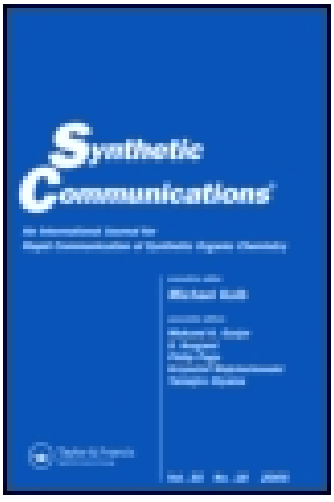

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Efficient and Industrially Viable Synthesis of Donepezil

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Published online: 30 Aug 2007.

To cite this article: R. Janaki Rama Rao , A. K. S. Bhujanga Rao & Y. L. N. Murthy (2007) Efficient and Industrially Viable Synthesis of Donepezil, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 37:17, 2847-2853, DOI: 10.1080/00397910701471477

To link to this article: http://dx.doi.org/10.1080/00397910701471477

Synthetic Communications®, 37: 2847–2853, 2007

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910701471477

Efficient and Industrially Viable Synthesis of Donepezil

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Abstract: An efficient, economically viable process has been developed for large-scale preparation of donepezil HCl (**1**), an anti-Alzheimer's agent. The process involves the condensation of 5,6-dimethoxy-1-indanone (**3**) and 1-benzyl-4-piperidinecarboxaldehyde (**4**) in the presence of alkalimetal carbonates at elevated temperature to yield 1-benzyl-4-[(5,6-dimethoxy-1-indanone)-2-yidenyl] methyl piperidine (**2**), the key intermediate in the synthesis of donepezil. Hydrogenation of **2** yields donepezil.

Keywords: anti-Alzheimer's agent, aqueous alkali metal carbonates, condensation, donepezil, economically viable

INTRODUCTION

Donepezil HCl (**1**) is a memory-enhancing drug useful in the treatment of Alzheimer's disease. Alzheimer's disease, the most common cause of dementia, is a neurodegenerative disorder characterized by a progressive deterioration of memory and cognition.[1] Donepezil HCl (**1**) is one of the most promising agents among the acetyl cholinesterase inhibitors. Donepezil HCl was introduced by Japanese pharmaceutical company Eisai.

Received in India November 4, 2006
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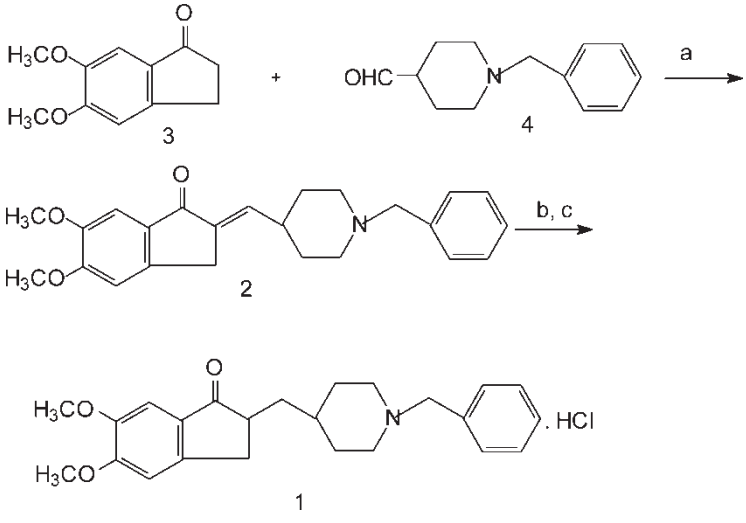
CHEMISTRY

Sugimoto and coworkers[2] described the synthesis of donepezil with an overall yield of 27.4%, which involves the condensation of 5,6-dimethoxy-1-indanone (**3**) and 1-benzyl-4-piperidinecarboxaldehyde (**4**) in the presence of n-BuLi as base, at −78°C in tetrahydrofuran/hexamethylphosphoric triamide (THF/HMPTA) solvents under anhydrous conditions (Scheme 1). The resulting compound (**2**) is isolated by column chromatography, hydrogenated over palladium carbon in THF solvent, followed by conversion to hydrochloride to afford donepezil hydrochloride (**1**). In this method, the donepezil base is also isolated by column chromatography.

