JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS
J Label Compd Radiopharm 2003; **46**: 131–138.
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jlcr.651

Research Article

Synthesis of *N*, *N*-diethyl-4-[phenyl-(piperidin-4-ylidene)methyl]-[*carboxy*-^{14}C]benzamide, a potent δ opioid receptor agonist

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Summary

The synthesis of carbon-14 labelled *N*,*N*-diethyl-4-[phenyl-(piperidin-4-ylidene)methyl]-benzamide is described. The radioisotope is introduced *via* an aryllithium reaction with $^{14}CO_2$ to form the labelled acid, which is subsequently transformed into the amide. Copyright © 2002 John Wiley & Sons, Ltd.

Key Words: δ agonist; benzamide; carbon-14; aryllithium

Introduction

N, *N*-Diethyl-4-[phenyl-(piperidine-4-ylidene)methyl]-benzamide [***1***, AR-M 390, Figure 1] is a potent, orally active opioid agonist, currently under investigation at AstraZeneca as one of a series of 4-[aryl-(piperidine-4-ylidene)methyl]-benzamides. It binds to the δ opioid receptor with high affinity, is a potent full agonist and has exceptional

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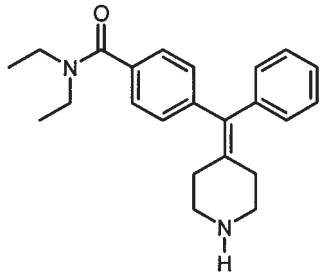
Received 11 March 2002
Revised 29 May 2002
Accepted 11 June 2002



AR-M 390, *1*

Figure 1.

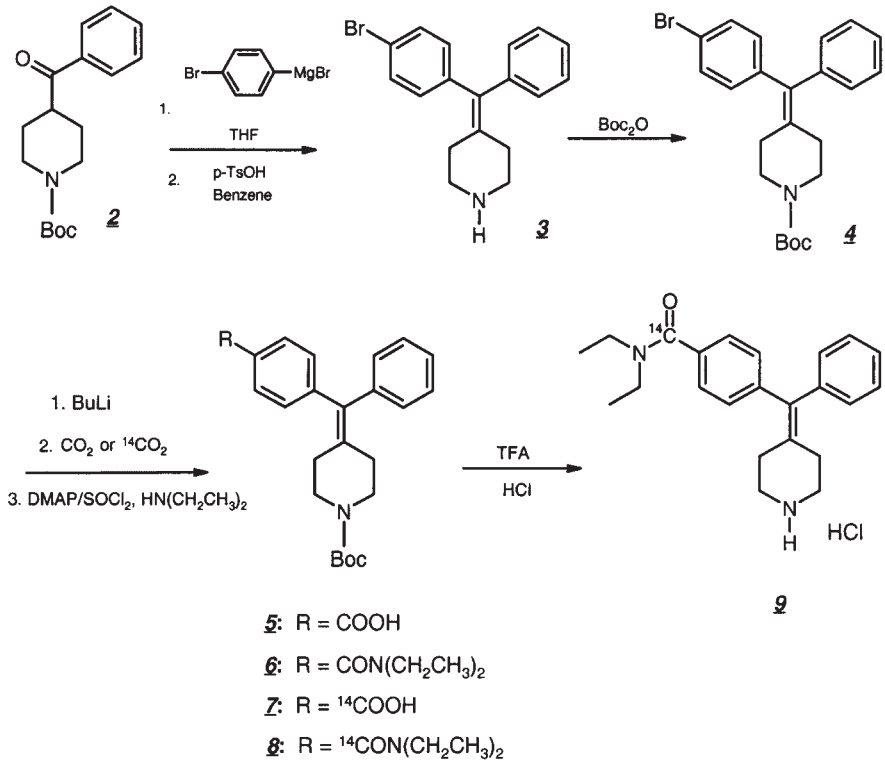
selectivity with respect to μ and κ opioid receptors[1]. During the pharmacological evaluation of AR-M 390, the compound was required labelled with carbon-14 to be used in autoradiographic studies. The synthesis of [^{14}C]AR-M 390 described here constitutes the general method used for the preparation of ^{14}C-labelled benzamides from this series.

Results and discussion

Results from metabolic studies of this class of compounds led us to choose to label AR-M 390 (*1*) with carbon-14 in its amide carbonyl group (Figure 1). This functionality remained attached to the main molecular structure in all the metabolites that were identified, suggesting that a label in this position would be ideal for elucidating the distribution of the compound.

