A facile solvent-free synthesis of high specific activity potassium [^{14}C]formate and ethyl [^{14}C]formate under microwave irradiation

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Potassium [^{14}C]cyanide was first hydrolysed to potassium [^{14}C]formate with dilute alkali under microwave (1300 W) irradiation for 8 min in a sealed glass ampoule. Potassium [^{14}C]formate was then esterified with triethyl orthophosphate under microwave irradiation for 20 min to furnish ethyl [^{14}C]formate having high specific radioactivity (50 mCi/mmol) in an yield of 98%.

Keywords: potassium [^{14}C]cyanide, microwave irradiation, potassium [^{14}C]formate, ethyl [^{14}C]formate

Ethyl [^{14}C]formate is a key synthon for the synthesis of ^{14}C labelled levocetrazine, sesquiterpenes and spirovetivane[1,2] which are required to study the absorption, distribution, metabolism and excretion of these molecules. The procedures reported in the literature for the preparation of potassium formate involve either hydrolysing potassium cyanide with alkali at high temperature for several hours[3-5] or catalytic reduction of either sodium bicarbonate[6-10] or carbon dioxide.[11] These procedures are not quite suitable for the preparation of high specific activity sodium/potassium [^{14}C]formate as prolonged heating at high temperature often leads to lower yields. Preparation of ethyl formate involves esterification of formic acid with calculated amounts of ethanol and sulfuric acid,[11,12] with ethyl phosphate or ethyl sulfate at high temperature,[13] with potassium hydroxide/methylsulphoxide and iodomethane[14] or by exclusive use of diazoethane.[7]

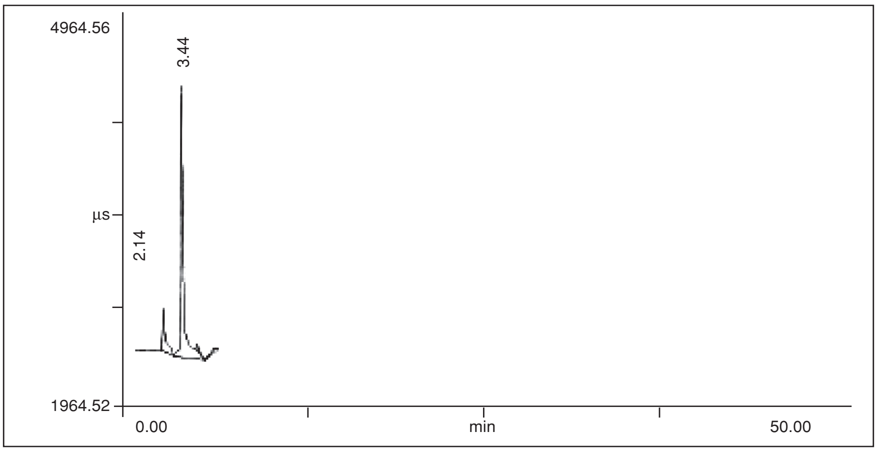
In our approach, potassium [^{14}C]cyanide was hydrolysed with dilute alkali under microwave irradiation for 8 min to give potassium [^{14}C]formate see CAUTION in Experimental section. After work-up, the product was confirmed by ion chromatography (retention time 3.44 min), HPLC (retention time 1.22 min) and IR (presence of band at 1710 cm^{-1} due to carbonyl group), on comparison with an authentic sample. Potassium [^{14}C]formate was esterified with triethyl phosphate under microwave (1300 W) irradiation for 20 min in a sealed ampoule. Formation of ethyl [^{14}C]formate was confirmed by IR spectroscopy (the shift of band from 1710 cm^{-1} to 1740 cm^{-1} in IR spectra) and HPLC (peak at r.t. 1.38 min). The analytical data were in good agreement with an authentic sample.

Experimental

CAUTION: Potassium cyanide is toxic and appropriate precautions should be taken.

Potassium [^{14}C]formate: Aqueous potassium hydroxide solution (0.1 ml, 1 M) was added to potassium [^{14}C]cyanide (0.12 mmol, 6 mCi., Sp activity 50 mCi/mmol) in a glass ampoule and sealed. The ampoule was heated in a domestic microwave oven (1300 W) for 8 min. The ampoule was cooled and the reaction mixture was taken up in 5 ml methanol. The methanol was distilled off and the residue was dried under a vacuum for 8 h to give potassium [^{14}C]formate (5.9 mCi, 98%) IR 1710 cm^{-1}.

Formation of potassium [^{14}C]formate was confirmed by ion exchange chromatography and HPLC, followed by liquid scintillation counting.



