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Synthesis of [^{11}C]-labelled Aldehydes

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The synthesis of benzaldehyde, anisaldehyde, 4-*tert*-butoxybenzaldehyde, veratraldehyde, piperonal and phenylacetaldehyde labelled with ^{11}C ($t_{\frac{1}{2}}$=20.3 min) in the 1-position is reported.

In the synthesis of the ^{11}C-labelled aldehydes, ^{11}C-carbon dioxide (produced by the ^{14}N(p,α) ^{11}C reaction on a nitrogen gas target) was trapped in the appropriate Grignard solution. The labelled salts obtained were then directly reduced by lithium aluminium hydride to give the corresponding [1-^{11}C]-alcohols. Oxidation of the labelled alcohols with tetrabutylammonium bichromate[1] gave the corresponding aldehydes in 60–95 % radiochemical yields within 5 min of the arrival of the lead-shielded trap at the chemistry laboratory. The ^{11}C-labelled acids and alcohols were obtained in 70–95 % radiochemical yields.

We also report the use of tetrabutylammonium bichromate[1] in the synthesis of unlabelled benzaldehyde, anisaldehyde and phenylacetaldehyde, starting from the corresponding alcohols.

Growing interest in the use of β^+-emitting radionuclides, such as ^{11}C, ^{13}N, ^{15}O and ^{18}F, in biology and medicine in recent years has been the important incentive in our research on the synthesis of compounds labelled with these radionuclides.[2] The synthetic strategies which can be used are severely limited by the time factor and the restricted number of labelled precursors available directly at the target or by rapid on-line synthesis.

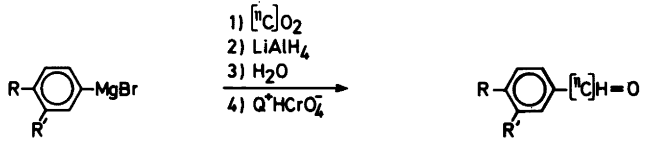
Some of these ^{11}C-labelled aromatic aldehydes have been used in the preparation of [3-^{11}C]-labelled phenylalanine, DOPA and tyrosine by a synthetic route including asymmetric synthesis, which will be reported elsewhere.[3] The [1-^{11}C]-phenylacetaldehyde may also be used in a Bücherer-Strecker synthesis to yield [2-^{11}C]-labelled aromatic amino acids.[4]

Grignard reactions have been used for the preparation of labelled acids, including [1-^{11}C]-benzoic acid,[5] for use as such or for the preparation of [1-^{11}C]-benzaldehyde.[6]

In this report, a rapid synthesis of [1-^{11}C]-labelled aldehydes is presented. The corresponding ^{11}C-labelled alcohols and acids have also been isolated in 70–95 % radiochemical yields.

DISCUSSION AND RESULTS

The ^{11}C-labelled aromatic and aliphatic aldehydes presented in this paper were prepared from the corresponding ^{11}C-labelled alcohols by oxidation according to routes shown in Schemes 1 and 2.



R,R'= H, OR

Scheme 1.

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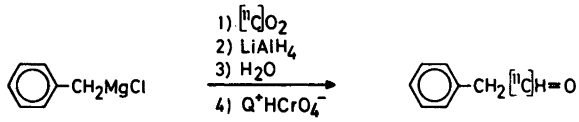


Scheme 2.

The [1-^{11}C]-carboxylic acids were obtained by trapping ^{11}C-carbon dioxide in the appropriate Grignard solution.

The trapping of ^{11}C-carbon dioxide in a Grignard solution depends on the concentration of the Grignard reagent and on the solvent, temperature and gas flow. The trapping efficiency varied from 80 to 95 % of total radioactivity (Table 1).

Reduction of the labelled acid salts with lithium aluminium hydride gave the corresponding alcohols (Table 2).

The labelled alcohols were oxidized to the corresponding aldehydes using various oxidation reagents. In one case chromic acid was used on a solid support[7] according to Wolf and coworkers.[6] This method worked very well in cold runs, but in "no carrier added" experiments radioactivity was lost in the columns containing the supported chromic acid in unacceptable and irreproducible amounts.

