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

C. Anaya de Parrodi^a, V. Vázquez^a, L. Quintero^b & E. Juaristi^c

^a Departamento de Química y Biología , Universidad de las Américas-Puebla , Santa Catarina Mártir, Cholula, Puebla, 72780, México

^b Centro de Investigación de la Facultad de Ciencias Químicas , Universidad Autónoma de Puebla , Puebla, 72570, México

^c Departamento de Química, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Apartado Postal 14-740, México, D.F., 07000, México Published online: 20 Aug 2006.

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

C. Anaya de Parrodi,^{1,*} V. Vázquez,¹ L. Quintero,^{2,*} and E. Juaristi³

¹Departamento de Química y Biología, Universidad de las Américas-Puebla, 72780, Santa Catarina Mártir, Cholula, Puebla, México ²Centro de Investigación de la Facultad de Ciencias Químicas, Universidad Autónoma de Puebla, 72570, Puebla, México ³Departamento de Química, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Apartado Postal 14-740, 07000 México, D.F., México

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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^{*}Corresponding authors. E-mail: anaya@mail.udlap.mx

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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 = H2, R = Me, *i*-Pr, *t*-Bu, *neo*-Pentyl, PhCH₂

Scheme 1.

One of the classical synthetic procedures for the formation of 1,2diamines 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 LiClO₄, LiBF₄ 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 LiClO₄catalyzed 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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TRANS-1,2-DIAMINOCYCLOHEXANE



^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_N^2 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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	$ \begin{array}{c} \mathcal{O}H \\ \mathcal{O}H $	CH ₃ SO ₂ Cl Et ₃ N/ r.t.	6a-c
Entry	R	Aziridine	Yield, ^a %
1	(S)-α-PhCH ₃ CH-	6a	70
2	PhCH ₂ -	6b	68
3	<i>c</i> -C ₅ H ₉ -	6с	68

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

^a Isolated product.

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

6a-0	$N - R + R' - NH_2$ c 4b-d	LiClO ₄ CH ₃ CN reflux	$(R) \qquad NH \\ (R) \qquad NH \\ (R) \qquad NH \\ R \\ 7a-d$	(S) NH (S) NH R
Entry	R	R'-NH ₂	Product	Yield, ^a %
1	(S)-α-PhCH ₃ CH-	4b , PhCH ₂ NH ₂	7a	90
2	PhCH ₂ -	4b , $PhCH_2NH_2$	7b	85
3	<i>c</i> -C ₅ H ₉ -	$\mathbf{4c}, c\text{-}\mathrm{C}_{5}\mathrm{H}_{9}\text{-}\mathrm{NH}_{2}$	7c	79
4	<i>c</i> -C ₅ H 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 ¹³C NMR spectra were recorded in



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 $CDCl_3$ 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 Na₂SO₄, filtered and concentrated *in vacuo* to afford the β-aminoalcohols **5a–c**.

trans-(1'S)2-N-[(\alpha-Phenylethyl)amino]cyclohexanols, 5a. See ref. 8

rac-trans-2-*N*-[(Benzyl)amino]cyclohexanols, **5b**.¹⁰ ¹H 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). ¹³C 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**. ¹H 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). ¹³C 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⁺⁺). Anal. calcd. C₁₁H₂₁ON (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 CH₂Cl₂ (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 Na₂SO₄, 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,2S,1'S)N-(α -Phenylethyl)cyclohexene aziridine, **6a**. ¹H NMR⁹ ¹³C NMR⁹[α]_D = -42.4(c = 1.0, CHCl₃), [Lit.⁹[α]_D = -42.4(c = 1.4, CHCl₃)].

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). ¹³C NMR: 20.7, 24.6, 38.6, 64.4, 126.6, 127.5, 128.3, 140.1. *m/z*: 187 (M⁺⁺).

N-(Cyclopentyl)cyclohexene aziridine, **6c**. ¹H NMR: 1.02 (m, 2H), 1.21 (m, 2H), 1.35 (m, 5H), 1.47 (m, 2H), 1.58 (m, 8H). ¹³C NMR: 20.6, 24.4, 24.8, 32.2, 37.3, 72.06. *m*/*z*: 165 (M⁺). Anal. calcd C₁₁H₁₉N (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 Na₂SO₄, filtered and concentrated *in vacuo* affording the 1,2-diamines **7a–d**.

trans-(1'*S*)-[*N*-(α-Phenylethyl)-*N*'-benzyl]-1,2-cyclohexanediamine **7a**. ¹H 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). ¹³C 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⁺⁺). Anal. calcd C₂₁H₂₈N₂ (308.4) C 81.78%, H 9.14%; found C 81.53%, H 9.17%. Copyright © Marcel Dekker, Inc. All rights reserved



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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**. ¹H 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). ¹³C 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⁺). 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**. ¹H 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). ¹³C 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⁺). Anal. calcd C₁₆H₃₀N₂ (250.4) C 76.75%, H 12.07%; found C 76.92%, H 12.12%.

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