the synthesis of [*I]MIBG via isotope exchange reaction has some distinct disadvantages. Firstly, by-products such as radiolabeled iodobenzylamine may be formed as impurities during the radioiodination.11 Secondly, due to the method of preparation the formulation contains a considerable amount of unlabeled cold MIBG, which may influence the pharmacokinetics of the radiolabeled form.2 Therefore, it would be advantageous to prepare [*I]MIBG containing virtually no cold MIBG. The first reported approaches to synthesize no-carrier-added [*I]MIBG relied on a tributylstannyl- or silyl-substituted precursor.13 In the latter case, radiochemical yields varied from 85–90% in addition to the formation of benzyl-, 3-chloro-, and 3-fluorobenzylguanidine as by-products. Recently, N,N′-bis((tert-butoxycarbonyl)-N-(3-trimethylstannyl)benzyl)guanidine prepared from the corresponding iodo derivative by Pd-catalyzed stannylation as (impure) oils in 43% and 57% yield, respectively, was used as precursor for iododestannylation.14,15

Our synthesis of [*I]MIBG is also based on iododestannylation of 3-(trimethylstannyl)benzylguanidine.14,15 Initially, the preparation of this precursor was tried in two steps by a literature procedure.16 First, 3-iodobenzylamine was treated with hexamethylditin and tetrakis(triphenylphosphine)palladium(0) to obtain the corresponding 3-(trimethylstannyl)benzylamine, which was described as a crystalline solid (mp 78 °C).16 However, it was found to be an oil (bp 98 °C/1 mmHg), which was also supported by literature.17 Furthermore, the yield of stannylation was unsatisfactorily low (25%). The second step was the conversion of the amine with cyanamide in the presence of a catalytic amount of HCl to the guanidine, which was claimed to be an oil. We repeated this transformation, but the result was inconclusive.

Therefore, it was decided to prepare the amine and the guanidine by a different approach (Scheme 1). Halogen-metal exchange in 3-iodobenzyl alcohol (1a) with t-BuLi (3.2 equiv) at −78 °C in anhydrous THF followed by 1.5 equivalents of Me3SnCl gave at best 23% of 3-(trimethylstannyl)benzyl alcohol (2). The yield could be increased to 69%, when t-BuLi was replaced by n-BuLi (3.2 equiv, 90 min, −78 °C, 1.5 equiv of Me3SnCl, THF). The yield was even better (93%), when 3-bromobenzyl alcohol (1b)
was used as the substrate (2.3 equiv of n-BuLi for halogen–lithium exchange at −78 °C in THF for 90 min, 2.1 equiv of Me3SnCl). This method was used previously for the preparation of 3-(tributylstannyl)benzyl alcohol.18

Scheme 1 Synthesis of precursor 6

The 3-(trimethylstannyl)benzyl alcohol (2) was converted into the azide17 by the Mitsunobu reaction in 82% yield and then reduced to the oily benzylamine 4 in 70% yield. The amine had been prepared earlier from (3-bromobenzyl)dimethylamine by Koldobsky et al. in three steps.17 The guanidinylation of 4 could have been effected, for example, by reaction with cyanamide,16 Mukaiyama’s reagent, and thioureas,20 or \(N,N′\)-bis(tert-butoxycarbonyl)-\(N′\)-triflylguanidine.21 None of this method was tried, as it had been found in the meantime that the Mitsunobu reaction of alcohol 2 with \(N,N′\)-bis(tert-butoxycarbonyl)guanidine could give a protected precursor in high yield, which could be purified by flash column chromatography. Alternatively, the benzyl alcohol could be transformed into the bromide, which is then reacted with the sodium salt of \(N,N′\)-bis(tert-butoxycarbonyl)guanidine.23 As the Mitsunobu reaction was our first choice, the protected guanidine was prepared first and the literature procedures were optimized (Scheme 2). Commercially available \(S\)-methylisothiourea hemisulfate was Boc-protected in 91% yield in the biphasic system NaHCO3/H2O/Boc2O/CH2Cl2. \(N\text{-}tert\text{-}Butoxycarbonyl\)methylisothiourea (8), formed as a side product (8%), could be removed easily by flash chromatography. Exchange of the methylthio group for amine with ammonia in methanol furnished the bis(Boc)-protected guanidine 9a in 95% yield.22 Interestingly, Feichtinger et al. reported that 9b was formed from guanidine and Boc2O under strong alkaline conditions in 59% yield.21 In the literature, structures19,22 9a and in one case22 9b are given for bis(Boc)-guanidine without providing evidence. To solve this ambiguity, a single crystal X-ray analysis was performed proving structure 9a for the solid state (Figure 1). We assume that this is also the structure of bis(Boc)-guanidine in solution.

