Preparation of 1-Hydrosilatrane, and Its Use in the Highly Practical Synthesis of Secondary and Tertiary Amines from Aldehydes and Ketones via Direct Reductive Amination

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Procedure (Note 1)

A. 1-Hydrosilatrane (2). A 1-L, three-necked (24/40 joints), round-bottomed flask containing a 5.0 cm x 0.5 cm Teflon-coated magnetic stir bar, is fitted with a reflux condenser. A rubber septum is attached to the top of the reflux condenser with a nitrogen inlet and an outlet needle, and a 24/40 glass stopper is attached to the side necks of the 1-L round-bottomed flask. The entire apparatus is flame-dried and, after removing the outlet needle, is allowed to cool to 23 °C under a flow of N₂. The glass stoppers are switched to rubber septa at this stage. The round-bottomed flask is charged in one portion with boratrane (6.28 g, 40 mmol, 1.0 equiv) (Note 2) through the side...
neck under a nitrogen flow. Then, using a 500-mL graduated cylinder, xylene (400 mL) (Note 2) is added in one portion through the side neck. Then, using a 20-mL plastic syringe, triethoxysilane (11.1 mL, 60 mmol, 1.5 equiv) (Notes 2 and 3) is added in one portion through the septum. Finally, aluminum ethoxide (0.12 g, 0.76 mmol, 0.019 equiv) (Note 2) is added in one portion through the side neck. The aluminum ethoxide turns into a black suspension, but the reaction mixture homogenizes within an hour. Cold water is run through the condenser and the apparatus is lowered into a silicone oil bath (Note 4) pre-heated to 177 °C on a hot plate equipped with a temperature probe (Figure 1).

![Figure 1. Reaction set-up (provided by checker)](image)

The reaction mixture is stirred over 4 h under reflux while maintaining the oil bath at 177 °C. The clear, colorless reaction mixture is removed from the oil to cool to 23 °C under nitrogen (Figure 2), followed shortly by crashing out of the product (Figure 3).
The round-bottomed flask, disassembled from the condenser, is cooled in an ice/water bath for an additional 15 min, followed by vacuum filtration using a Büchner funnel, a 1-L filter flask, and a 185-mm diameter Whatman filter paper. An additional 40 mL of cold (0 °C) xylenes is used to transfer residual product from the round-bottomed flask and to rinse the filter cake. White, fibrous solid remains and is dried on the funnel under vacuum for an additional 10 min (Figure 4).
The solid is transferred to a 100-mL, single-necked, round-bottomed flask (24/40 joint) containing a 2.5 cm x 0.6 cm rod-shaped stir bar. CH$_2$Cl$_2$ (60 mL) (Note 5) is added using a 100-mL graduated cylinder and the content is stirred for 5 min (Figure 5). The entire suspension is passed through a celite plug (Note 6) with the aid of air pressure and collected in a 250-mL, single-necked (24/40 joint), round-bottomed flask. The clear, colorless eluent is concentrated on a rotary evaporator (Note 7) for 30 min to remove the solvent to yield a fine, white, crystalline powder. Before use, the product is dried overnight under high vacuum (0.30 mmHg) for 12 h to yield 1-hydrosilatrane (2) (Figure 6) (5.20 g, 74% yield, >99.5% purity) (Note 8 and 9).

Figure 5. After dissolving in CH$_2$Cl$_2$ (provided by checker)

Figure 6. Final product (2)

B. N-(4-Methylbenzyl)aniline (4). A 50-mL, single-necked, round-bottomed flask (24/40 joint) containing a 1.2 cm x 0.8 cm egg-shaped stir bar is charged sequentially and in one portion with p-tolualdehyde (1.6 mL, 13.6 mmol, 1.0 equiv) (Note 10) and aniline (1.5 mL, 16.4 mmol, 1.2 equiv) (Note 10) using a 3-mL plastic syringe through the septum with a vent needle, resulting in a cloudy, opaque solution (Figure 7A). Following this, acetic acid (14 mL) (Note 10) is added over 15 sec via a 20-mL plastic syringe through the septum, resulting in a homogenous bright-yellow solution (Figure 7B). The reaction mixture is stirred and then 1-hydrosilatrane (4.80 g, 27.4 mmol,
2.0 equiv) (2) (Note 10) is added in one portion through the neck. The resulting opaque reaction mixture homogenizes as more silatrane dissolves (Figure 7C). After removing the vent needle, the reaction mixture is stirred over 3 h at 23 °C under ambient atmosphere.

