Palladium-mediated carboxylation of aryl halides (triflates) or benzyl halides using [^{13}C]/[^{11}C]carbon monoxide with tetrabutylammonium hydroxide or trimethylphenylammonium hydroxide

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[Carbonyl-^{11}C]carboxylic acids were synthesised using palladium-mediated reaction of [^{11}C]carbon monoxide with aryl halides/triflates and benzyl halides in combination with either tetrabutylammonium hydroxide or trimethylphenylammonium hydroxide. The radiochemical yields were in the range 20-85%. In a typical experiment starting with 2.1 GBq [^{11}C]carbon monoxide, 0.6 GBq of HPLC-purified 1-[carbonyl-^{11}C]naphthoic acid (**13**) was obtained within 25 min of the start of the carbonylation reaction (67% decay-corrected radiochemical yield). The specific radioactivity of [carbonyl-^{11}C]nicotinic acid (**17**) was in the order of 750 GBq μmol^{-1} using 10.0 μAh bombardment. [Carbonyl-^{13}C]nicotinic acid (**17**) was synthesised to verify the position of the labelling (δ 166.1) determined by ^{13}C NMR.

Introduction

Positron emission tomography (PET) is a powerful tool for non-invasive investigation of biologically active compounds *in vivo*. The increasing application of PET in nuclear medicine[1] and drug development[2] stimulates a need for further improvement of rapid and efficient methods for incorporation of [^{11}C]carbon in new tracers with high specific radioactivity.[3]

Zerovalent palladium mediated carbonylation of organohalides using [^{11}C]carbon monoxide and appropriate nucleophiles has been previously used for synthesis of ^{11}C-amides,[4] ^{11}C-imides[5] and ^{11}C-hydrazides.[6] However, the use of this method is limited to organohalides having no β-protons bound to sp^3 carbons due to the competing β-elimination.[7]

^{11}C-Carboxylic acids have been synthesised previously using either a Grignard reaction of phenylmagnesium chloride and [^{11}C]carbon dioxide[8,9] or *via* hydrolysis of the corresponding ^{11}C-nitrile.[10]

Here we report a mild and rapid method for synthesis of various [^{11}C]carboxylic acids using the corresponding organohalide or triflate with tetrakis(triphenylphosphine)-palladium(0), and [^{11}C]carbon monoxide to form the appropriate Pd–acyl complex followed by using a nucleophile substrate as a hydroxide source *i.e.* tetramethylammonium hydroxide or trimethylphenylammonium hydroxide.

Results and discussion

Grignard reactions with [^{11}C]carbon dioxide have been previously used for synthesis of [^{11}C]carboxylic acids. This approach is somewhat limited due to undesired side reactions and only a few examples of [^{11}C]carbon dioxide-derived ^{11}C-labelled acids have been reported.[8,9] Another drawback with this approach is isotopic dilution from atmospheric carbon dioxide (3.4×10^4 ppm). Furthermore, using the corresponding ^{11}C-nitrile derivatives followed by hydrolysis (in two steps) might limit the presence of some functional groups. Moreover longer reaction time is another disadvantage of the latter method.

In this report, [^{11}C]carboxylic acids were synthesised in a system equipped with a device for local reduction of [^{11}C]carbon dioxide to [^{11}C]carbon monoxide and a micro-autoclave (200 μl). The reaction mixture, containing tetrakis(triphenylphosphine)palladium(0), an aryl halide or triflate and tetramethylammonium hydroxide or trimethylphenylammonium hydroxide (as hydroxide donor), was transferred by anhydrous THF to a micro-autoclave at high pressure (35 Mpa). The micro-autoclave was then heated at 180 or 190 °C for 5 min before releasing the crude reaction mixture into a flask at reduced pressure. The target compounds and the corresponding halides or triflates are presented in Figs. 1 and 2. The results show that in nearly all cases trimethylphenylammonium hydroxide seems to be a suitable hydroxide source (Table 1). When an aqueous solution of sodium hydroxide (1 M) or water was used as hydroxide source, almost no product was obtained.

In order to investigate the scope and limitations of aryl bromide/iodide and triflate reactivity, the compounds **1**, **2**, **10** and **14** were synthesised using the corresponding halides or triflates **20**, **21**, **29** and **33** under comparable conditions. The results showed that the triflates are preferred to the corresponding bromides but a higher reaction temperature is required.

