

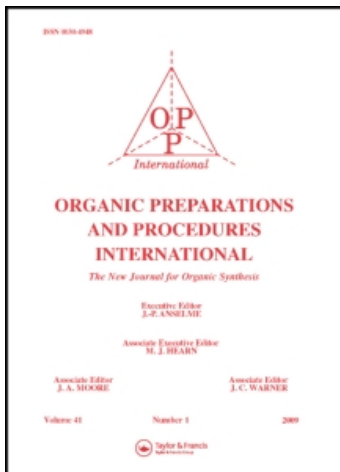
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Organic Preparations and Procedures International

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t902189982>

IMPROVED SYNTHESIS OF MIRTAZAPINE

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To cite this Article Rao, D. V. N. Srinivasa , Dandala, R. , Handa, V. K. , Sivakumaran, M. , Reddy, A. V. Raghava and Naidu, A. (2007) 'IMPROVED SYNTHESIS OF MIRTAZAPINE', *Organic Preparations and Procedures International*, 39: 4, 399 – 402

To link to this Article: DOI: 10.1080/00304940709458595

URL: <http://dx.doi.org/10.1080/00304940709458595>

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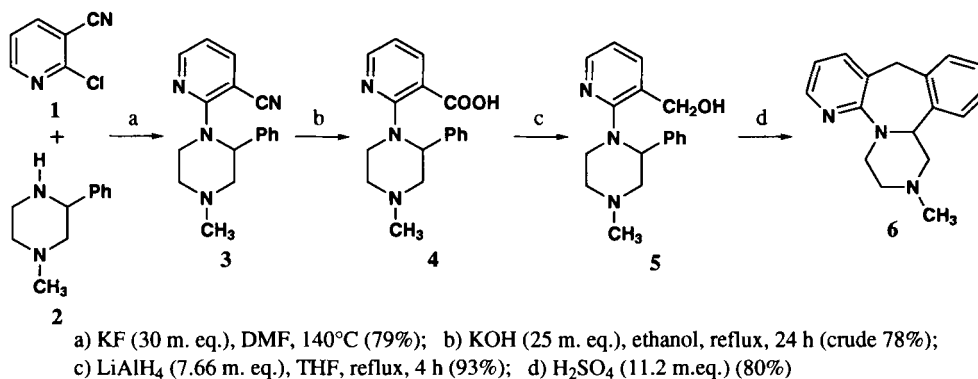
Submitted by
(11/27/06)

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Mirtazapine (**6**) has a tetracyclic chemical structure and belongs to the piperazino-azepine group of compounds with anti-depressant therapeutic effects. Mirtazapine is a racemate consisting of two pharmacologically active enantiomers, both of which contribute to the therapeutic effect.^{1,2} Three methods have been reported in the patent literature to prepare *mirtazapine*.³⁻⁵ The most studied synthesis of *mirtazapine*³ (Scheme 1) has some disadvantages in each stage, such as the need for column chromatography during the isolation of cyano compound (**3**), the use of large quantities of potassium hydroxide (~25 molar equivalents) and long reaction



Scheme 1

times (~25 h) during the preparation of carboxy compound (**4**); in addition, the use of lithium aluminum hydride (~7 molar equivalents) greatly enhances danger of fire hazard in commercialization during the preparation of hydroxymethyl compound (**5**), and the formation of lumps during the dehydrative cyclization to *mirtazapine* (**6**) slows down the completion of the reaction considerably. Some modifications have been suggested to overcome the drawbacks of the original sequence. Singer *et al.*⁴ reported a method for the hydrolysis of **3** to **4** with potassium hydroxide (11 molar equivalents) at higher temperature (140-145°C) and pressure. Although this modification has the advantage of reducing the time of the reaction and the amount of base, it is

necessary to conduct the reaction in an autoclave. Consideration of foregoing problems and limitations, led us to undertake an investigation to develop a process, which is cost effective and convenient for commercialization by systematically solving the problems associated with the above reported process at every stage.