The reaction mixture, now a pale-yellow solution (Figure 7D), is transferred to a 500-mL separatory funnel and diluted with CH₂Cl₂ (140 mL). (Note 5). Aqueous NaOH (1 M, 300 mL) (Note 11), which is added to the separatory funnel in 50 mL portions to minimize an exotherm, is used to wash the solution through inversion of the separatory funnel, with frequent venting (Figure 8) (Note 12). The organic layer is collected, and the aqueous layer is then extracted with CH₂Cl₂ (2 x 140 mL). The combined organic layer is washed with H₂O (100 mL) and dried over MgSO₄ (4 g) (Note 13) for 5 min with occasional swirling by hand and then filtered by gravity, using a plastic funnel and a 185-mm diameter Whatman filter paper, into a 1-L, single-necked, round-bottomed flask (24/40 joint).
Removal of the solvent by rotary evaporation is performed until the volume is small enough to transfer to a 100-mL single-necked, round-bottomed flask (24/40) (Note 14). After transferring the pale-yellow liquid to 100-mL single-necked, round-bottomed flask, an additional 10 mL of CH₂Cl₂ is used to transfer residual product from the 1-L round-bottomed flask. Final removal of the solvent by rotary evaporation (Note 15) yields a pale-yellow liquid (Figure 9), which is then placed in an oil bath preheated to 60 °C and further dried under high vacuum (0.30 mmHg) for 12 h. After cooling to 23 °C, the resulting solid (Figure 10) is washed with cold (0 °C) petroleum ether (1 mL) and, after the liquid is removed by trituration, is dried under high vacuum for 12 h (0.30 mmHg) (Note 16). The solid product is heated to 50 °C on a water bath until melted (~5 mins) and then cooled to 23 °C while under high vacuum (0.30 mmHg) overnight to yield the product N-(4-methylbenzyl)aniline (4) as a pale-brown crystalline solid (Figure 11) (2.22 g, 83% yield, 98.9% purity) (Notes 17 and 18).
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 https://www.acs.org/content/acs/en/about/governance/committees/chemicalsafety/hazard-assessment.html. 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 boratrane, triethoxysilane, xylenes, aluminum ethoxide, p-tolualdehyde, aniline, acetic acid, 1 M NaOH, and dichloromethane. Appropriate care must be taken when performing reactions at high temperatures. Triethoxysilane, in particular, must be handled in a fume hood.

2. Boratrane (97%) was obtained from Sigma-Aldrich. It can also be synthesized according to published procedure. Triethoxysilane (96%) was obtained from Alfa Aesar. Aluminum ethoxide (97%) was obtained from Sigma-Aldrich. All chemicals were used as received.

3. An excess of triethoxysilane was used to ensure full conversion and faster reaction time. Using less than 1.5 equivalents may result in incomplete conversion and slower reaction time.

4. Silicone oil bath was purchased from Alfa Aesar. Alternatively, a heating mantle works equally well for this protocol.

5. Dichloromethane (Reagent grade) was purchased from ACP chemicals and used as received.

6. A column was packed with glass wool and sand. Celite was added on top of the sand layer (1 inch). Glass wool was purchased from Thermo Scientific. Sand was purchased from Fisher Chemical. Celite was purchased from ACP chemicals.

7. The following rotary evaporator settings were used: 500 mmHg, 40 °C water bath, for 15 minutes. Then 40 mmHg, 40 °C water bath for 15 min.

8. Characterization data for compound (2): mp 250–256 °C; 1H NMR (700 MHz, CDCl3) δ: 2.87 (t, J = 5.9 Hz, 6H), 3.79 (t, J = 6.0 Hz, 6H), 3.88 (s, 1H); 13C NMR (176 MHz, CDCl3) δ: 51.0 (s), 57.1 (s); 29Si NMR (119 MHz, CDCl3) δ: −83.1 (s); FTIR (powder): 2974, 2934, 2885, 2085, 1860, 1456, 1348, 1268, 1166, 1082, 1019, 930, 910, 862, 752 cm⁻¹. The product is air- and moisture-stable and can be stored under air for several months. The purity of the product was determined by qNMR by dissolving 18.8 mg of pyraine (>99%, purchased from Sigma-Aldrich and used as
received) and 40.8 mg of compound (2) in 0.9 mL CDCl₃. The purity was determined to be >99.5%.

9. A second reaction on the same scale afforded the product (2) with 73% yield and 98.5% purity.

10. p-Tolualdehyde was purchased from Sigma-Aldrich (97%), aniline was purchased from Alfa Aesar (99+%), glacial acetic acid (ACS reagent grade) was purchased from ACP chemicals. All chemicals were used as received.

11. 1 M NaOH was made using NaOH pellets purchased from EMPLURA and used as received. A single washing of the organic solvent was performed using all 300 mL of aq NaOH, but the NaOH solution was added 50 mL portions to minimize exotherm concerns.

