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Note

Synthesis of labelled *N*-(4-hydroxy-[^{14}C(U)]phenyl)-2-[2,3-dihydro-3-oxo-l,2-benzisothiazol-2-yl-1,1-dioxide]acetamide

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Summary

The amidation of 2-[1,1-dioxide-3-oxo-1,2-benzisothiazole-2(3H)-yl] acetyl chloride with carbon-14-labelled 4-amino-[^{14}C(U)]phenol in NaOAc-HOAc buffer solution at -10°C gave *N*-(4-hydroxy-[^{14}C(U)]phenyl)-2-[2,3-dihydro-3-oxo-1,2-benziso-thiazol-2-yl-1,1-dioxide]acetamide in 82% yield. Subsequent hydrolysis with aqueous 0.5 N NaOH solution afforded the ring opened product *N*-(4-hydroxy-[^{14}C(U)]-phenyl)-2-[2-carboxy-phenylsulfonamido]acetamide in 80% yield. Copyright © 2005 John Wiley & Sons, Ltd.

Key Words: analgesic; anti-pyretic; acetaminophen; carbon-14

Introduction

The *N*-(4-hydroxyphenyl)-2-[1,1-dioxide-3-oxo-1,2-benzisothiazole-2(3H)-yl] acetamide (**1**) has been found to exhibit *in vivo* analgesic and anti-pyretic activity of equal or greater potency to that of acetaminophen while displaying no anti-inflammatory activity.[1,2] However, **1** lacks the hepatotoxicity associated with equal molar doses of acetaminophen.[1,2] The favorable safety profile of **1** has prompted further investigation toward the development of an orally delivered analgesic. To this end it became necessary to prepare carbon-14-labelled **1** and metabolite **2** for further characterization of the biological activity.

Results and discussion

The patented procedures for the preparation of **1** and related homologues were not suitable for the preparation of carbon-14-labelled **1** because the procedures

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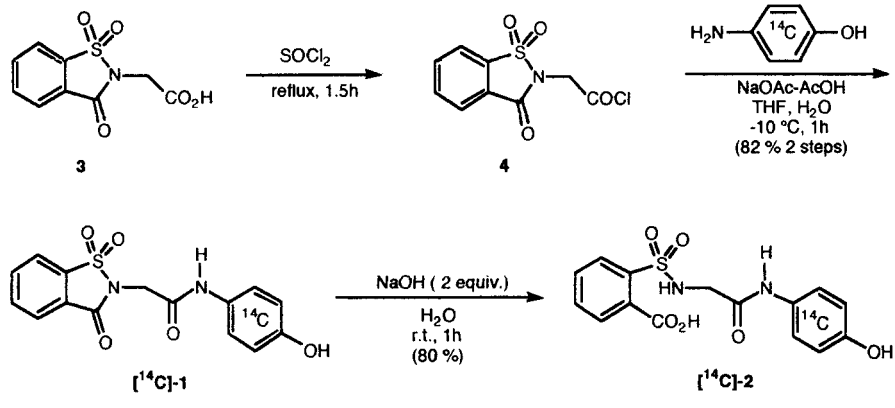
employed *N*, *N*′-dicyclohexylcarbodiimide (DCC) as a coupling reagent which complicated the work-up procedure and thus lowered the yield.[1,2] Our improved synthesis started with readily available 2-saccharin acetic acid (**3**) (Scheme 1). Treatment of **3** with thionyl chloride under reflux for 1.5 h gave the intermediate 2-saccharin acetyl chloride (**4**) that was used without further purification in the subsequent reaction. The acid chloride **4** was dissolved in dry THF and added dropwise over a period of 15 min to a pre-cooled buffer solution of aqueous saturated sodium acetate, acetic acid and 4-amino-[^{14}C(U)]phenol (1 mCi) at -10°C. The amidation reaction was completed quickly (30 min) to furnish [^{14}C]-**1** in 82% overall yield. The slow addition of the acid chloride solution was found to be critical for obtaining high yields. In addition, optimum yields for the overall procedure were obtained by using 1.35 equivalents of the acid **2** relative to the 4-aminophenol. This procedure was highly efficient and quite convenient. Pure product (> 95% by NMR) was obtained directly by pouring the reaction mixture into ice water followed by filtration and drying under vacuum. No column chromatography or recrystallizations were needed.



Scheme 1.

