A Concise Synthesis of Atipamezole

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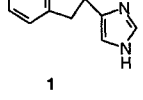
Atipamezole (**1**), a potent α_2 adrenergic receptor antagonist, was synthesized in four steps from dibromide **2** and 2,4-pentanedione.

Atipamezole (**1**) is a potent α_2 adrenergic receptor antagonist which is marketed by Orion-Farmos as a veterinary product to reverse the sedative effect produced by the α_2 agonist medetomidine. Atipamezole is also undergoing clinical evaluation as an antidiabetic as well as an antidepressant agent.[1] In addition, there are reports that this compound may be useful in the treatment of asthma, obesity, migraine,[2] and age related memory impairment and other cognitive disorders.[3] Recently, atipamezole was shown to reverse laparotomy-induced ileus,[4] and to reduce urine production in the rat.[5] Given its broad range of biological activities, and as part of a program directed at the identification of selective α adrenergic agents,[6] we were interested in evaluating the pharmacological profile of atipamezole in cloned human α adrenergic receptors. This paper focuses on the development of a concise synthesis of this interesting agent.[7]



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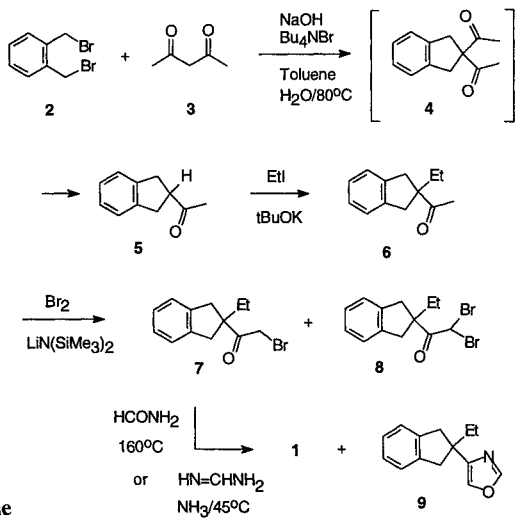
Several synthetic routes to atipamezole have been reported since 1985.[2,8] In general, these procedures were problematic because they were lengthy (up to eleven steps), reaction yields were not reported in many cases, or there were other synthetic difficulties.

We desired a process with fewer steps and involving an intermediate which could potentially be modified for the preparation of other atipamezole analogs. A compound such as 2-acetylindan (**5**, Scheme) serves as an ideal intermediate because it allows for aromatic ring functionalization as well as alkylation at C-2 of the indan ring with various alkylating agents to provide atipamezole analogs having different alkyl side chains.



Scheme

Although several syntheses of 2-acetylindan (**5**) have been documented, none was a simple, one-step preparation.[9] We observed that dibromide **2** reacted with 2,4-pentanedione (**3**) under phase transfer catalysis conditions to provide **5** in 63% yield in one step. Presumably, the initial reaction product was 2,2-diacetylindan (**4**) which underwent cleavage in the presence of sodium hydroxide to afford compound **5**.

When ketone **5** was treated with ethyl iodide and lithium bis(trimethylsilyl)amide in tetrahydrofuran, no desired product could be isolated. However, when ethylation was performed using potassium *tert*-butoxide as the base, an 88% yield of intermediate **6** was obtained.

Bromination of ketone **6** using bromine in dichloromethane[2] was sluggish and led to many byproducts including dibromo compound **8**. Bromination in acetic acid also yielded **8** as the major product. However, the process could be substantially improved by brominating the enolate generated from compound **6** after treatment with lithium bis(trimethylsilyl)amide.[10] Although dibromination was not eliminated, the desired monobromo compound **7** could be isolated in 56% yield.

When repeating a literature procedure[2] for converting bromo ketone **7** to atipamezole using formamide at 160°C, atipamezole was formed as the minor product. The major product in this reaction was the oxazole **9** which was obtained in 46% yield. The original documents which describe this reaction did not mention the formation of any oxazole, and the yield of the reaction was not given. By varying the reaction temperature (110 to 180°C), we did not dramatically improve the yield of **1** (< 30%). Nevertheless, the desired product could easily be separated from the oxazole because the former was soluble in aqueous hydrochloric acid from which the oxazole could be extracted away; subsequent basification and extraction of the acidic phase then afforded pure **1**. Therefore, no chromatography was necessary to isolate or purify the product.

