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Note

Synthesis of carbon-14 labelled l,5 diaryl-[5-^{14}C]-l,2,3-triazolines

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Summary

Two 1,2,3-triazoline anticonvulsants, 1-(4-methylsulphone-phenyl)-5-(4-methoxy-phenyl)-1,2,3-triazoline and l-(4-methylsulphone-phenyl)-5-phenyl-1,2,3-triazoline, both labelled with carbon-14 in the 5-position, have been synthesized as part of a 5-step sequence. Copyright © 2003 John Wiley & Sons, Ltd.

Key Words: triazoline; Schiff base; anticonvulsant; carbon-l4

Introduction

1,5-Diaryl-1,2,3-triazolines frequently exhibit anticonvulsant properties[1] and compare favourably with prototype antiepileptic drugs such as phenobarbitol, phenytoin, etc.[2] The presence of the methylsulphone group at the *para*-position of one of the phenyl rings has led to compounds with good anti-inflammatory properties.[3–6] To further elucidate the mechanism of action and to support on-going metabolism studies[7] the need arose to synthesise the corresponding carbon-14 compounds, with the label situated in a biologically stable site. In this paper we report the synthesis of two 1,5-diaryl-[5-^{14}C]-1,2,3-triazolines (la,b).

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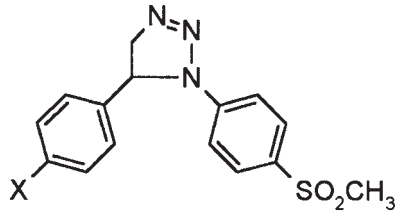
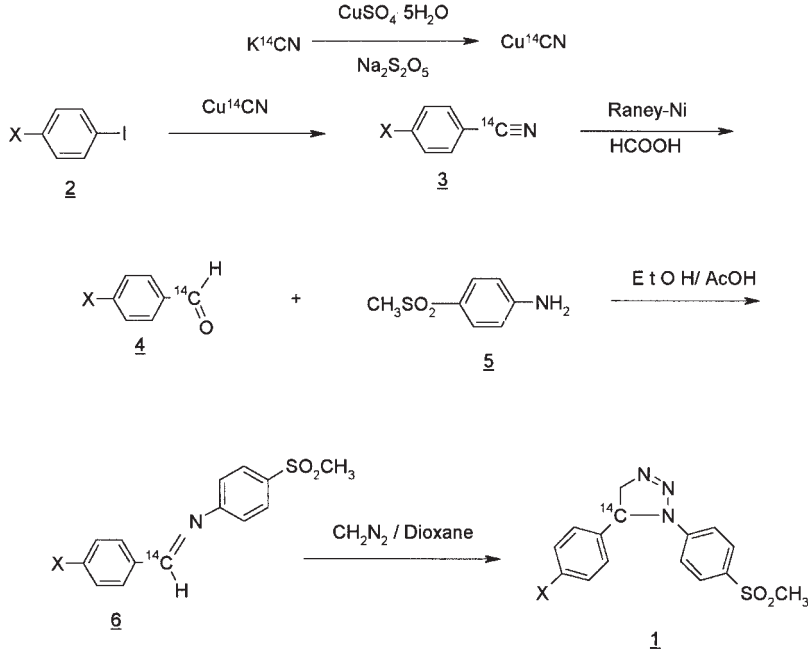


1 a X : CH_3O
b X : H

The desired product 1, was synthesized as part of a 5-stage sequence[8–12] (Scheme 1).



Scheme 1.

Experimental

Barium [^{14}C]-carbonate was purchased from Amersham Pharmacia Biotech (Amersham Place, Little Chalfont, Buckinghamshire, England HP7 9NA) and converted to potassium [^{14}C]-cyanide according to the standard procedure.[13] IR spectra were recorded on a Bruker FT-IR instrument and the ^{1}H-NMR

spectra on a Bruker DRX 500 (500 MHz) spectrometer. Radioactivity was determined using a Beckman LS6500 liquid scintillation spectrometer.

Copper(I) [^{14}C] cyanide

Copper(II) sulphate pentahydrate (1246 mg, 5 mmol) and water (3 ml) were stirred at 45°C. The resulting solution was treated with a solution of sodium metabisulphite (257 mg, 1.35 mmol) in water (1.5 ml). A solution of potassium hydroxide (115 mg, 2.05 mmol) and potassium [^{14}C]-cyanide (26 mCi, 260 mg, 4 mmol) in water (1.26 ml) was added dropwise over the course of 5 min. The resulting suspension was stirred at 45°C for 1 h, followed by 30 min at 23°C. The suspension was filtered, washed with water (4×4.5 ml), ethanol (2×4.5 ml), and ether (2×1.5 ml) and was dried under vacuum to give the title compound as a solid (23.74 mCi, 3.69 mmol, 332 mg) (yield: 91.3%).

4-Methoxy-benzonitrile-[cyano-^{14}C] 3a

A mixture of 4-iodo-anisole 2a (700 mg , 3 mmol) and copper(I) [^{14}C] cyanide (9.65 mCi, l.5 mmol, 135 mg) in *N*,*N*-dimethylformamide (5.8 ml) was stirred at reflux for 7 h. The solution was allowed to cool to room temperature and extracted with ethyl acetate (30 ml). The extract was washed with water followed by brine and dried over anhydrous sodium sulphate. Concentration under reduced pressure and purification by column chromatography on silica gel using (20%) ethylacetate: hexane as eluant gave (8.55 mCi, 1.33 mmol, 177 mg) of the title compound (yield: 88.56%). IR(KBr): 3085, 2980, 2230, 1600, 1510, 1460, 1160 Cm^{-1}, ^{1}H-NMR ($CDCl_3$, TMS): δ 7.6, d, 2H; δ 6.9, d, 2H; δ 3.9, s, 3H.

