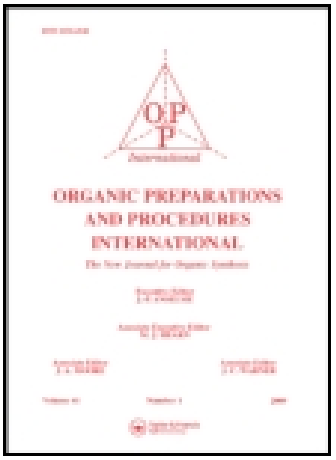

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Synthesis and Enantiomeric Resolution of Medetomidine

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Synthesis and Enantiomeric Resolution of Medetomidine

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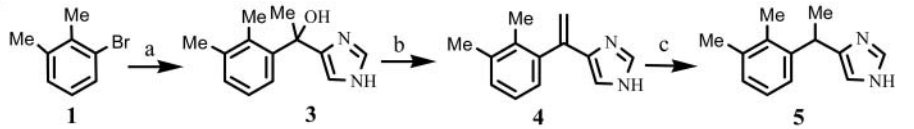
Medetomidine {4-[l-(2,3-dimethylphenyl)ethyl]-3*H*-imidazole], **5**} is a selective α_2-adrenoceptor agonist used in veterinary medicine for its analgesic and sedative properties.[1,2] It is also an alternative and environmentally acceptable anti-fouling biocide which impedes the settlement of barnacles at nanomolar concentrations and replaces toxic anti-fouling coatings based on heavy metals.[3–5] Several syntheses of *medetomidine* have been reported.[6–13]

The first method for the preparation of **5** and of other related 4-benzylimidazoles was described in a patent starting from 2,3-dimethylbromobenzene as shown in *Scheme 1*; unfortunately the yields were not reported.[6–8]



1 **3** **4** **5**

a) Mg, then methyl 4-imidazolecarboxylate (**2**) and immediately after MeMgBr;
b) $KHSO_4$, heat; c) H_2, Pd/C

Scheme 1

A second route, proceeding in 41% overall yield (*Scheme 2*),[9] also involved the reaction of the Grignard reagent derived from **1** with 4-(1-triphenylmethyl)imidazole carboxaldehyde (**6**).

In a third preparation, secondary carbinol **7** was obtained *via* the addition of 2,3-dimethylbenzaldehyde (**10**) to the Grignard reagent prepared from 4-iodo-(1-tripheny1-methyl)imidazole (**11**). Subsequent oxidation with MnO_2, addition of MeMgCl, deprotection and hydrogenolysis afforded **5** in ~60% overall yield (*Scheme 3*).[10]

Medetomidine has also been synthesized in four steps (overall yield ~79%) from 1-(*N,N*-dimethylsulfamoyl)imidazole which had been regioselectively protected at the 2-

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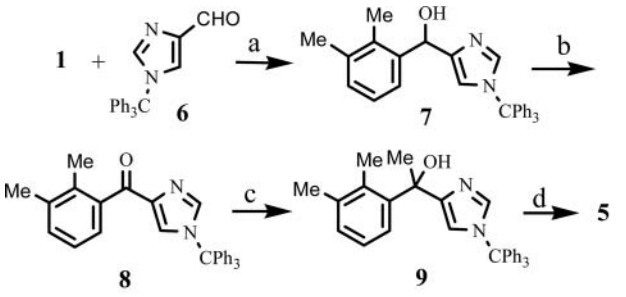
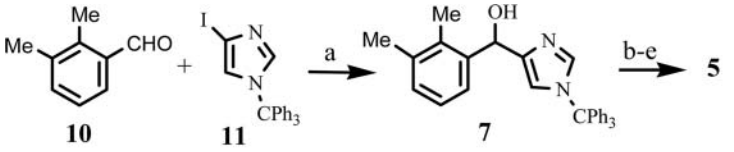


