Research Article

Journal of Labelled Compounds and Radiopharmaceuticals

Received 19 October 2009, Revised 20 January 2010, Accepted 25 February 2010 Published online 25 April 2010 in Wiley Interscience

(www.interscience.wiley.com) DOI: 10.1002/jlcr.1755

Palladium-catalyzed hydroxycarbonylation as the key step in the synthesis of a carbon-14 labeled Maxi-K channel blocker

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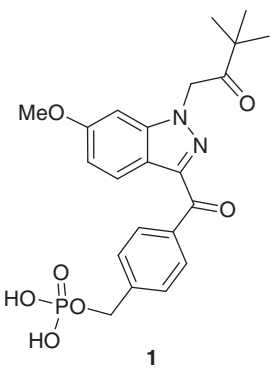
Carbon-14 labeled sodium formate was utilized for the preparation of a radiolabeled tracer to support the development of a Maxi-K channel blocker. Key to the process was a palladium-catalyzed hydroxycarbonylation of a bromoarene for installation of the radiolabel.

Keywords: Maxi-K channel; carbon-14; palladium-catalyzed hydroxycarbonylation; [^{14}C]carbon monoxide; carbonylation

Introduction

The movement of ions across cell membranes is a process that is controlled by the action of specialized pore-forming proteins called ion channels. The high-conductance, calcium-activated potassium (Maxi-K) channels are one such group of proteins that are present in many cell types throughout the body including epithelial, neuronal, endocrine, and smooth muscle tissue cells.[1] Maxi-K channel modulators have been reported for the treatment of glaucoma,[2] a disease characterized by increased intraocular pressure due to an imbalance between the production and the release of aqueous humor from the anterior section of the eye. In support of a medicinal chemistry program aimed at developing a Maxi-K channel blocker, the preparation of a carbon-14 labeled version of indazole (**1**) was required for drug metabolism studies.[3] Herein, we report the synthesis of this compound as well as a simple and efficient palladium-catalyzed hydroxycarbonylation utilizing carbon-14 sodium formate as a radiolabeled carbon monoxide source.



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Results and discussion

Our strategy for carbon-14 incorporation required the synthesis of a suitable unlabeled precursor (Scheme 1). The medicinal chemistry intermediate, 6-methoxy-1*H*-indazole-3-carbonitrile (**2**),[3] was treated with 4-bromophenylmagnesium iodide, formed *in situ* from isopropylmagnesium chloride and 1-bromo-4-iodobenzene, resulting in ketone (**3**). Alkylation of the basic nitrogen with 1-bromopinacolone in the presence of potassium carbonate provided (**4**), which would serve as the starting point for the introduction of the radiolabel, which was to be placed at the methylene carbon adjacent to the phosphate of compound (**1**).

The synthesis of carbon-14 labeled carbonyl derivatives from aryl halides can be achieved via palladium-catalyzed carbonylation; however, this process is limited by the efficiency in which one can generate and trap carbon-14 carbon monoxide.[4] Elmore has reported a procedure for the generation of carbon-14 carbon monoxide from the dehydration of formic acid with sulfuric acid and has applied this to the synthesis of carbon-14 labeled carbonyl derivatives via palladium catalysis.[5] This method results in moderate-to-high radiochemical yields and can be extended to the preparation of esters, amides, aldehydes, and ketones.

In the absence of high carbon monoxide or hydrogen pressure, reductive carbonylation often requires the slow addition of a reducing agent such as Bu_3SnH[6] or Et_3SiH[7] in order to minimize arene side products resulting from hydrodehalogenation. An alternative method first introduced by Okano utilizes sodium formate as a reducing agent at atmospheric carbon monoxide pressure.[8] We sought to combine the Elmore procedure for carbon-14 carbon monoxide

