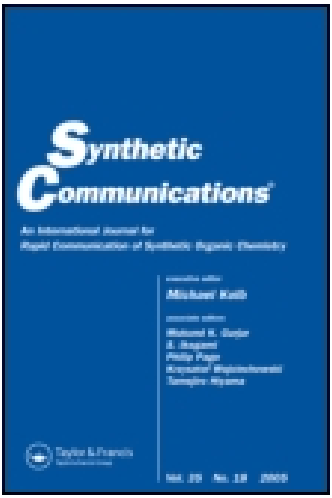

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Novel and Efficient Method to Synthesize N-Benzyl-4-Formyl-Piperidine

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Novel and Efficient Method to Synthesize N-Benzyl-4-Formyl-Piperidine

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ABSTRACT

A novel and efficient method was developed to synthesize N-benzyl-4-formyl-piperidine, a key intermediate of Donepezil (Aricept®). N-Benzyl-4-piperidone was reacted with dimethyloxosulfonium methylide to get epoxide, followed by rearrangement in the presence of magnesium bromide etherate to give target compound in high yield.

Key Words: N-Benzyl-4-formyl-piperidine; Epoxidation; Rearrangement.

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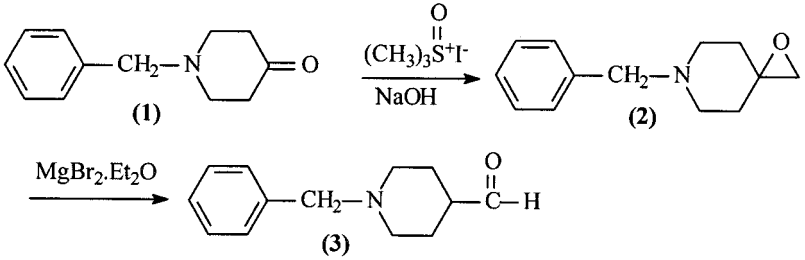
INTRODUCTION

Donepezil hydrochloride (Aricept®) is the most promising agent in the treatment of Alzheimer's diseases.[1] It was synthesized through the Aldol condensation of 5,6-dimethoxy-1-indanone and N-benzyl-4-formyl-piperidine, following double-bond reduction and hydrochlorination.[2] N-Benzyl-4-formyl-piperidine is the key intermediate of Donepeziln, and as reported in the literature, there are many approaches to its synthesis. Route A utilizes the Wittig reaction of (methoxymethyl) triphenylphosphonium chloride with N-benzyl-4-piperidone, followed by hydrolysis of the enol ether [2] to get the target compound. Similarly, in route B, trimethylsilyldiazomethane is condensed with N-benzyl-4-piperidone to get enamine, followed by hydrolysis to give the final product.[3] Route C is based on the partial reduction of N-benzyl-4-ethoxycarbonylpiperidine with sodium bis(2-methoxyethoxy) aluminum hydride (SMEAH) in the presence of N-methyl piperazine [4] or pyrrolidine.[5] All these methods commonly require expensive reagents, low temperature, and tedious procedures, thus we set out to find a more economical and efficient method.

There are many reports about the synthesis of aliphatic aldehyde via epoxide rearrangement catalyzed by mineral acid[6] or Lewis acid, such as boron trifluroride etherate,[7] magnesium bromide etherate,[8] lithium bromide,[9] and so on. Our literature survey showed there was no reference about the rearrangement of aza-cycle epoxide. So we tried the following new route to synthesize N-benzyl-4-formyl-piperidine (Sch. 1). The epoxide **(2)** was prepared from N-benzyl-4-piperidone **(1)** and dimethyloxosulfonium methylide[10] in high yield. Through wide scrutinization of catalysts in the rearrangement reaction of **(2)**, magnesium bromide etherate was picked out as the best one, and other factors affecting results of the reaction were carefully investigated. Results showed the title compound can be prepared economically and efficiently through this new route.



Scheme 1.

