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Straightforward synthesis of radioiodinated C_c-substituted o-carboranes: towards a versatile platform to enable the *in vivo* assessment of BNCT drug candidates†

K. B. Gona,^a J. L. V. N. P. Thota,^a Z. Baz,^a V. Gómez-Vallejo^b and J. Llop^{*a}

Due to their high boron content and rich chemistry, dicarba-*closo*-dodecaboranes (carboranes) are promising building blocks for the development of drug candidates with application in Boron Neutron Capture Therapy. However, the non-invasive determination of their pharmacokinetic properties to predict therapeutic efficacy is still a challenge. Herein, we have reported the unprecedented preparation of mono-[¹²⁵I] iodinated decaborane *via* a catalyst-assisted isotopic exchange. Subsequent reactions of the radiolabelled species with acetylenes in acetonitrile under microwave heating yield the corresponding ¹²⁵I-labelled, C_c-substituted *o*-carboranes with good overall radiochemical yields in short reaction times. The same synthetic strategy was successfully applied to the preparation of ¹³¹I-labelled analogues, and further extension to other radioisotopes of iodine such as ¹²⁴I (positron emitter) or ¹²³I (gamma emitter) can be envisaged. Hence, the general strategy reported here is suitable for the preparation of a wide range of radiolabelled C_c-substituted *o*-carborane derivatives. The labelled compounds might be subsequently investigated *in vivo* by using nuclear imaging techniques such as Single Photon Emission Computerized Tomography or Positron Emission Tomography.

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Introduction

Binary approaches to cancer therapy, in which two non- or low-toxicity components of the treatment require co-localization in the tumour to become effective, are promising strategies to improve patient outcomes and reduce side effects. One such binary approach, boron neutron capture therapy (BNCT), was proposed almost 80 years ago by Locher,¹ and involves the accumulation of the non-radioactive nuclide, boron-10 (¹⁰B), into the targeted area, followed by local irradiation with low energy thermal neutrons, which results in the rapid nuclear reaction ¹⁰B(n,α,γ)⁷Li. Alpha particles and ⁷Li recoil ions have high linear energy transfer (LET) and path lengths in the range of 4 to 10 μm. Hence, their deposition energy is limited to the diameter of a single cell, leading to selective cell damage and

death, while sparing healthy surrounding tissue and decreasing unwanted off-target side effects.

Besides presenting low or no toxicity, an ideal BNCT drug candidate should be able to deposit >20–35 μg ¹⁰B per g of tumour to secure therapeutic efficacy, and guarantee tumour-to-normal tissue and tumour-to-blood ratios greater than five to prevent damage to healthy tissue in the path of the neutron beam.² In addition, it should ideally incorporate (or enable the straightforward incorporation of) a positron or a gamma emitter to facilitate the determination of its pharmacokinetic properties using non-invasive, *in vivo* imaging techniques such as Positron Emission Tomography (PET) or Single Photon Emission Computerized Tomography (SPECT), to allow candidate-by-candidate screening to predict therapeutic efficacy.

1,2-Dicarba-*closo*-dodecaboranes (*ortho*-carboranes or *o*-carboranes) are polyhedral clusters containing boron, hydrogen and carbon atoms and were first reported in the early 1960s simultaneously by two groups.³ The unique physico-chemical properties of *o*-carboranes, *i.e.* rigid geometry, rich derivative chemistry, thermal and chemical stability and exceptional hydrophobic character, together with their high boron content, make them suitable building blocks for the preparation of

^aRadiochemistry and Nuclear Imaging Group, CIC biomaGUNE, Paseo Miramón 182, San Sebastián, 20009 Guipuzcoa, Spain. E-mail: jlllop@cicbiomagune.es; Tel: +34 943 00 53 33

^bRadiochemistry Platform, CIC biomaGUNE, Paseo Miramón 182, San Sebastián, 20009 Guipuzcoa, Spain