Benzonitrile-[cyano-^{14}C] 3b

The benzonitrile-[cyano-^{14}C] 3b was prepared according to the above described procedure by heating iodo-benzene 2b (610 mg, 3 mmol) and copper(I) [^{14}C] cyanide (9.65 mCi, l.5 mmol, 135 mg) in pyridine (yield: 79.6%). IR(KBr): 3092, 2240, 1600, 1490, 1450 Cm^{-1}.

4-Methoxy-benzaldehyde-[carbonyl-^{14}C] 4a

4-Methoxy-benzonitrile-[cyano-^{14}C] 3a (8.35 mCi, 1.3 mmol, 173 mg) was converted to 4-methoxy-benzaldehyde-[carbonyl-^{14}C] 4a by refluxing with Raney-Ni (173 mg) in 75% formic acid (2.6 ml) for 1 h. The product was purified by distillation under vacuum, to give (7.73 mCi, 1.2 mmol, 163 mg) of the title compound (yield: 92.6%), IR(KBr): 3083, 2960, 2860, 2740, 1680, 1600 Cm^{-1}.

Benzaldehyde-[carbonyl-^{14}C] 4b

The benzonitrile-[carbonyl-^{14}C] 4b was prepared according to the above described procedure (yield: 94.3%). IR(KBr): 3095, 2840, 2740, 1720, 1450 Cm^{-1}.

4-Methylsulphone-N-(4-methoxy-benzylidene)-aniline-[azomethine-^{14}C] 6a

The title compound was obtained by warming a mixture of 4-methoxy-benzaldehyde-[carbonyl-^{14}C] 4a (6.44 mCi, 1 mmol, 136 mg) and 4-methylsulphone aniline (1 mmol, 171 mg) in ethanol (0.5 ml) and acetic acid (0.3 ml) for 15 h. Recrystallization from THF/hexane (1:10) gave the title product (4.26 mCi, 0.66 mmol, 191 mg) in 66.15% yield. IR(KBr): 3040, 2950, 1630, 1570, 1510, 1305, 1140 Cm^{-1}, ^{1}H-NMR (DMSO-d_6): δ 8.56, s, 1H; δ 7.9, m, 4H; δ 7.46, m, 2H; δ 7.15, m, 2H; δ 3.85, s, 3H; δ 3.22, s, 3H.

4-Methylsulphone-N-(benzylidene)-aniline-[azomethine-^{14}C] 6b

The 4-methylsulphone-*N*-(benzylidene)-aniline-[azomethine-^{14}C] 6b was prepared according to the above described procedure by warming a mixture of benzaldehyde-[carbonyl-^{14}C] 4b (7.35 mCi, 1.14 mmol, 121 mg) and 4-methylsulphone aniline 5 (1.14 mmol, 195 mg) in ethanol (0.4 ml) and THF (0.4 ml) for 15 h. Recrystallization from THF/hexane (1:10) gave the title product (5.98 mCi, 0.93 mmol, 241 mg) in 81.3% yield. IR(KBr): 3090, 2940, 1640, 1580, 1310, 1150 Cm^{-1}, ^{1}H-NMR (DMSO-d_6): δ 8.65, s, lH; δ 7.96, m, 4H; δ 7.56, m, 3H; δ 7.45, m, 2H; δ 3.2, s, 3H.

Diazomethane

N-nitroso, *N*-methyl urea (2.5 g) was added in small portions and with shaking to a mixture of 1,4-dioxane (25 ml) and 40% potassium hydroxide solution (7.5 ml) kept at 8–10°C. The mixture was then carefully introduced into a separatory funnel and the lower alkaline layer was separated off. The dioxane layer was deep yellow in colour and contained approximately 0.7 g of diazomethane which was used immediately in the triazoline synthesis.

1-(4-Methylsulphone-phenyl)-5-phenyl-1,2,3-triazoline-[5-^{14}C] 1b

4-Methylsulphone-*N*-(benzylidene)-aniline-[azomethine-^{14}C] 6b (5.38 mCi, 0.84 mmol, 217 mg) was added with shaking to a cold freshly prepared solution of diazomethane (3 mmol) in dioxane (4.5 ml) contained in an Erlenmeyer flask. The reaction mixture was allowed to stand at room temperature for 5 days. At the end of this period, the mixture was filtered, cooled, and diluted with cold water (4.5 ml) with shaking, until a precipitate formed. Recrystallization from ethanol provided the title compound (4.41 mCi, 0.69 mmol, 208 mg). (yield: 82%).^{1}H-NMR (DMSO-d_6): δ 7.78,

m, 2H; δ 7.28 −7.37, m, 5H; δ 7.18, m, 2H; δ 5.34, q, 1H; δ 4.95, q, 1H; δ 4.38, q, 1H; δ 3.1, s, 3H.

1-(4-Methylsulphone-phenyl)-5-(4-methoxy-phenyl)-1,2,3-triazoline-[5-^{14}C] 1a

4-Methylsulphone-*N*-(4-methoxy benzylidene)-aniline-[azomethine-^{14}C] 6a (3.87 mCi, 0.6 mmol, 174 mg) was converted to the title compound according to the above described procedure by using (8 ml) of diazomethane solution. After 5 days, the mixture was worked up. Recrystallization using acetone/petroleum ether (1 : 10), gave the title compound. (1.85 mCi, 0.29 mmol, 96 mg) in 47.8% yield.

^{1}H-NMR(DMSO-d_6): δ 7.81, m, 2H; δ 7.4, m, 4H; δ 6.9, m, 2H; δ 5.3, q, 1H; δ 4.9, q, 1H; δ 4.35, q, 1H; δ 3.85, s, 3H; δ 3.22, s, 3H.

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