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COMMUNICATION

^{11}C-Carbonylation Through ^{11}C-Benzoyl Chlorides Using Tetrabutylammonium Chloride

Kenneth Dahl,[b] and Patrik Nordeman*[a]

Abstract: Aromatic carbon-11 containing acids, amides, esters and aldehydes were obtained through a novel ^{11}C-carbonylative reaction. In the two-step process, aryl iodides are first reacted with ^{11}CO and tetrabutylammonium chloride in a palladium-mediated reaction to yield ^{11}C-benzoyl chlorides *in situ*. The crude mixture is then further treated with either a hydroxyl, amine, alcohol or a hydride in a second vial to furnish the final ^{11}C-carbonyl product. The monodentate ligand tri-*tert*-butylphosphonium tetrafluoroborate was proven to be crucial for obtaining high radiochemical yield (RCY). A wide range of ^{11}C-carbonyl containing compounds were successfully radiolabeled in moderate to excellent RCYs, ranging from (41-93%). The synthetic retinoic acid Tamibarotene was obtained in a RCY of 89%, whereas the Boc-protected Procainamide was labelled in 68% RCY, which is a significantly increase (2-3 fold) in RCY compared to other published methods.

Introduction

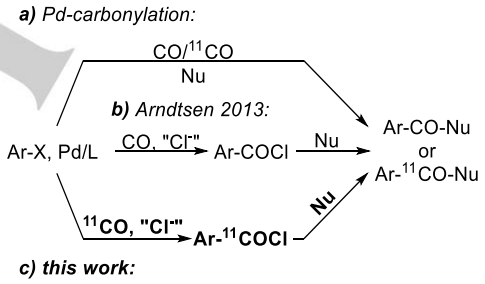
Carbon monoxide (CO) is as a diverse and useful building block for carbonyl compounds. Over the past two decades, substantial development in the field of organic catalysis using CO has been made.[1] In radiochemistry, carbon-11 (^{11}C, $t_{1/2}$ = 20.4 min) labelled carbon monoxide, ^{11}CO, can be obtained through the reduction of cyclotron-produced $^{11}CO_2$[2] and used in metal-mediated reactions much like those on a laboratory scale.[3] The substoichiometric (nmol) quantities of the gases requires specialized equipment and modified synthetic methods since time is of the essence.[4] In the literature there are examples of different approaches to retain the volatile ^{11}CO in the reaction chamber and to efficiently incorporate it into a molecule of interest.[2c-d, 5]

The palladium-mediated ^{11}C-carbonylation has since it was introduced in the mid-nineties[6] been an effective and selective method for the radiolabeling of amides, esters and other carbonyl containing molecules (Scheme 1a).[1,3]

In 2013, Arndtsen described the synthesis of aromatic amides by the aminocarbonylation of aryl compounds at ambient pressure of CO using a Pd-catalyzed approach in the presence of a chloride source. The method relies upon the intermediate formation of an acyl chloride which could further react with a nucleophile (Scheme 1b).[7] Inspired by these results we set out to develop a two-step method using ^{11}CO.

Carbon-11 labelled acid chlorides have previously been prepared via metals-mediated transformation starting from either $^{11}CO_2$[8a,b] or ^{11}CO[9]. However, these methodologies are all performed in two-steps and rely upon the initial formation of the corresponding carboxylic acid, followed by chlorination using corrosive reagent such as oxalyl chloride and thionyl chloride.

In this communication, we describe the ^{11}C-carbonylation of aryl compounds using a method in which ^{11}C-benzoyl chlorides are formed *in situ* and subsequently reacted with the desired nucleophile in a second reaction vial (Scheme 1c). In this way, an array of carbonyl compounds (amides, esters, alcohols and aldehydes) could be obtained using the same methodology.



Scheme 1. Pd-catalyzed and mediated carbonylation reactions using CO and ^{11}CO.

Results and Discussion

The initial screening of suitable reaction conditions is presented in Table 1. A model reaction constituting of iodobenzene, benzylamine, and bis(dibenzylideneacetone)palladium(0) was screened in combination with different chloride sources and phosphorus ligand at 120 °C for 5 min. In this study, the ^{11}CO was produced by on-line reduction of $^{11}CO_2$ over zinc at 400 °C and in the first step used within a 200 µL steel reaction chamber (µ-autoclave) submerged in an oil bath.[10] When the carbonylative step was complete (5 min), the mixture was automatically eluted into a 2 mL capped vial containing the nucleophile. The resulted solution was than heated (120 °C) for an additional 2 min using a heat block.