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candidates for BNCT drugs.^{4–6} Indeed, functionalized *o*-carboranes have been proposed as targeted boron-rich drugs able to selectively accumulate in tumour tissue.⁷

C_c-selectively functionalized *o*-carboranes can be obtained by treatment of *o*-carborane with a strong base (e.g., alkyl lithium salts) and subsequent reaction with an electrophile. Unfortunately, monolithiation of *o*-carboranes at carbon competes unfavourably with dilithiation, leading to complex mixtures. Alternatives for the preparation of mono-substituted *o*-carboranes, e.g. blocking one of the C_c positions with a –Si(Me)₂CMe₃ (TBDMS)⁸ or by using dimethoxyethane as a solvent,⁹ have been developed. Alternatively, the reaction of decaborane[‡] (B₁₀H₁₄) with a Lewis base to form a reactive complex (B₁₀H₁₂L₂),¹⁰ and further reaction with an alkyne can be used for the preparation of C_c-functionalized *o*-carboranes. This 2-step reaction usually offers variable chemical yields and requires longer reaction times (from several hours to days) at elevated temperatures, especially in the case of hindered alkynes.^{3a} Variants of the method including the use of ionic liquids¹¹ and the use of metal salts to enhance the yields have been reported, with satisfactory results.¹² These routes enable the preparation of a large collection of *o*-carborane derivatives, including BNCT drug candidates.¹³

Very recently, we have reported the mono-[¹⁸F]fluorination of *o*-carborane *via* nucleophilic substitution using the carbonyl iodonium salt as the precursor, and subsequent monofunctionalization at one of the C_c atoms by formation of the lithium salt and reaction with an aldehyde.¹⁴ The incorporation of the positron emitter (¹⁸F) enables external tracking after administration into living organisms using PET. Despite the usefulness and novelty of this strategy, post-radiolabelling chemical reactions and tedious work-up are required, limiting the widespread application of this methodology.

Radioiodination represents an attractive alternative to radiofluorination. The radioiodination of *nido*- and *closo*-derivatives of monocarbon carboranes,¹⁵ dodecahydro-*closo*-dodecaborate (2-),¹⁶ *nido*-*o*-carborane¹⁷ and dicarba-*nido*-undecaborate¹⁸ have been reported in the literature. Here, in continuation of these previous studies, and in pursuit of a general strategy for the preparation of radiolabelled *o*-carboranes, we report an unprecedented strategy. Our approach relies on the preparation of radiolabelled decaborane using ¹²⁵I (a radioactive isotope which decays by electron capture with a half-life of nearly 59 days) and catalytic isotopic exchange (Fig. 1).

Further reaction with alkynes using acetonitrile, which acts both as a Lewis base and as the solvent, yields the corresponding radiolabelled *o*-carborane derivatives in a one-pot, one-step reaction. The same synthetic strategy could be successfully translated to the preparation of analogues radiolabelled with ¹³¹I (a radioactive isotope which decays by beta and gamma emission, with a half-life of nearly 8 days). Hence,

[‡]Decaborane is a powerful toxin affecting the central nervous system, and can be absorbed through skin. It forms an explosive mixture with carbon tetrachloride. Special precaution must be taken for its manipulation.

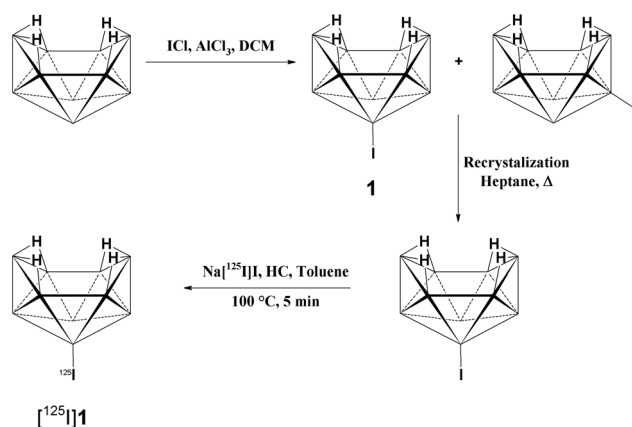


Fig. 1 Schematic synthesis and purification of 1-iododecaborane and radiolabelling by isotopic exchange using ¹²⁵I. The same synthetic strategy was used for the preparation of ¹³¹I-labelled derivatives.