a) Mg; b) MnO_2; c) MeMgBr; d) Et_3SiH, CF_3CO_2H, then H_2, Pd/C

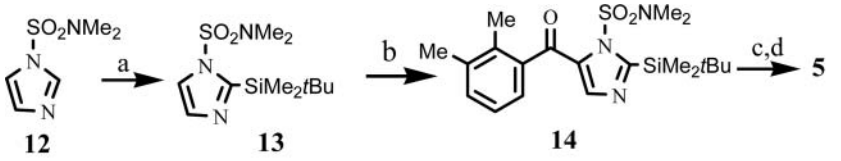
Scheme 2



a) *i*PrMgBr; b) MnO_2; c) MeMgCl; d) HCl, heat; e) H_2, Pd/C

Scheme 3

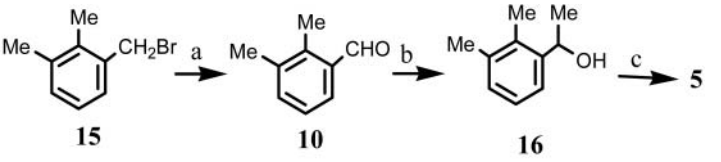
position using *t*-$BuMe_2SiCl$ (*Scheme 4*).[11] This method suffers from drawbacks such as two BuLi-metalations at -78 ° C, the use of lithium in liquid ammonia at -78 ° C, and the need for chromatographic purification.



a) BuLi, then *t*$BuMe_2SiCl$; b) BuLi, then 2,3-dimethylbenzoylchloride;
c) HCl, heat; d) MeLi, then Li, NH_3/NH_4Cl

Scheme 4

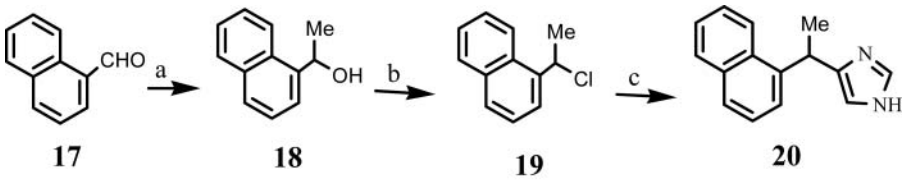
A more recent report described (without yields) the alkylation of *N*-(tri-methylsilyl)imidazole (TMSIm) with 1-(2,3-dimethylphenyl)-1-ethanol (**16**) in the presence of titanium tetrachloride for the preparation of *medetomidine* at room temperature (*Scheme 5*).[12] The same procedure has been performed *via* 1-(1-chloroethyl)2,3-dimethylbenzene (the chloro derivative of **16**) using TMSIm (400–500 mol%) and $TiCl_4$ (350–450 mol%), again without yields being reported.[13]



a) NaOEt, 2-nitropropane, ethanol, then NaOH; b) MeMgCl; c) $TiCl_4$, *N*-trimethylsilylimidazole

Scheme 5

The naphthalene analogue of *medetomidine* has also been synthesized *via* a three-step procedure (*Scheme 6*)[14–18] involving reaction of 1-naphthaldehyde (**17**) with MeMgI in ether followed by addition of $SOC1_2$ in toluene to give the crude chloro compound (**19**) in 97% yield. Treatment of **19** with *N*-trimethylsilylimidazole (TMSIm, 200 mol%) in the presence of $TiCl_4$ (200 mol%) in $CHC1_3$ gave 4-[1-(1-naphthylethyl)]-1*H*-imidazole (**20**) (~19%). The difference between this method and that previously outlined in *Scheme 5*,[12] lies in the fact that in the preceding method, the chlorination step does not exist and alkylation of *N*-trimethylsilylimidazole with 1-(2,3-dimethylphenyl)-1-ethanol (**16**) is performed directly in one-step using $TiCl_4$. The mechanism of the $TiCl_4$-promoted alkylation of carbonyl compounds has been reported previously.[19]

