J IRAN CHEM SOC
DOI 10.1007/s13738-017-1114-0

ORIGINAL PAPER

A novel and facile route for the synthesis of medetomidine as the α_2-adrenoceptor agonist

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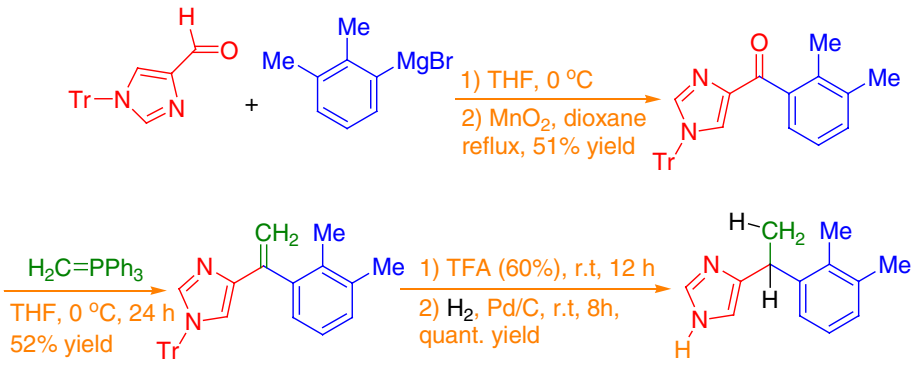
Received: 10 August 2016 / Accepted: 31 March 2017

Abstract We report here a novel and facile method for the synthesis of (±)-4(5)-[1-(2,3-dimethylphenyl)ethyl]-1*H*-imidazole (medetomidine) in a good yield in five steps. The method involves Wittig olefination of the phenylimidazolylketones, followed by a hydrogenation. We demonstrate that the Wittig alkenylation reaction provides a convenient step for the synthesis of medetomidine without requiring methylation and dehydration steps, which are problematic processes in the previous methods.

Graphical Abstract Novel route for the synthesis of medetomidine.



Keywords Imidazole · Medetomidine · Wittig reaction · α_2-adrenoceptor agonist · Methanone

Introduction

Imidazole derivartives are an important class of compounds that exhibit a variety of interesting and useful properties in biological activities [1–7]. Among the biologically active imidazole compounds, medetomidine is known as the prototype of a class of α_2-adrenoceptor agonist that shows a high degree of the sedative-analgetic effect [8]. The (*S*)-enantiomer of medetomidine is named dexmedetomidine

Electronic supplementary material The online version of this article (doi:10.1007/s13738-017-1114-0) contains supplementary material, which is available to authorized users.

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Published online: 08 April 2017

[9, 10] that is commercially available under trade name Precedex. This drug is used currently in clinic as anesthetic and offers sufficient sedation with sporadic side effect that allows surgeries without artificial ventilation of the patient (Fig. 1). The chiral form was obtained by enantiomeric separation of medetomidine using (+)-tartaric acid [11].

Several methods have been reported for the synthesis of medetomidine [12–20]. The first synthesis of medetomidine is reported in the patent literature and requires 7 steps to give low yield (<11%) starting from 2,3-dimethylbromobenzene via stepwise addition of two kinds of Grignard reagents [12].

Kudzma et al. [15] reported another approach for the synthesis of medetomidine (Scheme 1). In this method, the arylketone, prepared from 2,3-dimetheylbenzoyl chloride and the doubly protected imidazole *via* the regioselective lithiation, was treated with MeLi to give the tertiary alcohol, which was reduced with Li/NH_3 to give medetomidine. The method requires at least 8 synthetic steps, low temperatures, and high protection of moisture during the reaction.

Cordi et al. [16] reported a novel route starting from the protected imidazole carbaldehyde and 2,3-dimetheylphenylmagnesium bromide as shown in Scheme 2. In this route, the Grignard adduct was oxidized by MnO_2, and followed by subsequent addition of methylmagnesium bromide to give the tertiary alcohol. The authors emphasized that the tertiary alcohol was converted to the corresponding alkene in the presence of Et_3SiH and TFA in CH_2Cl_2 at a low temperature, and subsequent hydrogenation of the alkene over Pd/C gave medetomidine. However, no evidence is disclosed about the formation of the alkene. Moreover, in our hand, we cannot reproduce last three steps in the Cordi method to give medetomidine from tertiary carbinol as reported in the literature.

Purpose of this paper is to report an alternative method for the synthesis of medetomidine, in which the Cordi ketone was unambiguously transformed to the alkenyl compound by a Wittig olefination and subsequent hydrogenation gave medetomidine in good yield. We also disclose experimental details and the physical data for newly synthesized alkenyl compound **5**, which are not reported previously (Scheme 3).

