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Research Article

Efficient *in-loop* synthesis of high specific radioactivity [^{11}C]carfentanil

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Summary

The synthesis of the precursor for [^{11}C]carfentanil and the precursor labelling with ^{11}C have both been improved. The problem 'bottleneck' step in the carfentanil precursor synthesis, due to low chemical yield (14%) of intermediates nitrile into amide conversion, has been solved. Application of a H_2O_2/K_2CO_3/DMSO reaction method significantly increased the yield of this chemical transformation (up to 84%). A simple and straightforward synthesis of [^{11}C]carfentanil was achieved by combining *in-loop* methylation of the ammonia salt of the precursor by [^{11}C]CH_3I, using tetrabutylammonium hydroxide as a base, with a previously developed product purification procedure using a C2 extraction disc. A decay corrected yield with respect to [^{11}C]CH_3I of [^{11}C]carfentanil was 64 $\pm$ 12% ($n = 6$) with the synthesis time of 21 min. The radiochemical purity was >98%. Comparatively high specific radioactivity of [^{11}C]carfentanil [11.2 $\pm$ 4.8 Ci/μmol (EOS, $n = 5$)] was partially attributed to the use of [^{11}C]methane target gas for production of carbon-11 methyl iodide. Copyright © 2003 John Wiley & Sons, Ltd.

Key Words: [^{11}C]carfentanil; opioid receptor; in-loop synthesis

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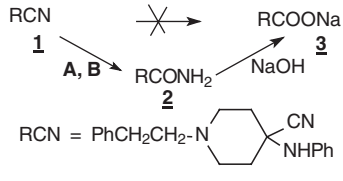
Introduction

Two approaches to the synthesis of the μ-opioid receptor agonist [^{11}C]carfentanil[1] have been previously reported. In the original procedure[2] radiolabelling was achieved by heating the sodium salt of the carboxylate precursor with [^{11}C]CH_3I followed by product purification on reverse-phase HPLC. This synthesis was significantly improved in a more recently published procedure[3] when ^{11}C-methylation of the ammonium salt of the precursor with [^{11}C]methyl triflate was followed by the product purification using a C2 extraction disc. We have further modified the [^{11}C]carfentanil synthesis by combining the [^{11}C]CH_3I methylation of the ammonium salt of the precursor, with the convenient 'In-Loop Method'[4–6] of labelling followed by product purification using a C2 extraction disc. An improvement of specific radioactivity was achieved by using [^{11}C]CH_4 (rather than [^{11}C]CO_2) generated in the target as the source of carbon-11 for the synthesis of [^{11}C]CH_3I.[7] We also report an improved procedure for the synthesis of the precursor to [^{11}C]carfentanil.

Results and discussion

During the synthesis of the carboxylic acid precursor to [^{11}C]carfentanil we encountered a problem of low yield ($<3\%$ ours; 14% literature)[8] for the conversion of nitrile **1** into amide **2** (Scheme 1, followed by hydrolysis to the acid). To bypass this 'bottleneck', direct conversion of nitrile **1** into the acid **3** was attempted; however, the reaction did not proceed under acidic or basic conditions. Heating of **1** with tetrafluorophthalic acid in the absence of solvent[9] also failed to yield the product. Among different methods available for the conversion of nitriles to amides[10] we choose H_2O_2/K_2CO_3/DMSO;[11] high-yield (84%) conversion of **1** to **2** was achieved at this conditions.



Scheme 1. Conversion of nitrile to carboxylic acid. A-concentrated H_2SO_4 (14% yield),[8] B-H_2O_2/DMSO/water (84% yield)