It was also found that ion-pair oxidation in water–ethyl acetate with tetrabutylammonium

Table 1. Summary of results regarding synthesis of ^{11}C-labelled acids.

Name	Solvent, conc. (M) (±0.01)	Trapping [a,b] eff. (%) (±2)	Radiochem.[c] yield (%) (±2)
[1-^{11}C]Benzoic acid	Ether (0.20)	85	>95
	THF (0.80)	90	>95
[1-^{11}C]-4-Methoxybenzoic acid	Ether (0.15)	80	>95
[1-^{11}C]-4-*t*-Butoxybenzoic acid	Ether/THF (1:1) (0.32)	90	>95
[1-^{11}C]-3,4-Dimethoxybenzoic acid	THF (0.30)	95	>95
[1-^{11}C]-3,4-Methylenedioxybenzoic acid	THF (1.47)	85	70
[1-^{11}C]Phenylacetic acid	THF (0.74)	80	90

[a] The trapping efficiency was calculated from the trapped amount of ^{11}C-activity and total radioactivity. [b] Temperature 0 °C, flow 24 ml/min. [c] The radiochemical yield was analysed by LC and counted on ^{11}C trapped in the Grignard solution.

Table 2. Summary of results regarding synthesis of ^{11}C-labelled alcohols.

Name	Radiochem.[a] yield (%) (±2)	Time[b] (min)
[1-^{11}C]Benzyl alcohol	>95	~2
[1-^{11}C]-4-Methoxybenzyl alcohol	>95	~2
[1-^{11}C]-4-*t*-Butoxybenzyl alcohol	>95	~2
[1-^{11}C]-3,4-Dimethoxybenzyl alcohol	>95	~2
[1-^{11}C]-3,4-Methylenedioxybenzyl alcohol	70	~2
[1-^{11}C]Phenethyl alcohol	90	~2

[a] The radiochemical yield was analysed by LC and counted on ^{11}C trapped in the Grignard solution. [b] The time calculation is based on the arrival of lead-shielded trap containing the activity at the chemistry laboratory.

hypochlorite[8] worked satisfactorily. However, one complication occurred in the synthesis of activated aromatic aldehydes, such as veratraldehyde, where competing chlorination took place.

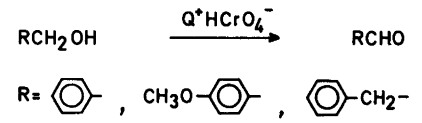
In a third approach, the oxidation was carried out using tetrabutylammonium bichromate[1] in 3 M sulfuric acid–ethyl acetate (Table 3). This method is now used routinely and works well.

Before the labelled aldehydes could be used for further synthesis, the organic phase had to be washed carefully with water. This method gives consistent results, with only a small amount of labelled acid present in the final product mixture. The washing procedure also removes labelled carbonate, which may be formed if the Grignard solution is no longer fresh. The only case of failure so far is that we have not been able to prepare indolyl-3-aldehyde in a large enough yield. In the synthesis of phenylacetaldehyde the yields are rather low (Tables 3 and 4).

The labelled aldehydes were then used without further purification in the synthesis of [3-^{11}C]-labelled phenylalanine, DOPA and tyrosine, as will be reported elsewhere.[3]

In the synthesis reported here, approximately 50–180 mCi ^{11}C-carbon dioxide of a specific radioactivity of the order of 10–100 mCi/μmol was used. Carrier carbon dioxide was not added in any case. Further developments in the technical handling of the synthesis are in progress, which may speed up the reaction time.

We also report the use of tetrabutylammonium bichromate[1] in the preparative synthesis of benzaldehyde, anisaldehyde and phenylacetaldehyde, starting from the corresponding alcohols (Scheme 3 and Table 4).



Scheme 3.

Table 3. Summary of results regarding synthesis of ^{11}C-labelled aldehydes.

Name	Radiochem.[a] yield (%) (±2)	Time[b] (min)
[1-^{11}C]Benzaldehyde	>95	~5
[1-^{11}C]Anisaldehyde	80	~5
[1-^{11}C]-4-*t*-Butoxybenzaldehyde	>95	~5
[1-^{11}C]Veratraldehyde	80	~5
[1-^{11}C]Piperonal	70	~5
[1-^{11}C]Phenylacetaldehyde	60	~5

[a] The radiochemical yield was analysed by LC and counted on ^{11}C trapped in the Grignard solution. [b] The time calculation is based on the arrival of the lead-shielded trap containing the activity at the chemistry laboratory.