Our initial experiments using tetrabutylammonium chloride as the chloride source and tri-*tert*-butylphosphonium tetrafluoroborate as the ligand with 50 µl of benzylamine resulted in an almost quantitative retention of ^{11}CO (trapping efficiency >95%) in the vial after flushing (Table 1, entry 1). The amide [^{11}C]**2** was obtained in an RCY of 81% as deducted by radio-HPLC. The

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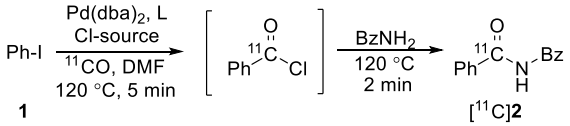
bidentate ligands, Xantphos and dppf, obtained the desired product in a RCY of 8% and 17%, respectively (Table 1, entries 2 and 4). However, when triphenylphosphine was used as the supporting ligand an RCY of 43% was reached (Table 1, entry 3). Changing the chloride source to benzyltriphenylphosphonium chloride, gave a somewhat reduced RCY (69%, Table 1, entry 5,). However, lowering the amount of amine had a positive effect on the reaction outcome. At a five-times lower benzyl amine concentration a slight increase in RCY was observed (87%, Table 1, entry 7). A further reduction of the amine concentration resulted in a reduced RCY (84%, Table 1, entry 8). Therefore, the method using 10 µl of benzylamine (90 µmol of nucleophile) was used throughout the work. Lastly, two control experiments were performed. When the chloride source was removed (Table 1, entry 9) a RCY of 41% was obtained, demonstrating the importance of the chloride source. Using a 5 mL reaction vial[5e] instead of the µ-autoclave gave a lower retention of [^{11}C]CO (63% TE) and provided [^{11}C]**2** in 66% RCP and 42% RCY.

Table 1. Optimization of the reaction conditions.

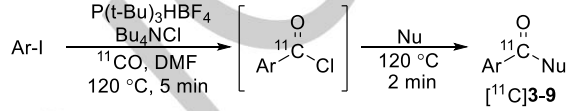


n[a]	Cl-source	Ligand	$BzNH_2$ (µl)	TE (%)	RCP (%)	RCY (%)
1	Bu_4NCl	P(*t*-Bu)$_3$HBF$_4$	50	>95	85	81
2	Bu_4NCl	Xantphos	50	>95	8	8
3	Bu_4NCl	PPh_3	50	90	48	43
4	Bu_4NCl	dppf	50	90	19	17
5	$BnPh_3PCl$	P(*t*-Bu)$_3$HBF$_4$	50	>95	73	69
6	Bu_4NCl	P(*t*-Bu)$_3$HBF$_4$	20	>95	85	81
7	Bu_4NCl	P(*t*-Bu)$_3$HBF$_4$	10	>95	92	87
8	Bu_4NCl	P(*t*-Bu)$_3$HBF$_4$	2	>95	88	84
9	-	P(*t*-Bu)$_3$HBF$_4$	10	>95	43	41
10[b]	Bu_4NCl	P(*t*-Bu)$_3$HBF$_4$	10	63	66	42

[a] Reaction conditions: Iodobenzene (20 µmol), $Pd(dba)_2$ (4 µmol), ligand (16 µmol for monodentate and 8 µmol for bidentate), Cl-source (70 µmol), DMF (400 µl), $BzNH_2$ (90 µmol). [b] A single 5 mL vial was used instead of the µ-autoclave. Average of two experiments. See supporting info for further information. The RCY was determined by radio-HPLC analysis of the crude product.

