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An Improved and Efficient Process for the Production of Donepezil Hydrochloride: Substitution of Sodium Hydroxide for *n*-Butyl Lithium via Phase Transfer Catalysis

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Abstract:

A simple, efficient and highly economic process for the production of donepezil hydrochloride (1), an anti-Alzheimer drug is reported. The process relies upon improved and large-scale synthesis of a key intermediate: 1-benzylpiperidine-4-carboxaldehyde (2), and the introduction of operationally simple chemistry at the penultimate stage wherein 2 is reacted with 5,6-dimethoxy indanone (3) in the presence of sodium hydroxide and a phase transfer catalyst (PTC) in a biphasic solvent to furnish the intermediate 4, which is reduced and directly treated with hydrochloric acid to furnish highly pure donepezil hydrochloride with desired polymorphic form. The improved process provides donepezil hydrochloride at considerably lower cost and allows the omission of hazardous chemicals.

Introduction

Process research and development in pharmaceutical companies aim to produce a process for the manufacture of a chemical intermediate or an active pharmaceutical ingredient (API) at minimal cost with high quality. However, the cost of the "product" is depend on the time of its inception in the market and decreases gradually as it becomes generic. Hence, the process chemistry plays an important role to gain the competitive advantage in pharmaceutical companies. In comparison, in the generic API industry, the issues are to be noninfringing and cost-effective all under stringent timeline. Exploring new routes or exploiting the existing chemical schemes to enhance the yield and quality are the potential solutions for the chemist engaged in the process development of generic APIs. In this report, we discuss our attempts to meet the process development aspects of donepezil hydrochloride (**1**), a well-known acetylcholinesterase inhibitor used for the treatment of Alzheimer's-type diseases such as memory loss and other neurodegenerative disorders.[1,2]

The first reported synthetic route by Sugimoto and coworkers[3] used a convergent approach to **1** with an overall yield of 27% that involved conversion of 1-benzyl-4-piperidone (**8**) to 1-benzylpiperidine-4-carboxaldehyde (**2**) in ether in the presence of *n*-butyl lithium (Figure 2). Condensation of **2** with 5,6-dimethoxy indanone (**3**) in the presence of a strong base such as *n*-butyl lithium and diisopropylamine in hexamethyl phosphoric amide (HMPA) under inert atmosphere at −78 °C, and finally catalytic reduction of the double bond compound **4** with 10% Pd/C in tetrahydrofuran (THF) furnished donepezil free base (Figure 1, Path A). This process suffered from several disadvantages: (a) use of hazardous and pyrophoric reagents such as *n*-butyl-lithium, (b) unacceptable process solvents such as hexane and HMPA, (c) the requirement for special equipment to attain the lower temperatures required for the condensation of **2** and **3** and (d) purification of **4** and free base of **1** by column chromatography.

Several other reported processes are either too long, lead to formation of several process-related impurities, use an expensive catalyst, or contain unacceptable operations such as palladium-catalyzed hydrogenation at pressures of 4 to 5 kg/cm^2 and thus are not safe for large-scale preparations[4–6] (Figure 1, paths B and C).

We report a scaleable and economic process for the large-scale synthesis (Scheme 1) of 1-benzylpiperidine-4-carboxaldehyde (**2**) starting from commercially available ethyl isonipecotate (**5**) followed by its condensation with 5,6-dimethoxyindanone (**3**) in the presence of sodium hydroxide (NaOH) under PTC conditions comprising water, dichloromethane (DCM), and a phase transfer catalyst to furnish **4** in 89% yield and 99.4% HPLC purity. This is followed by the reduction of **4** to furnish donepezil, followed by hydrochloride salt preparation in the same pot (Scheme 2).

