Efficient Synthesis of (S)-4(5)-[1-(2,3-Dimethylphenyl)ethyl]imidazole tartrate, the Potent $\alpha_2$ Adrenoceptor Agonist Dexmedetomidine

Alex A. Cordi $^a$, Thierry Persigand $^a$ & Jean-Pierre Lecouvé $^b$

$^a$ Institut de Recherches Servier, 11 rue des Moulineaux, 92150, Suresnes, France
$^b$ ORIL, 13 rue Auguste Desgenetais, BP 17, 76210, Bolbec, France

Published online: 15 Aug 2006.

To cite this article: Alex A. Cordi , Thierry Persigand & Jean-Pierre Lecouvé (1996): Efficient Synthesis of (S)-4(5)-[1-(2,3-Dimethylphenyl)ethyl]imidazole tartrate, the Potent $\alpha_2$ Adrenoceptor Agonist Dexmedetomidine, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 26:8, 1585-1593

To link to this article: http://dx.doi.org/10.1080/00397919608003527

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.tandfonline.com/page/terms-and-conditions
Efficient Synthesis of (S)-4(5)-[1-(2,3-Dimethylphenyl)ethyl]imidazole Tartrate, the Potent $\alpha_2$ Adrenoceptor Agonist Dexmedetomidine.

Alex A. Cordi$^a$, Thierry Persigand$^a$, Jean-Pierre Lecouvé$^b$.

$^a$ Institut de Recherches Servier, 11 rue des Moulineaux, 92150 Suresnes, France
$^b$ ORIL, 13 rue Auguste Desgenetais, BP 17, 76210 Bolbec, France

(S,R)-4(5)-[1-(2,3-Dimethylphenyl)ethyl]imidazole 5 is prepared in 41% yield, by a new reliable method from readily available starting materials. The separation of the enantiomers proceeds through the selective crystallisation of the (+)-tartrate of the (S) enantiomer 6 in the presence of the (R) enantiomer free base.

Dexmedetomidine (6) is the (S) enantiomer of 4(5)-[1-(2,3-dimethylphenyl)ethyl]imidazole. It is a very potent $\alpha_2$ adrenoceptor agonist which is currently evaluated in clinic as anaesthetic. According to patent literature, compound 6 is obtained by resolution of medetomidine (5, (S,R)-4(5)-[1-(2,3-dimethylphenyl)ethyl]imidazole) by repeated crystallizations of the (+)-tartraric acid salt in alcoholic media. The two reported syntheses of compound 5 suffer from drawbacks such as poor yield or low practicability (two BuLi-metalations at -78 °C; use of Li in liquid ammonia at -78 °C; chromatographic purification of an...
intermediate). We report herein a simple and efficient route to 6 which enables the synthesis of reasonable quantities of the enantiomerically pure compound in 8.5 % overall yield compared to 1.2 % overall yield for the patent published procedures.

Our synthesis starts from the readily available 4-(1-triphenylmethyl)imidazolecarboxaldehyde 1 which has previously been used in the preparation of $\alpha_2$ adrenoceptor agonists and antagonists. Addition of 2,3-dimethylphenylmagnesium bromide to 1 leads to the secondary carbinol which is easily oxidised to the ketone 3. Reaction of 3 with methylmagnesium bromide gives the tertiary carbinol 4. Simultaneous deprotection and dehydration followed by hydrogenation of the double bond leads to medetomidine 5 in 41 % overall yield starting from 1. It was hoped that 5 would be produced directly, in the conditions used for the deprotection, by capture with triethylsilane of the stabilised tertiary carbonium ion formed, however the deprotonation was apparently faster.

According to the procedure reported in the patent literature, we were able to isolate, after 8 crystallizations from ethanol, dexmedetomidine as (+)-tartrate in 7 % yield and in enantiomeric excess of 96 % (data not shown). Following the observation that the free base of dexmedetomidine was freely soluble in most organic solvents except alkanes and that the tartrate salts were poorly soluble in alcohol's, the crystallization of the (+)-tartrate of dexmedetomidine (S)-6 was attempted in ethanol in the presence of levmedetomidine (R)-6 free base. After 4 crystallizations, dexmedetomidine (+)-tartrate was recovered in 21 % yield and enantiomeric excess > 99 %.
These figures could supposedly be improved if, at each crystallization step, the thermodynamic equilibrium between the solid and the filtrate is reached by stirring the mixture for an extensive period of time. For instance, in an independent experience, a mixture of tartrate and free base in ethanol was stirred in ethanol, for 3 hours, to give an enantiomeric excess of 82 % whilst the same mixture stirred for
24 hours gave an enantiomeric excess of 86%. In addition, by adjusting accurately the quantity of tartaric acid to the quantity of the corresponding enantiomer present in the mixture, the success of the resolution is improved in term of overall yield and number of crystallizations but at the price of a more laborious procedure. Indeed, after each crystallization, the solid tartrate needs to be decomposed and the free base recovered by extraction and a new mixture weighed out. In conclusion, we would like to emphasise the use of "nonstoichiometric resolution conditions which have yet been little exploited but which appear in our hands as a useful alternative to the classical second Pasteurian resolution method.

