A FACILE SYNTHESIS OF SODIUM 3-[1-^{14}C]-ETHYL-7-ISOPROPYL-1-AZULENESULFONATE

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SUMMARY

Sodium 3-ethyl-7-isopropyl-1-azulenesulfonate 1, a new therapeutic agent for stomatitis, pharyngitis and ophthalmia was labelled with carbon-14 in the ethyl group attached to the azulene ring for use in metabolic studies. ^{14}C-labelled 1 with a specific activity of 1.98 GBq/mmol was prepared in four steps in 39.3% overall chemical yield from [1-^{14}C]acetic acid sodium salt.

Key Words: carbon-14 , sodium 3-[1-^{14}C]ethyl-7-isopropyl-1-azulene-sulfonate , stomatitis, pharyngitis , ophthalmia

INTRODUCTION

Sodium 3-ethyl-7-isopropyl-1-azulenesulfonate 1 is a candidate as an anti-inflammatory and anti-ulcer agent.[1,2] In order to develop 1 as a therapeutic agent for stomatitis, pharyngitis and ophthalmia, a high specific activity ^{14}C-labelling compound of 1 is required for the study of metabolism in animals. The synthesis of 1 has been reported by our laboratories[3] using the reaction of 2H-cyclohepta[b]furan-2-one with enamin.[4] However, this synthetic route was eight steps and the reaction yields were not satisfactory. We developed alternatively a synthesis to prepare the desired ^{14}C-labelling of compound 1 with a high specific activity. In this paper, we report a facile synthesis of a high specific activity of 1 which was labelled with carbon-14 at the ethyl group introduced into the azulene ring by the method of the Friedel-Craft reaction[5] and mild reduction with $NaBH_3CN$ in the presence of $BF_3 \cdot Et_2O$ in diglyme[6].

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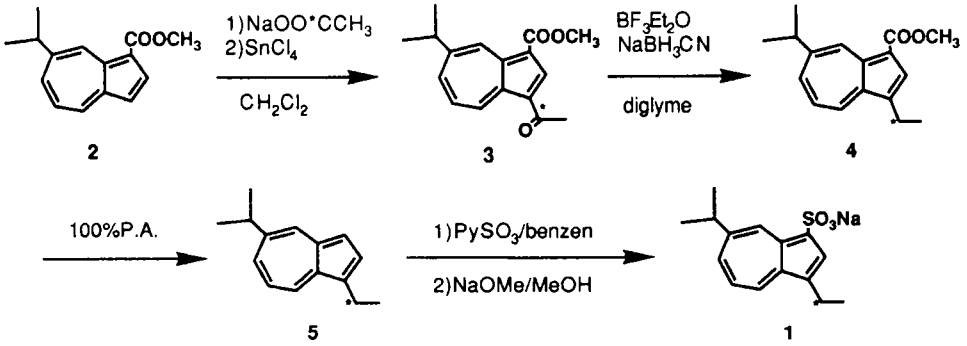
RESULTS AND DISCUSSION

Methyl 3-[1-^{14}C]acetyl-7-isopropylazulene-1-carboxylate 3 was prepared by reaction of methyl 7-isopropylazulene-1-carboxylate[7] with $SnCl_4$ in the presence of [1-^{14}C]acetyl chloride generated in situ from [1-^{14}C]acetic acid sodium salt upon the addition of $POCl_3$ in dichloromethane.

This Friedel-Crafts acylation at the 3 position on the azulene ring was obtained by the effect of electron-withdrawing 1-methoxy carbonyl group. Attempts to convert 3 into 4 by Wolff-Kishner reaction[8] and reduction with stronger hydride reagents [$LiBH_4$, $LiAlH_4$, DIBAH] were unsuccessful because of the low stability under the condition employed. However, reaction of compound 3 with the mild reducing agent cyano sodium borohydride ($NaBH_3CN$) in the presence of $BF_3 \cdot Et_2O$ and diglyme afforded 4 in 94.7% yield. Decarboxylation of 4 with 100% phosphoric acid afforded 5 in 92.5% yield. Sulfonation of 5 with a pyridine-sulfur trioxide complex in benzene followed by treatment with sodium methoxide afforded the sodium salt 1 in 93.4% yield (Scheme 1). We obtained 67.5 mg (436.6 MBq) of sodium 3-[1-^{14}C] ethyl-7-isopropyl-1-azulenesulfonate, 1 (specific activity : 1.98 MBq/mmol), radiochemical purity greater than 99% (RHPLC) in four steps from 46.6 mg (1.11 GBq) of the starting material, [1-^{14}C]acetic acid sodium salt.



