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Nosylaziridines: Activated Aziridine Electrophiles

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Abstract: Nosylaziridines are highly reactive electrophiles towards a variety of nucleophiles yielding the corresponding SN2 adducts without competing attack on the nosyl functionality (SNAr). The resulting primary nosylamide adducts can be readily cleaved under mild conditions to provide the primary amines.
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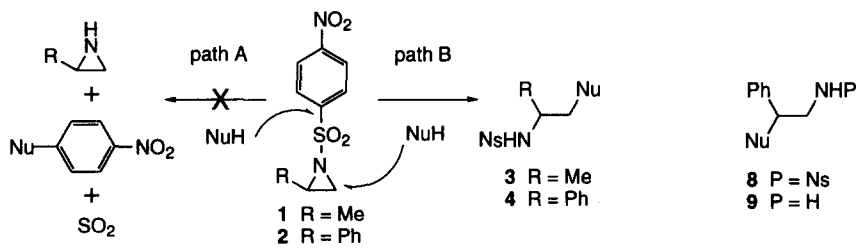
Aziridines have become popular electrophilic β-aminoethyl synthetic equivalents.[1] *N*-Arylsulfonyl aziridines are the most widely used activated aziridine electrophiles and they are readily prepared in optically active form.[2] However, subsequent cleavage of the arylsulfonyl group requires harsh conditions.[3] *N*-Acyl and *N*-carbalkoxy groups can also activate aziridines towards nucleophilic attack but they frequently suffer competitive attack on the carbonyl group.[4] Frequently the nucleophilic opening of activated and unactivated aziridines requires assistance by an acid or harsh reaction conditions.[5]

Scheme 1



It was postulated that a powerful electron withdrawing group such as 4-nitrobenzenesulfonyl (Ns = nosyl) would activate the aziridine ring towards nucleophilic attack (Scheme 1).[6] However, two pathways for nucleophilic attack of such nosylaziridines would be possible: path A, nucleophilic aromatic substitution (SNAr)[7] via the intermediate Meisenheimer complex or path B, nucleophilic attack at the aziridine carbon (SN2) to give the ring opened product. Herein we wish to report *nosylaziridines 1 and 2 readily undergo opening with a variety of nucleophiles such as amines, thiols, alkoxides, and cyanide to give the corresponding SN2 adducts in good yields without competing deprotection under mild conditions.*

Rate experiments demonstrated that nosylaziridines are 50-60 times more reactive than the corresponding tosylaziridines.[8] Nucleophilic attack on the 2-methyl-nosylaziridine **1**[9] occurred regiospecifically giving only the products resulting from attack on the less substituted center (Table 1).[10] Reaction of phenyl substituted aziridine **2**[11] with amine nucleophiles gave non-specific adduct formation. Interestingly however, reaction of

(*R*)-**2** with methanol gave only regioisomer **8i** resulting from attack on the benzylic center without any detectable loss of enantiomeric purity.[12]

The *N*-nosyl group of the ring-opened adducts can be cleaved under mild conditions (Scheme 2). Although we expected the nosylamide adducts could be deprotected with thiols, only secondary nosylamides have been deprotected in the literature.[13] Attempts at deprotection of the primary nosylamides employing the Fukuyama conditions (PhSH, K_2CO_3, DMF or thioglycolic acid, LiOH, DMF) resulted in sluggish reaction rates and incomplete reactions. Replacement of DMF with acetonitrile as the solvent resulted in complete deprotection within 24 h at 50°C and the addition of 2% DMSO (by vol) to the acetonitile shortened the reaction time to as little as 2 h.[14] In addition, prior conversion of the nosylamides to the Boc-nosylimide derivative **6** activates the nosyl group towards attack and cleavage by thiophenol.

