ORGANIC LETTERS

2001
Vol. 3, No. 8
1197−1200

# A Novel Type of Nucleophilic Substitution Reactions on Nonactivated Aromatic Compounds and Benzene Itself with Trimethylsiliconide Anions

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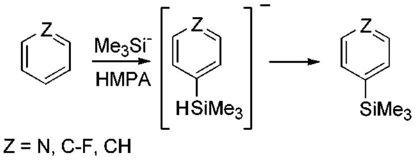
**Received February 6, 2001**

## ABSTRACT



**The reaction of fluorobenzene with Me$_3$Si$^-$ anion (1) in HMPA at room temperature surprisingly affords *o*- and *p*-fluorotrimethylsilylbenzenes (substitution of aromatic H for TMS, 76% yield) 7a and 7b and also 14% of trimethylsilylbenzene (2). Benzene itself reacts at 50 °C to furnish 4 in 45% yield. Pyridine affords *p*-trimethylsilylpyridine quantitatively. Mechanistic studies are presented.**

The available mechanisms to effect aromatic nucleophilic substitution vary greatly, depending on the aromatic moiety, the nucleophile, and the reaction conditions. During the past five decades, and after the landmark review of Bunnett and Zahler,[1] organic chemists have recognized that aromatic compounds can undergo nucleophilic substitution just as easily as they undergo electrophilic substitution.

Being interested in the reactions of triorganyltin ions as nucleophiles by the $S_{RN}1$ mechanism and their synthetic applications,[2] we decided to explore the triorganylsiliconide analogues. Although the reactions of these anions with haloarenes and haloheteroarenes to afford substitution products have previously been reported, mechanistic studies are sparse and dubious.[3,4]

Trimethylsiliconide anion (Me$_3$Si$^-$ (**1**)), generated from reaction of hexamethyldisilane with NaOMe, reacts with *p*-halotoluenes (Cl, Br, and I) to afford mainly the trimethylsilyl-substituted products (63−92%) and toluene as a minor product (4−26%) in HMPT as solvent.[4] There is 30% deuterium incorporation when the reaction is quenched with D$_2$O. On the other hand, when NaOCH$_3$ is replaced by NaOCD$_3$ in the reaction of *p*-iodotoluene and hexamethyldisilane, toluene is recovered with 64% of deuterium incorporation. From these results there appear to be at least two intermediates involved in this reaction.[4]

We prepared the highly basic and nucleophilic **1**,[5] in dry and de-oxygenated HMPA as solvent and allowed it to react with haloarenes under nitrogen. There is a fast dark (15 min) reaction between PhI and **1** to afford PhSiMe$_3$ (**2**) in 99% yield. PhBr and PhCl react in the same fashion to afford **2** in 89 and 71% yields, respectively, in 30-min reactions (Scheme 1).

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[1] Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 275.

[2] (a) Yammal, C. C.; Podesta, J. C.; Rossi, R. A. *J. Org. Chem.* **1992**, *57*, 5720. (b) Yammal, C. C.; Podesta, J. C.; Rossi, R. A *J. Organomet. Chem.* **1996**, *509*, 1. (c) Lockhart, M. T.; Chopa, A. B.; Rossi, R. A. *J. Organomet. Chem.* **1999**, *582*, 229. (d) Córsico, E. F.; Rossi, R. A. *Synlett* **2000**, 227. (e) Córsico, E. F.; Rossi, R. A *Synlett* **2000**, 230.

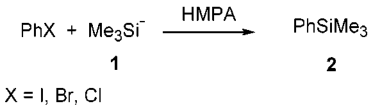
[3] (a) Gilman, H.; Wittemberg, D. *J. Org. Chem.* **1958**, *23*, 2677. (b) Benkeser, R. A.; Severson, R. G. *J. Org. Chem.* **1951**, *16*, 1424. (c) Brook, A. G.; Wolfe, S. *J. Am. Chem. Soc.* **1957**, *79*, 1431

[4] Dervan, P. B.; Shippey, M. A. *J. Org. Chem.* **1977**, *42*, 2654.