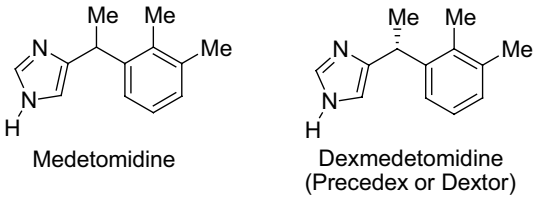


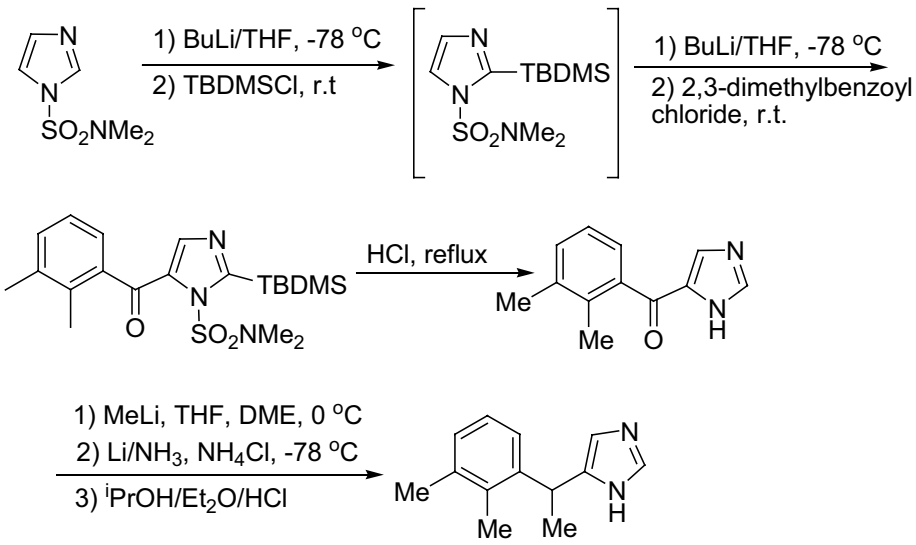
Fig. 1 Structures of medetomidine and dexmedetomidine

Materials and methods

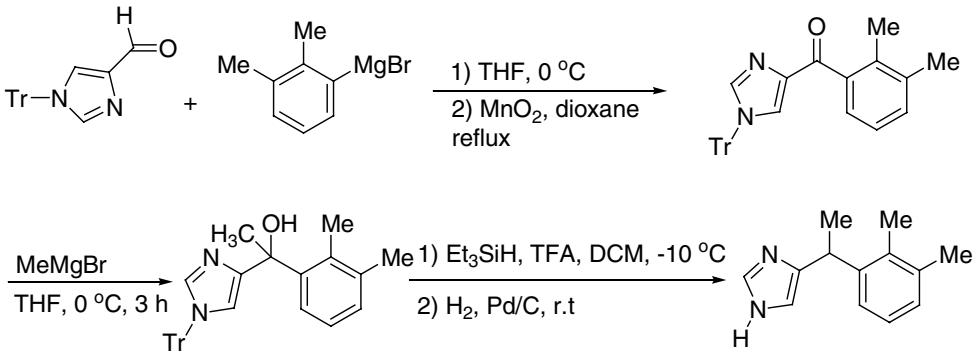
All chemicals were commercial products and distilled or recrystallized before use. NMR spectra were taken with a 400 MHz Bruker Avance instrument with the chemical shifts being reported as δ ppm and coupling constants expressed in Hertz. Silica gel column chromatography was carried out with Silica gel 100 (Merck No. 10184). Merck Silica gel 60 F254 plates (No. 5744) were used for the preparative TLC. Melting points are uncorrected.

X-ray crystal data of alkene **5** were collected by a Bruker SMART APEX II diffractometer. The structure was solved by a direct method using SHLEXS-97 (Scheldrik 1997) and refined with a full matrix laser-squares