When 1-fluoro-4-(iodomethyl)benzene (**29a**) was used instead of 1-(bromomethyl)-4-fluorobenzene (**29b**), the radiochemical yield of ^{11}C-carboxylic acid **10** was increased from 12% to 24% (using trimethylphenylammonium hydroxide, 25 μl, 37.5 mmol). Increasing the concentration of hydroxide source resulted in a lower yield (10%).

In the case of **14**, where the aryl bromide (**33a**) was used a yield of only 7% was obtained. However, when the corresponding triflate (**33b**) was employed the yield was increased to 39%.

2-Phenyl[carbonyl-^{11}C]propionic acid (**16**) was synthesised with a 14% yield using (1-bromoethyl)benzene, but to our surprise (1-iodoethyl)benzene gave no product.

The determined specific radioactivity for **17** was in the range 750 ± 30 GBq μmol^{-1} (n = 2) at 27 min after the end of bombardment (using 10.0 μAh). The specific radioactivity obtained indicates that there was no significant isotopic dilution during the synthesis after the radionuclide production.

Identification of the labelled compounds was made with analytical LC after addition of appropriate reference substances.

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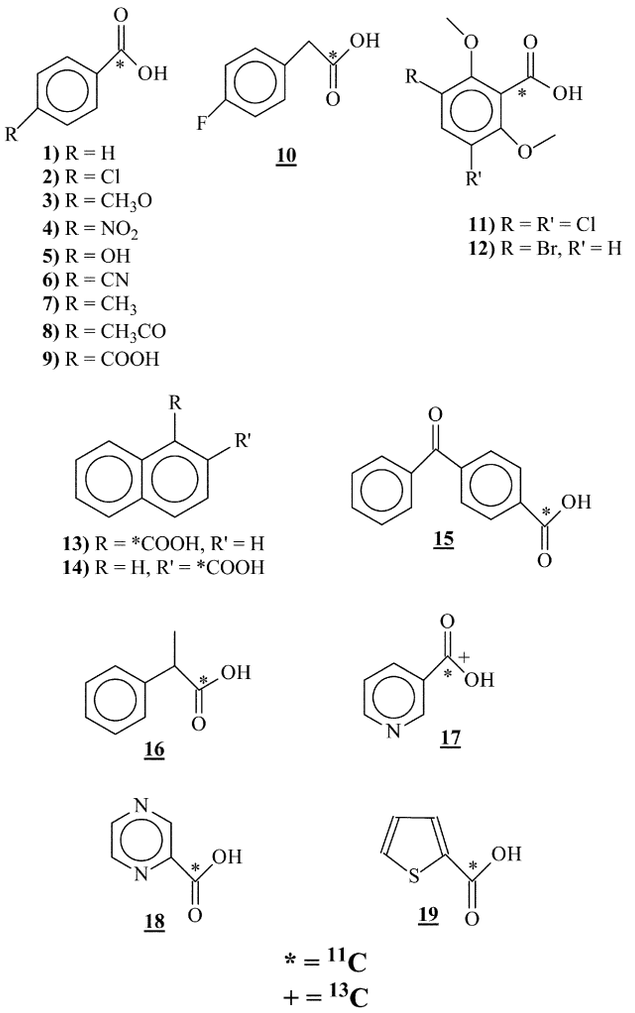

Fig. 1 Target compounds.

