A Convenient One-Pot Conversion of N-Boc-β-Aminoalcohols into N-Boc-Aziridines

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Abstract: This paper describes an efficient single step transformation of chiral N-protected β-amino alcohols into appropriate aziridines.

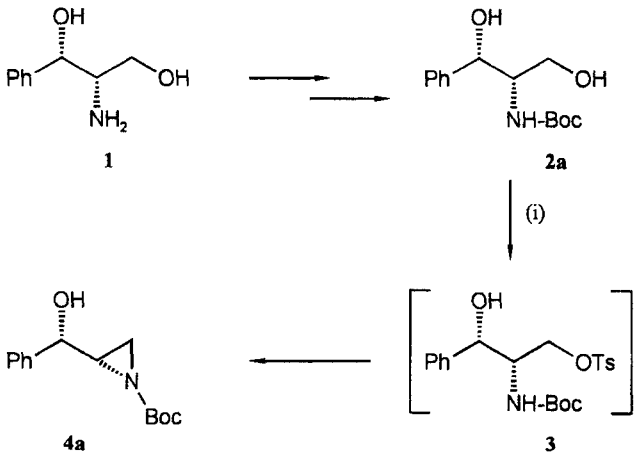
N-acyl aziridines are versatile synthons useful in many synthetic works. Their value for preparative chemists is essentially based on the high reactivity against various nucleophilic reagents. Compared with N-protected β-halogen-alkylamines, N-acyl aziridines must be characterised as rather soft electrophiles. Furthermore, elimination as typical side reaction of haloalkanes upon treatment with nucleophiles does not occur in the case of aziridines. Thus, ring opening reactions with N-, C-, O-, S-nucleophiles have been reported. Either sodium azide and anions of nitrogen heterocycles react with N-acyl aziridines in the presence of Lewis acids giving β-azido amines and N-(β-aminoalkyl) heterocycles respectively[1], whereas amines lead to 1,2-diamines without catalysts[2]. The reaction with organocopper compounds makes a variety of substituted amines accessible[3]. Derivatives of aziridine-2-carboxylic acid (Azy) are important synthons for the preparation of nonproteinogenic α-amino acids[4] and the Lewis acid-catalysed aziridine ring-opening with alcohols gives protected β-amino ethers[5]. Finally, a lot of β-mercaptoamines and β-alkylthioamines were prepared upon reaction with hydrogen sulphide or thiols[6].

Up to now N-acyl aziridines were prepared according to essentially three synthetic routes all starting with N-acyl-β-amino alcohols. The first method involves activation of the hydroxyl group by converting into tosylates or mesylates and subsequent ring-closure by means of strong bases (LiHMDS or NaH)[7]. The second method is most frequently used and applies the Mitsunobu reaction[5,8]. Thirdly N-acyl aziridines were prepared using the expensive and hazardous diethylamino sulfurtrifluoride (DAST)[9].

In this paper we describe a straightforward method of preparation of enantiomerically pure N-BOC aziridines **4** from N-BOC β-amino alcohols **2**. The BOC group was chosen in view of easy removal although our method should not be limited to this protective group.

During our investigations regarding the preparation of unnatural α-amino acids we were especially interested in synthetic protocols starting with the commercially available aminodiol **1**. After converting **1** into the O(1)- and N-protected derivative **2**[10] the 3-hydroxyl group should be transformed into a leaving group in order to enable subsequent chain elongation reactions. Thus, we attempted O-tosylation using a very mild method originally developed by Brandsma for propargylic alcohols[11]. It involves treatment of the alcohol with tosylchloride and an excess of powdered KOH in dry diethylether. If **1** is subjected to these conditions TLC monitoring of the reaction mixture indicates the formation of a primary product, presumably the expected tosylate **3** together with remaining reactants. Upon refluxing the mixture, intermediate **3** was surprisingly converted to aziridine **4** in excellent yields (Scheme 1).