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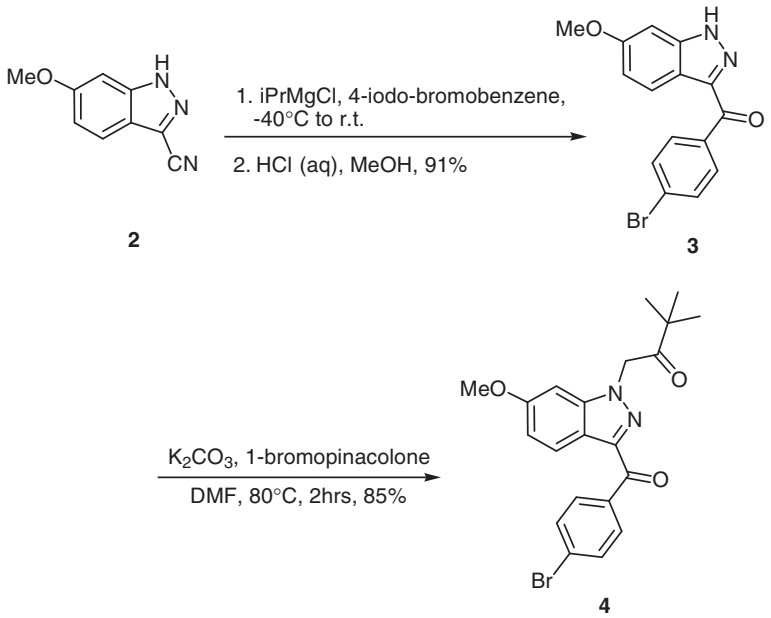


Scheme 1. Synthesis of radiolabeling precursor.

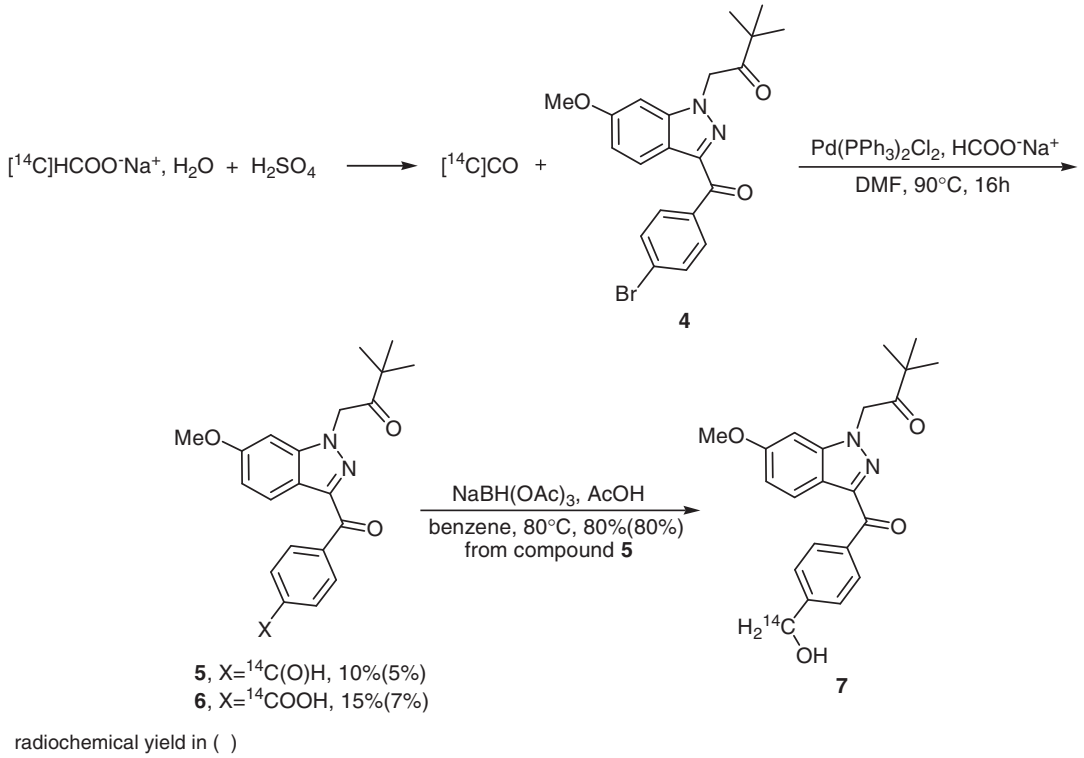
generation, with the use of sodium formate as a reducing agent, in an attempt to prepare a carbon-14 labeled aldehyde (Scheme 2). We envisioned that this compound could be converted to the benzylic alcohol via selective reduction in the presence of both ketone functionalities.

Radiolabeled carbon monoxide was generated using 2.1 equiv. of carbon-14 sodium formate and trapped into a separate flask containing the catalyst, solvent, and 1.5 equiv. of unlabeled sodium formate as the reducing agent. Unfortunately, we were only able to obtain the desired aldehyde (**5**) in 10% yield. The major product of the reaction was the carboxylic acid (**6**), which was isolated in 15% yield, with the remainder being unreacted bromide and a trace amount of the arene resulting from hydrodehalogenation. As expected, we were able to selectively reduce the aldehyde in the presence of both ketones by heating with sodium triacetoxyborohydride in benzene to obtain the benzylic alcohol (**7**). However, we required further synthetic steps to obtain our target compound and this led us to pursue a more efficient method for the introduction of the radiolabel.