Reagents were commercially available and of synthetic grade. Solvents were of analytical grade and used without further purification. $^1$H NMR spectra were recorded on Bruker 200 or 400 MHz spectrometers and are given in ppm relative to TMS. Infrared spectra were recorded on a Bruker Fourier transform spectrometer as nujol emulsion. All new substances were monospot by TLC and exhibited spectroscopic data consistent with the assigned structures. Elemental analyses (C, H, N) were performed on a Carlo Erba 1108 instrument. Melting points were obtained on a Reichert hot stage microscope and are uncorrected. Silica gel 60, Merck 230-400 mesh, was used for both flash and medium pressure chromatography. TLC were performed on pre-coated 5 x 10 cm, Merck silica gel 60 F254 plates (layer thickness 0.25 mm). Chiral HPLC was performed on Daicel OC column eluted with a mixture of heptane and isopropanol (90/10) and detection at 220 nm.

4-[(2,3-Dimethylphenyl)hydroxymethyl]-1-(triphenylmethyl) imidazole 2. A solution of 1-bromo-2,3-dimethylbenzene (11.5 g, 62 mmole) in THF (200 ml) was
added dropwise to magnesium turnings (1.5 g, 62 mmole) covered with THF (50 ml) containing one crystal of iodine. When around 10 % of the bromide was added, the suspension was heated to reflux. After discoloration of the solution had occurred, the addition of the bromide was continued under reflux. At the end of the addition, the solution was heated to reflux for one hour then cooled to room temperature. The decanted solution was added dropwise at 0°C to a solution of 1-(triphenylmethyl)imidazolecarboxaldehyde 1 (17.5 g, 52 mmole) in dry THF (225 ml). At the end of the addition, the mixture was allowed to warm to room temperature and the solution was stirred for 1.5 additional hour. A saturated NH₄Cl solution (500 ml) was then added, the aqueous phase extracted with dichloromethane (3 × 75 ml), the pooled organic extracts dried over MgSO₄ and the solvents evaporated under reduced pressure. Towards the end of the evaporation (=100 ml) a solid appeared which was filtered and washed with pentane, to give 12.3 g (52 % yield) of 2 as a white solid: mp 203 °C; ¹H NMR (CDCl₃) δ 7.5 (d, 1H), 7.4 (dd, 1H), 7.3 (m, 9H), 7.1 (m, 6H), 7.0-7.1 (m, 2H), 6.45 (d, 1H), 6.05 (s, 1H), 3.0-3.3 (m, 1H), 2.2 (s, 3H), 2.1 (s, 3H). IR: vOH = 3100-3400 cm⁻¹. TLC: CH₂Cl₂/EtOH (9/1).

C₃₁H₂₃N₂O calc. C 83.75 H 6.35 N 6.30 (444.58) found 83.29 6.30 6.23

4-[(2,3-Dimethylphenyl)carbonyl]-1-(triphenylmethyl) imidazole 3. A solution of 2 (12.3 g, 28 mmole) in dioxane (500 ml) was mixed with MnO₂ (24.1 g, 280 mmole) and heated to reflux with stirring for 5 h. The warm suspension was filtered on a celite bed, the solid washed with warm dioxane (2 × 50 ml) and the filtrate evaporated under reduced pressure. The residue was taken up in cyclohexane (100 ml) and ethylacetate (50 ml), and the solid was collected to give
11.2 g (90 % yield) of 3 as a white solid: mp 171 °C; 1H NMR (CDCl₃) δ 7.55 (d, 1H), 7.5 (dd, 1H), 7.35 (m, 9H), 7.05-7.4 (m, 3H), 7.15 (m, 6H), 2.3 (s, 3H), 2.25 (s, 3H). IR: ν_C=O = 1655 cm⁻¹. TLC: CH₂Cl₂/EtOH (9/1).

C₃₆H₃₆N₂O   calc.  C 84.13  H 5.92  N 6.33
(442.57)  found  84.15  5.98  6.29

4-[1-(2,3-Dimethylphenyl)-1-hydroxyethyl]-1-(triphenylmethyl) imidazole 4.

A solution of methylmagnesium bromide (16.6 ml, 3N in ether, 50 mmole) was added dropwise at 0 °C to a solution of 3 (11 g, 25 mmole) in THF (95 ml). At the end of the addition, the mixture was allowed to warm to room temperature and stirred for 2 h. The solution was cooled back to 0 °C, a saturated solution of NH₄Cl (15 ml) and CH₂Cl₂ (500 ml) were added and the organic solution was washed with water (3 × 100 ml) and saturated NaCl before drying over Na₂SO₄ and evaporation under reduced pressure. The solid residue was taken up in a mixture of warm cyclohexane/ethyl acetate (75 ml; 95/5), cooled and filtered to give 10.9 g (95 % yield) of 4 as a white solid: mp 225 °C; 1H NMR (CDCl₃) δ 7.5 (d, 1H), 7.45 (d, 1H), 7.3 (m, 9H), 7.15 (m, 6H), 7.05 (d, 2H), 6.5 (d, 1H), 3.1 (m, 1H), 2.2 (s, 3H), 2.1 (s, 3H), 1.9 (s, 3H). IR: ν_HOH = 3216 cm⁻¹. TLC: CH₂Cl₂/EtOH (9/1).