Scheme 2

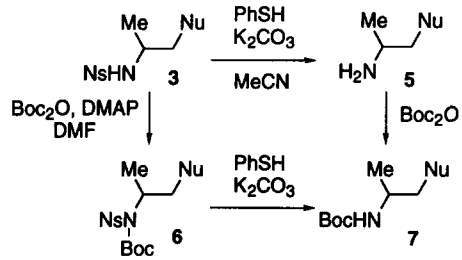


Table 1

		Reactions with Nucleophiles				Deprotection		
Entry	Aziridine	Reaction Conditions[a]	Nu	Adducts	%Yield	Method[b]	Product	%Yield
1	(*rac*)-**1**	n-HexylNH$_2$, 2 h	n-HexylNH	**3a**	86	A	**5a**	46
2	(*rac*)-**1**	BnNH$_2$, Et$_3$N, 2 h	BnNH	**3b**	92	A	**5b**	97
3	(*rac*)-**1**	Et$_2$NH, 2 h	Et$_2$N	**3c**	99	C	**7c**	92
4	(*rac*)-**1**	Pyrrolidine, Et$_3$N, 3 h	(CH$_2$)$_4$N	**3d**	98	C	**7d**	62
5	(*rac*)-**1**	Piperidine, Et$_3$N, 3 h	(CH$_2$)$_5$N	**3e**	98	C	**7e**	85
6	(*rac*)-**1**	Morpholine, Et$_3$N, 3 h	O(CH$_2$CH$_2$)$_2$N	**3f**	86	C	**5f**	73
7	(*rac*)-**1**	n-BuSH, Et$_3$N, 22 h	n-BuS	**3g**	80	B	**7g**	98
8	(*rac*)-**1**	BnSH, Et$_3$N, 2 h	BnS	**3h**	72	A	**5h**	99
9	(*rac*)-**1**	NaOMe, 2 h	MeO	**3i**	45	B	**7i**	92
10	(*rac*)-**1**	KCN, n-Bu$_4$NCN, 22 h	CN	**3j**	78	B	**7j**	74
11	(*R*)-**2**	BnNH$_2$, Et$_3$N, 4 h	BnNH	**4b, 8b**[c]	56	-	-	-
12	(*R*)-**2**	Piperidine, Et$_3$N, 4 h	(CH$_2$)$_5$N	**4e, 8e**[c]	78	-	-	-
13	(*R*)-**2**	MeOH, 60 h	MeO	**8i**	99	B	**9i**	79

(a) Reactions were carried out in THF (1 mL/mmol) at 30°C using 0.2 equiv of Et$_3$N where indicated and evaporated to dryness and the residue was purified by flash chromatography (silica gel, Merck, 70-230 mesh ASTM) unless otherwise stated: entry 1, 2 equiv of nucleophile; entry 3, 1.4 equiv of nucleophile; entry 9, NaOMe was used as a 25% solution in MeOH; entry 10, 1.4 equiv of nucleophile and 0.1 equiv of n-Bu$_4$NCN in 10:1 THF-water (0.2M); entry 13, MeOH was used as the reaction solvent (0.1M). (b) Method A: 3 equiv PhSH, 4 equiv K_2CO_3, MeCN, 50°C, 24 h; Method B: 3 equiv PhSH, 4 equiv K_2CO_3, 49:1 MeCN-DMSO, 50°C, 2-6 h then 5 equiv Boc$_2$O; Method C: 1.1 equiv Boc$_2$O, 1.1 equiv DMAP, DMF then 1.5 equiv PhSH, 3 equiv K_2CO_3. (c) An approximately 1:1 mole ratio mixture of the two regioisomers (NMR) was obtained. Enantiomeric purities were not determined.

In summary, nosylaziridines have been found to be highly reactive electrophiles towards a variety of nucleophiles in an SN2 sense and the resulting adducts can be deprotected under mild conditions. The nosylaziridines can be readily prepared from the corresponding alkenes.[15] The direct asymmetric nosylaziridination of alkenes is under investigation.

