Preparation of Tributyl(iodomethyl)stannane

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Procedure (Note 1)

A. Tributyl(chloromethyl)stannane (1). An oven-dried 500-mL pear-shaped recovery flask equipped with a 34 x 16 mm, Teflon-coated, oval magnetic stir bar is charged with anhydrous THF (150 mL) (Note 2) and N,N-diisopropylamine (10.6 mL, 7.65 g, 75.6 mmol, 1.1 equiv) (Note 3) via a syringe. The flask is fitted with a rubber septum and a nitrogen inlet needle, after which the stir rate is set to ca. 375 rpm (Figure 1A). The reaction is cooled to 0–5 °C using an ice/water bath before the dropwise addition of n-BuLi (47.8 mL, 75.6 mmol, 1.1 equiv) (Note 4) via a 20 mL syringe over 25 min (Figure 1B). The resulting clear pale-yellow solution is stirred further at 0–5 °C for 30 min before tributyltin hydride (18.5 mL, 20.0 g, 68.7 mmol, 1.0 equiv) (Note 5) is added dropwise via syringe over 15 min (Figure 1C). The resulting clear yellow solution is stirred further at 0–5 °C for 30 min before paraformaldehyde (2.30 g, 76.6 mmol, 1.1 equiv) (Note 6) is weighed under air into a glass vial and charged in one portion to the reaction flask.
The ice/water bath is removed, and the turbid yellow suspension is stirred at 25–27 °C for 3 h during which a discoloration takes place affording a turbid pale-yellow reaction mixture (Figure 1D).

The resulting turbid reaction solution is cooled in a dry ice-acetone bath for 30 min before methanesulfonyl chloride (6.40 mL, 9.47 g, 82.7 mmol, 1.2 equiv) (Note 7) is added dropwise via a syringe over 10 min (Figure 1E). The cooling bath is removed, and the resulting pale-yellow suspension is stirred at 25–27 °C for 10 h (Note 8) (Figure 1F). At this point water (100 mL) is added in one portion using a graduated cylinder and the mixture is stirred further for 15 min.

The contents of the reaction flask are transferred to a 500-mL separatory funnel containing hexanes (150 mL). The aqueous layer is separated and extracted with hexanes (2 x 60 mL). The combined organic layers are washed with saturated NaCl solution (2 x 50 mL), dried over anhydrous MgSO₄ (12 g), and filtered through a 150-mL sintered glass Büchner funnel (medium porosity, 66 mm diameter). The MgSO₄ is washed with hexanes (3 x 10 mL) and the combined filtrate is concentrated by rotary evaporation (40 °C, 20 mmHg) to afford ca. 26 g of a pale-yellow oil (Notes 9 and 10). This material is diluted with hexanes (15 mL) and deposited onto a column (90 mm diameter) of 550 g of silica gel (16 cm high) (Note 11) prepared as a slurry in hexanes. Elution is carried out with hexanes collecting 50-mL fractions. The desired product is obtained in fractions 25–46 (Note 12).
Mixed fractions 20–24 are collected separately and concentrated by rotary evaporation (40 °C, 20 mmHg). The resulting colorless oil is diluted with hexanes (10 mL) and loaded onto a column (60 mm diameter) of 300 g of silica gel (8.5 cm high) (Note 11) prepared as a slurry in hexanes. Elution is carried out with hexanes collecting 30-mL fractions. The desired product is obtained in fractions 16–27. All fractions containing pure product according to TLC (Note 9) are combined and concentrated by rotary evaporation (40 °C, 20 mmHg). Further concentration at 23 °C under 0.1 mmHg for 2 h provides 15.8 g (68%) of chloromethyl stannane 1 as a colorless oil (Figure 1G) (Notes 13, 14, 15, and 16).

B. Tributyl(iodomethyl)stannane (2). An oven-dried 500-mL pear-shaped recovery flask equipped with a 34 x 16 mm, Teflon-coated, oval magnetic stir bar is charged with acetone (125 mL) (Note 17) via a graduated cylinder and tributyl(chloromethyl)stannane (1) (10.5 g, 30.9 mmol, 1.0 equiv) (Note 13) from step A via a syringe over 10 min. The flask is fitted with a rubber septum and nitrogen inlet needle, after which the stir rate is set to ca. 375 rpm. Sodium iodide (9.50 g, 63.4 mmol, 2.0 equiv) (Note 18) is weighed in air into a glass vial and added in one portion to the reaction flask (Figure 2A). The colorless suspension is stirred at 25–27 °C for 8 h during which the mixture turns pale yellow (Note 19) (Figure 2B).