the general strategy reported here might be used for the efficient preparation of a variety of radiolabelled *o*-carboranes by using the same radiolabelled precursor (¹²⁵I-labelled or ¹³¹I-labelled iododecaborane) and just modifying the alkyne. Notably, translation of the methodology to other positron (¹²⁴I) or gamma (¹²³I) emitters, more convenient for their use in *in vivo* imaging, should be straightforward.

Results and discussion

The mono-iodination of decaborane under non-radioactive conditions was first undertaken. Experimentally, decaborane was reacted with iodine monochloride and anhydrous AlCl₃ in dichloromethane to obtain two positional isomers (1- and 2-iododecaboranes, see Fig. 1), which were separated by recrystallization in hot heptane following a previously reported method.¹⁹ Previous results suggest a higher propensity of 2-iododecaborane to undergo deiodination,¹⁹ and hence 1-iododecaborane was used in subsequent radiolabelling experiments and preparation of *o*-carborane derivatives.

¹²⁵I-radiolabelling was carried out by adapting the previously reported palladium catalyzed iodine exchange reaction on iodinated dicarba-*closo*-dodecaboranes.²⁰ Briefly, 1-iododecaborane (4.04 μmol) in toluene (100 μl) was reacted with 370 KBq (10 μCi) of Na[¹²⁵I]I (solution in 0.1 M aqueous NaOH) in the presence of Hermann's catalyst (HC, 0.1 mg in 100 μl of toluene) at 100 °C for 5 min (Fig. 1). Radiochemical conversion (RCC) values, as determined by high performance liquid chromatography (HPLC) using radiometric detection were 70 ± 4% (see Fig. S7A in the ESI† for an example of a chromatographic profile). Longer reaction times and higher temperature values led to a decrease in RCC, suggesting a progressive deiodination of the precursor and the labelled species in competition with the isotopic exchange reaction. The crude reaction mixture was finally purified by solid phase extraction (SPE) to remove the unreacted Na[¹²⁵I]I. With this



aim, the reaction mixture was diluted with water and passed through a C-18 cartridge, which was further rinsed with water. The final elution with acetonitrile (1 mL) yielded pure 1- ^{125}I iododecaborane in overall radiochemical yield of $58 \pm 7\%$ (see Fig. S7B† for the chromatographic profile of the purified product).

The work reported herein was first conducted with ^{125}I , which was selected for convenience (it is widely available) and economical reasons. However, the results can be translated to other radioisotopes of iodine, more convenient for imaging studies and with shorter half-lives such as ^{123}I (a gamma emitter with $T_{1/2} = 13.2$ h) or ^{124}I (a positron emitter with $T_{1/2} = 4.2$ days). In order to prove the suitability of the strategy when other iodine radioisotopes were used, the same procedure was repeated but Na^{131}I (solution in 0.1 M aqueous NaOH) was used as the labelling agent. Equivalent radiochemical yields ($56 \pm 4\%$) were achieved.

In order to develop a methodology applicable to shorter lived radioisotopes of iodine (such as the above mentioned ^{123}I and ^{124}I) we emphasized on developing a one-pot, one-step, fast and efficient method for the reaction of 1- ^{125}I iododecaborane (or 1- ^{131}I iododecaborane) with different alkynes to obtain radiolabelled substituted *o*-carboranes. Generally, strategies involving Lewis bases require two steps, and hence our first attempts were performed with ionic liquids under microwave heating. Despite not previously reported in the context of the preparation of *o*-carboranes in ionic liquids, microwave heating was expected to significantly decrease reaction times. This was tested in model compounds using decaborane as the precursor (see Table 1). Experimentally, decaborane and the corresponding alkynes (1 : 3 molar ratio) were dissolved in biphasic toluene/ionic liquid (1-butyl-3-methylimidazolium chloride, bmimCl) in a microwave vial and heated at 140 °C under microwave irradiation for 1 minute (Fig. 2, method A). Overall yields after purification for the six compounds assayed (2–7) ranged from $68 \pm 6\%$ to $85 \pm 7\%$, resulting in a significant reduction of the reaction time when compared to conventional heating, according to

