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Stereospecific isomerization of 2-(1-bromoalkyl)-1-sulfonylaziridines using magnesium bromide

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Abstract—Novel stereospecific isomerization of 2-(1-bromoalkyl)-1-sulfonylaziridines into 2-(bromomethyl)-3-alkyl-1-sulfonylaziridines using magnesium bromide is described. The suitable choice of solvent led to good yields and diastereoselectivites.

Aziridines are versatile intermediates for the synthesis of nitrogen-containing compounds via ring-opening[1] and ring-expansion reactions.[1f–h] Especially, 2-(1-haloalkyl)-1-sulfonylaziridines could be expected as nitrogen analogs of epihalohydrins.[2] Although several methods have been developed for the preparation of aziridines,[1a–c] there are few examples known for the synthesis of 2-(1-haloalkyl)-1-sulfonylaziridines, despite their potential as synthetic intermediates. For example, the iodocylization reaction of *N*-allylsulfonamides to give 2-(1′-iodoalkyl)-1-sulfonylaziridnes with moderate diastereoselectivity has been reported.[3,1c] Aziridination reaction of allyl halides with chloramine-T gives 2-(1′-bromoalkyl)-1-sulfonylaziridines.[4]

We have previously reported a novel stereospecfic isomerization of 3-substituted-3-bromo-1,2-epoxypropanes in the presence of magnesium bromide to produce 1-substituted-3-bromo-1,2-epoxypropanes.[5] We have now extended this study to the corresponding azridine derivatives.

In this present work, we report a practical stereoselective synthesis of 2-(bromomethyl)-3-alkyl-1-sulfonylaziridines **2** by rearrangement approach of 2-(1-bromoalkyl)-1-sulfonylaziridines **1**.

2-(1-Bromoalkyl)-1-sulfonylaziridines **1** are accessible from *N*-allylsulfonamides by modification of earlier methods.[6] Bromination of *N*-allylsulfonylamides and subsequent dehydrobromination afforded **1** in good yield with moderate diastereoselectivity. In all the cases studied, a single diastereomer was isolated in extremely valuable diastereomeric ratio after recrystallization. With the desired diastereomerically pure **1** in hand, we set out to examine the reactivity and diastereoselectivity of various **1** with metal bromide salts.

Initially, we investigated the reaction of **1a** with magnesium bromide in MeOH. A solution of **1a** (0.5 mmol) with 1.2 equiv of magnesium bromide was stirred in MeOH at 50 °C. After completion of the reaction (2 days), the reaction mixture was quenched by addition of water and extracted with toluene. Work-up and purification by silica gel column chromatography (*n*-hexane/AcOEt = 4/1) gave **2a** in 83% yield (Table 1, entry 1).[7] In a similar fashion, various metal bromides reacted smoothly with **1a** to give the isomeric **2a** in good yields (Table 1, entries 2–5). These reactions were quite stereoselective to give *cis*-**2a** exclusively, even though a diastereomerically impure **1a** ((2*R**,1′*R**)/(2*R**,1′*S**) = 83/17) was used (Table 1, entries 3–5). This high *cis*-stereoselectivity (*cis*/*trans* = > 98/2) suggests that the relative stability of *cis*-2-(bromomethyl)-3-alkyl-1-sulfonylaziridine **2a** is favored over the corresponding *trans*-**2a**. These results prompted us to investigate the reaction of (2*R**,1′*S**)-aziridine **1a** with magnesium bromide under the same reaction conditions. In the case of (2*R**,1′*S**)-**1a** the prospected *trans*-**2a** was not obtained. After prolonged reaction, only the ring-opening product **3** by MeOH was

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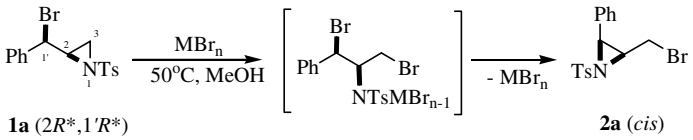
Table 1. Stereoselective isomerization of **1a** into **2a** by using different metal bromides

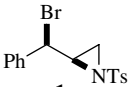
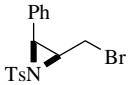
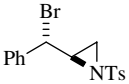
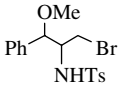
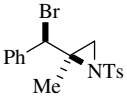
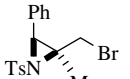
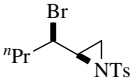
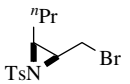
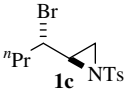
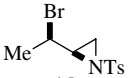
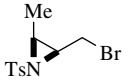
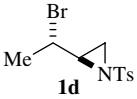
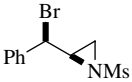
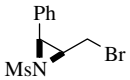


1a (2*R**,1′*R**) **2a** (*cis*)

