A Short Synthesis of Trimebutine, 2-Dimethylamino-2-phenylbutyl 3,4,5-trimethylbenzoate

Jin Yeon Kim,† Gwang-il An,‡ Kwon-Soo Chun,‡ and Hakjune Rhee*

†Department of Chemistry, Seonam University, Namwoen, Chunrabuk-do 590-170, Korea
‡Laboratory of Cyclotron Application, Korea Institute of Radiological & Medical Sciences, Seoul 139-706, Korea
*Department of Chemistry, Hanyang University, Ansan, Kyunggi-do 426-791, Korea. *E-mail: hrhee@hanyang.ac.kr*

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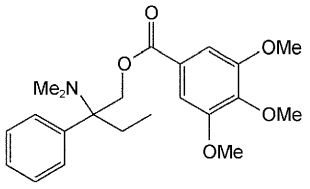
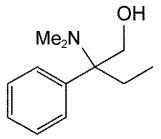
Trimebutine (**1**) maleate, 2-dimethylamino-2-phenylbutyl 3,4,5-trimethylbenzoate hydrogen maleate, has been used for the treatment of functional bowel disorders, including irritable bowel syndrome and postoperative ileus.[1] Due to its biological activities, the efficient synthesis of **1** would be challengeable. The synthesis of **1** and its analogues has been reported by several research groups.[2] An efficient and facile preparation method of a key intermediate, 2-dimethylamino-2-phenylbutanol (**2**), is important for the synthesis of trimebutine (**1**). Previously, amino alcohol **2** has been synthesized using Strecker protocol[2g] or more recently *via* 2-oxazolines.[2a]



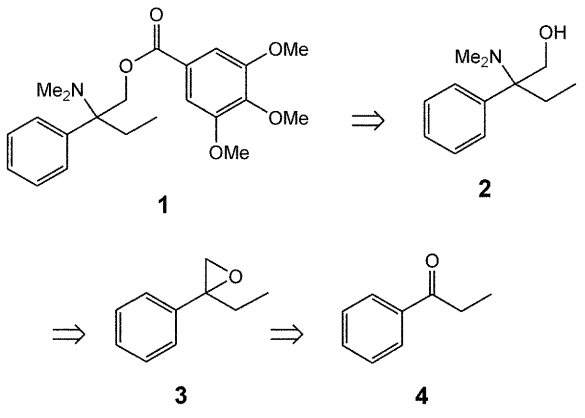
Trimebutine (1)

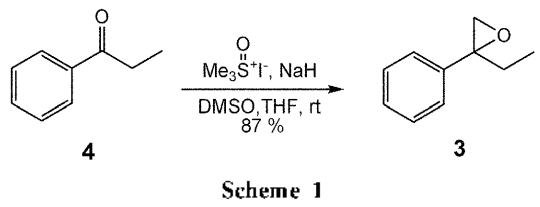


2-Dimethylamino-2-phenybutanol (2)

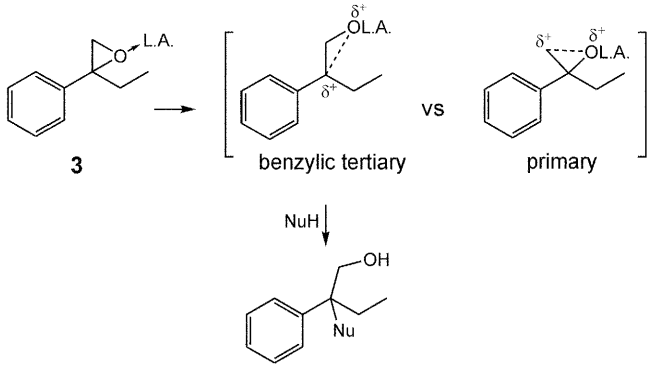
These methods need several reaction steps from the corresponding starting materials to amino alcohol **2** and seem to be inefficient procedures. In this paper, we report a short three-step synthesis of **1**.

We speculated a strategy for the synthesis of **1**. In this strategy, the key points will be how to prepare 1-ethyl-1-phenyloxirane (**3**) from propiophenone (**4**) and how to control the correct ring opening of the oxirane **3** by dimethylamine to amino alcohol **2**.