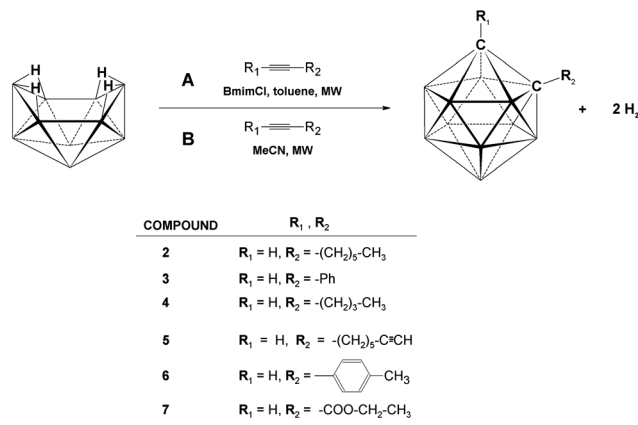


Fig. 2 Scheme of the reaction for the preparation of *o*-carborane derivatives using microwave (MW) heating; route A: using ionic liquids; route B: using acetonitrile both as the Lewis base and solvent.

published data (Table 1).¹² Unfortunately, the translation of these conditions to the preparation of ^{125}I - and ^{131}I -labelled analogues of compounds 2–7 resulted in low RCC values as determined by radio-HPLC (<5% in all cases). Longer reaction times (up to 20 min) only improved RCC values slightly up to 5–10%.

In pursuit of simple alternatives applicable to the preparation of radioiodinated *o*-carboranes, we assayed an experimental scenario based on a one-pot, one-step, microwave-assisted synthetic route without using ionic liquids. Exploratory studies were initially conducted with non-labelled decaborane; in a typical experiment, decaborane and alkyne (1 : 3 molar ratio) were dissolved in acetonitrile in a microwave vial and heated at 120 °C for 20 min under microwave irradiation (Fig. 2, method B). Excellent yields were obtained for the six alkynes assayed (65 ± 4 to $76 \pm 3\%$, Table 1), while reaction times could be significantly decreased when compared to reported values using the conventional 2-step method (e.g., 23 h for compound 2, 10 h for compound 3).

Despite the fact that this method proved successful for the preparation of the substituted carboranes reported here, the determination of the real scope of MW-assisted formation of *closo*-carborane derivatives and the effect of different parameters (e.g. chemical properties of the alkynes, polarity, size, etc.) on the reaction yield and formation of by-products would require assays using a larger collection of alkynes and a more systematic analysis. Such an investigation was out of the scope of the current work.

As a proof of concept that this strategy is suitable for the preparation of radiolabelled *o*-carboranes, these experimental conditions were applied to the preparation of four ^{125}I -labelled *o*-carboranes (Fig. 3). Experimentally, the purified labelled 1- ^{125}I iododecaborane was dissolved in 100 μl of acetonitrile in a 2 mL microwave vial. The corresponding alkyne (14 μmol), was added and the mixture was heated under microwave irradiation at 120 °C for 40 min. Good RCC values, as

Table 1 Formation of *o*-carborane derivatives by reaction of decaboranes with alkynes using ionic liquids (IL) and acetonitrile under microwave heating

