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A convenient method for synthesis of II-[^{14}C]-loxapine

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Abstract 8-Chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4]oxazepine labeled with carbon-14 in 11-position has been synthesized as part of a 5-step sequence from potassium [^{14}C] cyanide.

Key words dibenzoxazepine • carbon-14 • microwave heating

Introduction

Tricyclic ring systems, possessing the dibenzo structure joined to the central seven membered heterocyclic ring with a basic side chain, have been a rich source of biologically active molecular entities and frequently show effects on the central nervous system [10]. The precise mechanism of action of these compounds is not known [2]. Therefore to further elucidate the mechanism of action and to support ongoing metabolism studies, there arose a need for analogues of these compounds carbon-14 labeled in a biologically stable site. In our previous report [7], we reported a modified synthesis of 11-[^{14}C]-clozapine and in this paper a convenient method for the synthesis of 8-chloro-11-(4-methyl-1-piperazinyl)-11-[^{14}C]-dibenz[b,f][1,4]oxazepine is described.

Experimental

Barium ^{14}C-carbonate was purchased from Amersham Pharmacia Biotech UK Ltd. (Amersham Place, Little Chalfont, Buckinghamshire, England HP7 9NA) and converted to potassium [^{14}C] cyanide according to the standard procedure [8]. IR and ^{1}H-NMR spectra were recorded on Bruker FT-IR, Vector 22 instrument and Bruker DRX 500 (500 MHz) spectrometers, respectively. Radioactivity was determined with a Beckman LS6500 liquid scintillation spectrometer.

2-hydroxy-benzonitrile[cyano-^{14}C] potassium salt **2**

An aliquot of potassium [^{14}C] cyanide (114 mg, 337 MBq) was suspended in 1-methyl-2-pyrrolidinone (2.2 ml) and 2-iodo-phenol **1** (338 mg) together with cuprous iodide (324 mg) were added. The reaction mixture was stirred for 5 hours at 180°C, then the conversion was checked as complete by TLC. The

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solution was allowed to cool to room temperature and extracted into ethyl acetate (20 ml). The extract was washed with water followed by brine and dried over anhydrous sodium sulfate. After evaporation of the solvent and purification of the residue by column chromatography on silica gel using ethyl acetate:dichloromethane (1:20) as eluant, recrystallization followed.

2-hydroxy-benzonitrile[cyano-^{14}C] (173 mg, 279 MBq), was obtained. Then, to a stirred solution of potassium hyroxide (81.2 mg) in water (2 ml), 2-hydroxy-benzonitrile[cyano-^{14}C] (173 mg, 279 MBq) was added. The resulting mixture was stirred at room temperature for 30 min, and then concentrated under reduced pressure which afforded compound **2** (228 mg, 279 MBq).

IR(KBr): 3250, 2240, 1600, 1460, 1360 cm^{-1}

^{1}H-NMR($CDCl_3$): δ7.35(dd,1H), δ7.5(t,1H), δ7.28(bs,1H), δ7.08(d,1H), δ7(t,1H).

2-[(4-chloro-2-nitrophenyl)oxy]benzonitrile-[cyano-^{14}C] 4

To a mixture of 2-hydroxy-benzonitrile-[cyano-^{14}C] potassium salt **2** (228 mg, 279 MBq), in dry DMF (2.35 ml) 1,4 dichloro-2-nitrobenzene **3** (385 mg) was added, and then the resulting mixture was irradiated under microwave radiation (300 W, 5 min). The solution was then allowed to cool to room temperature and diluted with ethyl acetate (30 ml). This mixture was washed with water, followed by brine and then dried over anhydrous sodium sulfate. Concentration of this solution under reduced pressure gave a residue which was purified by silica gel chromatography using ethyl acetate:hexane (1:5) as eluant to give the title compound **4** (349 mg, 243 MBq).

IR(KBr): 3101, 2221, 1573, 1523, 1448, 1341, 1259, 1146, 1102, 850, 750 cm^{-1}

^{1}H-NMR($CDCl_3$): δ8.08(d,1H), δ7.7(d,1H), δ7.36(dd,1H), δ7.57(t,1H), δ7.28(t,1H), δ7.16(d,1H), δ6.88(d,1H).

2-[(4-chloro-2-nitrophenyl)oxy]-benzoamide[carboxy-^{14}C] 5

To a stirred solution of 2-[(4-chloro-2-nitrophenyl)oxy]-benzonitrile[cyano-^{14}C] **4** (349 mg, 243 MBq), in DMSO (10 ml) cooled in an ice bath was added H_2O_2 (30%, 7 ml) and cesium carbonate (2500 mg). The mixture was then allowed to warm up to room temperature. After six hours, distilled water (150 ml) and ethyl acetate (300 ml) were added to the mixture. The organic phase was separated, dried over anhydrous sodium sulfate, filtered and the solvent was then removed under reduced pressure. The product was purified by silica gel chromatography using ethyl acetate:hexane (1:5) as eluant to give the title compound **5** (234 mg, 153 MBq).

