Note

Journal of Labelled Compounds and Radiopharmaceuticals

Received 10 September 2012, Accepted 16 October 2012 Published online 27 November 2012 in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/jlcr.2983

The synthesis of [*carboxamido*-^{14}C]SAR240550, [*carboxamido*-^{14}C]Iniparib, via monocarboxylation of 1,4-diiodobenzene

Thomas J. Gregson,*† Andrew D. Kohler,† and Daniel W. Spurr†

1,4-Diiodobenzene was monolithiated with *n*-butyllithium and subsequently carboxylated with $^{14}CO_2$ in 86% yield. The resulting [*carboxyl*-^{14}C]-4-iodobenzoic acid was used in the synthesis of [*carboxamido*-^{14}C]SAR240550, [*carboxamido*-^{14}C]Iniparib.

Introduction

Iniparib (SAR240550, 4-iodo-3-nitrobenzamide) is a novel investigational agent for the treatment of various cancers.[1] The potential chemotherapeutic activity of this compound has long been recognised.[2] To enable ADME (absorption, distribution, metabolism and elimination) and human studies, [*carboxamido*-^{14}C] SAR240550 (**1**) was required. As initial metabolic studies had indicated that the amide carbon was metabolically stable, we decided that labelling in that position would be appropriate.

The key labelled intermediate, [*carboxyl*-^{14}C]-4-iodobenzoic acid (**2**), has previously been accessed by a number of means; (1) cyanation of 4-nitrobenzenediazonium salt, reduction and subsequent Sandmeyer reaction (75%);[3] (2) Rosenmund–von Braun monocyanation of 1,4-diiodobenzene followed by hydrolysis (<60%);[4] or (3) via 1-bromo-4-trimethylsilylbenzene with a lithium–bromide exchange quenched by $^{14}CO_2$ and then replacement of the silyl group with iodine using iodine monochloride (80%).[5] Other nonlabelled methods have been described, which appeared to be applicable to radiosynthesis and these include organozinc preparations from diiodobenzene,[6] copper-catalysed carboxylations of 4-iodophenylboronic esters[7] and isopropylmagnesium chloride reactions on fluorinated analogues.[8] However, direct monolithiation of diiodobenzene and CO_2 quench has not previously been reported. Although it has been suggested that such an approach might be difficult,[9] the formation and use of 4-iodophenylithium from 1,4-diiodobenzene and its reaction with electrophiles has been widely examined.[10] In a number of cases, concerns over the potential issues of disproportionation of 4-iodophenylithium to starting material and dilithiobenzene or reaction of the butyliodide to form 4-iodobutylbenzene were raised.[10a-b] Such side reactions have been observed when reaction times were extended due to large scale, or when temperatures were raised for the subsequent reaction. Notably, the formation of 4-bromophenylithium from 1,4-dibromobenzene is well-established[11] and this has been used as an intermediate to synthesise 4-bromobenzoic acid.[12] With this precedent in mind, we decided that the lithium exchange and subsequent carboxylation reaction on 1,4-diiodobenzene was worthy of re-examination.

Results and discussion

The preparation of [*carboxamido*-^{14}C]SAR240550 (**1**) is outlined in Scheme 1. Reaction of a tetrahydrofuran solution of 1,4-diiodobenzene at −78 °C with one equivalent of *n*-butyllithium and subsequent quenching with 0.9 equivalents of $^{14}CO_2$ generated from barium [^{14}C]carbonate afforded [*carboxyl*-^{14}C]-4-iodobenzoic acid in 86% radiochemical yield. In comparison with the previously described labelled syntheses, this is both the most direct and the highest yielding method. The remainder of the synthesis of [*carboxamido*-^{14}C]SAR240550 (**1**) required two simple steps; a nitration, which was achieved in 89% yield with a mixture of concentrated nitric and sulfuric acids affording the nitroaromatic (**3**), formation of the acyl chloride using thionyl chloride and subsequent amination using ammonium hydroxide in 60% yield. Thus, [*carboxamido*-^{14}C]SAR240550 (**1**), [*carboxamido*-^{14}C]Iniparib, was prepared rapidly and in 46% radiochemical yield and in doing so, we have demonstrated that [*carboxyl*-^{14}C]-4-iodobenzoic acid can be successfully prepared by the lithium–halogen exchange of 1,4-diiodobenzene and subsequent quenching with $^{14}CO_2$.