Compd	Alkyne	Y. IL ^a	Y. MeCN ^b	Y. CH ^c
2	1-Octyne	$85 \pm 7\%$	$75 \pm 7\%$	91%
3	Phenylacetylene	$68 \pm 6\%$	$65 \pm 4\%$	71%
4	1-Hexyne	$71 \pm 6\%$	$72 \pm 9\%$	NR
5	1,8-Nonadiyne	$72 \pm 6\%$	$71 \pm 7\%$	63%
6	4-Ethynyltoluene	$75 \pm 8\%$	$76 \pm 3\%$	NR
7	Ethyl propiolate	$72 \pm 4\%$	$69 \pm 5\%$	$84 \pm 4\%$

^aYield obtained in this work: microwave heating, reaction time of 1 min, using ionic liquids. ^bYield obtained in this work: microwave heating, reaction time of 20 min, using MeCN both as the Lewis base and solvent. ^cYield reported in the literature, using ionic liquids under conventional heating (CH) with reaction time of 7 min; NR: not reported in the literature.



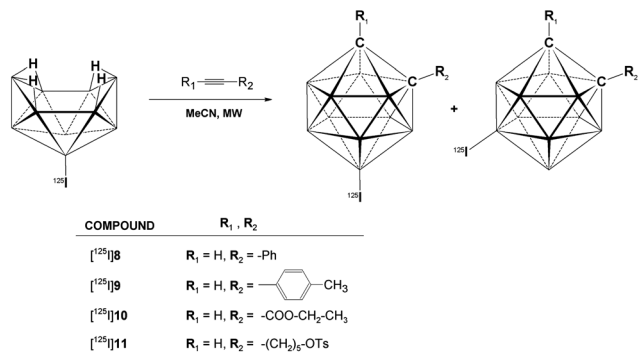


Fig. 3 Scheme of the reaction for the preparation of ¹²⁵I-labelled *o*-carborane derivatives using microwave (MW) heating and acetonitrile acting both as the solvent and as the Lewis base, under microwave heating. The same strategy was used for the preparation of ¹³¹I-labelled analogues.

Table 2 Preparation of ¹²⁵I-labelled *o*-carboranes using acetonitrile acting both as the solvent and as the Lewis base, under microwave heating

Compound	Alkyne	RCC (%)	RCY (%)
[¹²⁵ I]8	Phenylacetylene	69 ± 4	22 ± 3
[¹²⁵ I]9	4-Ethynyltoluene	89 ± 3	33 ± 2
[¹²⁵ I]10	Ethyl propiolate	84 ± 4	31 ± 3
[¹²⁵ I]11	6-Heptyn-1-yl <i>p</i> -toluenesulfonate	70 ± 5	36 ± 4

determined by radio-HPLC, were obtained (see Table 2). Subsequent purification using radio-HPLC yielded pure compounds with overall radio chemical yields (RCYs) of 22 ± 3%, 33 ± 2%, 31 ± 3% and 36 ± 4% for [¹²⁵I]8, [¹²⁵I]9, [¹²⁵I]10 and [¹²⁵I]11, respectively (Table 2). Compounds 8–11 were also prepared using ¹³¹I, with equivalent radiochemical conversion and yields. Identification of the labelled compounds was carried out by radio-HPLC and co-elution using reference standard compounds (Fig. S8–S11†).

It is worth mentioning that when the iodinated decaborane is used (both in radioactive and in non-radioactive conditions), the reaction with unsymmetrical acetylenes results in a mixture of two unavoidable positional isomers (see Fig. 3), with the iodine atom attached to the 9- and 12-positions. Separation of these isomers was out of the scope of this work, although it might be required for subsequent *in vivo* applications. This could be achieved, for example, using chiral HPLC. In addition, the values of specific activity should also be taken into consideration, as they may gain relevance when moving to *in vivo* studies. Because the labelling strategy relies on isotopic exchange and low amounts of radioactivity were used, the final specific activity values were estimated to be around 0.1 MBq μmol⁻¹, taking into account that 10 μCi (0.37 MBq) of radioiodine were used to label 1 mg of 1-iododecaborane. These values may be increased significantly by using higher amounts of radioactivity.

