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A novel synthesis of 3-aminoazetidines by ring transformation of 2-(bromomethyl)aziridines†

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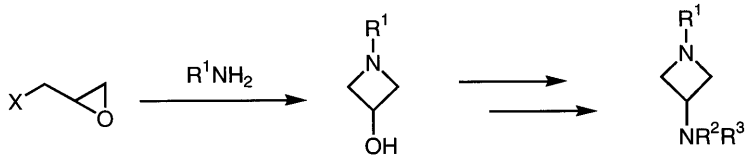
Abstract

A one-step approach to the biologically interesting 3-aminoazetidines is described. The reaction concerns a ring transformation of 1-arylsulfonyl-2-(halomethyl)aziridines with aliphatic amines under various reaction conditions.

Keywords: 3-aminoazetidines; aziridines; ring transformation.

Azetidines are an interesting class of four-membered heterocyclic compounds in terms of biological activities.[1] 3-Aminoazetidines **3** have received attention in recent years because of their antibacterial activities.[2] In most cases, 3-aminoazetidine derivatives have been obtained by functional group transformation of 3-hydroxyazetidines **2**. The preparation of the 3-hydroxyazetidines **2** by the reaction of epihalohydrins **1** with amines has been known for a long time (Scheme 1).[3] However, this reaction gives mostly low yields, although some improved methods have been published.[4]



1 **2** **3**

Scheme 1.

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† Dedicated to Prof. Dr. Gabor Bernath on the occasion of his 65th birthday.

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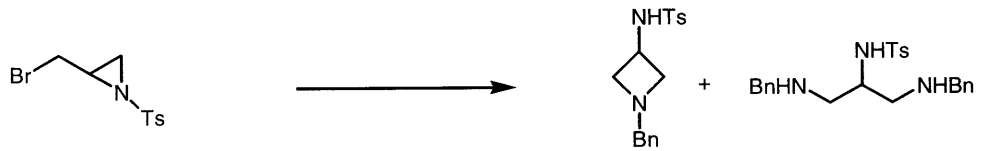
In the course of our synthetic study concerning small ring heterocycles, we were interested in exploring the possibility of constructing such 3-aminoazetidines by ring transformation of appropriately functionalized *N*-arylsulfonylaziridines.[5]

Activated aziridines which possess an electron withdrawing group on nitrogen exhibit similar reactivities as oxiranes towards nucleophiles such as amines.[6] Accordingly, we found a new synthetic method for 3-aminoazetidines **3** by the reaction of *N*-arylsulfonyl-2-(halomethyl)aziridines **4a** with aliphatic amines. In this reaction, 3-aminoazetidines **5** are obtained as *N*-sulfonyl-protected derivatives by a one-step reaction without any further functional group transformation.

N-*p*-Toluenesulfonyl-2-(bromomethyl)aziridine **4a** and *N*-methanesulfonyl-2-(bromomethyl)aziridine **4b** were easily obtained from allyl bromide by a modification of a method described in the literature.[5] *N*-Benzenesulfonyl-2-(chloromethyl)aziridine **4c** was also obtained by a similar method using chlorine gas instead of bromine.

When a solution of *N*-*p*-toluenesulfonyl-2-(bromomethyl)aziridine **4a** in tetrahydrofuran was refluxed with 2.4 equivalents of benzylamine (Method A) for 5 h, *N*-benzyl-3-*p*-toluenesulfonylamidoazetidine **5a** was obtained in 28% yield. Also 40% of 1,3-di(*N*-benzylamino)-2-*p*-toluenesulfonylamide **6a** was obtained as an undesirable side product. These observations can be explained by considering a second nucleophilic displacement process by the excess of benzylamine. In order to improve the yield of **5a** and to avoid the formation of **6a**, 1.2 equivalents of benzylamine and 1.2 equivalents of triethylamine were used (Method B).[7] As expected, **5a** was obtained in an higher yield of 37% (Scheme 2). On the other hand, when the reaction of aziridine **4a** was conducted in the presence of 2.4 equivalents of benzylamine at room temperature, the formation of 3-aminoazetidine **5a** was not observed (Method C). From the mechanistic point of view the reaction proceeds via a nucleophilic opening of 1-sulfonyl-2-(bromomethyl)aziridines **4a**, affording intermediate 3-halo-2-(*N*-sulfonyl)amidopropanes **7**, which undergo ring closure by intramolecular nucleophilic substitution to the title azetidines **5**.