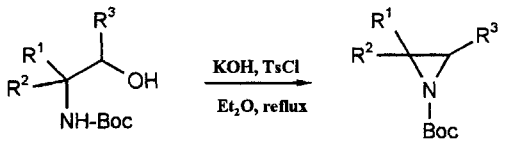
In order to prove whether this method is generally applicable we have treated some N-Boc-β-amino alcohols **2b-h** under the same conditions. Compounds **2** were prepared by N-protection of commercially available β-amino alcohols using di-*tert*-butyl dicarbonate. It should be mentioned that the reduction of N-BOC-α-amino acids according to Ho[5] is often a more convenient method for preparation of α-



Scheme 1. (i) TsCl, powdered KOH, Et_2O, reflux

unsubstituted compounds **2** (R^3 = H, see Table). In all cases we obtained the N-Boc-aziridines **4** in good to excellent yields [12].

Table. Ring-closure of *N*-BOC-β-amino alcohols **2**



Substrate	Product	R^1	R^2	R^3	conf. [a]	yield [c] (%)
2a	**4a**	[b]	H	H	*S*	78
2b	**4b**	Me	H	H	*S*	83
2c	**4c**	Et	H	H	*R*	72
2d	**4d**	*i*-Pr	H	H	*S*	75
2e	**4e**	Ph	H	H	*S*	89
2f	**4e**	H	H	Ph	*rac.*	99
2g	**4f**	Me	Me	H	-	79
2h	**4g**	*i*-Bu	H	H	*S*	85

[a] absolute configuration at C(2) of aziridines 4; [b] for R^1 see Scheme 1; [c] isolated yields

The reaction time depends mainly on the steric hindrance of the hydroxyl group. Thus, reaction of **2a-e,h** required *ca.* 4 h, whereas **2f,g** had fully disappeared after *ca.* 8 h. The stability of aziridines **4** bearing only alkyl substituents (**4a-d,g,h**) is remarkably higher than that of the phenyl-substituted compound **4e**. That especially appears during absorption on silica gel. While **4a-d,g,h** could be detected by TLC using mobile phases containing MeOH (usually mixtures of CH_2Cl_2 and

MeOH) the hitherto unknown 2-phenyl aziridine **4e** completely decomposed. Mixtures of petroleum ether / ethyl acetate are suitable both for TLC and flash cromatography in overcoming this problem. The ring closure of **2f** proved that also N-Boc α-substituted β-aminoalkanols undergo the described reaction. However compounds containing ester groups are not compatible with our reaction. Thus, upon treatment of N-Boc-serine methylester with KOH/TsCl no aziridine formation was observed, probably due to saponification of the ester group.

Finally, it should be mentioned that the O-tosyl derivative is isolable in the case of β-disubstituted aminoalcohols (**2g**).

Compared with previous methods, our procedure has fundamental advantages such as inexpensive reagents, simple work up and excellent yields.

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10. The preparation of **2a** was performed as follows: (i) *N*-protection using $(BOC)_2O$ / CH_2Cl_2 / reflux in the absence of any base, (ii) protection of the primary hydroxyl group using dimethylhexylsilyl chloride / imidazole / DMF, (iii) protection of the secondary hydroxyl group using BnBr / NaH / DMF, (iv) deprotection of the primary hydroxyl group using HF (40%, aqueous) / acetonitrile.
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12. Typical procedure: To a solution of **2** (10 mmol) and TsCl (12 mmol) in 200 ml dry diethyl ether was added KOH (40 mmol, freshly powdered with the help of a ball mill) at r.t. The stirred mixture was refluxed until TLC indicates disappearance of the reactants. If the reaction progress stagnates addition of additional powdered KOH (40 mmol) is useful. The mixture was poured into a separatory funnel filled with crushed ice. The organic phase was separated, washed with brine, dried with $MgSO_4$ and the solvent was removed under reduced pressure. The aziridines were purified by distillation (**2b-d, g,h**) or flash chromatography. It should be noted, that the crude products contain only traces of solvent mostly, whereas the reactants or byproducts are not detectable by NMR.