ACKNOWLEDGMENT We wish to thank Robert A. Reamer and Lisa DiMichele for their NMR support, and Gregory McManemin for his mass spectroscopic support.

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6. To our knowledge there have been no reported cases of nosylaziridine openings by direct nucleophilic attack on the aziridine ring. A recent report of the opening of an allylic nosylaziridine via SN2' attack by an organocuprate has appeared: Wipf, P.; Henninger, T.C. *J. Org. Chem.* **1997**, *62*, 1586-1587.

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8. The rates of reaction of **1** and the corresponding p-tosylaziridine with a nucleophile were determined by reaction of the arylsulfonylaziridine (0.12 mmol) with n-$PrNH_2$ (0.24 mmol) in d_8-THF (0.40 mL) at 30°C. The reactions were monitored by ^1H NMR and integration of the CH_3CHN and aryl protons. Rates were calculated, assuming second order kinetics (for the reaction of **1** with n-$PrNH_2$, k = 1.6 $M^{-1}min^{-1}$ and for the reaction of the corresponding tosylaziridine with n-$PrNH_2$, k = 0.028 $M^{-1}min^{-1}$). Similar results for the reactivity difference between **1** and the corresponding tosylaziridine were obtained with benzylamine and benzyl mercaptan as nucleophiles.

9. Preparation of **1**: A solution of 2-methylaziridine (5.71 g, 0.10 mol) and Et_3N (11.1 g, 0.11 mol) was added over 30 min to a solution of nosyl chloride (22.2 g, 0.10 mol) in CH_2Cl_2 (100 mL) maintained below -20°C. The mixture was warmed to 10°C over 30 min and washed with 1M NaH_2PO_4 (100 mL), water (100 mL), 5% aq $NaHCO_3$ (100 mL), and brine (100 mL). The organic phase was dried ($MgSO_4$) and evaporated. The residue was crystallized from 1:5:5 CH_2Cl_2-MTBE-hexane (110 mL) to provide **1** as a white crystalline solid (22.2 g, 92% yield); ^1H NMR (250 MHz, $CDCl_3$) δ 8.75 (d, *J* = 8.9 Hz, 2H), 8.13 (d, *J* = 8.9 Hz, 2H), 2.95 (m, 1H), 2.71 (d, *J* = 7.0 Hz, 1H), 2.12 (d, *J* = 4.7 Hz, 1H), 1.28 (d, *J* = 5.6 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 150.6, 144.2, 129.1, 124.3, 36.8, 35.5, 16.8.

10. The other regioisomer was not detectable and the regiochemistry of **3a-j** was confirmed by NMR analysis. Typical procedure, preparation of **3b**: a mixture of **1** (1.21 g, 5.00 mmol), $BnNH_2$ (0.54 g, 5.05 mmol), Et_3N (0.10 g, 1.0 mmol) and THF (5 mL) was stirred at 30°C for 2 h and evaporated. The residue was purified by flash chromatography (silica, MTBE) to provide **3b** as a colorless oil (1.61 g, 92% yield); ^1H NMR (250 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.6 Hz, 2H), 7.98 (d, *J* = 8.6 Hz, 2H),