The preparation of the metabolite [^{14}C]-**2** was achieved by treatment of [^{14}C]-**1** with aqueous 0.5 N NaOH solution. The hydrolysis reaction was completed within 1 h affording the ring open product [^{14}C]-**2** in 80% yield. The concentration of the NaOH solution greatly influenced the yield of the reaction as well as the formation of side products. At concentrations above 1 N NaOH an intractable mixture of hydrolysis products was obtained.

Experimental

4-Amino-[^{14}C(U)]phenol (1 mCi/ml, 55 mCi/mmol, in 0.01 N HCl) was purchased from American Radiolabeled Chemicals Inc. (St. Louis, Missouri). ^{1}H and ^{13}C NMR spectra were recorded on a Varian-400 MHz spectrometer at

ambient temperature in DMSO-d_6 (Cambridge Isotope Laboratories, Inc.). Melting points were recorded on a Hoover Mel-Temp apparatus and are uncorrected.

*Preparation of N-(4-hydroxy-[^{14}C(U)]-phenyl)-2-[1, 1-dioxide-3-oxo-1, 2-benzisothiazole-2(3H)-yl] acetamide ([^{14}C]-**1**)*

A mixture of 2-[1, 1-dioxide-3-oxo-1, 2-benzisothiazole-2(3H)-yl] acetic acid (326 mg, 1.35 mmol) and thionyl chloride (4 ml) was heated at reflux (external oil bath temperature of 82–85°C) for 1.5 h. The excess $SOCl_2$ was removed under reduced pressure and the resulting acid chloride **3** (1.35 mmol) was used without further purification in the subsequent reaction. The acid chloride **4** (*ca* 1.35 mmol) was dissolved in dry THF (2 ml) and added dropwise over a period of 15 min to a mixture of 4-aminophenol (108 mg, 0.99 mmol), 4-amino-[^{14}C(U)]-phenol (1 ml, 1 mCi/ml, 55 mCi/mmol, in 0.01 N HCl), $NaOAc \cdot 3H_2O$ (429 mg), HOAc (1.5 ml) and saturated NaOAc solution (0.6 ml) at −10°C. After the addition, the reaction mixture was stirred at −10°C for 1 h and poured into icewater (65 g). The precipitate was collected by vacuum filtration and dried under vacuum (0.1 mm Hg) overnight to furnish [^{14}C]-**1** (270 mg, specific activity: 1.09 mCi/mol) as a white solid in 82% yield. m.p. 202–204°C (lit.[1] 204–206°C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.06 (s, 1H, NH), 9.28 (s, 1H, OH), 8.37 (d, $J = 8.0$ Hz, 1H), 8.06–8.20 (m, 3H), 7.37 (d, $J = 8.0$ Hz, 2H), 6.73 (d, $J = 8.4$ Hz, 2H), 4.55 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.2, 159.4, 154.3, 137.6, 136.5, 136.0, 130.7, 127.1, 125.8, 122.3, 121.6, 115.8, 41.1.

*Preparation of N-(4-hydroxy-[^{14}C(U)]phenyl)-2-[2-carboxy-phenylsulfonamido]-acetamide ([^{14}C]-**2**)*

A mixture of [^{14}C]-**1** (330 mg, 1 mmol) and aqueous 0.5 N NaOH (4 ml) was stirred at room temperature for 1 h. The solution was acidified with 1 N HCl solution to pH **1** and extracted with EtOAc (2 × 15 ml). The extracts were combined, washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was triturated with hexanes. The resulting solid was recrystallized from ethyl acetate to give white crystals (281 mg, specific activity: 0.99 mCi/mol) in 80% yield. The purity of [^{14}C]-**2** (>99%) was established by HPLC analysis ($t_R = 15.8$ min) using a Waters HPLC system: Waters Nova-Pak C18 (3.9 × 150 mm) steel analytical column and an acetonitrile/water (0.1% trifluroacetic acid) gradient mobile phase (flow = 1 ml/min). m.p. 193–195°C. IR (KBr) 3364, 3320, 2969, 1702, 1645, 1608, 1536, 1401, 1332, 1271, 1156, 1108 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.10 (bs, 1H), 9.72 (s, 1H), 9.20 (s, 1H), 7.92 (d, $J = 8.0$ Hz, 1H), 7.64–7.78 (m, 3H), 7.42 (s, 1H), 7.20 (d, $J = 8.8$ Hz, 2H), 6.64 (d, $J = 8.8$ Hz, 2H),

3.71 (d, $J = 4.8$ Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.6, 165.1, 153.4, 137.4, 132.6, 132.4, 130.8, 129.8, 129.6, 128.5, 120.8, 114.9, 45.7.

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