[5] Kondo, F.; Sakurai, H. *J. Organomet. Chem.* **1975**, *92*, C46. Buncel, E.; Venkatachalam, T. K.; Edlund, U. *J. Organomet. Chem.* **1992**, *437*, 5. Sakurai, H.; Okada, A.; Kira, M.; Yonezawa, K. *Tetrahedron Lett.* **1971**, *19*, 1511.

10.1021/ol015666s CCC: $20.00

Scheme 1

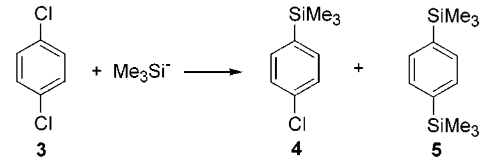


When an HMPA solution of *p*-chlorotoluene is allowed to react in the dark with **1**, only *p*-trimethylsilyltoluene is obtained in 90% yield. No *meta* isomer is observed in the reaction mixture. Minor amounts of toluene are also found ($<2\%$). The above reaction performed with an excess of NaOMe (an excellent hydrogen atom donor to aryl radicals)[6] does not lead to an increase in reduction product toluene.

2-Bromo-1,3,5-trimethylbenzene (bromomesitylene) reacts with **1** in HMPA, furnishing 2-trimethylsilyl-1,3,5-trimethylbenzene[7] in 48% yield, along with reduction product mesitylene (30% yield). These facts preclude a benzyne mechanism to be operating in the substitution reaction of halobenzenes with **1** in excess, in HMPA as solvent.

Upon reaction of *p*-dichlorobenzene (**3**) with **1** in HMPA, *p*-chlorotrimethylsilyl benzene[7] (**4**) (15%), *p*-bis(trimethylsilyl)benzene[7] (**5**) (71%), and traces of **2** (3%) are obtained (Scheme 2). This indicates that the reaction proceeds in a consecutive fashion (i.e., **4** being the precursor of **5**) in contrast to some nucleophilic disubstitutions via the $S_{RN}1$ mechanism that do not proceed through the monosubstitution intermediates.[8] There is a fast depletion of **3** concomitant with the appearance of **4**, which then decreases as **5** increases, indicating a stepwise mechanism (Figure 1).

Scheme 2



In all these examples, the substrates suffer an *ipso* substitution. Contrasting results are obtained with PhF (**6**). When **6** is allowed to react with **1** in HMPA, *o*- and *p*-fluorotrimethylsilylbenzenes (**7**)[9] are obtained in 76% overall yield, as well as some **2** (14%) (experiment 1, Table 1) (Scheme 3).[10]

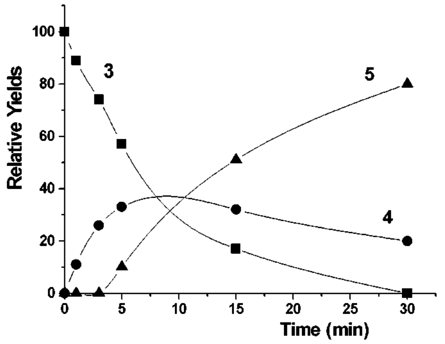


**Figure 1.** Relative yields of the disappearance of **3** and the formation of **4** and **5** in HMPA vs time.

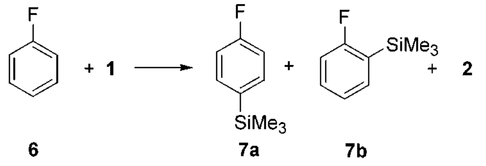
**Table 1.** Reactions of Aromatic Compounds with **1** in HMPA

| expt | substr (mM) | **1**, mM | time (min) | products (yield, %) |
|---|---|---|---|---|
| 1 | **6** (106) | 272 | 30 | **7** (76),[a] **2** (14) |
| 2 | $C_6D_5F$ (107) | 272 | 30 | **7**[b] (15), **2**[b] (9) |
| 3 | 8 (515)[c] | 927 | 120 | **9** (99) |
| 4 | **8** (618)[c] | 742 | 15 | **10** (99)[d] |
| 5 | **8** (494)[e] | 1480 | 15 | **11** (87),[f] **9** (9) |
| 6[g] | benzene (447) | 1480 | 2280 | **2** (20 |
| 7[h] | benzene (5634) | 1878 | 2304 | **2** (45) |
| 8 | benzene (223) | 1790 | 2280 | **2** (11) |
|  | $C_6D_6$ (223) |  |  | $C_6D_5SiMe_3$ (6.4) |

