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Highly Regioselective Opening of Optically Active N-Boc -2,3-Aziridino Alcohol Derivatives with Metal Halides

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Abstract: Chiral 3-substituted N-Boc-2,3-aziridino alcohols are opened in a regio and stereoselective fashion by $MgBr_2$; the obtained 3-bromo derivatives can be reduced and deprotected under mild conditions to the corresponding 1,2-amino alcohols.

We have recently described[1] two different and efficient methods for the regio and stereoselective opening of 3-substituted N-ethoxycarbonyl aziridine-2-carboxylates with metal halides. The important role played by 1,2-amino alcohols[2] as chiral auxiliaries and chiral building blocks in the preparation of biologically active compounds has prompted us to extend our study on aziridino alcohols.

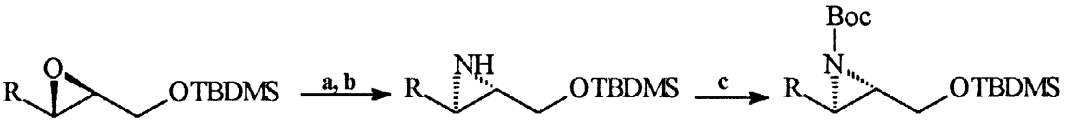
To our knowledge the regio and stereoselective opening of these substrates by halides has not yet been studied. In fact, although recent papers describe nucleophilic opening of aziridino alcohols with complex hydrides, organocuprates or aluminocuprates on 3-hydroxymethyl [3] or 3-phenyl aziridino alcohols,[4] no general methodology was reported on the reaction with metal halides.

Aziridino alcohols and esters require, for a stereo and regioselective opening under smooth conditions, an appropriate N-"activating" group, normally an electron withdrawing one. So far the tosyl group[5] was the most extensively employed in the ring opening of aziridino alcohols and esters; also N-carboxyethyl aziridino 2-carboxylates [1] were easily cleaved by halogen nucleophiles to afford, in a regio and stereocontrolled fashion, the corresponding 2-amino-3-halo or 2-halo-3-amino carboxylic esters. Some limitations in the use of the mentioned activating groups arise especially due to the rather strenuous conditions required for their removal.[6]

To our knowledge, a systematic use of the N-Boc protection and activation for aziridino alcohols and derivatives has never been reported, although N-Boc protection has been used with other aziridines.[7] Such protecting groups, should demonstrate the same ability as the others, in activating and directing the opening of the aziridine ring; furthermore the removal of the Boc group could be efficiently achieved by standard methodology (i.e. TFA catalysis).[8]

After the preparation of optically active aziridino alcohols (see scheme 1),[3] the N-Boc protection can be

Scheme 1



crude material

R = Me, Pr, Ph, i-Pr, Cyclohexyl

a: NaN_3, NH_4Cl, MeOH, reflux **b**: Ph_3P, CH_3CN, reflux. **c**: BOC_2O, DMAP, CH_2Cl_2, rt.

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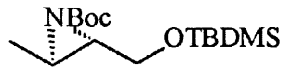
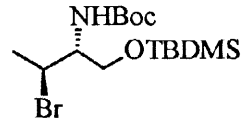
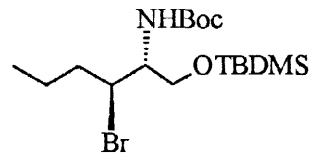
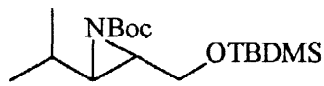
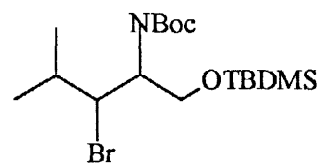
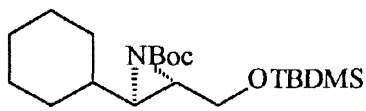
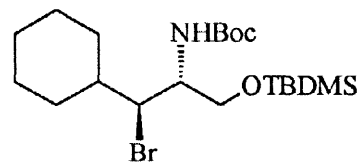
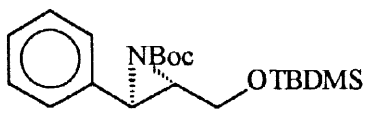
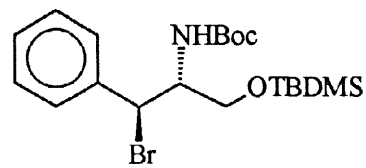
easily achieved on the crude aziridino alcohol derivatives, thus avoiding the difficult column separation of the non-protected aziridino alcohols. The final aziridino N-Boc, TBDMS-alcohols are quite stable compounds and easily purified by chromatography.[9]