We considered using the slow addition of Bu_3SnH to obtain the aldehyde as reported by Elmore[5], but we were discouraged by the need to use a syringe pump in addition to the double flask apparatus required for the gas generation. There has been considerable interest in the recent literature for the development of safer and environmentally benign carbonylation procedures, which do not use gaseous carbon monoxide.[9] One such procedure reported by Cacchi uses acetic anhydride and lithium formate as a carbon monoxide source, presumably through the formation and decomposition of acetic formic anhydride. This one pot procedure has been used to generate aryl carboxylic acids from aryl and vinyl halides and triflates.[10] In addition, preformed acetic formic anhydride has been used in the presence of Et_3SiH to prepare aryl aldehydes.[11] We set out to explore whether the Cacchi method was amenable to the preparation of carbon-14 labeled carboxylic acid derivatives, by applying it to the synthesis of our target compound.

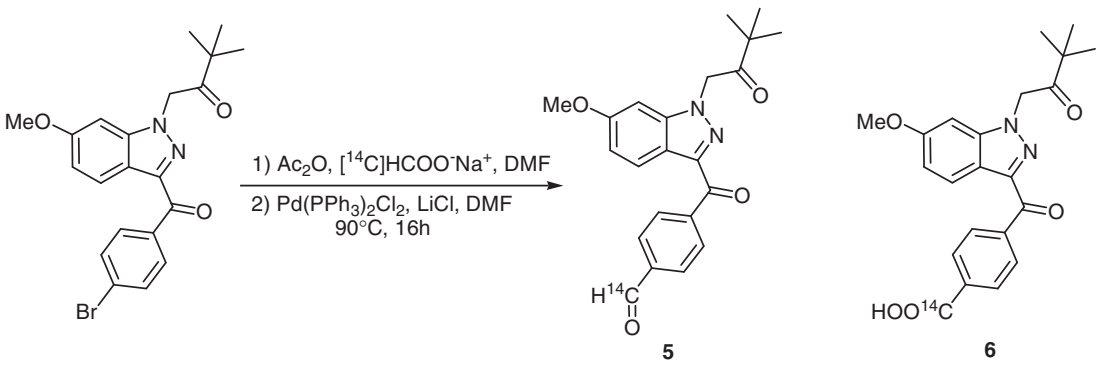
By using readily available carbon-14 labeled sodium formate as a surrogate for lithium formate, we explored a number of different reaction conditions as shown in Table 1. The Cacchi procedure uses three equivalents of the formate salt as the optimal reaction conditions. We first sought to reduce the amount of formate, since this is the source of the radiolabel. Using 1.4 equiv. of carbon-14 sodium formate (entry 1) we were able to obtain a 23% chemical yield and a 16% radiochemical yield of the carboxylic acid (**6**); however, none of the aldehyde was detected. With 2.3 equiv. of formate (entry 2), a 2:1 ratio of (**6**) to (**5**) was obtained in a moderate yield. The use of polymethylhydrosiloxane (PMHS)[12] as a hydride source (entry 3) completely inhibited the formation of radiolabeled products. However, incorporation of Et_3SiH (entry 4) resulted in selective formation of the aldehyde, albeit in low yield, with the major product arising from hydrodehalogenation of the bromide. Interestingly, complete selectivity for the carboxylic acid (**6**) was achieved with the highest yield by removing the amine base from the reaction. This is in contrast to Cacchi's report in which the presence of the base was determined to give the highest yields of carboxylic acid products.

With an efficient procedure to make the carboxylic acid (**6**) in hand, we reconsidered our synthetic plan and searched for a method to selectively reduce the carboxylic acid in the presence of both ketones. We were encouraged by the report from Taddei which details the reduction of aryl carboxylic acids to alcohols with hydrogen gas through the intermediacy of [1,3,5]triazine esters.[13] We therefore treated compound (**6**) with 2-chloro-4,6-dimethoxytriazine and NMM in dimethoxyethane to form the activated ester, which was subsequently hydrogenated over 10% Pd/C (Scheme 3). Using this method, we were able to obtain the desired alcohol (**7**) in 55% radiochemical yield, with the major byproduct (25% rcy) resulting from ketone reduction. A number of modifications of this procedure were attempted, but all failed to increase the selectivity of the reaction. However, due to the efficiency of the hydroxycarbonylation for the formation of the carboxylic acid, this method still resulted in greater than a 2-fold increase in radiochemical yield over the aldehyde route. The remainder of the synthesis was completed by converting alcohol (**7**) to the phosphate (**8**) via treatment with di-*tert*-butyl-*N,N*-diethylphosphoramidate in the presence



Scheme 2. Synthesis of carbon-14 labeled benzylic alcohol intermediate.