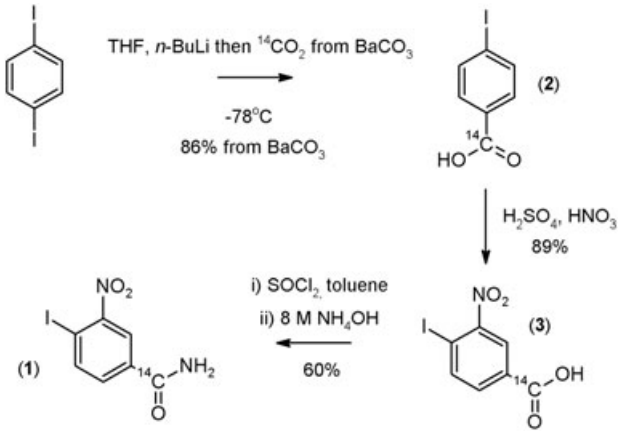
Experimental

Barium [^{14}C]carbonate was purchased from GE Healthcare. All steps were carried out at low specific activity prior to being repeated at high specific activity. High specific activity materials were characterised by comparative TLC (to known standards) and ^{1}H-NMR. Merck silica gel 60 F_{254} TLC plates (Merck KGaA, Darmstadt, Germany) were analysed by electronic autoradiography using a Packard A202401 model Instantimager (Packard Instrument Company, Meriden, Connecticut, USA) (since integrated into PerkinElmer, Waltham, Massachusetts, USA). Activities were determined by liquid scintillation analysis using a Packard Tri-Carb 1900TR (Packard Instrument Company, Meriden, Connecticut, USA) (since integrated into PerkinElmer, Waltham, Massachusetts, USA). ^{1}H-NMR data were recorded on a Bruker DRX 500 NMR instrument (Bruker Biospin Corporation, Billerica, Massachusetts, USA).

Sanofi-Aventis, Isotope Chemistry and Metabolite Synthesis, Willowburn Ave., Alnwick, Northumberland NE66 2JH, UK

**Correspondence to: Thomas J. Gregson, Covance Laboratories, Willowburn Avenue, Alnwick, Northumberland, NE66 2JH, UK.*
E-mail: tom.gregson@covance.com

† Covance Laboratories, Willowburn Avenue, Alnwick, Northumberland, NE66 2JH, UK.



Scheme 1. Synthesis of [*carboxamido*-^{14}C]SAR240550.

*[Carboxyl-^{14}C]-4-iodobenzoic acid (**2**)*

(The preparation was performed on a glass manifold attached to a high-vacuum pump). To a solution of 1,4-diiodobenzene (468 mg, 1.42 mmole) in tetrahydrofuran (3.5 mL) at −78 °C, *n*-butyllithium solution (2.5 M in hexanes, 570 μL, 1.42 mmole) was added dropwise. This afforded a yellow suspension that was stirred at −78 °C for 1 h 20 min before freezing with liquid nitrogen. In a separate flask containing concentrated sulfuric acid (6 mL), barium [^{14}C]carbonate (2696 MBq, 248 mg, 1.24 mmole) was introduced very slowly using a solid-addition tube. The [^{14}C]carbon dioxide thus produced was transferred to the frozen reaction mixture that was then sealed, taken to −78 °C and stirred for 3 h. The reaction mixture was then refrozen with liquid nitrogen and the vacuum was replaced with a flow of nitrogen. Aqueous ammonium chloride solution (2 M, 1.5 mL, 3 mmole) was added and the mixture was allowed to room temperature and stirred overnight under nitrogen. Aqueous sodium hydroxide solution (0.5 M, 20 mL) was added and the layers were separated. The organic phase was extracted with further aqueous sodium hydroxide (0.5 M, 20 mL). The aqueous layers were combined and aqueous hydrochloric acid (1 M, 25 mL) was added to afford a thick, white precipitate that was stirred for 10 min. Ethyl acetate (2 × 50 mL) was then used to extract the aqueous phase. Combined extractions were dried over anhydrous sodium sulfate, filtered and evaporated to afford [*carboxyl*-^{14}C]-4-iodobenzoic acid (**2**) as a white solid (2318 MBq, 1.07 mmole, 86% radiochemical yield). δ^H(DMSO-d^6) 7.68 (2H, d, J 8.5), 7.88 (2H, d, J 8.5), 13.0 (1H, broad s).