SCHEME 1

EXPERIMENTAL

[1-^{14}C]Acetic acid sodium salt [1.11 GBq, 1.98 GBq/mmol] was purchased from Amersham International plc. The reactions in the labelling synthesis were monitored by thin layer chromatography (TLC). Analytical TLC was carried out on a Merck silica gel 60 F_{254} plate (0.25

mm). Fuji Divison BM-820MH silica gel was used for column chromatography. Melting points were determined on a micro melting point apparatus. ^{1}H-NMR spectra were measured at 90MHz on a Hitachi R-90H Fourier Transform NMR spectrometer. Chemical shifts are quoted in parts per million (ppm) with tetramethylsilane as an internal standard, and coupling constants (J) are given in Hz. The following abbreviations are used: s = singlet, d = doublet, dd = doublet doublet, q = quartet, sept = septet, m = multiplet and bd = broad doublet. Infrared spectra were recorded on a Hitachi 270-30. These spectral data were obtained in trial experiments using unlabeled material. Radioactivity was determined with a Beckman LS-900 liquid scintillation counter using 2,5-diphenyl-oxazole in toluene and Triton X-100 as a liquid scintillator. The radio-high performance liquid chromatograph (Hitachi Co., Ltd., Japan) was equipped with a 655A UV detector (Hitachi Co.) and a RS-8000 Radioanalyzer (Toso). A stainless steel column packed with octadesyl silane (TSK-gel 80Tm, id 4.6×150mm) was used for analysis of 1. Operation conditions: mobile phase 20 mM phosphate Buffer (pH 6.0)/CH_3CN = 7:3 v/v ; flow rate 1.0 ml/min.: UV 285 nm: retention time of 1 30 min.

Methyl 3-[1-^{14}C]acethyl-7-isopropyl-1-azulenecarboxylate. 3

To a suspension of 46.6 mg, 0.57 mmol, specific activity 1.98 GBq/mmol, 1.11 GBq, of [1-^{14}C] acetic acid sodium salt in 3 ml of dichloromethane was added 0.1 ml of $POCl_3$ at 0°C, and the mixture was stirred for 20 min. at 0°C and for 2 hours at 40°C. A solution of methyl 7-isopropyl-azulene -1-carboxylate (194.5 mg, 0.85 mmol) of dichloromethane (2 ml) and $SnCl_4$ (0.1 ml, 0.85 mmol) was added dropwise to the above mixture, and the mixture was stirred at 0°C for 20 min. and for 30 min. at room temperature. The reaction mixture was quenched with ice-water, then extracted with dichloromethane. The extract was dried over anhydrous Na_2SO_4, and evaporated to give a red solid. This crude product was purified by column chromatography on silica with ethyl acetate/ n-hexane (1:4) as the eluent, to give 73.1 mg (47.4%) of 3 (534 MBq) as red solid. mp 104-105 °C, IR (KBr) cm^{-1}, 2950, 1700, 1650. ^{1}H-NMR ($CDCl_3$) δ =1.40 (6H, d, J=7.0Hz, isoprCH_3), 2.65 (3H, s, $COCH_3$), 3.30 (1H, sept, J=7.0Hz, isoprCH), 7.75 (1H, dd, J=10.0, 10.0Hz, C_5-H), 7.85 (1H, dd, J=10.0, 2.0Hz, C_6-H), 8.70 (1H, s, C_2-H), 9.80 (1H, d, J=10.0Hz, C_4-H), 9.88 (1H, d, J=2.0Hz, C_8-H).

