Journal of Labelled Compounds and Radiopharmaceuticals—Vol. XLI, No. 3

Synthesis of *p*-Di[1-^{13}C]ethoxybenzene from [1-^{13}C]Iodoethane with High Labeling Efficiency

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Summary

p-Di[1-^{13}C]ethoxybenzene was synthesized in high yield and with high labeling efficiency from hydroquinone and [1-^{13}C]iodoethane in the presence of a base in dry acetone. Some *p*-[1-^{13}C]ethoxyphenol was also formed, from which further *p*-di[1-^{13}C]ethoxybenzene could be synthesized.

Key words: *p*-di[1-^{13}C]ethoxybenzene, *p*-[1-^{13}C]ethoxyphenol, [1-^{13}C]-iodoethane, hydroquinone.

Introduction

We have already reported procedures for the synthesis of various ^{13}C-labelled compounds, utilizing the minimum number of reaction steps and taking care to maximize the yield from the labelled precursor.[1] We now report a synthesis of *p*-di[1-^{13}C]ethoxybenzene by dialkylation of hydroquinone with [1-^{13}C]iodoethane. The labelled product should be useful for metabolic studies of *p*-diethoxybenzene, which is used as a component of cosmetics.

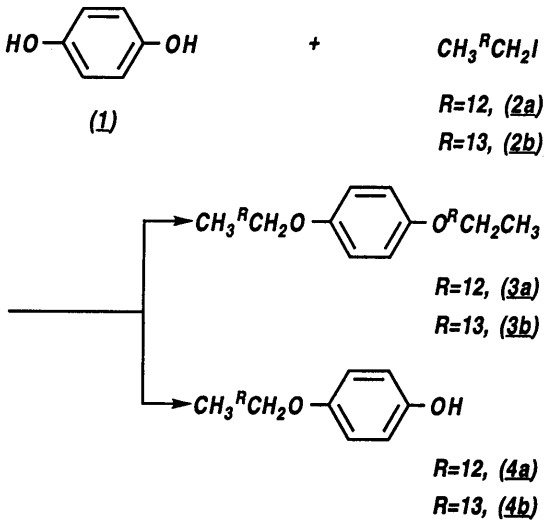
CCC 0362–4803/98/030235–07$17.50

Received 6 October1997
Revised 20 October 1997

Results and Discussion

p-Diethoxybenzene (3a) can be simply synthesized by diethylation of hydroquinone (1) with diethyl sulfate in high yield.[2] However, it is difficult to synthesize ^{13}C-labelled diethyl sulfate.

As shown in scheme 1, Loupy *et al.* reported a method for the synthesis of *p*-diethoxybenzene (3a) from hydroquinone (1), iodoethane (2a) and tetrabutylammonium bromide (TBAB; a phase-transfer catalyst), in the absence of a solvent, in 90 % yield from hydroquinone (1), without formation of *p*-ethoxyphenol (4a).[3] We examined the synthesis of *p*-diethoxybenzene (3a) by this method (Method A), using various amounts of iodoethane (2a) as shown in table 1. The conversion yield from iodoethane (2a) reached 77 % as the amount of iodoethane (2a) was reduced from 3.0 to 2.1 eq. (run 3 in table 1), though the yield from hydroquinone (1) was submaximal under this condition.



Scheme 1; Synthesis of p-Diethoxybenzene (3a) and p-Di[1-^{13}C]ethoxybenzene (3b)

Table 1; Yields of p-Diethoxybenzene (3a) in Method A

Run		1	2	3
2a	(g)	14.43	12.03	10.0
	(mmol)	92.52	77.13	64.11
	(eq.)	3.0	2.5	2.1
3a	(g)	4.96	4.66	4.11
Yield from 1	(%)	97	91	80
Yield from 2a	(%)	65	72	77

1 (3.4 g, 30.88 mmol), potassium hydroxide (85 %, 5.1 g, 77.26 mmol, 2.5 eq.) and tetrabutylammonium bromide (TBAB, 390 mg, 9 % relative to the quantity of potassium hydroxide) were used. Reaction temperature was 70 °C, and reaction time was 70 hr. All values of equivalents (eq.) are based on 1.