Finally, 9a and 3-(trimethylstannyl)benzyl alcohol (2) were reacted in a Mitsunobu reaction with Ph3P/DIAD (diisopropyl azodicarboxylate) in anhydrous toluene to give the desired precursor 10, which was isolated by flash chromatography (87%) (Scheme 3).22 Satisfyingly, precursor 10 crystallized (from hexanes) to give colorless crystals. The same precursor had been prepared earlier as an oil by the reaction of 3-iodobenzyl bromide with the sodium salt of bis(Boc)-guanidine, followed by exchange of the iodine for trimethyltin using Pd(Ph3P)4/Me6Sn2 (57%).15 Iododestannylation and removal of protecting groups furnished the tracer.

When this work was finished, we found that the bis(Boc)-protected guanidine is commercially available. Thus, our synthesis comprises just two steps starting from 3-bromo-benzyl alcohol, which is also commercially available. As the precursor was described as an oil (chemical purity 94%) in the literature and ours was crystalline, and although the \(1\text{H} \) NMR spectra were virtually identical, we decided to perform a single crystal X-ray structure analysis (Figure 2). Satisfyingly, it proved the structure of com-

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Figure 1 Molecular structure of 9a with hydrogen bonds as dashed lines

Scheme 2 Improved synthesis of bis(Boc)-guanidine 9a

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Radioiodination of the precursor \( \text{N,N'-bis(Boc)-N-(3-trimethylstannylbenzyl)} \)guanidine (10) with no-carrier-added \([\text{I}^{123}]\)NaI and N-chlorosuccinimide (NCS) as an in situ oxidizing agent has been recently reported. Rossouw et al. described the use of 2000 \( \mu \)g of NCS as an oxidant – a 10-fold mass excess relative to precursor 10 – which appeared to us as nonoptimal. We argued that the large excess of NCS could interfere with the final purification of the tracer by HPLC or by using a solid phase cartridge. Therefore, it was decided to replace NCS with chloramine-T, also a well known oxidizing agent.\(^{25,26}\) The reaction of 200 \( \mu \)g of 10 dissolved in MeOH–AcOH with no-carrier-added \([\text{I}^{131}]\)NaI and only 60 \( \mu \)g of chloramine-T at room temperature resulted in the almost quantitative formation of the bis(Boc)-protected 3-[\text{I}^{131}]iodobenzylguanidine intermediate \([\text{I}^{131}]\)11. Here, the labeling reaction was monitored by radio TLC. Since the reaction mixture contained acetic acid, a slight removal of the Boc groups from \([\text{I}^{131}]\)11 was observed already during labeling. After deactivation of the oxidant with sodium metabisulfite, the complete removal of the protecting groups was performed with \( \text{CF}_3\text{CO}_2\text{H} \) at 110 °C for 10 minutes to give the crude \([\text{I}^{131}]\)MIBG ([\text{I}^{131}]12). After neutralization with NaOH, the labeled \([\text{I}^{131}]\)MIBG was purified by semi-preparative HPLC. Up to 98% of the starting radioactivity could be isolated as \([\text{I}^{131}]\)MIBG. A small amount of unreacted \([\text{I}^{131}]\)NaI was detected in the reaction mixture, but no significant quantities of by-products were found. The solvent was gently removed at 35 °C under reduced pressure from the pooled fractions containing \([\text{I}^{131}]\)MIBG. The dry residue was redissolved in phosphate-buffered saline–5% EtOH. To prevent decomposition by radiolysis 2,5-dihydroxybenzoic acid and benzyl alcohol were added as preservatives.\(^{27,28}\) \([\text{I}^{131}]\)MIBG was isolated with an overall radiochemical yield of 81 ± 3% (\( n = 4 \)).

