Microwave assisted fast and clean conversion of mesylate to azide: Synthesis of (1S,2R/1R,2S)-1-azido-2-carbocyclic amines as immediate precursors to versatile 1,2-cis-diamines

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An efficient and rapid conversion of mesylate to azide under microwave irradiation has been carried out. It proceeds through inversion of configuration from chiral mesylates to provide optically pure cis-azides, immediate precursors of vicinal-cis-1,2-diamines. These diamines can serve as metal ligands in asymmetric catalysis and their derivatives can be employed as medicinal agents.

Keywords: Mesylate, azide, microwave irradiation, diamines, asymmetric catalysis, medicinal agent

IPC: Int.Cl. C07D

In synthetic organic chemistry, azido compounds are versatile precursors to access a variety of amino compounds such as 1,2-aminoalcohols, 1,2-diamines and β-aminoacids. Efficient methods available for the reduction of azide to amines has made the azide functionality a synthon of choice to access amino compounds and their potential derivatives. Routine conversion of alcohol to azide functionality involves mesylation or tosylation followed by nucleophilic displacement by azide anion. A large variety of mesylates like primary, secondary and sterically hindered mesylates have been used to access azides. Mesylates react with azide nucleophile often very slowly, requiring prolonged reaction times and high temperatures. Under such circumstances, some reactive mesylates undergo decomposition, rearrangement, intramolecular cyclizations and prolonged reaction times may cause racemization. In particular, conversion of hindered mesylate to azide requires very harsh conditions and even impossible in some cases. Thus, an alternative rapid and efficient microwave assisted transformation of mesylate to azides will be of interest to many organic chemists and in a recent example, microwave irradiation was employed for the azidation of tosylate. The microwave-enhanced organic reactions are rapidly gaining acceptance and popularity since it provides opportunity to complete the reactions in minutes and have manifold application in academia and industry.

Results and Discussion
During the course of our work, we were interested in making azide from sterically hindered mesylate substrates such as 1-9, 11-14 shown in Schemes I and II. The conventional synthetic procedure involved heating of the mesylate with NaN₃ (8.0 eq.) in DMF for 5-12 hr at 65-70°C. In microwave method the reaction mixture was treated with microwave radiation in microwave oven following the microwave organic reaction enhancement techniques (MORE). The reactions were carried out in a conical flask covered with a filter funnel to prevent the spillage during the irradiation. The reaction mixture was irradiated with microwave in 1-6 cycles of 2 min each followed by 1 min rest until complete conversion of the starting material. The domestic microwave oven of 800 watt at power level of 5 in a scale of 10 raised the temperature of the reaction mixture to 90°C in 10 min. The temperature was maintained at 90°C by controlling the power level depending on conversion time of substrate and then allowed to cool to room temperature. The conversions monitored by TLC were very clean and no trace of impurities was found. DMF was a solvent of choice as in conventional method.
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because of its high boiling point (153°C) and polarity resulting in very good microwave absorption medium. The results are summarized in Tables I and II. The nucleophile NaN₃ used was 1.5-2.0 eq. as compared to 8.0 eq. in conventional method. The products were easily purified by just filtration column chromatography to achieve high purity. Almost complete conversion was observed within short periods, leading to high enantiopurities of azide products and no recemization occurred. The optical rotations and other characterization data were in agreement with the reported data.

The mesylate 7 being unstable, underwent neighboring group assisted rearrangement to give slight amount of cyclic aziridine impurity. Interestingly, the inactive and sterically hindered mesylate 9 gave the azide 10 under microwave irradiation as the exclusive product, which was not possible by conventional method (Scheme I, Table I). Conversion of carbocyclic mesylates such as 11-14 into corresponding azides by conventional methods was accompanied by formation of a side product, identified as the cyclic urea (Scheme III, 19) in 7-10% yield, where the structure was confirmed by NMR and X-ray crystallography (Figure 1). This is probably formed by the thermal decomposition of azide accompanied by the rearrangement with the adjacent carbamate (Boc) functionality (Scheme III). However, under
microwave irradiation, no such impurities were observed. In general, conversions of trans-cyclohexyl (pentyl) mesylates are very rapid with slightly improved optical purities of the products (Scheme II, Table II). Azidation of mesylate accompanied by the inversion of configuration is clearly seen from the crystal structures of mesylate 12 and corresponding azide product 16 (Figure 2). The carbocyclic 1,2-diamines were obtained by the reduction of these amino azides as reported.