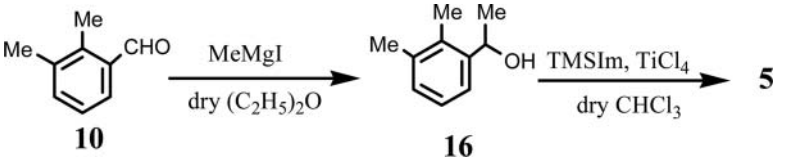


a) MeMgI; b) $SOCl_2$, heat; c) $TiCl_4$, *N*-trimethylsilylimidazole

Scheme 6

The final attempt to prepare of *medetomidine* involved the construction of the imidazole ring *via* a seven-step process starting from commercially available 2,3-dimethylbenzoic acid.[20]

The simplest and most practical method for the preparation of *medetomidine* would be based of that used for the naphthalene analogue (*Scheme 6*). However, the final step of this approach starting from 2,3-dimethylbenzaldehyde (**10**) and TMSIm (*Scheme 7*) proceeds in only 20% yield. Therefore the two-step procedure for the preparation of *medetomidine* **(5)** was re-examined under different reaction conditions such as proportional amount of reactants, reaction time, and order of the addition of reactants as determined using the Taguchi method.[21–23]



Scheme 7

Addition of aldehyde **10** to a solution of an excess methylmagnesium iodide in ether (see *Experimental Section*; the reverse mode of addition leads to coagulation and decrease in the yield) gave 90–95% yield of **16.** Acidification with excess 2N HCl (200 mol%) and stirring for 5 minutes of stirring converted the alcoholate to the alcohol. Longer contact times between the 2N HCl solution and the reaction mixture caused dehydration of the product and formation of the ethylenic compound leading to a change in the color of the organic phase from yellow to red. Other important modifications were accomplished during the work-up of the second step, by inverting the order of the addition of reaction mixture and water and by addition of the NaOH solution in two stages to the aqueous phase. Addition of the final reaction mixture to water (and not the reverse) increased the yield of the second step (by 40%). A two-step increase of the pH of aqueous phase caused Ti $(OH)_4$ (formed after addition of final reaction mixture to water) to precipitate at low pH prior to the isolation of *medetomidine* as the free base at high pH. Indeed the precipitation of $Ti(OH)_4$ occurred at a pH between 0.3 (for concentrated solutions) and 2.5 (for dilute solutions). Thus, the pH of the aqueous phase was first adjusted to 3.0–3.5 (by NaOH solution) to promote the precipitation of $Ti(OH)_4$ which was removed by filtration. *Medetomidine hydrochloride* (formed after addition of final reaction mixture to water) is freely soluble in water. The second addition of the NaOH solution to the filtrate to give a pH of 11–12, allowed the separation of *medetomidine* as the free base from the aqueous solution as a coagulated and sticky precipitate.

Since the naphthalene analogue of *medetomidine* (**20**) has similar biological effects and 1-naphthaldehyde (**17**) is much less expensive than 2,3-dimethylbenzaldehyde, it was used to determine optimized conditions for the final step. Although time was found to be not a major factor, the concentration of TMSIm, of $TiCl_4$ and of 1-(naphthalen-1-yl)ethanol (**18**) did have significant effects on the yield of **20;** it was determined that a ratio of 6:6:1 for TMSIm, $TiCl_4$ and **18** was optimal for the synthesis of **20**. However, an increase in the amount of $TiCl_4$ did not change the yield significantly. These conditions were used in our procedure to prepare racemic *medetomidine*.

Medetromidine is a racemate of the enantiomeric *levomedetomidine* and *dexmedetomidine. Dexmedetomidine* (the *S*-enantiomer), marketed under the brand name *Precedex* (Hospira, Inc.) in the United States, is used in intensive care units and by anesthesiologists. It is relatively unique in its ability to provide sedation without causing respiratory depression. Unlike *rac-medetomidine* and *dexmedetomidine*, *levomedetomidine* only provides sedation or analgesia at high doses in rats and mice[24] and its excretion from the body is four times more rapid than *rac-medetomidine* and *dexmedetomidine* in dogs.[25-] Dexmedetomidine was obtained by resolution of (±)-medetomidine via fractional crystallization of its diastereoisomeric salt with (+)-tartaric acid (as resolving agent) in alcoholic media. [9, 26]

