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PREPARATION OF *trans*-1,2-DIAMINO-1,2-DIMETHYLCYCLOHEXANE *via* HIGHLY STEREOSELECTIVE OLEFIN OXIDATION BY DINITROGEN TETROXIDE

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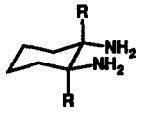
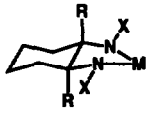
Summary: Reaction of N_2O_4 with 1,2-dimethylcyclohexene led to the corresponding dinitro compound **4** with high *trans* stereoselectivity (>30:1). Catalytic hydrogenation of **4** with $Pd(OH)_2$ on carbon afforded a quantitative yield of (*d,l*)-1,2-diamino-1,2-dimethylcyclohexane, which was resolved to pure enantiomers with mandelic acid. This approach constitutes a simple and potentially general route to interesting new chiral auxiliaries.

C_2-symmetric 1,2-diamines and their derivatives are emerging as extremely valuable chiral auxiliaries with broad applications in asymmetric synthesis.[1,2] The utility of hindered diamines with well-defined steric properties has led us to investigate compounds with the general structure of **1** (Figure 1). The parent compound (**2**, R = H) is available commercially in optically pure form, and it has been employed successfully as an auxiliary in a variety of asymmetric reactions.[2] On the other hand, disubstituted derivatives where R is an alkyl or aryl group are not known. Axially-locked substituents on **1** are expected to have a significant steric influence on a chelated metal (e.g. **A**), leading to highly dissymmetric reactive sites for certain processes.



1 R = alkyl or aryl
1a R = CH_3
2 R = H

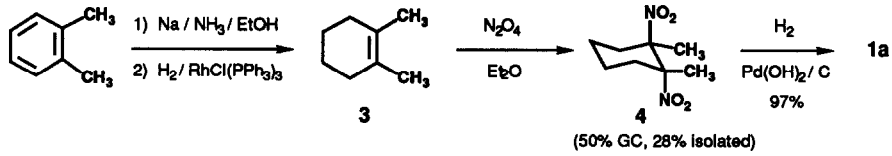


A

Despite the structural simplicity of **1**, available methods for amine synthesis do not provide a straightforward approach to this class of compounds. Neither classical Curtius-type rearrangement chemistry,[3] Ritter reactions, addition reactions,[4,5] nor modern imine coupling methods[6] are well-suited to the preparation of *trans*-1,2-diamines adjacent to tertiary centers. We report here that addition of dinitrogen tetroxide to 1,2-dimethylcyclohexene provides a simple and convenient entry to the corresponding *trans*-1,2-dinitro product, which can be reduced quantitatively to **1a** (R = CH_3) by hydrogenation. The synthesis of **1a** has been carried out on multi-gram scale, and it highlights the utility of N_2O_4 as a practical reagent for the preparation of hindered chiral diamines.

The requisite alkene precursor to **1a**, 1,2-dimethylcyclohexene (**3**), is available commercially but it is rather expensive.[7] Preparation of **3** from *o*-xylene was accomplished by a Birch reduction/ Wilkinson hydrogenation sequence (Scheme 1),[8] leading to a mixture containing predominantly **3**, with *o*-xylene and 1,6-dimethylcyclohexene as minor contaminants. As a result of the high crystallinity of dinitro derivative **4** (*vide infra*), the presence of these impurities does not have an adverse effect on the subsequent steps and the mixture can be used without further purification.

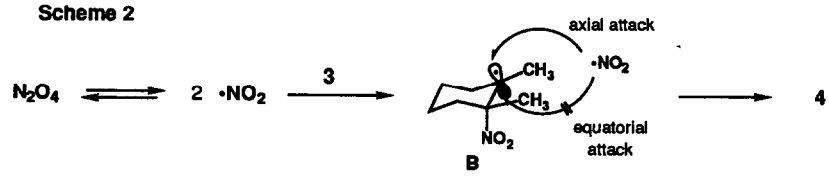
Scheme 1



Slow addition of **3** to an ethereal solution of N_2O_4 at 0°C leads to a mixture containing approximately 50% **4** and several minor products. If the reaction is run under a stream of oxygen, the yield of **4** is unaffected but its purification is facilitated. Analytically pure **4** can be obtained by treatment with base and extractive removal of water-soluble impurities and recrystallization of the remaining mixture. While isolation by this method results in modest product recovery (28% overall isolated yield based on **3**), the procedure is simple and readily adaptable to large scale. Alternatively, isolation of **4** with nearly complete recovery (i.e. up to 50% yield) is achievable on smaller scale by flash chromatography.

