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Large-scale synthesis of no-carrier-added [^{123}I]mIBG, using two different stannylated precursors

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The clinical advantages of no-carrier-added (n.c.a) radioiodinated meta-iodobenzylguanidine ([*I]mIBG) over its carrier-added (c.a.) analogue have previously been reported. A large-scale synthesis of n.c.a. [^{123}I]mIBG was therefore investigated in this study, using a slightly adapted literature method. Two *bis* (t-butyloxycarbonyl)-protected (*bis*-Boc) stannylated benzylguanidine precursors were prepared. The *bis*-Boc-trimethylstannyl precursor was used to optimize radioiodination conditions. *N*-chlorosuccinimide (NCS) was used as oxidant. An HPLC method was developed to monitor radioiodination and de-protection steps. Amounts of 200 g precursor and 2000 g NCS resulted in HPLC yields of Boc-protected radioiodinated compounds in excess of 90%. De-protection was carried out with trifluoroacetic acid at 110°C. A robust solid phase extraction method was developed to purify reaction mixtures. Radiochemical yields at radioactivity levels ranging between 1900 and 3280 MBq were 85 ± 2.2% (*n* = 4). A twice scaled up reaction at 5340 MBq gave a similar yield. Radiochemical purities were in excess of 98% and the specific activity estimated at approximately 1 TBq.µmol^{-1}. Yields obtained from an HPLC-purified *bis*-Boc-tributylstannyl precursor were generally lower and ranged from 61 to 81%. Results obtained in this study suggest that n.c.a [^{123}I]mIBG could be synthesized on a GBq scale.

Keywords: mIBG; 123I; no-carrier-added; stannylated; precursors

Introduction

The diagnostic and therapeutic applications of radioiodinated *meta*-iodobenzylguanidine (mIBG) in oncology and cardiology are well documented[1,2]. Currently, isotopic exchange is the radioiodination method of choice.[3–5] During the past 10–15 years the synthesis and applications of no-carrier-added (n.c.a.) [*I]mIBG,[3–9] as well as other 4-substituted mIBG analogues,[10,11] have also been described. It has been suggested that n.c.a. [*I]mIBG might have certain clinical advantages over its carrier-added (c.a.) analogue. In oncology, the n.c.a. product shows an apparent higher uptake in neuroblastoma[4] and pheochromocytoma[12] cells. Furthermore, the administration of high doses of cold mIBG during therapeutic applications of c.a. [^{131}I]mIBG might result in pharmacological side effects.[5] In radioimaging, n.c.a. [^{123}I]mIBG gives a significantly higher myocardial uptake associated with better contrast between the heart and neighbouring organs.[6] The nuclear medicine community could certainly benefit from the availability of n.c.a. [*I]mIBG, as its limited availability might be the reason for the lack in progress in larger-scale clinical research efforts.[9] This prompted us to investigate the synthesis of this product.

In South Africa, iThemba LABS is the sole producer of c.a. [^{123}I]mIBG. Owing to the location of this facility the product reaches distant users only 24 h post production. Consequently, activities supplied to all users are calibrated at 12:00 h following the production day. This necessitates a large-scale production with high yields in order to compensate for decay. Whereas radiolabelling yields for c.a. [^{123}I]mIBG via isotope exchange are generally consistently in excess of 90%, n.c.a. radioiodination yields are generally more variable. The radioiodination method of choice should therefore be selected very carefully. Various methods for the synthesis of n.c.a. [*I]mIBG have been documented using various labelling precursors such as 3-tributylstannyl-,[7] 3-trimethylstannyl,[8] 3-trimethylsilyl[3,4,6] and 3-bromobenzylguanidine[7,9] derivatives, as well as a polymer-supported 3-benzylguanidinium reagent.[5] More recently, the utilization of the fluorous labelling strategy, using a highly fluorinated tin precursor, was also described.[13] This method, however, makes use of relatively complicated precursor synthesis procedures as well as fairly expensive fluorous solid-phase extraction cartridges. A few methods also describe the use of protected guanidine precursors.[8,11] This approach appears to be very sensible as the sparing solubility of free guanidines in aprotic organic solvents could complicate the synthesis of lipophilic precursors. When selecting the most appropriate radioiodination method, issues such as the ease of preparation and stability of the precursor and the accomplishment of optimal radiochemical yields should all be considered.

