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A general method for deprotection of *N*-toluenesulfonyl aziridines using sodium naphthalenide

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Abstract

Deprotection of a variety of *N*-tosylaziridines with sodium naphthalenide provided the corresponding *N-H*-aziridines in excellent yield. No single electron transfer (SET) induced aziridine ring opening was seen under the conditions employed for the deprotection reaction. © 1999 Elsevier Science Ltd. All rights reserved.

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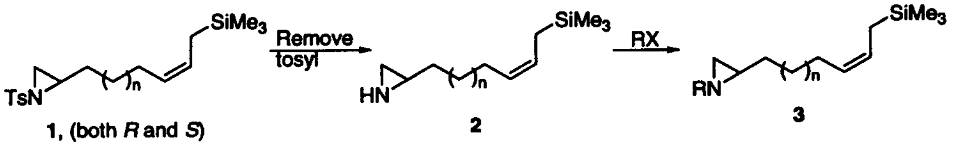
We recently reported a novel synthesis of optically pure *N*-tosyl aziridine-allylsilane **1** via a ring opening/closing reaction of *N*-tosyl-*O*-tosylaziridine methanols.[1] For some of our related work,[2] we needed access to enantiopure aziridine-allylsilanes which had protecting groups on the aziridine nitrogen other than tosyl.

An attractive method to access differentially substituted aziridine-allylsilanes such as **3**, would be by deprotection of *N*-tosylaziridine-allylsilane **1** to provide aziridine **2**, followed by reaction of **2** with the substituent of choice (Scheme 1). We perceived that this methodology could be a useful general procedure for the synthesis of a variety of differentially *N*-substituted aziridines from a single *N*-tosylaziridine precursor. This combined with the fact that chiral and racemic *N*-tosylaziridines can be easily synthesized from the corresponding olefins using methodology developed by Mansuy[3] and others,[4] were compelling reasons to explore such deprotections.



Scheme 1.

A difficulty typically encountered in deprotection reactions of aziridines, is the competing ring opening reaction.[5,6] This ring opening reaction can potentially be avoided, if the nitrogen protecting group is

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one which does not strongly activate the aziridine towards ring opening such as trityl,[7a] phosphinyl,[7b] sulfinyl,[7c] or alkoxy.[7d] Removal of *N*-tosyl groups is substrate dependent and typically requires harsh conditions such as HBr/AcOH.[8] One would not expect an aziridine ring to be stable under these conditions. It was not surprising that there were very few reports in the literature of deprotection of *N*-tosylaziridines.[9] Several reports have indicated that *N*-sulfonyl aziridines undergo N–S cleavage prior to ring opening under SET (single electron transfer) reaction conditions. We thus felt that an investigation into the scope and limitations of sodium naphthalenide for the deprotection of *N*-tosyl aziridines would be a generally useful study.

Deprotection of **4**[1] using sodium naphthalenide[10] (3 equiv. in THF) as the reducing agent at 0°C provided us with the desired aziridine **5** in 52% yield (Table 1). The yield improved to 69% when sodium naphthalenide was added dropwise (see experimental)[11] to a cold (–78°C) solution of aziridine **4**. The best results were obtained when the deprotection was carried out in DME as opposed to THF.

Deprotection of the tosyl group in **6**[1,12] provided the aziridine **7** in excellent yield (89%). The reaction worked equally well when the adjacent protecting group is benzyl (76%) as in case of aziridine **8**[12] to provide **9**.[13] Thus, the conditions are mild enough that even the reductively labile benzyl ethers are stable under the reaction conditions.

We next attempted to deprotect the known aziridine *t*-butyl ester **10**.[14] Unfortunately, this resulted in decomposition of **10** and none of the desired product was seen either by TLC or in ^{1}H NMR of the crude reaction mixture. Decomposition in this case could have resulted from attack of the intermediate nitrogen anion onto the carbonyl carbon of the ester group. Decomposition could have also resulted from cleavage of the C–N bond of the aziridine ring, adjacent to the carbonyl group.[15] To test for this possibility, we synthesized the aziridine *t*-butylamide **11**.[15] Deprotection of the amide **11** provided us with the desired aziridine **12** in excellent yield (93%). This result indicated that presence of an adjacent carbonyl group does not necessarily lead to decomposition.

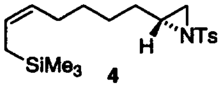
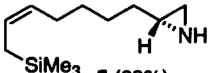
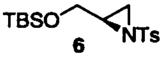
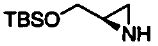
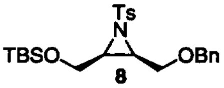
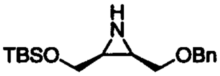
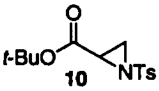
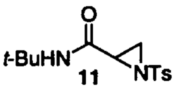
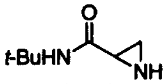
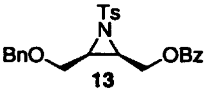
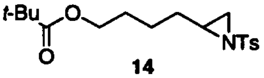
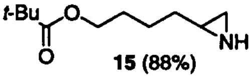
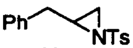
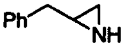
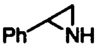
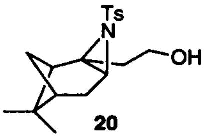
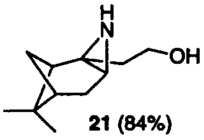
We next examined the compatibility of an ester linkage at other positions within the molecule. To this end the benzoate ester **13** and the pivalate ester **14** were prepared from the corresponding alcohols.[16] Deprotection of **13** resulted in decomposition. It was not readily apparent if the decomposition resulted due to SET to the benzoyl carbonyl[9a,b] or due to a fragmentation reaction facilitated by a relatively good leaving group adjacent to the aziridine ring. This is in contrast to the report by Katoh in which an acyloxy group adjacent to an aziridine was retained.[9e]

Deprotection of the tosyl group in **14**, provided the desired aziridine **15** (63%) which was contaminated with a small amount of the corresponding *O,N*-dipivalate aziridine (15%). This problem was avoided simply by carrying out the reaction in more dilute conditions (0.07 M in DME), which eliminated an intermolecular acyl transfer reaction to provide the deprotected aziridine **15** (88%).

