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An easy method and two steps for synthesis of the medetomidine with high yield

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Abstract: A two step method (consisting of transformation of aldehyde to alcohol and addition of imidazole group) was used for the synthesis of naphtalenic derivative of medetomidine and the optimized conditions were then applied to the synthesis of medetomidine. Thus, after optimization of first step (preparation of chiral alcohol), the various reaction parameters that affect the yield of naphtalenic derivative of medetomidine following second step were determined. then produced alcohol was treated by TMS-imidazole in the presence titanium tetrachloride in anhydrous chloroform and the reaction mixture is worked up of by two step addition of sodium hydroxide. The same conditions applied in the synthesis of medetomidine has afforded the same result (99% yield). NMR spectra were obtained on a Bruker DPX-250 instrument (250 MHz for ^{1}H and 62.5 MHz for ^{13}C), and $CDCl_3$ and DMSO-d_6 were used as solvents; chemical shifts are reported in δ (ppm) from TMS for ^{13}C and ^{1}H. Gas chromatogram (GC) spectra were recorded on Varian (STAR 3400CX) spectrometer with a packed column (10% OV-101 CWHP 80/100, 2m x 1.8") and a He flow rate of 10 ml/min. Electronic ionization GC-MS spectra were recorded on a Varian (SATURN 4D) spectrometer using an ionization current of 8 μA with a capillary column (DB-5MS, 0.1 micron, 30 m x 0.250 mm). Only m/z values having intensities of more than 10% are given, and retention times are reported with a He flow rate of 10 ml/min. HPLC analyses were performed on a Knauer EA 4300F equipped with a UV detector (215 nm), model 2600, and a C_{18} column (250 x 4.6 mm) with an eluent (H_2O/EtOH, 25:75) flow rate of 1 mL/min. Melting points were obtained on a Mettler FP61 apparatus.

Keywords: Synthesis, Medetomidine, TMS-imidazole, Naphtalenic, 1-(Naphthalen-1-yl)ethanol**.**

Introduction

Medetomidine (4(5)-[l-(2,3-dimethylphenyl)ethyl] imidazole) (**4**) is an agonist of receptors as adrenergic alpha-2 in certain parts of the brain and is used in veterinary medicine for its analgesic and sedative properties [1,2]. It is the racemate of dexmedetomidine (its S-enantiomer) used by intensive care units and anesthesiologists, and marketed under the brand name precedex (Hospira, Inc.) in the United States. It is relatively unique in its ability to provide sedation without causing respiratory depression. Medetomidine is also an alternative, environmentally acceptable candidate antifouling biocide which impedes settlement of barnacles in the nanomolar range and replaces toxic antifouling coatings based on heavy metals [3-5].

The synthesis of medetomidine and other 4-benzyl-substituted imidazole was first reported (without yield notification) by the Farmos Group Limited in Finland (pathway I Scheme **1**) [6-8].

Another synthesis method was consisted to use 4-(1-tripheny1methyl) imidazolecarboxaldehyde as starting material (pathway II Scheme **1**) [9]. Addition of 2,3-dimethylphenylmagnesium bromide to this compound has led to the secondary carbinol which was easily oxidized to the ketone. Reaction of ketone with methyl magnesium bromide has given the tertiary carbinol. Simultaneous deprotection and dehydration followed