The various parameters (temperature, stirring time and solvent amount) for this process also determined by the Taguchi method, were used to optimize the diastetreoisomeric resolution of *medetomidine*. The results indicate that temperature, stirring time and volume of solvent play significant roles in the generation of enantiomeric excesses. A temperature of 5°C, a stirring time of 4 h and 6 mL of ethanol for 0.15 g of (±)-*medetomidine* and 0.056 g. of (+)-tartaric acid (50 mole%) were found to be optimal to produce *medetomidine* with maximum enantiomeric excess. Thus, on a ~50 mmol scale, a total volume of 125 mL ethanol was used at 5°C for a total stirring time of 16 h to perform one diasteroisomeric step and three consecutive fractional crystallizations to obtain *dexmedetomidine* with an overall yield of 26% and an enantiomeric excess of 99% as described in the *Experimental Section*. In contrast to previous results,[9,26] our optimized

procedure is more efficient, requiring less solvent and stirring time to achieve higher enantiomeric excess.

In conclusion, the two-step procedure for the preparation of *medetomidine* (**5**) and its naphthalene analogue **20** has been reinvestigated, and the second step has been optimized with respect to the proportional amounts of reactants, order of addition, time of reaction and work-up procedure. At the optimized conditions, the product of the second step was obtained in high purity and quantitative yield. Major modifications were carried out on the work-up procedure of the second step, and a six-fold excess of $TiCl_4$ and TMSIm. Secondly, it has been shown that various factors such as temperature, stirring time and volume of solvent have significant effects on the diastereoisomeric resolution of *medetomidine*; its final enantiomeric excess was optimized.

Experimental Section

NMR spectra were obtained on a Bruker DPX-250 instrument (250 MHz for ^1H 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 ^1H. Gas chromatography (GC) was performed on a Varian (Star 3400CX) instrument with a packed column (10% OV-101 CWHP 80/100, 2m x 1.8") and a He flow rate of 10 mL/min. Electron impact 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 $\times$ 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 of the synthesis products were performed on a Knauer EA 4300F equipped with a UV detector (215 nm), vendor model 2600, and a C_{18} column (250 $\times$ 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. *N*-Trimethylsilylimidazole (Merck, 97%), 2,3-dimethylbenzaldehyde (Aldrich, 97%) and 1-naphthaldehyde (Alfa-Ceasar, 97%) were used without purification. For the diastereoisomeric resolution of *medetomidine*, the suspensions were stirred at a constant stirring speed of 700 rpm in a 100 mL jacketed glass beaker connected to a thermostated water bath (Julabo F12, $\pm$0.1 °C). All samples were analyzed by HPLC using a *CHIRAL-AGP* column (150 mm $\times$ 4 mm, 5 μm, Illkrich) and a mobile phase of 1% 2-propanol in 20 mM acetate buffer at pH 5.0 with a flow rate of 0.9 mL/min.

Preparation of 1-(2,3-Dimethylphenyl)ethanol (16).- Magnesium turnings (2.9 g, 0.12 g.-atom) were added over 15 min to a solution of methyl iodide (9.3 mL, 21.0 g, 0.15 mol) in 200 mL of dry diethyl ether with cooling in an ice-water bath and stirring during 5 h. A solution of 2,3-dimethylbenzaldehyde (**10**) (13.0 mL, 13.4 g, 0.10 mol) in 50 mL of diethyl ether was added dropwise to the solution of MeMgI (cooled in an ice-water bath), and the reaction mixture was stirred for 3 h at room temperature. The crude reaction mixture was treated with 100 mL of 2 N HCI over 2 min, and the organic layer was separated, washed with brine (2 $\times$ 250 mL) and dried over $CaCl_2$. Evaporation of the solvent under reduced pressure gave 13.8 g (92%) of the alcohol (**2**) as a viscous colorless liquid.

^1H 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 (%)): 135 (19), 133 (52), 132 (90), 117 (26), 107 (100), 105 (37), 91 (34).