Analytical data for aziridines **4**:

4a: $[\alpha]_D$ = -28.1 ° (c=1.5, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 9H), 2.02 (d, 1H, *J* = 3.8 Hz), 2.23 (d, 1H, *J* = 6.3 Hz), 2.73 - 2.79 (m, 1H), 4.15 (d, 1H, *J* = 6.4 Hz), 7.25 - 7.30 (m, 10H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 27.9 (CH_3), 28.3 (CH_2), 41.9 (CH), 70.5 (CH_2), 81.3 (CH), 127.2 (CH), 127.4 (CH), 127.6 (CH), 128.2 (CH), 128.3 (CH), 138.3 (C_q), 138.8 (C_q), 162.0 (CO). **4b**: $[\alpha]_D^{20}$ = +39.2 ° (c=1, CH_2Cl_2). n_D^{20} = 1.4265. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.27 (d, 3H, *J* = 5.3 Hz), 1.46 (s, 9H), 1.88 (d, 1H, *J* = 3.8 Hz), 2.23 (d, 1H, *J* = 6.0 Hz), 2.42-2.47 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 17.8 (CH_3), 28.3 (CH_3), 32.9 (CH_2), 33.9 (CH), 81.3 (C_q), 162.8 (CO). **4c**: $[\alpha]_D^{20}$ = -50.4° (c=1, CH_2Cl_2). n_D^{22} = 1.4256. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.03 (t, 3 H, *J* = 7.53 Hz, CH_3), 1.43-1.58 (m, 11H), 1.91 (d, 1H, *J* = 3.8 Hz), 2.23 (d, 1H, *J* = 6.03 Hz), 2.32 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 11.2 (CH_3), 25.7 (CH_2), 28.3 (CH_3), 31.7 (CH_2), 39.8 (CH), 81.1 (C_q), 163.0 (CO). **4d**: $[\alpha]_D^{20}$ = +57.6 (c=1, CH_2Cl_2). n_D^{21} = 1.4261. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.97 (d, 3H, *J* = 6.8 Hz), 1.06 (d, 3H, *J* = 6.6 Hz), 1.37 - 1.53 (m, 10 H), 1.94 (d, 1H, *J* = 3.9 Hz), 2.10-2.16 (m, 1 H), 2.22 (d, 1 H, *J* = 6.3 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 19.0 (CH_3), 19.6 (CH_3), 27.8 (CH_3), 30.5 (CH_2), 30.9 (CH), 44.3 (CH), 80.6 (C_q), 162.8 (CO). **4e**: $[\alpha]_D^{20}$ = -163.5 (c=1, CH_2Cl_2). n_D^{20} = 1.5064. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.44 (s, 9H), 2.26 (d, 1H, *J* = 3.6 Hz), 2.62 (d, 1H, *J* = 6.3 Hz), 3.40 - 3.44 (m, 1H), 7.25 - 7.29 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 27.9 (CH_3), 34.8 (CH_2), 39.3 (CH), 81.4 (C_q), 126.3 (CH), 127.7 (CH), 128.4 (CH), 137.2 (C_q), 162.1 (CO). **4g**: n_D^{20} = 1.4272. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.29 (s, 6H), 1.47 (s, 9H), 2.09 (s, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 22.8 (CH_3), 28.1 (CH_3), 38.3 (CH_2), 40.4 (C_q), 80.7 (C_q), 161.4 (CO). **4h**: $[\alpha]_D^{22}$ = +43.9 (c=1, CH_2Cl_2). n_D^{20} = 1.4319. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.97 (d, 2H, *J* = 2.0 Hz), 1.0 (d, 2H, *J* = 1.8 Hz), 1.21- 1.31 (m, 1H), 1.36 - 1.43 (m, 1H), 1.45 (s, 9H), 1.82 - 1.89 (m, 1H), 1.88 (d, 1H, *J* = 3.7 Hz), 2.26 (d, 1H, *J* = 6.3 Hz), 2.36 - 2.41 (m ,1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 22.0 (CH_3), 22.7 (CH_3), 26.9 (CH), 27.9 (CH_3), 31.8 (CH_2), 36.8 (CH), 41.3 (CH_2), 80.7 (C_q), 162.6 (CO).