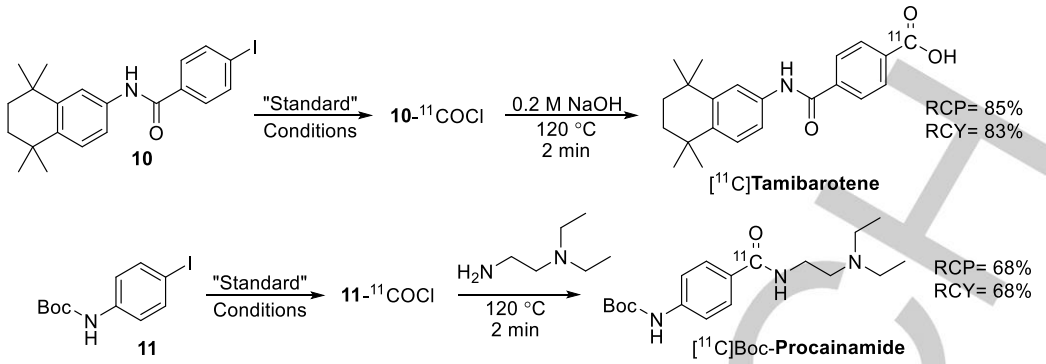
The best reaction conditions (Table 1, entry 7) were next used in the radiosynthesis of a diverse set of carbonyl compounds. The results from the screening are summarized in Table 2. For all the investigated reactions, the trapping efficiency was over 95%. When the sparely reactive amine, aniline, was used as the nucleophile a RCY of 21% (Table 2, entry 1) was obtained. However, an improved RCY of 85% was observed when the inorganic strong base, K_2CO_3, was used (Table 2, entry 2) during the second acetylation step. This is an important observation since this approach using the insoluble K_2CO_3 could not be used in the online carbonylative µ-autoclave system. With *p*-iodoanisole as the substrate and *n*-hexylamine as nucleophile, the desired ^{11}C-labelled amide ([^{11}C]**5**) was produced in a RCY of 80%(Table 2, entry 3). In a preparative run using these reagents, starting with 6 GBq (162 mCi) of $^{11}CO_2$, 1.66 GBq (45 mCi) of the isolated product ([^{11}C]**5**) was obtained 69% (decay corrected RCY based on initial $^{11}CO_2$) with a high RCP (>99%).

Table 2. Scope and limitations of the developed method.



n[a]	Ar-I	Nucleophile	Product	RCP (%)	RCY (%)
1	**1**	$PhNH_2$	[^{11}C]**3**	24	21
2	**1**	$PhNH_2/K_2CO_3$	[^{11}C]**3**	88	85
3	**4**	H_2N-*n*-Hex	[^{11}C]**5**	83	80
4	**1**	MeOH	[^{11}C]**6**	83	79
5	**1**	25% aq. NH_3	[^{11}C]**7**	12	10
6	**4**	40% aq. Bu_4NOH	[^{11}C]**8**	41	41
7	**4**	0.2 M NaOH	[^{11}C]**8**	93	93
8	**4**	NaH	[^{11}C]**9**	55	55
9	**4**	Et_3SiH	[^{11}C]**9**	50	49

[a] Reaction conditions: Iodobenzene (20 µmol), $Pd(dba)_2$ (4 µmol), P(*t*-Bu)$_3$HBF$_4$ (16 µmol), Bu_4NCl (70 µmol), DMF (400 µl), nucleophile (90 µmol). See supporting info for further information. For all reactions, the retention of activity in the reaction vial after flushing with N_2 (trapping efficiency) was >97%. Average of two experiments. [b] Formation of benzoic acid (88% RCP). The RCY was determined by radio-HPLC analysis of the crude product.



Scheme 2. Radiosynthesis of [^{11}C]Tamibarotene and Boc protected [^{11}C]Procainamide. Average of two experiments. The RCY was determined by radio-HPLC analysis of the crude product. See supporting information for further information.

Moreover, the methyl ester, [^{11}C]**6,** was obtained in a reproducible RCY of 79% (Table 2, entry 4) using methanol as nucleophile. Aqueous ammonia (25%) furnished the desired benzamide, [^{11}C]**7**, in merely RCY (10%, Table 2, entry 5). The analysis of the crude sample by analytical HPLC determined the benzoic acid as the major impurity (80%), which could be explained by the excess of water in the ammonia. As expected, when the reagent was changed to anhydrous grade ammonia in THF,[11] the RCY increased to 64% with only traces of the benzoic acid being formed (Table 2, entry 6).

In an attempt to produce 4-methoxybenzoic acid using 40% aq. tetrabutylammonium hydroxide (Bu_4NOH) as the nucleophile resulted in a RCY of 41% (Table 2, entry 7). However, by simply changing the hydroxide source to aq. NaOH (0.2 M) produced the desired compound in almost quantitative yield (93%, Table 2, entry 8). Finally, the aldehyde [^{11}C]**9** (Table 2, entry 9) was synthesized in a RCY of 55% using NaH as the hydride source. The yield was slightly lower when the hydride source was replaced with trietylsilane (49%, Table 2, entry 10).