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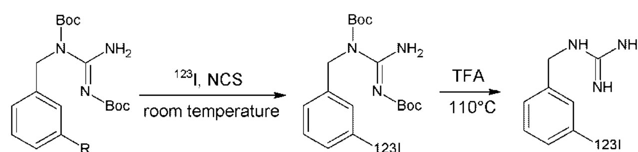
Halodesilylation reaction yields are generally lower than halodestannylation yields,[3,14] but silylated precursors are more stable than their stannylated counterparts. A *bis*(*t*-butyloxycarbonyl) (*bis*-Boc) protected trimethylstannylated benzylguanidine precursor, however, was claimed to be very stable at a low storage temperature.[8] We eventually decided upon the latter method in which a halo-destannylation procedure with a Boc-protected precursor, using various radioisotopes of iodine (excluding ^{123}I), as well as ^{211}At, had been successfully employed.[8] Since the maximum scale of radioiodination was only 37 Mbq, the primary goal of this study was to establish whether this method was adaptable for a larger-scale preparation of n.c.a. [^{123}I]mIBG. This necessitated an optimization of radioiodination conditions. In addition, we also synthesized and utilized a Boc-protected tributylstannyl precursor in order to compare radiochemical yields with those obtained from the protected trimethylstannyl analogue. High Performance Liquid chromatography (HPLC) methods were also developed to determine the chemical purities of precursors and to monitor the progress of radioiodination and de-protection steps. In an attempt to simplify the purification of crude reaction mixtures, we also developed and applied a solid phase extraction procedure, as opposed to the more conventional HPLC purification. The latter could be cumbersome and time-consuming, especially when handling large amounts of radioactivity.

Results and discussion

The intermediate *N, N′-bis*(*tert*-butyloxycarbonyl)-3-iodobenzylguanidine (*bis*-Boc-mIBG) was synthesized from 3-iodobenzyl alcohol using the Mitsunobu protocol, following a procedure that was reported for an analogous compound.[11] *N,N′-bis*(*tert*-butyloxycarbonyl)-3-trimethylstannylbenzylguanidine (*bis*-Boc-mTMSBG **1**) was synthesized and purified according to a slightly adapted literature method.[8] It was obtained in a yield of 43% with a chemical purity of about 94% as determined by HPLC Method A (see Table 1 for retention time (RT) data). The purified product contained a trace (less than 1%) of *bis*-Boc-mIBG. *Bis*-Boc-3-tributylstannylbenzylguanidine (*bis*-Boc-mTBSBG **2**) was synthesized according to conventional methods. Successive silica gel column chromatography yielded **2** with a chemical purity of about 92% as determined by HPLC (column B, Method C). Additional HPLC purification was required for optimal radioiodination yields (see later). Both precursors remained stable in methanol solutions kept at −10°C for periods exceeding two months.

The entire radiosynthesis sequence is shown in Scheme 1. Radioiodination conditions were based upon those described in literature,[8] using *N*-chlorosuccinimide (NCS) as oxidant. Reactions were performed at room temperature instead of 70°C in order to prevent the possible cleavage of the protecting groups during radioiodination. Precursor **1** was used to roughly optimize reaction conditions with regards to the precursor and NCS content. Reactions were monitored on HPLC (column A, Method B). The RT data in Table 1 show that two or three radioiodinated species were formed (RT = 30–35 min). One of these species (RT = 33.5 min) was only formed when precursor **2** was used (see discussion later). The relative intensities of the other two peaks followed a random distribution, the one having the longer RT always being predominant. They were assumed to be the mono- and *bis*-Boc-derivatives of [^{123}I]mIBG because treatment with trifluoroacetic acid (TFA) resulted in the disappearance of both species with the simultaneous formation of only one product ([^{123}I]mIBG).

Low and inconsistent HPLC radiochemical yields were obtained using 50–100 ug of precursor together with 100–300 ug of NCS (Table 2). Increasing the NCS content to 2000 ug, while maintaining the same levels of precursor, resulted in higher but still somewhat inconsistent yields. Increasing the precursor content to 200 ug resulted in consistently high HPLC yields at radioactivity levels up to nearly 3300 MBq. The HPLC yields were also backed up by good and consistent isolated yields (see later). These optimized conditions were also applied to the radioiodination of the tributylstannyl precursor **2**. Silica gel purified **2** resulted in the formation of a considerable amount of a radioiodinated impurity with RT = 33.5 min (Method B), leading to poor [^{123}I]mIBG radiochemical yields (see Table 3). The impurity was identified as Boc-*m*-[^{123}I]iodobenzylamine since TFA treatment of an HPLC-facilitated isolated fraction led to the formation of *m*-[^{123}I]iodobenzylamine (RT = 8.5 min). HPLC-purified precursor **2** did not generate the impurity, suggesting that the latter had resulted from the presence of a trace amount of its Boc-stannylated analogue in the silica gel purified precursor **2**.