The enantiomers of **4** elute with baseline separation on an analytical commercial chiral capillary GC column,[9] confirming the *trans* stereochemical disposition of the nitro groups. The extremely high (>30:1) *trans*-selectivity of N_2O_4 addition constitutes a most striking feature of the reaction. Although dinitration of certain olefins has been reported,[10] this is the first case in which the stereochemical outcome is completely unambiguous, as both nitro groups in **4** are bound to non-epimerizable tertiary centers. The stereoselectivity may be rationalized within Shechter's[11] proposed free-radical mechanism for N_2O_4 additions to alkenes, with a free and relatively long-lived tertiary radical **B** undergoing less hindered axial attack by $\bullet NO_2$ to afford **4** (Scheme 2). Mixtures of *cis* and *trans*-dinitro products are obtained in additions to alkenes where the steric bias in the putative radical intermediate is low.[11] If olefin **3** and N_2O_4 are mixed directly, high molecular weight side-products are formed at the expense of **4**, presumably due to oligomerization reactions undergone by **B** with additional olefin present. Slow addition of substrate and the presence of excess N_2O_4 are thus crucial to the success of the dinitration reaction, as these conditions favor capture of the putative intermediate by $\bullet NO_2$.

Scheme 2



Hydrogenation of **4** was catalyzed cleanly by $Pd(OH)_2$ on carbon under 45 psi H_2, and the resulting racemic diamine **1a** was purified by distillation. Under identical conditions, Pd on carbon was completely ineffective as a reduction catalyst. The four-step synthesis of **1a** from *o*-xylene was thus carried out in 14.2% overall yield and required no chromatographic separations. Resolution with (+)-mandelic acid leads to optically pure (*R,R*)-(–)-**1a**.[12] The absolute configuration of the diamine was established from the relative stereochemistry of its mandelate salt, as determined by an X-ray crystal structure analysis.

Applications of this methodology to the preparation of other chiral 1,2-diamines and the utility of **1a** and derived compounds as chiral ligands in asymmetric catalysis are currently under investigation in our laboratories.

Acknowledgments.

We are grateful to Mr. Alexander Muci for preliminary studies directed toward the preparation of **1a**, and to Ming Tao for valuable experimental assistance. We thank Dr. Scott R. Wilson for carrying out the X-ray crystal structure analysis. This work was supported in part by a Presidential Young Investigator Award from the National Science Foundation (CHE-9057740), and by generous matching contributions from the Monsanto Company, the Rohm and Haas Company, and Merck & Company.

Preparation of *trans*-1,2-Dimethyl-1,2-dinitrocyclohexane (4). *CAUTION! Dinitrogen tetroxide (bp 21°C) is toxic and should only be handled in an efficient hood.*[13] Crude 1,2-dimethylcyclohexene prepared from *o*-xylene (see above)[8] (43.8 g, 0.306 mol of **3** based on the composition of the mixture) in 100 mL of dry ether was added dropwise to a stirred solution of 65.0 g of N_2O_4 (0.706 mol) in 600 mL ether over a period of 6 h at 0°C with a slow stream of O_2 bubbling through the reaction mixture. After the addition, the mixture was poured into 1 L of ice/water and allowed to warm to room temperature overnight. The organic phase was separated and the solvent was removed. The residue was then dissolved in 500 mL of 1:2 Et_2O/hexane and washed with 8 x 300 mL of H_2O (until the washings were neutral), dried over Na_2SO_4, and evaporated to give an oil. The oil was dissolved in 100 mL of EtOH and added slowly to 1000 mL of 2 M NaOH solution, and the mixture was stirred for 10 h at room temperature. The dark brown mixture was then extracted with 3 x 300 mL of Et_2O, the combined extracts were dried over Na_2SO_4 and evaporated. The residue was recrystallized twice from hexane to give 17.32 g of pure **4** as large crystals (28%, 14.2% overall from *o*-xylene), mp 206-208°C. IR (KBr): 1549, 1532, 1441, 1389, 1348, 1097, 887, 864 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.77 (s, 6H, 2 x CH_3), δ 1.50-2.50 (m, 8H) ppm; ^{13}C NMR: δ 91.7, 35.0, 21.8, 20.0 ppm. Anal. Calcd for $C_8H_{14}N_2O_4$: C, 47.52; H, 6.98; N, 13.85. Found: C, 47.51; H, 6.97; N, 13.84.

