Organic Bases as Additives to Improve the Radiochemical Yields of [^{11}C]Ketones Prepared by the Suzuki Coupling Reaction

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Keywords: [^{11}C]/(^{13}C)Carbon monoxide / Carbonylation / Organic base / Positron emission tomography / Suzuki cross-coupling

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The Suzuki cross-coupling reaction was employed in the syntheses of eight new [^{11}C-carbonyl]ketones. The reactions between the corresponding boronic acids and the corresponding triflates were performed in the presence of [^{11}C]carbon monoxide and a palladium(0) complex as the catalyst. Lithium bromide was added to facilitate the reactions, and different bases were tested to improve the radiochemical yields. All the ketones were synthesised, with the achievement of isolated radiochemical yields (decay-corrected) of between 14 and 74%. Important improvements in the radiochemical yield were achieved by use of tetrabutylammonium fluoride in the synthesis of ketones incorporating alkyl groups, while potassium *tert*-butoxide was the best base among those tested for improving the radiochemical yields in the syntheses of biaryl ketones. The optimal amount of base was determined in all cases. Only for compounds **3e** and **3h** were better radiochemical yields obtained when no base was used. No radiochemical impurities were detected after isolation of the compounds. The specific radioactivity for compound **3a** was determined, and a value of 200 GBq/μmol was obtained. Compound **3b** was labelled simultaneously with [^{11}C] and (^{13}C)carbon monoxide and the position of the labelled atom was determined and confirmed by ^{13}C NMR spectrometry. Tetrabutylammonium fluoride and potassium *tert*-butoxide are reported as useful bases for Suzuki carbonylation with [^{11}C]/(^{13}C)carbon monoxide.

Introduction

The increasing use of Positron Emission Tomography (PET) as a diagnostic technique and as a tool in drug development[1] has stimulated the development of new radiotracers. Of all the β^+-emitting radionuclides, ^{11}C is most attractive, due to its interesting radioactive properties ($t_{1/2}$ = 20.4 min, 100% β^+-emission). Moreover, carbon is present in all organic molecules. Because of these unique properties, there is a need for rapid and efficient incorporation of [^{11}C]carbon into prospective radiopharmaceuticals, not only to increase the number of radiolabeled compounds but also to give the option of labelling a determinate compound in different positions.[2]

The radionuclide ^{11}C can be introduced into organic molecules in different ways, including *S*-, *O*- and *N*-methylation with [^{11}C]methyl iodide or triflate,[3] *N*-cyanation with ^{11}CNBr,[4] ^{11}C−C bond-forming reactions such as carboxylation through the use of $^{11}CO_2$ and Grignard reagents,[5] coupling reactions with [^{11}C]methyl iodide or triflate,[6] and palladium-[7] and selenium-mediated[8] carbonylation with [^{11}C]carbon monoxide. During the last few years, we have focussed on the development of new ^{11}C-labelled radiotracers through incorporation of [^{11}C]carbon monoxide, so far primarily by palladium-mediated reactions.[9] The low solubility and reactivity[10] makes it difficult to trap [^{11}C]carbon monoxide in a reaction mixture by conventional methods. In a fully automated system, [^{11}C]carbon monoxide was trapped on silica cooled by liquid nitrogen, concentrated to a small volume, and transferred into a microautoclave (200 μL) that could be pressurised to 30−40 MPa. This technique allows the synthesis of [^{11}C-carbonyl]compounds in high radiochemical yields and with good specific radioactivities in relatively short synthesis times.

Recently, [^{11}C]carbon monoxide has been shown to be a versatile reagent for the synthesis of [^{11}C]ketones by Suzuki carbonylation reactions.[11] In conventional Suzuki carbonylation reactions, arylboronic acids were treated with aryl or benzyl electrophiles and carbon monoxide in the presence of a palladium catalyst in order to prepare biaryl or aryl-benzyl ketones.[12] The potential of aryl halides as precursors in Suzuki carbonylation reactions with [^{11}C]carbon monoxide has been reported previously.[11b] However, the use of aryl triflates as alternatives to halides has not

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DOI: 10.1002/ejoc.200400038

previously been demonstrated. We showed that aryl triflates[11a] are good alternatives to aryl halides for the production of [^{11}C]ketones by Suzuki carbonylation, and prepared [^{11}C]ketones incorporating either two aromatic residues or one aromatic and one alkyl group with good trapping efficiency (conversion of [^{11}C]carbon monoxide to products) and moderate to high decay-corrected radiochemical yields. LiBr was added to promote the cross-coupling carbonylation reaction and/or to prevent premature catalyst decomposition.[13] Suzuki coupling reactions, however, are usually carried out in the presence of a base. The active base is believed to assist the formation of a boronate anion that is capable of effecting borane to palladium transmetallation.[14] In our previous work good results were obtained when no base was used. In the current work, aryl triflates and different aromatic and aliphatic boronic acids have been tested as precursors for the synthesis of ^{11}C-labelled ketones. The radiochemical yields for some boronic acids, especially those with long alkyl chains, were very low. An attempt to improve the radiochemical yields by exploring the effects of different organic bases was performed.

