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Utilisation of [11C]-labelled boron carbonyl complexes in palladium carbonylation reaction

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Received (in Cambridge, UK) 19th November 2003, Accepted 22nd December 2003

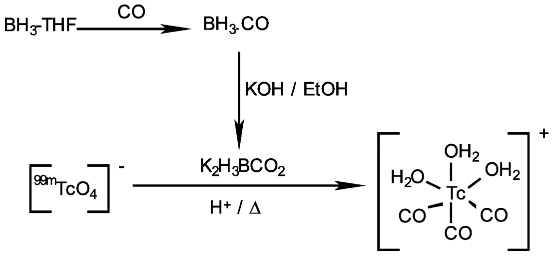
The use of the [^{11}C]$BH_3{\cdot}CO$ complex as a source of carbon monoxide in the carbonylation of iodobenzene catalysed by palladium(0) is described, which allows the synthesis of an amide and a lactone in a straightforward manner.

The use of [^{11}C]carbon monoxide for the synthesis of radiolabelled molecules in the field of positron emission tomography (PET) has become increasingly accessible due to the pioneering work of several groups using palladium-mediated carbonylation of organohalides.[1] This attractive reaction has to face the problem of low solubility of carbon monoxide in most solvents, which makes it difficult to work with. However, methods have been developed to facilitate the trapping of [^{11}C]CO in small volumes of solvents, which are applicable for micromolar scale reactions used in radiolabelling synthesis. They rely on the use of [^{11}C]CO under high pressure, or even recirculation of [^{11}C]CO, in order to maintain adequately high levels in solution.[1a–e] Nevertheless these methods require sophisticated automated robotic systems and specialised equipment for the handling of [^{11}C]CO.

In an effort to develop new methods to label molecules with PET isotopes, we inititated a project focused on the establishment of new procedures to trap and react [^{11}C]CO. Recently, Alberto *et al.* demonstrated the ability to prepare a technetium(I) carbonyl complex [$^{99m}Tc(OH_2)_3(CO)_3$]$^+$ using a boron-based carbonylating agent ($K_2[H_3BCO_2]$) (Scheme 1).[2] This in turn was prepared by passing CO through a tetrahydrofuran (THF) solution of $BH_3{\cdot}THF$ to give H_3BCO, followed by its reaction *in situ* with an alcoholic solution of potassium hydroxide affording $K_2[H_3BCO_2]$. If such a method could be adapted to trap and release [^{11}C]CO, its relative simplicity would make it extremely useful in PET chemistry. Moreover, it has been demonstrated in 1979 that the insertion of [^{11}C]CO into organoboranes at atmospheric pressure, followed by an oxidation of the reaction product could lead to [^{11}C]aldehydes. However this method was limited to the synthesis of [^{11}C]octanal.[3]

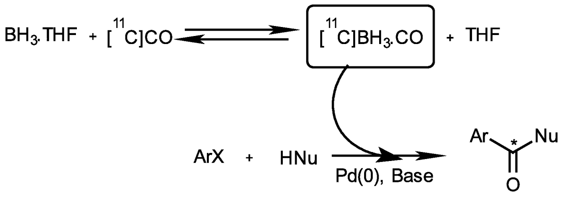
In order to investigate the validity of the method, we decided to study carbonylation reactions of organohalides catalysed by palladium(0) at atmospheric pressure (Scheme 2).

Based on Scheme 2, the amide and ester formation were first studied, using [^{11}C]*N*-benzylbenzamide **1** and [^{11}C]phthalide **2** as model compounds (Fig. 1). The reactions were run in one-pot by mixing iodobenzene and *N*-benzylamine for **1** or 2-bromobenzyl alcohol for **2** with 30 mol% of palladium(0) catalyst prepared *in situ* from $Pd(OAc)_2$ and PPh_3.



