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Efficient Synthesis of 2-(Trimethylsilyl)phenyl Trifluoromethanesulfonate: A Versatile Precursor to *o*-Benzyne

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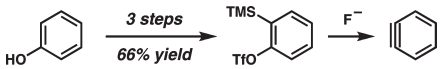
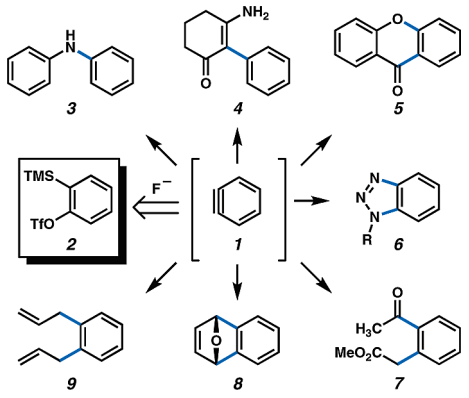


An efficient procedure for the gram-scale preparation of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate, a versatile precursor to *o*-benzyne, is presented. The three-step sequence utilizes phenol as the starting material, requires only one chromatographic purification, and ultimately delivers the desired silyltriflate in 66% overall yield.

o-Benzyne (**1**) has garnered much attention as a valuable synthetic building block (Scheme 1).[1] Although a number of

SCHEME 1. Silyltriflate 2 and Synthetic Applications of *o*-Benzyne



methods for benzyne generation have been discovered, Kobayashi's mild fluoride-induced formation of benzyne (**1**) from 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**2**) has proven most versatile.[2] The use of **2** as a precursor to benzyne has enabled the synthesis of substituted aromatic compounds and has spawned the discovery of many new chemical reactions (e.g., **1** → **3**–**9**).[1,3]

Despite the importance of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**2**) in modern organic synthesis, literature procedures for its preparation are sparse. In Kobayashi's original report, the benzyne precursor was synthesized from *o*-chlorophenol (**10**) by a sequence involving conversion to bis(silylated) intermediate **11**, followed by lithiation/triflation (Figure 1).[2] A recent paper describes a synthesis of **2** in three

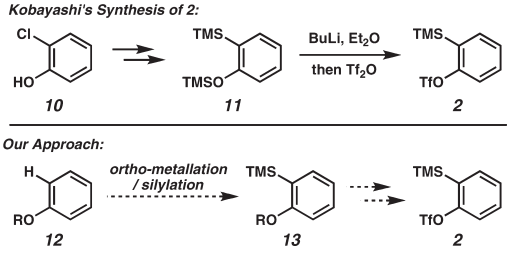
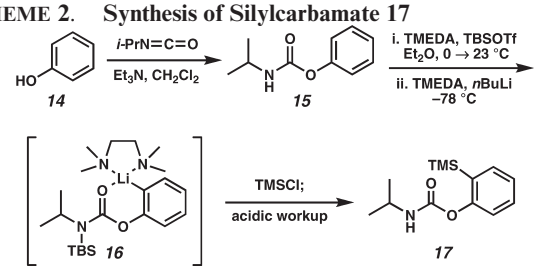


FIGURE 1. Approaches to silyltriflate **2**.

steps from 2-bromophenol, using an analogous strategy.[4] We envisioned that an alternative synthesis of silyltriflate **2** could be implemented by using phenol as the starting material. In this approach, ortho-metalation of a suitably protected phenol derivative would provide a means to introduce the necessary trimethylsilyl substituent (**12** → **13**) en route to the coveted benzyne precursor **2**.[5]

The pioneering studies by Snieckus in the area of directed-metalation chemistry[6] led us to examine the use of arylcarbamates as intermediates in our planned synthesis of **2**. Although both *N*,*N*-dialkylcarbamate and *N*-monoalkyl carbamate derivatives of phenol could easily be prepared and utilized for the desired metalation/silylation, we elected to focus on monoalkyl derivatives which would be more readily cleaved at a later stage. Thus, phenol (**14**) was allowed to react with isopropyl isocyanate in the presence of cat. Et_3N to provide carbamate **15** in quantitative yield (Scheme 2). Using the one-pot procedure developed by Snieckus and Hoppe,[7] crude **15** underwent *N*-silylation,

SCHEME 2. Synthesis of Silylcarbamate 17



(1) (a) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701–730. (b) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 502–528. (c) Sanz, R. *Org. Prep. Proced. Int.* **2008**, *40*, 217–291.