Preparation of *trans*-1,2-Dimethyl-1,2-diaminocyclohexane (1a). The dinitro compound **3** (14.95 g, 73.9 mmol) was dissolved in 100 ml of acetic acid and hydrogenated in the presence of $Pd(OH)_2$ on carbon (5.0 g, Aldrich) under 3 atm of H_2 until the uptake of H_2 ceased. The mixture was then filtered and the catalyst was washed with 2 x 30 mL of EtOH. The filtrate and washings were combined, the solvents were removed under vacuum, and the residue was dissolved in 100 mL of H_2O and then treated with 1 N NaOH until the solution pH reached 12. The mixture was then extracted with 3 x 200 mL of CH_2Cl_2, the combined organic layers were dried over Na_2SO_4, and solvent was evaporated under vacuum. The crude diamine was then distilled to give 10.23 g of pure product, bp 100-102°C/3 mm Hg, yield 97%, mp 89-90°C. IR (KBr): 3409, 3318, 2936, 1630, 1586, 1534, 1441, 1379 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.09 (s, 6H, 2 x CH_3), 1.35-1.57 (m, 12 H) ppm; ^{13}C NMR: δ 54.1, 38.2, 23.6, 22.5 ppm. Anal. Calcd for $C_8H_{18}N_2$: C, 67.55; H, 12.75; N, 19.70. Found: C, 67.75; H, 12.65; N, 19.34.

Resolution of (1*R*,2*R*)- and (1*S*,2*S*)-1,2-Dimethyl-1,2-cyclohexanediamine. To a solution of 9.25 g (0.065 mol) of the racemic diamine in 100 mL of EtOH was added a solution of 19.78 g (0.130 mol) of (*S*)-(+)-mandelic acid in 100 mL of EtOH and the mixture was refluxed for 30 min and then cooled to room temperature. The crystals thus formed were collected by filtration, and recrystallized four times from EtOH to give pure (1*R*,2*R*)-1,2-dimethyl-1,2-cyclohexanediammonium bis-(*S*)-mandelate (5.95 g), $[\alpha]_D^{23} = +72.6°$ (c 0.5, H_2O). The diamine was obtained as a white crystalline solid by treatment of the salt with 1 NaOH solution (100 mL), extraction with CH_2Cl_2 (3 x 100 mL) and evaporation of the solvent. mp 88-9°C. $[\alpha]_D^{23} = -15.8°$ (c 1.0, 1N HCl). The (1*S*,2*S*)-(+)-diamine was similarly obtained by recrystallization of its *bis*-(*R*)-mandelate salt three times from EtOH.

Notes and References

1. For some leading examples, see: (a) Corey, E.J.; Imwinkelried, R.; Pikul, S.; Xiang, Y.B. *J. Am. Chem. Soc.* **1989**, *111*, 5493. (b) Corey, E.J.; Kim, S.S. *J. Am. Chem. Soc.* **1990**, *112*, 4976. (c) Yamada, T.; Narasaka, K. *Chem. Lett.* **1986**, 131. (d) Zhang, W.; Loebach, J.L.; Wilson, S.R.; Jacobsen, E.N. *J. Am. Chem. Soc.* **1990**, *112*, 2801. (e) Tomioka, K.; Nakajima, M.; Koga, K. *J. Am. Chem. Soc.* **1987**, *109*, 6213. (f) Oishi, T.; Hirama, M. *J. Org. Chem.* **1989**, *54*, 5834. (g) Corey, E.J.; Jardine, P.; Virgil, S.; Yuen, P.W.; Connel, R.D. *J. Am. Chem. Soc.* **1989**, *111*, 9243. (h) Bolm, C.; Zehnder, M.; Bur, D. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 205. (i) Tomioka, K.; Shindo, M.; Koga, K. *J. Am. Chem. Soc.* **1989**, *111*, 8266. (j) Cuvinot, D.; Mangeney, P.; Alexakis, A.; Normant, J.-F.; Lellouche, J.-P. *J. Org. Chem.* **1989**, *54*, 2420.

