

## Note

# Preparation of [carboxy-<sup>13</sup>C]4-nitrophenylacetic acid

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## Summary

Reaction of sodium [<sup>13</sup>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

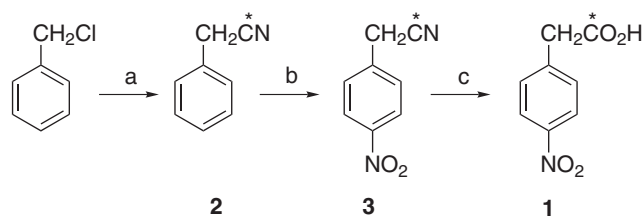
## Introduction

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 <sup>13</sup>C in its carboxy group. The quantity of [<sup>12</sup>C]CO<sub>2</sub> formed from the test substance could then be related to the quantity of [<sup>13</sup>C]CO<sub>2</sub> formed from the standard using the relative intensity of the normal and isotopic CO<sub>2</sub> bands in the IR spectra. 4-Nitrophenylacetic acid **1** (as its anion) is known to photodecarboxylate with high quantum yield<sup>1</sup> 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<sup>2</sup> described these procedures and reviewed relevant literature on unwanted dimeric by-products that are formed when displacement is

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**Scheme 1.** Reagents: (a)  $\text{Na}^{[13]\text{C}}\text{CN}$ -aq. EtOH, then thiourea; (b)  $\text{NH}_4\text{NO}_3$ -TFAA; (c)  $\text{H}_2\text{O}$ - $\text{H}_2\text{SO}_4$ -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,<sup>3</sup> sodium  $^{[13]\text{C}}$ cyanide was allowed to react with excess benzyl chloride in aqueous ethanol, and residual benzyl chloride was then destroyed with thiourea. Benzyl  $^{[13]\text{C}}$ cyanide has been reported by other workers who used either the original aqueous ethanol procedure<sup>3,4</sup> or in better yield in acetonitrile with 18-crown-6 as catalyst.<sup>5</sup> Our modified procedure gave labelled benzyl cyanide with 75% isotope utilization. Nitration of benzyl cyanide with nitric-sulfuric acid mixture is well known,<sup>6</sup> but for small-scale work ammonium nitrate in TFAA<sup>7</sup> was more convenient and gave the 2- and 4-nitro isomers in  $\sim 1:3$  ratio. Flash chromatography gave pure 4-nitrobenzyl cyanide **3** in 50% yield. Acidic hydrolysis as described<sup>6</sup> then yielded the required acid **1**.

## Experimental

Sodium  $^{[13]\text{C}}$ cyanide (99% isotopic abundance) was from Cambridge Isotope Laboratories, Andover, MA. Flash chromatography was on Merck 9385 silical gel. NMR spectra were determined in  $\text{CDCl}_3$  on either JEOL FX90Q or Varian Unityplus 500 spectrometers.

### Benzyl $^{[13]\text{C}}$ 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  $^{[13]\text{C}}$ 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  $\text{Et}_2\text{O}$  and water. The organic phase was washed with water, dried and evaporated to a yellow oil and purified by flash chromatography.

graphy [EtOAc–light petroleum, 1:9] to give **2** (1.76 g, 74.6%), <sup>1</sup>H-NMR (90 MHz): δ 7.33 (5H, br s, Ar-H), 3.73 (2H, d, <sup>2</sup>J<sub>C-H</sub> = 10.5 Hz, CH<sub>2</sub>).

#### 4-Nitrobenzyl [<sup>13</sup>C]cyanide **3**

Ammonium nitrate (1.15 g, 14.4 mmol) and trifluoroacetic anhydride (14.4 ml) were added to benzyl [<sup>13</sup>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<sub>2</sub>O. The organic phase was washed with aq. NaHCO<sub>3</sub> 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<sub>f</sub> values in the same solvent were 0.40 and 0.36 for the 2- and 4-nitro isomers, respectively. 4-Nitrobenzyl [<sup>13</sup>C]cyanide **3** was obtained as a pale yellow solid (1.16 g, 50%) that was used without further purification. <sup>1</sup>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, <sup>2</sup>J<sub>C-H</sub> = 10.6 Hz, CH<sub>2</sub>).

#### [carboxy-<sup>13</sup>C]4-Nitrophenylacetic acid **1**

The cyanide **3** (1.1 g, 6.75 mmol) was mixed with water (2.2 ml), concentrated H<sub>2</sub>SO<sub>4</sub> (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<sub>2</sub>O. The organic extract was dried and evaporated to give [carboxy-<sup>13</sup>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<sub>max</sub> 287 nm (ε 10 900 M<sup>-1</sup> cm<sup>-1</sup>); <sup>1</sup>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, <sup>2</sup>J<sub>C-H</sub> = 7.8 Hz, CH<sub>2</sub>).

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