To further exemplify the developed method, we set out to synthesize two biologically active compounds of more complexity, Tamibarotene and Procainamide (Scheme 2). The radiosynthesis of the synthetic retinoic acid Tamibarotene has previously been labeled by us and others in RCYs ranging from 12-39%.[12] Using the above developed procedure, we were able to obtain the desired ^{11}C-labelled carboxylic acid in 83% RCY (RCP 85%) starting from the aryl iodide **10**. Furthermore, we have previously described the radiosynthesis of the Boc-protected Procainamide using a three component reaction, which resulted in a RCY of 29±4%.[2d] However, using this newly developed methodology, the [^{11}C]Boc-Procainamide were successfully radiolabeled in a 68% RCY (RCP 68%) from aryl iodide **11** and *N*,*N*-diethylethylenediamine. For both of these compounds, in comparison to previously described methods, a staggering 2-3 fold increase in RCY were observed. These results clearly exemplify the usefulness of this present method. Finally, in a recent study using carbon-12 CO, a carbonylative methodology was described using 4-dimethylaminopyridine (DMAP) as mediator to form stable aroylating reagents.[13] In an attempt to apply this method to ^{11}CO radiochemistry resulted in a complex reaction mixture with only trace amount of the desired product.

Conclusions

In conclusion, we have developed a general protocol for ^{11}C-carbonylation of aryl iodides using a two-step method. ^{11}C-Benzoyl chloride is formed in the first step and subsequently reacted with a nucleophile in a second vial. The method is compatible to form amides, esters, acids and aldehydes from the corresponding aryl iodide. Two biologically interesting molecules, Tamibarotene and Procainamide, were successfully labelled in 83% and 68% RCY, respectively, which is significant improvement in yields (2-3 fold) compared to previous reports. A natural extension of the current study would be to include other halides or pseudo-halides, however, this work is ongoing but deemed to be outside the scope of this communication.

Experimental Section

An oven dried 0.8 mL vial was loaded with $Pd(dba)_2$ (2.3 mg, 4 µmol) and P(*t*-Bu)$_3$HBF$_4$ (4.7 mg, 16 µmol), capped and then flushed with He for 1 min. Dry DMF (400 µL) was added, the vial was vortexed and then heated on a heatblock (120 °C) for 30 seconds. To a second oven dried 0.8 mL vial was added aryl iodide (20 µmol) and Bu_4NCl (20 mg, 70 µmol). The vial was capped, flushed with He for 1 min where after the content of the first vial was added. The vial was vortexed and then the content was added onto the loop of the carbonylation apparatus (Figure S1).[2b,10] When the reaction was finished, the content was ejected into a capped 2 mL vial containing the nucleophile (90 µmol) in 50 µL of dry DMF. The vial was then heated on a heating block at 120 °C for 2 min, cooled for 1 min and then flushed with N_2 to establish the trapping efficiency (% non-volatile radioactivity). An aliquot was taken, diluted with 200 µL 50 mM AMF pH 3.5 /MeCN (1:1) and analysed on analytical radio-HPLC to determine the RCP and RCY.

Keywords: Carbon-11 • Carbonylation • Positron emission tomography • Benzoyl chlorides • Palladium

[1] A. Brennführer, H. Neumann, M. Beller. *Angew. Chem. Int. Ed.* **2009**, *48*, 4114-4133.

[2] a) S. K. Zeisler, M. Nader, A. Theobald, F. Oberdorfer, *Appl. Radiat. Isotopes* **1997**, *48*, 1091-1095. b) K. Dahl, O. Itsenko,O. Rahman, J. Ulin, C. O. Sjöberg, P. Sandblom, L. A. Larsson, M. Schou, C. Halldin, *J. Labelled Comp. Radiopharm.* **2015**, *58*, 220-225. c). C. Taddei, S.

Bongarzone, A. K. Haji Dheere, A. D. Gee, *Chem. Commun.* **2015**, 51, 11795-11797. d) P. Nordeman, S. D. Friis, T. L. Andersen, H. Audrain, M. Larhed, T. Skrydstrup, G. Antoni, *Chem. Eur. J.* **2015**, *21*, 17601-17604.