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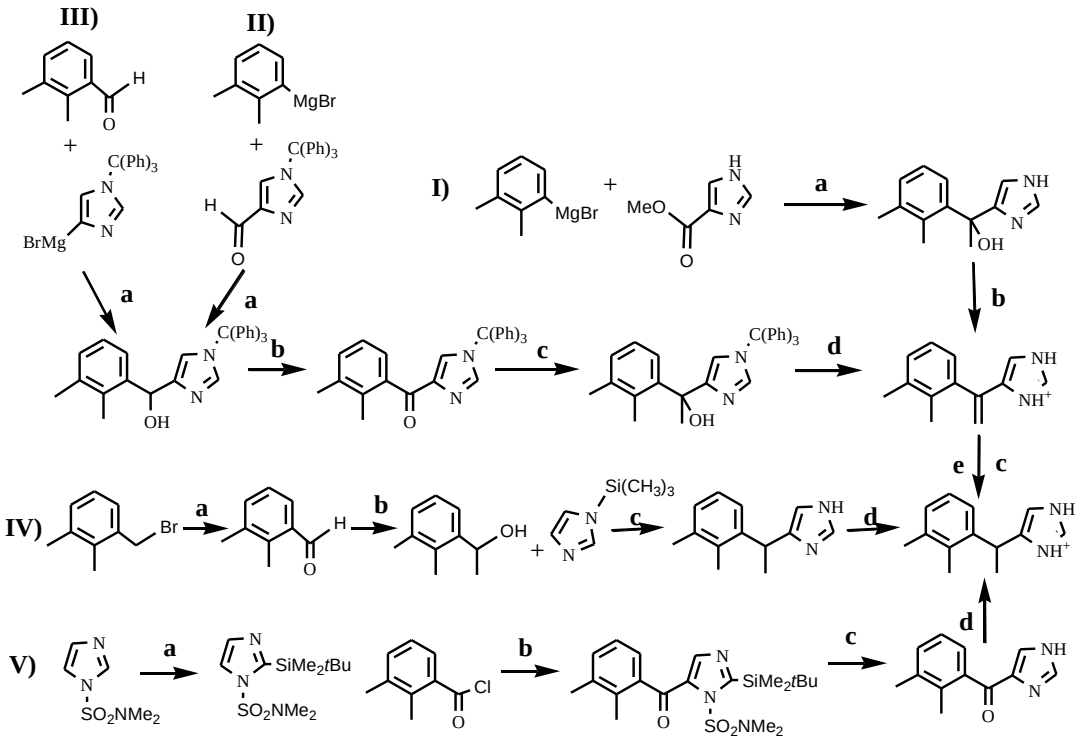
by hydrogenation of the double bond has led to medetomidine in 41 % overall yield. In another attempt to prepare medetomidine (without yield notification), the secondary carbinol was synthesized *via* 2,3-dimethyl benzaldehyde and 4-(1-tripheny1methyl) imidazole magnesium bromide (pathway III Scheme **1**) [10].

Medetomidine was also prepared in four steps in 79% overall yield from 1-(N,N-dimethylsulfamoyl) imidazole by bis protection, regioselective lithiation followed by an efficient tandem addition-reduction of the resulting 2,3-dimethylbenzoylchloride adduct with lithium/ammonia/ammonium chloride (pathway V, Scheme **1**) [11]. This method suffer from drawbacks such as two BuLi-metalations at -78 °C; use of Li in liquid ammonia at -78 °C and chromatographic purification.

More recent report (without yield notification) underlined the usage of 2,3-dimethyl benzaldehyde (commercial or synthesized form) and N-trimethyl silylimidazole for the preparation of medetomidine at relatively moderate temperature (pathway IV, Scheme **1**) [12, 13].



I: a) 1:MeMgBr, 2: H_2SO_4; b) $KHSO_4$, Heating; c) H_2, Pd/C (overall yield not reported) [6-8]. II: a) THF 0 °C; b) MnO_2, Dioxan, Reflux; c) MeMgBr, THF, 0 °C; d) Et_3SiH, CH_2Cl_2, CF_3CO_2H, -10 °C; e) H_2, Pd/C, 2N HCl, RT (~41% overall yield) [9]. III: a) 1h, RT; b) CH_2Cl_2, MnO_2, reflux, 2 h; c) 1:THF and Ar, MeMgBr, 0 °C, 2: stirring 3.5 h at 25 °C, 3: NH_4Cl; d) aq. HCl, reflux 2h; e) MeOH, Pd/C, H_2, stirred at 45 °C for 1.5 h (~60% overall yield) [10]. IV: a) 1: NaOEt,2-nitropropane, ethanol, r.t., 2: NaOH; b) MeMgBr, THF, r.t. ; c) CH_2Cl_2, $TiCl_4$, r.t.; d) HCl 37%, Toluene, Dean-Stark apparatus (overall yield not reported) [12, 13]. V): a) 1: BuLi, THF, -78 C, 0.5 h, 2: TBDMSCl, r.t., 3h; b) 1: BuLi, THF, 0.5 h, 2: dimethyl benzyl chloride, r.t., 16h; c) HCl 1.5 N, reflux, 1 h d) 1: MeLi, THF, DME, 0 C, 2: Li, NH_3, NH_4Cl, -78 C, 15 min (~85% overall yield) [11].