Results and Discussion

The [^{11}C]ketones (compounds **3a−3h**, Figure 1) were synthesised by Suzuki carbonylation. The reaction was performed in a microautoclave of 200 μL volume. The corresponding aryl triflates (compounds **1a** and **1b**, Figure 2) and the corresponding boronic acids (compounds **2a−2g**, Figure 3), were allowed to react in the presence of low concentrations (typically ca 10^{-4} M) of [^{11}C]carbon monoxide, tetrakis(triphenylphosphane)palladium(0) and LiBr (Scheme 1). The conversion of carbon monoxide into products (trapping efficiency) was between 53% and 85%, and isolated radiochemical yields of between 14% and 74% were obtained after around 35 min from the end of bombardment (EOB). The specific radioactivity was determined for compound **1**. For this purpose, the experiment was carried out under the same conditions but with an integrated bombardment current of 10 μAh in contrast to the corresponding value of 1−2 μAh used in the other experiments. Starting from 9.62 GBq [^{11}C]carbon monoxide, 7.76 GBq of product was obtained after degassing (trapping efficiency 83%). After 29 min from EOB, 3.27 GBq of isolated product was obtained. The concentration of product in the final solution was determined by LC-MS, and a value of 4.0 μM was obtained, giving a specific radioactivity of 200 GBq/μmol. In order to confirm the position of the labelled atom, a synthesis of compound **3b** was carried out with both [^{11}C] and (^{13}C)carbon monoxide simultaneously. The product was purified by semi-preparative HPLC and analysed by ^{13}C NMR spectroscopy. A signal at δ = 193.0 ppm corresponding to the carbonyl group of the reference compound was observed. The identities of the compounds were determined by co-injection of reference compounds with the labelled compounds. Final characterisation of all the compounds was performed by LC-MS.

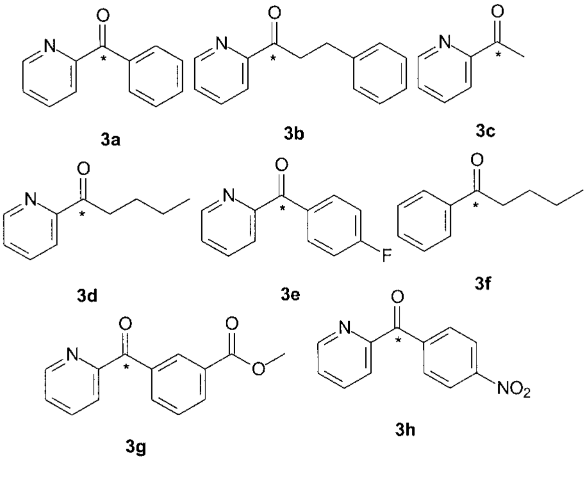


Figure 1. Target compounds (* = ^{11}C)

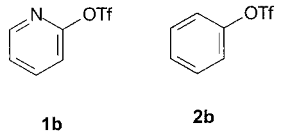


Figure 2. Aryl triflates used

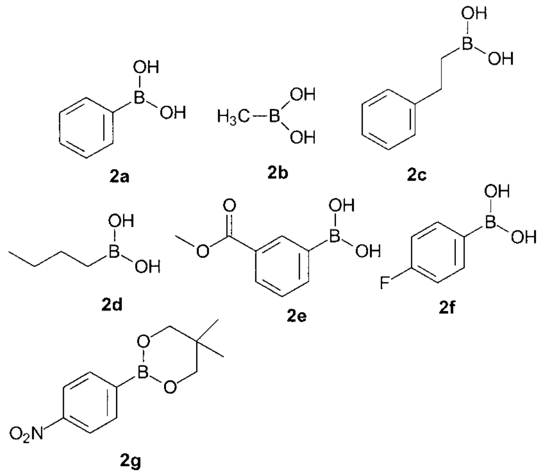
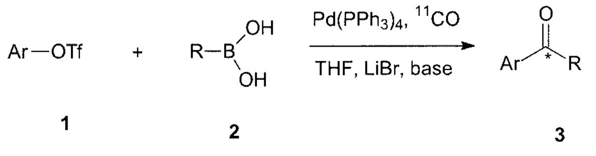