Sr No	Retn. Time	Height	Area	Area %	Peak Type	Area/ Height
1	2.14	16454	5944718	13.7364	BP	0.247
2	3.44	101753	35503919	82.0383	PB	0.238
3	4.54	3022	876979	2.0264	TTT	0.198
4	5.82	1410	951625	2.1989	PB	0.461
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Fig. 1 Ion chromatogram of potassium [^{14}C]formate.

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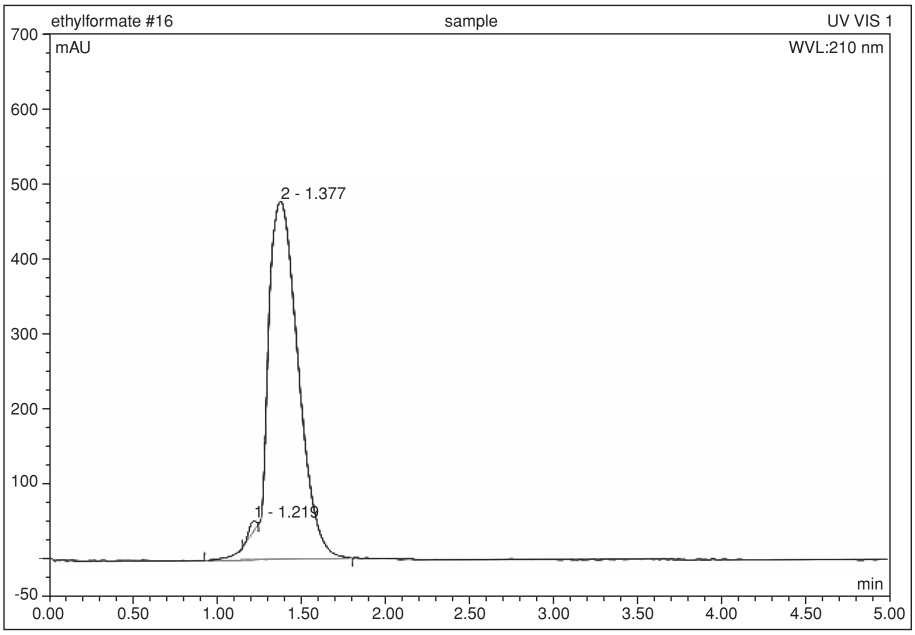

No	Retn. Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	1.22	n.a.	12.026	0.697	0.68	n.a.	Ru
2	1.38	n.a.	478.682	101.292	99.32	n.a.	BMB
Total:			490.708	101.989	100.00	0.000	

Fig. 2 HPLC of ethyl [^{14}C]formate.

Ion exchange chromatography: Column: Anion exchanger ION Pack AS9/HC 250 × 4.6 mm; Mobile Phase : Disodium carbonate (9 mmol) + sodium hydrogen carbonate (1 mmol); Detector : Conductivity; Flow 1 ml/min; Retention time 3.44 min (see Fig. 1).

HPLC: Column : C-18, BDS Hypersil 100 x 4.6 mm; Mobile Phase : Methanol; Detector UV : 240 nm; Flow rate : 1.00 ml/min; Potassium formate, retention time 1.22 min.

Ethyl [^{14}C]formate: Triethyl phosphate (0.2 mmol, 360 µl) was added to potassium [^{14}C]formate 0.1 mmol (5 mCi, 50 mCi/mmol) in a glass ampoule. The sealed ampoule was heated in a domestic microwave oven for 20 min. The ampoule was cooled and the reaction mixture was taken up in 15 ml tetrahydrofuran. Ethyl [^{14}C]formate was distilled along with tetrahydrofuran at 55–60 °C (4.9 mCi, 98 %).

Formation of ethyl [^{14}C]formate was confirmed by IR (1740 cm^{-1}) and HPLC followed by liquid scintillation counting

HPLC: Column : C18, BDS Hypersil 100 x 4.6 mm; Mobile Phase : Methanol; Detector UV : 210 nm; Flow rate : 1.00 ml/min; Ethyl formate retention time 1.38 min (see Fig. 1); Sodium formate, retention time 1.22 min

The authors wish to express their thanks to Mr J.K. Ghosh, Chief Executive, BRIT, and Dr D. Padmanabhan, Manager LC/ILCJ, BRIT for their support and encouragement. Thanks are also due to Mr. N. Jayachandran Manager LC/ILCJ, BRIT for his help in analysing the samples by ion chromatography and HPLC and Mrs Neelambari M Parkar for the in-house preparation and supply of potassium [^{14}C]cyanide.

Received 4 May 2005; accepted 27 July 2005
Paper 05/3221

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