Table 1. Comparison of hydroxycarbonylation conditions

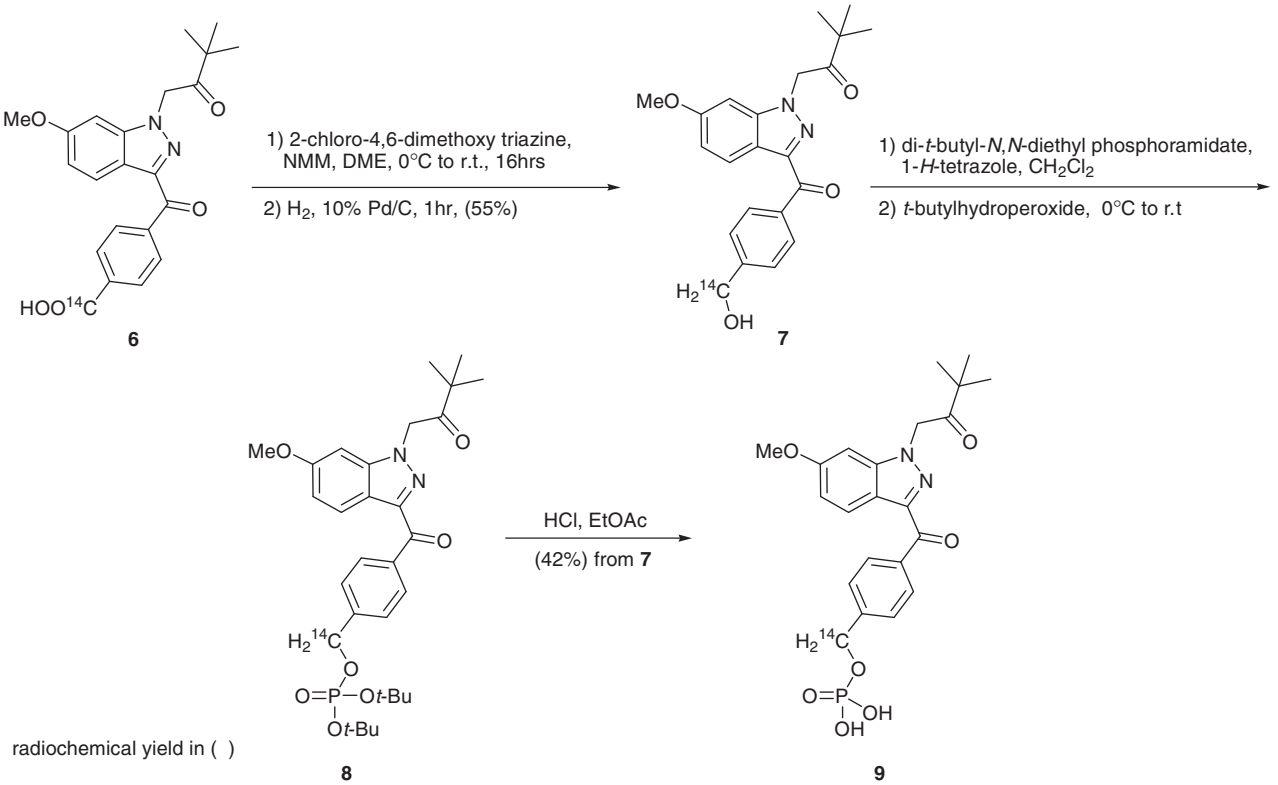


1) 1.4 eq. $[^{14}C]HCOO^-Na^+$, 2 eq. $(i\text{-Pr})_2NEt$	0 %	23%(16%)
2) 2.3 eq. $[^{14}C]HCOO^-Na^+$, 2 eq. $(i\text{-Pr})_2NEt$	20%(10%)	46%(23%)
3) 2.3 eq. $[^{14}C]HCOO^-Na^+$, 2 eq. $(i\text{-Pr})_2NEt$, 1.4 eq. PMHS	0%	0%
4) 2.3 eq. $[^{14}C]HCOO^-Na^+$, 2 eq. $(i\text{-Pr})_2NEt$, 1 eq. Et_3SiH	20%(9%)	0%
5) 2.3 eq. $[^{14}C]HCOO^-Na^+$	0%	72%(32%)

Radiochemical yield in parentheses.

of tetrazole, followed by *in situ* oxidation with *tert*-butylhydroperoxide. Removal of the *tert*-butyl esters with HCl in ethyl acetate, followed by HPLC purification, resulted in the target radiotracer (**9**).