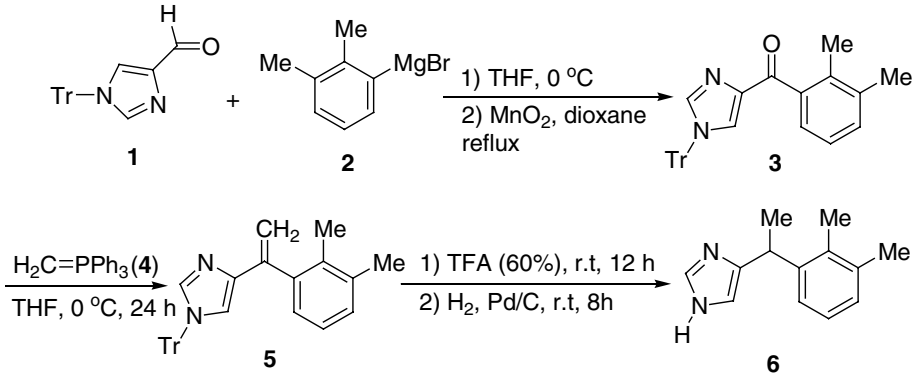
Scheme 1 Kudzma et al. method



Scheme 2 Cordi et al. method



Scheme 3 Our method



method. Molecular formula = $C_{32}H_{28}N_2$, MW = 440.56, triclinic, space group= $P-1$, a = 9.6788(9) Å, b = 9.8481(9) Å, c = 14.8413(14) Å, V=1205.37(19) Å3, T=90 K, Z=2, D_x=1.214 Mg/m^3, (Mo-Kα) = 0.71073 Å, R=0.0210 over independent reflections. Crystallographic data (excluding structure factors) for the X-ray crystal structure analysis reported in this paper have been deposited with the Cambridge Crystallographic Data Center (CCDC) as supplementary publication No. CCDC 1465213; copies of these data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax:+44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Preparation of (2,3-Dimethylphenyl)(1-trityl-1H-imidazol-4-yl)methanone (3) This compound was obtained according to the method reported by Cordi et al. [16]. The product gave satisfactory spectral data in accordance with the assigned structure and literature report. A white solid; mp: 171–172 °C {Lit [16]. 171 °C}; ^{1}H NMR ($CDCl_3$, 400 MHz): 2.28 (s, 3H, CH_3), 2.31 (s, 3H), 7.12–7.39 (m, 18H, Ar), 7.52 (d, 1H, J = 1.2 Hz), 7.60 (d, 1H, J = 1.2 Hz), ^{13}C NMR ($CDCl_3$, 100.6 MHz): 16.7, 20.3, 76.2, 124.8, 126.1, 128.3, 128.4, 128.5, 129.7, 131.6, 134.7, 137.7, 139.5, 140.1, 141.1, 141.7, 192.8.

Procedure for the preparation 4-(1-(2,3-dimethylphenyl)vinyl)-1-trityl-1H-imidazole (5) A solution of methyltriphenyl phosphonium bromide (2.5 g, 7.1 mmol) in dry THF (80 mL) under Ar atmosphere was treated with butyllithium (2.5 M hexane solution, 5 mL) dropwise at 0 °C, and the reaction mixture was stirred for 1 h at 0 °C. A solution of (2,3-dimethylphenyl)(1-trityl-1H-imidazol-4-yl) methanone **3** (1 g, 2.26 mmol) in dry THF (10 mL) was added dropwise to the reaction mixture, and the resulting mixture was stirred for 24 h at 0 °C. Then, the reaction mixture was quenched with water (30 mL), and the solvent was removed under reduced pressure. The residue was dissolved in $CHCl_3$ (100 mL) and washed with water (2 × 50 mL) and saturated NaCl. Separated organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was subjected to flash column chromatography on silica gel. Elution with EtOAc/*n*-hexane (1:9 to 9:1) gave pure product **5** (0.52 g) in 52% yield. Analytical samples of compound **5** for X-ray analysis were obtained by recrystallizing several times from a mixture of EtOAc/*n*-hexane. The product **5** gave satisfactory spectral data in accord with the assigned structure. A white solid; mp: 200–204 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): 2.00 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 5.04 (d, 1H, J = 1.6 Hz, =CH_2), 6.14 (d, 1H, J = 1.6 Hz, =CH_2)

6.28–7.50 (m, 20H, Ar), ^{13}C NMR ($CDCl_3$, 100.6 MHz): 16.7, 20.4, 75.4, 120.3, 125.2, 127.4, 128.0, 128.1, 128.1, 128.7, 128.8, 129.7, 129.8, 134.5, 136.7, 139.1, 140.8, 142.2. HRMS for $C_{32}H_{29}N_2$ calculated [MH] 441.2330; found m/z= 441.2332.

