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Synthesis of triphenylsilyl[$^{14}C_2$]acetylene for use in a Sonogashira reaction

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Silylacetylenes are useful coupling partners for aromatic halides in the Sonogashira reaction and a C-14 labeled version of this useful synthon would allow ready access to a wide variety of arylalkynes. $Ca^{14}C_2$ was converted to triphenylsilyl[$^{14}C_2$]acetylene using two related routes in 65% yield, and the resulting [$^{14}C_2$]acetylene was coupled with an aryl halide to give the target triphenylsilylarylacetylene (2) in 40% yield.

Keywords: triphenylsilylacetylene; calcium carbide; Songashira reaction

Introduction

Carbon–carbon triple bonds are important structural motifs in organic chemistry. They can be found in drug and drug candidate molecules, such as ethinylestradiol and mGluR5 receptor antagonists,[1,2] and enediyne antibiotics, such as Neocarzinostatin,[3] and they provide ready access to numerous other functional groups via well-precedented transformations. The synthetic accessibility of aryl alkynes was dramatically improved with the report of what has come to be known as the Sonogashira reaction in 1975.[4] This reaction involves the Pd-catalyzed coupling of a monosubstituted alkyne with an aryl or alkenyl halide or triflate.[4–6]

Many different Pd-containing catalysts have been demonstrated to catalyze the reaction; these catalysts can be divided into two broad classes of ligated and ligand free. Ligated catalysts vary considerably; $Pd(PPh_3)_4$, palladacycles, and *N*-heterocyclic carbene containing Pd catalysts have shown good efficacy in catalyzing the coupling. Traditionally, the Sonogashira reaction uses a copper(I) co-catalyst to generate the copper alkyne which then undergoes transmetalation to give the palladium alkyne. These conditions can lead to byproduct formation (dimerization) via the Glaser coupling that occurs under very similar reaction conditions.[7] Dimerization can be reduced by slow addition of the alkyne to the reaction mixture[8] and by running the reaction under a H_2 atmosphere.[9] There have also been numerous reports of copper-free conditions that completely eliminate the need for a copper co-catalyst.[10–12]

Despite the utility of this chemistry, there are few reports in the literature of the use of C-13 or C-14 labeled acetylenes in Sonogashira reactions.[13] This is due, in part, to the difficulty in preparing the requisite alkyne and to the low yields inherent in the Sonogashira when the alkyne is used as the limiting reagent.

Experimental

General

$Ca^{14}C_2$ was obtained from American Radiolabeled Chemical Company and contained considerable non-radioactive impurities. Multiple analyses were performed to determine the specific activity of the material, and they gave a specific activity of 15 μCi/mg. There was considerable variation in the specific activity measurements (12–23 μCi/mg) due to the heterogeneity of the material. The radioactive portion of the calcium carbide had a specific activity of 117 mCi/mmol. All other reagents were obtained from Aldrich or Acros and were used without purification. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker Avance 500 and were referenced to the residual solvent peak (7.26). Preparative HPLC purifications were performed using a 250 × 21.2-mm Phenomenex Luna C-18(2) column and MeCN-0.1% Formic acid as the eluent. Analytical HPLC analyses were performed using an Agilent 1100 series HPLC system on a Phenomenex Luna C-18(2) column using a gradient of 50–100% MeCN-0.1% TFA over 10 min followed by a 5-min wash with 100% MeCN.