Although radiolabelling of the sodium salt of the [^{11}C]carfentanil carboxylate precursor was successfully achieved in the absence of base,[2] in our hands the reaction of [^{11}C]CH_3I with either sodium or ammonium salts of the precursor in DMF or DMSO resulted in very low yields ($<2\%$) of the product. Addition of base [tetrabutylammonium hydroxide (TBA^+OH^-), 1 equivalent], however, considerably improved the product yield. The rise of the yield may be attributed to the formation of a more reactive ion pair with the soft TBA^+ cation compared to the harder sodium or ammonium cations and/or an increase of the precursor solubility in DMF. We found that the yield of [^{11}C]carfentanil was further increased, and the procedure simplified, by carrying out the reaction of the precursor with [^{11}C]CH_3I inside of a Tefzel tubing loop (1 mm i.d., 2 ml volume). A decay corrected yield with respect to [^{11}C]CH_3I of [^{11}C]carfentanil was $64 \pm 12\%$ ($n = 6$) with the synthesis time of 21 min.The radiochemical purity was $>98\%$. The residual precursor, which lacks carfentanil physiological activity, was detected by reverse-phase HPLC at the level 4–5 μg per batch of the final product.

The specific radioactivity (11.2 ± 4.8 Ci/μmol, EOS; 23.2 ± 10 Ci/μmol, EOB; $n = 5$) of [^{11}C]carfentanil obtained in our syntheses is significantly higher than that previously reported for this radiotracer. It can be attributed to the short radiosynthesis time and preponderantly the use of the [^{11}C]CH_4 target[7] (which eliminates dilution of carbon-11 with carbon-12 from the atmospheric CO_2). Although high EOB specific radioactivities of radiotracers synthesized from [^{11}C]CH_3I (>10 Ci/μmol)[12,13] can be obtained when [^{11}C]CO_2 targets are used, in many reported radiosyntheses the values lie below 5 Ci/μmol.

Experimental

All chemicals were acquired from Aldrich Chemical Co. An authentic sample of carfentanil was donated by R. F. Dannals (John Hopkins University, Baltimore, MD). NMR spectra were recorded with a Brucker 400 MHz NMR spectrometer. [^{11}C]CH_3I was produced from [^{11}C]CH_4 generated in target[7] using a homemade automatic gas-phase synthesiser following a standard synthetic route.[12,14,15] The chemical and radiochemical purity along with specific radioactivity were determined by radio TLC (Macherey-Nagel polygram sil G/UV_{254} plastic-back TLC plates, 4×8 cm) and analytical radio HPLC in the

presence of authentic unlabeled compound as a carrier. HPLC: Phenomenex, Synergi Max-RP, 4 μm, 250 × 4.6 mm column; eluent, 30 mM ammonium acetate-30% CH_3CN; flow rate, 2 ml/min; t_R ([^{11}C]carfentanil precursor) 3.0 min. Waters, Nova-Pak C18, 3.9 × 150 mm column; eluent, 30 mM ammonium acetate-70% CH_3CN; flow rate, 2 ml/min; t_R ([^{11}C]carfentanil) 1.6 min.TLC: 5% triethylamine-(1:1 ethyl acetate: hexane), Rf ([^{11}C]carfentanil) 0.48.

*4-Anilino-1-(2-phenylethyl)piperidine-4-carboxamide (**2**) (Scheme 1)*

Potassium carbonate (7 mg, 0.05 mmol) was added to the solution of 4-anilino-1-(2-phenylethyl)piperidine-4-carbonitrile (**1**, 100 mg, 0.33 mmol) in DMSO (0.6 ml). Hydrogen peroxide (30 wt%, 80 μl, 0.78 mmol) was slowly added, and the mixture was left overnight while stirring. After addition of water (3.6 ml), crystals were isolated, washed with water and vacuum-dried to produce 89 mg (0.28 mmol, 84% yield) of white solid. Mp 184°C (literature 189.5°C).[8] TLC, 20% water-acetonitrile, 1 drop of 85% aquous H_3PO_4 per 6 ml of eluent, R_f 0.48. (Amide **2** obtained using H_2O_2/K_2CO_3/DMSO reaction method had an identical TLC R_f and 1°C difference in melting points with amide prepared using concentrated H_2SO_4 as described in the literature.[8])