Entry	Substrate ((2*R**,1′*R**)/(2*R**,1′*S**))[b]	MBr_n (equiv)	Time/day	Yield[a] (*cis*/*trans*)[b]
1	>98/2	$MgBr_2$ (1.2)	2	83 (>98/2)
2	>98/2	LiBr (1.2)	2	69 (>98/2)
3	87/13	KBr (1.2)	2	76 (>98/2)
4	87/13	NaBr (1.2)	2	82 (>98/2)
5	87/13	Bu_4NBr (1.2)	2	77 (>98/2)

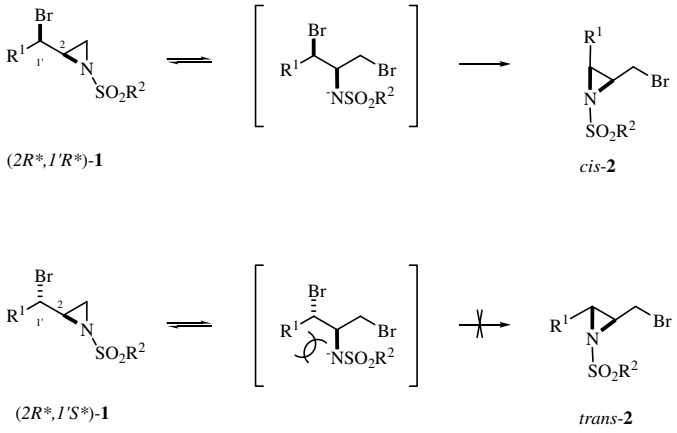
[a] Yields of isolated products.
[b] Diastereomeric ratios were determined by ^1H NMR analysis. The indication of >98/2 means that a single diastereoisomer was observed.

Table 2. Stereoselective isomerization of various substituted **1** with $MgBr_2$ in MeOH

Entry	Substrate ((2*R**,1′*R**)/(2*R**,1′*S**))[b]		$MgBr_2$ (equiv)	Time/day	Product	Yield[a] (*cis*/*trans*[b])
1	 **1a**	(>98/2)	1.2	2	 **2a**	83 (>98/2)
2	 **1a**	(2/>98)	1.2	6	 **3**	72
3	 **1b**	(>98/2)	1.2	2	 **2b**	89 (>98/2)
4	 **1c**	(>98/2)	1.2	6	 **2c**	71 (>98/2)
5	 **1c**	(2/>98)	1.2	6	recovd.	
6	 **1d**	(>98/2)	1.2	6	 **2d**	56 (>98/2)
7	 **1d**	(2/>98)	1.2	7	recovd.	
8	 **1e**	(96/4)	1.2	2	 **2e**	72 (>98/2)

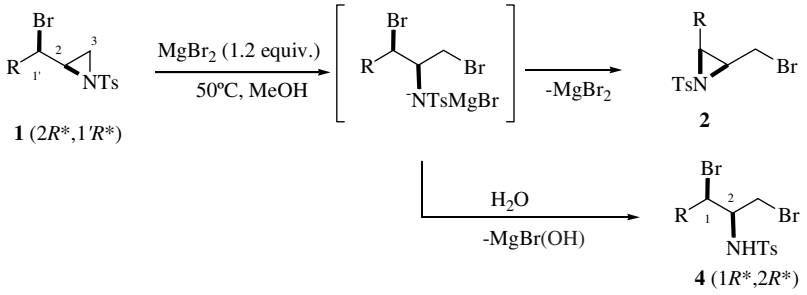
[a] Yields of isolated products.
[b] Diastereomeric ratios were determined by ^1H NMR analysis. The indication of >98/2 and 2/>98 means that a single diastereoisomer was observed.

obtained in 72% yield (Table 2, entry 2). In a similar fashion, use of (2*R**,1′*S**)-**1c**,**d** resulted in recovery of the starting substrates **1c**,**d** (entries 5 and 7). This clearly shows that the (2*R**,1′*R**)-**1c**,**d** are more prone to afford the rearranged products than (2*R**, 1′*S**)-**1c**,**d** (entries 4–7). As the most sterically hindered substituent of **1a**, **1c**, and **1d** is the *p*-toluenesulfonyl group on the nitrogen, *cis*-aziridines **2a**, **2c**, and **2d**, which possess less hindered substituents such as a bromomethyl, propyl, or phenyl group in the same direction, would be the thermodynamically more stable stereoisomer (Scheme 1).[8]



Scheme 1.