Triphenylsilyl[$^{14}C_2$]acetylene: Route A

A two-necked, round-bottomed flask containing 775 mg (approx 15 μCi/mg, 12 mCi, 0.10 mmol) of $Ca^{14}C_2$ was fitted with a septum and was connected to a vacuum manifold through a gas drying tube containing drierite. The other port on the manifold was connected to a two-necked, round-bottomed flask that had a septum in one port and a drying tube containing K_2CO_3 connected to the gas manifold in the other. The apparatus was evacuated and the valve leading to the vacuum closed. Water (2.5 ml) was added to the $Ca^{14}C_2$ through the septum and the resulting slurry was stirred at rt. While the water was being added, the other flask was cooled in liquid nitrogen to trap the resulting gases. After 5 min of condensing [$^{14}C_2$]acetylene, the valve connecting the flask to the manifold was closed. A solution of 3 ml of 3 M EtMgBr in Et_2O and 4 ml of THF (under a N_2 atmosphere) was added via cannula to the cold acetylene and the solution was stirred for 30 min at 0°C and then at room

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temperature for 1 h. A solution of 2.01 g (6.83 mmol) of triphenylchlorosilane in 4 ml of THF was added and the solution was stirred overnight under N_2. The reaction was diluted with 20 ml of water and was extracted four times with 20 ml of Et_2O. The combined organic layers were washed twice with 25 ml of brine and 25 ml of H_2O and was dried ($MgSO_4$). Filtration followed by concentration gave 9.2 mCi of triphenylsilyl[$^{14}C_2$]-acetylene (radiochemical purity 94%), which was purified by silica gel chromatography (100% hexane) to give 7.7 mCi (radiochemical purity >98%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.78 (s, 1 H), 7.38 (*m*, 9H), 7.66 (d, *J* = 6.71 Hz, 6 H).

Route B

A solution of 64 mg (0.12 mmol, 13.4 mCi) of 1,2-*bis*(triphenylsilyl)[$^{14}C_2$]acetylene in 20 ml of THF and 200 µl of MeOH was stirred as 50 µl (50 µmol) of 1 M *n*-Bu_4NF in THF was added. The solution was stirred rapidly for 20 min at room temperature and was then passed through a light silica Sep-Pak® cartridge, which was subsequently washed with 10 ml of THF. The volatiles were removed and the residue was purified by preparative HPLC (50–100% over 10 min then hold for 10 min) to give 11.4 mCi (29 mg, >98% radiochemical purity) of triphenylsilyl[$^{14}C_2$]acetylene.

*1,2-*Bis*(triphenylsilyl)[$^{14}C_2$]acetylene*

[$^{14}C_2$]Acetylene was generated as was described in route A for the generation of triphenylsilyl[$^{14}C_2$]acetylene using 962 mg (15 µCi/mg, 14 mCi) of $Ca^{14}C_2$ and 2.9 ml of water. To the two-necked receiving flask was added a solution of 2.4 ml of 1.6 M (3.8 mmol) *n*-BuLi in hexane in 15 ml of THF through the sidearm. The reaction vessel was then warmed to −78°C and was stirred for 25 min. A solution of 1.12 g (3.80 mmol) of triphenylchlorosilane in 6 ml of tetrahydrofuran was added, and the solution was stirred at −78°C for 30 min, at 0°C for 3 h, and then at room temperature overnight. The reaction mixture was diluted with 30 ml of water and was extracted four times with 30 ml of Et_2O. The combined organic layers were washed three times with 20 ml of water and then dried ($MgSO_4$). After filtering, the solvent was removed and the residue was taken up in 10 ml of MeCN. The solution was cooled at 0°C for 1 h and was then filtered. The filtrate was then purified by preparative HPLC (50 to 100% over 20 min) in three batches to give 10.6 mCi as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.40 (*m*, 18 H) 7.69 (d, *J* = 6.7 Hz, 12 H).

Isoindolone ***1***

A mixture of 0.19 mmol of **2**, 0.44 mg (2.3 µmol) of CuI, and 5.37 mg (7.65 µmol) of dichloro*bis*(triphenylphosphine)palladium(II) under a H_2 atmosphere was stirred for 20 min and then 85 µl (0.61 mmol) of NEt_3 was added and the solution was warmed to 80 C. A carefully degassed solution of 4.3 mCi (0.038 mmol, 11 mg) triphenylsilyl[$^{14}C_2$]acetylene in 1 ml of MeCN was added dropwise over 20 min. The solution was heated at 80°C for 1.5 h and was then concentrated to dryness under a stream of nitrogen. Purification by preparative HPLC (75–100% over 5 min then hold at 100% MeCN for 10 min) afforded 1.84 mCi of Isoindolone **1** (43%, >98% radiochemical purity with a specific activity of 117 mCi/mmol).