The radioactive carbon atom at this position could be incorporated by the reaction between an organolithium precursor and $^{14}CO_2$, forming the corresponding labelled carboxylic acid, which would serve as the precursor for the preparation of the amide. The starting material was prepared from the *t*-Boc-protected amino ketone *2* (Scheme 1).

The Grignard reaction between 4-bromo-phenylmagnesium bromide and ketone *2* produced the corresponding alcohol, which was dehydrated in refluxing benzene in the presence of *p*-TsOH. Under these reaction conditions, the *N*-protecting group was also cleaved off



Scheme 1.

to furnish amine ***3***, which was re-protected with di-*tert*-butyl dicarbonate to give compound ***4***.

The remaining steps of the synthesis, which constitute the radiosynthesis, were first validated with non-radioactive material. The protected amino bromide ***4*** was subjected to halogen–lithium exchange by treatment with *n*-butyllithium at $-78^{\circ}C$ to give the corresponding aryl–lithium reagent. This was reacted with carbon dioxide, generated by the action of concentrated sulfuric acid on barium carbonate, to provide the acid ***5***. The reaction was performed on a vacuum manifold. Treatment of the acid ***5*** with thionyl chloride/DMAP at $-20^{\circ}C$, formed the acid chloride which was coupled, *in situ*, with diethylamine to give amide ***6***.

When this procedure was applied to the preparation of the carbon-14 labelled material, the reaction with $^{14}CO_2$ produced acid ***7*** in 44% yield. The acid ***7*** was transformed into the amide ***8*** (90% yield), which was

subsequently treated with TFA/CH_2Cl_2 to provide [^{14}C]AR-M 390. The compound was purified by column chromatography, from which one fraction was treated with HCl/EtOH to produce the hydrochloride **9** with a specific activity of 48.7 mCi/mmol.

Experimental

Melting points were determined on a Thomas–Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Pragon 100 FT-IR spectrometer. NMR spectra were recorded on a Varian Unity Plus 400 MHz spectrometer with $(CH_3)_4Si$ (TMS) as the internal reference. Elemental analyses were performed by Canadian Microanalytical Service Ltd., Delta, British Columbia and the results were within $\pm 0.4\%$ of the theoretical values unless otherwise indicated. Radiochemical purity was determined by TLC using a Raytest Rita 92 detector or with HPLC connected to a Packard Radiomatic 500TR detector. The HPLC-system was a Luna C18-column with CH_3CN containing 0.04% HCOOH in H_2O as eluent (18:82% at $t = 0$ and 25:75% at $t = 6$ min, postrun 3 min). Flow rate: 0.6 mL/min. Radioactivity was measured in a Packard Tri-Carb 2300TR liquid scintillation spectrometer using Packard Ultima Gold as counting medium. *n*-BuLi was purchased from Aldrich and the concentration determined by titration with diphenylacetic acid[2]. Drying of organic extracts was performed with Na_2SO_4.

*4-Bromo-[phenyl-(piperidin-4-ylidene)methyl]-benzene, (**3**)*

To a solution of *N-tert*-butoxycarbonyl-4-benzoylpiperidine (**2**)[1], (6.65 g, 23 mmol) in THF (30 mL) cooled by an ice-water bath, was added 4-bromo-phenylmagnesium bromide (1 M in THF, 25 mL). When the addition was completed, the cooling bath was removed and the reaction mixture refluxed for 2 h. The mixture was cooled to room temperature and saturated aqueous NH_4Cl was added followed by diethyl ether. The organic layer was separated and washed with brine, dried and evaporated to dryness. The residual oil was mixed with benzene (150 mL) and *p*-TsOH $\times$ H_2O (8.6 g) and heated to reflux with water removal by means of a Dean–Stark trap. After 2 h the water had ceased to form and the reaction mixture was cooled to room temperature. 2 M HCl was added followed by diethyl ether. The

aqueous layer was separated, washed with diethyl ether and made basic (pH ~ 10) with solid NaOH. Extraction with diethyl ether gave, after drying and evaporation of the solvent, a solid residue of crude compound ***3*** (6.10 g, 81% yield). An analytical sample was converted to the HCl-salt and recrystallized from EtOH–diethyl ether. M.p. 187–189°C. ^{1}H NMR ($CDCl_3$, TMS): δ 2.69 (4 H, m), 3.21 (4 H, m), 6.88–6.98 (2 H, m), 6.99–7.09 (2 H, m), 7.20–7.34 (3 H, m), 7.36–7.45 (2 H, m), 9.77 (2 H, br s,). ^{13}C NMR ($CDCl_3$, TMS): δ 28.11, 45.09, 121.32, 127.40, 128.50, 129.17, 129.42, 130.90, 131.59, 138.97, 140.44. Anal. ($C_{18}H_{19}BrClN$): C, H, N.