2. (a) Hanessian, S.; Delorme, D.; Beaudoin, S.; Leblanc, Y. *J. Am. Chem. Soc.* **1984**, *106*, 5754. (b) Tokles, M.; Snyder, J.K. *Tetrahedron Lett.* **1986**, *27*, 3951. (c) Nakajima, K.; Sasaki, C.; Kojima, M.; Aoyama, T.; Ohba, S.; Saito, Y.; Fujita, J. *Chem. Lett.* **1987**, 2189. (d) Nakajima, K.; Kojima, M.; Fujita, J. *Chem. Lett.* **1986**, 1483.

3. Curtius and related rearrangement reactions are generally either ineffective with tertiary migrating groups, or they afford very poor yields in the preparation of 1,2-diamines. See: a) Wallis, E.S.; Lane, J.F. *Org. React.* **1946**, *3*, 267. b) Wolf, H. *Org. React.* **1946**, *3*, 307. c) Smith, P.A.S. *Org. React.* **1946**, *3*, 337.

4. Known transition metal-mediated diamination reactions are *cis*-stereospecific. See, for example: (a) Chong, A.O.; Oshima, K.; Sharpless, K.B. *J. Am. Chem. Soc.* **1977**, *99*, 3420. (b) Becker, P.N.; Bergman, R.G. *Organometallics* **1983**, 2, 787. (c) Bäckvall, J.E. *Tetrahedron Lett.* **1978**, 163.

5. (a) Kohn, H.; Jung, S.-H. *J. Am. Chem. Soc.* **1983**, *105*, 4106 (b) Jung, S.-H.; Kohn, H. *Tetrahedron Lett.* **1984**, *25*, 399. (c) Fristad, W.E.; Brandvold, T.A.; Peterson, J.R.; Thompson, S.R. *J. Org. Chem.* **1985**, *50*, 3647. (d) Moriarty, R.M.; Khosrowshahi, J.S. *Tetrahedron Lett.* **1986**, *27*, 2809.

6. For leading references, see: Roskamp, E.J.; Pedersen, S.F. *J. Am. Chem. Soc.* **1987**, *109*, 3152.

7. Wiley Organics (Coshocton, Ohio) lists the price of 1,2-dimethylcyclohexene at $42 / 5g.

8. Birch, A.J.; Walker, K.A.M. *Aust. J. Chem.* **1971**, *24*, 513.

9. J&W Scientific (Folsom, CA) Cyclodex-B column, 30 m x 0.25 mm I.D., 0.25 μm film.

10. (a) Levy, N.; Scaife, C.W. *J.Chem. Soc.* **1946**, 1093. (b) Baldock, H.; Levy, N.; Scaife, C.W. *J.Chem. Soc.* **1949**, 2627. (c) Cambell, K.N.; Shavel, J.; Cambell, B.K. *J. Am. Chem. Soc.* **1953**, *75*, 2420. (d) Schechter, H.; Conrad, F. *J. Am. Chem. Soc.* **1953**, *75*, 5610. (e) Brand, J.C.D.; Stevens, I.D.R. *J.Chem. Soc.* **1958**, 629.

11. Shechter, H.; Garkikes, J.J.; Cantrell, T.S.; Tiers, G.V.D. *J. Am. Chem. Soc.* **1967**, *89*, 3005.

12. The optical purity of **1** was ascertained by analysis of the bis-3,5-dinitrobenzamide derivative by HPLC on a Pirkle covalently-bound *N*-1-naphthylleucine column (Regis). We are grateful to Mr. Christopher Welch and to Professor Pirkle for their invaluable assistance.

13. For notes on the handling of N_2O_4, see *Org. Synth., Coll. Vol. V*, **1973**, 336.

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