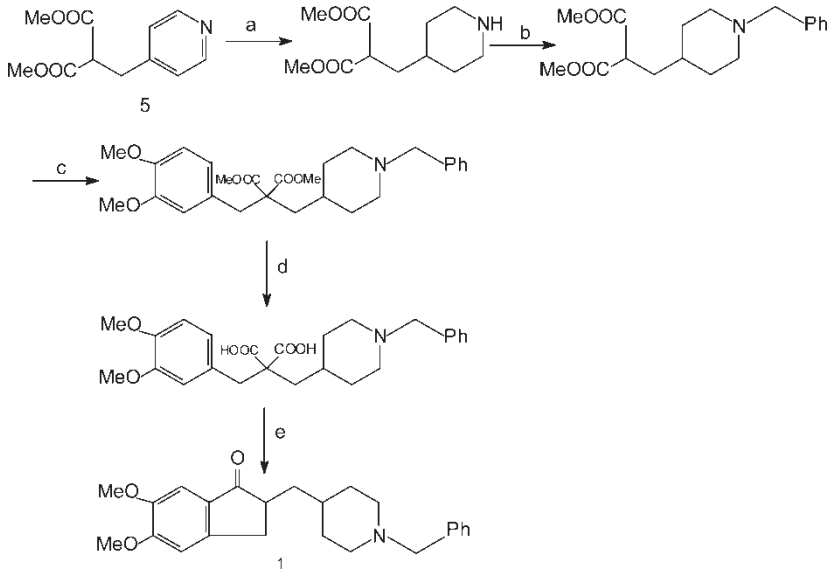
The process described is not suitable for large-scale production, because of subzero temperature requirements (−78°C) and use of raw materials such as BuLi, diisopropylamine, and THF/HMPTA that are either expensive, hazardous, or toxic. Anhydrous conditions are required to protect n-BuLi from moisture. Isolations of compounds **2** and **1** involve column chromatography, which is time-consuming and limits the batch size.

The other process reported for condensation of 5,6-dimethoxy-1-indanone (**3**) and 1-benzyl-4-piperidinecarboxaldehyde (**4**) employs sodium methoxide in THF solvent.[3] This process also has disadvantages such as the moisture-sensitive nature of sodium methoxide.

Gutman and his coworkers[4] established a new method for preparation of donepezil (**1**) (Scheme 2) using dimethyl-(4-pyridylmethylene)malonate (**5**) and 3,4-dimethoxy benzylchloride as key intermediates. The preparation of



Scheme 1. Reagents and conditions: a = n-BuLi/THF/HMPTA, −78°C, 2 h; b = H_2-10% Pd-C/THF, 25°C, 6 h; c = HCl-EtOAc.