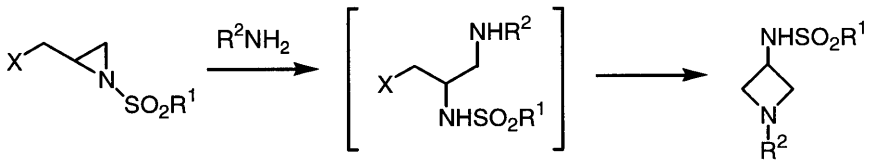


	4a	**5a**	**6a**
Method A	2.4 equiv. $PhCH_2NH_2$, THF, reflux 5h	28%	40%
Method B	1.2 equiv. $PhCH_2NH_2$, 1.2 equiv. Et_3N, THF, reflux 5h	37%	19%
Method C	2.4 equiv. $PhCH_2NH_2$, THF, rt 64h	0%	62%

Scheme 2.

As presented in Table 1, the same reaction did not give good results in toluene or methanol (entries 4, 5). THF appeared to be the solvent of choice. With the purpose of activation of the aziridine **4a**, $Yb(OTf)_3$ was added as a Lewis catalyst[8], but no azetidine **5a** was produced at all (entry 6). In order to extend the scope and synthetic utility of the reaction, the reactions of other commercially available amines were studied. 1-Cyclohexyl- and 1-*t*-butyl-3-*p*-toluene–sulfonylamidoazetidines (**5b**, **5c**) were easily synthesized from **4a** in moderate yields (entries 7–9).

Table 1
Ring transformation of 1-sulfonyl-2-(halomethyl)aziridines **4** into 1-alkyl-3-aminoazetidines **5**



7

4a: R^1 = *p*-Tol, X = Br
4b: R^1 = Me, X = Br
4c: R^1 = Ph, X = Br
4d: R^1 = Ph, X = Cl
4e: R^1 = 4-$CF_3C_6H_4$, X = Br

5a: R^1 = *p*-Tol, R^2 = $PhCH_2$
5b: R^1 = *p*-Tol, R^2 = *t*-Bu
5c: R^1 = *p*-Tol, R^2 = Cyclohexyl
5d: R^1 = Ph, R^2 = $PhCH_2$
5e: R^1 = 4-$CF_3C_6H_4$, R^2 = $PhCH_2$

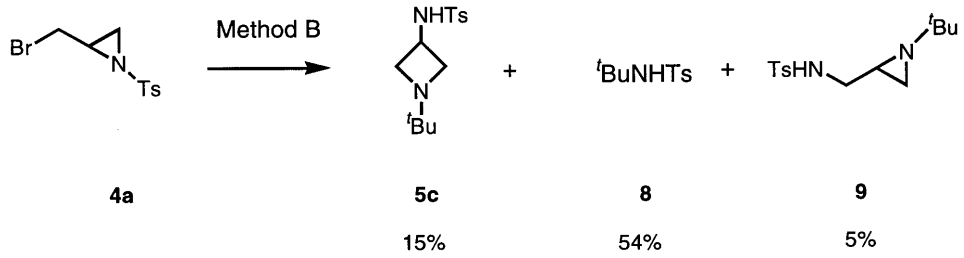
Entry	R^1	X	R^2	Solvent	Method[a]	Yield of **5** (%)[b]
1	*p*-Tol	Br	$PhCH_2$	THF	A	28
2	*p*-Tol	Br	$PhCH_2$	THF	B	37
3	*p*-Tol	Br	$PhCH_2$	THF	C	0
4	*p*-Tol	Br	$PhCH_2$	Toluene	B[c]	19
5	*p*-Tol	Br	$PhCH_2$	MeOH	B[c]	Trace
6[d]	*p*-Tol	Br	$PhCH_2$	THF	B	0
7	*p*-Tol	Br	*t*-Bu	THF	A	38
8	*p*-Tol	Br	*t*-Bu	THF	B	15
9	*p*-Tol	Br	Cyclohexyl	THF	B	13
10	*p*-Tol	Br	Diphenylmethyl	THF	B	0
11	*p*-Tol	Br	*p*-Tol	THF	B	0
12	Me	Br	$PhCH_2$	THF	B	0
13	Ph	Br	$PhCH_2$	THF	B	36
14	Ph	Br	*t*-Bu	THF	B	27
15	Ph	Cl	$PhCH_2$	THF	B	22
16	4-$CF_3C_6H_4$	Br	$PhCH_2$	THF	B	28

