[Chem. Pharm. Bull. 33(12)5562—5564(1985)]

A Synthesis of ^{14}C-Labeled Sodium 2-[*o*-[(2,6-Dichlorophenyl)-amino]phenyl]acetate ([^{14}C]Diclofenac Sodium)

YOSHIHIRO HORIO,[1] YASUHIRO TORISAWA, and SHIRO IKEGAMI*

Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa 199-01, Japan

(Received April 17, 1985)

A synthesis of sodium 2-[*o*-[(2,6-dichlorophenyl)amino]phenyl]acetate labeled with a carbon-14 atom at the 1-position was accomplished efficiently by using potassium [^{14}C]cyanide, in 5 steps starting from *o*-(chloromethyl)iodobenzene.

Keywords——potassium [^{14}C]cyanide; cyanation; 18-crown-6; hydrolysis; [^{14}C]diclofenac sodium

Sodium 2-[*o*-[(2,6-dichlorophenyl)amino]phenyl]acetate (diclofenac sodium) (**1**) is a potent anti-inflammatory agent that is in clinical use. In various rheumatic disorders, its therapeutic effect was found to be similar to or better than those of indomethacin, acetylsalicylic acid (ASA), phenylbutazone and ibuprofen.[2] In order to extend its applicability as a drug, it became necessary to synthesize diclofenac sodium labeled with a carbon-14 atom for studies of the drug distribution in the ocular tissues of rabbits. Thus, this paper describes an efficient synthesis of [^{14}C]diclofenac sodium (**1**). In order to obtain the highest possible incorporation of a cheap isotopic material such as potassium or sodium [^{14}C]cyanide ([^{14}C]KCN), the present synthesis utilized a newly developed route based on the Ullmann-type coupling reaction as a key step after the introduction of a carbon-14 atom.

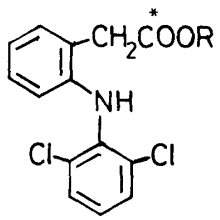
The synthesis commenced with the preparation of labeled (*o*-iodophenyl)acetonitrile (**5**) by the cyanation of *o*-(chloromethyl)iodobenzene (**4**) with [^{14}C]KCN in the presence of 18-crown-6 in acetonitrile (CH_3CN)[3] (83% chemical and 95% radiochemical yields[4]). The conventional method for cyanation by treatment with KCN in ethanol (EtOH) gave lower yields (50—70% yields).[5]

Hydrolysis of **5** in 18 N H_2SO_4 gave the corresponding carboxylic acid (**6**) in 72.5% yield; this product was esterified in MeOH–CH_2Cl_2 in the presence of a catalytic amount of H_2SO_4 to afford the methyl ester (**7**) in 96% yield.

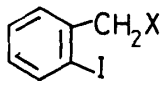
The amination reaction of the ester (**7**) with 2,6-dichloroaniline using cuprous iodide–potassium carbonate as a coupling reagent in toluene yielded the desired diphenylamine (**3**) in 74.2% yield.[6]

The conversion of **3** into diclofenac sodium (**1**) was accomplished in the following way. After base-promoted hydrolysis of **3**, the carboxylic acid (**2**) was isolated by acidification of the reaction mixture. Then, the acid (**2**) was converted to the sodium salt (**1**) by using an equimolar amount of sodium hydroxide in water, and the salt was purified by recrystallization from water to give the pure salt (**1**) in 51.5% yield.

Thus, a synthesis of ^{14}C-labeled diclofenac sodium was achieved in 22% overall yield. The radiochemical purity of [^{14}C]diclofenac sodium thus obtained was examined by measuring a thin layer chromatogram (TLC) with a radiochromatoscanner and by autoradiographic analysis. The product was found to be pure both chemically and radiochemically.



1: R=Na
2: R=H
3: R=CH_3



4: X=Cl
5: X=C*N
6: X=C*OOH
7: X=C*OOCH$_3$
C*=^{14}C

Chart 1

Experimental

Material and General Procedure——^{14}C-Labeled KCN was purchased from The Radiochemical Centre, Amersham, U.K. *o*-(Chloromethyl)iodobenzene was purchased from Aldrich Chemical Co. Column chromatography was carried out over silica gel (C-200, Wakogel, Japan) and TLC on silica gel plates (Art. 5715, Kieselgel 60F_{254}, Merk) containing a fluorescent indicator. The spots were detected under ultraviolet (UV) light (254 nm). Radioactivity was measured in the usual toluene scintillator (2,5-diphenyloxazole (PPO)) with a liquid scintillation counter (Aloka LSC 900), and radioactivity on TLC was recorded with a two-dimensional radiochromatogram scanner (Packard Model 7230). Acetonitrile, toluene and dichloromethane were used after distillation.