RESULTS AND DISCUSSION

In the course of our research, we found that catalysts played a crucial role in the rearrangement reaction of **(2)**. Two mineral acids (dilute sulfate acid, perchlorate acid) and several Lewis acids (boron trifluroride etherate, zinc chloride, aluminum chloride, lithium bromide, and magnesium bromide etherate) were tested in the course of the experiments. When diluted sulfate acid, perchlorate acid, or boron trifluroride etherate was used, no target compound was produced. The yields of the target compound were very poor (19%, 25%, and 27%, respectively) when zinc chloride, aluminum chloride, or lithium bromide was used as the catalyst, while magnesium bromide etherate showed promising results in a similar reaction condition. Three additional factors (catalyst/substrate ratio, solvent, and reaction temperature) affecting the results of the reaction were carefully investigated, as shown in Table 1.

The results in Table 1 show that changing solvents and temperature remarkably affected the yields of reactions. This was probably related to the solubility of magnesium bromide etherate in different solvents and temperature; it cannot be well dissolved in THF or Et_2O even under reflux, while in benzene, toluene, and chloroform, magnesium bromide etherate can be completely dissolved at about 40°C. When temperature rose to 50°C or higher, magnesium bromide etherate would partly decompose to lose diethyl ether and cause the reduction of yields. So we chose entry 8 as the optimum reaction condition.

Table 1. The selection of the reaction conditions.[a]

Entry	Solvent	Cat/sub (mol/mol)	Temp (°C)	Yield (%)
1	Et_2O	2/1	20	38
2	THF	2/1	40	45
3	$CHCl_3$	1/1	40	46
4	$CHCl_3$	2/1	40	82
4	Toluene	2/1	20	56
5	Toluene	2/1	40	83
6	Benzene	1/1	20	53
7	Benzene	2/1	20	65
8	Benzene	2/1	40	86
9	Benzene	3/1	40	82
10	Benzene	4/1	40	81
11	Benzene	2/1	60	65
12	Benzene	2/1	80	58

[a]Magnesium bromide etherate was used as the catalyst.

EXPERIMENTAL

^{1}HNMR spectra were recorded on a Brucker ADVANCE-400 MHz spectrometer using $CDCl_3$ as solvent and $SiMe_4$ as internal standard. Infrared spectra were recorded on a Bruck Vector 200 spectrometer. ESIMS were measured on an ESQUIRE-LC-00075 spectrometer.

GENERAL PROCEDURE

At room temperature, to a well-stirred mixture of N-benzyl-4-piperidone **(1)** (18.9 g, 0.1 mol), $(CH_3)_3S^+OI^-$ (24.2 g, 0.11 mol), and tetrabutylammonium bromide (0.5 g, 1.5 mmol) in 200 mL toluene, was added dropwise a solution of NaOH (6.0 g, 0.15 mol) in 60 mL of water. The resulting mixture was warmed to 80°C and stirred for 4 h. The organic phase was separated and the water phase was extracted with toluene. The combined organic phase was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give epoxide **(2)** (19.2 g, 94.6% yield), which could be directly used in the next reaction without further purification. Infrared (IR) (KBr, cm^{-1}): 3028, 2919, 2799, 1598, 1495, 1452, 1129, 739. ^{1}H-NMR: δ 1.49 (2 H, m, C-CH_2), 1.76 (2 H, m, C-CH_2), 2.50 (6 H, m, 2N-CH_2, O-CH_2), 3.53 (2 H, s, N-CH_2-Ph), 7.20 (5 H, m, Ph).

Freshly prepared magnesium bromide etherate (0.2 mol) was dissolved in 200 mL anhydrous benzene, warmed to 40°C, and a solution of epoxide **(2)** (20.3 g 0.1 mol) in 20 mL anhydrous benzene was added in one portion. The mixture was stirred for 20 min, quenched by 50 mL of water, and extracted with ethyl acetate. The extracts were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give crude product, and then purified by reduced pressure distillation [boiling point (bp) 126–128°C/0.12 kpa, (5) 130–134°C/1 mmHg] to get colorless oil 17.5 g (86.2% yield). IR (KBr, cm^{-1}): 3027, 2922, 2804, 2760, 1723, 1601, 1452, 738. ^{1}HNMR: δ 1.71 (2 H, m, C-CH_2), 1.90 (2 H, m, C-CH_2), 2.12 (2 H, m, N-CH_2), 2.28 (1 H, m, CH), 2.83 $\sim$ 2.87 (2 H, m, N-CH_2), 3.54 (2 H, s, N-CH_2-Ph), 7.28 (5 H, m, Ph), 9.68 (1 H, d, J = 1.2 Hz, H-C=O). MS (ESI): m/z 204 (M + H).

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