[3] a) B. Långström, O. Itsenko, O. Rahman, *J. Label. Comp. Radiopharm.* **2007**, *50*, 794-810. b) O. Rahman, *J. Labelled Comp. Radiopharm.* **2015**, *58*, 86-98. c) S. Kealey, A. D. Gee, P. W. Miller, *J. Labelled Comp. Radiopharm.* **2014**, *57*, 195-201. d) B. H. Rotstein, S. H: Liang; M. S. Placzek, J. M. Hooker, A. D. Gee, F. Dolle, A. A. Wilson, N. Vasdev, *Chem. Soc. Rev.* **2016**, *45*, 4708-4726.

[4] a) P. W: Miller, N. J. Long, R. Vilar, A. D. Gee, *Angew. Chem. Int. Ed.* **2008**, *47*, 8998-9033. b) V. W. Pike, *Curr. Med. Chem.* **2016**, *23*, 1818-1869.

[5] a) S. Kealey, P. W. Miller, N. J. Long, C. Plisson, L. Martarello, A. D. Gee, *Chem. Commun.* **2009**, *25*, 3696-3698. b) T. Kihlberg, B. Långström, *J. Org. Chem.* **1999**, *64*, 9201-9205. c) K. Dahl, M. Schou, N. Amini, C. Halldin, *Eur. J. Org. Chem.* **2013**, *7*, 1228-1231. d) J. Eriksson, J. van den Hoek, A. D. Windhorst, *J. Labelled Comp. Radiopharm.* **2012**, *55*, 223-228. e) T. L. Andersen, S. D. Friis, H. Audrain, P. Nordeman, G. Antoni, T. Skrydstrup, *J. Am. Chem. Soc.* **2015**, *137*, 1548-1555.

[6] Y. Andersson, B. Långstrom, *J. Chem. Soc. Perk. T. 1* **1995**, *4*, 287-289.

[7] a) J. S: Quesnel; B. A. Arndtsen, *J. Am. Chem. Soc.* **2013**, *135*, 16841-16844. b) J. S. Quesnel, L. V: Kayser; A. Fabrikant, B. A. Arndtsen, *Chem. Eur. J.* **2015**, *21*, 9550-9555.

[8] a) S.K. Luthra, V.W. Pike, F. Brady. *Int. Appl. Radiat. Isot.* **1990**, *26*, 471-476. b) P. Riss, S. Lu, S. Telu, F. Aigbirhio, V.W. Pike. **2012**, *Angew. Chem. Int. Ed.* 51, *2698*-2702.

[9] J. Eriksson, O. Aberg, B. Langstrom, *Eur. J. Org. Chem.* **2007**, *455-461*.

[10] T: Kihlberg, B. Långström, *Method and Apparatus for Production and use of [^{11}C]Carbon Monoxide in Labelling Synthesis. PCT/SE02/01222*, **2002**.

[11] To a 2 mL capped and ventilated vial containing 200 µL of anhydrous THF was bubbled NH_3 gas for 2 min to produce a saturated solution.

[12] a) M. Takashima-Hirano, H. Ishii, M. Suzuki, *ACS Med. Chem. Lett.* **2012**, *3*, 804-807. b) The ^{11}C-carbonylation of corresponding aryl iodide precursor using MeOH as nucleophile with a subsequent basic hydrolysis has been evaluated in our lab resulting in a RCY of 16±4%.

[13] J. S. Quesnel, A. Fabrikant, B. A. Arndtsen, *Chem. Sci.* **2016**, *7*, 295-300.

10.1002/ejoc.201700268

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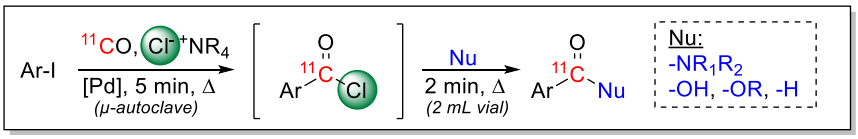

Carbon-11 Radiochemistry*

Kenneth Dahl,[b] and Patrik Nordeman[a]*

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^{11}C-Carbonylation Through ^{11}C-Benzoyl Chlorides Using Tetrabutylammonium Chloride

A novel radiochemical method for the ^{11}C-carbonylation is presented. The two-step protocol relies upon an intermediate ^{11}C-acyl chloride which is further reacted with a desired nucleophile to produce amides, benzoic acids, esters and aldehydes. An increased RCY of [^{11}C]Tamibarotene and Boc protected [^{11}C]Procainamide is presented using the developed method.

*one or two words that highlight the emphasis of the paper or the field of the study