We also tried to synthesize *p*-diethoxybenzene (3a) by using Williamson's ether reaction[4] (Method B). As shown in scheme 1, reaction of hydroquinone (1) and iodoethane (2a) in the presence of potassium carbonate in dry acetone gave *p*-diethoxybenzene (3a) and *p*-ethoxyphenol (4a), which were easily separated by silica gel chromatography. As shown in table 2, the reaction was conducted with various amounts of iodoethane (2a) and dry acetone. With a given quantity of dry acetone, a decrease in the amount of iodoethane (2a) caused the yield of *p*-diethoxybenzene (3a) from hydroquinone (1) to decrease, the yield of *p*-diethoxybenzene (3a) from iodoethane (2a) to increase, and the yield of *p*-ethoxyphenol (4a) from hydroquinone (1) or iodoethane (2a) to increase. With a given amount of iodoethane (2a), a decrease in the amount of dry acetone caused the yield of *p*-diethoxybenzene (3a) from hydroquinone (1) or iodoethane (2a) to increase, and the yield of *p*-ethoxyphenol (4a) from hydroquinone (1) or iodoethane (2a) to decrease. The best yield from iodoethane (2a) was 80 %

in run 6. In addition, 5 % of iodoethane (2a) was converted to *p*-ethoxyphenol (4a), from which further *p*-diethoxybenzene (3a) could be synthesized, so that the overall conversion yield from iodoethane (2a) reached 85 %.

Finally, *p*-di[1-^{13}C]ethoxybenzene (3b) was synthesized from hydroquinone (1) and [1-^{13}C]iodoethane (2b) under the conditions of run 6 in method B to afford *p*-di[1-^{13}C]ethoxybenzene (3b) in a high yield, with efficient use of [1-^{13}C]iodoethane (2b).

Table 2; Yields of p-Diethoxybenzene (3a) and p-Ethoxyphenol (4a) in Method B

Run		1	2	3	4	5	6
acetone	(ml)	100	100	100	50	50	50
2a	(g)	14.43	12.09	10.00	14.43	12.09	10.00
	(mmol)	92.52	77.51	64.11	92.52	77.51	64.11
	(eq.)	3.0	2.5	2.1	3.0	2.5	2.1
3a	(g)	4.74	4.41	3.85	5.03	4.75	4.25
Yield from 1	(%)	92	86	75	98	93	83
Yield from 2a	(%)	62	68	72	65	74	80
4a	(mg)	209	426	670	74	170	460
Yield from 1	(%)	5	10	16	2	4	11
Yield from 2a	(%)	2	4	8	1	2	5
Total yield of 3a and 4a							
from 1	(%)	97	96	91	100	96	94
from 2a	(%)	63	72	80	66	75	85

1 (3.4 g, 30.88 mmol) and potassium carbonate (10.7 g, 77.42 mmol, 2.5 eq.) were used. Reaction temperature was 70 °C, and reaction time was 70 hr. All values of equivalents (eq.) are based on 1.

Experimental

Materials

[1-^{13}C]Iodoethane (99 atom % ^{13}C) was purchased from C. I. L..

Instruments

Melting point determinations were carried on a Yanaco micro melting point apparatus, Model MP, without correction. ^{1}H and ^{13}C-NMR spectra were recorded on a JEOL GSX-400 (^{1}H: 400 MHz and ^{13}C: 100 MHz) spectrometer. IR spectra were recorded on a JASCO VALOR-III FT-IR spectrometer. EI-MS were obtained on a Fisons Instruments VG Analytical AutoSpec spectrometer with a DEC VAX-4000 Model 60 data system. Elemental analysis was conducted with a Perkin-Elmer Model 240B apparatus.

Synthesis of p-Diethoxybenzene (3a)

Method A

Hydroquinone (1) (3.4 g, 30.88 mmol), potassium hydroxide (85 %, 5.1 g, 77.26 mmol, 2.5 eq.) and tetrabutylammonium bromide (390 mg, 9 % of the quantity of potassium hydroxide) were stirred at room temperature for 15 min under argon. Iodoethane (2a) (10.0 g, 64.11 mmol, 2.1 eq.) was added dropwise to this mixture, and the whole was heated at 70 °C for 70 hr. Water (50 ml) was added to the reaction mixture. The whole was neutralized with concentrated hydrochloric acid, then extracted with ether (50 ml x 3). The extracts were dried over magnesium sulfate and evaporated. Chromatography of the residue on silica gel and elution with ether:hexane (1:10) gave *p*-diethoxybenzene (3a) (4.11 g, 80 % from hydroquinone (1) or 77 % from iodoethane (2a)), m.p. 69.6~70.9 °C; ^{1}H-NMR ($CDCl_3$) δ: 1.38 (t, 6H, *J*=6.93 Hz, $C\underline{H}_3CH_2O$), 3.98 (q, 4H, *J*=6.93 Hz, $CH_3C\underline{H}_2O$), 6.82 (s, 4H, phenyl protons); ^{13}C-NMR ($CDCl_3$) δ: 14.9 (2C, $\underline{C}H_3CH_2O$), 64.0 (2C, $CH_3\underline{C}H_2O$), 115.4 (4C, phenyl carbons), 153.0 (2C, phenyl carbons); FT-IR

(KBr) cm^{-1}: 1236 (COC); EI-MS *m/z* (rel. int. %): 166 (M^+, 62.5), 110 (100); *Anal.* Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.19; H, 8.45.