Preparation of Medetomidine 4-[1-(2,3-Dimethylphenyl)ethyl)]-1H-imidazole (5).- A solution of *N*-trimethylsilylimidazole (64.1 g, 67.3 mL, 0.46 mol) was added to a solution of $TiCl_4$ (87.1 g, 50.3 mL, 0.46 mol) in 100 mL of dry chloroform (cooled in an ice-water bath) over a period of 30 min. The resulting orange-colored mixture was stirred for an additional 2 h, and then a solution of compound **16** (11.5 g, 0.077 mol) in 100 mL of dry chloroform was added in one portion to the reaction mixture (cooled in an ice-water bath) which was then stirred for 6 h at room temperature. The reaction was quenched by the dropwise addition to water (500 mL) with stirring after which the aqueous layer was separated and extracted with 50 mL of methylene chloride and the methylene chloride extract was discarded. Then 2 N NaOH (210 mL) was added to raise the pH of aqueous layer to 3.5–4.0. After removal fof the precipitated $Ti(OH)_4$ thus produced by filtration, 2 N NaOH (20 mL) was added to bring the pH of the aqueous filtrate to about 12. During the addition of the sodium hydroxide solution, *medetomidine* precipitated as a viscous, very thick substance that coagulated affording 15.4 g (100%) of the target product **5** as a pale-yellow solid, mp. 83–92 ° C.

^{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.

Preparation of 1-(Naphthalen-1-yl)ethanol (18).- Reaction of methylmagnesium iodide [prepared from magnesium (2.9 g, 0.12 g-atom) and methyl iodide (9.3 mL, 21 g, 0.15 mol)], with 1-naphthaldehyde (**17**) (13.6 mL, 15.6 g, 0.10 mol) as above afforded **18** (16.3 g, 0.095 mol, 95% yield) as a pale green solid., mp 60–63°C.

^{1}H NMR ($CDCl_3$): δ 1.67 (d, J = 6.5 Hz, 3H, $CHCH_3$), 5.66 (q, J = 6.5 Hz, 1H, $CHCH_3$), 7.26–8.13 (m, 7H, naphthyl). ^{13}C NMR ($CDCl_3$): δ 24.3, 67.1, 122.0, 123.2, 125.5 (2C), 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).

Preparation of 4-(1-(Naphthalen-1-yl)ethyl)-1H-imidazole (20).- Reaction of $TiCl_4$ (12.9 mL, 22.7 g, 0.12 mol), *N*-trimethylsilylimidazole (16.8 g, 17.4 mL, 0.12 mol), and **18** (3.4 g, 0.02 mol) as above afforded 4.4 g of **20** (0.02 mol, 100% yield). mp 161–166 ° C, *Lit.*[14] mp 175–176°C.

^{1}H NMR ($CDCl_3$): δ 1.71 (d, J = 7 Hz, 3H, $CHCH_3$), 4.84 (q, J = 7 Hz, 1H, $CHCH_3$), 6.68–8.01 (m, 7H, naphthyl). ^{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).

Multigram-Scale Diastereoisomeric Resolution of Medetomidine.- To a solution of (±)-*medetomidine* (9.8 g, 0.049 mol) in absolute ethanol (62 mL) was added (+)-tartaric acid (3.7 g, 0.024 mol); the suspension was heated until complete dissolution and then stirred for 4 h at 5°C. The white solid (6.5 g, 38%, *ee* 84%) was collected and fractionally crystallized three consecutive times from ethanol by stirring for 4 h at 5°C. The first fractional crystallization of 6.5 g of diastereisoomeric salt obtained above from 24 mL of ethanol afforded 5.8 g (89%, *ee* 92%) of a white solid. The second consecutive fractional crystallization of diastereoisomeric salt obtained above from 21 mL of ethanol led to 4.9 g (85%, *ee* 98%) of a white solid. The third consecutive fractional crystallization of diastereoisomeric salt obtained above from 18 mL of ethanol produced 4.4 g (90%,*ee*

99%) of a white solid. Thus, the overall yield was 26% (or 52% based on the amount of *dexmedetomidine tartarate* salt present in the original diastereoisomeric mixture).

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