Results and Discussion

Our focus during process development was mainly on three aspects: (a) developing an improved process for the manufacture of 1-benzylpiperidine-4-carboxaldehyde (**2**), (b) condensing intermediate **2** with **3** without hazardous or pyrophoric reagents or unacceptable process solvents and conditions, and (c)

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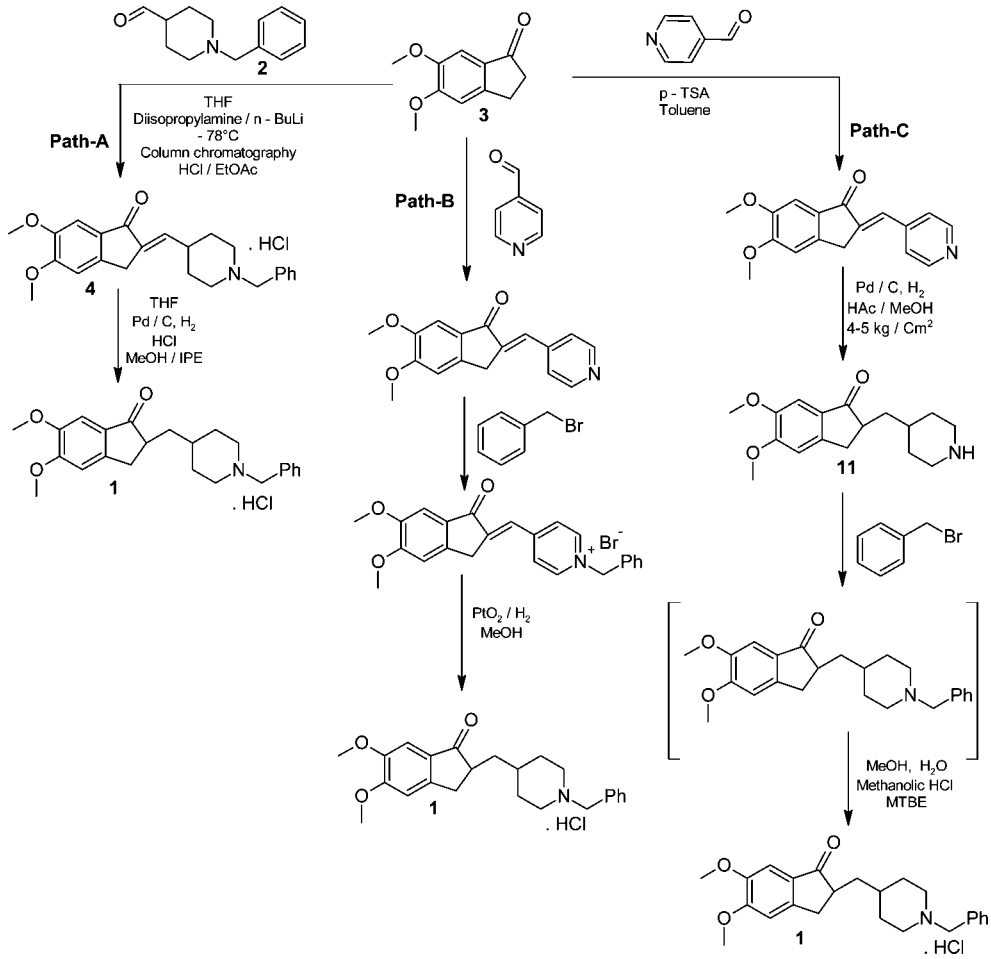
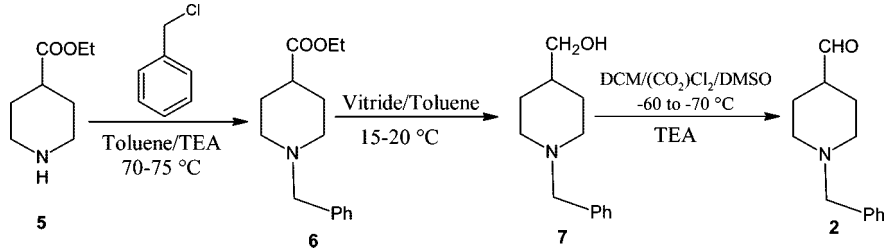


Figure 1. **Reported synthetic approaches for donepzil hydrochloride.**

Scheme 1. **Process for the preparation of 2**



isolation of the desired polymorphic form of the hydrochloride salt in desired purity while avoiding the isolation of the free base.