Scheme 1

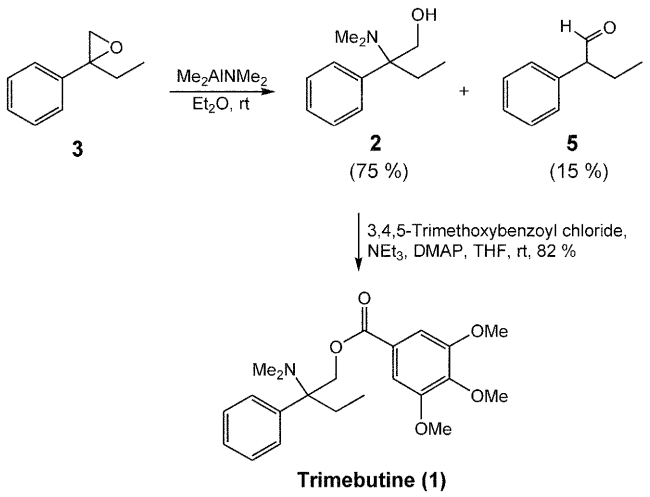


Scheme 2

It is well known that the formation of oxiranes is easily achieved from the corresponding aldehydes and ketones *via* sulfur ylide chemistry.[2a,3] Thus, the reaction of ketone **4** with trimethylsulfoxonium iodide in the presence of sodium hydride yielded the anticipated oxirane **3** in 87 % (Scheme 1).

Regioselective ring-opening of oxirane **3** mediated by Lewis acid can be expected to occur as shown in Scheme 2. The preferential α-attack on oxirane **3** can be explained in terms of the stability of the intermediate benzylic tertiary carbocation. Several research groups reported Lewis acid catalyzed or stoichiometric aminolysis and azidolysis of oxirane compounds.[4] It should be also considered that Lewis acid-promoted rearrangement of epoxides[5] can occur in this reaction.

We tried the aminolysis of oxirane **3** with stoichiometric amount of dimethylaluminum amide, which was prepared by mixing dimethylamine and trimethylaluminum.[4g] Then, simultaneous addition of oxirane **3** into the reaction mixture at room temperature afforded, after hydrolysis, amino alcohol **2** and 2-phenylbutanal (**5**) in 75 and 15%, respectively. Following a precedent procedure,[2c] the synthesis of **1**



Scheme 3

was then completed (Scheme 3).

In summary, we have accomplished the synthesis of **1** from **4** in three steps and 54% overall yield through intramolecular Lewis acid mediated aminolysis of oxirane **3**. Investigation on the intermolecular Lewis acid-catalyzed ring-opening of oxirane **3** to amino alcohol **2** for practical reactions is now under way.

Experimental Section

All reactions were carried out under an inert atmosphere of argon. TLC was conducted on E. Merck 60 F254 aluminum backed silica gel plates (0.2 mm) with a fluorescent indicator. Developed plates were visualized under UV light, with iodine staining, or by dipping in 2.0% phosphomolybdic acid solution and then heating. Flash column chromatography was performed using Merck silica gel 60 (230-400 mesh) under positive pressure of air according to the procedure of Still.[6] Reagents and solvents were of reagent grade, and solvents were purified by the known procedure[7] before use. ^{1}H NMR and ^{13}C NMR spectral data were obtained on a Varian Gemini 300 (300 MHz) spectrometer. Infrared spectra were recorded using a BioRad FT-IR spectrophotometer with internal calibration. High-resolution mass spectra were recorded on a JEOL SX102A mass spectrometer.

Synthesis of 1-ethyl-1-phenyloxirane (3). A solution of trimethylsulfoxonium iodide (2.20 g, 10.0 mmol) in DMSO (30.0 mL) was added to a suspension of NaH (0.45 g, 13.3 mmol, 60% in mineral oil) in DMSO (5.0 mL) at 25 °C. The mixture was stirred for 1 h and then propiophenone (**4**) (1.0 mL, 7.5 mmol) in THF (10 mL) was added. The resulting mixture was stirred at 25 °C for 10 h under argon. It was poured into diethyl ether-brine solution (200 mL, 1 : 1, v/v). The organic phase was separated, dried with anhydrous $MgSO_4$, and concentrated by rotary-evaporation. The residue was purified by flash column chromatography (*n*-hexane/ethyl acetate, 10 : 1, v/v, R_f – 0.80) to give a pale yellow oil **3** (0.97 g, 87%): IR (neat) 3060, 2972, 1496 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.27-7.37 (m, 5H), 2.95 (d, J – 5.7 Hz, 1H), 2.72 (d, J = 5.4Hz, 1H), 2.25 (m, 1H), 1.79 (m, 1H), 0.93 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 140.03, 128.32, 127.50, 126.06, 61.15, 55.54, 28.52, 9.29; HRMS (EI) *m z* calcd. for ($C_{10}H_{12}O$): 148.0888, found 148.0880.

