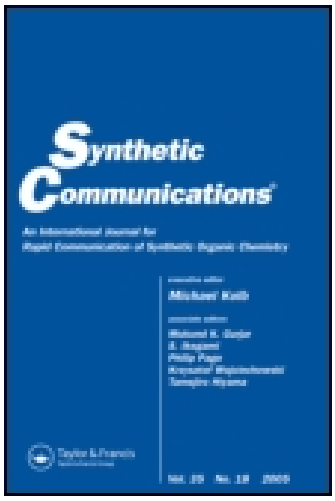

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PREPARATION OF TRANS-1,2-DIAMINOCYCLOHEXANE DERIVATIVES BY LITHIUM PERCHLORATE CATALYZED RING OPENING OF AZIRIDINES

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PREPARATION OF *TRANS*-1,2-DIAMINOCYCLOHEXANE DERIVATIVES BY LITHIUM PERCHLORATE CATALYZED RING OPENING OF AZIRIDINES

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ABSTRACT

N,*N*′-Dialkylated *trans*-1,2-diaminocyclohexane derivatives were synthesized with good overall yield via reaction of the corresponding *N*-alkylated cyclohexene aziridine with amines, in the presence of lithium perchlorate as catalyst.

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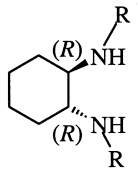
INTRODUCTION

There are numerous recent examples of the use of chiral 1,2-diamines in the field of asymmetric synthesis and molecular recognition.[1] Some of the most widely used ligands incorporating a vicinal diamine moiety are derivatives of *trans*-1,2-diaminocyclohexane, **1**.[2] In addition, *N*,*N*′-dialkylated derivatives **2** have been recently exploited as stereodirecting reagents or ligands in asymmetric synthesis, with applications continuing to increase (Scheme 1).[2]



1, R = H
2, R = Me, *i*-Pr, *t*-Bu, *neo*-Pentyl, $PhCH_2$

Scheme 1.

One of the classical synthetic procedures for the formation of 1,2-diamines is the ring opening of aziridines with amines; nevertheless, this method has limited application due to the low nucleophilicity of amines and the relative scarcity of aziridine starting materials.[3,4]

Interestingly, Crotti *et al.*[5] reported the ring opening reaction of epoxides and oxetanes in the presence of various metal based-salts, such as $LiClO_4$, $LiBF_4$ and lanthanide(III) triflates. In particular, Yamamoto *et al.*[7] studied the aminolysis of *N*-Boc, *N*-Ts, and *N*-Bn-protected aziridines catalyzed by lanthanoid triflates. Besides, other reports of the use of lithium salts to facilitate the opening of epoxides have recently appeared.[6–8]

This paper describes a useful extension of the above idea, the $LiClO_4$-catalyzed aminolysis of aziridines conveniently prepared from ubiquitous epoxides.[9]

RESULTS AND DISCUSSION

The synthesis of several vicinal diamines was carried via the $LiClO_4$-catalyzed aminolysis of *N*-alkylated aziridines derived from cyclohexene oxide (Table 1).

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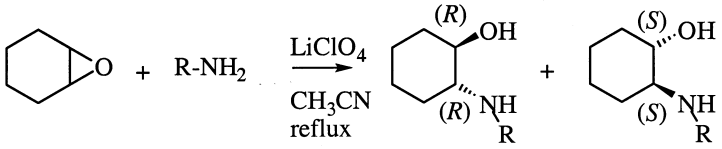
Table 1. Aminolysis of Cyclohexene Oxide, **3**



3 **4a-c** **5a-c**

Entry	4	Yield,[a] %
1	**4a**, (*S*)-α-Ph(CH_3)CHNH_2	98
2	**4b**, PhCH_2NH_2	95
3	**4c**, *c*-C_5H_9-NH_2	97

[a] Isolated product.