(a) Development of an Improved and Economic Process for Manufacture of 1-Benzyl Piperidine-4-carboxaldehyde (2). The 1-benzylpiperidine moiety, also present in a wide variety of bioactive compounds,[7] is the principle cost-contributing intermediate in the synthesis of donepezil hydrochloride. Reported approaches[3a,8] involve: (a) Wittig olefination of 1-benzylpiperidine-4-one (**8**) followed by acid hydrolysis to produce **2** (Figure 2, Path A); or (b) treating **8** with the expensive reagent trimethylsulphonium iodide followed by opening the obtained epoxide **10** with magnesium bromide in ether to yield **2** (Figure 2, Path B). Both approaches either require pyrophoric or expensive or unstable reagents, and flammable solvents or inconvenient workups make the process unsafe on large scale.

In our approach (Scheme 1) we used cheap and commercially available ethyl isonipicotate (**5**) as the starting material. Treatment of **5** with benzyl chloride in toluene in the presence of triethylamine afforded the compound **6** in 95% yield and 99% GC purity, which was reduced using Vitride in toluene solution to furnish the alcohol **7** in 97% yield and 97% GC purity. Swern oxidation of **7** furnished **2** in 73% yield and 98% GC purity after distillation.

(b) Condensation of Aldehyde 2 with 3. As it was clear that butyl lithium was not desired, we have tried optimizing

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(9) Progress of the reaction mass was monitored by HPLC with Inertsil C-18, 250 mm × 4.6 mm, 5 μm; mobile phase: buffer and methanol in the ratio of 50:50 (v/v); buffer: 0.1 M KH_2PO_4 in water at pH adjusted to 5−6 with triethylamine; flow rate: 0.9 mL/min: wave length: 230 nm.

Scheme 2. **Modified process for donepezil hydrochloride 1**

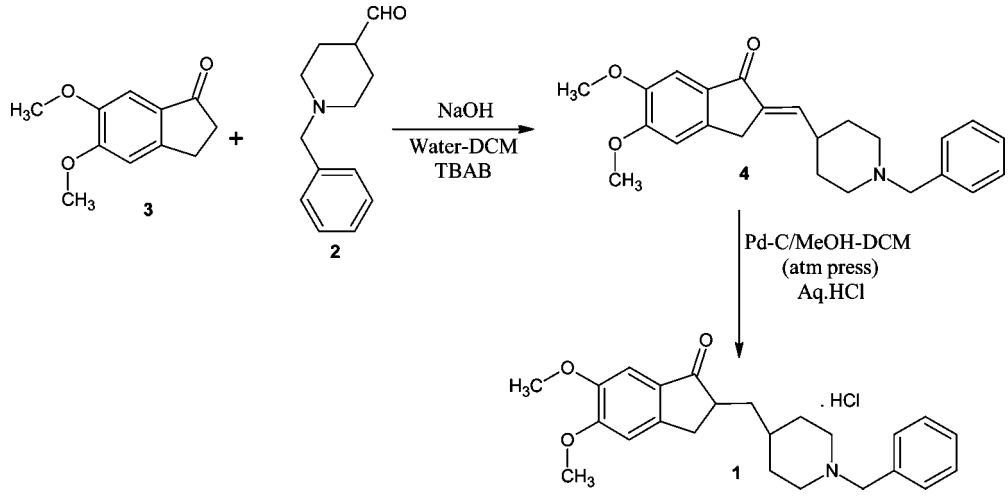

Table 1. **Efficiency of acetone and toluene system for purification of 4**

		HPLC purity of crude **4**		HPLC purity after recrystallization in acetone:toluene (5v/5v)	
s. no.	batch no.	**4** (%)	SMUI[a] (%)	**4** (%)	SMUI[a] (%)
1	DON/A031/1A/36	98.40	0.34	99.54	0.20
2	DON/A031/1A/37	93.57	2.84	99.21	0.41
3	DON/A031/1A/38	88.85	1.92	99.08	0.26

[a] SMUI = single maximum unknown impurities.

the condensation process using different bases such as sodium ethoxide, sodium methoxide, potassium *tert*-butoxide, potassium hydroxide, and sodium hydroxide in various solvents.