The purity of \([\text{I}^{131}]\)MIBG was assessed with radio TLC and radio HPLC by comparison with an authentic nonradioactive reference sample. The amount of cold MIBG (2 \( \mu \)g) in a batch of \([\text{I}^{131}]\)MIBG, was determined by HPLC, resulting in a specific activity of >11 GBq/\( \mu \)mol. The radiochemical purity of the isolated \([\text{I}^{131}]\)MIBG was >99% and the final formulations remained stable for more than 20 hours.

In conclusion, we have developed a concise synthesis of a trimethylstannylated precursor, which allows a no-carrier-added labeling with radioidine to form \([\text{I}]\)MIBG. As a novel approach, the radiolabeling reaction was carried out successfully using chloramine-T as oxidant. It was shown that the \([\text{I}]\)MIBG could be obtained in high yield and purity under mild reaction conditions. The labeling process appears to be amenable for automation, which is applicable to all radioiodine isotopes and allows large scale routine production of \([\text{I}]\)MIBG for radiopharmaceutical use.
A mixture of \( ^{13} \text{C} \) NMR spectra (J modulated) were measured in CDCl\(_3\) at 300 K on a Bruker Avance DRX 400 spectrometer at 400.13 MHz and 100.63 MHz, respectively. Chemical shifts were referenced to residual CHCl\(_3\) (\( \delta = 7.24 \)) and CDCl\(_3\) (\( \delta = 77.00 \)). IR spectra were run on a PerkinElmer 1600 FT-IR spectrometer; liquid samples were measured as films on a silicon disc. Crystal structures were analyzed using a Bruker AXS APEX CCD diffractometer. TLC was carried out on a 0.25 mm thick Merck plates, silica gel 60M (230–400 mesh). Spots were visualized by UV and/or dipping the plate into a solution of \((\text{NH}_4)_6\text{Mo}_7\text{O}_{24} \cdot 4\text{H}_2\text{O} (23.0 \text{ g})\) and of \(\text{Ce} (\text{SO}_4) \cdot 4\text{H}_2\text{O} (1.0 \text{ g})\) in \(10\% \text{ aq H}_2\text{SO}_4 (500 \text{ mL})\), followed by heating with a heat gun. \(\text{S-Methylisothioureasulfate}\) was obtained from Aldrich. Melting points were determined on a Reichert Thermovar instrument and are uncorrected.

**Radiosynthesis**

No-carrier-added \[^{119}\text{Na}\] in 0.1 M \(\text{NaOH}\) was obtained from PerkinElmer (Boston, MA, USA). The radioactivity was measured in a Capintec CRC15 dose calibrator (Ramsey, NJ, USA). Analytical high-performance liquid chromatography (HPLC) analyses were performed on an Agilent 1200 system (Böblingen, Germany) equipped with a quaternary pump, autosampler, and a variable wavelength spectrophotometer, which was connected in series with a Raytest radioactivity detector (Straubenhardt, Germany). Data were collected by Raytest radio chromatography software. Radio-TLCs were evaluated using an electronic autoradiograph (Canberra-Packard, Watford, UK).

**3-(Trimethylstannyl)benzyl Alcohol (2)**

- **Synthesis**: A solution of \(\text{tert-butoxy carbonyl)-guanidine (9a)}\) was added dropwise to a solution of \(3\)-(trimethylstannyl)benzyl alcohol \(\text{(117/119Sn,C) = 35.9 Hz}\), \(128.2 \) [s, \(\delta = 171.40 (2\ C), 28.00 (6\ C), 14.79\).]
- **1H NMR (DMSO-d\(_6\))**: \(\delta = 10.28 (\text{br s, } 1\ H), 8.51 (\text{br s, } 2\ H), 1.41 (\text{s, } 18\ H).
- **13C NMR (DMSO-d\(_6\))**: \(\delta = 158.5 (2\ C), 158.2 (\text{br s, } 9.75 (2\ C), 27.8 (6\ C)).

The \(1\ H\) NMR spectrum was identical to that of literature; \(21\) no \(13\ C\) NMR and IR spectra were given.