C₁₂H₁₄N₂O   calc.  C 83.81  H 6.59  N 6.11
(458.61)  found  84.47  6.55  6.01

(S,R)-4(5)-[1-(2,3-Dimethylphenyl)ethyl]imidazole; Medetomidine 5.

Trifluoroacetic acid (17.5 ml, 25.5 g, 224 mmole) was added dropwise at -10 °C to a solution of 4 (10.3 g, 22.4 mmole) and triethylsilane (13 g, 112 mmole) in CH₂Cl₂ (500 ml). After 4h, the temperature was raised to room temperature and
the solution was stirred overnight. The organic solution was washed with saturated NaHCO₃ (4 × 100 ml), and water (100 ml), dried over MgSO₄ and evaporated under reduced pressure. The residue was taken up in ether (500 ml), extracted with 2N HCl (4 × 25 ml) and the aqueous solution was hydrogenated (1 bar, room temperature) in the presence of Pd/C (5 %) for 2 h. The catalyst was filtered on celite and the aqueous solution neutralised with concentrated NaOH (35 %, ≈ 16 ml) and extracted with ether (4 × 125 ml). Pooled organic solutions were dried over MgSO₄, evaporated under reduced pressure and crystallized from a mixture of cyclohexane/toluene (50 ml, 99/1) to give 4.1 g (93 % yield) of 5 as a white solid: mp 172 °C; ¹H NMR (CDCl₃) δ 7.4 (d, 1H), 6.9-7.1 (m, 3H), 6.75 (m, 1H), 4.4 (q, 1H), 2.3 (s, 3H), 2.2 (s, 3H), 1.6 (d, 3H). IR: νOH and/or νNH = 3500 and 1700 cm⁻¹. TLC: CH₂Cl₂/EtOH/NH₃ (9/1.8/0.2).

C₁₁H₁₆N₂  calc.  C 77.96  H 8.05  N 13.99
(200.29)  found  77.69  7.98  13.82

(S)-4(5)-[1-(2,3-Dimethylphenyl)ethyl]imidazole  (+)-tartrate;

Dexmedetomidine 6. (+)-Tartaric acid (1.1 g, 7.37 mmole) was added to 5 (2.95 g, 14.75 mmole) dissolved in absolute ethanol (59 ml). The suspension was heated to reflux until complete-dissolution and stirred for 20 h at room temperature before filtration of the white solid (2.05 g, purity 27/73). The solid was suspended by stirring for 18 h in ethanol (60 ml) and filtered (1.58 g, purity: 17.5/82.5). The new solid was suspended by stirring for 66 h in ethanol (51 ml) and filtered (1.21 g, purity: 4/96). The solid was dissolved in water (20 ml) and the solution neutralised with 1N NaOH (4 ml). The solution was extracted with ether (2 × 100 ml) and the organic solution dried over MgSO₄ and evaporated under reduced pressure. The residue (655 mg, 3.28 mmole) was dissolved in hot ethanol (40 ml)
with (+)-tartaric acid (471 mg, 3.14 mmole) and the solution was stirred at room temperature overnight. The solid was filtered to give 6 (824 mg, purity: 0.5/99.5, 21 % overall yield): mp 184 °C; ¹H NMR (CDCl₃) δ 7.75 (s, 1H), 6.85-7.05 (m, 3H), 6.8 (s, 1H), 4.35 (q, 1H), 4.25 (s, 2H), 2.2 (s, 3H), 2.25 (s, 3H), 1.5 (d, 3H), the five exchangeable protons appears as a broad absorption which can not be characterized with accuracy. IR: νOH and/or νNH = 3150-3455 cm⁻¹; νOH acid and/or νNH⁺ = 1800-3000 cm⁻¹; νC=O and νC=O⁺ = 1708 cm⁻¹; νC=O = 1624 cm⁻¹; νC=O(COO⁻) = 1584 cm⁻¹. Optical purity was determined as > 99% by HPLC chromatography over a Daicel OC column eluted with a mixture of heptane and isopropanol (9/1), UV detection at 220 nm.

C₁₁H₁₆N₂C₄H₆O₈ calc. C 58.28  H 6.33  N 8.00
(350.37) found  57.98  6.36  7.73

References

8 Cordi, A.A.; Snyers, M.P.; Giraud-Mangin, D.; Van der Maesen, C.; Van Hoeck,
DEXMEDETOMIDINE

J.-P.; Beuze, S.; Ellens, E; Napora, F.; Gillet, C.L.; Gorissen, H.; Calderon, P.;


10 Jacques, J.; Collet, A.; Wilen, S.H. In *Enantiomers, Racemates and Resolutions;*

(Received in The Netherlands 30 September 1995)