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An Improved Process for the Synthesis of 5-Bromo-3-(1-methylpiperidin-4-yl)-1*H*-indole: A Key Intermediate in the Synthesis of Naratriptan Hydrochloride

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Abstract:

An improved process has been developed for the synthesis of 5-bromo-3-(1-methylpiperidin-4-yl)-1*H*-indole, a key intermediate of naratriptan hydrochloride, which is used as a drug for migraine. A novel one-pot synthetic procedure using triethyl silane was developed for scale-up.

Introduction

Naratriptan is an important drug for the treatment of acute attack of migraine,[1] exhibiting high affinity for 5-HT_{1D} receptor.[2,3] It acquires the majority of market as migraine drugs. In the literature, many processes are described for the synthesis of naratriptan.[4−7] An important route for the synthesis of naratriptan is shown in Scheme 1 and the interesting key intermediate in the synthesis is 5-bromo-3-(1-methylpiperidin-4-yl)-1*H*-indole (**4**). Preparation of **4** involves the condensation of *N*-methylpiperidone **2** with 5-bromoindole (**1**) under basic conditions to give (**3**), which on catalytic hydrogenation gives **4**. Reduction of **3** may be done by using $NaBH_4$/AcOH,[13−16] which overcomes the difficulties of handling catalytic hydrogenation.

In general, alkylation on the C3 of indole includes use of alkyl halides under basic conditions, which suffers from low efficiency and regioselectivity (C3 to N1). Aldehydes and ketones can be used as alkylating agents; under basic conditions they give alkenes, which require reduction, an additional step. However, in acidic conditions they invariably give bis derivatives. Silane reduction[8−12] is preferred to the above-mentioned methods, as it gives **4** without the formation of intermediate **3**.

Results and Discussion

Synthesis of 5-bromo-3-(1-methylpiperidin-4-ly)-1*H*-indole (**4**) (Scheme 2) involves condensation of **1** and **2**, in the presence of KOH and ethanol as solvent at reflux temperature,[4,5] followed by reduction of **3**. During our optimization experiments, we found that the purification of unreacted **3** from **4** is difficult, leads to low yield, and also produces many impurities in the final product **4**. To obtain **4** in good yield, without impurity **3** (less than 0.05%), sodium borohydride reduction was optimized by varying different parameters (Table 1). Better results were obtained with sodium borohydride and acetic acid at a temperature range of 40−45 °C (entry 2, Table 1). Other advantages of the use of sodium borohydride are lower cost and easy handling.

A novel route has been developed for the synthesis of **4** by using silane for reductive alkylation (Scheme 3). The author[12] noted that very strong acid and very weak acids are not active in reductive alkylation, in our experiments, we found that strong acid can be used (Table 2) with triethylsilane for reductive alkylation, but weak acids fail to give the desired product. The reductive alkylation process has the advantage of less reaction time (30 min to 3 h) and also reduces the isolation of intermediate **3**. The optimized process gives good yield and purity in shorter time (entry 5, Table 2).

Conclusion

We have developed a scaleable process for the synthesis of 5-bromo-3-(1-methylpiperidin-4-ly)-1*H*-indole (**4**) by

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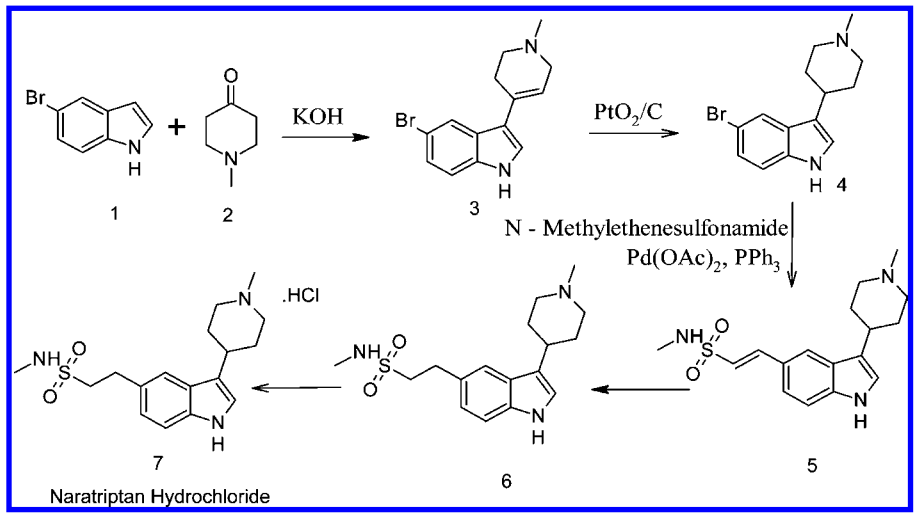
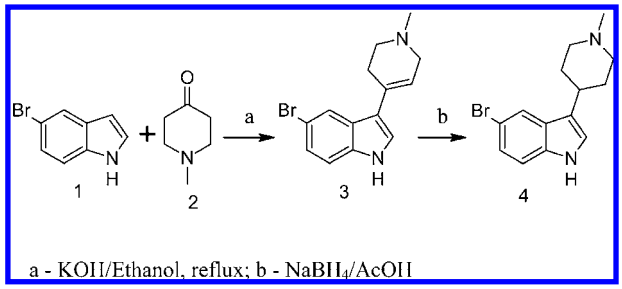
Scheme 1. **Naratriptan hydrochloride**