*[Carboxyl-^{14}C]-4-iodo-3-nitrobenzoic acid (**3**)*

Concentrated sulfuric acid (1.15 mL) was added to [*carboxyl*-^{14}C]-4-iodobenzoic acid (**2**) (2269 MBq, 1.04 mmole) affording a red suspension. A mixture of concentrated sulfuric acid with concentrated nitric acid (0.5 mL, 1:2 vol) was then added and the mixture was stirred under nitrogen. A yellow solution was formed with a white solid adhering to the sides of the flask. By manipulation of the flask, the majority of the solid was moved into solution and was stirred overnight. Cold water (5 °C, 12 mL) was added to the reaction mixture producing a yellow precipitate. Ethyl acetate (12 mL) was then added which dissolved the precipitate, and the phases were separated. The aqueous layer was further extracted with ethyl acetate (30 mL), and the combined organics were dried over anhydrous magnesium sulfate, filtered and evaporated to afford a yellow solid. This was purified by column chromatography on silica gel eluting rapidly with 7% methanol, 1% acetic acid in dichloromethane to afford [*carboxyl*-^{14}C]-4-iodo-3-nitrobenzoic acid (**3**) as a fine, yellow powder (2028 MBq, 0.93 mmole, 89% radiochemical yield). δ^H(DMSO-d^6) 7.85 (1H, dd, J 2.0, 8.0), 8.23 (1H, d, J 8.0), 8.31 (1H, d, J 2.0).

*[Carboxamido-^{14}C]-4-iodo-3-nitrobenzamide (**1**)*

[*Carboxyl*-^{14}C]-4-iodo-3-nitrobenzoic acid (**3**) (1860 MBq, 0.86 mmole) was partially dissolved in toluene (1.10 mL). *N,N*-Dimethylformamide was then added and the vessel was put under an atmosphere of nitrogen. Thionyl chloride (0.13 mL) was added to the reaction flask, which caused dissolution of the yellow solid. The reaction was heated to 96 °C for 2 h. The reaction was then allowed to cool and the solvent and thionyl chloride were removed under vacuum. The acyl chloride thus produced was dissolved in tetrahydrofuran (0.6 mL) and this was then added, over 1 min, to a stirred solution of ammonium hydroxide (25–30% as NH_3, 2.38 mL). The reaction was allowed to stir for 1 h 15 min under nitrogen before being diluted with ethyl acetate (7 mL). The phases were separated and the aqueous layer was extracted with ethyl acetate (4 × 8 mL). The organic phases were combined and chromatographed on silica gel, using ethyl acetate as eluant. This yielded [*carboxamido*-^{14}C]-4-iodo-3-nitrobenzamide (**1**) (1124 MBq, 0.52 mmole, 60% radiochemical yield) as a yellow solid. δ^H(DMSO-d^6) 7.72 (1H, broad s), 7.84 (1H, dd, J 2.0, 8.5), 8.22 (1H, d, J 8.5), 8.25 (1H, broad s), 8.34 (1H, d, J 2.0).

Acknowledgements

The authors wish to thank Dr. S. J. Byard for the NMR spectra and Dr. G. J. Ellames for the assistance in editing the manuscript.

Conflict of Interest

The authors did not report any conflict of interest.