Scheme 1: Synthesis of medetomidine.

Similar method was used previously for the synthesis of naphthalene derivative of medetomidine (Scheme **2**) [14], the properties of which was reported [14-18]. Following this procedure, 1-Naphthaldehyde (**1'**) was treated with MeMgI in ether followed by addition of $SOC1_2$ in toluene to give the crude chloro compound (**3'**) in 97% yield. Chloro compound was treated with 1-(trimethylsily1)imidazole in the presence of $TiCl_4$ in $CHC1_3$ to give 4-[1-(1-naphthyl)ethyl)]-1H-imidazole (**4'**) in ~19 % overall yield. The difference of this method with those previously underlined, lies to the fact that in the precedent method, the chlorination step and adjunction of the imidazole ring is performed by $TiCl_4$ in one conjoint step. While for the naphthalene derivative two distinct steps concerning chlorination step (by $SOCl_2$) and adjunction of imidazole ring have been considered. The mechanism of $TiCl_4$-promoted alkylation of carbonyl compound has been reported previously [19, 20].

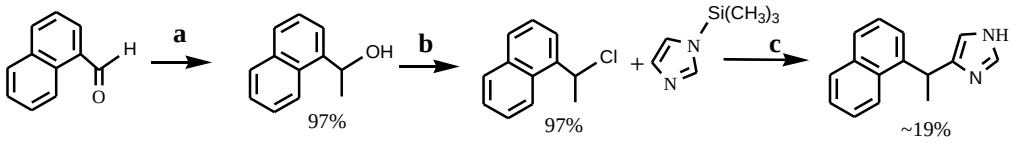
Last tentative to the preparation of medetomidine consist to a way in which the imidazole ring is built up during a multi-step process (7 steps) starting from commercially available, 2,3-dimethyl-benzoic acid [21].

Simplest practical and versatile method for the preparation of medetomidine seem to be those using 2,3-dimethyl benzaldehyde (**1**) and 1-(trimethylsilyl) imidazole as starting materials and performed following a three steps procedure (like Scheme **2**). But this method has inconvenient of low overall yield (~20). Herein, we intended to reinvestigate and optimize the three step procedure (Scheme **2**) for the preparation of medetomidine (**4**) and its naphthalenic derivative (**4'**) and to propose an industrially friendly scalable procedure for medetomidine synthesis.

Results and discussion

2,3-dimethyl benzaldehyde (**1**) is one of the starting materials from which medetomidine can be produced following a versatile and scalable method (Scheme **1** pathways III and IV and Scheme **2**). But this compound is expensive and the yield following these method are mediocre (~20%). 1-naphtaldehyde (**1'**) (pricing 0.1 of **1**) is an analogue of **1** (substituted in positions 1 and 3) and naphthalenic derivative of medetomidine (**4'**) present similar biological effects that medetomidine (**4**). Herein, the three steps procedure for the preparation of **4'** and **4** is reconsidered. For each step, different reaction condition (regarding proportional amount of reactant, reaction time, and addition order of reactant) were investigated.

