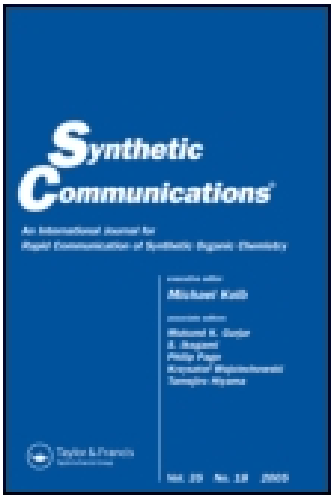

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New Synthesis of Donepezil Through Palladium-Catalyzed Hydrogenation Approach

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Abstract: A new, economical, and efficient process has been developed for large-scale synthesis of donepezil **1**, an anti-Alzheimer's drug. The process involves palladium-catalyzed hydrogenation of (2E)-5,6-dimethoxy-2-(pyridin-4-ylmethylene)indan-1-one **6** to provide 5,6-dimethoxy-2-(piperidin-4-ylmethyl)indan-1-one **8** as a key step.

Keywords: Anti-Alzheimer's drug, donepezil, economic synthesis, palladium-catalyzed hydrogenation

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INTRODUCTION

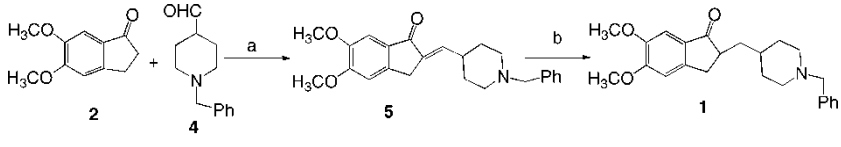
Alzheimer's disease, the most common cause of dementia, is a neurodegenerative disorder characterized by a progressive deterioration of memory and cognition.[1] Among the group of clinically useful marketed acetyl cholinesterase inhibitors, donepezil **1** is one of the promising agents for the treatment of this type of disease. It is effective for the treatment of various conditions involving memory loss, such as Alzheimer's disease and other neurodegenerative disorders.[2]

Sugimoto and coworkers[3] accomplished the synthesis of **1** with an overall yield of 27.4%, where in the aldol condensation of 5,6-dimethoxy-indan-1-one **2**, 1-benzyl piperidine-4-carboxaldehyde **4** served as a key step of synthesis to yield **5**, which upon debenzylation resulted donepezil **1** (Scheme 1). This process has additional obstacles for the large-scale production because of subzero temperature requirements ($-78^{\circ}C$) and hazardous chemicals such as n-butyl lithium.

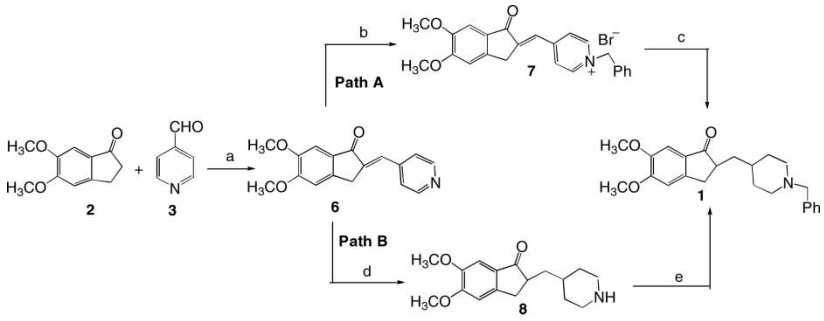
Several other syntheses of **1** have been reported,[4] which are either too long or contain unacceptable operations and thus are not suitable for large-scale preparation. Stephen Lensky[5] reported an efficient three-step synthesis for **1** involving hydrogenation of pyridine analogue **7** using expensive platinum oxide (Scheme 2, path A). This process was found to be highly expensive because of the high cost of platinum oxide. Attempts to replace platinum oxide with less expensive 5% palladium carbon always resulted in debenzylated products **8** and **11**.