Benzyl 1-(2-phenylethyl)-4-[phenyl(propionyl)amino]piperidine-4-carboxylate

Prepared as per the literature.[8] ^{1}H NMR ($CDCl_3$, δ) 7.43-7.33 (m, 8 H, -$C_6\underline{H}_5$), 7.29-7.20 (m, 5 H, -$C_6\underline{H}_5$), 7.16–7.14 (t, 2 H, -$C_6\underline{H}_5$), 3.35 (d, 2 H, 11.5 Hz, -$C\underline{H}_2CH_2$-), 3.15–3.05 (m, 2 H, -$C\underline{H}_2CH_2$-), 3.02–2.95 (m, 2 H, -$C\underline{H}_2CH_2$-), 2.52–2.35 (m, 4 H, -$C\underline{H}_2CH_2$-), 2.15 (s, 2 H, -$C\underline{H}_2$Ph), 1.86 (q, 2 H, 7.4 Hz, -$C\underline{H}_2CH_3$), 0.92 (t, 3 H, 7.5 Hz, $C\underline{H}_3$-). ESI MS: MH^+ 381.4 (F.W. 381.5). Mp 186°C (literature 188°C).[8]

Precursor synthesis (sodium or ammonium 1-(2-phenylethyl)-4-[phenyl (propionyl)amino]piperidine-4-carboxylate)

Carfentanil precursor in the form of the sodium or ammonium salts was synthesized in six steps starting from 1-(2-phenylethyl)-4-piperidone as previously described[3,8] with the exception of the modifications outlined above. The total yield of the six-step synthesis was 4.3%. The sodium salt of the precursor was recrystallized from acetonitrile-water.

[^{11}C]Carfentanil: Synthesis in reaction vessel

The sodium or ammonium salts of the precursor (1 mg, 2.6 μmol) were suspended in 0.15 ml of anhydrous DMF or DMSO. In the 'base-added' experiments tetrabutylammonium hydroxide (TBA^+OH^-, 2.6 μl of 1 M solution in methanol) was added to the mixture. [^{11}C]CH_3I in the flow of helium was bubbled through the reaction mixture either at ambient temperature (when DMSO was used as a reaction solvent) or at –42°C (acetonitrile-dry ice bath, DMF-solvent). The reaction vessel was heated for 7 min at 50°C; a small fraction of the solution (5–30 μl) was quenched with 1:1 ethanol:water (0.5 mL) and analysed. In one synthesis, purification of [^{11}C]carfentanil was achieved on C2 disc following published procedure.[3] The radiotracer yield was 50% (EOB) after 29 min of synthesis.

[^{11}C]Carfentanil: In-loop synthesis

Ammonium salt of the precursor (1 mg, 2.6 μmol) was suspended in 70–100 μl of DMF. After the addition of TBA^+OH^- (2.6 μl of 1 M solution in methanol), the mixture was loaded into the 2 mL, 1 mm i.d. Tefzel tubing loop (Upchurch Sci., Oak Harbor, WA). After [^{11}C]CH_3I in a flow of helium (flow rate, 15 ml/min) was blown through the loop (typically $>95\%$ of [^{11}C]CH_3I was retained on the loop), the reaction was allowed to proceed for 5 min at ambient temperature. The loop was washed with 4 ml of 0.15 M aqueous NH_3, and [^{11}C]carfentanil was purified on a C2 extraction disc according to published procedure.[3] Final solution of [^{11}C]carfentanil was filtered through the sterile Millipore, Millex-GV 0.22 μm filter into the sterile vial. The use of an anion exchange cartridge for final purification of the radiotracer was not required because [^{11}C]carfentanil as eluted from the C2 disc was chemically and radiochemically pure.

Conclusion

[^{11}C]Carfentanil was conveniently synthesized with the *in-loop* method by reaction of the ammonium salt of the carboxylate precursor with [^{11}C]CH_3I in DMF in the presence of base. Purification of the radiotracer on a C2 extraction disc was achieved following the published method.[3] The chemical yield of the synthesis of the precursor was also improved (from 14 to 84%). This simple radiolabelling procedure, which combines *in-loop* radiosynthesis with product

purification on extraction disc, may be widely applicable for the syntheses of other PET radiotracers.

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