1,2-Diamines are an important class of compounds, with applications as medicinal agents, chiral auxiliaries or as metal ligands in catalytic asymmetric synthesis. They are also present in many natural products with potential biological properties. Utilizations of the optically pure vicinal 1-azido-2-carbocyclic amines and their derivatives lead to the development of synthetic methods for the preparation of 1,2-diamines in their optically pure form. As compared to trans-1,2-cyclohexyl diamines, cis-1,2-cyclohexyl (pentyl) diamines have not been exploited to their full potential, in medicinal chemistry and in catalytic asymmetric synthesis. This is perhaps due to difficulty in obtaining chirally pure cis-1,2-cyclic diamines. We recently demonstrated the potential of these cis-1,2-diamines (both cyclohexyl and cyclopentyl) in designing constrained PNA analogues for DNA and RNA discrimination. The microwave procedure discussed here would be helpful in access a variety of such

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* for azides 2 (c 2.28, CH2Cl2) at 20°C.
* for azides 4 (c 1.37, CH2Cl2) at 20°C
* for azides 6 (c 0.52, CHCl3) at 20°C
* no transformation

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* for cyclopentyl azides (c 1.0, CH2Cl2) at 20°C.
* for cyclohexyl azides (c 1.5, CH2Cl2) at 20°C.
optically pure azido precursors.
In all the microwave irradiation experiments involving formation of azide products, no incidents have been observed. The sophisticated single mode microwave reactors enable the fine control of temperature and pressure during the microwave reactions, ensuring the safety.
In summary, this report demonstrates the use of microwave-assisted synthesis of substituted azides, which are immediate precursors of amine functionality. This procedure is efficient, rapid, clean and high yielding process, and a better alternative to conventional method. Our synthesis provides an easy access to the optically pure enantiomers of cis-1,2-cyclohexyl and cyclopentyl diamines, which are otherwise difficult to obtain from other methods as compared to trans-diamines which are commercially available.

Experimental Section
General. Melting points of samples were determined in open capillary tubes on Bruker melting point apparatus B-540 and are uncorrected. IR spectra were recorded on an infrared Fourier Transform spectrophotometer using KBr pellets or as neat; $^1$H and $^{13}$C NMR spectra on Bruker 200 MHz and 500 MHz NMR spectrometers (chemical shifts in δ, ppm) and mass spectra were obtained either by FAB or LCMS techniques. Column chromatographic separations were performed using silica gel 60-120 mesh, solvent systems 10-25% EtOAc-pet. ether and pure DCM to 3% MeOH/DCM.

Conventional method. A stirred mixture of the (1S,2S)-2-(N-t-Boc-amino)cyclopentan-1-methyl sulfoxonate 13 (700 mg, 2.5 mmoles) and NaN₃ (1.3 g, 20.0 mmoles) in DMF (5 mL) under nitrogen atmosphere was heated at 68-70°C for 5-6 hr. After cooling the reaction mixture, the solvent was evaporated under reduced pressure. The residue was extracted into ethyl acetate (10 mL × 2) and dried over Na₂SO₄. The organic layer was removed and the crude product was purified by column chromatography (EtOAc-pet. ether) to afford white solid of (1R,2S)-2-(N-t-Boc-amino)-1-azidocyclopentane 17, yield 91%, [a]_D⁻²⁻¹₁₆⁰°C (c 1.0, CH₂Cl₂), and the side product 19 (yield 7%).

cis-Cyclopentyl-1,3-urea 19: m.p. 143.0°C; IR (KBr): 3280.69, 3016.46, 2970.17, 1745.46, 1409.87, 1244.0, 1215.07, 1114.78, 1039.56, 991.34, 946.98, 756.04 cm⁻¹; $^1$H NMR (CDCl₃, 200 MHz); δH 1.25-1.75 (m, 4H), 1.75-1.9 (s, 2H), 3.9-4.1 (s, 1H), 4.75-4.9 (s, 1H), 6.5-6.85 (bd, 2H); $^{13}$C NMR (CDCl₃, 200 MHz); δC 21.5, 33.7, 34.1, 56.5, 81.9, 160.3; Anal. Calcd for C₆H₁₀N₂O: C, 57.14; H, 7.93; N, 22.22. Found: C, 56.91; H, 7.97; N, 21.87 (%); MS, LCMS: 128.03 [M+2]⁺.
Crystallographic data for compound 19. Single crystal of cis-cyclopentyl-1,3-urea 19 (colourless needles) was obtained from ethyl acetate and petroleum ether. X-ray intensity data was collected on a Bruker SMART APEX CCD diffractometer at room temperature.

Crystal data of cis-cyclopentyl-1,3-urea 19 (C<sub>6</sub>H<sub>10</sub>N<sub>2</sub>O); M = 126.16; Crystal system: Monoclinic; Crystal dimensions: 0.75 x 0.14 x 0.13 mm, a = 10.322(3), b = 5.5641(18), c = 11.284(4) Å, space group P 2(1), V = 643.5 (4) Å<sup>3</sup>, Z = 4, D<sub>c</sub> = 1.302 g cm<sup>-3</sup>, μ [Mo-Kα] = 0.091 mm<sup>-1</sup>, T = 293(2) K, F(000) = 272, Max. and min. transmission 0.9882 and 0.9347, 3149 reflections collected, 2090 unique [T > 2σ (T)], S = 1.116, R value 0.0595, wR<sup>2</sup> = 0.1559 (all data R = 0.0638, wR<sup>2</sup> = 0.1543). CCDC No. 49728 contains the supplementary crystallographic data for this compound.