In our approach **8** is identified as the suitable intermediate to prepare donepezil **1.** Reported synthesis[4a] of **8** involves five stages with much less overall yield and is commercially not feasible for large-scale production. Interestingly, no attempts were made in the literature to reduce the pyridine moiety of the potential and cheaply available intermediate **6**.

Here in we report an economic and efficient synthesis[6] (Scheme 2, path B) for donepezil **1**. The first step of our synthesis commenced from commercially available 5,6-dimethoxy-indan-1-one **2**, which was condensed with isonicotinaldehyde **3** in a modification of a literature procedure[5] to furnish the known intermediate **6** in 95.8% yield. With **6** in hand, hydrogenation of pyridine ring[7] was attempted utilizing palladium carbon. Two major impurities **9** and **10** (Fig. 1) were observed as a result of a competitive side reaction of



Scheme 1. Reagents and conditions: a = n-BuLi/THF/$-78^{\circ}C$/2 h, b = 10% PD-C/THF/rt/6 h.



Scheme 2. a = *P*-TSA/toluene/reflux/5 h; b = benzyl bromide/acetonitrile/reflux/2 h; c = PtO_2/MeOH/rt/24 h; d = 5% Pd-C/MeOH-HAc/60–65°C/6.5–7.0 h; e = benzyl bromide/IPA : MeOH (1 : 1)/60–65°C/11–12 h.

carbonyl moiety. With systematic screening of reaction conditions (reaction temperature, reaction time, hydrogen pressure, choice of solvent, etc.) the best result was obtained by hydrogenating **6** in methanol under a hydrogen pressure of 3.5–4.0 kg/cm^2 at 60–65°C for 6–7 h to accomplish **8** with 90% yield and 98.5% purity by HPLC. Finally in the last step, which involves benzylation of **8**, we learned that the nature of solvent and quantity of benzylbromide plays critical role in controlling obvious competitive dibenzyl product **12.** Our approach to understanding this benzylation chemistry began witha literature-reported procedure[4a] (benzyl bromide, IPE, 60–65°C, triethanolamine) that resulted in poor yield (19.5%) with dibenzylated impurity **12** (>15% by TLC). We tried solvents such as acetone, dichloromethane, acetonitrile, isopropylether, and dichloromethane, but they produced poor yields. Interestingly, usage of a 1 : 1 mixture of isopropylalcohol–water produced exclusively dibenzyl impurity **12.** Among the set of solvents screened treatment of **8** with 1 eq. of benzyl bromide/sodium

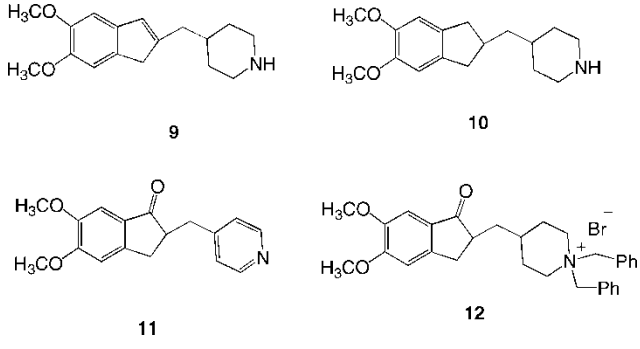


Figure 1. Observed process impurities.

carbonate in ethanol or 1 : 1 mixture of isopropanol–methanol produced fruitful results with satisfactory yield (65%) of **1**, as well facilitated ejecting an unwanted dibenzyl by-product as a filterable solid from the reaction mass. The spectroscopic data of our process samples **8** and **1** were well in agreement with those reported previously.[4a]

In summary, we present an economically competitive synthesis of donepezil **1**, which was obtained from 5,6-dimethoxy-indan-1-one **2** in three steps with overall yield of 56.0% using commercially available and less expensive raw materials and reagents. Although the moderate yield of the final step affected the overall yield of the process, the hydrogenation of (2E)-5,6-dimethoxy-2-(pyridin-4-ylmethylene)indan-1-one **6** in 90% yield employing less-expensive palladium carbon reduced the overall cost by twofold from that of the platinum oxide process.[5] To the best of our knowledge, our approach is the most economically advantageous among all the reported syntheses because of its yields and less-expensive raw materials and reagents.