(2) Himeshima, Y.; Sonada, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211–1214.

(3) For represenative examples, see: (a) Liu, Z.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3198–3209. (b) Ramtohul, Y. K.; Chartrand, A. *Org. Lett.* **2007**, *9*, 1029–1032. (c) Shi, F.; Waldo, J. P.; Chen, Y.; Larock, R. C. *Org. Lett.* **2008**, *10*, 2409–2412. (d) Liu, Z.; Shi, F.; Martinez, P. D. G.; Raminelli, C.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 219–226. (e) Hayes, M. E.; Shinokubo, H.; Danheiser, R. L. *Org. Lett.* **2005**, *7*, 3917–3920. (f) Liu, Z.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 223–232.

(4) Wu, Q.-c.; Li, B.-s.; Shi, C.-q.; Chen, Y.-x. *Hecheng Huaxue* **2007**, *15*, 111–113.

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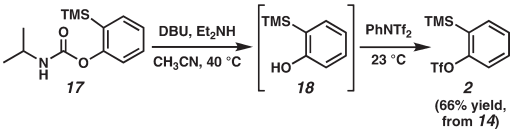
followed by ortho-lithiation to provide intermediate **16**, which in turn was quenched with TMSCl to install the necessary trimethylsilyl substituent. After workup, the desired silylcarbamate **17** was obtained without the need for chromatographic purification. Notably, this robust protocol could be carried out reliably on multigram scale.

To access the desired silyltriflate, a number of methods for carbamate cleavage/triflation were explored. Although stepwise routes provided initial success, we ultimately uncovered a one-pot procedure that allowed for the conversion of carbamate **17** to silyltriflate **2** (Scheme 3). Exposure of carbamate

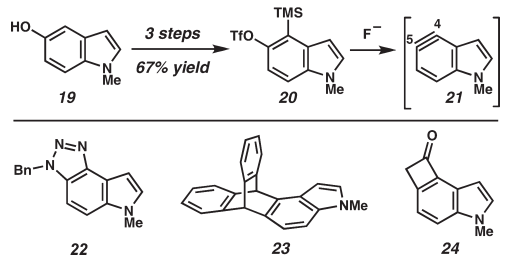
SCHEME 3. Synthesis of Silyltriflate 2



17 to DBU and Et_2NH in CH_3CN at 40 °C furnished intermediate *o*-silylphenol **18**.[8] After the reaction mixture was cooled to room temperature, a solution of $PhNTf_2$ in CH_3CN was introduced to facilitate triflation. Following purification by flash chromatography, silyltriflate **2** was obtained as a colorless oil in 66% yield, over the three steps. With use of this sequence, 5 g of phenol can be smoothly converted to > 10 g of **2**.

It is expected that our method for the conversion of phenol to silyltriflate **2** will be amenable to the synthesis of other aryne precursors. For instance, our laboratory has utilized the methodology to elaborate hydroxyindole **19** to indolylsilyltriflate **20** (Scheme 4) in 67% yield over three steps.[9]

SCHEME 4. Synthesis of Indolyne Precursor 20



Silyltriflate **20** provides a means to generate indolyne **21**, which in turn serves as a valuable precursor to a variety of novel indole derivatives (e.g., **22**−**24**).[9]

In summary, we have developed an efficient procedure for the gram-scale preparation of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate, a versatile precursor to *o*-benzyne. The three-step sequence utilizes phenol as the starting material, requires only one chromatographic purification, and ultimately delivers silyltriflate **2** in 66% overall yield. We expect the method will also prove amenable to the synthesis of other aryne precursors.

(5) 2-(Trimethylsilyl)phenyl trifluoromethanesulfonate may be purchased at a cost of over $110 per five grams from Aldrich or TCI America.

(6) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933.

(7) (a) Kauch, M.; Snieckus, V.; Hoppe, D. *J. Org. Chem.* **2005**, *70*, 7149–7158. (b) Kauch, M.; Hoppe, D. *Synthesis* **2006**, 1578–1589.

(8) Et_2NH serves as a scavenger for isopropyl isocyanate, which is liberated in the reaction; 1,1-diethyl-3-isopropylurea is formed as a byproduct.

(9) Bronner, S. M.; Bahnck, K. B.; Garg, N. K. *Org. Lett.* **2009**, *11*, 1007–1010.