The addition order of reactant in the first step is predominant and the addition of MeMgI solution to aldehyde solution (**1** or **1'**) has decreased the yield to ~50%. Using 20% molar excess of Mg and 50% molar excess of MeI for the preparation of MeMgI and addition of aldehyde solution (**1** or **1'**) to MeMgI solution have afforded higher yield (~90-95%). Inversing the addition order caused coagulation of the precipitate and decreased the yield to ~50%. Usage of excess amount of HCl 2N (200 mol%) at the end of reaction for 5 minutes is sufficient for transformation of ROMgI to ROH. Longer time of contact between HCl 2N solution and the reaction mixture caused dehydration of the product and formation of ethylenic compound, changing the color of the organic phase from yellow to red.



1' **2'** **3'** **4'**

a) 1:MeMgI, ether, r.t., 2h, 2: HCl 2N; b) $SOCl_2$, toluene, reflux, 4h; c) $CHCl_3$, $TiCl_4$, r.t., 12 h (~20% overall yield.

Scheme 2: Synthesis of naphthalene derivative of medetomidine.

Another important modifications were accomplished on the workup of the final step, by inversing the addition order of reaction mixture and water and two steps addition of NaOH 2N solution to the aqueous phase. Addition of final reaction mixture to water (and no inverse) increase the yield of the last step. Two steps increasing of the pH of aqueous phase allowed firstly to separate $Ti(OH)_4$ (formed after addition of final reaction mixture to water) as precipitate from the reaction mixture at low pH and then separation of medetomidine hydrochloride as free base at high pH. In fact, the precipitation of $Ti(OH)_4$ occurred at pH between 0.3 (for concentrated solutions) and 2.5 (for diluted solutions). Thus, at the workup step the pH of aqueous phase was first adjusted by NaOH 2N solution on 3.0-3.5 for filtration of precipitated $Ti(OH)_4$.

Conclusion

In conclusion, the tow steps procedure for the preparation of medetomidine (**4)** and its naphthalenic derivative (**4'**) has been reconsidered and optimized the conditions for each steps concerning the proportional amounts of reactant, time of reaction and work-up procedure have been stated. At the optimized conditions, the product of each step have been obtained with high purity and yield (without need of further purification). The major modification was made on the work-up procedure of the second step and triple uses of $TiCl_4$ and TMSI compared to **2** or **2'**.

Experimental

Preparation of naphtalenic derivative of medetomidine:

Naphtalenic derivative of medetomidine was prepared as the same two steps procedure and

following results concerning the yield (from cited quantities of row material) and product analysis have been obtained.

First step: Preparation of 1-(naphthalene-1-yl)ethanol (2'):

Magnesium (2.9 g, 0.12 mol), methyl iodide (9.3 ml, 21 g, 0.15 mol), and 1-naphthaldehyde (**1'**) (13.6 ml, 15.6 g, 0.1 mol) afforded 16.3 g **2'** (0.095 mol, 95% yield). ^{1}H NMR ($CDCl_3$): δ 1.67 (d, j=6.5 Hz, 3H, $CH(CH_3)$), 5.66 (q, j=6.5 Hz, 1H, $CH(CH_3)$), 7.26-8.13 (m, 7H, naphenthyl). ^{13}C NMR ($CDCl_3$): δ 24.3, 67.1, 122.0, 123.2, 125.5(2), 126.0, 127.9, 128.9, 130.3, 133.8, 141.4. GC: retention time: 7.9 min (T_{col}=200 °C). GC-MS: retention time: 8.0 min (T_{col}=150 °C); m/z (intensity (%)): 173(11), 172(100), 155(75), 129(33).

Second step: Preparation of 4-(1-(naphthalene-1-yl)ethyl)-1H-imidazole (4'):

$TiCl_4$ (12.9 ml, 22.7 g, 0.12 mol), TMSI (terimethyl silyl imidazole) (16.8 g, 17.4 ml, 0.12 mol), and the compound **2'** (3.4 g, 0.02 mol) affording 4.4 g of **4'** (0.02 mol, y=99%). ^{1}H NMR ($CDCl_3$): δ 1.71 (d, j=7 Hz, 3H, $CH(CH_3)$), 4.84 (q, j=7 Hz, 1H, $CH(CH_3)$), 6.68-8.01 (m, 7H, naphenthyl). ^{13}C NMR ($CDCl_3$): δ 20.9, 33.5, 117.4, 123.3, 124.4, 125.5, 125.6, 126.0, 127.2, 128.9, 131.3, 134.0, 134.3, 140.8, 140.9. GC-MS: retention time: 11.3 min (T_{col}=150 °C) ; m/z (intensity (%)): 224(15), 223(100), 222(55), 221(15), 207(14).