Scheme 2



Scheme 3

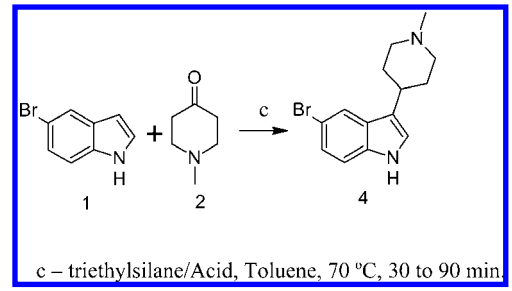


Table 1. **Experimental results of $NaBH_4$ reduction**

sl. no.	$NaBH_4$[a]	acetic acid[a]	temperature (°C)	% yield	% purity[b]
1	2	3	RT	95.4	96.3
2	2	3	45	98.9	99.5
3	3	3	RT	91.4	92.0
4	3	3	45	93.2	93.5
5	3	4	RT	80.5	90.5
6	3	4	45	85.6	92.3
7	3	5	RT	93.0	92.8
8	3	5	45	94.7	95.1
9	5	7	RT	82.0	93.5
10	5	7	45	84.8	96.1

[a] Taken in terms of mol equiv with respect to product **3**. [b] Purity is obtained by HPLC analysis. RT - room temperature 23 to 26 °C. % yield as on isolated basis.

Table 2. **Experimental result of triethylsilane reduction**

sl. no.	acids	% yield	purity[a]
1	Cl_3CCOOH	21.5	99.2
2	CF_3COOH	23.2	99.3
3	CH_3COOH	22.1	99.2
4	H_2SO_4	79.2	99.5
5	CH_3SO_3H	96.8	99.8
6	CF_3SO_3H	91.2	99.6

[a] Purity is obtained by HPLC analysis; % yield and purity obtained after column purification.

reduction of **3** with sodium borohydride. A new one-pot process for the synthesis of **4** by reductive alkylation method using triethylsilane in methanesulfonic acid has also been developed.

Experimental Details

All reagents and solvents were used as received from commercial suppliers, unless otherwise stated. All equipment was inspected visually for cleanliness and integrity before use. Analytical HPLC was performed on an Agilent 1200 system with UV detection at a wavelength of 230 nm using Inertsil 3 V ODS 5 μ 4.6 mm × 250 mm column, and eluting with the 0.1% *o*-phosphoric acid solution/acetonitrile (7:3). Melting point was determined using a Buchi melting point B-540 model and are uncorrected.

Experimental Procedure

5-Bromo-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-ly)-1*H*-indole (3). A 2-L reactor charged with 5-bromoindole (**1**) (500 g, 2.5 mol), *N*-methyl-4-piperidone (**2**) (317.1 g, 2.8 mol), KOH (28.6 g, 0.5 mol), and 1500 mL of ethanol. The solution was heated to reflux for 7 h. The solution was cooled to 0−5 °C, the separated solid was filtered, washed with 300 mL of cold ethanol, and dried in oven at 50 °C under reduced pressure to give 658 g (95%) of product. Mp: 266−268 °C. Purity 99.5% by HPLC, *m*/*z* 291 and 293 with 1:1 intensity.

5-Bromo-3-(1-methylpiperidin-4-ly)-1*H*-indole (4) Using $NaBH_4$. A 2 L reactor charged with **3** (250 g, 0.86 mol), $NaBH_4$ (65 g, 1.72 mol), 1250 mL of tetrahydrofuran. The solution was heated to 45 °C. Acetic acid (123.8 g, 2.58 mol) was added dropwise over a period of 1 h; the solution stirred for 2 h at 45 °C. Slowly the 150 mL of conc. HCl added was added, and the mixture was cooled to room temperature. Water (1500 mL) was poured into the mixture, and the THF was distilled off. The sticky, separated solid was stirred at 5 °C for 30 min and basified to pH 8 using 10% $NaHCO_3$. The separated solid was

filtered and dried in an oven at 50 °C under reduced pressure to give 250.5 g (99.5%) of product. Mp: 169−171 °C. Purity 99.8% by HPLC.

5-Bromo-3-(1-methylpiperidin-4-ly)-1*H*-indole (4) Using Triethylsilane. A 2-L reactor was charged with triethylsilane (445.4 g, 3.84 mol), methanesulfonic acid (184.3 g, 1.92 mol), 5-bromoindole (**1**) (250 g, 1.25 mol), and toluene (1 L). The solution was heated to 70 °C, and a solution of *N*-methyl-1-piperidone (**2**) (159 g, 1.4 mol) in toluene (250 mL) was added dropwise. The resulting solution was heated to 70 °C for 30 min to drive the reaction to completion as judged by HPLC. The solution was cooled to 5 °C and quenched with 10% aqueous sodium bicarbonate (1 L). Solid that separated in the biphase system was filtered, washed with water (500 mL), and dried in an oven at 50 °C under reduced pressure to give 373.7 g (91.2%) of product. Mp: 169−171 °C. Purity 98.5% by HPLC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (1H, b) for indole N−H confirmed by D_20 exchange. ^{1}H NMR δ 7.76 (1H, s), 7.25 (2H, m), 6.98 (1H, s), 3.01 (2H, d), 2.75 (1H, m), 2.36 (3H, s), 2.15 (2H, m), 2.03 (2H, d), 1.82 (2H, q). ^{13}C NMR ($CDCl_3$, 300 MHz) δ 32.80 (2C, d), 46.42 (1C, s), 56.30 (2C, s), 112.50 (2C, d), 120.96 (1C, s), 121.66 (1C, s), 124.72 (2C, s), 128.44 (1C, s), 135.01 (1C, s). *m*/*z* 293 and 295 with 1:1 intensity.

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