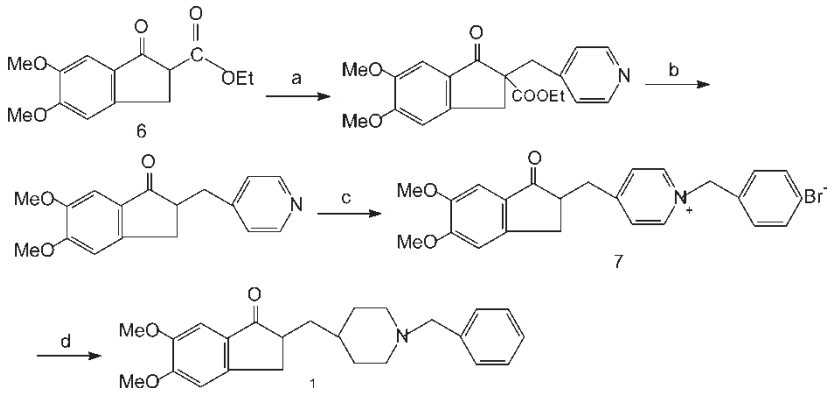


Scheme 2. Reagents and conditions: a = H_2-10% Pd-C/AcOH, 60°C; b = benzyl chloride/Na_2CO_3, 60–65°C, 12 h; c = 60% NaH/3,4-dimethoxy benzylchloride/THF, reflux; d = KOH, reflux; e = P_2O_5/methanesulphonic acid, 55–65°C.

intermediate dimethyl-(4-pyridyl methylene)malonate (**5**) involves the raw material 4-pyridinecarboxaldehyde, which is expensive and not readily available. The process is lengthy, and column chromatography is employed to isolate donepezil, thus rendering the process industrially unviable.

Iimura and coworkers[5] invented a novel method for the preparation of donepezil (**1**) (Scheme 3). The process involves the condensation of 5,6-dimethoxy-2-ethoxycarbonyl-1-indanone (**6**) with 4-pyridylmethyl chloride, in the presence of sodium hydride, followed by decarbalkoxylation, benzylation, and ring reduction of quaternary salt with platinum oxide. This process is also beset with the following disadvantages: 4-Pyridylmethyl chloride is a lachrymator and is not readily available. The preparation of this intermediate involves 4-picoline-N-oxide, which is hygroscopic. C-Acetylation of 4-picoline-N-oxide, hydrolysis, and chlorination are experimental conditions that cannot be handled easily at a plant level. The condensation reaction between **6** and 4-pyridylmethyl chloride requires anhydrous conditions. Hydrogenation of the quaternary salt **7** requires expensive PtO_2 catalyst.

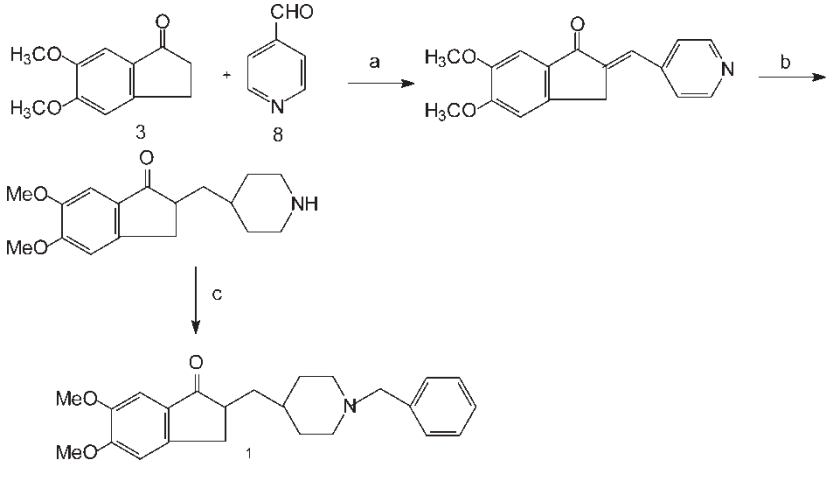
Chandrasekhar and his coworkers[6] prepared donepezil by condensing 5,6-dimethoxy-1-indanone (**3**) with 4-pyridinecarboxaldehyde (**8**) followed by catalytic hydrogenation and benzylation (Scheme 4). 4-Pyridinecarboxaldehyde is expensive and not commercially available, and benzylbromide used for benzylation is a severe lachrymator, posing difficulties on large scale.



Scheme 3. Reagents and conditions: a = 60% NaH/4-pyridylmethyl chloride; b = KOH/MeOH, reflux; c = benzyl bromide/CH_3CN, reflux; d = H_2-PtO_2, 25°C.