IR(KBr): 3689, 3354, 3026, 1661, 1577, 1494, 1455, 1345, 1262, 1158, 1094 cm^{-1}

^{1}H-NMR($CDCl_3$): δ11.56(bs,2H), δ8.92(d,1H), δ8.33(d,1H), δ7.6–7.7(m,2H), δ7.55(t,1H), δ7.09(d,1H), δ7.02(t,1H).

8-Chloro-10-hydro-dibenzo[b,f][1,4]oxazepine-11-one[11-^{14}C] 6

To a mixture of 2-[(4-chloro-2-nitrophenyl)oxy]-benzoamide[carboxy-^{14}C] **5** (234 mg, 153 MBq), and anhydrous stannous chloride (578 mg) in absolute ethanol (9.5 ml) glacial acetic acid (1.2 ml) was added, and the mixture was refluxed for 35–40 hours. The solution was then cooled to room temperature and neutralized with concentrated ammonium hydroxide. After addition of ethyl acetate (400 ml) and stirring the mixture, the organic layer was separated, washed with water and brine and dried over anhydrous sodium sufate. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography using dichloromethane:hexane(1:1) as eluant to give the title compound **6** (137 mg, 107 MBq).

IR(KBr): 3325, 1625, 1550, 1490, 1420, 1375, 1250, 1050, 780 cm^{-1}

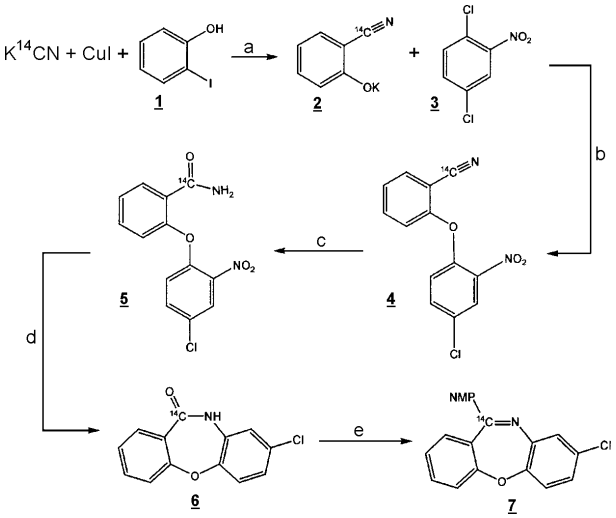
^{1}H-NMR($CDCl_3$): δ12.75–13.3(bs,1H), δ8.07(d,1H), δ7.65–7.81(m,2H), δ7.41(t,1H), δ7.31(m,1H), δ7.04(d,2H).

8-Chloro-11-(4-methyl-1-piperazinyl)-11-[^{14}C]-dibenz[b,f][1,4]oxazepine 7

The conversion of 8-chloro-10-hydro-dibenzo[b,f][1,4]oxazepine-11-one[11-^{14}C] **6** to the title compound **7** was then carried out according to the previously reported procedure [4].

Result and discussion

In this approach, according to the synthetic pathway shown in Scheme 1, after conversion of 2-hydroxy benzonitrile [cyano-^{14}C] (derived by addition of potassium [^{14}C] cyanide and cuprous iodide to 2-iodo phenol [9] **1**) to its potassium salt **2**, it was coupled with



Scheme 1. a – 1-methyl-2-pyrrolidinon/KOH(aq); b – DMF, MW; c – H_2O_2 30%, Cs_2CO_3, dimethyl sulfoxide; d – anhydrous $SnCl_2$, CH_3COOH, absolute ethanol; e – $POCl_3$, NMP, N,N-dimethyl aniline.

1,4-dichloro-2-nitrobenzene **3** in DMF under microwave irradiation [3].
The hydrolysis of nitrile **4** to the amide **5** was resulted in good yield in the presence of cesium carbonate, DMSO, and hydrogen peroxide 30% [1]. The reduction of the nitro group and the cyclization were accomplished in one step in the presence of stannous chloride in acetic acid as the reducing agent [6], and the key oxazepine-11-one-[11-^{14}C] **6** was produced in good yield. The conversion of the key oxazepine-11-one [11-^{14}C] **6** to 8-chloro-11-(4-methyl-1-piperazinyl)-11-[^{14}C]-dibenz [b,f][1,4]oxazepine **7** was then carried out according to the procedure of Liegeois *et al*. [5].

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