Aminolysis of cyclohexene oxide **3** with primary amines, (*S*)-α-phenylethylamine, **4a**, benzylamine, **4b**, and cyclopentylamine, **4c**, in the presence of an equivalent of lithium perchlorate in acetonitrile, heating to reflux for *ca*. 20 h, afforded in excellent yield (95–98%) the corresponding *trans*-*N*-alkyl-1,2-aminocyclohexanols **5a–c** (Table 1).

β-Aminoalcohols **5a–c** were then converted into the corresponding *N*-alkyl-cyclohexene aziridines **6a–c** via *in-situ* intramolecular S_N2 displacement of the mesylated alcohol by the amine, in 68–70% yields (Table 2).[9]

Finally, ring opening of aziridines **6a–c** was achieved by aminolysis with primary amines **4a–c** as well as piperidine, **4d**, catalyzed by lithium perchlorate (equimolar amount, heating to reflux in acetonitrile). As expected, the ring opening of the aziridines is completely stereoselective, leading to *trans* (enantiomeric) **7b**, **7c**, and **7d**, and *trans* (diastereomeric) **7a**, with no evidence for *cis* products (Table 3).

In summary, the present procedure for the synthesis of *trans*-1,2-diaminocyclohexane derivatives from cyclohexene oxide in the presence of lithium perchlorate as catalyst proceeds in good yield (52–60% overall).

EXPERIMENTAL

Melting points were recorded on a Melt–Temp apparatus and are uncorrected. Optical rotations $[\alpha]_D$ were measured at room temperature in

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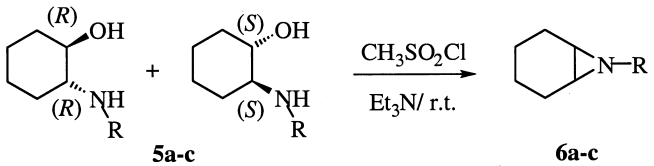
Table 2. Synthesis of *N*-Alkyl Cyclohexene Aziridines, **6a–c**

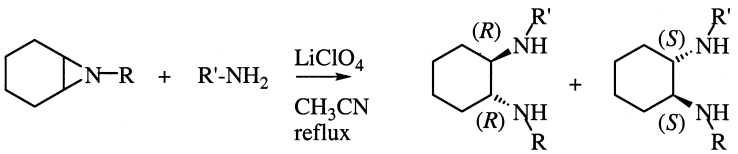


5a-c **6a-c**

Entry	R	Aziridine	Yield,[a] %
1	(*S*)-α-$PhCH_3CH$-	**6a**	70
2	$PhCH_2$-	**6b**	68
3	*c*-C_5H_9-	**6c**	68

[a] Isolated product.

Table 3. Aminolysis of Aziridines **6a–c** to Give 1,2-Diamines **7a–d**



6a-c **4b-d** **7a-d**

Entry	R	R'-NH_2	Product	Yield,[a] %
1	(*S*)-α-$PhCH_3CH$-	**4b**, $PhCH_2NH_2$	**7a**	90
2	$PhCH_2$-	**4b**, $PhCH_2NH_2$	**7b**	85
3	*c*-C_5H_9-	**4c**, *c*-C_5H_9-NH_2	**7c**	79
4	*c*-C_5H_9-	**4d**, $C_5H_{11}N$	**7d**	75

[a] Isolated product.

0.1 dm cells, using a Perkin–Elmer 241 spectrophotometer. All reagents were purchased from Aldrich Chemical Co. Analytical TLC plates and silica gel (230–400 mesh) were purchased from Merck.

All operations were carried under a nitrogen atmosphere. All glassware was dried in an oven at 120°C and cooled to room temperature under nitrogen atmosphere before use. ^1H and ^{13}C NMR spectra were recorded in

$CDCl_3$ as solvent with tetramethylsilane (TMS) as an internal standard on a 400 MHz JEOL spectrometer. Chemical shifts are given as δ values (ppm). Mass Spectra were recorded on a Varian Saturn II spectrometer.