In this paper we wish to present our results on the regio- and stereoselective opening of 2,3-aziridino alcohols N-Boc activated with metal halides.

Table 1. C-3 Regioselective opening of N-Boc-aziridino alcohols with $MgBr_2$

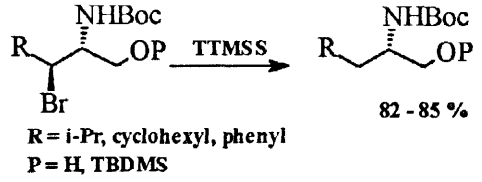
N-Boc-Aziridino alcohols [a]	Main product	C-3/C-2 [b, c]
 **1**		>99 / 1
 **2**		> 99 / 1
 **3**		> 99 / 1
 **4**		> 99 / 1
 **5**		> 99 / 1

[a] Compound **1, 2, 4, 5** are optically active [b] Chemical yields of the isolated products are nearly quantitative [c] The ratio has been determined by ^{1}H-NMR analysis

As shown in table 1, chiral N-Boc protected aziridino alcohols (compounds **1, 2, 4, 5**) or racemic (compound **3**) were subjected to our reaction conditions ($MgBr_2$)[1,10] with excellent C-3 regioselectivity and almost quantitative yield.[11,12] The reaction regioselectivity is not affected by the bulky substituent on C-3 position (compound **3, 4**); moreover the very mild reaction conditions are suitable for the presence of other functional groups.[13]

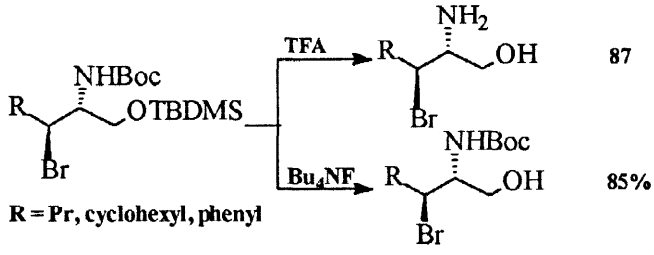
The obtained β-halogen derivatives can be transformed into the corresponding 1,2-amino alcohols N- and O-protected using Bu_3SnH [11] or TTMSS (Tris(trimethylsilyl)silane),[14] with excellent chemoselectivity and high yield (scheme 2).[15]

Scheme 2



As anticipated (see above) the removal of the Boc group can now be easily carried out with TFA (trifluoroacetic acid). In these conditions the TBDMS group is also removed and this allows one to obtain the deprotected 1,2-amino alcohols directly.[16a] Interestingly the use of Bu_4NF allows the selective removal of OTBDMS without cleaving the N-Boc protection (scheme 3),[16b] thus eventually allowing the further elaboration of the hydroxyl group.

Scheme 3



In conclusion we believe that the described methodology with the use of N-Boc protection represents an important improvement in the regio and stereoselective opening of chiral 2,3-aziridino alcohols by the use of extremely mild reaction conditions and for its wide range of applicability.

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5 See review on the preparation and reactions of aziridines :Tanner, D., *Angew. Chem. Int. Ed. Engl.* , **1994**, *33*, 599 and references therein.

6 *Protective groups in Organic Synthesis* Green, T. W.; Wuts, P. G. M.; John Wiley & Sons, Inc. **1991**, pg 317 and 379.