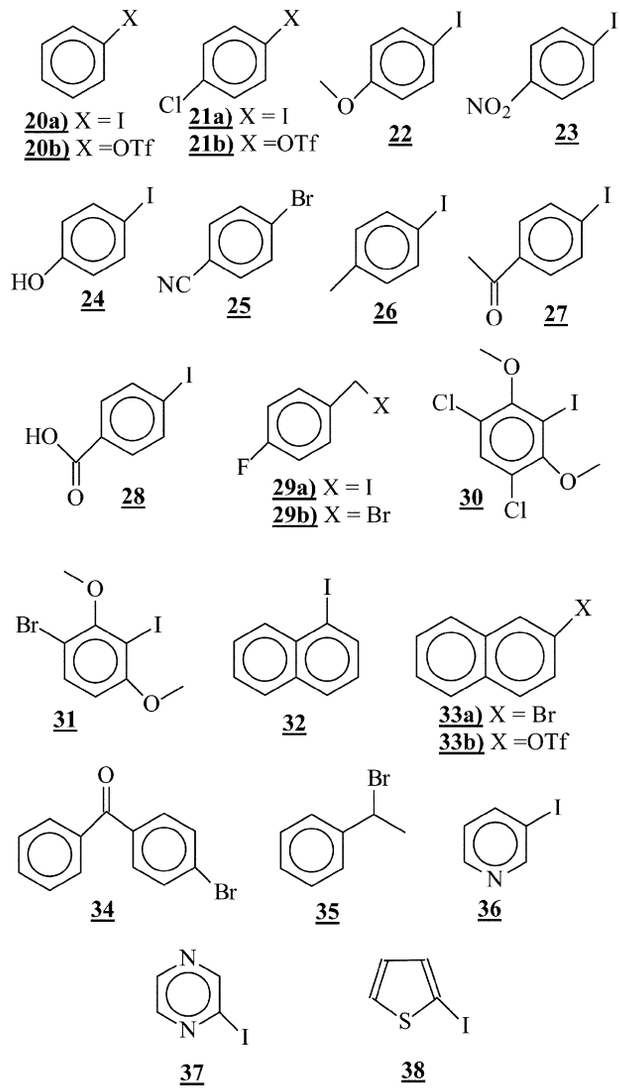

Fig. 2 Aryl halides/triflates.

Additional confirmation of the identity of compounds **3**, **8**, **11**, **12**, **15**, **17**–**19** was made by LC-MS. The identity of [carbonyl-^{11}C]nicotinic acid was confirmed using ^{13}C NMR analysis of [carbonyl-^{13}C]nicotinic acid, which was prepared using the same procedure. The ^{13}C signal at 166.1 ppm corresponded to the ^{13}C signal from the carbonyl carbon of authentic nicotinic acid.

In comparison to labelling reactions using [^{11}C]carbon dioxide or [^{11}C]cyanide, the scope of the palladium-mediated carbonylation with [^{11}C]carbon monoxide is not limited to the synthesis of various [^{11}C]carboxylic acids. A further advantage is that higher specific radioactivities may be obtained and the synthesis can be easily automated. One disadvantage of using this approach is a lower yield due to the competing β-hydride elimination, when organohalides having β-hydrogen bound to sp^3 carbons are used.

Conclusions

The use of tetrakis(triphenylphosphine)palladium(0) with [^{11}C]carbon monoxide and the organohalide in combination with tetramethylammonium hydroxide or trimethylphenylammonium hydroxide (as nucleophilic source) is an efficient method for the synthesis of [carbonyl-^{11}C]carboxylic acids with high specific radioactivity. According to our observations triflates[11] might be suitable as precursors for the synthesis of [^{11}C]carboxylic acids. This is potentially valuable for ^{11}C-labelling since carboxylic acids are important intermediates which can be converted into other functional groups such as esters, acid chlorides, amides and aldehydes.

Experimental

General

[^{11}C]Carbon dioxide was produced with a cyclotron, and reduced to [^{11}C]carbon monoxide by passing though a zinc furnace at 400 °C.[12,13] This was concentrated and enclosed with the reaction mixture in a micro-autoclave (200 µl).

Liquid chromatographic analysis (LC) was performed with a Beckman 126 gradient pump and a Beckman 166 variable wavelength UV-detector in series with a β$^+$-flow detector. The following mobile phases were used: 0.05 M ammonium formate pH 3.5 (A), acetonitrile–water (50 : 7) (B), acetonitrile (C) and 0.01 M formic acid (D). For analytical LC a Jones Chromatography Genesis C_{18}, 4 µm, 250 × 4.6 mm id column was used at a flow rate of 1.5 ml min^{-1}. For semi-preparative LC, a Jones Chromatography Genesis C_{18}, 4 µm, 250 × 10 mm (id), column was used at a flow rate of 4 ml min^{-1}. "Synthia", an automated synthesis system,[14] was used for LC injection and fraction collection. Data collection and LC control were performed with the use of a Beckman System Gold chromatography software package.

Radioactivity was measured using an ion chamber (Veenstra Instrumenten bv, VDC-202). For measurements of radioactivity during synthesis, a portable dose-rate meter was used.