![Figure 2. Color change through the course of the reaction](image)

The resulting suspension is concentrated by rotary evaporation (40 °C, 40 mmHg) to afford a colorless oil containing excess sodium iodide and formed sodium chloride precipitates (Figure 3).
The resulting mixture is suspended in hexanes (30 mL) and filtered over a 45 g silica gel plug (3 cm high) (Note 11) in a 150-mL sintered glass Büchner funnel (medium porosity, 66 mm diameter) rinsing with hexanes (8 x 50 mL). The colorless filtrate is concentrated on a rotavap (40 °C, 20 mmHg) and at 23 °C under 0.1 mmHg for 2 h to afford 12.3 g (92%) of iodomethyl stannane 2 as a colorless oil (Figure 3B) (Notes 16, 20, 21, and 22).

Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of “Prudent Practices in the Laboratory” (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical. See also “Identifying and Evaluating Hazards in Research Laboratories” (American Chemical Society, 2015) which is available via the associated website “Hazard Assessment in Research Laboratories” at
In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with, as well as the proper procedures for tetrahydrofuran, \(N,N\)-diisopropylamine, \(n\)-butyllithium, tributyltin hydride, paraformaldehyde, methanesulfonyl chloride, hexanes, magnesium sulfate, sodium chloride, silica gel, acetone, sodium iodide, and sodium chloride. Tributyltin hydride and other tributyltin derivatives are moderately toxic. Those reagents should only be handled by individuals trained in their proper and safe use.

2. Tetrahydrofuran (low water inhibitor free HPLC grade) was purchased from Sigma-Aldrich and purified by pressure filtration through activated alumina immediately prior to use.

3. \(N,N\)-Diisopropylamine (≥99.5%) was obtained from Sigma-Aldrich and distilled from calcium hydride at 83–86 °C (760 mmHg) prior to use.

4. \(n\)-Butyllithium (1.60 M in hexanes under AcroSeal) was purchased from Sigma-Aldrich and titrated prior to use. The concentration was determined to be 1.58 M according to the reported procedure from Watson, S. C.; Eastham, J. F. J. Organomet. Chem. 1967, 9, 165–168.

5. Tributyltin hydride (97% containing 0.05% BHT as stabilizer) was purchased from Sigma-Aldrich and used as received.

6. Paraformaldehyde (95%) was purchased from Sigma-Aldrich and used as received.

7. Methanesulfonyl chloride (98%) was purchased from Alfa Aesar and used as received.

8. The reaction progress was not monitored as the intermediate mesylate is rather unstable.

9. TLC analysis (hexanes with \(\text{KMnO}_4\) stain visualization): Hexabutyldistannane sideproduct (\(R_f = 0.87\)) and tributyl(chloromethyl)stannane (1) (\(R_f = 0.74\)). The tributyl(chloromethyl)stannane (1) is not visible using UV 254 nm as the visualization technique.

10. The \(\text{KMnO}_4\) stain was prepared using 1.5 g of \(\text{KMnO}_4\) and 10 g of \(\text{K}_2\text{CO}_3\) dissolved in 200 mL of water and 1.25 mL of 10% w/v NaOH solution.

11. High-purity silica gel grade (9385), pore size 60 Å, 230–400 mesh particle size purchased from Sigma-Aldrich.

12. Purification is followed using TLC analysis on Silica gel (hexanes with UV 254 nm and \(\text{KMnO}_4\) stain visualization): Hexabutyldistannane sideproduct (\(R_f = 0.87\)) and tributyl(chloromethyl)stannane (1) (\(R_f =
The tributyl(chloromethyl)stannane (1) is not visible using UV 254 nm as the visualization technique.

Some fractions contain minor amounts of Bu₃SnOSnBu₃ and Bu₃SnH as impurities; see TLC in Note 12. The second column is not necessary for synthetic purposes as the impurity (ca. 5%) does not affect the follow-up reaction and only slightly diminishes (≤ 5% difference) the yield in following alkylation steps. The second purification was done to meet the purity standards on the publication and improve the yield of pure material.

13. Tributyl(chloromethyl)stannane (1) was prepared according to a modified procedure of Seitz et al.²

14. A second reaction on the same scale provided 16.2 g (69%) of the identical product. Tributyl(chloromethyl)stannane (1) decomposes over time when stored neat at ambient temperature. This reagent should be stored as a degassed 1 M solution in hexanes at –10 °C and used within the next few days for best results. The purification of the reaction crude after 7-10 days at –28 °C, provided 8.40 g (36% yield) of the compound 1.