References

[1] a) J. O'Shaughnessy, C. Osborne, J. Pippen, M. Yoffe, D. Patt, G. Monaghan, C. Rocha, V. Ossovskaya, B. Sherman, C. Bradley, *J. Clin. Oncol.* **2009**, *27*, 18s, Abstr 3; b) S. Kopetz, M. M. Mita, I. Mok, K. K. Sankhala, J. Moseley, B. M. Sherman, C. R. Bradley, A. W. Tolcher, *J. Clin. Oncol.* **2008**, *26*, 20s, Abstr 3577; c) J. J. Mahany, N. Lewis, E. I. Heath, P. M. LoRusso, M. M. Mita, J. Rodon, A. W. Tolcher, B. M. Sherman, C. R. Bradley, K. P. Papadopoulos, *J. Clin. Oncol.* **2008**, *26*, 20s, Abstr 3579.
[2] a) P. I. Bauer, J. Mendeleyeva, E. Kirsten, J. A. Comstock, A. Hakam, K. G. Buki, E. Kun, *Biochem. Pharmacol.* **2002**, *63*, 455; b) J. Mendeleyev, E. Kirsten, A. Hakam, K. G. Buki, E. Kun, *Biochem. Pharmacol.* **1995**, *50*, 705.
[3] M. F. Moreau, D. Parry, M. Bayle, J. Papon, P. Labarre, A. Veyre, *J. Labelled Compd. Rad.* **1995**, *36*, 805.
[4] D. D. O'Bannon, W. J. Wheeler, B. C. Peterson, in Synthesis and Applications of Isotopically Labeled Compounds 2003, (Eds.: D. C. Dean, C. N. Filer, K. E. McCarthy), John Wiley and Sons Ltd., Chichester, **2004**, 365.
[5] I. V. Ekhato, C. C. Huang, *J. Labelled Compd. Rad.* **1994**, *34*, 213.
[6] K. Kobayashi, Y. Kondo, *Org. Lett.* **2009**, *11*, 2035.
[7] J. Takaya, S. Tadami, K. Ukai, N. Iwasawa, *Org. Lett.* **2008**, *10*, 2697.
[8] T. Rausis, M. Schlosser, *Eur. J. Org. Chem.* **2002**, 3351.
[9] R. Voges, J. R. Heys, T. Moenius, Preparation of Compounds Labeled with Tritium and Carbon-14, John Wiley and Sons Ltd., Chichester, **2009**, 215.
[10] a) D. S. Ennis, D. C. Lathbury, A. Wanders, D. Watts, *Org. Process Res. Dev.* **1998**, *2*, 287; b) D. Schollmeyer, O. V. Shishkin, T. Rühl, M. O. Vysotsky, *Cryst. Eng. Comm.* **2008**, *10*, 715; c) Y. S. Cho, S. D. Yang, Y. S. Suh, K. S. Chun, S. H. Ahn, S. J. Lim, S. M. Lim, K. H. Yu, *Korean J. Nucl. Med.* **2000**, *34*, 410; d) J. Langer, H. Görls, M. Westerhausen, *Inorg. Chem. Commun.* **2007**, *10*, 853; e) E. Gallienne, G. G. Muccioli, D. M. Lambert, M. Shipman, *Tetrahedron Lett.* **2008**, *49*, 6495; f) B. D. Steinberg, L. T. Scott, *Angew. Chem. Int. Ed.* **2009**, *48*, 5400; g) H. Takaba, H. Omachi, Y. Yamamoto, J. Bouffard, K. Itami, *Angew. Chem.* **2009**, *121*, 6228.
[11] a) L. S. Chen, C. Tamborski, *J. Fluorine Chem.* **1981/1982**, *19*(1), 43; b) M. Wander, P. J. C. Hausoul, L. A. J. M. Sliedregt, B. J. van Steen, G. van Koten, R. J. M. Klein Gebbink, *Organometallics* **2009**, *28*, 4406.
[12] H. Gilman, W. Langham, F. W. Moore, *J. Am. Chem. Soc.* **1940**, *62*, 2327.