In summary, we have successfully applied a one-pot hydroxycarbonylation procedure to the synthesis of a carbon-14 labeled Maxi-K channel blocker. Furthermore, through careful control of the reaction conditions we were able to obtain complete selectivity for the aryl carboxylic acid over the aryl aldehyde with moderate radiochemical yields. This allowed us to obtain our target compound via a slight modification of our original route. We envision the one-pot hydroxycarbonylation



Scheme 3. Completing the synthesis of the carbon-14 labeled Maxi-K channel blocker.

protocol to have broad utility in radiosynthesis laboratories due to its operational simplicity.

Experimental

Materials and methods

All reagents and solvents were purchased from commercial sources and used without further purification. Sodium [^{14}C]formate was purchased from Amersham Radiochemicals. 6-Methoxy-1*H*-indazole-3-carbonitrile **2** was prepared by Merck Medicinal Chemistry according to reference 3. Radioactivity was measured with a Packard Tri-Carb 1000TR Liquid Scintillation Analyzer. ^{1}H NMR spectra (400 MHz) were measured at 400 MHz on a Varian Inova Spectrometer. Chemical shifts are reported as δ parts per million (ppm) downfield from tetramethylsilane. An Agilent series 1100 HPLC system coupled to a Packard Radiomatic 525TR Flow Scintillation Analyzer was used to monitor reactions and check for purity. The following conditions were used unless otherwise noted: Zorbax XDB C8 column, 4.6 $\times$ 150 mm, 5% acetonitrile:H_2O (0.1% TFA) to 100% acetonitrile, 15 min linear gradient, 1 mL/min. Preparative HPLC was performed using Varian Pro Star Model 210 pumps coupled to a Shimadzu SPD-10A UV/Vis detector. LC/MS and specific activity measurements were obtained by electrospray ionization using an Agilent 1100 Series LC/MSD. After injection, samples were loaded onto a 4.6 $\times$ 150 mm Zorbax XDB C8 column and eluted directly into the mass spectrometer using a linear gradient of acetonitrile in water with ammonium formate as a mobile phase modifier. Specific activity was calculated by comparison of the ratio of carbon-14/carbon-12 for the tracer against the unlabeled reference.

(4-Bromophenyl)(6-methoxy-1H-indazol-3-yl)methanone (3)

To a suspension of 1-bromo-4-iodobenzene (1.7 g, 6.0 mmol) in THF (3 mL) at -40°C was added dropwise a 2 M solution of isopropylmagnesium chloride (3.0 mL, 6 mmol) in THF. After 4 h at that same temperature, a solution of 6-Methoxy-1*H*-indazole-3-carbonitrile **2** (519 mg, 3.0 mmol) in THF (4.5 mL) was added and the mixture was stirred for 15 min and then allowed to warm to room temperature, at which time 2 N HCl (7.5 mL) was added and stirring was continued for an additional 2 h. The reaction mixture was extracted with methylene chloride (3 $\times$ 75 mL). The organic extracts were combined, washed with water (1 $\times$ 50 mL), and dried over sodium sulfate. Evaporation under reduced pressure yielded a yellow solid (907 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.30 (1H, broad s), 8.30 (1H, d, J = 8.89 Hz), 8.22–8.19 (2H, m), 7.68–7.64 (2H, m), 7.04 (1H, dd, J = 8.90, 2.14 Hz), 6.92 (1H, d, J = 2.11 Hz), 3.93 (3H, s). MS (ESI$^+$) $[M+H]^+$ 330.9.

1-{3-[(4-Bromophenyl)carbonyl]-6-methoxy-1H-indazol-1-yl}-3,3-dimethylbutan-2-one (4)

To a solution of **3** (741 mg, 2.23 mmol) in DMF (7 mL) was added potassium carbonate (754 mg, 5.45 mmol) and 1-bromopinacolone (647 μL, 4.80 mmol) and the mixture was heated at 80°C for 4 h. The reaction was quenched with water (50 mL) and extracted into diethyl ether (3 $\times$ 50 mL). The organic extracts were combined, washed with water (1 $\times$ 50 mL), and dried over sodium sulfate. Evaporation under reduced pressure yielded a light yellow residue, which was triturated with warm diethyl ether (100 mL) and aged at 0°C for 1 h. The solids were collected on a filter funnel and dried in a vacuum pistol overnight to give a white solid (816 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (1H,

d, $J = 8.90$ Hz), 8.18–8.14 (2H, m), 7.64–7.60 (2H, m), 7.01 (1H, dd, $J = 8.91$, 2.08 Hz), 6.52 (1H, d, $J = 2.06$ Hz), 5.39 (3H, s), 3.86 (3H, s), 1.34 (9H, s). MS (ESI^+) $[M+H]^+$ 429.0.