Table 4. Results and experimental conditions in the synthesis of unlabelled aldehydes.

Experimental conditions	Benzaldehyde	Anisaldehyde	Phenylacetaldehyde
3 M sulfuric acid (cm^3)	10.0	10.0	40.0
Ethyl acetate (cm^3)	20.0	20.0	80.0
Tetrabutylammonium bisulfate (g)	2.5	2.5	5.0
Sodium dichromate (g)	7.5	10.0	5.0
Alcohol (mmol) (g)	94.2 (10.0)	73.4 (10.0)	83.2 (10.0)
Reaction time (min)	2	2	30
2 M sodium hydroxide (cm^3)	15.0	15.0	60
Yield (%) (g)	65 (6.6)	55 (5.6)	30 (3.1)
B.p. (°C/mmHg)	85/30	140/30	105/40

EXPERIMENTAL

General. The ^{11}C was produced at the Tandem Van de Graaff accelerator at the University of Uppsala by using the $^{14}N(p,\alpha)^{11}C$-reaction on a nitrogen gas target.[2] The ^{11}C-carbon dioxide was trapped in the reaction vessel containing the appropriate Grignard solution. After trapping, the magnesium salts of the labelled acids were kept in a lead-shielded trap during transport to the chemistry laboratory.

LC-analysis was carried out on a Hewlett-Packard 1084 B equipped with a variable wavelength detector in series with a β^+-flow-detector.[9] In the analysis a 25 cm×0.4 cm (i.d.) C-18-Nucleosil, 10 μm was used. GLC-analysis was carried out on a Hewlett-Packard 5880. ^1H and ^{13}C NMR were performed on a JEOL FX-100. The concentration of Grignard reagent was determined by the method of Gilman.[10]

General synthetic procedure. [1-^{11}C]-aldehydes (Schemes 1 and 2 and Table 3). Reagent: tetrabutylammonium bichromate. A nitrogen gas stream containing ^{11}C-carbon dioxide from the gas target was passed through a solution kept at 0 °C and containing 2.0 cm^3 of the appropriate aryl(benzyl)magnesium halide solution. The ^{11}C-carbon dioxide was trapped in the Grignard solution for 4–8 min and the solution containing the magnesium salt of the labelled acid was transported to the chemistry laboratory. Then, 0.4 cm^3 of a 1 M lithium aluminium hydride solution in ether was added to the reaction vessel, equipped with a magnetic stirrer and a septum. The reduction was performed for 1 min at room temperature. After hydrolysis with 2.0 cm^3 water and addition of 1.5 cm^3 ether and removal of the aqueous phase, a two-phase mixture containing 2.0 cm^3 ethyl acetate, 1.0 cm^3 3 M sulfuric acid, 0.25 g tetrabutylammonium bisulfate and 0.50 g sodium dichromate (0.25 g in the preparation of phenylacetaldehyde) was added. After 1 min LC-analysis showed >95 % ^{11}C-labelled aldehyde.

LC-analysis of the reaction mixture was performed on a reverse phase system on the C-18 column using solvent A: 0.10 M sodium acetate, pH 4.50 and B: 96 % ethanol, as eluents. The following LC-programme was used: Flow 3.0 cm^3; time 0–4.5, gradient B 20–30; time 4.5–5.0, gradient B 30–80; time 5.0–9.0, B=80 isocratic; time 9.0–10.0 gradient B 80–20.

Synthesis of unlabelled aldehydes. The following general procedure was used (details in Table 4). In a reaction flask, equipped with a reflux condenser, magnetic stirrer and kept under N_2 atmosphere, were introduced 3 M sulfuric acid, ethyl acetate, tetrabutylammonium bisulfate and sodium dichromate. The appropriate alcohol was then added to the solution at room temperature. After reaction, 2 M sodium hydroxide was added and the mixture was extracted with ether. The organic phase was washed with saturated sodium chloride and dried over magnesium sulfate. Evaporation and distillation of the residue gave the required product.

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