We were pleased to discover that the use of sodium hydroxide in the presence of a PTC such as tetrabutyl ammonium bromide in the mixed-solvent system such as water and either toluene or DCM yielded the donepezil precursor **4** in high yield and good purity. Such chemistry avoids (1) the use of the hazardous reagents *n*-butyl lithium and HMPA, (2) cryogenic temperatures, and (3) column purification. The combination of dichloromethane with water was chosen for further optimization as the toluene−water mixture posed a problem during the isolation of crude **4**, as toluene requires higher temperature for distillation and also forms an azeotrope with the water. The condensation reaction performed in the absence of PTC did not undergo completion even after 55−60 h at 40−45 °C and led to formation of several impurities with the yield of 55−60% in 70−75% HPLC purity.

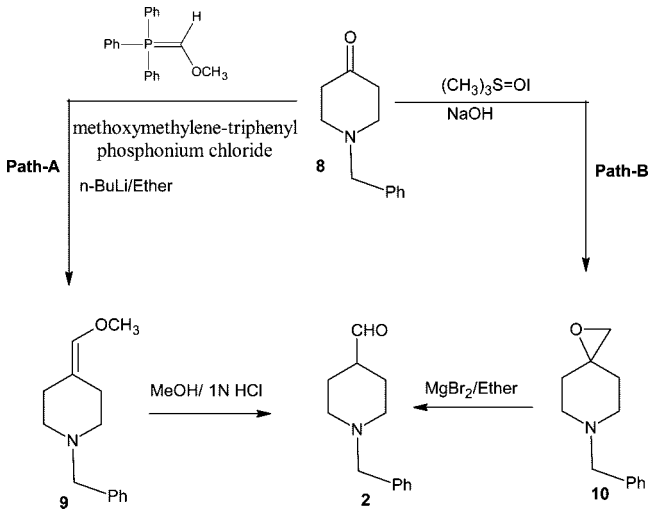

Figure 2. **Reported approaches for the preparation of 2.**

The workup process involves stripping the solvents at 40−45 °C followed by dilution with water and filtration to yield the crude intermediate (**4**) in quantitative yield. This was further purified by recrystallization in a mixture of acetone and toluene to produce 99% pure **4** in 88% overall yield. Crude **4** of 88.85%−98.40% purity could be efficiently purified (Table 1).

(c) Preparation of Donepezil Hydrochloride. The reduction of the exocyclic double bond of **4** was achieved by changing the published solvent, THF, to a 2:1 ratio of methanol and DCM. The reduction was performed using 10% Pd/C and once complete, the reaction mass was filtered. The organic layer was concentrated to yield the crude donepezil as a thick syrup containing around 80−90% of donepezil, ∼10−20% of the debenzylated impurity (**11**) and one unknown impurity ∼0.2% at 0.55 RRT. These impurities were efficiently removed by designing pH-based extractions. The thick syrup was diluted with water, the pH was adjusted to 1−2 with concentrated HCl, and the donepezil hydrochloride was extracted in dichloromethane. This was washed and concentrated to yield a thick syrup containing the donepezil hydrochloride in 99.0−99.6% HPLC purity with a drastic decrease in impurities (Table 2). A small additional purification has been attained by dissolution of the residue into water, adjusting the pH to 9−10, and extracting the donepezil into toluene. The toluene layer was distilled to yield a syrup containing donepezil of 99.7−99.8% HPLC purity. The salt was reformed by adding ethanol and water, and by adding conc. HCl until the pH of the mass was 2−3. The desired polymorph of donepezil hydrochloride was isolated by adding diisopropyl ether as an anti-solvent. The solid

Table 2. **HPLC analysis data of donepezil in the downstream process and after final isolation**

sr no.	batch no.	cmpd name	reaction mass (%)	residue after solvent distillation (%)	residue after acidic workup (%)	residue after basic workup (%)	final donepezil HCL purity (%)
1	DON[f-I]01PP08001	donepezil hydrochloride	79.93	79.80	99.62	99.81	99.91
		debenzylated impurity (**11**)	19.58	19.58	0.06	0.05	0.03
		0.55 RRT	0.23	0.23	0.03	0.03	0.02
2	DON[f-I]01PP08002	donepezil hydrochloride	86.53	85.95	99.69	99.75	99.92
		debenzylated impurity (**11**)	13.03	13.66	0.13	0.04	0.01
		0.55 RRT	0.24	0.22	0.04	0.03	0.03
3	DON[f-I]01PP08003	donepezil hydrochloride	88.27	88.27	99.80	99.85	99.92
		debenzylated impurity (**11**)	11.33	11.33	0.06	0.01	0.01
		0.55 RRT	0.24	0.24	0.04	0.03	0.02

crystals were filtered and dried under vacuum to yield **1** with 99.9% HPLC purity. Experimental results of pilot-plant batches are shown in Table 2.