4-{[1-(3,3-Dimethyl-2-oxobutyl)-6-methoxy-1H-indazol-3-yl]-carbonyl}(formyl-^{14}C)benzaldehyde (5) and 4-{[1-(3,3-dimethyl-2-oxobutyl)-6-methoxy-1H-indazol-3-yl]carbonyl}(carboxy-^{14}C)benzoic acid (6) by Elmore method with sodium formate as a reducing agent

In a 3-neck 50 mL round-bottomed flask connected to a vacuum manifold was added sodium [^{14}C]formate (65 mg, 0.90 mmol, 49.5 mCi, 55 mCi/mmol) and water (2 mL). The flask was fitted with a dropping funnel capped with a rubber septum and a 90° bent adapter attached to a 10 mL recovery flask containing **4** (185 mg, 0.430 mmol), sodium formate (44 mg, 0.645 mmol), $Pd(PPh_3)_2Cl_2$ (15 mg, 0.022 mmol), and DMF (1 mL). The entire system was evacuated to 0.01 mm Hg and concentrated sulfuric acid (5 mL) was added via the dropping funnel. The 3-neck flask was heated at 70°C for 1 h at which time it was removed from the oil bath, the recovery flask was placed inside, and the temperature was increased to 90°C and held for 16 h. The reaction mixture was cooled to room temperature and the vacuum was released. Water (2 mL) and 1 N NaOH (2 mL) were added and the mixture was extracted with ethyl acetate (3×5 mL). The combined extracts had a total radioactivity of 3.8 mCi (5% rcy) by liquid scintillation counting. After drying over sodium sulfate and evaporation under reduced pressure, the resulting brown residue containing **5**, which had a radiochemical purity of 66.7% by HPLC ($t_R = 13.0$ min), was taken on directly to the next step. The alkaline aqueous layer was then adjusted to pH = 6 with concentrated hydrochloric acid and extracted with ethyl acetate (3×5 mL). The organic extracts were combined and dried over sodium sulfate. Evaporation under reduced pressure yielded a residue that was dissolved in 2:1 methanol:DMSO (3 mL) and subjected to preparative chromatography (Phenomenex Luna C18(2) column, 21.2×250 mm, 35–65% acetonitrile:H_2O (0.1% TFA), 30 min linear gradient, 20 mL/min, 3×1 mL injections). 4.0 mCi (7% rcy) of **6** was obtained, which had a radiochemical purity of 89.8% by HPLC ($t_R = 11.8$ min). ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (2H, d, $J = 8.04$ Hz), 8.19 (1H, d, $J = 8.91$ Hz), 8.13 (2H, d, $J = 8.08$ Hz), 7.01 (1H, dd, $J = 9.00$, 1.40 Hz), 6.91 (1H, d, $J = 1.40$ Hz), 5.68 (2H, s), 3.88 (3H, s), 1.33 (9H, s). MS (ESI^+) $[M+H]^+$ 397.5.

1-[3-({4-[Hydroxy(^{14}C)methyl]phenyl}carbonyl)-6-methoxy-1H-indazol-1-yl]-3,3-dimethylbutan-2-one (7) from (5)

To the crude residue containing **5** (2.5 mCi, 0.045 mmol) was added benzene (2 mL), acetic acid (10 μL, 0.175 mmol), and sodium triacetoxyborohydride (23 mg, 0.108 mmol). The mixture was purged with nitrogen gas and heated at reflux for 1 h. The reaction was diluted with acetonitrile (2 mL) and passed through a 0.45 μM filter. Evaporation under reduced pressure yielded a residue, which was dissolved in acetonitrile (1.5 mL) and subjected to preparative chromatography (Phenomenex Luna C18(2) column, 21.2×250 mm, 40% acetonitrile:H_2O (0.1% TFA) to 70% acetonitrile, 30 min linear gradient, 20 mL/min, 1×1.5 mL injections). 2.0 mCi (80% rcy) of **7** was obtained, which had a radiochemical purity of 99.9% by HPLC ($t_R = 11.5$ min). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (1H, d, $J = 8.92$ Hz), 8.26 (2H, d, $J = 8.07$ Hz), 7.54–7.47 (3H, m), 7.11 (1H, d, $J = 8.93$ Hz), 5.87 (2H, s), 4.81 (2H, s), 4.02 (3H, s), 1.33 (9H, s). MS (ESI^+) $[M+H]^+$ 383.0.