Scheme 1. Radiosynthesis of n.c.a. [123I]mIBG from precursors bis-Boc-mTMSBG 1 (R = trimethylstannyl) or bis-Boc-mTBSBG 2 (R = tributylstannyl).

Table 1. Peak retention times and anticipated identities of various species in HPLC chromatograms

HPLC column	HPLC method	Retention time (min)	Anticipated species
A	A	17.0	*bis*-Boc-mIBG
		22.1	*bis*-Boc-mTMSBG
A	B	2.9	[^{123}I]iodide
		4.2	benzylguanidine
		8.5	m-[^{123}I]iodobenzylamine
		13.5	[^{123}I]mIBG
		30.5	mono-Boc-[^{123}I]mIBG
		33.5	Boc-m-[^{123}I]iodobenzylamine
		35.0	*bis*-Boc-[^{123}I]mIBG
B	C	16.5	*bis*-Boc-mTBSBG

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Table 2. Radiochemical yields (RCY) of Boc-[^{123}I]mIBG and [^{123}I]mIBG from *bis*-Boc-mTMSBG **1** as a function of precursor and *N*-chlorosuccinimide (NCS) quantities

Mass precursor (μg)	Mass NCS (μg)	Starting radioactivity (MBq)	HPLC RCY[a] (%)		Isolated RCY[b] (%)	
50	100	37–140	39 ± 4.2	(*n* = 2)	ND	
100	100	30–140	12 ± 11.1	(*n* = 3)	ND	
100	300	37–180	50 ± 28.2	(*n* = 3)	ND	
50	2000	115–130	87 ± 18.3	(*n* = 5)	ND	
50	2000	325–850	60 ± 37.9	(*n* = 3)	ND	
100	2000	484–2170	74 ± 22.9	(*n* = 4)	ND	
200	2000	1900–3280	98 ± 1.4	(*n* = 4)	85 ± 2.2	(*n* = 4)
200	2000	6530	90	(*n* = 1)	69	(*n* = 1)
400	4000	5340	99	(*n* = 1)	86	(*n* = 1)

[a]As assessed by analytical HPLC, sum of all Boc-[^{123}I]mIBG species in chromatogram expressed as percentage of total number of radiopeaks.
[b]Isolated yield of n.c.a. [^{123}I]mIBG after TFA de-protection and Sep-Pak purification, expressed as percentage of the starting activity (decay-corrected).ND = not determined.

Table 3. Radiochemical yields (RCY) of Boc-[^{123}I]mIBG and [^{123}I]mIBG from *bis*-Boc-mTBSBG **2**, using 200 μg precursor and 2000 μg *N*-chlorosuccinimide

Precursor purification method	Starting radioactivity (MBq)	HPLC RCY[a] (%)	Isolated RCY[b] (%)
Silica gel	122	27	ND
	2370	32	43
	2886	40	56
HPLC C18	2225	91	70
	2564	98	81
	3467	85	61

[a]As assessed by analytical HPLC, sum of all Boc-[^{123}I]mIBG species in chromatogram expressed as percentage of total number of radiopeaks.
[b]Isolated yield of n.c.a. [^{123}I]mIBG after TFA de-protection and Sep-Pak purification, expressed as percentage of the starting activity (decay-corrected). ND = not determined.

Boc-*m*-tributylstannylbenzylamine was probably formed as a by-product during the catalytic conversion of *bis*-Boc-mIBG to precursor **2** and is seemingly not easily separable from **2** via silica gel chromatography. Even at trace level concentration it generated a relatively large amount of its radioiodinated counterpart.

Reaction mixtures were treated with TFA at 110°C for 15 min in order to completely convert all Boc-species to [^{123}I]mIBG. The de-protection was monitored by means of HPLC (Method B). The retention time of [^{123}I]mIBG was in accordance with that of authentic mIBG. The progress of the de-protection step was also once monitored at room temperature, using precursor 1. Under this condition the radiochromatogram showed after 50 min a predominant peak at RT = 30.5 min (probably mono-Boc-[^{123}I]mIBG) and only a trace of a peak at RT = 35.0 min (probably *bis*-Boc-[^{123}I]mIBG). No [^{123}I]mIBG was detected. After heating the mixture, the [^{123}I]mIBG peak appeared at the expense of both of the formerly mentioned two. These observations suggest that the de-protection only occurs partially at room temperature and support the earlier assumptions made regarding the identities of the formed species.