15. Tributyl(chloromethyl)stannane (1) has the following physical and spectroscopic properties: Rf = 0.74 (hexanes; KMnO₄ visualization; Merck Millipore TLC Silica gel 60 F254 plates); ¹H NMR (CDCl₃, 400 MHz) δ: 0.90 (t, J = 7.3 Hz, 9H), 0.97–1.01 (m, 6H), 1.32 (dq, J = 14.3, 7.2 Hz, 6H), 1.49–1.57 (m, 6H), 3.06 (t, J(¹¹⁷/¹¹⁹Sn-¹H) = 16.1 Hz, 2H); ¹³C NMR (CDCl₃, 101 MHz) δ: 9.6, 13.8, 24.5, 27.4, 29.0; HRMS (EI) calculated for C₁₂H₂₇Sn [M – CH₂Cl]⁺ 291.1129, found 291.1132 and calculated for C₉H₂₀ClSn [M – C₄H₉]⁺ 283.0270, found 283.0264; IR (film): 3015, 2969, 2654, 2926, 1738, 1456, 1365, 1228, 1216, 1206, 876, 692, 664, 527, 515 cm⁻¹; Purity of the product was not assessed due to the instability of the product, which was quickly taken on to the second step.
16. $^1$H NMR chemical shifts are expressed in parts per million ($\delta$) downfield from tetramethylsilane (with the CHCl$_3$ peak at 7.26 ppm used as a standard). $^{13}$C NMR chemical shifts are expressed in parts per million ($\delta$) downfield from tetramethylsilane (with the central peak of CHCl$_3$ at 77.00 ppm used as a standard) and $^{117}/^{119}$Sn–$^{13}$C couplings are not reported.

17. Acetone (≥99.5% analytical reagent grade) was purchased from Fisher Scientific and used as received.

18. Sodium iodide (puriss. p. a. ≥99.0%) was purchased from Sigma-Aldrich and used as received.

19. The progress of the reaction was not monitored.

20. Tributyl(iodomethyl)stannane (2) was prepared according to a modified procedure of Seitz et al.$^2$

21. A second run on the same scale provided 12.6 g (95%) of the identical product. Tributyl(iodomethyl)stannane (2) decomposes over time when stored neat at ambient temperature. This reagent should be stored as a degassed 1 M solution in hexanes at −10 °C and used within a few days for best results.

22. Tributyl(iodomethyl)stannane (2) has the following physical and spectroscopic properties: $R_f = 0.76$ (hexanes; KMnO$_4$ visualization; Merck Millipore TLC Silica gel 60 F254 plates); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$: 0.90 (t, $J = 7.3$ Hz, 9H), 0.96–1.00 (m, 6H), 1.32 (dq, $J = 14.2$, 7.2 Hz, 6H), 1.49–1.57 (m, 6H), 1.94 (t, $J^{117/119}$Sn-1H) = 18.0 Hz, 2H); $^{13}$C NMR (CDCl$_3$, 101 MHz) $\delta$: 10.8, 13.8, 27.4, 29.0; HRMS (EI) calculated for C$_{12}$H$_{27}$Sn [M–CH$_2$I]$^+$ 291.11292, found 291.11326 and calculated for C$_9$H$_{20}$Sn [M–C$_4$H$_9$] $^+$ 374.96262, found 374.96257; IR (film): 2954, 2924, 2871, 2848, 1739, 1456, 1375, 1365, 1228, 1217, 875, 692, 664, 588, 515, 456 cm$^{-1}$; Purity was assessed as >95% via Q NMR using 4′-nitroacetophenone as the internal standard.

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The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in
the Laboratory” (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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Discussion

The development of transition metal-catalyzed cross-coupling reactions has greatly influenced the manner in which the synthesis of complex organic molecules is approached. A wide variety of methods are now available for the formation of C(sp2)–C(sp2) bonds, and more recent work has focused on the use of C(sp3) electrophiles and nucleophiles. Access to functionalized aliphatic building blocks for such potential cross-coupling efforts are sought after, and organotin reagents remain one of the best approaches. While their applications have been hampered by challenges in removing organotin residues from the final products, organotin reagents often allow for mild processes tolerating a wide variety of functional groups. Their popularity is also due to their air- and moisture-stable nature, and their wide-availability.
Tributyl(iodomethyl)stannane (2) has been used as an electrophile in the preparation of $\alpha$-heteroalkylstannanes nucleophiles such as $\alpha$-tributylstannylmethyl ethers, amines, or sulfides as in SnAP reagents for the preparation of functionalized, unprotected N-heterocycles (Scheme 1).\textsuperscript{10,11}

Scheme 1. Preparation of an $\alpha$-tributylstannanemethyl ether and its application in the synthesis of a functionalized morpholines.

