

Guanidines as a Nitrogen Source for Direct Conversion of Epoxides to Aziridines

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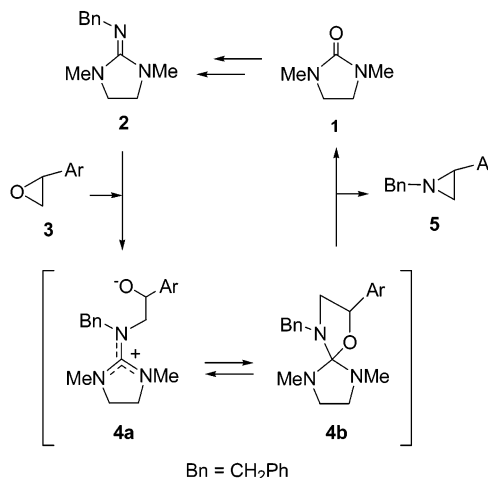
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Abstract: Direct conversion of epoxides to aziridines was achieved with guanidines as a nitrogen source. Stereochemical inversion at the chiral centers of epoxides was observed without loss of optical purity.

Aziridines are some of the most versatile synthetic intermediates for the synthesis of biologically active *N*-containing compounds.¹ Normally, aziridines are synthesized via reactions of nitrenes and olefins or carbenes and imines, and intramolecular cyclization of β -amino alcohol derivatives.² We have reported a unique method for the synthesis of aziridines from guanidinium salts derived from ureas such as 1,3-dimethylimidazolidin-2-one (DMI; **1**) and aromatic aldehydes, and its application to asymmetric synthesis by using the corresponding chiral template.³ The proposed reaction mechanism may involve the formation of spiro intermediates (like **4b** in Scheme 1) from guanidinium ylides and aromatic aldehydes via betains (like **4a** in Scheme 1), which undergo acid catalysis fragmentation to yield aziridines and **1**. We would expect the reaction of guanidines **2**, derived from **1**, with epoxides **3** to afford analogous betain species **4a**, which would then produce the corresponding aziridines **5** and **1** via spiro intermediates **4b** (Scheme 1). Until now, a few examples of direct conversion of epoxides to aziridines with iminophosphorane as a nitrogen source have been reported;⁴ however, problems still remain in partial racemization of the product.^{4c} Now we describe herein our preliminary approaches to direct conversion of epoxides to aziridines using guanidine as a nitrogen source.

Guanidines **2** were prepared from 2-chloro-1,3-dimethylimidazolidinium chloride (DMC) and primary amines

SCHEME 1. A Strategy for Direct Conversion of Epoxides to Aziridines



according to the reported procedure.⁵ Several epoxides were purchased or prepared by either simple epoxidation of the corresponding olefins or methylenation of aldehydes with trimethylsulfonium ylide.⁶ Heating guanidine **2a** and racemic styrene oxide [(±)-**3a**] at 70 °C without a solvent for 24 h afforded the expected aziridine (±)-**5a** in 16% yield together with urea **1** (15%) (entry 1, Table 1). Reactions in several solvents showed that the yields depended on the solvent. When the reaction was carried out in DMF or THF, the yield was not improved compared with the solvent-free conditions (entries 2 and 3). A higher yield was observed in CH₃CN (entry 4). The use of EtOH resulted in the formation of a complex mixture that was formed because of the instability of **5a** in EtOH (entry 5). Chloroform gave the best result, in which **5a** was produced in 65% yield despite a long reaction time (entry 6). The use of toluene resulted in low yield (entry 7).

The ¹H NMR spectrum of the crude product obtained with chloroform as a solvent showed lower field-shifted signals assignable to the salt⁷ of **2a** compared to the original ones. Thus, reactions in the presence of a basic additive were examined (Table 2); however, no improvement was found (entries 1–4). On the other hand, reaction in the presence of 10 mol % of *p*-toluenesulfonic acid hydrate (TsOH·H₂O) in toluene afforded (±)-**5a** in 77% yield (entry 5). Although a similar result was obtained in replacement of the solvent from toluene to benzene (entry 6), the yield was lowered when the reaction was carried out under azeotropic conditions, suggesting that a small amount of water is necessary for this reaction (entry 7). Low yield was also observed in chloroform under the acidic condition (entry 8). In the previous paper³ it was noted that SiO₂ played a crucial role for the formation of aziridine products. However,

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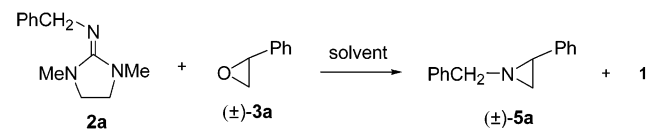
(7) A trace of acid may generate from the chloroform used as solvent.

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TABLE 1. Synthesis of Aziridine (\pm)-5a from Guanidine 2a and Racemic Styrene Oxide [(\pm)-3a]

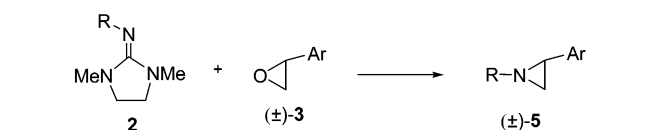
entry	solvent	conditions	yield (%) ^a	
			(\pm)-5a	1
1	none	70 °C, 24 h	16	15
2	DMF	75 °C, 41 h	9	15
3	THF	reflux, 7 d	10	7
4	CH ₃ CN	reflux, 40 h	48	23
5	EtOH	rt, 2 d	<i>b</i>	<i>b</i>
6	CHCl ₃	reflux, 7 d	65	72
7	toluene	75 °C, 41 h	2	8

^a Calculated yields by ¹H NMR, but not optimized. ^b Complex mixture.