*4-Bromo-[(phenyl-(N-tert-butoxycarbonyl)piperidin-4-ylidene) methyl]-benzene, (**4**)*

To a mixture of amine ***3*** (6.10 g, 18.6 mmol) and $KHCO_3$ (4.0 g, 40 mmol) in H_2O/THF (20 mL/15 mL) was added di-*tert*-butyl dicarbonate (4.9 g, 22.5 mmol). The mixture was refluxed for 1 h and after cooling to room temperature, EtOAc (100 ml) was added. The organic layer was separated and washed with H_2O (2 × 75 mL) and dried. Evaporation to dryness left a solid residue, which was crystallized from EtOAc–hexane to give 5.50 g (69% yield) of compound ***4***. M.p, 120–123°C. ^{1}H NMR ($CDCl_3$, TMS): δ 1.46 (9 H, s), 2.30–2.33 (4 H, m), 3.44–3.46 (4 H, m), 6.98 (2 H, d, $J = 8.0$ Hz), 7.05–7.13 (2 H, m), 7.18–7.32 (3 H, m), 7.40 (2 H, d, $J = 8.0$ Hz). ^{13}C NMR ($CDCl_3$, TMS): δ 28.44, 31.56, 45.12, 79.57, 120.57, 126.75, 128.18, 129.64, 131.52, 135.17, 136.19, 141.05, 141.63, 154.80. Anal. ($C_{23}H_{26}BrNO_2$): C, H, N.

*4-[(Phenyl-(N-tert-butoxycarbonyl)piperidin-4-ylidene)methyl]-benzoic acid, (**5**)*

On a vacuum manifold, *n*-BuLi (1.4 M in hexane, 0.7 mL, 0.98 mmol) was added at −78°C to a solution of aryl bromide ***4*** (402 mg, 0.94 mmol) in THF (5 mL). The mixture was stirred at −78°C for 1 h after which CO_2 (from $BaCO_3$, 200 mg, 1 mmol and conc. H_2SO_4) was introduced during 15 min. The temperature was maintained for another 15 min and then the stirring was continued at room temperature. After 4 h, H_2O was added to the reaction mixture followed by 1 M citric acid to pH ~ 3. The organic layer was separated, washed with H_2O and dried. After evaporation of the solvent to dryness, the residue was

recrystallized from EtOAc–heptane to give acid **5** (123 mg, 33% yield). M.p. 216–217°C. IR (KBr): ν 2974, 1719, 1692 cm^{-1}. ^1H NMR ($CDCl_3$, TMS): δ 1.43 (9 H, s), 2.23–2.36 (4 H, m), 3.38–3.50 (4 H, m), 7.04–7.09 (2 H, m), 7.18 (2 H, d, $J = 8.6$ Hz), 7.20–7.30 (3 H, m), 7.99 (2 H, d, $J = 8.6$ Hz).). ^{13}C NMR ($CDCl_3$, TMS): δ 28.44, 31.60, 45.03, 79.69, 126.90, 127.43, 128.27, 129.69, 129.86, 130.07, 135.94, 136.50, 141.33, 147.85, 154.83, 171.11. Anal. ($C_{24}H_{27}NO_4$): C, H, N.

*N,N-Diethyl-4-[(phenyl-(N-tert-butoxycarbonyl)piperidin-4-ylidene) methyl]-benzamide, (**6**)*

To a solution of DMAP (83 mg, 0.68 mmol) in CH_2Cl_2 (2.5 mL) at -20°C, $SOCl_2$ (40 μL, 0.54 mmol) was added dropwise. A precipitate was formed while the mixture was stirred for 15 min. To the slurry, the acid **5** (120 mg, 0.31 mmol) in CH_2Cl_2 (1 mL) was added and after 15 min at -20°C the mixture had become a clear solution. Diethylamine (150 μL, 1.48 mmol) was added and the cooling bath removed. After stirring overnight, the reaction mixture was washed with 1 M citric acid, H_2O and dried. Evaporation to dryness provided the amide **6** (104 mg, 75% yield). M.p. 121–123°C, (EtOAC–hexane). IR (KBr): ν cm^{-1}. ^1H NMR ($CDCl_3$, TMS): δ 1.13 (3 H, br s), 1.23 (3 H br s), 1.46 (9 H, s), 2.25–2.40 (4 H, m), 3.29 (2 H, br s), 3.40–3.52 (4 H, m), 3.54 (2 H br s), 7.08–7.12 (2 H, m), 7.14 (2 H, d, $J = 8.0$ Hz), 7.20–7.26 (1 H, m), 7.26–7.30 (2 H, m), 7.31 (2 H, d, $J = 8.0$ Hz). ^{13}C NMR ($CDCl_3$, TMS): δ 12.85, 14.24, 28.40, 31.50, 39.15, 43.26, 45.41, 79.50, 126.21, 126.64, 128.08, 129.65, 129.69, 135.13, 135.26, 136.58, 141.71, 143.03, 154.75, 171.08. Anal. ($C_{28}H_{36}N_2O_3$); C, H, N.