In any case, we investigated formamidine[11] as an alternative reagent. Mechanistically, this reagent was expected to be less likely to produce oxazole byproduct while, perhaps, increasing the yield of imidazole.

However, varying the quantity of the reagent (120 to 250 mol%), the nature of the solvent (DMF, EtOH, MeOH, pyridine, CH_2Cl_2, NH_3), the reaction temperature (−15 to 78°C), and the nature of the base ($NaHCO_3$, Na_2CO_3, Et_3N, NH_3, pyridine) did not increase the yield of the desired product. Nonetheless, we did not detect the formation of oxazole in these reactions.

In conclusion, we have accomplished a four-step synthesis of the potent α_2 adrenergic receptor antagonist atipamezole. Although the last step is low-yielding, the conciseness of the synthesis and the ease of isolating the final compound should make this synthesis an attractive al-

ternative to the previously disclosed procedures. Moreover, 2-acetylindan **(5)** has been prepared in one step and serves as a potentially useful intermediate for the preparation of other structurally related compounds.

All reagents and solvents were purchased from Aldrich Chemical Co., Inc. and used without further purification. Melting points (uncorrected) were determined on a Mel-Temp apparatus in open capillary tubes. ^{1}H and ^{13}C NMR spectra were recorded on a GE QE Plus 300 MHz spectrometer referenced to residual $CHCl_3$. Infrared spectra were obtained on a Nicolet 205 FT-IR spectrometer. Mass spectra were obtained by Oneida Research Services, Inc. in New York. Elemental analyses were performed at Robertson Microlit Laboratories, Inc. in New Jersey. Satisfactory microanalyses were obtained for all new compounds: C ± 0.07, H ± 0.1 (Exception: **5**, C + 0.51).

2-Acetylindan (5):
To a suspension of Bu_4NBr (0.62 g, 2 mmol) in H_2O (18 mL) containing NaOH (8.80 g, 0.22 mol) was added α,α′-dibromo-*o*-xylene (**2**; 10.02 g, 38 mmol) in toluene (50 mL), followed by the dropwise addition of 2,4-pentanedione (**3**; 3.80 g, 38 mmol) in toluene (10 mL). The mixture was then heated at 80 °C for 5 h. Upon cooling to r.t., the organic layer was separated and the aqueous layer was extracted with toluene (60 mL). The combined organic phase was washed with H_2O (50 mL), dried ($MgSO_4$), filtered and concentrated to afford a light orange oil (6.14 g). It was dissolved in CCl_4 and flash chromatographed over silica gel (210 g) eluting with EtOAc/hexane (1:20) to give **5** as a pale yellow oil (3.83 g, 63 % yield).

^{1}H NMR ($CDCl_3$): δ = 7.21–7.12 (m, 4H), 3.43 (m, 1H), 3.18 (m, 2H), 3.15 (m, 2H), 2.23 (s, 3H).

^{13}C NMR ($CDCl_3$): δ = 29.1, 35.6, 52.5, 125.1, 127.3, 142.1, 210.0.

IR (Film): $\nu = 1713\ cm^{-1}$.

MS (CI): $m/z = 161\ (MH^+)$.

2-Acetyl-2-ethylindan (6):[12]
A solution of 2-acetylindan (**5**; 2.66 g, 16.60 mmol) in anhydr. THF (8 mL) was added dropwise to a solution of *t*-BuOK in THF (1 M, 17.4 mL, 17.4 mmol) which was cooled by a dry ice-acetone bath. After 15 min, EtI (1.3 mL, 16.25 mmol) was added dropwise to the reaction mixture. It was allowed to warm to r.t. over 5 h and then stirred for another hour. Ice water (10 mL) was added and the organic layer was separated. The aqueous layer was extracted with EtOAc (2 × 15 mL), and the combined organic phase was dried ($MgSO_4$), filtered and concentrated to give an orange oil (3.08 g). It was dissolved in CCl_4 and flash chromatographed over silica gel (180 g) eluting with EtOAc/hexane (1:30 and then 1:25) to afford **6** as a pale yellow oil (2.75 g, 88 % yield).