Synthesis of 2-dimethylamino-2-phenylbutanol (2). A solution of dimethylamine (7.4 mmol, 3.7 mL in 2 *M* THF solution) in diethyl ether (20 mL) was added to $AlMe_3$ (7.4 mmol, 3.7 mL in 2 *M* toluene solution) at 25 °C under argon. After being stirred for 0.5 h, 1-ethyl-1-phenyloxirane (**3**) (0.91 g, 6.53 mmol) was added to the reaction mixture. The resulting mixture was stirred for 10 h and was quenched with 0.5 *N* NaOH solution (15 mL). The organic layer was washed with 0.1 *N* HCl solution (10 mL) and dried over $MgSO_4$, then the filtrate was concentrated. The residue was purified by flash column chromatography to afford a colorless oil **2** (*n*-hexane/ethyl acetate, 5 : 1, v/v, R_f = 0.30, 0.95 g, 75%) and a byproduct, 2-phenylbutanal (**5**) (*n*-hexane/ethyl acetate, 5 : 1, v/v, R_f = 0.90, 0.15 g, 15%).

2-Dimethylamino-2-phenylbutanol (**2**): IR (neat) 3400 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.23-7.38 (m, 5H), 4.01 (dd, J = 10.5, 1.2 Hz, 1H), 3.77 (d, 10.2 Hz, 1H), 2.25 (s, 6H), 2.02 (m, 1H), 1.88 (m, 1H), 0.72 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ146.51, 127.91, 126.06, 125.44, 73.96, 69.78, 47.34, 34.90, 7.69; HRMS (EI) *m z* calcd. for ($C_{12}H_{19}NO$): 193.1467, found 193.1461.

2-Phenylbutanal (**5**): ^{1}H NMR (300 MHz, $CDCl_3$) δ9.64 (d, J – 0.9 Hz, 1H), 7.14-7.53 (m, 5H), 3.37 (t, J – 7.2 Hz, 1H), 2.11 (m, 1H), 1.78 (m, 1H), 0.88 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ200.83, 140.00, 129.01, 128.81, 127.51, 60.92, 22.70, 14.09; MS (EI) *m z* 148 (M^+), 125, 111, 97, 83, 69, 57.

Synthesis of trimebutine, 2-dimethylamino-2-phenylbutyl 3,4,5-trimethylbenzoate (1). To a solution of amino alcohol **2** (0.50 g, 2.6 mmol) in THF (15 mL) were added 3,4,5-trimethoxybenzoyl chloride (0.67 g, 2.9 mmol), triethylamine (0.41 mL, 2.9 mmol), and dimethylaminopyridine (0.016 g, 0.13 mmol). The reaction mixture was stirred at room temperature for 12 h. It was poured into brine solution (30 mL) and extracted with ethyl acetate (10 mL × 3). The organic phase was separated, washed with saturated aqueous $NaHCO_3$ (10 mL) and brine solution (10 mL), dried with anhydrous $MgSO_4$, and concentrated by rotary-evaporation. The residue was purified by flash column chromatography (*n*-hexane/ethyl acetate, 5 : 1, v/v, R_f = 0.26) to give a colorless gummy solid **1** (0.82 g, 82%): ^{1}H NMR (300 MHz, $CDCl_3$) δ7.47 (d, J = 7.8 Hz, 2H), 7.32 (t, J = 7.7 Hz, 2H), 7.21 (t, J = 7.2 Hz, 1H), 7.17 (s, 2H), 4.84 (d, J = 12.0 Hz, 1H), 4.73 (d, J – 12.3 Hz, 1H), 3.87 (s, 3H), 3.80 (s, 6H), 2.39 (s, 6H), 1.89 (m, 2H), 0.72 (t, J = 7.4 Hz, 3H).

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