Figure 3. Organoboranes used



Ar = 2-pyridyl, phenyl; R = phenyl, 2-phenylethyl, methyl, *n*-butyl, 4-fluorophenyl, 3-(methoxycarbonyl)-phenyl, 4 nitrophenyl. * = ^{11}C

Scheme 1

Table 1. Trapping efficiencies and radiochemical yields for [^{11}C]ketones shown in Figure 1

Entry	Product	Aryl triflates	Organo-boranes	Base	*T*/°C	TE (%)	RCY[a] (%)	RCY[b] (%)
1	**3a**	**1a**	**2a**	No base	150	70 ± 10[c]	59 ± 8[c]	–
2	**3a**	**1a**	**2a**	K-*t*BuO[d]	150	85 ± 9[c]	78 ± 9[c]	74 ± 7[e]
3	**3b**	**1a**	**2c**	No Base	170	22	8	–
4	**3b**	**1a**	**2c**	TBAF[f]	170	63 ± 6[c]	55 ± 6[c]	43 ± 3[e]
5	**3c**	**1a**	**2b**	No Base	170	40	0	–
6	**3c**	**1a**	**2b**	TBAF[f]	170	53 ± 1[c]	42 ± 3[c]	33 ± 2[e]
7	**3d**	**1a**	**2d**	No base	170	32	28	–
8	**3d**	**1a**	**2d**	TBAF[f]	170	58	52	–
9	**3d**	**1a**	**2d**	TBAF[f]	190	74 ± 6[c]	61 ± 5[c]	49 ± 3[e]
10	**3e**	**1a**	**2f**	No base	150	84 ± 2[c]	83 ± 2[c]	67 ± 4[e]
11	**3e**	**1a**	**2f**	K-*t*BuO[d]	150	52	26	–
12	**3f**	1b	**2d**	No base	170	52	6	–
13	**3f**	1b	**2d**	TBAF[f]	170	84 ± 5[c]	35 ± 1[c]	24 ± 3[e]
14	**3g**	**1a**	**2e**	No Base	170	60	54	–
15	**3g**	**1a**	**2e**	K-*t*BuO[d]	170	83 ± 4[c]	80 ± 3[c]	49 ± 4[e]
16	**3h**	**1a**	**2g**	No Base	150	57 ± 6[c]	21 ± 4[c]	14 ± 1[e]
17	**3h**	**1a**	**2g**	K-*t*BuO[d]	150	43	13	–
18	**3h**	**1a**	**2g**	TBAF[f]	150	22	5	–
19	**3b**	**1a**	**2c**	K-*t*BuO[d]]	150	91	3	–
20	**3b**	**1a**	**2c**	LiEtO[d]	150	57	7	–
21	**3b**	**1a**	**2c**	TEA[d]	150	10	3	–
22	**3b**	**1a**	**2c**	TBAF[d]	150	53	44	–
23	**3a**	**1a**	**2a**	TEA	150	72	69	–
24	**3a**	**1a**	**2a**	TBAF[f]	150	23	4	–

[a] Radiochemical yield, non isolated, decay-corrected. [b] Radiochemical yield, isolated, decay-corrected. [c] Average values from at least 3 experiments. [d] Base concentration 40 mM, base/boronic acid molar ratio 1:5. [e] Average values from 2 experiments. [f] Base concentration 45 mM, base/boronic acid molar ratio 1:4.5. TE: trapping efficiency (fraction of radioactivity left in the crude product after purge with nitrogen) decay-corrected. RCY.