7 See for some selected examples: a) Satake, A.; Shimizu, I.; Yamamoto, A. *Synlett* **1995**, 64. b) Ezquerra, J.; Pedregal, C.; Lamas, C. *Tetrahedron Lett.* **1996**, *37*, 683. c) McCort, I.; Dureault, A.;Depezay, J. *Tetrahedron Lett.* **1996**, *37*, 7717. d) Funaki, I.; Thijs, L.; Zwanenburg, B.

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8 During the preparation of the manuscript we have been made aware of the use of the nosyl N-protecting group in the nucleophilic opening of 1,2-aziridines (Maligres, P. E.; See, M. M.; Askin, D.; Reider, P. J. *Tetrahedron Lett.* **1997**,*38*, 5253).

9. Also crude aziridine-2-carboxylates (prepared from the corresponding optically active α,β-epoxy esters according to Legters, J.; Thijs, L.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*,), can be easily protected to the corresponding N-BOC derivatives and easily purified by flash chromatography .

10. For related previous opening of 2,3- epoxy alcohols and esters with metal halides see a) Bonini, C.; Righi, G. Review: *Synthesis* **1994**, *3*, 225. b) Bonini, C.; Chiummiento, L.; Federici, C.; Funicello, M.; Righi, G.; Rossi, L. *Tetrahedron Lett.* **1994**, *35*, 797. c) Bonini, C.; Federici, C.; Righi, G.; Rossi, L. *J. Org. Chem.* **1995**, *60*, 4803. d) Bonini, C.; Righi, G.; Rumboldt, G. *Tetrahedron* **1995**, *51*, 13401. e) Bonini, C.; Righi, G.;Rumboldt, G. *J. Org. Chem.* **1996**, *61*, 3557.

11. General procedure: To a solution of N-Boc-2,3 aziridino alcohol derivative (1 mmol) in Et_2O (10 mL) $MgBr_2.Et_2O$ (258 mg, 2 meq) was added. The solution was stirred at room temperature for 4h (TLC monitoring), filtered and washed with brine. The organic layers were then dried over Na_2SO_4 and evaporated *in vacuo*. The crude mixture was checked by ^1H and ^{13}C-NMR for determining the regio and diastereomeric ratio.

12. Some attempts to utilise LiBr / Amberlyst 15 system as for 2,3-epoxy alcohols [10b,c] gave rise only to a mixture of products, probably due to the partial deprotection of the OTBDMS group. However also on the hydroxy unprotected aziridines the use of LiBr afforded a mixture of regioisomers with a fair regioselectivity (C3/C2 = 84/16).We have also performed the opening reaction with some N-protected tosyl and carboxyethyl aziridines: we have found $MgBr_2$ the best reagent for an excellent C-3 attack, with regio and chemical yields compared to those reported in Table 1.

13. The reaction was also performed on two model N-Boc protected aziridino-2-carboxylates affording the corresponding N-Boc-α-amino-β-bromo esters in the same excellent regiochemical yields (unpublished results).

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15. Our two steps procedure to the 1,2-amino alcohols favourable competes (82-85% overall yield) with the alternative direct opening with $LiAlH_4$ and DIBAL [5] (75% and 40% yield respectively).

16. a) To a solution of 3-bromo derivative (1 mmol) in CH_2Cl_2 (12 mL) a solution of TFA (50% in CH_2Cl_2, 6.2mL) was added. The solution was stirred at room temperature for 12h (TLC monitoring), diluted with Et_2O and washed with $NaHCO_3$ sol.sat. The organic layers were then dried over Na_2SO_4, evaporated *in vacuo* and purified by flash chromatography afforded the deprotected amino alcohol. b) To a solution of 3-bromo derivative (1 mmol) in THF (10.6 ml/g) Bu_4NF (2 mL, sol.1 M in THF) was added at 0°C. The solution was stirred at room temperature for 1h (TLC monitoring) and concentrated in vacuo. The residue was diluted with AcOEt and washed with NaCl sol.sat. The organic layers were then dried over Na_2SO_4, evaporated in vacuo and purified by flash chromatography afforded the N-Boc-amino alcohol.