Experimental section

General

Decaborane was purchased from Katchem Ltd (Prague, Czech Republic); all other reagents (analytical grade purity) were purchased from Aldrich Chemical Co. and used without further purification. Dry solvents, stored over 4 Å molecular sieves, were also purchased from Aldrich Chemical Co. 6-Heptyn-1-yl *p*-toluenesulfonate was prepared following a previously described method.²¹ All reactions were carried out under a nitrogen atmosphere and followed by thin-layer chromatography carried out on silica gel 60 F₂₅₄ plates (Macherey-Nagel). Visualization was accomplished with a UV source (254, 365 nm) and by treatment with an acidic solution of 1% PdCl₂ in methanol. Carboranes were charred as black spots on TLC. Microwave reactions were conducted using a Biotage Initiator Exp Eu system, and a power of 400 W was used. All the reactions were performed in the vials specified by the manufacturer. Manual chromatography was performed with silica gel 60 (70–230 mesh) from Scharlau. ¹H, ¹¹B and ¹³C-NMR spectra were recorded on a 500 MHz Avance III Bruker spectrometer. To explain the multiplicities, the following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

Synthetic procedure for microwave assisted alkyne-insertion to decaborane in ionic liquid

In a clean and dry microwave vial, decaborane (1.636 mmol) and alkyne (5.235 mmol) were solved in biphasic toluene (8 ml)/bmimCl (0.818 mmol). The vial was purged with nitrogen, properly capped, and reacted under microwave heating (140 °C, 1 min). After cooling, the organic layer was withdrawn and the ionic liquid layer was extracted with ether (10 ml). The combined organic layer was evaporated and the crude reaction mixture was purified by silica gel column. The column was eluted with hexane (except for compound 4, which was eluted with 30% ethyl acetate in hexane), the product fractions were combined and the solvent was evaporated using a rotary evaporator.

Synthetic procedure for microwave assisted alkyne-insertion to decaborane in the absence of ionic liquid

In a clean and dry microwave vial, decaborane (1.636 mmol) and alkyne (5.235 mmol) were dissolved in acetonitrile (8 ml). The vial was purged with nitrogen gas, properly capped and reacted under microwave heating (120 °C, 20 min). After cooling, the solvent was evaporated and the residue was purified by silica gel column. The column was eluted with hexane (except for compound 4, which was eluted with 30% ethyl acetate in hexane), the product fractions were combined and the solvent was evaporated using a rotary evaporator.

Synthesis of 1-iododecaborane

A previously described procedure was used.¹⁹ Briefly: in a 100 ml SNRB flask, decaborane (5.00 g, 40.1 mmol) was dissolved in anhydrous dichloromethane (35 mL). Anhydrous



AlCl_3 (0.546 g, 4.03 mmol) was added, the mixture was cooled to 0 °C and a solution of ICl (2.08 mL, 41.5 mmol) in 20 mL of anhydrous dichloromethane was added dropwise. The dark brown reaction mixture was heated to reflux for 5 h. The reaction mixture was filtered and the solvent was evaporated to dryness. Recrystallization of the crude reaction mixture from hot heptane gave pure 2-iododecaborane. 1-Iododecaborane was isolated by recrystallization of mother liquor.

Synthetic procedure for microwave assisted alkyne-insertion to 1-iododecaborane

In a cleaned and dry microwave vial, 1-iododecaborane (1.636 mmol) and alkyne (5.235 mmol) were dissolved in acetonitrile (8 mL). The vial was purged with nitrogen gas, properly capped and reacted under microwave heating (120 °C, 60 min). After cooling, the solvent was evaporated and the residue was purified by silica gel column chromatography. The column was eluted with 4% ethyl acetate/hexane, the product fractions were combined and the solvent was evaporated using a rotary evaporator.