The previously used[11a] reaction conditions were applied in the initial experiments, and high trapping efficiencies and radiochemical yields (decay-corrected and determined by analytical HPLC) were obtained for some compounds (entries 1, 10, 14 and 16 in Table 1), but for other compounds (entries 3, 5, 7 and 12 in Table 1) both trapping efficiencies and radiochemical yields were low. Among these compounds, **3b**, **3c**, **3d** and **3f** each have the feature that the starting boronic acid contained alkyl chains. The low radiochemical yields thus seemed to be associated with the presence of saturated chains in the starting boronic acid. The effects of different organic bases, such as potassium *tert*-butoxide (1 M solution in THF), lithium ethoxide (1 M solution in THF), tetrabutylammonium fluoride (TBAF, 1 M solution in THF) and triethylamine (pure reagent) were investigated in order to improve the radiochemical yield for compound **3b** (entries 19–22 in Table 1). In the original version of the Suzuki cross-coupling reaction,[15] good yields were obtained with the addition of a twofold excess of base. In our case, this mol/mol ratio cannot be applied directly because of the small amount of [^{11}C]carbon monoxide present in the reaction mixture. The amount of base was therefore optimised for all compounds, and the optimal concentrations were much lower (base/boronic acid molar ratios around 1:5) than those described for carbonylation reactions in previous reports (base/boronic acid molar ratios around 2:1).[13] For compound **3b**, important improvements both in the trapping efficiency and in the radiochemical yield were obtained with TBAF, while no improvement in the radiochemical yield was observed for the other bases. Further experiments to optimise the reaction temperature were carried out, with the use of the same concentration of TBAF (base/boronic acid molar ratio 1:5). Three reaction temperatures – 150, 170 and 190 °C – were employed, and the best radiochemical yield was obtained at 170 °C, while at 190 °C the trapping efficiency was increased but the purity was reduced, resulting in an overall negative effect on the radiochemical yield. After optimisation of the reaction temperature, the relative amount of base was also optimised. Several experiments were carried out under identical conditions (reagent amounts specified above, $T = 170$ °C) but with variation in the amount of TBAF used, and both trapping efficiency and radiochemical yield reached their maxima at a base concentration around 45 mM (base/boronic acid molar ratio, 1:4.5). These conditions were chosen for further experiments focused on determining the isolated yield (entry 4, Table 1). A trapping efficiency of around 63% and isolated yields of around 43% were obtained for compound **3b** under these conditions. For the preparation of other labelled alkyl-aryl ketones, the temperature and the relative amount of base were optimised as described for compound **3b**. Non-isolated radiochemical yields of 42%, 61% and 35% were obtained for compounds **3c**, **3d** and **3f** (entries 6, 9 and 13, respectively, in Table 1) under optimal conditions. An improvement in the radiochemical yields by 30−40% was observed when TBAF was used as the base.

Different results were obtained in reactions involving an aromatic boronic acid (compounds **3a**, **3e** and **3g**). The use of TBAF reduced the radiochemical yield for compound **3a** (entries 1 and 24 in Table 1), while the use of triethylamine produced only a slight improvement (entry 23). The best results, however, were obtained when potassium *tert*-butoxide was used (entry 2), providing a trapping efficiency of 85% and an isolated radiochemical yield around 74%. In the case of compound **3g** (entries 14 and 15 in Table 1), the use of potassium *tert*-butoxide improved the non-isolated radiochemical yield from 54% to around 80%. Surprisingly, the radiochemical yield for compound **3e** was reduced when potassium *tert*-butoxide was used (entries 10 and 11 in Table 1), and the best result was obtained when no base was added, resulting in an isolated radiochemical yield of 67%. Compound **3h** (Entry 16 in Table 1) was synthesised from a boronic ester (compound **2g**, Figure 3) instead of boronic acid, and the radiochemical yield was 21%. The added base did not improve the radiochemical yield of this compound.

From this investigation it can be concluded that the radiochemical yield in the synthesis of [^{11}C]/(^{13}C)ketones by Suzuki cross-coupling carbonylation can often be improved by addition of an organic base. It has been found that tetrabutylammonium fluoride is the best base for ketones synthesised from an alkyl boronic acid, while potassium *tert*-butoxide is the best option when the starting reagent is an aromatic boronic acid. Only in two cases out of eight were better results obtained without any base.

Experimental Section

General: 2-Pyridyl trifluoromethanesulfonate, phenyl trifluoromethanesulfonate, phenylboronic acid, methylboronic acid, butylboronic acid, tetrakis(triphenylphosphane)palladium(0), anhydrous lithium bromide, potassium *tert*-butoxide (1 M solution in THF), tetrabutylammonium fluoride (1 M solution in THF), ammonium formate, formic acid, 2-acetylpyridine, valerophenone, phenyl pyridyl ketone and potassium phosphate were purchased from Aldrich. 3-Methoxycarbonylphenylboronic acid, 4-nitrophenylboronic acid neopentylglycol ester, 4-fluorophenylboronic acid and phenethylboronic acid were purchased from Frontier Scientific. THF was distilled from sodium/benzophenone under nitrogen before use. The rest of the solvents were HPLC quality grade and were used without further treatment.

[^{11}C]Carbon was produced in a Scanditronix MC-17 cyclotron at the Uppsala Imanet AB by use of the ^{14}N(p,α)^{11}C reaction in a gas target containing nitrogen (AGA, Nitrogen 6.0) and 0.05% oxygen (AGA, Oxygen 4.8) bombarded with 17 MeV protons and with 45 μA beam current for about 1.5 minutes (integrated current 1 μAh). [^{11}C]Carbon was obtained as [^{11}C]carbon dioxide. [^{11}C]Carbon monoxide was produced by reduction of [^{11}C]carbon dioxide in a zinc furnace at 400 °C in a remote-controlled workstation.[16] For the determination of the specific activity (performed only for compound **3a**), an integrated current of 10 μAh was used.