7.35-7.18 (m, 5H), 3.61 (A-B q, J = 21.2, 13.3 Hz, 2H), 3.34 (m, 1H), 2.57 (m, 2H), 1.13 (d, J = 6.6 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 146.5, 139.3, 128.6, 128.3, 127.9, 127.4, 124.2, 53.2, 53.1, 49.2, 19.6. Preparation of **3g**: Similar reaction conditions as above, starting with n-BuSH. The residue was purified by flash chromatography (silica, 1:9 EtOAc-hexane) to provide **3g** as a colorless oil (1.33 g, 80% yield); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.36 (d, J = 8.9 Hz, 2H), 8.09 (d, J = 8.9 Hz, 2H), 5.09 (d, J = 6.8 Hz, 1H), 3.51 (m, 1H), 2.56 (d, J = 6.1 Hz, 2H), 2.35 (td, J = 7.3, 2.7 Hz, 2H), 1.48-1.22 (m, 4H), 1.20 (d, J = 6.5 Hz, 3H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 150.0, 146.6, 128.4, 124.3, 49.4, 39.3, 32.5, 31.6, 21.9, 21.1, 13.6. Preparation of **3i**: a mixture of **1** (1.21 g, 5.00 mmol), 25% NaOMe in MeOH (1.14 mL, 5.00 mmol) and THF (5 mL) was stirred at 30°C for 2 h and evaporated. The residue was purified by flash chromatography (silica, 2:2:1 CH_2Cl_2-MTBE-hexane) to provide **3i** as a white crystalline solid (0.62 g, 45% yield); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.28 (d, J = 8.8 Hz, 2H), 8.02 (d, J = 8.8 Hz, 2H), 3.46 (m, 1H), 3.16 (d, J = 5.3 Hz, 2H), 3.12 (s, 3H), 1.03 (d, J = 6.9 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 149.9, 147.2, 128.2, 124.1, 75.5, 58.7, 49.5, 18.2.

11. Nosyl aziridine **2** was prepared from *(R)*-phenylglycinol by a method similar to that described in the literature: Ibuka, T.; Mimura, N.; Aoyama, H.; Akaji, M.; Ohno, H.; Miwa, Y.; Taga, T.; Nakai, K.; Tamamura, H.; Fujii, N. *J. Org. Chem.* **1997**, *62*, 999-1015. Preparation of *(R)*-**2**: *(R)*-phenylglycinol-nosylamide was prepared from *(R)*-phenylglycinol in a procedure similar to that described for the preparation of **1**. Diethylazodicarboxylate (DEAD) (9.58 g, 55 mmol) was added over 15 min to a solution of *(R)*-phenylglycinol-nosylamide (15.8 g, 49 mmol) and PPh_3 (14.4 g, 50 mmol) in THF (75 mL) maintained below 2°C. The mixture was warmed to 20°C over 16 h, and evaporated. The residue was purified by flash chromatography (silica, 1:2 hexane-CH_2Cl_2) and crystallization from 2:7:10 CH_2Cl_2-MTBE-hexane (190 mL) to provide *(R)*-**2** as a white crystalline solid (11.1 g, 75% yield); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.38 (d, J = 7.0 Hz, 2H), 8.19 (d, J = 7.0 Hz, 2H), 7.34-7.20 (m, 5H), 3.91 (dd, J = 7.3, 4.6 Hz, 1H), 3.11 (d, J = 7.3 Hz, 1H), 2.51 (d, J = 4.6 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 150.6, 143.9, 134.2, 129.2, 128.8, 126.5, 124.4, 41.9, 36.6.

12. The other regioisomer was not detectable and the regiochemistry of **8i** was confirmed by NMR analysis. Preparation of **8i**: A mixture of **2** (1.52 g, 5 mmol) (>99% ee) and MeOH (40 mL) was stirred at 45°C for 16 h and evaporated to provide crude **8i** as a white crystalline solid (1.68 g, 100%, >98% purity by HPLC). The crude residue was purified by crystallization from 1:2:4 CH_2Cl_2-MTBE-hexane (35 mL) to provide **8i** as a white crystalline solid (1.56 g, 93% yield); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.33 (d, J = 8.9 Hz, 2H), 8.01 (d, J = 8.9 Hz, 2H), 7.98-7.18 (m, 5H), 5.40 (dd, J = 8.6, 3.4 Hz, 1H), 4.26 (dd, J = 8.9, 3.6 Hz, 1H), 3.31 (ddd, J = 12.6, 8.6, 3.6 Hz, 1H), 3.17 (s, 3H), 3.03 (ddd, J = 12.7, 9.0, 3.6 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 150.0, 145.9, 137.8, 128.8, 128.6, 128.3, 126.6, 81.9, 56.8, 49.3. Enantiomeric purities of **2** (>99% ee) and **8i** (>99% ee) were monitored by supercritical fluid chromatography (SFC). SFC conditions: Chiralpak AD 250 × 4.6 mm column, isocratic elution with 4% MeOH, 96% supercritical CO_2 then gradient to 32% MeOH, 68% supercritical CO_2 at 300 bar over 28 min, 1 mL/min flow at 35°C with detection at 220 nm, retention times: *(S)*-**2** = 16.6 min, *(R)*-**2** = 18.3 min, **8i** antipodes = 20.4, 23.4 min. The absolute configuration of the product **8i** has not been determined.