Synthesis of ^{125}I - and ^{131}I -labelled 1-iododecaborane

All the solvents were degassed for 10 minutes before use. 1 μL [^{125}I]NaI (solution in 0.1 M NaOH, Perkin Elmer) or [^{131}I]NaI (solution in 0.1 M NaOH, Perkin Elmer) and 200 μL of acetonitrile (Sigma-Aldrich) were introduced in a 2.5 mL vial. The vial was heated at 100 °C for 5 min under a constant helium flow to evaporate all the solvents. After complete evaporation, 1 mg of the precursor dissolved in 100 μL of toluene and 0.1 mg (0.101 μmol) of Herrmann's catalyst (*trans*-bis(acetato) bis[*o*-(di-*o*-tolylphosphino)benzyl] dipalladium(II), HC) dissolved in 100 μL of toluene were added. Reaction conditions were: $T = 100$ °C, and $t = 5$ min. After completion of the reaction, the solvent was removed by a constant helium flow and the radiochemical conversion was determined by radio-HPLC. Analytical conditions were: stationary phase: Mediterranea SEA18 column (15 \times 0.46 cm); mobile phase A: 0.1 M ammonium formate (AMF) buffer pH = 3.9, B: acetonitrile; flow rate = 1 mL min^{-1} . The following gradient was used: initial: A-80% & B-20%; 2 min: A-80% & B-20%; 12 min: A-20% & B-80%; 16 min: A-20% & B-80%; 17 min: A-80% & B-20%; 20 min: A-80% & B-20%. Injected volume was 20 μL .

Synthesis of ^{125}I - and ^{131}I -labelled *o*-carboranes

In a clean and dry microwave vial, ^{125}I - or ^{131}I -labelled 1-iododecaborane and alkyne (2 μL) were dissolved in acetonitrile (100 μL). The vial was purged with nitrogen, properly capped and reacted under microwave heating (120 °C, 60 min). After completion of the reaction, RCC was determined by radio-HPLC, using the same experimental conditions as explained above. For compound **11**, analytical conditions were: stationary phase: Mediterranea SEA18 column (25 \times 1.0 cm); mobile phase A: 0.1 M ammonium formate (AMF) buffer pH = 3.9, B: acetonitrile; flow rate = 5 mL min^{-1} ; the following gradient was used: initial: A-60% & B-40%; 6 min: A-60% & B-40%; 12 min: A-20% & B-80%; 24 min: A-20% & B-80%; 28 min: A-60% &

B-40%; 30 min: A-60% & B-40%. Identification of the desired products was achieved by co-elution using a reference standard.

Conclusions

In conclusion, a straightforward methodology for the preparation of ^{125}I - and ^{131}I -labelled 1-iododecaborane is reported for the first time. Subsequent reactions with alkynes using acetonitrile as the solvent under microwave heating results in the formation of the corresponding radiolabelled *o*-carborane derivatives through a one-pot, one-step reaction, with excellent yields in short reaction times. The experimental conditions might be directly translated to the preparation of radiolabelled carborane analogues using other radioisotopes of iodine such as ^{124}I or ^{123}I , which are more appropriate to conduct subsequent *in vivo* imaging studies. Hence, the combination of the methodologies developed herein may enable the preparation of a wide range of radioiodinated *o*-carborane derivatives, whose potential suitability as BNCT drug candidates might be easily investigated using non-invasive, *in vivo* imaging techniques such as PET and SPECT. The preparation of radiolabelled carborane-bearing biomolecules is currently being explored using the methodology reported here. Notably, the presence of a tosyl group in compound **11** may enable subsequent functionalization for the incorporation of biologically active moieties and achievement of more complex structures.

