Technical Note

Convenient Method for Synthesis of l-Methamphetamine

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Enantioselective analysis of methamphetamine (MA) and amphetamine (AP) is necessary in forensic drug analysis. In general, standard materials are required for performing forensic investigation and also for developing new analytical methods. However, l-MA is not commercially available in Japan and only a few reports are available on the enantioselective synthesis of l-MA. We developed a new and convenient method for the synthesis of l-MA using d-norephedrine (d-NE) as a starting material. d-NE was treated with 1,1′-carbonyldiimidazole to produce the corresponding cyclic carbonate, and the product was treated with sodium hydride and iodomethane to form mono-N-methylated amine derivative, which was treated with palladium on activated carbon in hydrogen atmosphere for catalytic reduction. After the addition of aqueous hydrogen chloride (HCl), l-MA was obtained as its HCl salt (total yield 58%).

Key words: Synthesis, l-methamphetamine, d-norephedrine

Introduction

Methamphetamine (MA) and amphetamine (AP) are strong central nervous system stimulants. The use of these drugs is strictly regulated in Japan. Every year, many people are arrested for the use and/or possession of MA in Japan1), making it the most important drug in the field of forensic science. Since MA and AP have an asymmetric carbon, they have two optically active isomers, d- and l-forms. Although the d-isomer ((S)−(+−)−MA) is widely abused, the Vicks Vapor Inhaler, which is available as over-the-counter drug in USA, contains (R)−(−)−MA (l-MA)2). Moreover, l-MA is a metabolites of l-deprenyl (a drug for Parkinson’s disease)2). Furthermore, MA products produced from clandestine laboratories sometimes contain both enantiomers. The ratio of these enantiomers provides information about the source and synthetic route of MA. Therefore, the analysis of the enantiomeric ratio of MA is very important, and many analytical methods have been developed3−7).

Authentic MA is required as a standard material for enantiomeric analysis and for developing new analytical methods. Although d-MA is commercially available, l- and dl-MA can not be supplied in Japan. Consequently, for the above mentioned purposes, it is necessary to synthesize l-MA. A few studies reported on the
synthesis of MA from ephedrine (EP)\(^8\), phenyl-2-propanone (P2P)\(^9\), and phenylalanine (PHE)\(^10\). EP is easily prepared from natural products such as ephedra plants, and natural EP is in the l-form (\((1S, 2R)-(+-)\)-EP), which has the same stereochemical configuration as d-MA at the C-2 position. To obtain l-MA with this method, as a starting material it is necessary to use (1R, 2S)-(+-)EP (\((d)-\)EP), which is not commercially available in Japan. Synthesis of MA from P2P causes its racemization. PHE can be used to synthesize MA enantioselectively; however, this method is complicated. Instead, (1S, 2R)-(+-)norephedrine (d-NE), which has a structure similar to d-EP, is commercially available. In this study, d-NE was chosen as a starting material, and an convenient method was developed for the enantioselective synthesis of l-MA.

Materials and Methods

1. Reagents

d-MA hydrochloride and dl-AP sulfate were purchased from Dainippon Pharmaceutical (Osaka, Japan) and Takeda Pharmaceutical (Osaka, Japan), respectively. d-NE, l-NE, palladium on activated carbon (Pd/C), 1 M hydrochloric acid (HCl), and Celite (No. 500) were purchased from Wako Pure Chemicals Industries (Osaka, Japan). Sodium hydride (NaH), iodomethane (MeI), and trifluoroacetic anhydride (anhydrous TFA) were purchased from Kanto Chemical (Tokyo, Japan). 1,1′-Carbonyldiimidazole was purchased from Aldrich (Steinheim, Germany). Other solvents were used as reagent grade.

2. Instruments

Gas chromatography (GC) was performed with a HP 6890 series (Hewlett-Packard, Palo Alto, CA, USA), equipped with a hydrogen flame ionization detector. The analytical column was DB-1 (30 m × 0.25 mm id, 0.25-μm thick film; J&W Scientific, Rancho, Cordova, CA, USA). Temperature conditions were as follows: initial temperature was 130°C, which was increased to 190°C at the rate of 10°C/min, and was further increased to 280°C at 20°C/min. The flow of carrier gas (helium) was maintained at 1.0 ml/min in constant flow mode. The temperature of injection port and detector was 250°C, and the split ratio was 50:1.