[a] See Scheme 1.
[b] Isolated yield.
[c] The reaction has conducted in another solvent.
[d] 10 mol% of $Yb(OTf)_3$ was used.

In the case of *t*-butylamine, a considerable amount of *N*-*t*-butyl-*p*-toluenesulfonylamide **8** and a small amount of aziridine derivative **9** were obtained. This observation confirms that the sterically hindered amine cannot have easy access towards the aziridine ring of **4a** (Scheme 3).

However, diphenylmethylamine and *p*-toluidine did not give the corresponding azetidine under the given reaction conditions (entries 10 and 11). The reaction of 1-methanesulfonyl-2-(bromomethyl)azetidine **4b** with benzylamine in THF under reflux did not give the desired azetidine **5** (entry 12).

On the other hand, treatment of aziridine **4c** or **4d** with benzylamine gave azetidine **5d** in 36 and 22% isolated yield, respectively (entries 13 and 15). In the case of *N*-(4-trifluoromethylbenzenesulfonyl)aziridine **4e**, the electron-withdrawing influence did not give a remarkable influence on the yield of azetidine **5e** (entry 16).



4a **5c** **8** **9**

15% 54% 5%

Scheme 3.

In conclusion, an efficient and straightforward method for the preparation of protected 3-aminoazetidines was developed. These azetidines were obtained by a one-step conversion from 1-arylsulfonyl-2-(bromomethyl)aziridines. The yields are low but acceptable in view of the one-step procedure and known difficulties in the preparation of 3-aminoazetidines.

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7. In a typical procedure for Method B, benzylamine (0.64 g, 6.0 mmol) and triethylamine (0.61 g, 6.0 mmol) were added to a stirred solution of 1-*p*-toluenesulfonyl-2-(bromomethyl)aziridine **4a** (1.45 g, 5.0 mmol) in dry THF (15 ml) and the mixture was refluxed for 5 h. Then water was added, and the reaction mixture was extracted three times with dichloromethane. The organic phases were washed with brine, dried ($MgSO_4$) and the solvent was evaporated in vacuo. The residue was chromatographed on silica gel (ethyl acetate:petroleum ether 1:1). 1-Benzyl-3-*p*-toluenesulfonylamido)azetidine **5a** was obtained in 37% yield and 1,3-di(*N*-benzylamino)-2-*p*-toluenesulfonylamide **6a** in 19% yield. The spectroscopic data of **5a** are as follows: ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.42 (3H, s), 2.76 (2H, td, $J=6.6$, 2.0 Hz), 3.45 (2H, td, $J=6.6$, 2.0 Hz), 3.50 (2H, s), 3.95 (1H, m), 5.25 (1H, br s), 7.0–7.2 (7H, m), 7.6–7.7 (2H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 21.56, 44.08, 61.78, 63.23, 126.99, 127.22, 126.39, 129.85, 137.28, 137.41, 143.70. IR (neat) 3261, 3029, 2839, 1597, 1495, 1328, 1150 cm^{-1}; MS (70 eV, rel. intensity) m/z 317 (0.17, M^++1), 161 (58), 120 (54), 91 (100).
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