TFA-treated reaction mixtures were purified on a C18 solid phase extraction cartridge (Sep-Pak). Reaction mixtures were treated with base prior to the Sep-Pak procedure in order to neutralize the organic acids and raise the pH to approximately 6.3. At a lower pH the product was sometimes partially eluted during the water wash step. Free radioiodide, the only major radioactive contaminant in TFA-treated reaction mixtures when using precursor **1**, was quantitatively eluted with water. N.c.a. [^{123}I]mIBG was eluted with a 0.1% H_3PO_4/absolute ethanol (75:25) mixture and was present in the second to fourth 1 ml eluted fraction, rendering 3 ml in total. The amount of activity retained by the Sep-Pak cartridge ranged between 3 and 5% of the starting activity. The use of this biologically compatible eluant eliminates the need for an evaporation step, as would have been the case if a toxic solvent such as methanol were used. It also minimises the possibility of the co-elution of non-polar impurities. The eluate could be readily converted into a pharmaceutically usable product by adding phosphate buffer for pH control, as well as saline solution to reduce the ethanol content.

Under optimized conditions, precursor **1** gave consistent Sep-Pak-isolated radiochemical yields, averaging 85% at radioactivity levels ranging from 1900 to 3280 MBq (see Table 2). When the activity level was doubled by increasing the volume of radio-iodide, without increasing the precursor mass, the yield dropped (Table 2, second last entry). A single two-fold scale-up of the whole reaction at an activity level of 5340 MBq gave a similar

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yield as before (Table 2, last entry). A semi-purified precursor **2** gave relatively poor isolated radiochemical yields (see Table 3 and discussion earlier). HPLC-purified **2** gave improved yields, albeit generally inferior to those given by precursor **1**. Radiochemical purities of all isolated products were in excess of 98%.

Sep-Pak purification also removed the major cold substances of the reaction mixture, as verified by means of HPLC UV analysis. The combined product-containing Sep-Pak fraction, obtained from a two-fold scaled-up reaction, was analysed for the presence of traces of NCS [Method B; 50 μl (60 MBq) injected]. This injection volume related to a theoretically maximum amount of 66 μg (500 nmol) of NCS, should all of the original 4000 μg NCS be present. When compared with the HPLC chromatogram of a NCS standard (RT = 3.1 min), less than the detection limit of about 5 nmol NCS/60 MBq could be detected. This suggests that most of the NCS, if not all, was removed during the water elution step. The harsh de-protection reaction conditions did not only lead to the complete removal of the Boc groups, but also resulted in the degradation of the precursor to the proton-destannylated derivative benzylguanidine. This was validated by treating *bis*-Boc-mTMSBG with TFA at 100°C and doing an HPLC analysis of a methanol solution of the TFA-evaporated residue (Method B, column A). A peak with the same RT as benzylguanidine was displayed. The latter had been synthesized from benzylamine hydrochloride and cyanamide according to the mIBG synthesis method of Wieland *et al.*[15] A semi-quantitative analysis suggested a near quantitative conversion of *bis*-Boc-mTMSBG to benzylguanidine. In order to demonstrate that the latter co-elutes with the other polar components during Sep-Pak purification, a radioiodination/de-protection/Sep-Pak procedure was simulated under cold conditions. The amount of benzylguanidine in each eluted fraction was determined by means of HPLC (Method B), using a benzylguanidine standard. Approximately 92% of the theoretically expected amount of benzylguanidine formed was present in the first 9 ml water eluate. No detectable traces of benzylguanidine were observed in the H_3PO_4/ethanol product fractions. Inductively Coupled Plasma (ICP) analysis of the latter showed the presence of trace amounts of tin (probably in the form of trimethylstannyl trifluoroacetate) up to a level of about 9 ppm. After dilution with buffer and saline, this figure should drop to about 3 ppm. At this level the product should probably be safe for clinical use, but this should nevertheless be confirmed by animal toxicity studies.