Table 3. Effect of various solvents on the reaction of aziridine **1** with magnesium bromide



Entry	Substrate ((2*R**,1′*R**)/(2*R**,1′*S**))[b]	Solvent	Time/day	Yield[a]	
				4; ((1*R**,2*R**)/(1*R**,2*S**))[b]	**2**; (*cis*/*trans*)[b]
1	**1a** R = Ph (>98/2)	MeOH	2	0	83 (>98/2)
2	**1a** R = Ph (87/13)	^{i}PrOH	2	Trace	52 (>98/2)
3	**1a** R = Ph (87/13)	^{t}BuOH	2	60 (>98/2)	0
4	**1a** R = Ph (87/13)	THF	2	65 (>98/2)	0
5	**1a** R = Ph (>98/2)	MeCN	4	Complex mixture	
6	**1a** R = Ph (>98/2)	DMF	4	0	38 (>98/2)
7	**1c** R = ^{n}Pr (>98/2)	MeOH	7	Trace	71 (>98/2)
8	**1c** R = ^{n}Pr (>98/2)	^{t}BuOH	7	85 (>98/2)	0
9	**1c** R = ^{n}Pr (>98/2)	THF	7	97 (>98/2)	0

[a] Yields of isolated products.
[b] Diastereomeric ratios were determined by ^{1}H NMR analysis. The indication of >98/2 means that a single diastereoisomer was observed.

As shown in Table 2, various types of methyl, propyl, and phenyl-substituted aziridines **1a**–**e** were converted to their corresponding *cis*-aziridines **2a**–**e**. All products were characterized by ^{1}H, ^{13}C, NMR, and IR spectra and also by comparison with authentic samples.[5,8] The ratio of diastereoisomers of both **1** and **2** was determined by ^{1}H NMR spectrum.

Our previous work concerning epoxy derivatives had suggested that the trend of the isomerization is considerably dependent on the solvent. When the reactions were conducted in MeCN, THF, ^{t}BuOH, and ^{i}PrOH, only dibromo alcohols, which correspond to the reaction intermediate, were obtained after usual work-up. On the other hand, in the case of DMF and MeOH, the isomerization proceeded to give the corresponding bromoalkylepoxides as regioisomers.[5]

Similar trends were observed in the cases of **1a** and **1c**. As Table 3 shows, the solvent with higher dielectric constant such as ^{i}PrOH and DMF comparable to that of MeOH gave the rearranged products **2a**[8] and **2c** (entries 1, 2, 6, and 7). In contrast, a less polar solvent such as ^{t}BuOH and THF gave only the ring-opening product **4**, which correspond to the intermediates of the isomerization reaction (entries 3, 4, 8, and 9). These results could be explained by the fact that a polar solvent such as MeOH/DMF is able to solvate magnesium bromide. Thus, the rearrangement proceeded to afford **2** as the thermodynamically more stable regioisomer. On the contrary, in the cases of THF and ^{t}BuOH, magnesium bromide was not solvated sufficiently, thus the most stable species in the reaction system would be a magnesium salt of the dibromo-intermediates. Then, **4** were obtained as the final products after usual work-up.

In summary, we have developed a novel isomerization method for the stereoselective synthesis of 2-(bromomethyl)-3-alkyl-1-(sulfonyl)aziridines **2**. During the systematic exploration of the reaction conditions of 2-(1-bromoalkyl)-1-sulfonylaziridines **1** with magnesium bromide, it was possible to extend the methodology to a stereoselective preparation of *cis*-2-(bromomethyl)-3-alkyl-1-(sulfonyl)aziridines **2**.

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7. *cis*-2-(Bromomethyl)-3-phenyl-1-tosylaziridine (**2a**); A typical procedure is as follows: To a solution of aziridine **1a** (183 mg, 0.50 mmol) in MeOH (2.5 mL) was added $MgBr_2$ (110 mg, 0.60 mmol), and the reaction mixture was stirred at 50 °C for 48 h. After completion of the reaction, the mixture was quenched with water, then extracted by toluene. The organic layer was dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (*n*-hexane/AcOEt = 4/1) to afford **2a** (152 mg, 83%). Colorless crystal, mp 85–86 °C, IR (KBr) 3310, 1595, 1494, 1325, 1159 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) $\delta = 2.45$ (3H, s), 2.93 (1H, dd, $J = 10.8$, 7.2 Hz), 3.16 (1H, dd, $J = 10.8$, 6.6 Hz), 3.42 (1H, q, $J = 6.9$ Hz), 4.14 (1H, d, $J = 6.9$ Hz), 7.33 (7H, m), 7.91 (2H, d, $J = 8.4$ Hz), ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 21.71$, 27.04, 45.34, 46.66, 127.54, 128.26, 128.39, 128.43, 128.51, 129.78, 131.16, 144.97. MS (EI, 70 eV) *m*/*z* (%): 286 (6.7, M^+-Br), 212 (77, M^+-Ts), 210 (78, M^+-Ts), 130 (100, $M^+-Ts-Br$).
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