Aminolysis of Ciclohexene Oxide. General Procedure

In a dry two necked flask provided with addition funnel condenser and magnetic stirrer, was placed with stirring and under argon an equimolar mixture of cyclohexene oxide (**3**, 10 mmol) and anhydrous lithium perchlorate (10 mmol) in freshly distilled acetonitrile (*ca*. 10 ml) until complete dissolution of the lithium salt. The reaction mixture was cooled in an ice water bath before the dropwise addition of the amine (**4a–c**, 10 mmol). The resulting solution was then heated to reflux until the reaction was complete (*ca*. 20 h). Water (25 ml) was added to the reaction mixture and the organic phase was extracted with CH_2Cl_2 (3×25 ml). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the β-aminoalcohols **5a–c**.

trans-(*1′S*)2-*N*-[(α-Phenylethyl)amino]cyclohexanols, 5a. See ref. 8

rac-trans-2-*N*-[(Benzyl)amino]cyclohexanols, **5b**.[10] ^{1}H NMR: 0.99 (m, 1H), 1.25 (m, 3H), 1.68 (m, 2H), 1.99 (m, 1H), 2.15 (m, 1H), 2.29 (m, 1H), 2.56 (broad, 2H), 3.20 (m, 1H), 3.67 (d, 1H, $J = 12.8$), 3.93 (d, 1H, $J = 12.8$), 7.21–7.40 (m, 5H). ^{13}C NMR: 24.4, 25.2, 30.5, 33.5, 50.8, 63.1, 73.8, 127.1, 128.2, 128.5, 140.4. *m*/*z*: 205 (M^+).

rac-trans-2-*N*-[(Cyclopentyl)amino]cyclohexanols, **5c**. ^{1}H NMR: 0.86 (m, 2H), 1.18 (m, 4H), 1.46 (m, 3H), 1.60 (m, 4H), 1.77 (m, 1H), 1.93 (m, 1H), 2.05 (m, 1H), 2.14 (m, 1H), 2.77 (broad, 2H), 3.00 (m, 1H), 3.13 (q, 1H, $J = 6.6$). ^{13}C NMR: 23.7, 23.8, 24.4, 25.2, 30.7, 32.9, 33.5, 34.3, 56.2, 61.9, 73.5. *m*/*z*: 183 ($M^{+\cdot}$). Anal. calcd. $C_{11}H_{21}ON$ (183.3) C 72.09%, H 11.54%; found C 71.81%, H 11.59%.

Preparation of *N*-Alkyl-cyclohexene Aziridines. General Procedure

In a two necked flask provided with an addition funnel, condenser and a magnetic stirrer, under argon the mixture of β-aminoalcohols (10 mmol, **5a–c**) and dry triethylamine (5 ml) were dissolved in dry CH_2Cl_2 (20 ml). To the ice cooled mixture was added dropwise a solution of methanesulfonyl

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chloride (10 mmol) in dry CH_2Cl_2 (5 ml). The reaction mixture was stirred at 0°C until no more β-aminoalcohols **5a–c** were detected by TLC (*ca.* 24 h), and then the *in situ* mesylated compounds were allowed to warm to rt for *ca.* 8 h to give the desired product. The cool reaction mixture was poured over ice cooled 1 N HCl (30 ml) and the organic layer was extracted with CH_2Cl_2 (3×25 ml). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude products were purified by flash chromatography to provide aziridine **6a–c** as a liquid. Vacuum distillation afforded pure aziridines as colorless liquid.

(1R,2*S*,1′*S*)*N*-(α-Phenylethyl)cyclohexene aziridine, **6a**. ^{1}H NMR[9] ^{13}C NMR[9] $[\alpha]_D = -42.4$ (c = 1.0, $CHCl_3$), [Lit.[9] $[\alpha]_D = -42.4$ (c = 1.4, $CHCl_3$)].