Scheme 1

The first attempts with our set-up† showed that the conversion of [^{11}C]CO to the [^{11}C]$BH_3{\cdot}CO$ complex and the trapping efficiency of the [^{11}C]$BH_3{\cdot}CO$ complex in the reaction mixture at −78 °C were very high (> 90%). However, the aminocarbonylation of iodobenzene was sluggish and difficult to reproduce. Analytical HPLC of the crude mixture showed the presence of the desired product **1** in low yields (Table 1, entry 1). Changing the temperature or the reaction time did not improve the yields. Suspecting the presence of $BH_3{\cdot}THF$ in the reaction mixture to be the problem, its neutralisation by the addition of water to the solvent had a dramatic effect on the process of the reaction, as seen in Table 1. The best conditions found afforded a radiochemical yield of 47% when 1% of water in THF and a temperature between 70 and 120 °C were



Scheme 2

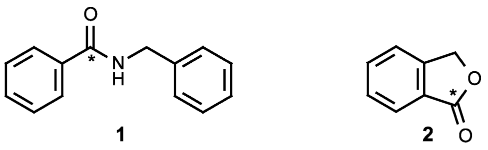


Fig. 1

Table 1 Study of the [^{11}C]aminocarbonylation of iodobenzene: synthesis of [^{11}C]*N*-Benzylbenzamide **1**

Entry	Base[a]	Solvent	Trapping temp./°C	Reaction temp./°C (time/min)	Radiochemical yield of product[b] (%)
1	TEA	THF	−78	110 (10)	1.7
2	TEA	THF + 20% H_2O	0	120 (8)	7
3	TEA	THF + 2% H_2O	−78	120 (8)	30
4	TEA	THF + 1% H_2O	−78	50 (8)	17
5	TEA	THF + 1% H_2O	−78	70 (8)	47
6	TEA	THF + 1% H_2O	−78	85 (8)	47
7	TEA	THF + 1% H_2O	−78	120 (8)	47
8	TEA	THF + 1% H_2O	−78	140 (8)	28
9	DBU	THF + 1% H_2O	−78	120 (8)	Traces
10	Pyridine	THF + 1% H_2O	−78	80 (8)	36
11	TMP	THF + 1% H_2O	−78	120 (8)	8
12	Benzylamine	THF + 1% H_2O	−78	90 (8)	20
13	TEA	DMF + 1% H_2O	−50	90 (8)	23
14	TEA	Dichloroethane	−20	110 (8)	12

[a] 1.2 eq. of base was used in all cases, except for entry 4 where 3 eq. of benzylamine were used. [b] Radiochemical yield was based on the total radioactivity trapped at the end of synthesis (EOS) in the reaction vial, corrected for decay.

DOI: 10.1039/b314982j

used (entries 5–7). For entry 2, the trapping temperature of the [^{11}C]borane carbonyl complex in the reaction vial was restricted to 0 °C because of the high amount of water present (20% in THF). This increase in temperature caused a large decrease in the trapping efficiency explaining the low radiochemical yield of the product (7%).

The influence of bases and solvents was also investigated in order to improve the radiochemical yields. In our case, the choice of base is very important for the amidation reaction (Table 1, entries 5–7 and 9–12). However, no correlation between the strength of the bases and the outcome of the reaction were observed as previously described in the literature.[4] Using the strong base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), only traces of product were seen on the analytical HPLC of the crude material (Table 1, entry 9). Weaker bases like pyridine, or intermediate bases like 2,2,6,6-tetramethylpiperidine (TMP) and benzylamine, gave radiochemical yields of 36, 8 and 20%, respectively (Table 1, entries 10–12), which was not as effective as with triethylamine (TEA) (47% radiochemical yield) (Table 1, entries 5–7).