The specific activity (SA) was not directly determined, as the cold mIBG content of the product fractions was below the detection limit of the instrumentation. By quantifying the trace of *bis*-Boc-mIBG in the *bis*-Boc-mTMSBG precursor, using HPLC (Method A) and a *bis*-Boc-mIBG standard, and assuming that it would all be converted to mIBG upon TFA treatment, a SA value of approximately 1.0 TBq.μmol^{-1} was estimated. This estimate was based on the maximum radiochemical yield obtained directly after purification. The SA of the [^{123}I]iodine used was also in excess of 1 TBq.μmol^{-1}. It should be noted that in this particular case the SA of the [^{123}I]mIBG was limited by the purity of the precursor and that a higher SA should theoretically be possible, using a purer precursor.

Experimental

General

All reagents and chemicals were obtained from either Sigma-Aldrich or Fluka. Pharmaceutical grade water was used throughout. The ^{1}H NMR spectra were collected on a Varian ^{Unity}*Inova* 400 MHz NMR spectrometer. TMS was added as a reference standard to sample solutions. Tin analysis was done on a Jobin-Yvon Ultima Inductively Coupled Plasma spectrometer (ICP). Radioactivity measurements were carried out in a Vinten Isocal II Radionuclide Assay Calibrator. Sep-Pak C18 cartridges (500 mg C18, 3 cc) were obtained from Waters. Cartridges were conditioned by elution with 4 ml methanol, followed by 3 ml water. *N, N′-bis*(*tert*-butyloxycarbonyl)-3-iodobenzylguanidine (*bis*-Boc-mIBG) was synthesized from 3-iodobenzyl alcohol, similarly to a literature procedure[11].

HPLC analysis

HPLC was performed on an Agilent 1100 Series pump, equipped with a HP 1100 Series Control Module for binary gradient elution and a Rheodyne Model 7725 injector. The column outlet was connected to a Spectra Series UV100 detector, set at 254 nm, which was coupled in series with a Carroll&Ramsey Model 105S-1 CsI(Tl) radiation detector. A Phenomenex Luna C18 (250 × 4.6 mm, 5 μm) [column A] and a Phenomenex Synergi column C12 (150 × 4.6 mm, 4 μm) [column B] were used. Chromatograms were recorded on a dual channel Chromatopac C-R8A from Shimadzu. The following HPLC methods were used (all elutions were carried out at 1 ml/min):

HPLC Method A: Mobile phase: A (water), B (acetonitrile). 0–10 min: isocratic elution with 80% B; 10–20 min: linear gradient change to 100% B; 20–30 min: isocratic elution with 100% B.

HPLC Method B: Mobile phase: A (water/methanol = 60/40 (v/v), containing 1 g guanidinium carbonate and 1 ml acetic acid/litre of mixture), B (water), C (methanol). 0–17 min: isocratic elution with 100% A; 17–22 min: linear gradient change to 100% B; 22–27 min: linear gradient change to 30% B/70% C; 27–30 min: linear gradient change to 100% C; 30–40 min: isocratic elution with 100% C.

HPLC Method C: Mobile phase: A (water), B (acetonitrile). 0–3 min: isocratic elution with 75% B; 3–6 min: linear gradient change to 100% B; 6–25 min: isocratic elution with 100% B.

Chemistry

N, N′-bis(*tert-butyloxycarbonyl)-3-trimethylstannylbenzylguanidine* (bis-*Boc-mTMSBG)* ***1***

A mixture of *bis*-Boc-mIBG (57 mg; 0.12 mmol), hexamethylditin (92 mg; 0.28 mmol) and *bis*(triphenylphosphine)palladium dichloride (10 mg) in dry dioxane (5 ml) was heated and stirred in an oil bath at 100°C for 2 h. The reaction mixture was subsequently filtered, and the filtrate concentrated under reduced pressure with heating. The oily residue was dissolved in a small amount of ethyl acetate and the solution loaded onto a column filled with silica gel in hexanes. The column was eluted with approximately 45 ml hexanes, followed by 30 ml 10% (v/v) ethyl acetate in hexanes and finally 30 ml 20% (v/v) ethyl acetate in hexanes (6 × 5 ml fractions). The product-containing fractions from the latter eluate were combined and evaporated to dryness to yield 26 mg (43%) of an oily product: ^{1}H NMR ($CDCl_3$) δ: 0.27 (s, 9H), 1.35 (s, 9H), 1.49 (s, 9H), 5.17 (s, 2H), 7.18–7.42 (m, 4H), 9.45 (br s, 2H).