Gas chromatography-mass spectrometry (GC/MS) was performed with Shimadzu model GCMS-QP5050A (Shimadzu, Kyoto, Japan), equipped with a Class 5000 data processing system. The analytical column was BETA DEX™ 225 (30 m × 0.25 mm id, 0.25-μm thick film; Supelco, Inc., Bellefonte, PA, USA). Temperature conditions were as follows: initial temperature was 80°C, which was increased to 200°C at 5°C/min and held for 6 min. The flow of carrier gas (helium) was maintained at 1.0 ml/min in constant flow mode. The temperature of the injection port and transfer line was 250°C and 280°C, respectively, and the split ratio was 10:1. Mass spectra were obtained by electron ionization mode at an ionization energy of 70 eV in the scanning mode.

Melting point was recorded on a MP–500D melting point apparatus (Yanaco, Kyoto, Japan). Optical ratios were measured on a P-10303 polarimeter (Jasco, Tokyo, Japan). Fourier transform infrared spectrophotometry (FTIR) analysis was measured on a FTIR–8600PC (Shimadzu, Kyoto, Japan). EI-MS (positive ion mode) and FAB-MS (positive ion mode; matrix: 4-nitrobenzyl alcohol) spectra were obtained on a JMS-FABmate (JEOL, Tokyo, Japan) and a JMS-HX110 instruments (JEOL), respectively.

3. Chromatographic analysis

To monitor synthetic reactions and estimate optical purities, GC and GC/MS analysis were performed, respectively. Samples for GC and GC/MS analysis were prepared as follow. In GC analysis, each reaction mixture, with concentration of approximately 1% (w/v), was injected (reaction A), after quenching with methanol (MeOH) (reaction B) or being filtered (reaction C). In GC/MS analysis, the dichloromethane (CH₂Cl₂) solution containing d-NE and compound 4 (1 mg/ml) was mixed with excess anhydrous TFA, and heated at 50°C for 15 min. The mixtures were then injected into
the GC/MS instrument.

4. Experimental

(4R, 5S)-4-Methyl-5-phenyl-1,3-oxazolidin-2-one (2)

1,1′-Carbonyldiimidazole (1.17 g, 7.3 mmol) was added to a solution of d-NE (1) (1.0 g, 6.6 mmol) in CH₂Cl₂ (100 ml), and the mixture was stirred at room temperature for 75 min. H₂O (50 ml) was added to the reacting mixture and stirred constantly to remove excess 1,1′-carbonyldiimidazole. The organic layer was washed with H₂O (30 ml × 2) and brine (300 ml), dried over Na₂SO₄, and evaporated under reduced pressure to give crude (2) (1.38 g as a pale yellow crystal, 66%): EI-MS m/z (%): 107 (100), 79 (27), 177 (15) [M⁺], 77 (9), FAB-MS m/z: 178 [M+H]⁺. This crude product was used in the next reaction without further purification.

(4R, 5S)-3,4-Dimethyl-5-phenyl-1,3-oxazolidin-2-one (3)

60% NaH (527 mg, 13.2 mmol) was added to a solution of (2) (1.38 g, crude) in DMF (100 ml) and the mixture was stirred at room temperature for 30 min. Mel (496 µl, 7.9 mmol) was added to the mixture and stirred constantly at room temperature for 30 min. After MeOH (2 ml) was added, the mixture was partitioned between ethyl acetate (300 ml) and H₂O (300 ml), and the organic layer was washed with H₂O (300 ml × 2) and brine (300 ml), dried over Na₂SO₄, and evaporated under reduced pressure to give crude (3) (1.11 g as a pale yellow crystal, 88%): EI-MS m/z (%): 57 (100), 191 (65) [M⁺], 58 (41), 176 (18), 147 (17), 117 (11), 132 (10), 91 (9), 77 (9), FAB-MS m/z: 192 [M+H]⁺. This crude product was used in the next reaction without further purification.