Concerning the solvent, THF proved to be the most effective. Dimethylformamide (DMF) and 1,2-dichloroethane gave a radiochemical yield of product of 23 and 12%, respectively (Table 1, entries 13 and 14). The polarity of the solvent did not influence the process of the carbonylation in our case. The low yields observed may be explained by a low trapping efficiency of the [^{11}C]BH_3·CO complex in the reaction vial as in these two cases higher temperature bath than −78 °C had to be used, because of the higher freezing point of these two solvents.

Employing the above conditions (1% of water in THF with TEA as a base) for the synthesis of the [^{11}C]phthalide **2**, a radiochemical yield of 27% of product could be obtained (Table 2, entry 1). The influence of the amount of palladium catalyst was then studied, and the results showed that 30 mol% catalyst gave the best results (Table 2, entries 1–3). An increase of catalyst did not enhance the radiochemical yield (Table 2, entry 3). Another study was performed by reacting 2-bromobenzyl alcohol with the [^{11}C]BH_3·CO complex catalysed by 30 mol% of Pd(0) and 5 equivalents of potassium carbonate in THF containing 1% of water (knowing that potassium carbonate had been successfully used for direct or carbonylative Suzuki couplings[5]). Unfortunately, only traces of product on the analytical HPLC of the crude were detectable (Table 2, entries 4 and 5). Changing the solvent from THF to dioxane did not lead to an improvement (Table 2, entry 6).

In summary, the use of the [^{11}C]BH_3·CO complex in carbonylation reactions catalysed by palladium(0) has shown to be an interesting new tool in PET-chemistry, as it allows the easy trapping of [^{11}C]CO under the form of a boran complex at −78 °C under atmospheric pressure. The application of this methodology allowed the synthesis of an amide and a lactone in useful radiochemical yields. Further optimisation is currently under way, and it is expected that the method can be extended to other substrates, which could give access to a whole new range of PET probes for *in vivo* imaging. In addition to the radiolabelling chemistry, we believe that BH_3·CO complex could be of interest for carbonylation reactions in general.

Table 2 [^{11}C]carbonylation reaction applied to the synthesis of an ester: synthesis of phthalide **2**

Entry	Base	Solvent	Trapping temp./°C	Reaction temp./°C	Radiochemical yield of product[a] (%)
1	TEA	THF + 1% H_2O	−78	90 (8)	27[b]
2	TEA	THF + 1% H_2O	−78	90 (8)	26[c]
3	TEA	THF + 1% H_2O	−78	120 (8)	20[d]
4	K_2CO_3	THF + 1% H_2O	−78	100 (4)	Traces
5	K_2CO_3	THF + 1% H_2O	−78	120 (5)	Traces
6	K_2CO_3	Dioxane + 1% H_2O	−78	80 (4)	Traces

[a] Radiochemical yield was based on the total radioactivity trapped at the end of synthesis (EOS) in the reaction vial, corrected for decay. [b] The reaction was run with 30 mol% palladium(0) catalyst. [c] The reaction was run with 20 mol% palladium(0) catalyst. [d] The reaction was run with 36 mol% palladium(0) catalyst.

Notes and references

† Our set-up consisted of a series of four different vials. The first vial, filled with 4 Å molecular sieves and cooled at −192 °C, was used to trap the produced [^{11}C]carbon monoxide. The second vial contained a solution of BH_3·THF at room temperature, where the [^{11}C]CO, carried with a flow of nitrogen, was passed through after its release at room temperature from the molecular sieves, forming the desired [^{11}C]BH_3·CO complex. This complex was further carried through an empty vial cooled at −60 °C in order to condense the THF, and was finally passed through the reaction vial containing the reactants in solution cooled at −78 °C, where it was efficiently trapped. After 6 min of the trapping process, time necessary to reach a maximum of radioactivity, the reaction vial was heated for 5–15 min. The crude product was filtered through a 0.45 μm filter and analysed using analytical radio HPLC. The desired end-product was identified by co-injection with a non-radioactive reference. The given yields of the product are based on the final radioactivity trapped in the reaction vial at EOS.

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