[1-^{14}C](*o*-Iodophenyl)acetonitrile (5)——[^{14}C]KCN (9.66 mg, 0.15 mmol, 8 mCi) was added to a solution of *o*-(chloromethyl)iodobenzene (160 mg, 0.62 mmol) in CH_3CN (2 ml) containing 18-crown-6 (70 mg, 0.26 mmol). The mixture was refluxed with stirring for 30 min, and then further KCN (8.5 mg, 0.13 mmol) was added to the reaction mixture. The mixture was refluxed for an additional 3 h with stirring. After evaporation under reduced pressure, the residue was extracted with Et_2O. The extract was washed with satd. aq. NaCl and dried over $MgSO_4$. Removal of the solvent *in vacuo* left a yellow residue which was purified by silica gel (7 g) column chromatography (*n*-hexane–Et_2O (19 : 1)) to give **5** (56.3 mg) in 83% yield based on KCN. Specific radioactivity was 117.9 μCi/mg.

[1-^{14}C](*o*-Iodophenyl)acetic Acid (6)——A solution of **5** (56.3 mg, 0.23 mmol, 117.9 μCi/mg) in 18 N H_2SO_4 (3 ml) was heated at 120 °C (bath temperature) with stirring for 3 h. The solution was diluted with water and extracted with Et_2O. The acid (**6**) was transfered to basic aqueous solution by shaking the ethereal extract with satd. aq. $NaHCO_3$ and the aqueous layer was acidified with 4 N HCl to pH 1—2, and again extracted with Et_2O. The extract was washed with satd. aq. NaCl and dried over $MgSO_4$. Removal of Et_2O gave **6** (44 mg, 72.5%).

Methyl [1-^{14}C]-2-[*o*-[(2,6-Dichlorophenyl)amino]phenyl]acetate (3)——A mixture of **7** (44.5 mg, 0.14 mmol), catalytic amount of conc. H_2SO_4 in CH_2Cl_2 (3 ml) was refluxed with stirring for 2 h. The mixture was cooled and diluted with Et_2O. The organic layer was washed with satd. aq. NaCl and dried over $MgSO_4$. Removal of the solvents afforded **7** (44.5 mg, 96%).

Methyl [1-^{14}C]-2-[*o*-[(2,6-Dichlorophenyl)amino]phenyl]acetate (3)——A mixture of **7** (44.5 mg, 0.14 mmol), 2,6-dichloroaniline (90 mg, 0.55 mmol), anhydrous K_2CO_3 (600 mg, 4.32 mmol) and CuI (50 mg, 0.26 mmol) in toluene was refluxed with stirring for 50 h. After cooling, the mixture was diluted with Et_2O and filtered. Removal of the solvents gave a residue, which was purified by silica gel (10 g) column chromatography (*n*-hexane–Et_2O (9 : 1)) to give **3** (37 mg, 74.2%) in 42.9% overall yield. Specific radioactivity was 92.7 μCi/mg.

Sodium [1-^{14}C]-2-[*o*-[(2,6-Dichlorophenyl)amino]phenyl]acetate (Diclofenac Sodium) (1)——A solution of **3** (37 mg, 0.12 mmol, 92.7 μCi/mg) and 2 M NaOH (0.3 ml) in EtOH (2 ml) was refluxed with stirring for 3 h. The mixture was concentrated under reduced pressure to give the residue, which was acidified with 4 N HCl to pH 1—2, and extracted with Et_2O. The extract was washed with satd. aq. NaCl and dried over $MgSO_4$. Removal of Et_2O gave [1-^{14}C]-2-[*o*-[(2,6-dichlorophenyl)amino]phenyl]acetic acid (**2**) (26.6 mg, 0.09 mmol, 74.6%). The acid (**2**) was dissolved in NaOH solution (4 mg, 0.1 mmol, in 0.3 ml), and the solution was decolorized by adding activated charcoal at 60—70 °C for 10 min. After filtration, the filtrate was allowed to stand at 5 °C for 20 h. The separated crystals (**1**) were collected (12 mg) by filtration, and further crystals (7.5 mg) were obtained by evaporation of the mother liquor, followed by recrystallization from H_2O (0.3 ml). The total yield of **1** was 19.5 mg (51.5%). Specific radioactivity was 90 μCi/mg. The purity of **1** was determined by measurement of the TLC (silica gel plate, 20 × 5 cm, $CHCl_3$–MeOH (9 : 1)) with a radiochromatoscanner and by autoradiographic analysis (X-ray film (Fuji 150 SAIFTY)). The purity found to be more than 99%.

References and Notes

1) Visiting scientist from *Research Institute, Wakamoto Pharmaceutical Co., Ltd., Kanate, Ohimachi,*

Ashigarakamigun, Kanagawa 258, Japan.

2) P. M. Matru, J. Pensonen, P. Salmela, O. Suchonen, and T. Sanck, *Scand. J. Rheumatol.*, **22**, 51 (1978).
3) D. Landini, F. Montanari, and F. M. Pirisi, *J. Chem. Soc., Chem. Commun.*, **1974**, 879; M. Cinquini, F. Montanari, and P. Tundo, *ibid.*, **1975**, 393.
4) The portionwise addition of potassium cyanide ([^{14}C]KCN + KCN) resulted in high incorporation of the isotope into the substrate (**4**).
5) W. S. Rapson and R. G. Shuttleworth, *J. Chem. Soc.*, **1941**, 487.
6) J. W. Schulenberg and S. Archer, *Org. React.*, **14**, 1-51 (1965); F. Nohara, Brit. UK Patent Appl. 2027028 (1981) [*Chem. Abstr.*, **94**, 15402*x* (1981)].