perform the substitution/deprotection process in a one pot sequence, as exemplified starting with chloride **31** and **11**. In these cases, the chlorides were simply refluxed with methanol and then heated after removal of the solvent, to give **32** or **33**. Alternatively, silver(I)-promoted hydrolytic cleavage of the *N*-cyanomethyl moiety was also operative and gave **33** and **34** from **16** and **22**, respectively (Scheme 3).



Scheme 3.

In conclusion, this methodology affords a convenient and flexible preparation of chiral β-aminoethers and 1,2-diamines. The produced compounds can be envisioned as valuable starting material for the synthesis of peraza[8] or azacrown[9] chiral macrocycles, as well as di- or polyamine chiral bases[10] used in asymmetric synthesis.

Acknowledgements

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Supplementary data

Supplementary data contains experimental procedures and characterisation for new compounds. Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.02.016.

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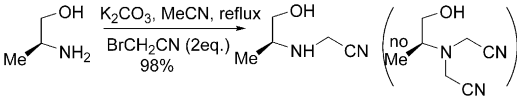
8. Perhaps the more spectacular illustration of this deactivation is the fact that trials of dicyanomethylation of a β-amino alcohols such as (*S*)-alaninol, even under forcing conditions, cleanly stops at the monoalkylation step:



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10. See inter alia: (a) Bassindale, M. J.; Crawford, J. J.; Henderson, K. W.; Kerr, W. J. *Tetrahedron Lett.* **2004**, *45*, 4175–4179; (b) Hutchinson, P. C.; Heightman, T. D.; Procter, D. J. *J. Org. Chem.* **2004**, *69*, 790–801; (c) Johansson, A. J.; Abrahamsson, P.; Davidsson, Ö. *Tetrahedron: Asymmetry* **2003**, *14*, 1261–1266; (d) Amedjkouh, M.; Pettersen, D.; Lill, S. O. N.; Davidsson, Ö.; Ahlberg, P. *Chem. Eur. J.* **2001**, *7*, 4368–4377; (e) Colman, B.; de Sousa, S. E.; O'Brien, P.; Towers, T. D.; Watson, W. *Tetrahedron: Asymmetry* **1999**, *10*, 4175–4182.