JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS
J Label Compd Radiopharm 2005; **48**: 231–233.
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jlcr.917

Note

Preparation of [carboxy-^{13}C]4-nitrophenylacetic acid

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Summary

Reaction of sodium [^{13}C]cyanide with excess benzyl chloride gave ~75% utilization of the isotope. Subsequent nitration, isomer separation and hydrolysis of the nitrile gave the required carboxy-labelled 4-nitrophenylacetic acid. Copyright © 2005 John Wiley & Sons, Ltd.

Key Words: nitration; chromatography; NMR spectra

Introduction

As part of a quantitative study of photodecarboxylation reactions using rapid-scan IR spectroscopy, we needed a compound that undergoes efficient photodecarboxylation and that could easily be labelled with ^{13}C in its carboxy group. The quantity of [^{12}C]CO_2 formed from the test substance could then be related to the quantity of [^{13}C]CO_2 formed from the standard using the relative intensity of the normal and isotopic CO_2 bands in the IR spectra. 4-Nitrophenylacetic acid **1** (as its anion) is known to photodecarboxylate with high quantum yield[1] and appeared to be a suitable choice.

Results and discussion

A simple route to isotopically labelled **1** should *a priori* be available by displacement on 4-nitrobenzyl chloride or bromide with labelled cyanide ion, followed by hydrolysis. Although such procedures have been described (preferably with a mixture of NaCN and HCN, or the equivalent produced by adding a strong acid such as TFA to NaCN), they are inefficient in terms of cyanide incorporation, so are not well suited for isotopic synthesis. Kalir and Mualem[2] described these procedures and reviewed relevant literature on unwanted dimeric by-products that are formed when displacement is

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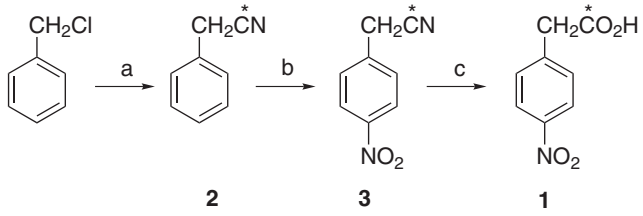
Received 19 November 2004
Accepted 22 November 2004



Scheme 1. Reagents: (a) Na[^{13}C]CN–aq. EtOH, then thiourea; (b) NH_4NO_3–TFAA; (c) H_2O–H_2SO_4–HOAc, heat

attempted without HCN. The most direct alternative route to **1** involves preparation of labelled benzyl cyanide **2**, followed by nitration, isolation of the required 4-nitrobenzyl cyanide **3** and acidic hydrolysis (Scheme 1). These steps have been described previously, but we report here their adaptation to small-scale isotopic synthesis.

In a modification of a known procedure,[3] sodium [^{13}C]cyanide was allowed to react with excess benzyl chloride in aqueous ethanol, and residual benzyl chloride was then destroyed with thiourea. Benzyl [^{13}C]cyanide has been reported by other workers who used either the original aqueous ethanol procedure[3,4] or in better yield in acetonitrile with 18-crown-6 as catalyst.[5] Our modified procedure gave labelled benzyl cyanide with 75% isotope utilization. Nitration of benzyl cyanide with nitric–sulfuric acid mixture is well known,[6] but for small-scale work ammonium nitrate in TFAA[7] was more convenient and gave the 2- and 4-nitro isomers in ~1:3 ratio. Flash chromatography gave pure 4-nitrobenzyl cyanide **3** in 50% yield. Acidic hydrolysis as described[6] then yielded the required acid **1**.

Experimental

Sodium [^{13}C]cyanide (99% isotopic abundance) was from Cambridge Isotope Laboratories, Andover, MA. Flash chromatography was on Merck 9385 silical gel. NMR spectra were determined in $CDCl_3$ on either JEOL FX90Q or Varian Unityplus 500 spectrometers.

Benzyl [^{13}C]cyanide **2**

A solution of benzyl chloride (4.0 g, 31.6 mmol) in EtOH (5 ml) was added dropwise over 45 min to a solution of sodium [^{13}C]cyanide (1.0 g, 20 mmol) in water (1.8 ml) and the mixture was refluxed for 6 h. Thiourea (1.14 g, 15 mmol) and EtOH (10 ml) were added and the mixture was refluxed for a further 1 h. The solution was concentrated under reduced pressure and partitioned between Et_2O and water. The organic phase was washed with water, dried and evaporated to a yellow oil and purified by flash chromato-

graphy [EtOAc–light petroleum, 1:9] to give **2** (1.76 g, 74.6%), ^{1}H-NMR (90 MHz): δ 7.33 (5H, br s, Ar-H), 3.73 (2H, d, $^{2}J_{C\text{-}H} = 10.5$ Hz, CH_2).

4-Nitrobenzyl [^{13}C]cyanide **3**

Ammonium nitrate (1.15 g, 14.4 mmol) and trifluoroacetic anhydride (14.4 ml) were added to benzyl [^{13}C]cyanide **2** (1.7 g, 14.4 mmol) and the solution was stirred at room temperature. It warmed spontaneously to reflux within 15 min and was stirred for a further 1.25 h at room temperature, then diluted carefully with water (70 ml) and the aqueous layer was extracted with Et_2O. The organic phase was washed with aq. $NaHCO_3$ and brine, dried and evaporated. The mixture of isotopic 2- and 4-nitrobenzyl cyanides was separated by flash chromatography (EtOAc–light petroleum, 1:1). Silica gel TLC R_f values in the same solvent were 0.40 and 0.36 for the 2- and 4-nitro isomers, respectively. 4-Nitrobenzyl [^{13}C]cyanide **3** was obtained as a pale yellow solid (1.16 g, 50%) that was used without further purification. ^{1}H-NMR (90 MHz): δ 8.25 (2H, d, $J = 8.7$ Hz, Ar-H3,5), 7.54 (2H, d, $J = 8.7$ Hz, Ar-H2,6), 3.88 (2H, d, $^{2}J_{C\text{-}H} = 10.6$ Hz, CH_2).

[carboxy-^{13}C]4-Nitrophenylacetic acid **1**

The cyanide **3** (1.1 g, 6.75 mmol) was mixed with water (2.2 ml), concentrated H_2SO_4 (2.2 ml) and glacial acetic acid (2.2 ml) and refluxed for 1 h. The mixture was diluted with water (55 ml) and extracted with Et_2O. The organic extract was dried and evaporated to give [carboxy-^{13}C]4-nitrophenylacetic acid **1** as beige crystals (1.1 g, 90%) m.p. 149–151°C (from aqueous ethanol). UV [EtOH–25 mM Na phosphate, pH 7 (1:9 v/v)]: λ_{max} 287 nm (ε 10 900 $M^{-1}\,cm^{-1}$); ^{1}H-NMR (500 MHz): δ 8.21 (2H, d, $J = 8.7$ Hz, Ar-H3,5), 7.47 (2H, d, $J = 8.7$ Hz, Ar-H2,6) 3.78 (2H, d, $^{2}J_{C\text{-}H} = 7.8$ Hz, CH_2).

Acknowledgements

We are grateful to the MRC Biomedical NMR Centre for access to facilities.

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