Experimental Section

Carbamate 15. To a stirred solution of phenol (5.00 g, 53.1 mmol) in CH_2Cl_2 (177 mL) was added *i*-PrNCO (7.80 mL, 79.65 mmol, 1.5 equiv), followed by NEt_3 (1.50 mL, 10.6 mmol, 0.2 equiv). The solution was stirred at 23 °C for 2 h, then concentrated to dryness in vacuo to provide carbamate **15** as a white powder, which was used in the subsequent step without purification. R_f 0.23 (2:1 hexanes:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (t, J = 8 Hz, 2H), 7.20 (t, J = 7.5 Hz, 1H), 7.13 (d, J = 8 Hz, 2H), 4.86 (s, 1H), 3.94−3.87 (m, 1H), 1.23 (d, J = 8.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9, 151.2, 129.5, 125.4, 121.8, 43.6, 23.1; IR (film) 3290, 2972, 1696, 1535 cm^{-1}; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{10}H_{14}NO_2$ 180.1024, found 180.1026.

Silylcarbamate 17. The crude carbamate **15** was dissolved in ether (530 mL) at 0 °C and TMEDA (9.40 mL, 58.41 mmol, 1.1 equiv) was added followed by a solution of TBSOTf in *n*-pentane (1.30 M, 44.9 mL, 58.41 mmol, 1.1 equiv). The mixture was allowed to stir at 0 °C for 5 min, and then was warmed to 23 °C over 30 min. Additional TMEDA (17 mL, 106.2 mmol, 2 equiv) was added, and the reaction was cooled to −78 °C. A solution of *n*-BuLi in hexanes (2.12 M, 50.09 mL, 106.2 mmol, 2.0 equiv) was added dropwise over 70 min. The mixture was stirred at −78 °C for 1 h, then neat TMSCl (23.59 mL, 185.9 mmol, 3.5 equiv) was added dropwise over 35 min. The resulting mixture was stirred at −78 °C for 85 min, quenched with saturated aqueous $NaHSO_4$ (200 mL), and allowed to warm to 23 °C over 45 min with vigorous stirring. The organic layer was separated, washed successively with saturated aqueous $NaHSO_4$ (1 × 300 mL) and brine (1 × 300 mL), then dried over Na_2SO_4. Evaporation under reduced pressure afforded crude silylcarbamate **17**. R_f 0.75 (2:1 hexanes:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, J = 7.5, 6 Hz, 1H), 7.38 (td, J = 7.5, 1.5 Hz, 1H), 7.20 (t, J = 7.5 Hz, 1H), 7.11 (d, J = 8 Hz, 1H), 4.86 (d, J = 7 Hz, 1H), 4.00−3.90 (m, 1H), 1.25 (d, J = 6.5 Hz, 6H), 0.30 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 154.0, 135.0, 131.8, 130.5, 125.2, 122.4, 43.6, 23.1, −0.7; IR (film) 3320, 2968, 1705 cm^{-1}; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{13}H_{22}NO_2Si$ 252.1420, found 252.1418.

Silyltriflate 2. To a solution of crude silylcarbamate **17** in MeCN (530 mL) was added DBU (11.9 mL, 79.7 mmol, 1.5 equiv) and Et_2NH (6.59 mL, 63.7 mmol, 1.2 equiv). The resulting mixture was placed in a heating bath maintained at 40 °C for 45 min, then allowed to cool to 23 °C. Next, a solution of $PhNTf_2$ (28.5 g, 79.7 mmol, 1.5 equiv) in MeCN (155 mL) was added via cannula over 20 min. After being stirred for 2 h, the reaction mixture was washed successively with saturated aqueous $NaHSO_4$ (2 × 300 mL) and 10% aqueous NaOH (2 × 300 mL), then dried over Na_2SO_4. Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (199:1 hexanes:EtOAc) to provide 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **2** (10.4 g, 66% yield over 3 steps) as a colorless oil. R_f 0.80 (2:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (dd, J = 7.5, 2.0 Hz, 1H), 7.46 (m, 1H), 7.36 (m, 2H), 0.40 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 136.5, 132.8, 131.5, 127.7, 119.7, 118.7 (q, J = 318 Hz, CF_3), −0.6; IR (film) 2960, 1419, 1206 cm^{-1}; HRMS-ESI (m/z) $[M + NH_4]^+$ calcd for $C_{10}H_{17}F_3NO_3S$-Si 316.0651, found 316.0650.

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Supporting Information Available: ^{1}HNMR and ^{13}CNMR spectra for compounds **15**, **17**, and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.