Several other syntheses of donepezil have been reported,[7] which are either too long or contain unacceptable operations and thus are not suitable for plant-scale operations.

We have focused primarily on the Sugimoto process of condensation of 5,6-dimethoxy-1-indanone (**3**) and 1-benzyl-4-piperidinecarboxaldehyde (**4**) (Scheme 1) to improve and render it economically viable. Alkalimetal carbonates are chosen as base instead of n-BuLi, and aqueous aliphatic alcohols are chosen as reaction media. Reaction is carried out at reflux temperatures, and hydrogenation of compound **2** is carried out in methanol instead of THF.



Scheme 4. Reagents and conditions: a = TsOH/toluene, reflux, 5 h; b = H_2-5% Pd-C/MeOH-HOAc, 60–65°C, 6.5–7.0 h; c = benzyl bromide/IPA: MeOH (1:1), 60–65°C, 11–12 h.

Thus we report herein an excellent synthetic method for condensation of commercially available 5,6-dimethoxy-1-indanone (**3**), with 1-benzyl-4-piperidenecarboxaldehyde (**4**), in the presence of potassium carbonate, in aqueous methanol medium at reflux temperature (Scheme 5).

The alkylidene derivative (**2**) is isolated by a simple crystallization technique with no need to carry out column chromatography. Yields are in the range of 75–80%, and purity of the product is >96% by high performance liquid chromatography (HPLC). This purity is sufficient to proceed to the next stage (hydrogenation).

Donepezil is prepared by carrying out hydrogenation of **2** with 10% palladium carbon as catalyst in methanol solvent at 25°C for 2 h. Here also the product is isolated without involving column chromatography.

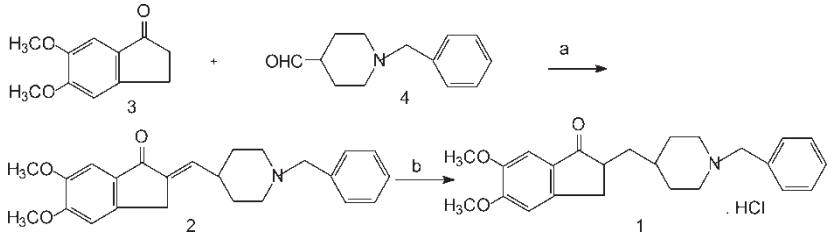
After hydrogenation of the intermediate **2**, thin-layer chromatography (TLC) of the reaction mass shows two polar impurities (**9** and **10**) in about 2% level.

In summary, we present an economically and industrially viable synthesis of donepezil HCl, which is obtained from 5,6-dimethoxy-1-indanone (**3**) in two steps by employing commercially available, less expensive, nontoxic raw materials by simplified experimental conditions and isolation procedures.

EXPERIMENTAL

Preparation of 1-Benzyl-4-[(5,6-dimethoxy-1-indanone)2-ylidenyl] methyl-piperidine (2)

5,6-Dimethoxy-1-indanone (**3**, 61 g, 0.32 mol) was dissolved in methanol (610 ml) under stirring at a temperature of 45–50°C. The solution was heated to reflux temperature. Aqueous potassium carbonate solution (potassium carbonate 305 g (2.20 mol), water 305 ml) was added to the reaction mass dropwise over 30–40 min. After an additional 20 min of stirring, 1-benzyl-4-piperidinecarboxaldehyde (**4**, 83.08 g, 0.409 mol) was added dropwise to the reaction mass. The pale brown suspension was maintained at a bath temperature of 75°C for a period of 2.5 h.



Scheme 5. Reagents and conditions: a = potassium carbonate, water/methanol, reflux, 2.5 h; b = H_2-10% Pd-C/MeOH, 25°C, 2 h, 1.5 N aqueous HCl.