12. A white insoluble suspension formed as the additional volume of aq. NaOH increased. The solution became clear after the addition of 300 mL NaOH.

13. MgSO₄ was purchased from Alfa Aesar (powder, anhydrous, 99.5%).

14. The following rotary evaporator settings were used: 520 mmHg, 40 °C.

15. The following rotary evaporator settings were used: 412 mmHg, 50 °C water bath for 20 min.

16. Petroleum ether was purchased from Sigma-Aldrich (ACS grade) and used as received.

17. Characterization data for compound (4): mp 42–45 °C; ¹H NMR (700 MHz, CDCl₃) δ: 2.38 (s, 3H), 3.96 (br, 1H), 4.29 (s, 2H), 6.65 (d, J = 7.9 Hz, 2H), 6.74 (t, J = 7.3 Hz, 1H), 7.22–7.15 (m, 4H), 7.28 (d, J = 7.8 Hz, 2H); ¹³C NMR (176 MHz, CDCl₃): 21.2, 48.2, 112.9, 117.6, 127.7, 129.4, 129.4, 136.5, 137.0, 148.3; FTIR (neat): 3417, 3015, 2914, 1600, 1510, 1438, 1323, 1269, 1178, 1097, 1042, 983. HRMS: (ESI) calc’d for C₁₄H₁₆N [M + H]⁺: 198.1277. Found: 198.1278. The product is stable and can be stored under air for several months. The purity of the product was determined by qNMR by dissolving 13.9 mg of pyrazine (>99%, purchased from Sigma-Aldrich and used as received) and 32.0 mg of compound (4) in 0.9 mL CDCl₃. The purity was determined to be 98.9%. Based on this % purity determination, the mass of product is 2.19 g (82%).

18. A second reaction on the half-scale afforded the product (4) with 90% yield and >99.5% purity.
Working with Hazardous Chemicals

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.

In some articles in Organic Syntheses, chemical-specific hazards are highlighted in red “Caution Notes” within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in Organic Syntheses are provided as published and are conducted at one's own risk. Organic Syntheses, Inc., its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

Discussion

The synthesis of amines is highly desired for their wide range of applications from pharmaceuticals to fine chemicals. By far the most practical method to prepare amines is through direct reduction amination (DRA), which involves reacting an amine with an aldehyde/ketone to generate an imine or an iminium, which is then reduced to the corresponding amine. The most common reducing agents used are NaBH₃CN and NaBH(OAc)₃ due to their widespread availability and the mild reaction
conditions required.\textsuperscript{5,6} However, there are certain drawbacks associated with their usage: NaBH\textsubscript{3}CN is toxic and forms toxic by-products upon workup, NaBH(OAc)\textsubscript{3} is not compatible with some aromatic ketones or amines.\textsuperscript{6,7}

Organosilanes can be used as alternatives to borohydrides as reducing agents for DRA reactions.\textsuperscript{8} Polymethylhydrosiloxane (PMHS) has been shown to carry out these reactions and presents certain advantages over the borohydride reducing agents mentioned such as its non-toxicity, low price, and inertness in the presence of an activator.\textsuperscript{9} However, they require activating catalysts, such as TFA, Bu\textsubscript{2}SnCl, or InCl\textsubscript{3} to promote reduction.\textsuperscript{10,11,12} The use of these catalysts introduces issues such as incompatibility with acid-labile functional groups, toxicity, and cost, which are undesirable.

Our lab recently demonstrated a DRA method using aldehydes and ketones to access secondary and tertiary amines using 1-hydrosilatrane (2) as the reducing agent.\textsuperscript{13} (We have also used hydrosilatrane to carry out reduction of aryl aldehydes to alcohols,\textsuperscript{2} reduction of ketones to alcohols,\textsuperscript{14} and reductive acetylation of aldehydes;\textsuperscript{15} we have also published asymmetric versions of the ketone reduction\textsuperscript{16} to secondary alcohols and the DRA\textsuperscript{17} of ketones.) Hydrosilatrane is easily prepared and is air- and moisture-stable making it easy to handle. The preparation of secondary amines requires AcOH as the solvent while tertiary amines can be accessed under neat conditions. This method is applicable to alkyl- and aryl- amines and shows broad functional group tolerance. The factors mentioned make this an attractive alternative method to access secondary and tertiary amines via DRA. A selection of the substrate scope for the preparation of secondary amines and tertiary amines from aldehydes and ketones is shown in Tables 1-4 below.