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N, N′-bis(tert-butyloxycarbonyl)-3-tributylstannylbenzylguanidine (bis-Boc-mTBSBG) **2**

Bis-Boc-mIBG (35 mg; 0.07 mmol) was dissolved in dry dioxane (2 ml). A stream of nitrogen was bubbled through the solution for 1 min, and tetrakis(triphenylphosphine)palladium (8 mg) and *bis*(tributyltin) (172 mg; 0.3 mmol) was added. The reaction vial was again flushed with nitrogen and the mixture was heated in an oil bath at 115°C for 3 h. The reaction mixture was subsequently concentrated under a stream of nitrogen with heating. The concentrated mixture was loaded onto a column filled with silica gel in hexanes. The column was eluted with approximately 35 ml hexanes, followed by 25 ml 10% (v/v) ethyl acetate in hexanes. The product-containing fractions from the latter eluate were combined and evaporated to dryness to yield 22 mg (47%) of an impure oily product. The latter was combined with a product from another batch (18 mg) and subjected to further silica gel purification, using 10% (v/v) ethyl acetate in petroleum ether, to obtain a semi-pure product: ^{1}H NMR ($CDCl_3$) δ: 0.86–0.9 (m, 9H, SnBu), 1.01–1.08 (m, 6H, SnBu), 1.26–1.36 (m, 15H, Boc, SnBu), 1.46–1.56 (m, 15H, Boc, SnBu), 5.17 (s, 2H), 7.2–7.45 (m, 4H), 9.45 (br s, 2H). Additional HPLC purification was carried out by injecting a solution of semi-pure **2** (500 μg) in methanol (50 μl) on column B and using Method C to elute the mixture. The product fraction (RT = 16.5 min) was collected and evaporated to dryness under a stream of nitrogen and slight heating. The residue (approximately 450–500 μg) was re-dissolved in methanol (50 μl).

Radiochemistry

No-carrier-added [^{123}I]iodine was locally produced by means of the ^{127}I(p,5n)^{123}Xe→^{123}I route, using a 66 MeV proton beam, and recovered in 0.01 M NaOH. The latter solution was reduced in volume approximately 10 times by means of evaporation, therefore effectively rendering a NaOH concentration of approximately 0.1M.

A solution of the respective precursor (50–200 μg) in methanol (20 μl) was added to glacial acetic acid (200 μl). A solution of ^{123}I in approximately 0.1M NaOH (50 μl) was added, followed by a solution of NCS (100–2000 μg) in glacial acetic acid (50 μl). When 100 μl ^{123}I was used, additional acetic acid (100 μl) was added. The mixture was stirred for 15 min at room temperature and then quenched with a solution of $Na_2S_2O_5$ (90–1800 μg) in water (45 μl). A small aliquot of the reaction mixture was withdrawn for routine HPLC analysis. Neat TFA (100 μl) was then added and the mixture stirred and heated in a sealed vial at 110°C for 15 min. Another small aliquot was taken for HPLC analysis, and the reaction mixture subsequently neutralized with 5 M NaOH (1.1 ml). The mixture was loaded onto a pre-conditioned Sep-Pak cartridge (500 mg C18) and passed through, using vacuum. The empty reaction vial was rinsed with water (4 ml), which was subsequently passed through the cartridge. The latter was eluted with a further 14 ml water, followed by a mixture of 0.1% H_3PO_4/absolute ethanol = 75:25 (v/v) (1 ml). The cartridge was subsequently eluted with a further four to five 1 ml portions of the same mixture. The activities in the individual fractions were counted and those in the product-containing fractions were expressed as percentages of the starting activity (decay-corrected). When the reaction was scaled up twice under optimized conditions, a two-fold increase of all chemical and radiochemical ingredients and solvents, including the quantity of water used for Sep-Pak elutions, was implemented. The quantity of eluant used to elute the product, however, was not adjusted accordingly.

Conclusion

The described optimized method for the production of n.c.a. [^{123}I]mIBG proved to be reliable and results appear to be reproducible. Radiochemical yields obtained from a Boc-protected trimethylstannyl precursor were generally higher than those obtained from its tributylstannyl counterpart. The described Sep-Pak purification process appears to be robust up to activity levels of at least 5.3 GBq. Certain features of the procedure such as the chemical degradation of the precursor and the selective elution of the degradation products from the Sep-Pak make a chromatographic separation of the radiolabelled product from its precursor unnecessary. The results of this study suggest that n.c.a [^{123}I]mIBG could be synthesized on a GBq scale, using a relatively simple purification procedure. This should enable medical scientists to embark on more extensive clinical trials.

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