A CONVENIENT SYNTHESIS OF [CARBONYL-^{14}C]-4-HYDROXYBENZALDEHYDE

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SUMMARY

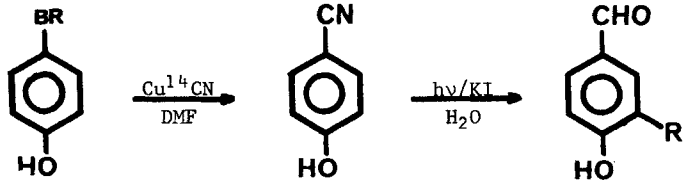
A two-step synthesis of the title compound from [cyano-^{14}C]-copper(I) cyanide is described. The method is extensible to the preparation of carbonyl-labelled 3,4-dihydroxybenzaldehyde.

Key Words: [carbonyl-^{14}C]-4-hydroxybenzaldehyde,
[carbonyl]-labelled 3,4-dihydroxybenzaldehyde

INTRODUCTION

The aromatic aldehydes, 4-hydroxy- and 3,4-dihydroxybenzaldehyde (1 and 2, respectively) are key intermediates in the chemical synthesis of the phenylethylamine neuro-amines (1), aromatic amino acids such as tyrosine (2), and the related ketoacids (2-4). Previously described syntheses of carbonyl-labelled 1 have involved multi-step procedures from $^{14}CO_2$ (5-7) or K^{14}CN (8); a simplified procedure for the preparation of [carbonyl-^{14}C]-1 has been described, but isolated yields and specific activities were not reported (9). Syntheses of [carbonyl-^{14}C]-2 by multi-step procedures from either $^{14}CO_2$ (10) or K^{14}CN (11) have also been described.

We now report a convenient synthesis of [carbonyl-^{14}C]-1 which proceeds in only two steps from Cu^{14}CN, according to the following scheme:



1. R = H
2. R = OH

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In experiments with unlabelled material, we have also obtained 2 by the route shown, starting from 4-bromocatechol.

The key features of our synthesis are the following: quantitative conversion of $Na^{14}CN$ to $Cu^{14}CN$ by the standard procedure (12, 13); direct conversion of 4-bromophenol to [cyano-^{14}C]-4-cyanophenol without the use of a protecting group; and reduction of the nitrile group to the aldehyde by a modification of the method of Omura (14). The photochemical reduction of the nitrile functionality to aldehyde proceeded in high yield in aqueous solution when iodide ion was used as the electron donor. This method circumvents the experimental problems associated with the micro-scale use of the metal hydride reducing agents (5, 6, 10) or active metal catalysts (8, 9, 11) which have been used in previous syntheses of [carbonyl-^{14}C]-1.

EXPERIMENTAL

[Cyano-^{14}C]-4-cyanophenol: In a 10 mL flask, [^{14}C]-copper(I) cyanide (89 mg, 1 mmole S. A. 2.93 mCi/mmole, prepared from $Na^{14}CN$ (12, 13)), 4-bromophenol (173 mg, 1.1 mmole) and DMF (2 mL, dried by distillation from P_2O_5) were refluxed under nitrogen for 3½ h. The reaction mixture was then cooled and diluted with a solution of ferric chloride hydrate (1.5 g) in water (3 mL) and concentrated HCl (1 mL). The resulting mixture was warmed at 50-60° until no oily layer was visible, and while warm was extracted with ether. The ether extract was washed with water, dried (Na_2SO_4) and evaporated. The residue was then chromatographed on silica gel using benzene, benzene-ether (1:1) and ether, successively, as eluents. Unreacted 4-bromophenol was removed in the benzene fractions; pure 4-cyanophenol was eluted by ether. Isolated yields in successive experiments varied from 40 to 55 percent.

[Carbonyl-^{14}C]-4-hydroxybenzaldehyde (1): A solution of [cyano-^{14}C]-cyanophenol (25 mg, S.A. 2.93 mCi/mmole), and potassium iodide (1.4 g) in 0.09 M aqueous potassium hydroxide (25 mL) was irradiated for 8 h under a nitrogen atmosphere with an Hanovia 140 W Hg lamp (unfiltered). The reaction mixture was then cooled, acidified (10% HCl) to pH 4.5, and extracted with ethyl acetate (4 x 25 mL). The extract was washed (1 M sodium thiosulphate, (20 mL),

followed by water (10 mL)), dried (Na_2SO_4) and evaporated. The residue was freed of residual sulphur by sublimation under vacuum, leaving pure 1 (20 mg, 80%), S.A. 2.93 mCi/mmole.

4-Cyanocatechol: 4-Bromocatechol (189 mg, 1 mmole) and copper(I) cyanide (89 mg, 1 mmole) were heated in refluxing dry DMF (2 mL) under nitrogen for 5 h. The reaction mixture was cooled and worked up as described above, to yield the title compound (56 mg, 41%).

3,4-Dihydroxybenzaldehyde (2): 4-Cyanocatechol was reduced photolytically by the procedure described above, using an irradiation time of 12 h. The title compound was obtained as the sole product.

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