The reaction mass was then cooled to room temperature, diluted with water (640 ml), and extracted with CH_2Cl_2 (600 ml × 2). The combined organic layer was washed with demineralized water (600 ml × 2), and the separated organic layer was dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to afford a brown solid. The solid was recrystallized in CH_2Cl_2/isopropylether to yield an off-white solid (92 g, 77%), mp 170–174°C.

Data

IR (KBr): υ 3003 (aromatic C-H), 2929 (aliphatic C-H), 1690 (>C═O), 1647 (C═C), 1603 (aromatic C═C). ^{1}H NMR (200 MH_Z, $CDCl_3$): δ 1.6–1.8 (m, 5H), 2.0–2.2 (m, 2H), 2.3–2.4 (m, 1H), 2.9–3.0 (m, 2H), 3.5 (s, 2H), 3.6 (s, 2H), 3.9 (s, 3H), 4.0 (s, 3H), 6.7 (d, 1H), 6.9 (s, 1H), 7.3–7.4 (m, 5H). ^{13}C NMR (200 MH_Z, $CDCl_3$): δ 29.2, 31.0, 37.0, 52.8, 55.76, 55.90, 63.17, 104.60, 106.95, 126.61, 127.82, 128.76, 131.41, 135.31, 137.94, 139.36, 144.15, 149.12, 154.92, 192.00. Mass (m/e) = 378.3 (M + 1), 271.1, 188.1.

Preparation of Donepezil HCl (1)

The compound **2** obtained (30 g, 0.079 mol) in methanol (600 ml) and 10% palladium carbon (3.0 g) was hydrogenated at room temperature and 1 atm for 2 h. Thin-layer chromatography (TLC) was checked for completion of reaction. The reaction mixture was filtered through a hyflow bed, and the filtrate was distilled off at temperatures less than 60°C under reduced pressure to yield a yellow product (31 g).

To this crude material, 1.5 N aqueous HCl (140 ml) was added and stirred for 15 min at room temperature. To this cloudy liquid, demineralized water (95 ml) was added and stirred for another 15 min at room temperature. The aqueous phase was extracted with EtOAc (2 × 65 ml), and the organic layer was discarded. The aqueous phase was extracted with $CHCl_3$ (2 × 190 ml). The organic layer was washed with demineralized water (2 × 190 ml). The aqueous layer was discarded. The organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated at temperatures less than 60°C under reduced pressure to yield an off-white foamy solid [25 g, donepezil HCl (**1**)].

The obtained solid was recrystallized in MeOH/isoprpoylether (1:1, 75 ml). After 1 h of stirring at 5°C, the product was filtered off, washed with isopropylether (100 ml), and dried in vacuum at 30 mm for 6 h at room temperature to afford donepezil HCl (21.6 g, 65%, 99.8% HPLC purity).

Data

IR (KBr): υ 3588.7 (>N-H), 3004.5 (aromatic C-H), 1684.6 (>C═O), 1316 and 1266.1 (-OCH_3). ^{1}H NMR (200 MH_Z, $CDCl_3$): δ 1.2–1.4 (m, 4H), 1.6–1.8 (t, 2H), 1.8–2.1 (m, 3H), 2.6–3.0 (m, 4H), 3.2–3.4 (dd, 1H), 3.45–3.55 (s, 2H), 3.9 (s, 3H), 4.0 (s, 3H), 6.9 (s, 1H), 7.2 (s, 1H), 7.3–7.4 (m, 5H). ^{13}C NMR (200 MH_Z, $CDCl_3$): δ 31.66, 32.87, 33.14, 34.27, 38.52, 45.25, 53.58, 55.83, 55.96, 63.21, 104.13, 107.16, 126.59, 127.84, 128.87, 129.03, 138.28, 148.42, 149.15, 155.16, 207.27. Mass (m/e): 380.1 (M + 1), 362.2, 288.1, 243.1, 172.1.

ACKNOWLEDGMENT

The authors thank the management of Natco Pharma Ltd. for supporting this work. The technical service from the analytical division of Natco Research Centre is gratefully acknowledged.

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