In the analysis of the ^{11}C-labelled compounds, unlabelled reference substances were used for comparison in all the LC runs. The identities of synthesised compounds were determined

Table 1 Radiochemical yields and synthesis parameters for the ^{11}C-labelled carboxylic acids shown in Fig. 1

Compound	Method[a]	Trapping efficiency (%)[b]	Radiochemical yield (%)[c]	LC-MS (ESI$^+$)[d] *m*/*z* [M + H]$^+$
1	[e]A (7)	91 ± 4	59 ± 4	—
	[f]B (5)	88 ± 2	78 ± 2	
	[g]C (2)	79 ± 1	85 ± 1	
2	A (1)	98	35	—
	B (2)	76 ± 1	77 ± 1	
	C (2)	81 ± 1	75 ± 1	
3	B (4)	91 ± 1	76 ± 1	153
4	A (1)	68	46	—
	B (2)	71 ± 2	74 ± 2	
5	A (2)	55 ± 4	40 ± 8	—
	B (4)	94 ± 2	21 ± 4	
6	A (1)	79	31	—
7	B (3)	85 ± 3	70 ± 2	—
8	A (2)	93 ± 2	26 ± 5	165
	B (2)	79 ± 1	73 ± 2	
9	A (2)	92 ± 2	33 ± 3	—
10	B (2)	86 ± 1	24 ± 1	—
11	B (2)	60 ± 1	50 ± 2	252
12	B (2)	89 ± 1	42 ± 1	262
13	A (1)	96	23	—
	B (2)	93 ± 2	66 ± 1	
14	B (3)	80 ± 4	7 ± 2	—
	C (2)	72 ± 1	39 ± 1	
15	A (2)	95 ± 3	10 ± 1	227
	B (1)	67	25	
16	B (3)	19 ± 2	14 ± 3[h]	—
17	A (4)	96 ± 3	20 ± 8	124
	B (2)	77 ± 1	65 ± 3	
18	A (2)	88 ± 1	4 ± 1	125
	B (3)	82 ± 1	75 ± 1	
19	B (2)	57 ± 1	68 ± 1	129

[a] Values in parentheses show number of runs. [b] Decay-corrected, the fraction of radioactivity left in the crude product after purging with nitrogen. [c] Decay-corrected, calculated from the amount of radioactivity in the crude product before nitrogen purge, and the radioactivity of the LC-purified product. [d] Using mobile phases C and D. [e] $Me_4N^+OH^-$ was used as hydroxide source. [f] $Me_3PhN^+OH^-$ was used as hydroxide source. [g] The appropriate triflate was used instead of halide. [h] Analytical radiochemical yield determined by LC.

using ^{1}H and ^{13}C NMR and LC-MS. NMR spectra were recorded on a Varian XL 300 (300 MHz) with chloroform-d_1 as internal standard. LC-MS was performed using a Micromass VG Quattro with electrospray ionisation using mobile phases C and D. A Beckman 126 pump, a CMA 240 autosampler and an XTerra™ MS C_{18} 3.5 μm, 4.6 × 100 mm column were used for the LC-MS separation with mobile phases C and D.

THF was distilled under nitrogen from sodium–benzophenone.

All chemicals were purchased from Aldrich or Chemtronica (Sweden). Compounds **21b**,[15] **29a**,[16] **30** and **31**[17] were synthesised according to the literature.

4-Chlorophenyl trifluoromethanesulfonate (21b)

To an ice-cooled solution of 4-chlorophenol (0.88 g, 6.86 mmol) in dry pyridine (10 ml) trifluoromethanesulfonic anhydride (1.50 ml, 8.92 mmol) was slowly added under argon atmosphere. The mixture was stirred at room temperature for 2.5 h and refluxed for an additional 1 h. The solvent was removed under reduced pressure and the residue was partitioned between water and methylene chloride. The aqueous layer was extracted with methylene chloride (3 × 70 ml). The combined organic phases were dried over $MgSO_4$, concentrated and purified by flash chromatography using ethyl acetate–pentane (1 : 1) to give the title compound (1.30 g, 71%). GC-MS: *m*/*z* = 261, 129.

1-Fluoro-4-(iodomethyl)benzene (29a)

Hydriodic acid (57%, 10 ml) was added to (4-fluorophenyl)-methanol (2.65 g, 21.0 mmol) at room temperature. The reaction mixture was refluxed for 1 h then cooled to room temperature, diluted with ether (30 ml) followed by washing with saturated $Na_2S_2O_3$ (50 ml), and then brine (40 ml). The organic phase was dried over $MgSO_4$, and concentrated by evaporation of the volatile fraction by vacuum. The crude product was purified by flash silica gel column chromatography. Elution with pentane yielded the title compound (4.84 g, 98%). GC-MS: *m*/*z* = 236, 109.