[a] **7a** and **7b** elute together in our VPC conditions. A ratio of ca. 60:40 is found for the two isomers according to $^1$H NMR spectroscopy. [b] Deuterated **7a**, **7b**, and **2**; $C_6D_5F$ was recovered in 78% yield. [c] Quenched with water. [d] Isolated as **9** (92%). [e] Quenched with ethyl chloroformate. [f] Isolated in 78% yield. [g] Duplicate experiments, ratio $C_6H_6$:**1** = 0.3. Yield of **2** based on benzene. [h] At 50 °C, ratio $C_6H_6$:**1** = 3. Yield of **2** based on **1**.

A plot of product formation vs time indicates that the production of **7** and **2** occurs simultaneously, as two competitive reactions (Figure 2): a fast nucleophilic substitution reaction by **1** on the benzene ring to yield **7** and a fluorine-atom replacement by **1** to furnish **2**. At prolonged reaction times (6 h) there is a decrease in the yield of product **7**, and small amounts of *o*- and *p*-bis(trimethylsilyl)benzenes

Scheme 3



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(6) Tomaselli, G. A.; Bunnett, J. F. *J. Org. Chem.* **1992**, *57*, 2710. Tomaselli, G. A.; Cui, J. J.; Chen, Q. F.; Bunnett, J. F. *J. Chem. Soc., Perkin Trans. 2* **1992**, 9. Bunnett, J. F. *Acc. Chem. Res.* **1992**, *25*, 2.

(7) Spectroscopic data for these compounds are in agreement with published data: Haubold, W.; Herdtle, J.; Gollinger, W.; Einholz, W. *J. Organomet. Chem.* **1986**, *315*, 1.

(8) Bunnett, J. F.; Creary, X. *J. Org. Chem.* **1974**, *39*, 3611. Bunnett, J. F.; Shafer, S. J. *J. Org. Chem.* **1978**, *43*, 1873.

(9) The spectroscopic evidence agrees well with the published spectra, see: Freeburger, M. E.; Hughes, M.; Buell, G. R.; Tierman, T. O.; Splatter, L. *J. Org. Chem.* **1971**, *36*, 933. See also: Nishimura, J.; Fukurawa, J.; Kawabata, N. *J. Organomet. Chem.* **1971**, *29*, 237. Cartledge, F. K.; Riedel, K. H. *J. Organomet. Chem.* **1972**, *34*, 11. Moerlin, S. M. *J. Organomet. Chem.* **1987**, *319*, 29. Eaborn, C.; Jaura, K. L.; Walton, D. R. M. *J. Chem. Soc.* **1964**, 1198.

(10) Products **3a** and **3b** were quantified together. There is **3a**:**3b** ratio of ca. 60:40.

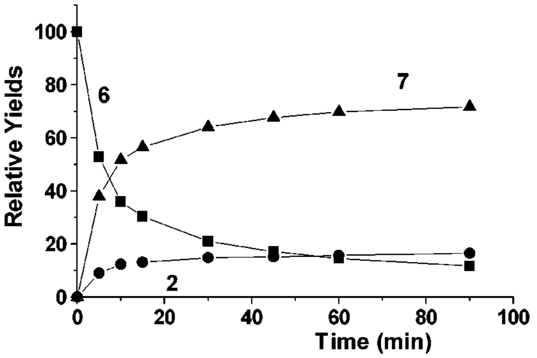


**Figure 2.** Relative yields for the disappearance of **2** and formation of **3** and **4** in HMPA vs time.

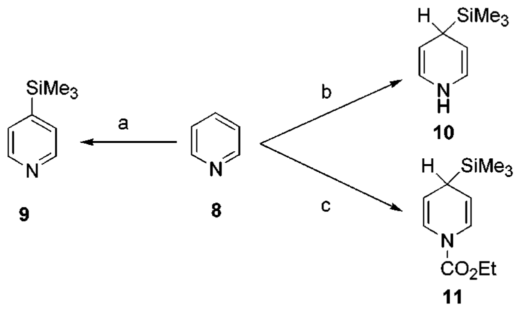
are obtained (5%).[11] *o*- and *p*-bis(trimethylsilyl)benzenes arise from further reaction of *o*- and *p*-fluorotrimethylsilylbenzenes **7** with **1**.

