AN EFFICIENT PROCESS OF ONDANSETRON SYNTHESIS

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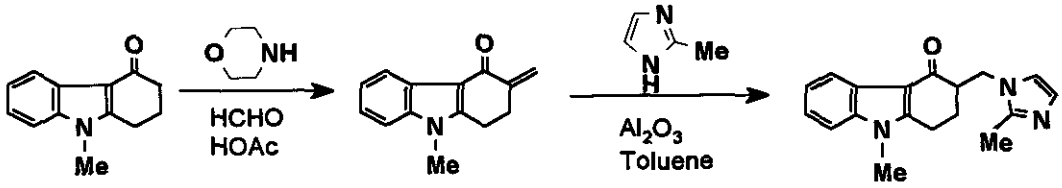
Abstract - An efficient and practical two-step synthesis of ondansetron (1) was accomplished from readily available *N*-methyltetrahydrocarbazolone (2) *via* direct Mannich α-methylenation and alumina catalyzed Michael addition resulting in a 70% overall yield

Ondansetron (1), a tetrahydrocarbazolone derivative with imidazolylmethyl group, is one of the potent selective 5-HT_3 receptor antagonists used to prevent severe vomiting caused by cancer chemotherapy and radiotherapy.[1] Several processes for the preparation of ondansetron have been published.[2] However, most of the published processes for ondansetron synthesis have drawbacks such as lengthy steps, the use of dangerous and expensive reagents, and steps involving technology that is not suitable for industrial scale use.

In this note we wish to describe a concise, efficient route for the production of ondansetron (1) from readily available *N*-methyltetrahydrocarbazolone (2)[3] employing direct Mannich α-methylenation and alumina catalyzed Michael addition of imidazole to exocyclic α,β-unsaturated ketone (3) as the key steps, as shown in the following Scheme.



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The introduction of α-methylene group to *N*-methyltetrahydrocarbazolone (2) by a known procedure[2a] involves several synthetic operations (α-dialkylaminomethylation, quaternization, and elimination). The application of other existing Mannich-related protocols[4] was unsatisfactory when applied to *N*-methyltetrahydrocarbazolone (2). After some experimentation, we found that simple treatment of *N*-methyltetrahydrocarbzolone (2) with paraformaldehyde or 37% aqueous formaldehyde solution in the presence of

catalytic or stoichiometric amounts[5] of a secondary amine (preferably morpholine) in refluxing acetic acid directly furnished the desired exocyclic α,β-unsaturated ketone (**3**). This product was then used for the next reaction without further purification (85% crude yield).

The conjugate addition of 2-methylimidazole to exocyclic α,β-unsaturated ketone (**3**) is known to proceed in low yield after a long reaction time (43%; 20 h).[2a] To our delight, alumina catalyzed conjugate addition of 2-methylimidazole to α-methylene ketone (**3**) under Pelletier's conditions,[6] followed by a simple workup, afforded a quantitative yield of ondansetron (**1**) as a colorless crystalline material in a much shorter reaction time (4 h).

In summary, a practical two-step synthetic Scheme for ondansetron synthesis was developed, based upon direct Mannich α-methylenation and alumina catalyzed Michael addition. Our present improved process for ondansetron synthesis proceeds in a 70% overall yield for two steps and is amenable to large-scale industrial synthesis.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker AC-200 spectrometer in $CDCl_3$ containing TMS as the internal standard. Chemical shifts are given in parts per million (ppm) downfield from TMS. Coupling constants (J) are given in Hz. Infrared (IR) spectra were recorded on a Midac M2000.

1,2-Dihydro-9-methyl-3-methylenecarbazol-4(3*H*)-one (3). The mixture of 1,2,3,9-tetrahydro-9-methyl-4*H*-carbazol-4-one (**2**, 50 mmol, 10 g) and morpholine (25 mmol, 2.2 mL) in 90 mL of glacial acetic acid was heated to reflux. To this refluxing mixture, paraformaldehyde (6.81 g) was added portionwise over 5 h. Alternatively, a 37% aquous formaldehyde solution (22.8 mL) was added dropwise over 5 h. After completion of the reaction, acetic acid was stripped off under reduced pressure and the residue was diluted with ethyl acetate. The organic layer was washed succesively with 10% aqueous hydrochloric acid, saturated sodium bicarbonate solution, water, and brine, and then dried over anhydrous magnesium sulfate. Evaporation of the solvent resulted in 9.02 g (85%) of residue, which was used for the next step without further purification. Purification of the crude material by silica gel chromatography (1:1 ethyl acetate/hexane) resulted in 7.5 g (70%) of the pure product. **3** : ^{1}H-NMR ($CDCl_3$) δ 3.00 (m, 4H), 3.70 (s, 3H), 5.36 (d, 1H, J = 1.5 Hz), 6.13 (d, 1H, J = 1.5 Hz), 7.29 (m, 3H), 8.32 (m, 1H); IR (KBr) 1651, 1593, 1576, 1478, 1468 cm^{-1}

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1*H*-imidazol-1-yl)]-4*H*-carbazol-4-

one (1). The mixture of crude 1,2,3,9-tetrahydro-9-methyl-3-methylene-4*H*-carbazol-4-one (**3**, 42.75 mmol, 9.02 g), 2-methylimidazole (127 mmol, 10.5 g) and alumina (22 g) in 225 mL of toluene was heated to reflux for 4 h. The reaction mixture was cooled to rt and filtered. The filter cake was extracted with chloroform, and the alumina was filtered off. The chloroform layer was washed with water and brine succesively, and dried over anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure and trituration with 180 mL of ethyl acetate provided a white crystaline compound (**1**) (10.4 g) in an overall yield of 70% from *N*-methyl-tetrahydrocarbazolone (**2**). 1 : mp 223 ℃(decomp); ^{1}H-NMR ($CDCl_3$) δ 1.90 (m, 1H), 2.18 (m, 1H), 2.41 (s, 3H), 2.90 (m, 3H), 3.65 (s, 3H), 4.04 (dd, 1H, J = 8.8 Hz, 14 Hz), 4.63 (dd, 1H, J = 4.4 Hz, 14 Hz), 6.85 (d, 1H, J = 1 Hz), 6.88 (d, 1H, J = 1 Hz), 7.28 (m, 3H), 8.22 (m,1H); IR (KBr) 1622, 1578, 1481, 1458 cm^{-1}.

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5. Morpholine is regenerated in the course of reaction and thus it can be used in a catalytic amount.
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