Conclusion

A new, improved, cost-effective and scaleable process for donepezil hydrochloride (**1**) via condensation of **2** with **3** in the presence of PTC is provided.

Experimental Section

General. All reagents, solvents, and processing aids are commercial products and were used as received. For reactions run of pilot scale, glass-lined reactors having variable rate agitation, at −100 to 150 °C jacket temperature range, were used for the Swern oxidation. ^{1}H NMR spectra were recorded in $CDCl_3$ and DMSO using a Varian Gemini 400 MHz FT NMR spectrometer; the chemical shifts are reported in δ ppm relative to TMS.

Ethyl-1-benzylpiperidin-4-carboxylate (6). To a stirred solution of ethyl isonipecotate (**5**, 5.0 kg, 31.84 mol) in toluene (11 L) was added slowly the solution of benzyl chloride (4.04 kg, 31.84 mol) in toluene (5 L) at 10−15 °C over 2−3 h. Triethyl amine (3.85 kg, 38.21 mol) was charged, temperature of the reaction mass was raised to 70−75 °C and maintained for 6−7 h. Water (5 L) was added at 25−35 °C and stirred, and the toluene layer was separated from the reaction mass, washed with water (10 L), and distilled under vacuum to afford compound **6** as a syrup. Yield: 7.5 kg (95%); MS; *m*/*z* 248 ($M^+ + 1$). ^{1}H NMR ($CDCl_3$): δ 7.18−7.31 (m, 5 H), 4.09−4.14 (q, 2 H), 3.5 (s, 2 H), 2.8−2.9 (m, 4 H), 2.0−2.27 (m, 1 H), 1.74−1.88 (m, 4 H), 1.22−1.25 (m, 3 H); Purity by GC: 99.19%.

(1-Benzylpiperidin-4-yl)methanol (7). To a stirred solution of **6** (7.5 kg, 30.36 mol) in toluene (22.5 L), was added Vitride (10.51 kg, 36.43 mol, 70 wt %/wt in toluene) diluted with toluene (10 L) at 15−20 °C. The contents were stirred for 2−3 h at 25−30 °C, quenched slowly over 10% sodium hydroxide solution (3.75 L) and then with water (3.75 L). Contents were stirred for 30 min, and the toluene layer was separated, washed with water (4.0 L), and with a saturated solution of sodium chloride (4.0 L) and then distilled off to give compound **7** as a syrup. Yield: 6.03 kg (97%). MS; *m*/*z* 206 ($M^+ + 1$); ^{1}H NMR ($CDCl_3$): δ 7.22−7.31 (m, 5 H), 3.70 (s, 2 H), 3.45−3.48 (d, 2 H), 2.22−2.26 (m, 4 H), 1.94 (m, 1 H), 1.74−1.78 (m, 4 H); Purity by GC: 97.50%.

1-Benzylpiperidine-4-carbaldehyde (2). A stirred solution of dichloromethane (12 L) and oxalyl chloride (3.74 kg, 29.46 mol) was cooled to −65 to −60 °C, and the solution of dimethyl sulfoxide (3.53 kg, 45.26 mol) in dichloromethane (93 L) was added between −65 to −60 °C over 2−3 h. The solution of **7** (4.0 kg, 19.51 mol) in dichloromethane (12 L) was added over 1−2 h at −65 to −60 °C. The reaction mixture was stirred for 3−4 h, and then the temperature was raised to −50 to −45 °C. Triethyl amine (9.95 kg, 98.52 mol) was added followed by water (12 L), and the mixture stirred for 30 min before the separation of the organic layer. The organic layer was washed with water (6 L) at 10–15 °C, and the pH was adjusted with 1 N HCl until the aqueous layer showed pH 7−8. The organic layer was separated, washed with water (6.0 L), and distilled under 500−600 mmHg vacuum to furnish **2** as pure syrup. Yield: 2.89 kg (73%). MS; *m*/*z* 204 ($M^+ + 1$). ^{1}H NMR ($CDCl_3$): δ 9.65 (s, 1 H), 7.23−7.32 (m, 5 H), 3.48−3.50 (s, 2 H), 1.45−2.95 (m, 9 H). Purity by GC: 97.00%.