Method B

Potassium carbonate (10.7 g, 77.42 mmol, 2.5 eq.) was added to a solution of hydroquinone (1) (3.4 g, 30.88 mmol) in dry acetone (50 ml) under argon. Iodoethane (2a) (10.0 g, 64.11 mmol, 2.1 eq.) was added dropwise to this suspension, and the whole was heated under reflux for 70 hr. Solids in the reaction mixture were removed by filtration, and the filtrate was evaporated. The residue was dissolved in ether (100 ml), and this solution was washed with water (50 ml x 2) and brine (50 ml), dried over magnesium sulfate and evaporated. Chromatography of the residue on silica gel and elution with ether:hexane (1:10) gave *p*-diethoxybenzene (3a) (4.25 g, 83 % from hydroquinone (1) or 80 % from iodoethane (2a)) and elution with ether:hexane (1:5) gave *p*-ethoxyphenol (4a) (460 mg, 11 % from hydroquinone (1) or 5 % from iodoethane (2a)). The combined yield of *p*-diethoxybenzene (3a) and *p*-ethoxyphenol (4a) was 94 % from hydroquinone (1) and 85 % from iodoethane (2a). The analytical data of *p*-diethoxybenzene (3a) were the same as for the product obtained by method A, and those of *p*-ethoxyphenol (4a) were as follows: m.p. 64.6~65.9 °C; ^{1}H-NMR ($CDCl_3$) δ: 1.38 (t, 3H, *J*=6.93 Hz, $C\underline{H}_3CH_2O$), 3.97 (q, 2H, *J*=6.93 Hz, $CH_3C\underline{H}_2O$), 6.77 (m, 4H, phenyl protons); ^{13}C-NMR ($CDCl_3$) δ: 14.9 (1C, $\underline{C}H_3CH_2O$), 64.1 (1C, $CH_3\underline{C}H_2O$), 115.7 (2C, phenyl carbons), 116.0 (2C, phenyl carbons), 149.4 (1C, phenyl carbon), 153.0 (1C, phenyl carbon); FT-IR (KBr) cm^{-1}: 3367 (OH), 1230 (COC); EI-MS *m/z* (rel. int. %): 138 (M^+, 58.7), 110 (100); *Anal.* Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.59; H, 7.41.

Analytical Data of p-Di[1-^{13}C]ethoxybenzene (3b)

M.p. 69.8~70.7 °C; ^{1}H-NMR ($CDCl_3$) δ: 1.38 (dt, 6H, $J_{^1H^{13}C}$=4.62 Hz, *J*=6.93 Hz, $C\underline{H}_3{}^{13}CH_2O$), 3.97 (dq, 4H, $J_{^1H^{13}C}$=142.96 Hz, *J*=6.93 Hz, $CH_3{}^{13}C\underline{H}_2O$),

6.81 (s, 4H, phenyl protons); ^{13}C-NMR ($CDCl_3$) δ: 64.0 ($CH_3{}^{13}\underline{C}H_2O$); FT-IR (KBr) cm^{-1}: 1236 (COC); EI-MS *m/z* (rel. int. %): 168 (M^+, 62.5), 110 (100).

Analytical Data of p-[1-^{13}C]Ethoxyphenol (4b)

M.p. 64.3~65.5 °C; ^{1}H-NMR ($CDCl_3$) δ: 1.38 (dt, 3H, J_{1H13C}=4.37 Hz, J=6.93 Hz, $C\underline{H}_3{}^{13}CH_2O$), 3.97 (dq, 2H, J_{1H13C}=142.97 Hz, J=6.93 Hz, $CH_3{}^{13}C\underline{H}_2O$), 6.77 (m, 4H, phenyl protons); ^{13}C-NMR ($CDCl_3$) δ: 64.1 ($CH_3{}^{13}\underline{C}H_2O$); FT-IR (KBr) cm^{-1}: 3368 (OH), 1230 (COC); EI-MS *m/z* (rel. int. %): 139 (M^+, 56.2), 110 (100).

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