1,5-Dichloro-3-iodo-2,4-dimethoxybenzene (30)

3,5-Dichloro-2,6-dimethoxybenzoic acid (0.50 g, 2.0 mmol), iodine (0.81 g, 3.2 mmol) and mercury(II) oxide (0.22 g, 1.0 mmol) were dissolved in nitrobenzene (10 ml). The reaction mixture was heated at 160–165 °C for 2 h under an argon atmosphere and then left to cool to room temperature overnight. The resulting mixture was washed with NaOH (1.5 M, 50 ml), dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (ether–pentane, 20 : 80) to obtain 0.50 g, 75% of **30**. δ_H (300 MHz, $CDCl_3$): 7.43 (s, 1H), 3.86 (s, 6H). ^{13}C NMR (300 MHz, $CDCl_3$): 155.5, 134.5, 130.8, 129.3, 123.4, 92.2, 60.5. GC-MS: *m*/*z* = 334, 332.

1-Bromo-3-iodo-2,4-dimethoxybenzene (31)

The synthesis was performed as described for **30** except that 3-bromo-2,6-dimethoxybenzoic acid was used. The purified compound **31** was obtained (72%). δ_H (300 MHz, $CDCl_3$): 7.45 (d, 1H), 6.49 (d, 1H), 3.80–3.85 (d, 6H). ^{13}C NMR (300 MHz, $CDCl_3$): 159.0, 157.3, 133.1, 107.9, 107.4, 85.0, 60.4, 55.8. GC-MS: *m*/*z* = 344, 342.

Labelling experiments

General procedure A. Tetrakis(triphenylphosphine)-palladium(0) (≈ 3 μmol) and the appropriate halide (≈ 9 μmol)

were placed in a vial (1 ml). The vial was flushed with nitrogen then dry THF (220 μl) was added. The resulting mixture was heated (70 °C, 1 min) and kept at room temperature for 10–15 min. An aqueous solution of tetramethylammonium hydroxide (1.5 M, 25 μl, 37.5 μmol) was added and shaken just before injection into the micro-autoclave (200 μl) at high pressure (35 Mpa), pre-charged with [^{11}C]carbon monoxide. The mixture was heated at 180 °C for 5 min and the crude product transferred to a pre-evacuated vial (5 ml). The micro-autoclave was washed with THF (250 μl), which was collected into the same vial. The radioactivity of the vial was measured before and after purging with nitrogen. The solvent was reduced to 0.1 ml by heating at 80 °C and flushing with nitrogen. The crude mixture was dissolved in acetonitrile–water before injection onto the semi-preparative LC using solvent A and B or C. The identity and radiochemical purity of the collected fraction were analysed by analytical LC and LC-MS.

General procedure B. The synthesis was performed as above using an aqueous solution of trimethylphenylammonium hydroxide (1.6 M, 25 μl, 40 μmol) instead of tetramethylammonium hydroxide (1.5 M, 25 μl, 37.5 μmol).

General procedure C. The synthesis was performed as described in method A but using aryl triflate (≈ 9 μmol) instead of aryl halide and heating at 190 °C.

[Carbonyl-^{13}C]nicotinic acid (17)

In a vial (1 ml) were placed tetrakis(triphenylphosphine)-palladium(0) (8 mg, 6.9 μmol) and 3-iodopyridine (**36**) (5.4 mg, 26.4 μmol) dissolved in anhydrous THF (150 μl) and trimethylphenylammonium hydroxide (75 μl, 123 μmol), as previously described in method B. The resulting reaction mixture and [^{13}C]carbon monoxide (1 ml) were transferred to the micro-autoclave, which was pre-charged with [^{11}C]carbon monoxide. The micro-autoclave was heated at 180 °C for 20 min. The crude product was transferred to a vial with reduced pressure and the volatile fraction was removed by heating at 50 °C and purging with nitrogen. Acetonitrile (0.4 ml) and then water (1.0 ml) was added and the resulting solution was purified on the semi-preparative LC as described before, to obtain the desired product (78%). ^{13}C NMR (300 MHz, $CDCl_3$): 166.1.

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