2-(1-Benzylpiperidin-4-ylmethylene)-5,6-dimethoxy-indan-1-one (4). A stirred solution of 5,6-dimethoxy indanone (**3**, 2.0 kg, 10.41 mol), dichloromethane (10 L), and TBAB (0.34 kg) was cooled to 15−20 °C. To the above solution was added 10% sodium hydroxide solution (7.0 L) over 1−1.5 h at 15−20 °C and stirred for 30 min. Further was added **2** (2.54 kg, 12.51mol) at 15−20 °C over 1−2 h, and the temperature was raised to 40−45 °C and maintained for 5−6 h. After completion of the reaction (by TLC, mobile phase: DCM:methanol: ammonia = 9:1:0.1 mL), the mixture was distilled to remove the dichloromethane. The suspension was diluted with water (20 L); the solid was filtered and washed with water to furnish crude **4**.The obtained crude **4** (3.9 kg wet weight) was dissolved in a previously mixed solution of toluene (10 L) and acetone (10 L) and stirred for 30 min at 55−60 °C. The solution was cooled to 5−10 °C and maintained for 1 h. The crystalline solid was filtered, washed with acetone (1.0L),and dried under vacuum (650−700 mmHg) to afford pure **4** as a white crystalline solid. Yield: 3.46 kg (88%). MS; *m*/*z* 378 ($M^+ + 1$): ^{1}H NMR (DMSO): δ 7.20−7.32 (m, 5 H), 7.13−7.15 (s, 1 H), 7.10−7.13 (s, 1 H), 6.4−6.45 (d, 1 H), 3.90 (s, 3 H), 3.80 (s, 3 H), 3.58−3.62 (s, 2 H), 3.43−3.46 (s, 2 H), 1.32−2.80 (m, 9 H). Purity by HPLC 99.54%.

Donepezil Hydrochloride (1). A mixture of **4** (1.0 kg, 2.65 mol), dichloromethane (5 L), methanol (10 L), and 10% palladium on carbon (50 gm, 50% wet) were cooled to 15−20 °C, and hydrogen gas was bubbled into the reaction mass until

the completion of reaction by HPLC.[9] The catalyst was removed by filtration, and the filtrate was distilled off to yield a thick residue. The residue was dissolved in dichloromethane (2.0 L), water was added (5.0 L), and the pH was adjusted between 1−2 using conc. hydrochloric acid; the mixture stirred for 15−20 min, and the organic layer was separated and stored. The aqueous layer was further extracted with dichloromethane (2.0 L × 2), the combined organic layer was washed with water and brine and distilled to yield the thick residue. The residue was dissolved in water (5.0 L), toluene was added (4.0 L), and the pH of the aqueous layer was adjusted to 9−10 using aqueous ammonium hydroxide. The toluene layer was separated, and the aqueous layer was re-extracted with toluene (2.0 L). The combined toluene layer was washed with water and brine and then distilled to get the residue. This was dissolved in ethanol (6.0 L) and water (0.35 L), and the pH of the resulting solution was adjusted to 2.0 to 2.5 using conc. hydrochloric acid. The mass was cooled to 0−5 °C, and diisopropyl ether was added (9.0 L); the mixture stirred for 1−2 h, and the obtained crystalline solid was filtered off and dried under vacuum at 50−55 °C to yield donepezil hydrochloride with desired polymorphic form characterized by PXRD. Yield 0.72 kg (63%); MS; *m/z* 380 ($M^+ + 1$). ^{1}H NMR (DMSO): δ 7.4 − 7.59 (m, 5 H), 7.08 (s, 1 H), 7.04 (s, 1 H), 4.25 (s, 2 H), 3.85 (s, 3 H), 3.77 (s, 3 H), 3.19−3.30 (m, 3 H), 2.50−2.90 (m, 4 H), 1.27−1.91 (m, 7 H).

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