Preparation of medetomidine:

First step: Preparation of 1-(2,3-dimethylphenyl) ethanol (2).

Magnesium (2.9 g, 0.12 mol) was added during 15 min to a solution of methyl iodide (9.3 ml, 21 g, 0.15 mol) in 200 ml of dry diethyl ether with cooling in an ice-water bath and stirring during 5h. A solution of 2,3-dimethylbenzaldehyde (**1**) (13 ml, 13.4 g, 0.1 mol) in 50 ml of diethyl ether was added (dropwised) to the prepared solution of MeMgI dry with cooling in an ice-water bath, and the resulting reaction mixture was stirred for 3 h at room temperature. The reaction mixture was treated with 100 ml of 2N HCI during 2 min, and the organic layer was separated from the aqueous layer. The organic layer was washed with brine (2 x 250 ml) and dried over $CaCl_2$. Evaporation of the solvent under reduced pressure gave 13.8 g (92%) of the alcohol as a viscous liquid. ^{1}H NMR ($CDCl_3$): δ 2.23 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 1.46 (d, j=6.25 Hz, 3H, $CH(CH_3)$), 5.19 (q, j=6.25 Hz, 1H, $CH(CH_3)$), 7.1-7.4 (m, 3H, Phenyl). ^{13}C NMR ($CDCl_3$): δ 14.5, 20.6, 24.0, 67.2, 122.2, 125.8, 128.9, 132.9, 136.9, 143.7. GC: retention time: 3.2 min (T_{col}=200 °C). GC-MS: retention time: 3.8 min (T_{col}=150 °C) ; m/z (intensity (%)): 91 (34), 105 (37), 107 (100), 117 (26), 132 (90), 133 (52), 135 (19).

Second step: Preparation of medetomidine (4-(1-(2,3-dimethylphenyl)ethyl)-1H-imidazole(4):

A solution of TMSI (tetra methyl silyl imidazole) (64.1 g, 67.3 ml, 0.46 mol) was added to the solution of $TiCl_4$ (87.1 g, 50.3 ml, 0.46 mol) in 100 ml of dry chloroform with cooling in an ice-water bath for 30 min. The resulting orange colored mixture was stirred for an additional 2h, and then a solution of the compound **2** (11.5 g, 0.077 mol) in 100 ml of dry chloroform was added to the reaction mixture with cooling in an ice-water bath. The reaction mixture was stirred for 9 h at ambient temperature. The reaction mixture was added drop-wised to water (500 ml) and stirred for 10 min. Aqueous layer was separated and washed with methylene chloride (50 ml). Then 2 N NaOH (210 ml) was added to raise the pH of aqueous layer until 3.5-4. After filtration of the produced precipitate ($Ti(OH)_4$), 2 N NaOH was added against to make basic aqueous layer (pH~12). During the addition of 2N NaOH to the aqueous layer, medetomidine hydrochloride was precipitated as a viscose, very thickly and coagulated compound affording 15.5 g of target product (77 mmol, y=99%).^{1}H NMR ($CDCl_3$): δ 2.15 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 1.52 (d, j=7.5 Hz, 3H, $CH(CH_3)$), 4.32 (q, j=7.5 Hz, 1H, $CH(CH_3)$), 6.63-7.25 (m, 5H, Phenyl and imidazole), 10.26 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 14.7, 20.8, 21.0, 34.2, 117.1, 124.7, 125.6, 127.9, 134.1, 134.6, 136.8, 141.4, 143.4. GC-MS: retention time: 3.8 min (T_{col}=250 °C); m/z (intensity (%)): 201 (100). HPLC: retention time: 3.8 min.

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