During the condensation of 1-methyl-3-phenylpiperazine⁶ with 2-chloronicotinonitrile in dimethylformamide using potassium fluoride, two major impurities identified as 2-dimethylamino-3-cyanopyridine and 4-formyl-1-methyl-3-phenylpiperazine, were formed in 17% and 25%, respectively. These impurities were shown to be generated from the hydrolysis of dimethylformamide, to formic acid and dimethylamine in presence of strong base at higher temperatures. Reaction of dimethylamine with **1** leads to 2-dimethylamino-3-cyanopyridine while formylation of **2** accounts for the formation of 4-formyl-1-methyl-3-phenylpiperazine; the validity of these reactions was confirmed by independent synthesis.

Once the behavior of this condensation reaction was understood, experiments were carried out under nitrogen and it was found that formation of these impurities were under control (<5%) and thus purification of **3** is not required. It is likely that, the gaseous side-product, dimethylamine, is driven out during the operation. In the next step, alkaline hydrolysis of this crude material provides highly pure carboxylic acid **4**. We attempted to hydrolyze the cyano group of compound **3** by different known methods and found that hydrolysis proceeds rapidly at higher temperatures. An increase in the temperature accelerated the hydrolysis and with a lesser molar quantity of base. Replacement of ethanol with high boiling ethylene glycol in the presence of sodium hydroxide (7 molar equivalents) reduced the time cycle for completion of the reaction (7 hrs) at 130°C, thus avoiding the need to use an autoclave. Carboxylic acid **4** was reduced to carbinol **5** in 97% yield with commercially available *synhydride* [sodium bis(2-methoxyethoxy)aluminum hydride] in toluene, thus avoiding the use of hazardous lithium aluminum hydride and of expensive tetrahydrofuran. Finally, the cyclization step was simplified by controlled addition of a solution of carbinol **5** in methylene chloride to sulfuric acid, thus eliminating the problems associated with the lumps; the product was obtained in 91% yield and high purity.

In summary, we report a simplified route for the synthesis of *mirtazapine*. This procedure is industrially less problematic and has the advantage of higher yields, mild reaction conditions, easier work-up, shortened reaction times. Mirtazapine thus obtained is highly pure making this process an attractive alternative to the reported procedures.

EXPERIMENTAL SECTION

Mps were determined using Polmon melting point apparatus and are not corrected. ¹H NMR spectra were recorded on Bruker 300 MHz spectrometer in deuteriochloroform. Chemical shifts are reported in δ from tetramethylsilane as an internal standard. The electrospray ionization mass spectra were determined on Perkin Elmer PE SCIEX-API 2000 mass spectrometer.

Synthesis of 1-(3-Cyanopyridyl-2)-2-phenyl-4-methylpiperazine (3).- To a stirred solution of 1-methyl-3-phenylpiperazine (125 g, 0.71 mol) and 2-chloronicotinonitrile (98.4 g, 0.71 mol) in dimethylformamide (525 mL), was added anhydrous potassium fluoride (123.6 g, 2.13 mol) while nitrogen was bubbled through. The temperature was maintained at 140°C with stirring. The progress of the reaction was monitored by HPLC. After 6 hrs, dimethylformamide was removed by distillation under reduced pressure. The concentrated mass was cooled and water (625 mL) was added. The product was extracted into ethyl acetate (1 x 500 mL, 1 x 250 mL) and the combined ethyl acetate extract was washed with 10% aqueous sodium chloride solution (125 mL). The ethyl acetate layer was dried and evaporated under reduced pressure to afford the product (195.5 g, 99%) as a dark brown viscous oily residue. This product was hydrolyzed as such in the next stage.