We then examined the compatibility of aromatic rings under the deprotection conditions. The known aziridines **16**[17] and **18**[4a] were deprotected. The deprotected aziridine **17**[18] was obtained in excellent yield (89% from **16**) when the reaction was carried out at –78°C. However, none of the desired product **17** was obtained when the reaction was carried out at 0°C. The deprotected aziridine **19** (64% from **18**)[19] was obtained along with a small amount of *N*-tosylphenethylamine (19%), which arose from reduction of the benzylic C–N bond of the aziridine ring. This result was not entirely unexpected, as deprotection of **18** using SmI_2 had provided only *N*-tosylphenethylamine.[9c]

Lastly, we looked at the deprotection of a strained bicyclic *N*-tosyl aziridine **20**, derived from (–)-nopol. Protection of the hydroxyl group in nopol with TBSCl, followed by aziridination using PhINTs[4a] provided the corresponding *N*-tosylaziridine, which was then desilylated using nBu$_4$NF to provide aziridine **20**. Deprotection of **20** provided the desired deprotected aziridine **21** (84%). The successful

Table 1
Deprotection of *N*-tosylaziridines using Na-naphthalenide[11]

Entry	Reactant	Product (yield)
1[a]	 **4**	 **5** (69%)
2	 **6**	 **7** (89%)
3	 **8**	 **9** (76%)
4	 **10**	decomp.
5	 **11**	 **12** (93%)
6	 **13**	decomp.
7[b]	 **14**	 **15** (88%)
8	 **16**	 **17** (89%)
9[c]	 **18**	 **19** (64%)
10	 **20**	 **21** (84%)

[a] This reaction was carried out in THF. [b] This reaction was carried out 0.07M in DME.
[c] *N*-tosylphenethyl-amine (19%) was also recovered from this reaction.

deprotection of **20** also indicates that a hydroxyl group adjacent to the aziridine ring is tolerated in the deprotection reaction.

We have developed a useful protocol for the deprotection of *N*-tosylaziridines using sodium naphthalenide. A wide variety of functionality is tolerated under the reaction conditions employed for the deprotection reaction. This deprotection reaction could be a useful procedure for the synthesis of different *N*-protected aziridines from a single *N*-tosylaziridine precursor. This method should also be useful for the deprotection of other *N*-arenesulfonyl aziridines.

Acknowledgements

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11. Experimental: Finely chopped sodium metal (0.12 g, 5 mmol) and naphthalene (0.72 g, 5.5 mmol) were dissolved in DME (5 mL). The reaction was stirred for 2 h, to provide a dark green solution.[10] The desired *N*-tosylaziridine (0.25 mmol) in DME (1 mL) was cooled to –78°C. The Na-naphthalenide solution was added dropwise to the reaction via a syringe, until a dark green color persisted for 5 min. The reaction was quenched at –78°C with 1–2 drops of water (to discharge the green color) and the reaction was diluted with Et_2O to provide a cloudy solution which was dried ($MgSO_4$), filtered and concentrated. Purification (2–5% MeOH in $CHCl_3$, silica gel) provided the *N-H*-aziridines. NOTE: care should be exercised while isolating the final aziridines, most of which are slightly volatile. All new starting and product aziridines showed satisfactory ^1H, ^{13}C NMR and HRMS data. ^1H and ^{13}C NMR data for new compounds: Data for **7**: ^1H NMR ($CDCl_3$) δ 3.68 (d, 2H, J=3.9), 2.08 (m, 1H), 1.62 (d, 1H, J=5.5), 1.51 (d, 1H, J=3.5), 0.85 (s, 9H), 0.03 (s, 6H). ^{13}C NMR δ 63.3, 31.1, 25.8, 21.9, 18.3, –5.4, –5.41. Data for **12**: ^1H NMR ($CDCl_3$) δ 6.22 (br, 1H), 2.36 (br, 1H), 1.83 (br, 1H), 1.75 (br, 1H), 1.35 (s, 9H). ^{13}C NMR δ 169.8, 51.1, 30.9, 28.7, 26. Data for **15**: ^1H NMR ($CDCl_3$) δ 4.0 (t, 2H, J=6.5), 1.88 (m, 1H), 1.69 (d, 1H, J=5.8), 1.6 (m, 2H), 1.5–1.3 (m, 6H), 1.25 (d, 1H, J=3.6), 1.13 (s, 9H). ^{13}C NMR δ 178.5, 64.2, 38.7, 34.2, 30.1, 28.6, 27.2, 25.8, 25. Data for **21**: ^1H NMR ($CDCl_3$) δ 3.65 (m, 2H), 2.56 (br, 2H), 2.17 (d, 1H, J=5.8), 2.1 (m, 1H), 2.03 (t, overlapped, 2H, J=5.9), 2.0 (m, 1H), 1.81 (dd, 1H, J=14.8, 2.7), 1.58 (m, 1H), 1.55 (m, 1H), 1.26 (s, 3H), 1.17 (t, 2H, J=10.7), 0.93 (s, 3H). ^{13}C NMR δ 59.3, 44.6, 41.2, 41, 40.9, 37.1, 32.3, 27.1, 26.8, 26.1, 20.4.
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