Methyl 3-[1-^{14}C]ethyl-7-isopropylazulene-1-carboxylate. 4

A solution of compound 3 (73.1 mg, 0.27 mmol, 534 MBq) in 2.5 ml of ether and 2.5 ml of diglyme was cooled at 0°C. $BF_3 \cdot Et_2O$ (0.18 ml, 0.81 mmol) was added and the mixture stirred at 0°C for 30 min. To the reaction mixture was slowly added 100 mg (1.60 mmol) of cyano sodium borohydride dissolved in 5 ml of diglyme and the mixture stirred at room temperature for 30 min. The reaction mixture was quenched with ice-water, then extracted with ethyl acetate. The extract was dried over anhydrous Na_2SO_4, and evaporated to give a violet solid. This crude product was purified by column chromatography on silica with ethyl acetate/n-hexane (1:5) as the eluent, to give 65.4 mg (94.7%) of 4 (515 MBq), as violet solid. mp 64-66°C. ^{1}H-NMR ($CDCl_3$) δ =1.39 (6H, d, J=7.0Hz, isoprCH_3), 1.40 (3H, t, J=7.5Hz, -$CH_2C\underline{H}_3$), 3.02 (2H, q, J=7.5Hz, -$C\underline{H}_2CH_3$), 3.16 (1H, sept, J=7.0Hz, isoprCH), 3.95 (3H, s, -$COOCH_3$), 7.38 (1H, d, J=10.0Hz, C_5-H), 7.70 (1H, bd, J=10.0Hz, C_6-H), 8.24 (1H, s, C_2-H), 8.28 (1H, d, J=10.0Hz, C_4-H), 9.70 (1H, d, J=2.0Hz, C_8-H).

1-[1-^{14}C]Ethyl-5-isopropylazulene. 5

A mixture of 4 (65.4 mg, 0.26 mmol, 515 MBq) and 100% phosphoric acid (10 ml) was heated at 100°C for 10 min, cooled and poured into water (50 ml), then extracted with ethyl acetate. The extract was dried over anhydrous Na_2SO_4, and evaporated to give a blue violet oil. This crude product was purified by column chromatography on silica with n-hexane as the eluent, to give 5 (46.8 mg, 455 MBq, 92.5%). ^{1}H-NMR ($CDCl_3$) δ =1.34 (6H, d, J=7.0Hz, isoprCH_3), 1.36 (3H, t, J=7.6Hz, -$CH_2C\underline{H}_3$), 3.06 (2H, q, J=7.6Hz, -$C\underline{H}_2CH_3$), 3.01 (1H, sept, isoprCH), 6.87-8.37 (6H, m, azulene ring).

Sodium 3-[1-^{14}C]ethyl-7-isopropyl-1-azulenesulfonate. 1

A mixture of 5 (46.8 mg, 0.23 mmol, 455 MBq) and pyridine-sulfur trioxide (110.9 mg, 0.69 mmol) in benzene 10 ml was stirred under reflux 3 hours. The mixture was concentrated under reduced pressure and the resulting solid dissolved in methyl alcohol (5 ml) and 28% NaOMe (200

mg) was added at 0°C. After stirring at room temperature for 2 hours, the solution was concentrated under reduced pressure and water (30 ml) was added to the mixture and the whole was extracted with *n* -butyl alcohol . The extract was dried over anhydrous Na_2SO_4, and evaporated to give a violet solid. This crude product was purified by column chromatography on silica with chloroform/methyl-alcohol (1:3) as the eluent followed by recrystallization from ethyl alcohol to give 67.5 mg (93.4%) of 1 (436.6 MBq, specific activity : 1.98 GBq/mmol) as a violet solid. mp 178-179°C, IR (KBr) cm^{-1}, 3430, 1175, 1050. ^{1}H-NMR (CD_3OD) δ =1.36 (3H, t, J=7.5Hz, -$CH_2\underline{CH_3}$), 1.40 (6H, d, J=7.0Hz, isoprCH_3), 3.04 (2H, q, J=7.5Hz, -$\underline{CH_2}CH_3$), 3.18 (1H, sept, J=7.0Hz, isoprCH), 7.25 (1H, d, J=9.6Hz, C_5-H), 7.70 (1H, bd, J=10.0Hz, C_6-H), 8.04 (1H, s, C_2-H), 8.29 (1H, dd, J=9.6, 1.2Hz, C_4-H), 9.21 (1H, d, J=2.0Hz, C_8-H).

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