\textit{Table 1. Scope for aldehydes and primary amines for DRA to form secondary amines}

\[
\begin{array}{ccc}
\text{R}^1\text{O} & + & \text{H}_2\text{N}^\cdot\text{R}^2 \\
\text{AcOH, rt, 1h} & \rightarrow & \text{R}^1\text{N}^\cdot\text{R}^2 \\
\text{Me}_2\text{N} & 93\% & \text{Ph} & 93\% & \text{Bn} & 98\% & \text{Bn} & 80\%
\end{array}
\]
Table 2. Scope for aldehydes and secondary amines for DRA to form tertiary amines

\[
\text{R}^1\text{N}^\text{Et} + (\text{i-Pr})_2\text{SiO} + \text{R}^2\text{HN}^\text{Ph} + \text{MeO} + \text{R}^3\text{N}^\text{Bn} \rightarrow \text{R}^1\text{~N}^\text{R}^2\text{~N}^\text{R}^3
\]

80%  87%  97%  90%

Table 3. Scope for ketones and primary amines for DRA to form secondary amines

\[
\text{O} + \text{R}^1\text{~R}^2 + \text{H}_2\text{N}^\text{R}^3 \rightarrow \text{R}^1\text{~N}^\text{R}^2\text{~R}^3
\]

98%  76%  92%  72%

Table 4. Scope for ketones and secondary amines for DRA to form tertiary amines

\[
\text{O} + \text{HN}^\text{R}^2 + \text{HN}^\text{R}^3 + \text{CHCl}_3 \rightarrow \text{R}^1\text{~N}^\text{R}^2\text{~R}^3
\]

91%  85%  75%  80%
References

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**Appendix**

**Chemical Abstracts Nomenclature (Registry Number)**

Boratrane: 2,8,9-Trioxa-5-aza-1-borabicyclo[3.3.3]undecane; (283-56-7)
Triethoxysilane: Silane, triethoxy-; (998-30-1)
Aluminum ethoxide: Ethanol, aluminum salt (3:1); (555-75-9)
Xylenes: Benzene, dimethyl-; (1330-20-7)
1-Hydrosilatrane: 2,8,9-Trioxa-5-aza-1-silabicyclo[3.3.3]undecane; (283-60-3)
P-Tolualdehyde: Benzaldehyde, 4-methyl-; (104-87-0)
Aniline: Benzenamine; (62-53-3)
N-(4-Methylbenzyl)aniline: Benzenemethanamine, 4-methyl-N-phenyl-; (15818-64-1)

Fawwaz Azam was born in tropical Penang, Malaysia and raised in Dubai, United Arab Emirates. He moved to Toronto, Canada in 2014 and obtained his BSc in Chemistry from the University of Toronto in 2018. He is currently in the MSc program in Molecular Science at Ryerson University, where his research focuses on developing new synthetic organic methods using silanes.
Marc J. Adler is an Assistant Professor in the Department of Chemistry & Biology at Ryerson University (Canada). He was born in San Diego, CA (USA), received degrees in chemistry from University of California, Berkeley (USA, BSc) and Duke University (USA, Ph.D.), and further trained as a postdoctoral researcher at Yale University (USA) and University of Oxford (UK). He began his independent academic career at Northern Illinois University (USA). He loves family and friends, and lives by the motto “stay far from timid, only make moves when your heart’s in it, and live the phrase ‘sky’s the limit’” (Christopher Wallace).

Jin Su Ham received his B. S. and M. S. in chemistry from KAIST where he worked in the lab of Prof. Hee-Yoon Lee, researching total synthesis of natural products. After 9-years of industrial experience at SK Innovation, he is currently a Ph.D. student in the laboratories of Prof. Richmond Sarpong at UC Berkeley. His research focuses on developing new synthetic methods using transition metal catalysis.
1-Hydrosilatrane \(^1\)H NMR (700 MHz, CDCl\(_3\))
1-Hydrosilatrane $^{13}$C NMR (176 MHz, CDCl$_3$)
1-Hydrosilatrane $^{29}$Si NMR (119 MHz, CDCl$_3$)
N-(4-methylbenzyl)aniline $^1$H NMR (700 MHz, CDCl$_3$)
*N*-(4-methylbenzyl)aniline $^{13}$C NMR (176 MHz, CDCl$_3$)
1-Hydrosilatrane + pyrazine $^1$H NMR (700 MHz, CDCl$_3$)

Purity = 99.6%
Sample weight: 40.8 mg, and mol weight: 175.26
Using Reference Compound: pyrazine (18.8 mg, 99+% purity, mol weight=80.09)
Sample Integral : 0.247 (1 H)
Reference Integral: 1.000 (4 H)
N-(4-methylbenzyl)aniline + pyrazine $^1$H NMR (700 MHz, CDCl$_3$)

Purity = 98.9%
Sample weight: 32.0 mg, and mol weight: 197.28
Using Reference Compound: pyrazine (13.9 mg, 99+% purity, mol weight=80.09)
Sample Integral: 0.462 (2 H)
Reference Integral: 1.000 (4 H)