Results and discussion

Isoindolone **1** was required labeled with C-14 in a metabolically stable position for use as a synthetic intermediate. Although it is possible to incorporate the C-14 label into the isoindolone ring of **2** via the medicinal chemistry approach, the synthesis would have been quite long and low yielding.[14] The next step in the medicinal chemistry synthesis afforded the opportunity to incorporate C-14 via a Sonogashira reaction. This had the advantage of late-stage incorporation of radioactivity while avoiding some of the difficult, low-yielding steps found in the preparation of **2** (Scheme 1). However, to the best of our knowledge, a Sonogashira reaction using a C-14 labeled acetylene has not been reported previously although it has been conducted on an acetylene containing a S-35 labeled side chain.[15]

The medicinal chemistry route utilized trimethylsilylacetylene as a coupling partner in the Sonogashira reaction. This reagent is not readily available in C-14 labeled form; hence, we decided to

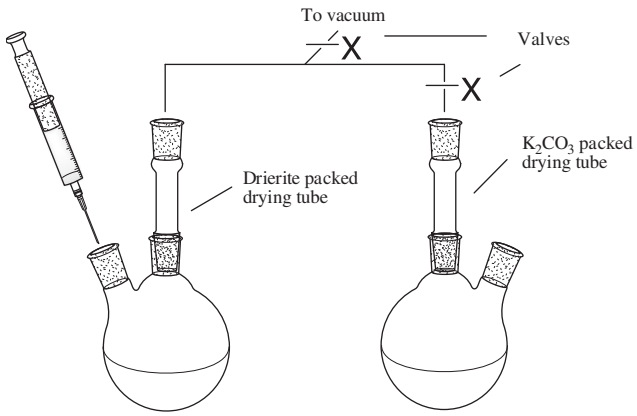
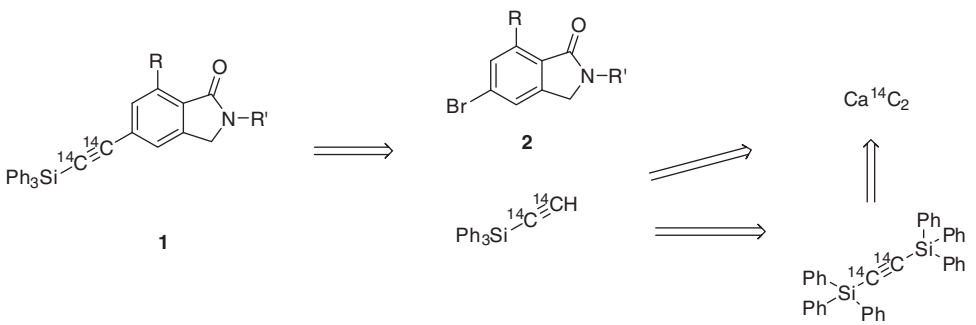
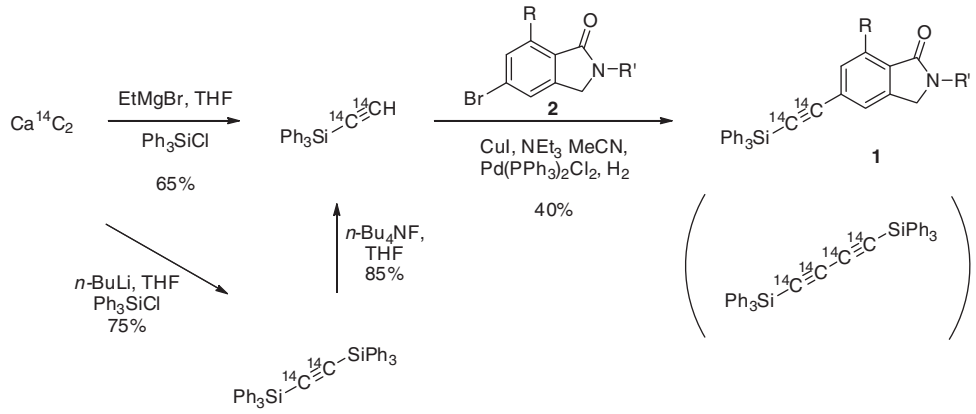