In competition experiments of **6** (426 mM) and perdeuteriofluorobenzene ($C_6D_5F$, 426 mM), toward **1** (426 mM, 2 h), a primary deuterium kinetic isotope effect,[12] DKIE ($k_H/k_D = 3.2 \pm 0.1$), is found for the formation of compound **7**. This is in agreement with loss of hydride as the rate-limiting step from a $\sigma^H$ adduct. No DKIE is observed for the formation of product **2** (fluorine as leaving group) ($k_H/k_D = 1.0 \pm 0.1$).

Formation of compound **7** entails loss of hydrogen as leaving group, whereas to form product **2** the formal leaving group is fluorine. With loss of hydrogen being a rate-determining step in the formation of **7** (but not in the formation of **2**), this should also be reflected in the relative yields of products **7**:**2** when $C_6D_5F$ and **6** are used as substrates, respectively. When $C_6D_5F$ is allowed to react with **1**, a **7**:**2** product ratio of ca. 1.7 (experiment 2, Table 1) is observed, in contrast to a **7**:**2** ratio of 5.4, (experiment 1, Table 1) when **6** is utilized as substrate.

Given the remarkable reactivity of **1**, we estimated that an aromatic moiety even without a formal leaving group such as pyridine (**8**) would be able to react with **1**. Upon reaction of **1** with **8** (2 h) and subsequent quenching with water, 4-trimethylsilylpyridine (**9**) is obtained in quantitative yield (99% yield).[13] At shorter reaction times (15 min), dihydro derivative **10** is obtained (99%, isolated as **9** in 92% yield). When the above reaction (15 min) is quenched with ethyl chloroformate, urethane **11** is obtained in 87% isolated yield, along with minor amounts of **9** (9% yield) (Table 1, experiments 3−5) (Scheme 4).[14]

**Scheme 4**[a]



[a] Reagents and conditions:( a) (i) **1** (2 h); (ii) $H_2O$; (b) (i) **1** (15 min); (ii) $H_2O$; (c) (i) **1** (15 min); (ii) $ClCO_2Et$.

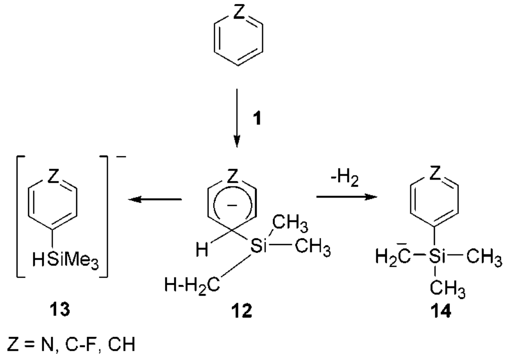
The intrinsic reactivity of **1** toward **6** and **8** led us to consider benzene itself as a candidate to undergo substitution by **1**. When benzene is allowed to react with **1** under similar experimental conditions, **2** is obtained in 20% yield (48 h) (Table 1, experiment 6). When the reaction is performed at 50 °C the yield of **2** rises to 45% (experiment 7, Table 1).

A primary kinetic isotope effect,[12] 1.7 ± 0.1, is observed when benzene-$d_6$ is placed in competition with ordinary benzene (Table 1, experiment 8).

In other competition experiments we determined the relative reactivity pattern of halobenzenes (toward **1**) and found values for PhI (3.5), PhBr (1.9), and PhF (0.08)[15] vs *p*-chlorotoluene as unity. These results show that the span in reactivity between the four halogens toward **1** is, from PhF to PhI, only about 44.