Synthesis of 1-(3-Carboxypyridyl-2)-2-phenyl-4-methylpiperazine (4).- Compound 3 obtained above and sodium hydroxide (168.8 g, 4.44 mol) were added to ethylene glycol (400 mL) and heated to 130°C for 7 h. with stirring. The reaction mass was cooled to 30°C and water (750 mL) was added. The pH was adjusted to 6.5-7.0 with conc. hydrochloric acid and the product was extracted into methylene chloride (4 x 1000 mL). The methylene chloride layer was evaporated under reduced pressure and ethanol (400 mL) was added to precipitate the product. The precipitated product was collected and dried to give 132 g (63%) of 4 as a white solid, mp. 160-161°C, *lit.*³ 161-162°C. ¹H NMR: δ 2.45 (s, 3H, N-CH₃), 2.55-3.50 (m, 6H, C₃H₂, C₅H₂ and C₆H₂), 4.80 (dd, 1H, C₂H), 7.12-8.53 (m, 8H, Ar-H); mass m/z: 298.0.

Synthesis of 1-(3-Hydroxypyridyl-2)-2-phenyl-4-methylpiperazine (5).- To a suspension of compound 4 (100 g, 0.34 mol) in toluene (750 mL), was added sodium *bis*(2-methoxyethoxy)aluminum hydride (91.70 g, 0.84 mol) under a nitrogen atmosphere. After 2h. at 55-60°C with stirring, the mass temperature was cooled to 10°C, and 20% sodium hydroxide solution (220 mL) was added. The organic layer was separated at 45-50°C, dried and was evaporated under reduced pressure. Diisopropyl ether (300 mL) was added to precipitate the product. The resulting precipitate was collected and dried to afford (92 g, 97%) of 5 as a white solid, mp. 124-125°C, *lit.*³ 124-126°C. ¹H NMR: δ 2.36 (s, 3H, N-CH₃), 2.29-3.18 (m, 6H, C₃H₂, C₅H₂ and C₆H₂), 4.62 and 4.86 (CH₂OH), 4.70 (dd, 1H, C₂H), 5.34 (brs, 1H, OH), 6.85-8.15 (m, 8H, Ar-H); mass m/z: 284.2.

Synthesis of Mirtazapine (6).- To conc. sulfuric acid (150 mL), was slowly added a solution of compound 5 (75 g, 0.26 mol) in methylene chloride (150 mL) at 38-42°C. After refluxing for 3 h. with stirring, the reaction mixture was poured into ice water (750 mL) while keeping the temperature below 30°C. The pH was adjusted to 10.5 with 20% sodium hydroxide solution and the product was extracted into methylene chloride (1 x 600 mL, 1 x 225 mL). The methylene chloride layer was dried and evaporated under reduced pressure and diisopropyl ether (160 mL) was added to precipitate the product. The precipitated product was collected and dried to afford (64 g, 91%) of 6 as a white solid having purity 99.9% by HPLC, mp. 115-116°C, *lit.*³ 114-116°C. ¹H

NMR: δ 2.33/2.96 (2 m, each 1H, C₃H), 2.36 (s, 3H, N-CH₃), 2.50/2.85 (2m, each 1 H, C₁H), 3.40/4.51 (2d, each 1H, C₁₀H), 3.49/3.69 (2m, each 1H, C₄H), 4.35 (dd, 1H, C_{14b}H), 6.70-8.16 (m, 7H, Ar-H).

Acknowledgment.- The authors thank the management of Aurobindo Pharma Limited and gratefully acknowledge the assistance of Mr. K. C. Vara Prasad in the preparation of the manuscript.

REFERENCES

1. T. de Boer, G. Maura, M. Raiteri, C. J. de Vos, J. Wieringa and R. P. Pinder, *Neuropharmacology*, **27**, 399 (1988).
2. T. de Boer, G. S. F. Ruigt and H. H. G. Berendsen, *Human Psychopharm*, **10**, S107 (1955).
3. W. J. van der Burg, *DE 2614406*; *Chem. Abstr.*, **86**, 29883b (1977).
4. C. Singer, A. Liberman and N. Finkelstein, *PCT WO 0062782*; *Chem. Abstr.*, **133**, 321900d (2000).
5. K. Iishi and K. Yoshikawa, *US Patent 6,437,120*; *Chem. Abstr.*, **135**, 33494y (2001).
6. D. V. N. Srinivasa Rao, D. Ramesh, V. K. Handa, M. Sivakumaran and A. Naidu, *Arkivoc*, **14**, 1 (2006).