Figure 1. Apparatus for generating [$^{14}C_2$]acetylene and reacting it with BuLi or EtMgBr.



Scheme 1. Retrosynthetic analysis for isoindolone **1**.



Scheme 2. Synthesis of isoindolone **1** from $Ca^{14}C_2$.

prepare it from C-14 acetylene; however, after verifying that triphenylsilylacetylene (TPSA) was also an effective coupling partner, it was decided to target that alkyne instead to reduce the volatility of the C-14-labeled intermediate.

Two approaches to the preparation of [$^{14}C_2$]TPSA were investigated: (1) a one-step deprotonation–alkylation approach and (2) a two-step deprotonation *bis*-alkylation, deprotection approach. These approaches are depicted in Scheme 1. In both the approaches, addition of water to $Ca^{14}C_2$ produces acetylene gas, which is transferred via a vacuum manifold to a reaction flask using standard vacuum transfer methodology (Figure 1).[16] The [$^{14}C_2$]acetylene gas was passed through a column containing $CaCO_3$ and then through a column containing K_2CO_3 to dry it prior to anion formation.

For the direct, one-step approach, a solution of ethylmagnesium bromide was added to the condensed acetylene and the solution was then warmed to 0°C (Scheme 2).[17] After complete anion formation, a solution of triphenylsilyl chloride was introduced into the reaction mixture, and the solution was stirred overnight. Purification by silica gel chromatography afforded a yield of 65%.

The two-step approach involved the one-pot *bis*-alkylation of acetylene; the anion of acetylene was formed using *n*-BuLi and was captured with triphenylsilyl chloride. The *bis*-silyl adduct was then purified by preparative HPLC and then monodeprotected to afford the target triphenylsilyl[$^{14}C_2$]acetylene in 64% yield.

Both routes provided the modest yields of the target triphenylsilyl[$^{14}C_2$]acetylene. The procedures were complicated by non-radioactive impurities in the $Ca^{14}C_2$. This made exact quantitation of the amount of radioactive $Ca^{14}C_2$ being added difficult. However, in both the procedures, excess base was used which alleviated the concern that some of the C-14 acetylene would remain unreacted due to inadequate amount of base or triphenylsilyl chloride.

The Sonogashira reaction proved to be a challenge. Initial attempts to couple the [$^{14}C_2$]TPSA using the medicinal chemistry procedure, resulted in either dimerization of the acetylene or in no reaction. After probing many different conditions, we discovered that no conversion of the [$^{14}C_2$]TPSA to the target product occurred unless the alkyne was purified by preparative HPLC. Presumably, a non-radioactive impurity that was not removed during silica gel chromatography interfered with the reaction. The use of MeCN as solvent gave a higher yield than the use of a amine solvent such as diisopropylamine. Slow addition of the alkyne to the reaction mixture and the use of a H_2 atmosphere in place of argon dramatically reduced the amount of homocoupling. However, the reaction yield was still highly variable (from 15% to 75% with 40% being the norm) and so the Sonogashira reaction was conducted multiple times in small batches and the products combined to mitigate the loss in case a reaction gave a poor yield. No reduction of the triple bond to give alkene or alkane products was observed by LC/MS although if this reduction occurred prior to the Sonogashira coupling, it likely would not have been observed.

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