^{1}H NMR ($CDCl_3$): δ = 7.18–7.10 (m, 4H), 3.36 (d, 2H, *J* = 16.0 Hz), 2.83 (d, 2H, *J* = 15.9 Hz), 2.17 (s, 3H), 1.78 (q, 2H, *J* = 7.5 Hz), 0.81 (t, 3H, *J* = 7.5 Hz).

^{13}C NMR ($CDCl_3$): δ = 10.2, 26.5, 31.5, 40.9, 61.5, 125.2, 127.2, 141.8, 212.1.

IR (Film): $\nu = 1704\ cm^{-1}$.

MS (CI): $m/z = 189\ (MH^+)$.

2-Bromoacetyl-2-ethylindan (7):[12]
Compound **6** (300 mg, 1.59 mmol) was dissolved in anhydr. THF (3 mL) and added dropwise to $(Me_3Si)_2NLi$ in THF (1 M, 1.7 mL, 1.7 mmol) cooled by a dry ice-acetone bath. The solution was allowed to warm to r.t. and then cooled again to −78 °C. Br_2 (85 µL, 1.65 mmol) was added. After 15 min, $NaHCO_3$ solution (5 mL) was added. Extraction with EtOAc (3 × 3 mL) gave a yellow oil. It was dissolved in CCl_4 and flash chromatographed over silica gel (30 g) eluting with EtOAc/hexane (1:40) to afford **7** as a colorless oil (239 mg, 56 % yield).

^{1}H NMR ($CDCl_3$): δ = 7.16 (m, 4H), 4.11 (s, 2H), 3.40 (d, 2H, *J* = 16.1 Hz), 2.92 (d, 2H, *J* = 16.1 Hz), 1.81 (q, 2H, *J* = 7.4 Hz), 0.85 (t, 3H, *J* = 7.4 Hz).

^{13}C NMR ($CDCl_3$): δ = 10.3, 31.6, 32.9, 41.4, 61.1, 125.2, 127.5, 141.2, 204.6.

IR (Film): $\nu = 1720, 1716\ cm^{-1}$.

MS (CI): $m/z = 267, 269\ (MH^+)$.

Atipamezole (1):
Compound **7** (270 mg, 1.01 mmol) was heated at 160 °C in formamide (2 mL) for 30 min. The solution was cooled by a water bath when water (2 mL) was added followed by 1 N HCl (2 mL). The mixture was washed with CH_2Cl_2 (2 × 4 mL), basified with NH_4OH to pH 9 and extracted with EtOAc (2 × 4 mL). The extract was washed with H_2O, dried ($MgSO_4$), filtered and concentrated to give **1** as a yellow solid (48 mg, 22 % yield). Recrystallization of this solid from benzene/hexane afforded an analytical sample as tan crystals (41 mg); mp 122–126 °C [Lit.[2] mp (HCl salt) 211–215 °C].

^{1}H NMR ($CDCl_3$): δ = 7.56 (s, 1H), 7.20 (m, 2H), 7.14 (m, 2H), 6.77 (s, 1H), 3.26 (d, 2H, *J* = 15.5 Hz), 3.09 (d, 2H, *J* = 15.7 Hz), 1.91 (q, 2H, *J* = 7.4 Hz), 0.80 (t, 3H, *J* = 7.4 Hz).

Alternatively, compound **7** was treated with formamidine acetate (120–250 mol %) in liquid ammonia and heated at 45 °C in a sealed pressure tube overnight. After the solvent was evaporated off, the residue was triturated with Na_2CO_3 solution and extracted with EtOAc. The crude product from the organic extract was then flash chromatographed over silica gel eluting with EtOAc/Et_3N (20:1) to give compound **1**; yield: < 30 %.

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