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Notes and references

- 1 G. L. Locher, *Am. J. Roentgenol. Radium Ther.*, 1936, **36**, 1.
- 2 R. F. Barfh, A. H. Soloway, R. G. Fairchild and R. M. Brugger, *Cancer*, 1992, **70**, 2995.
- 3 (a) T. L. Heying, J. W. Ager Jr., S. L. Clark, D. J. Mangold, H. L. Goldstein, M. Hillman, R. J. Polak and J. W. Szymanski, *Inorg. Chem.*, 1963, **2**, 1089; (b) M. M. Fein, J. Bobinski, N. Mayes, N. Schwartz and M. S. Cohen, *Inorg. Chem.*, 1963, **2**, 1111.
- 4 M. F. Hawthorne, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 950.
- 5 A. H. Soloway, W. Tjarks, B. A. Arnum, F. G. Rong, R. F. Barth, I. M. Codogni and J. G. Wilson, *Chem. Rev.*, 1998, **98**, 1515.
- 6 R. F. Barth, J. A. Coderre, M. G. H. Vicente and T. E. Blue, *Clin. Cancer Res.*, 2005, **11**, 3987.



- 7 (a) Y. H. Zhu, *J. Am. Chem. Soc.*, 2005, **127**, 9875; (b) G. Calabrese and E. J. Barbu, *Mater. Chem.*, 2008, **18**, 4864.
- 8 S. B. Kahl and R. A. Kasar, *J. Am. Chem. Soc.*, 1996, **118**, 1223.
- 9 C. Viñas, R. Benakki, F. Teixidor and J. Casabó, *Inorg. Chem.*, 1995, **34**, 3844.
- 10 R. Schaeffer, *J. Am. Chem. Soc.*, 1957, **79**, 1006.
- 11 Y. Li, P. J. Carroll and L. G. Sneddon, *Inorg. Chem.*, 2008, **47**, 9193.
- 12 A. Toppino, A. R. Genady, M. E. El-Zaria, J. Reeve, F. Mostofian, J. Kent and J. F. Valliant, *Inorg. Chem.*, 2013, **52**, 8743.
- 13 (a) G. B. Giovenzana, L. Lay, D. Monti, G. Palmisano and L. Panza, *Tetrahedron*, 1999, **55**, 14123; (b) H. Minegishi, T. Matsukawa and H. Nakamura, *ChemMedChem.*, 2013, **8**, 265; (c) R. Tiwari, A. Toppino, H. K. Agarwal, T. Huo, Y. Byun, J. Gallucci, S. Hasabelnaby, A. Khalil, A. Goudah, R. A. Baiocchi, M. V. Darby, R. F. Barth and W. Tjarks, *Inorg. Chem.*, 2012, **51**, 629.
- 14 K. B. Gona, V. Gómez-Vallejo, D. Padro and J. Llop, *Chem. Commun.*, 2013, **49**, 11491.
- 15 D. S. Wilbur, D. K. Hamlin, R. R. Srivastava and M. K. Chyan, *Nucl. Med. Biol.*, 2004, **31**, 523.
- 16 O. Lebeda, A. Orlova, V. Tolmachev, H. Lundqvist, J. Carlsson and S. Sjöberg, *Spec. Publ. – R. Soc. Chem.*, 2000, **253**, 148.
- 17 A. E. C. Green, L. E. Harrington and J. F. Valliant, *Can. J. Chem.*, 2008, **86**, 1063.
- 18 S. Ghirmai, J. Malmquist, H. Lundqvist, V. Tolmachev and S. Sjöberg, *J. Labelled Compd. Radiopharm.*, 2004, **47**, 557.
- 19 A. V. Safronov, Y. V. Sevryugina, S. S. Jalisatgi, R. D. Kennedy, C. L. Barnes and M. F. Hawthorne, *Inorg. Chem.*, 2012, **51**, 2629.
- 20 K. J. Winberg, G. Barberà, L. Eriksson, F. Teixidor, V. Tolmachev, C. Viñas and S. Sjöberg, *J. Organomet. Chem.*, 2003, **680**, 188.
- 21 F. F. Knapp, P. C. Srivastava, A. P. Callahan, E. B. Cunningham, G. W. Kabalka and K. A. R. Sastry, *J. Med. Chem.*, 1984, **27**, 57.