N-(Benzyl)cyclohexene aziridine, **6b**.[7a,c] ^{1}H NMR: 1.17 (m, 2H), 1.39 (m, 2H), 1.58 (s, 2H), 1.75 (m, 2H), 1.86 (m, 2H), 3.43 (s, 2H), 7.09–7.45 (m, 5H). ^{13}C NMR: 20.7, 24.6, 38.6, 64.4, 126.6, 127.5, 128.3, 140.1. *m*/*z*: 187 ($M^{+\cdot}$).

N-(Cyclopentyl)cyclohexene aziridine, **6c**. ^{1}H NMR: 1.02 (m, 2H), 1.21 (m, 2H), 1.35 (m, 5H), 1.47 (m, 2H), 1.58 (m, 8H). ^{13}C NMR: 20.6, 24.4, 24.8, 32.2, 37.3, 72.06. *m*/*z*: 165 ($M^{+\cdot}$). Anal. calcd $C_{11}H_{19}N$ (165.2) C 79.95%, H 11.58%; found C 80.17%, H 11.49%.

Aminolysis of *N*-Alkyl-cyclohexene Aziridines 6a–c. General Procedure

In a dry two necked flask provided with an addition funnel, condenser and a magnetic stirrer, was placed with stirring and under argon an equimolar mixture of *N*-alkyl-cyclohexene aziridine **6a–c** (10 mmol) and anhydrous lithium perchlorate (10 mmol) in freshly dried acetonitrile (*ca.* 10 ml) until complete dissolution of the lithium salt. The reaction mixture was cooled in an ice-water bath to 0°C before the dropwise addition of the amine (10 mmol, **4a–d**). The resulting solution was then heated to reflux until the reaction was complete, *ca.* 30 h. Water was added to the reaction mixture and the organic phase was extracted with CH_2Cl_2 (3×25 ml). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* affording the 1,2-diamines **7a–d**.

trans-(1′*S*)-[*N*-(α-Phenylethyl)-*N*′-benzyl]-1,2-cyclohexanediamine **7a**. ^{1}H NMR: 0.85 (m, 1H), 1.20 (m, 3H), 1.35 (d, 3H, $J = 6.6$), 1.65 (m, 3H), 1.92 (m, 2H), 2.18 (m, 2H), 2.38 (m, 1H), 3.66 (d, 1H, $J = 13.2$), 3.82 (q, 1H, $J = 6.6$), 3.91 (d, 1H, $J = 13.2$), 7.15–7.44 (m, 10H). ^{13}C NMR: 23.9, 24.9, 25.0, 25.4, 31.6, 32.7, 32.6, 51.1, 54.1, 55.8, 57.8, 59.7, 61.4, 61.5, 126.6, 126.9, 128.0, 128.1, 128.4, 141.3, 146.0, 147.6. *m*/*z*: 308 ($M^{+\cdot}$). Anal. calcd $C_{21}H_{28}N_2$ (308.4) C 81.78%, H 9.14%; found C 81.53%, H 9.17%.

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***Rac-trans-N,N′-Bis*(benzyl)-1,2-cyclohexanediamine 7b. See ref. 11**

rac-trans-N,N′-bis(cyclopentyl)-1,2-cyclohexanediamine **7c**. ^{1}H NMR: 0.86 (m, 2H), 1.28 (m, 4H), 1.42 (m, 4H), 1.64 (m, 9H), 1.92 (m, 6H), 2.39 (m, 2H), 3.06 (m, 1H), 3.81 (m, 1H), 4.47 (m, 1H). ^{13}C NMR: 23.7, 23.8, 24.6, 28.9, 30.0, 30.1, 31.4, 35.9, 52.7, 53.5, 58.5, 59.8, 63.2. *m/z*: 250 ($M^{+\cdot}$). Anal. calcd $C_{16}H_{30}N_2$ (250.4) C 76.75%, H 12.07%; found C 76.28%, H 11.98%.