4-{[1-(3,3-Dimethyl-2-oxobutyl)-6-methoxy-1H-indazol-3-yl]-carbonyl}(formyl-^{14}C)benzaldehyde (5) via *in situ* formation of [^{14}C] carbon monoxide

In a 0.5–2 mL Biotage microwave vial was placed sodium [^{14}C]formate (17 mg, 0.242 mmol, 13.3 mCi, 55 mCi/mmol), DMF (1 mL), and *N*,*N*-diisopropylethylamine (36 μL, 0.210 mmol). A rubber septum was placed on the vial and the mixture was purged with argon gas. Acetic anhydride (20 μL, 0.210 mmol) was added, the septum was quickly removed, and a crimp cap was placed on the vial. The mixture was stirred at room temperature for 1 h. In a separate vial was placed **4** (45 mg, 0.105 mmol), $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol), lithium chloride (9.0 mg, 0.221 mmol), DMF (500 μL), and triethylsilane (16 μL, 0.105 mmol). A rubber septum was placed on the vial and the mixture was purged with argon gas. An argon-filled balloon was inserted through the septum of the vial containing the sodium [^{14}C]formate mixture and the substrate/catalyst mixture was added via syringe. The crimp cap was quickly removed and replaced with a new one and the mixture was heated at 90°C overnight. The reaction mixture was cooled to room temperature, diluted with water (2 mL), and extracted with ethyl acetate (3×5 mL). The organic extracts were combined, washed with water (1×5 mL), and dried over sodium sulfate. Evaporation under reduced pressure yielded a residue, which was dissolved in acetonitrile (1 mL) and subjected to preparative chromatography (Phenomenex Luna C18(2) column, 21.2×250 mm, 40% acetonitrile:H_2O (0.1% TFA) to 70% acetonitrile, 30 min linear gradient, 20 mL/min, 1 mL injection). 1.2 mCi (9% rcy) of **5** was obtained, which had a radiochemical purity of 99.5% by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.13 (1H, s), 8.39–8.35 (3H, m), 8.00 (2H, d, $J = 8.09$ Hz), 7.13 (1H, d, $J = 8.92$ Hz), 5.86 (2H, s), 4.02 (3H, s), 1.33 (9H, s). MS (ESI^+) $[M+H]^+$ 381.0.

4-{[1-(3,3-Dimethyl-2-oxobutyl)-6-methoxy-1H-indazol-3-yl]-carbonyl}(carboxy-^{14}C)benzoic acid (6) via *in situ* formation of [^{14}C] carbon monoxide

In a 0.5–2 mL Biotage microwave vial was placed sodium [^{14}C]formate (23.2 mg, 0.329 mmol, 18.2 mCi, 55 mCi/mmol) and DMF (1 mL). A rubber septum was placed on the vial and the mixture was purged with argon gas. Acetic anhydride (28.2 μL, 0.298 mmol) was added, the septum was quickly removed, and a crimp cap was placed on the vial. The mixture was stirred at room temperature for one hour. In a separate vial was placed **4** (64 mg, 0.149 mmol), $Pd(PPh_3)_2Cl_2$ (5.3 mg, 0.008 mmol), lithium chloride (13.3 mg 0.313 mmol), and DMF (1 mL). A rubber septum was placed on the vial and the mixture was purged with argon gas. An argon filled balloon was then inserted through the septum of the vial containing the sodium [^{14}C]formate mixture and the substrate/catalyst mixture was added via syringe. The crimp cap was quickly removed and replaced with a new one and the mixture was heated at 90°C overnight. The reaction mixture was cooled to room temperature and evaporated under reduced pressure. The residue was partitioned between 1 N NaOH (4 mL) and ethyl acetate (5 mL). The alkaline aqueous layer was adjusted to pH = 6 with concentrated hydrochloric acid and extracted with ethyl acetate (3×5 mL). The combined extracts had a total radioactivity of 6.7 mCi (32% rcy) by liquid scintillation counting.

After drying over sodium sulfate and evaporation under reduced pressure, the resulting residue containing **6**, which had a radiochemical purity of 88.4% by HPLC, was taken on directly to the next step. ^{1}H NMR and MS data were consistent with that given for the sample prepared by the alternate method described above.