l-Methamphetamine hydrochloride (4)

A mixture of (3) (1.11 g, crude) and Pd on carbon (20%, 50 mg) in MeOH (100 ml) was vigorously stirred under H₂ atmosphere at room temperature for 20 h. The mixture was filtered through a Celite pad, and the filtrate was evaporated under reduced pressure. 1 M aq. HCl (10 ml) was added to the residue to form HCl salt, and the mixture was evaporated under reduced pressure. The residue was purified by recrystallization from diethyl ether-chloroform to give (4) (0.71 g as a white crystal, 66%): mp 173–175°C (ref.¹¹ 171–173°C); [α]D²² = 15.6° (c 1.0, CHCl₃) (ref.¹¹ [α]D = 16.3° (c 0.52, water)). IR (KBr) cm⁻¹: 2461, 1605, 1489, 1456, 1387, 1356, 1082, 1061, 748, 700, 463. (This spectrum was the same as the spectrum of d-MA hydrochloride). EI-MS m/z (%): 58 (100), 91 (4), FAB-MS m/z: 150 [M+H]⁺. Anal. Calcd for C₁₀H₁₆ClN: (mol wt. 185.10) C, 64.68; H, 8.68; Cl, 19.09; N, 7.54. Found: C, 64.31; H, 8.48; Cl, 19.15; N, 7.48.

Fig. 1 The synthetic scheme of l-methamphetamine hydrochloride from d-norephedrine.
Total yield (in three steps) was 58%.

Results and Discussion

In the earlier reports\textsuperscript{12,13}, the enantiomers of compounds 2 and 3 were prepared from \textit{l}-NE and \textit{l}-EP, respectively, under similar conditions as in reaction A, and compound 2 was obtained from \textit{d}-NE treated with diethylcarbonate and potassium carbonate in good yield (83%), whereas there was no report on the synthesis of MA from compound 3. In this study, we have developed a highly efficient enantioselective preparation method of \textit{l}-MA using the commercially available \textit{d}-NE (1) as the starting material. Each step was handled with ease and the obtained materials were in a pure form that was acceptable in the field of forensic science. In our method, unreacted reagents were almost removed by washing with water and by filtration, and a few by-products were formed by monitoring with GC analysis. In gas chromatograms (Fig. 2), peaks other than those of compounds 1–4 and solvents were determined to be imidazole (Fig. 2(b)), MeOH (Fig. 2(c)), and glycerol (Fig. 2(d)). Imidazole and glycerol were removed with the washing and recrystallization process, respectively. Furthermore, each reaction could be terminated rapidly, except reaction C, and it took only a few days to perform the total reactions. The total yield (58%) was satisfactory to obtain authentic standards.

Optical purities of \textit{d}-NE and compound 4 were estimated by GC/MS analysis. The total ion chromatograms are shown in Fig. 3. The retention time and mass spectra of \textit{d}-NE, \textit{d}-MA, and \textit{d} or \textit{l}-AP were consistent with those of the standard materials, and the mass spectra of \textit{l}-NE-bisTFA and \textit{d}-MA-TFA have the same patterns as \textit{d}-NE-bisTFA and \textit{l}-MA-TFA, respectively. Because commercially available \textit{d}-NE material contained trace amount of \textit{l}-NE as an original impurity, it is reasonable that compound 4 contained trace amount of \textit{d}-MA which was derived from \textit{l}-NE. Furthermore, it contained trace amounts of \textit{d} or \textit{l}-AP as

![Gas chromatograms](image-url)
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![Image](image.png)

Fig. 3 Total ion chromatograms of TFA-derivatives of starting materials (a) and synthetic products (b).
(a) Main peak: \( d \)-NE-bisTFA; minor peak: \( l \)-NE-bisTFA. (b) Main peak: \( l \)-MA-TFA; minor peaks: \( d \)-MA-TFA, \( d \) or \( l \)-AP-TFA.

synthetic by-products.

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