trans-[*N*-(cyclopentyl)-*N′*-(piperidinyl)]-1,2-cyclohexanediamine **7d**. ^{1}H NMR: 1.18 (m, 6H), 1.52 (m, 16H), 1.90 (m, 2H), 2.27 (m, 2H), 2.38 (m, 1H), 2.56 (m, 2H), 3.07 (m, 1H). ^{13}C NMR: 22.0, 23.6, 23.7, 24.8, 25.1, 27.0, 32.5, 34.6, 49.5, 56.2, 57.9, 68.2. *m/z*: 250 ($M^{+\cdot}$). Anal. calcd $C_{16}H_{30}N_2$ (250.4) C 76.75%, H 12.07%; found C 76.92%, H 12.12%.

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REFERENCES

1. For a detailed review, see: Lucet, D.; Le Gall, T.; Mioskowski, Ch. Angew. Chem. Int. Ed. **1998**, *37*, 2580.
2. For an excellent review, see: Bennani, Y.L.; Hanessian, S. Chem. Rev. **1997**, *97*, 3161.
3. For an authoritative review on aziridine formation, see: Tanner, D. Angew. Chem. Int. Ed. **1994**, *33*, 599.
4. For a general discussion on aziridine conversion to 1,2-diamines, see: Kemp, J.E.G. In *Comprehensive Organic Synthesis*, Trost, B.M.; Fleming, I., Eds.; Pergamon Press, Oxford, 1991, vol. 7, p. 469.
5. a) Crotti, P.; Di Bussolo, V.; Favero, L.; Macchia, F.; Pineschi, M. Tetrahedron Lett. **1996**, *37*, 1675. b) Chini, M.; Crotti, P.; Favero, L.; Macchia, F.; Pineschi, M. Tetrahedron Lett. **1994**, *35*, 433. c) Crotti, P.; Favero, L.; Macchia, F.; Pineschi, M. *ibid*. **1994**, *35*, 7089. d) Chini, M.; Crotti, P.; Gardelli, C.; Macchia, F. Synlett. **1992**, 673. e) Chini, M.; Crotti, P.; Flippin, L.A.; Macchia, F. J. Org. Chem. **1991**, *56*, 5939. f) Chini, M.; Crotti, P.; Macchia, F. Tetrahedron Lett. **1990**, *31*, 4661.
6. a) Ganesan, A.; Chng, B.L. Bioorg. Med. Chem. Lett. **1997**, *7*, 1511. b) Markovic, F.; Dimitrijevic, G.; Aleksic, V. J. Chem. Research (S) **1997**, *66*.

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7. a) Meguro, M.; Yamamoto, Y. Heterocycles **1996**, *43*, 2473. b) Meguro, M.; Asao, N.; Yamamoto, Y. J. Chem. Soc. Perkin Trans. I **1994**, 2597. c) Meguro, M.; Asao, N.; Yamamoto, Y. Tetrahedron Lett. **1994**, *35*, 7395.
8. de Parrodi, C.A.; Quintero-Cortés, L.; Juaristi, E. Anal. Quím. Int. Ed. **1996**, *92*, 400, and references cited therein.
9. For a preliminary report, see: de Parrodi, C.A.; Moreno, G.E.; Quintero, L.; Juaristi, E. Tetrahedron: Asymmetry **1998**, *9*, 2093.
10. Yamamoto, Y.; Asao, N.; Meguro, M.; Tsukada, N.; Nemoto, H.; Sadayori, N.; Wilson, J.G.; Nakamura, H. J. Chem. Soc. Chem. Commun. **1993**, 1201.
11. Denmark, S.E.; Stadler, H.; Dorow, R.L.; Kim, J.H. J. Org. Chem. **1991**, *56*, 5063–5079.

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