*4-[(Phenyl-(N-tert-butoxycarbonyl)piperidin-4-ylidene)methyl]-[carboxy-^{14}C]benzoic acid, (**7**)*

To a stirred solution of bromide **4** (431 mg, 1 mmol) in THF (5 mL), in a flask attached to a vacuum manifold, was added dropwise at -78°C, a solution of *n*-BuLi (1 mL, 1.6 M in hexane). After 75 min at this temperature, $^{14}CO_2$ (from $Ba^{14}CO_3$, 50 mCi, 55 mCi/mmol) was introduced, the cooling bath removed and the reaction mixture left overnight to reach room temperature. To the yellow solution, 1 M aqueous citric acid was added (pH $\sim$ 3) followed by diethyl ether (5 mL). The organic layer was separated, washed with H_2O, dried and evaporated to dryness. The residue was purified by flash chromato-

graphy on a SiO_2 column using EtOAc: *n*-hexane (1:1) with HOAc (2%) as eluent. The main fraction (210 mg, 19.7 mCi) of an oil, crystallized by the addition of EtOAc providing the acid **7** (158 mg) with a radiochemical purity of 96%, as determined by TLC in the same system.

*N,N-Diethyl-4-[(phenyl-(N-tert-butoxycarbonyl)piperidin-4-ylidene) methyl]-[carboxy-^{14}C]benzamide, (**8**)*

To a solution of DMAP (85 mg, 0.7 mmol) in CH_2Cl_2 (2.5 mL) was added $SOCl_2$ (50 µl, 0.67 mmol) at −20°C. A white precipitate was formed and after 15 min of stirring, the acid **7** (158 mg, 0.40 mmol) in CH_2Cl_2 (3 mL) was added, dropwise, keeping the temperature between −25 and −20°C. The stirring was continued at the same temperature while the precipitate dissolved. After 15 min, diethylamine (150 mg, 2 mmol) was added and the stirring continued for 1 h. 2 M HCl (2 mL) was added and the organic layer separated, washed with 1 M aqueous citric acid, H_2O and dried. Evaporation to dryness left benzamide **8** as a glass [162 mg, 14.9 mCi, radiochemical purity: 95.7%, as determined by TLC: SiO_2/hexanes–EtOAc, (1:1)] which was used in the next step.

*N,N-Diethyl-4-[(phenyl-(piperidin-4-ylidene)methyl]-[carboxy-^{14}C] benzamide hydrochloride, (**9**)*

The compound **8** was dissolved in CH_2Cl_2 (1 mL) and trifluoroacetic acid (TFA) (100 µL) was added. The mixture was stirred at room temperature and after 2 h, TLC indicated 29% conversion and more TFA (50 µL) was added. After another hour, TLC indicated 53% conversion and 100 µL of TFA was added and the stirring continued. After 1 h, CH_2Cl_2 (3 mL) was added and the pH adjusted to ~ 10 with 2 M NaOH. The organic layer was separated, washed with H_2O and dried. Evaporation to dryness left a residue (109 mg) which was purified on a SiO_2 column using CH_2Cl_2 (w. drops of conc. NH_3) with a gradient of MeOH as eluent. Three fractions containing the base of compound **9** were collected (tot. 88 mg). The first fraction (55 mg) was treated with HCl in EtOH to furnish the compound **9** (6.6 mCi, spec. act: 48.7 mCi/mmol, radiochemical purity: 99.4% by HPLC and 98.1% by TLC, [SiO_2/CH_2Cl_2–MeOH–NH_4OH (9:1:drps)].

Acknowledgements

The author is grateful to Mr Peter Ström, AstraZeneca R&D Lund, Sweden, for providing laboratory space and equipment.

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