Procedure for the preparation of medetomidine (6) A solution of **5** (88 mg, 0.2 mmol) in aqueous TFA solution (60%, 5 mL) was stirred overnight. The solvents were evaporated, and the residue was diluted with $CHCl_3$ (15 mL) and treated with HCl solution (10%, 15 mL). The organic layer was washed again with HCl solution (10%, 3 × 5 mL). The combined acidic solutions were neutralized to pH~10 and then extracted with $CHCl_3$ (4 × 20 mL). The organics were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give trityl-deprotected **5**. To a solution of trityl-deprotected **5** in MeOH (4 mL) was hydrogenated over 10% Pd/C (3 mg) at 40 Psi of hydrogen for 8 h. The catalyst was filtered through celite. The celite pad was washed with MeOH (2 × 10 mL). The combined filtrate was concentrated *in vacuo* to give 36 mg (95%) of medetomidine **6**. The product gave satisfactory spectral data in accordance with the assigned structure and literature report [16]. Yellow viscous oil; ^{1}H NMR ($CDCl_3$, 400 MHz): 1.57 (d, 3H, $J = 7.2$ Hz, CH_3), 2.20 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 4.38 (q, 1H, $J = 7.2$ Hz, CH), 6.17 (s, 1H), 6.90–7.05 (m, 3H), 7.40 (s, 1H), 7.50–8.0 (br, 1H); ^{13} C NMR ($CDCl_3$, 100.6 MHz): 15.5, 21.5, 21.7, 34.9, 125.4, 126.4, 128.8, 134.9, 135.3, 137.7, 143.8; analytically calculated for $C_{13}H_{16}N_2$, C, 77.96; H, 8.05; N, 13.99; found: C, 77.65; H, 8.33; N, 13.69.

Results and discussion

Treatment of 1-trityl-1-H-imidazole-4-carboxaldehyde **1** [21] with 2,3-dimethylphenylmagnesium bromide **2** (prepared by reaction of 2,3-dimethyl phenylbromide with magnesium metal in THF) followed by oxidation of resulting tertiary alcohol with manganese oxide to form methanone **3** as reported in the literature. Wittig reaction is a very convenient, general, and useful method for the conversion of aldehyde or ketones to alkenes. Phosphorus ylides are used as a Wittig reagent that easily generated from a phosphonium salt.[8] Addition of [$MePPh_3$]Br to a solution of butyllithium in THF forms Wittig reagent $CH_2{=}PPh_3$ **4**, which is allowed to react *in situ* with methanone **3** under an argon atmosphere to give 4-(1-(2,3-dimethylphenyl)vinyl)-1H-imidazole **5** in 52% yield. The structure of **5** was unambiguously determined by X-ray crystallographic analysis. ORTEP drawing of alkene **5** is shown in Fig. 2 [22–24].

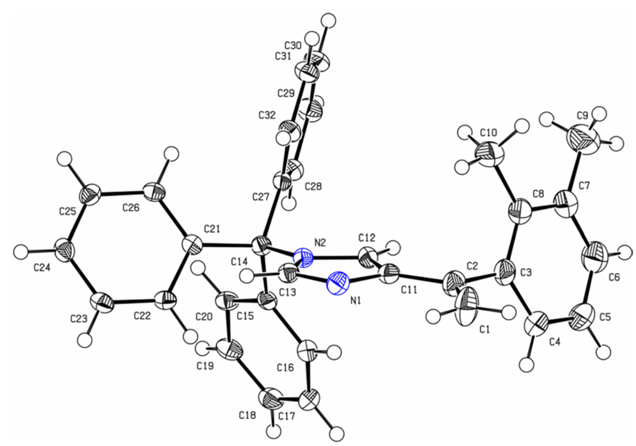


Fig. 2 ORTEP drawing of compound **5**

Trityl protecting group is readily removed from alkene **5** using a mixture of TFA/H_2O (60:40 v/v) at ambient temperature in nearly quantitative yield. Subsequent treatment of crude deprotected free base with hydrogen gaseous in the presence of 10% palladium on charcoal for 8 h afforded medetomidine **6** in quantitatively yield.

In summary, we report herein a novel and simple route for the synthesis of medetomidine *via* the reaction of easily available Wittig reagent CH_2PPh_3 with methanone **5**. The alkenylation reaction gave compound **5** which readily converted to medetomidine **6** *via* deprotection and hydrogenation processes. Mild reaction condition, relatively good yield, a simple workup, and clean reactions make this method an attractive and a useful contribution to current methodology.

Supplementary Material

Copies of ^{1}H NMR and ^{13}C NMR for compounds **1**, **3**, **5**, **6** and X-ray data of compound **5**. Supplementary data associated with this article can be found, in the online version.

Acknowledgements The Iran National Science Foundation (INSF) is thanked for supporting this work. The authors also thank Mr. Haruhiko Fukaya, Tokyo University of Pharmacy and Life Sciences for his helps carrying out the X-ray crystallographic analysis.

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