EXPERIMENTAL

Experimental Procedure for 6

A mixture of compounds **2** (100.0 g, 0.52 mol), **3** (78.0 g, 0.728 mol), and *p*-toluene sulfonic acid (138.4 g, 0.804 mol) in toluene (1250 mL) were heated to reflux using a water separator for 6 h. The resulting solid was filtered and slurried in 10% $NaHCO_3$ solution (1200 mL) and filtered. The filter cake was washed with water (1000 mL) and dried at 80°C to afford pure **6** as pale yellow solid (140.0 g, 95.6%, 99.64% purity by HPLC).

Note

Initially hydrogenation of **6** was carried out using 5% Pd-C in neat acetic acid at 60–65°C and a hydrogen pressure of 4.0 kg/cm^2 for 16 h. HPLC analysis of the product yielded under these conditions recorded a content of 1.37% and 22.42% of **9** and **10** respectively. Interestingly, only impurity **9** was observed (18.9% by HPLC) when methanol was used as solvent in the presence of 1.2 eq. of acetic acid in these reaction conditions. Further optimization of time (6–7 h) and temperature (60–65°C) enabled these two impurities to be controlled to a level of $<0.25\%$ by HPLC.

Experimental Conditions for 8

The hydrogenation experiments were carried out in a clean and dry autoclave. The appropriate quantities of **6**, solvent, acetic acid, and the catalyst were

added. Before heating the autoclave to the required temperature, it was repeatedly purged first with nitrogen and then with hydrogen at room temperature in the absence of agitation. Once the required temperature was reached, hydrogen pressure was applied to obtain the desired pressure of hydrogen. As the reaction proceeded, the consumed hydrogen was replenished so as to maintain a constant pressure in the autoclave.

Experimental Procedure for 8

A mixture of compound **4** (100.0 g, 0.35 mol), 5% palladium on activated carbon (25.0 g), acetic acid (25.6 g, 0.42 mol), and methanol (1800 mL) were heated to 60–65°C at a hydrogen pressure of 4.0 kg/cm^2 for 7.0 h. Reaction was monitored until the content of **11** complied to a limit of 5–10% by TLC. After cooling the flask to room temperature, the catalyst was filtered off, the solvent was removed under vaccum, and the residue was dissolved in water (1000 mL). The aqueous solution was treated with dichloromethane (3 × 200 mL), basified to a pH of ~13.0, and extracted with dichloromethane (3 × 300 mL). Dichloromethane was dried and evaporated under vacuum and treated with n-heptane (500 mL) to afford a crystalline 5,6-dimethoxy-2-(piperidin-4-ylmethyl)indan-1-one **8** (92.0 g, 90.0%, 98.5% purity by HPLC).

Experimental Procedure for 1

A mixture of compound **8** (150 g, 0.519 mol), sodium carbonate (33.0 g, 0.311 mol), and 1 : 1 mixture of isoproponal and methanol (1500 mL) were heated to 60–65°C. Benzyl bromide (88.74 g, 0.518 mol) was added slowly, and the mixture was stirred at 60–65°C for 11 h. After cooling the flask to room temperature, the unwanted by-product **12** was filtered off, and water (1650 mL) was added to the filtrate. Then the pH of the aqueous solution was adjusted to 7.5–8.2 and was extracted with toluene (5 × 750 mL). The combined organic phases were distilled and treated with toluene–petether (150 : 300 mL) to precipitate donepezil free base as a white crystalline solid (128 g, 65.0%, 97.5% purity by HPLC).

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