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14. Preparation of **5b**: A mixture of **3b** (193 mg, 0.2 mmol), PhSH (66 mg, 0.6 mmol), K_2CO_3 (111 mg, 0.8 mmol), and MeCN (5 mL) was stirred at 50°C for 24 h and evaporated. The residue was purified by flash chromatography (silica, 1:1 EtOAc-MeOH) to provide **5b** as a colorless oil (88 mg, 97% yield); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.32-7.17 (m, 5H), 3.69 (A-B q, J = 15.5, 13.3 Hz, 2H), 2.87 (m, 1H), 2.53 (dd, J = 12.0, 4.2 Hz, 1H), 2.30 (dd, J = 12.0, 8.5 Hz, 1H), 0.97 (d, J = 6.4 Hz, 3H). Preparation of **7g**: A mixture of **3g** (70 mg, 0.2 mmol), PhSH (66 mg, 0.6 mmol), K_2CO_3 (111 mg, 0.8 mmol) and 49:1 MeCN-DMSO (5 mL) was stirred at 50°C for 3 h. Boc_2O (218 mg, 1 mmol), was added and the mixture was stirred at 25°C for 1 h and evaporated. The residue was purified by flash chromatography (silica, 9:1 hexane-EtOAc) to provide **7g** as a colorless oil (51 mg, 98% yield); ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.62 (br m, 1H), 3.82 (br m, 1H), 2.63 (td, J = 13.2, 5.0 Hz, 2H), 2.53 (t, J = 7.4 Hz, 2H), 1.68-1.31 (m, 4H), 1.43 (s, 9H), 1.19 (d, J = 6.8 Hz, 3H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 155.1, 79.9, 46.2, 39.0, 32.7, 31.8, 28.4, 21.9, 20.0, 13.7. Preparation of **7i**: Similar reaction conditions as above, starting with **3i**. The residue was purified by flash chromatography (silica, 3:1 hexane-EtOAc) to provide **7i** as a colorless oil (44 mg, 92% yield); ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.69 (br m, 1H), 3.80 (br m, 1H), 3.34 (s, 3H), 3.31 (d, J = 4.4 Hz, 2H), 1.43 (s, 9H), 1.14 (d, J = 6.6 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 155.4, 79.1, 75.8, 59.0, 46.0, 28.4, 17.9.

15. Preparation of (rac)-**2**: A suspension of styrene (5.21 g, 50 mmol), PhI=NNs (2.02 g, 5.00 mmol), $Cu(OTf)_2$ (90 mg, 0.25 mmol) and MeCN (10 mL) was stirred at 20°C for 18 h and the resulting green homogenous mixture was evaporated. The residue was dissolved in CH_2Cl_2 (30 mL), filtered through silica (15 g) and evaporated. The residue was crystallized from 1:1:2 CH_2Cl_2-MTBE-hexane (20 mL) to provide (rac)-**2** as a white crystalline solid (858 mg, 56% yield). The preparation of PhI=NNs was similar to that described in the literature: (a) Besenyei, G.; Nemeth, S.; Simandi, L.I. *Tetrahedron Lett.* **1993**, *34*, 6105-6106. (b) Yamada, Y.; Yamamoto, T.; Okawara, M. *Chem. Lett.* **1975**, 361-362.

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