Microwave irradiation. The mixture of mesylate (1S,2S)-19 (ref. 16) (700 mg, 2.5 mmoles) and NaN<sub>3</sub> (0.32 g, 5.0 mmoles) in DMF (5 mL) was taken in a conical flask covered with filter funnel. The above reaction mixture was irradiated in a microwave oven (BPL-Sanyo) at 90°C for 12 min. The reaction periods were standardized by irradiating the reaction mixtures in 1-6 cycles, each of 2 min interval and 1 min rest. DMF (100 mL) was placed in another vessel and irradiated simultaneously. The progress of the reaction was monitored by TLC (in every 2 min interval). After cooling to room temperature, the solvent evaporated and the residue was extracted in to EtOAc (10 mL x 2) and dried over Na<sub>2</sub>SO<sub>4</sub>. The organic layer was removed and passed through the silica gel column to give the azide (1R,2S) 17, yield 97%, [α]<sub>D</sub><sup>20</sup> -17° (c 1.0, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 81.0°C; IR (KBr): 3442.7, 3014.53, 2935, 2977.8, 2935.4, 2113.84, 1706.88 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz): δ<sub>H</sub> 0.9-1.45 (m, 1H, CH<sub>2</sub> t-Boc), 1.65-2.0 (m, 4H, C<sub>2</sub>H<sub>5</sub>, C<sub>3</sub>H<sub>2</sub>), 3.7-4.1 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>), 4.6-5.0 (bd, 1H, carbamate NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 200 MHz): δ<sub>C</sub> 19.8, 28.2, 29.0, 54.7, 64.1, 79.4, 154.3; Anal. Calcd for C<sub>10</sub>H<sub>16</sub>N<sub>3</sub>O<sub>2</sub>: C, 55.19; H, 5.31; N, 18.19 (%); LCMS: 305.0 [M+1], 205.0 [M+1-t Boc].

(2S,4S)-4-Azido-N-1-benzoxycarbonyl proline methyl ester 4: Yield 99%, IR (Neat): 3365.5, 2977.8, 2935.4, 2104.19, 1695.31, 1392.51, 1265.2, 1164.9, 1118.6, 773.4 cm<sup>-1</sup>; [α]<sub>D</sub><sup>20</sup> -11.0 (c 0.52, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz): δ<sub>H</sub> 4.20-4.5 (bd, 1H, C<sub>2</sub>H<sub>2</sub>), 4.05-3.90 (m, 1H, C<sub>2</sub>H<sub>2</sub>), 3.75 (m, 2H, CH<sub>2</sub>), 4.25-4.20 (m, 1H, t-Boc), 3.65-3.55 (m, 2H, t-Boc), 3.3-2.5 (m, 1H), 2.55-2.0 (m, 1H), 1.45-1.1 (s, <sup>13</sup>C NMR (CDCl<sub>3</sub>, 200 MHz): δ<sub>C</sub> 27.9, 33.5, 51.3, 52.7, 55.5, 58.6, 79.8, 153.4; Anal. Calcd for C<sub>10</sub>H<sub>16</sub>N<sub>3</sub>O<sub>2</sub>: C, 54.94; H, 6.36; N, 11.98. Found: C, 54.76; H, 6.71; N, 11.68 (%); MS (FAB<sup>+</sup>): 268 [M+1].

(1S,2R)-2-(N-t-Boc-amino)-1-azidocyclopentane 15: Yield 97%; [α]<sub>D</sub><sup>20</sup> +117° (c 1.0, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 81.0°C; IR (KBr): 3442.7, 3014.53, 2935.4, 2113.84, 1706.88 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz): δ<sub>H</sub> 1.0-1.45 (m, 11H, 4-CH<sub>2</sub> t-Boc), 1.65-2.0 (m, 4H, 5-CH<sub>2</sub>, 3-CH<sub>2</sub>), 3.7-4.1 (m, 2H, 1-CH<sub>2</sub>-CH<sub>2</sub>), 4.6-5.0 (bd, 1H, carbamate NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 200 MHz): δ<sub>C</sub> 19.8, 28.2, 28.7, 29.0, 54.7, 64.1, 79.4, 155.3; Anal. Calcd for C<sub>10</sub>H<sub>16</sub>N<sub>3</sub>O<sub>2</sub>: C, 53.09; H, 7.96; N, 24.77. Found: C, 52.55; H, 7.98; N, 24.71 (%); MS (FAB<sup>+</sup>): 227 [M+1], 171 (100%) [M+1-N<sub>3</sub>], 127 (15%) [M+1-t Boc].

(1R, 2R)-2-(N-t-Butoxycarbonylaminocyclohexan-1-methyl sulphonate 12: Crystal data: C<sub>3</sub>H<sub>3</sub>N<sub>2</sub>O<sub>4</sub>S, M = 293.37° Crystal system Orthorhombic; Crystal dimensions: 0.67 x 0.08 x 0.04 mm, a =
Acknowledgement

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References and Notes


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16 Cyclohexyl mesylates are unstable to acidic conditions as the compounds were decomposed on silica gel column when attempted to purify, where as cyclohexyl mesylates are very stable.