TABLE 2. Effects of Additives on the Reaction of Guanidine 2a and Epoxide (\pm)-3a

entry	solvent	additive	conditions	yield (%) ^a of (\pm)-5a
1	CHCl ₃	Et ₃ N ^b	reflux, 4 d	51
2	CHCl ₃	pyridine ^b	reflux, 54 h	53
3	CHCl ₃	TMG ^{b,c}	reflux, 7 d	53
4	CHCl ₃	K ₂ CO ₃ ^b	reflux, 7 d	38
5	toluene	TsOH·H ₂ O ^d	reflux, 80 h	77
6	benzene	TsOH·H ₂ O ^d	reflux, 7 d	68
7 ^e	benzene	TsOH·H ₂ O ^d	reflux, 7 d	22
8	CHCl ₃	TsOH·H ₂ O ^d	reflux, 5 d	21
9	CH ₃ CN	SiO ₂ ^f	reflux, 35 h	<10

^a Calculated yields by ¹H NMR, but not optimized. ^b 1 molar equiv. ^c 1,1,3,3-Tetramethylguanidine. ^d A catalytic amount (0.1 molar equiv). ^e Using Dean–Stark apparatus. ^f 1 g per 1 mM.

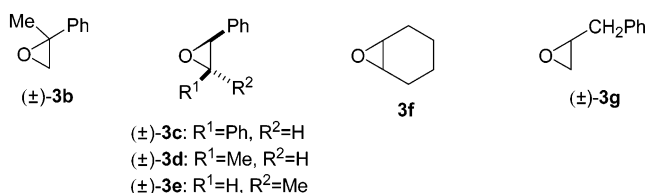
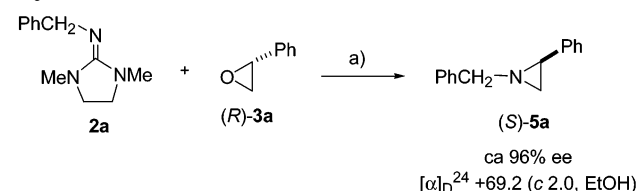
TABLE 3. Substituent Effects on the Aziridine Formation

entry	R in 2	Ar in (\pm)-3	conditions ^a	yield (%) ^b of (\pm)-5
1	allyl	Ph	A	60
2	CH ₂ CO ₂ ^t Bu	Ph	A	54
3	ⁱ Pr	Ph	A	29
4	Ph	Ph	B	no reaction
5	CH ₂ Ph	<i>o</i> -MeOPh	B	46
6	CH ₂ Ph	<i>p</i> -MeOPh	B	61 ^c
7	CH ₂ Ph	<i>p</i> -MePh	B	40 ^c
8	CH ₂ Ph	<i>p</i> -ClPh	B	55 ^c

^a A: reflux in toluene with TsOH·H₂O (0.1 molar equiv) for 3.5 d. B: reflux in CHCl₃ for 7 d. ^b Isolated yields, but not optimized. ^c Calculated yields by ¹H NMR, but not optimized.

utilization of SiO₂ resulted in a trace amount of production of 5a due to the instability of 5a against SiO₂ (entry 9).

We next examined the reaction using substrates with a different substituent (Table 3). Guanidines with a primary alkyl group on the imino nitrogen gave aziridine products (entries 1 and 2), but the reaction was suppressed in the case of a secondary alkyl-substituted

**FIGURE 1. Epoxides examined for the conversion.****SCHEME 2. Reaction of Guanidine 2a and Chiral Styrene Oxide (*R*)-3a^a**

^a Reagents and conditions: (a) TsOH·H₂O (1 molar equiv), toluene reflux, 90 h (41%).

guanidine (entry 3). The reaction was sluggish with *N*-phenylguanidine because of low nucleophilicity (entry 4). No acceleration was observed even when electron-rich styrene oxides were used (entries 5–8). Unfortunately, reactions were retarded with use of 1,1-disubstituted 3b, 1,2-disubstituted epoxides 3c–e, and aliphatic epoxides 3f and 3g shown in Figure 1.

A trial with chiral (*R*)-styrene oxide⁸ (*R*)-3a afforded (*S*)-aziridine (*S*)-5a in 41% yield (Scheme 2). The absolute configuration of the product was determined by optical rotation {[α]_D²⁴ +69.2 (c 2.0, EtOH)},⁹ showing that inversion of configuration occurred during the reaction. Optical purity of the product was estimated as ca. 96% ee from chiral HPLC analysis (DAICEL CHIRALCEL OD-H, hexane only, 254 nm, 1.2 mL/min). Thus, high retention of chirality should be expected in this direct conversion of epoxides to aziridines.

In summary, we have established a direct conversion method of epoxides to aziridines with guanidine as a nitrogen source. This reaction proceeds via inversion of configuration at the asymmetric carbon on styrene oxides with high chirality control. Detailed mechanistic studies and the application of aziridines¹⁰ to the synthesis of natural products are under way in our laboratory.

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Supporting Information Available: Experimental procedures for this work. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(8) Purchased from Aldrich, 95% ee.

(9) Kawamoto et al. reported the optical rotation of (*R*)-5a with 98% ee to be [α]_D²⁰ −49.4 (c 2.0, EtOH) [Kawamoto, A.; Wills, M. *Tetrahedron: Asymmetry* **2000**, *11*, 3257–3261]. The lower value may be due to the lability of 5a in EtOH.

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