1-[3-({4-[Hydroxy(^{14}C)methyl]phenyl}carbonyl)-6-methoxy-1H-indazol-1-yl]-3,3-dimethylbutan-2-one (7) from (6)

To a solution of 2-chloro-4,6-dimethoxytriazine (28.7 mg, 0.163 mmol) in DMF (1 mL) at 0°C was added 4-methylmorpholine (18.8 μL, 0.171 mmol). A precipitate immediately formed. The mixture was removed via syringe and added to a suspension of **6** (7.2 mCi, 0.131 mmol) in dimethoxyethane (2 mL) at 0°C. The reaction was warmed to room temperature and stirred for 16 h at which time it was passed through a 0.45 μM filter. The filter was rinsed with additional dimethoxyethane (2 mL) and the filtrate was transferred to a 15 mL recovery flask. The flask was purged with nitrogen and 10 wt% palladium on carbon (10 mg, 0.009 mmol) was added. The mixture was then stirred under a balloon of hydrogen for 1 h. The catalyst was removed by filtration and the filtrate was evaporated under reduced pressure. The residue was dissolved in acetonitrile (3 mL) and subjected to preparative chromatography (Phenomenex Luna C18(2) column, 21.2 × 250 mm, 40% acetonitrile:H_2O (0.1% TFA) to 70% acetonitrile, 30 min linear gradient, 20 mL/min, 2 × 1.5 mL injections). 4.0 mCi (55% rcy) of **7** was obtained, which had a radiochemical purity of 99.9% by HPLC. ^{1}H NMR and MS data were consistent with that given for the sample prepared by the alternate method described above.

Di-*tert*-butyl(4-{[1-(3,3-dimethyl-2-oxobutyl)-6-methoxy-1*H*-indazol-3-yl]carbonyl}phenyl)(^{14}C)methyl phosphate (8)

To a solution of **7** (5.9 mCi, 0.111 mmol) in dichloromethane (3 mL) under an argon atmosphere was added a solution of tetrazole in acetonitrile (740 μL, 0.45 M, 0.333 mmol) followed by di-*tert*-butyl *N,N*-diethylphosphoramidite (59 μL, 0.211 mmol). The reaction was stirred for 30 min at room temperature and cooled to 0°C, at which time *tert*-butyl hydroperoxide in decane (111 μL, 5 M, 0.555 mmol) was added. After 30 min, a solution of 1 M sodium sulfite (250 μL) was added and stirring was continued for a further 5 min. The mixture was diluted with ethyl acetate (10 mL) and washed with brine (5 mL). The organic layer, which had a total radioactivity of 5.5 mCi by liquid scintillation counting and a radiochemical purity of 88.2% by HPLC (t_R = 14.3 min), was taken on directly to the next step.

(4-{[1-(3,3-Dimethyl-2-oxobutyl)-6-methoxy-1*H*-indazol-3-yl]-carbonyl}phenyl)(^{14}C)methyl dihydrogen phosphate (9)

The ethyl acetate solution containing **8** was evaporated under reduced pressure and diluted with a solution of saturated HCl in ethyl acetate (2 mL). The solution was stirred at room temperature for 2 h, at which time it was concentrated to dryness, dissolved in methanol (2 mL), and subjected to preparative chromatography (Phenomenex Synergi Max RP column, 21.2 × 250 mm, 25% acetonitrile:H_2O (0.1% $HClO_4$) to 55% acetonitrile, 30 min linear gradient, 20 mL/min, 2 × 1 mL injections). 2.5 mCi (42% rcy from **7**) of **9** was obtained, which had a radiochemical purity of 99.2% by HPLC (Phenomenex Luna C8 column, 4.6 × 250 mm, 60% acetonitrile:H_2O (0.1% $HClO_4$), t_R = 12.5 min, 1 mL/min) and a specific activity of 53.1 mCi/mmol. ^{1}H NMR (400 MHz, CD_3OD) δ 8.25 (2H, d, *J* = 7.50 Hz), 8.18 (1H, d, *J* = 7.50 Hz), 7.60 (2H, d, *J* = 7.60 Hz), 7.00 (1H, d, 7.50 Hz), 6.90 (1H, broad s), 5.65 (2H, s), 5.10 (2H, broad s), 3.90 (3H, S), 1.35 (9H, s). MS (ESI$^+$) $[M+H]^+$ 463.0.

Acknowledgements

We thank Mr Herb Jenkins of Merck Analytical Research for analytical support and Dr Jeffrey Hale of Merck Medicinal Chemistry for helpful discussions related to phosphate chemistry.

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