Liquid chromatographic (LC) analysis was performed with a Beckman 126 gradient pump and a Beckman 166 variable wavelength UV detector, connected to a β^+-flow detector. The following mobile phases were used: 0.05 M ammonium formate, pH = 3.5 (A); acetonitrile/water: 50/7 (B) and pure acetonitrile (C). For analytical LC, a Jones chromatography Genesis C_{18}, 4 μm, 250 × 4.6 mm (i.d.) column (flow of 1.5 mL/min, mobile phase A-B 70/30, linear gradient to 0/100 within 8 minutes) was used. For semipreparative LC, a Jones chromatography Genesis C_{18}, 4 μm, 250 × 10 mm (i.d.) column was used at a flow of 4 mL/min (mobile phase A/C 50/50, linear gradient to 0/100 over 10 minutes).

Synthia, an automated synthesis system,[17] was used for the carbonylation, LC injection and fraction collection. Data collection and LC control were performed by use of a Beckman System Gold chromatography software package.

For identification of the synthesised ^{11}C-labelled compounds, reference compounds (when available) were co-injected during the HPLC analyses. The concentration of compound **3a** in a purified fraction (used for the calculation of specific radioactivity) was determined by LC-MS. For LC-MS, the following mobile phases were used: methanol/water 95:5 10 mM in formic acid (D) and 10 mM aqueous solution of formic acid (E). A Kromasil C_{18} 5 μm, 100 × 4.6 mm (i.d.) column (flow of 1.0 mL/min, mobile phase D-E 30/70, linear gradient to 100/0 within 6 minutes) was used. MS was performed on a Fisons VG Platform mass spectrometer with atmospheric pressure chemical ionisation (APcI). ^{13}C NMR was performed on a Varian Unity-400 (400 MHz) spectrometer. Chemical shifts are referred to tetramethylsilane. $CDCl_3$ was used as reference.

Radioactivity was measured in an ion chamber (Veenstra Instrumented bv, VCD-202). For coarse estimations of radioactivity during production, a portable dose-rate meter, obtained from Långenäs Eltekniska AB, was used.

Synthesis of [Carbonyl-^{11}C]Ketones 3a−3h: Tetrakis(triphenylphosphane)palladium(0) (5.0 mg, 4.3 μmol) was dissolved in dry THF (150 μ*L*), and 2-pyridyl trifluoromethanesulfonate (5 μL, 32.5 μmol) was added. After the mixture had briefly been shaken, lithium bromide (10 μL of 40 mg/mL solution in THF, 4.6 mmol) was added. In a second vial, the corresponding boronic acid (41 μmol) was dissolved in dry THF (150 μL). When needed, the required amount of base was added to this second vial. Solutions from vials 1 and 2 were mixed and injected into the injection loop of the synthesis system. The resulting solution was transferred (with the help of a HPLC pump) to the autoclave, precharged with [^{11}C]carbon monoxide in helium. The microautoclave was heated (temperature between 150 and 190 °C) for 5 min. After completion of reaction, the crude product was collected in a 5 mL septum-fitted pre-evacuated vial. The radioactivity was measured before and after purging with nitrogen. The mixture was concentrated to less than 0.2 mL by heating at 65 °C under a nitrogen flux (for compound **3f**, the evaporation step was avoided because a considerable amount of radioactivity was lost during this step, probably due to the high vapour pressure of the labelled compound). Acetonitrile/water: 1:1 (2 mL) was added, and the resulting solution was injected into the semi-preparative HPLC system. The fraction containing the purified product was collected in a 10 mL vial, and the activity was measured. A small sample of the collected fraction was injected into the analytical HPLC system to measure the radiochemical purity. After decay, the collected fraction was analysed by LC-MS to verify the identity of the compound. For compound **3a**, LC-MS was used to determine the specific activity of the compound. For this purpose, 1, 5 and 10 μM solutions of benzoylpyridine were prepared and injected into the LC-MS system in order to provide the calibration curve.

LC-MS (APcI$^+$): The presence of the $[M - H]^+$ species was confirmed for compounds **3a**−**3h**; ions with *m*/*z* of 184, 212, 122, 164, 202, 163, 242 and 229 were found for compounds **3a**−**3h**, respectively.

Acknowledgments

We thank Mr. Martin Lavén for support with the LC-MS analysis. The Swedish Research Council is acknowledged for its support by grant K3464 (B. L.).

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Received January 20, 2004