**Crystal Structure**

Crystal data: \(\text{C}_{26}\text{H}_{28}\text{N}_{2}\text{O}_{4}\), \(\text{FW} = 259.31\), colorless prism of \(0.57 \times 0.28 \times 0.26 \text{ mm}\) from hexanes, \(T = 100(2)\ K\), triclinic, space group \(P\overline{1}\), \(a = 11.6836(5) \AA, b = 16.1253(6) \AA, c = 16.3857(6) \AA, \alpha = 88.442(2)^\circ, \beta = 84.200(2)^\circ, \gamma = 70.064(2)^\circ, V = 3489.15(19)\ \text{Å}^3, Z = 8 (Z' = 4), D = 1.193\ \text{g cm}^{-3}, \mu = 0.091\ \text{mm}^{-1}, I(\text{MoK\alpha}) = 0.71073\ \text{Å}. \) Of 68471 reflections measured, 16771 were unique. Refinement of \(F^2\) using the program SHELXTL concluded with \(R = 0.0664\) and \(wR = 0.1229\) for 689 parameters and all data. The structure contains four chemically identical but crystallographically different molecules assembled in bis-NH–N hydrogen bonded pairs.

**N,N'-Bis(tert-butoxycarbonyl)-N-(3-trimethylstannylbenzyl)guanidine (10)**

A solution of \(N,N'-\text{bis(tert-butoxycarbonyl)}\)-guanidine \(\text{(9a)}\) in \(\text{MeOH} (18\ mL, 11.7 \text{ g N}_3\) in \(70\ mL\) of anhyd \(\text{MeOH}\) was added to \(N,N'-\text{bis(tert-butoxycarbonyl)}\)-S-methylisothiourea \(\text{(7)}\) \(0.283\ g, 82\%\) as a colorless oil. The \(1H\) NMR spectrum was identical with that of literature; \(21\) no \(13\ C\) NMR and IR spectra were given.

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Anal. Calcld for C_{23}H_{35}N_3O_4Sn: C, 49.24; H, 6.89; N, 8.20. Found: C, 49.57; H, 6.99; N, 8.27.

Crystal Structure

Crystal data: C_{23}H_{35}N_3O_4Sn, FW = 512.21, colorless oval of 0.45 × 0.34 × 0.28 mm from DMF, T = 100(2) K, monoclinic, space group P2_1/c, a = 11.8026(7) Å, b = 12.7556(8) Å, c = 16.6750(10) Å, β = 102.388(1°), V = 2452(3) Å^3, Z = 4, D_{c} = 1.388 g cm^{-3}, μ(MoKα) = 0.71073 Å. Of 44175 reflections measured, 7150 were unique. Refinement of F^2 using the program SHELXTL concluded with R1 = 0.0252 and wR2 = 0.0626 for 271 parameters and all data.

3-[^{131}I]iodobenzylguanidine ([^{131}I]MIBG, [^{131}I]12)

The labeling was performed in a sealed conical vial. To a solution of 0.05 M phosphate-buffered saline (pH 4.5)–EtOH–benzylamine-T (20 \mu L), and [^{131}I]NaI (in 0.1 M NaOH, 6 \mu g, 0.39 \mu Ci) was added 2,5-dihydroxybenzoic acid (100 \mu g, 0.2 mg, 0.39 \mu Ci) to form the intermediate [^{131}I]1 (TLC: MeOH–2 M ammonia–1 M NH_4NO_3 (27:2:1); R_f = 0.54). The reaction mixture was adjusted to pH 4 with aq 2 M NaOH (600 \mu L) and the crude product was purified via HPLC (Prontosil C18-asc-EGS column, 5 \mu m, 10 × 250 mm, Bischoff; liquid phase: MeOH–2 M ammonia–1 M NH_4NO_3, 27:2:1; R_f = 0.77). The reaction was quenched with aq Na_2S_2O_3 (50 \mu L, 4 \mu g, 4 \mu Ci). Afterwards, CF_3CO_2H (100 \mu L) was added and the isolated fraction (44.6 \mu g, 45.9 MBq) was purified using the program SHELXTL concluded with R1 = 0.0252 and wR2 = 0.0626 for 271 parameters and all data.

Acknowledgment

This work was supported by Grant No. L420-N19 from the Austrian Science Fund (FWF). We thank S. Felsing for recording the NMR spectra.

References


(30) CCDC 873052 (9a) and 859313 (52) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.ac.uk/data_request/cif.
(31) PAPER Synthesis 2012, 44, 3387–3391