Tributyl(iodomethyl)stannane (2) is also a useful reagent for the preparation of precursors that generate more reactive nucleophiles, via tin-lithium exchange, used in $\mathrm{[2,3]}$-sigmatropic Wittig rearrangements or react further with other electrophiles such as ketones (Scheme 2).\textsuperscript{8,12}

Scheme 2. $\mathrm{[2,3]}$-Sigmatropic Wittig rearrangement

Therefore, tributyl(iodomethyl)stannane (2) allows for the facile access of various air- and moisture-stable C(sp3) nucleophiles ready for further transformations.
References

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Appendix

Chemical Abstracts Nomenclature (Registry Number)

\(N,N\)-Diisopropylamine: \(N\)-(Propan-2-yl)propan-2-amine; (108-18-9)
\(n\)-BuLi: \(n\)-Butyllithium; (109-72-8)
Tributyltin hydride: Tributylstannane; (688-73-3)
Paraformaldehyde: Polyoxymethylene; (30525-89-4)
Methanesulfonyl chloride; (124-63-0)
Sodium iodide; (7681-82-5)

Michael U. Luescher was born in 1985 in Switzerland and was trained as a medicinal chemistry laboratory technician at the Novartis Pharma AG (Switzerland). He then moved on to earn a BSc and MSc degree in chemistry in 2010 and 2012 from the University of Basel under the supervision of Professor Karl Gademann. Afterwards, he joined Professor Jeffrey W. Bode at ETH Zurich (Switzerland) investigating SnAP reagents where he received his Ph.D. in 2017. He is currently a post-doctoral fellow in the laboratory of Professor Emily Balaskus at Harvard University.

Chalupat Jindakun received his BSc and MSc in Organic Chemistry from Mahidol University in Bangkok (Thailand). In 2016, he received a Royal Thai Government Scholarship to pursue his doctoral studies in organic chemistry under the guidance of Professor Jeffrey W. Bode at ETH Zurich (Switzerland) where he is currently investigating SnAP reagents for the preparation functionalized, of NH-free N-heterocycles.
Jeffrey W. Bode studied at Trinity University in San Antonio, TX (USA). Following doctoral studies at the California Institute of Technology (USA) and ETH Zurich and postdoctoral research at the Tokyo Institute of Technology (Japan), he began his independent academic career at UC Santa Barbara (USA) in 2003. He moved to the University of Pennsylvania as an Associate Professor in 2007 and to ETH Zurich as a Full Professor in 2010. Since 2013, he is also a Principal Investigator and Visiting Professor at the Institute of Transformative Biomolecules (WPI-ITbM) at Nagoya University (Japan).

Rahul Mondal completed his master’s degree in chemistry in 2016 at the Indian Institute of Technology Kanpur. He then joined Prof. D. Maiti’s group at the Indian Institute Technology Bombay to work as Research Assistant. In August 2017, he started his PhD studies in Prof. Cristina Nevado’s group at the University of Zurich.

Estíbaliz Merino obtained her Ph.D. degree from the Autónoma University (Madrid-Spain). After a postdoctoral stay with Prof. Magnus Rueping at Goethe University Frankfurt and RWTH-Aachen University in Germany, she worked with Prof. Avelino Corma in Instituto de Tecnología Química-CSIC (Valencia) and Prof. Félix Sánchez in Instituto de Química Orgánica General-CSIC (Madrid) in Spain. At present, she is research associate in Prof. Cristina Nevado’s group in University of Zürich. She is interested in the synthesis of natural products using catalytic tools and in the development of new materials with application in heterogeneous catalysis.
\( \text{Bu}_3\text{SnI} + \text{MeOC}_6\text{H}_4\text{NO}_2 \)

Int = Average of normalized integrals values
MW = Molecular weight
P = Purity (as percent value)
m = mass
n = number of protons giving rise to a given NMR signal (The total number of protons is set to one because an average of all normalized integrals is carried out)

\[
\begin{align*}
n_{\text{IS}} &= 1 \\
\text{Int}_{\text{IS}} &= 1.021 \\
\text{MW}_{\text{IS}} &= 165.15 \text{ g/mol} \\
m_{\text{IS}} &= 8.26 \text{ mg} \\
P_{\text{IS}} &= 98 \%
\end{align*}
\]

\[
\begin{align*}
n_2 &= 1 \\
\text{Int}_2 &= 1.066 \\
\text{MW}_2 &= 432.03 \text{ g/mol} \\
m_2 &= 23.02 \text{ mg}
\end{align*}
\]

\[
P \text{ [%]} = \frac{n_{\text{IS}} \cdot \text{Int}_2 \cdot \text{MW}_2 \cdot m_{\text{IS}}}{n_2 \cdot \text{Int}_{\text{IS}} \cdot \text{MW}_{\text{IS}} \cdot m_2} \cdot P_{\text{IS}} = 96 \%
\]