The formation of substitution products can be rationalized as arising from attack of **1** on the aromatic moiety to yield the $\sigma^H$ adduct **12** (Scheme 5). This adduct could proceed to products through hydride ion elimination.[16] A more plausible route to products could be hydride shift to form the pentacoordinate silicon species **13**,[17] which can persist in an anionic form until quenching of the reaction, with consequent

**Scheme 5**



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[11] Identified by GC-MS and compared with the authentic samples.

[12] Determination of the relative concentrations of deuterated and nondeuterated products were carried out by GC/MS analysis (Shimadzu GC-17 A Series, DB5-MS 30 m × 0.2 mm × 0.18 mm film column, integrated to a Shimadzu GCMS-QP 5050A mass selective detector) by mass selective integration.

[13] The spectroscopic evidence agrees well with the published spectra, see: Sulzbach, R. A. *J. Organomet. Chem.* **1970**, *24*, 307.

[14] For the methyl chloroformate adduct, see: Fowler, F. *J. Org. Chem.* **1972**, *37*, 1321.

[15] Taking only into account the *ipso* substitution product on substrate **2**, i.e., **4**, the relative reactivity is ca. 0.016.

evolution of molecular hydrogen. Hydrogen gas can also be envisaged as evolving from a species such as **12** through deprotonation of the ancillary methyl group from the trimethylsilyl substituent, to furnish anion **14** (Scheme 5). However, when the reaction is quenched with methyl iodide, ion **14** was not trapped. Other mechanistic possibilities may also be considered.

With respect to halobenzenes, the reactivity order found (PhI > PhBr > PhCl > PhF) toward **1** is in agreement with both HME and ET reactions, except that the span in reactivity is only of about 44. The span in reactivity in competition experiments of the four halobenzenes toward acetone enolate anion in $S_{RN}1$ reactions is over 100 000.[18] On the other hand, PhI reacts with $Me_3Sn^-$ ions by HME in a fast reaction, whereas PhCl does not by this mechanism.[2a,c]

Another mechanistic possibility for the *ipso* trimethylsilylsustitution products from halobenzenes could be the formation of a $\sigma^X$ complex that evolves to a pentacoordinate intermediate, from which the substitution product ensues.[19]

The reactivity order is also opposed to that found in $S_NAr$ reactions. However, in the mechanism proposed a transfer of the leaving group (X = halogen or H in Scheme 5) to silicon is envisaged, to form a pentacoordinate species and not to free halide ions, as occurs in ordinary $S_NAr$ reactions.

As far as we know, there is no precedent for silylation of aromatic compounds to replace hydrogen through the action of trialkylsiliconide ions. The operation of a $\sigma$ adduct-type reaction is due to the powerful nucleophilicity of **1** in HMPA that can effect substitution on substrates otherwise unreactive with nucleophiles, including benzene.

Further work is in progress to shed more light on the mechanistic aspects of these reactions, as well as reactions with other substituted benzene rings and heteroarenes.

**Acknowledgment.** We thank Professor Joseph F. Bunnett for his comments and valuable suggestions. This work was supported in part by the SECYT, National University of Córdoba, FONCYT, CONICOR, and CONICET, Argentina.

**Supporting Information Available:** Experimental procedures and spectroscopic data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) (a) It is known that under certain conditions the hydrogen atom can indeed be substituted (vicarious nucleophilic substitution, VNS). This elimination is assisted by a leaving group (generally X, ArO, RO, ArS) and therefore does not imply hydride ion elimination. The VNS requires the presence of an EWG such as nitro or cyano, which stabilizes the $\sigma^H$ adduct.[16b] Lately, alkyl-hydroperoxide anions have been employed for the introduction of the hydroxy functionality on the aromatic moiety,[16c] and more recently it has been reported that the reaction of nitroarenes with a large excess of potassium methoxide leads to removal of the *ipso* hydrogen to form a dianion.[16d] (b) Makosza, M.; Miniarski, J. *Acc. Chem. Res.* **1987**, *20*, 143. (c) Makosza, M.; Sienkiewicz, K. *J. Org. Chem.* **1998**, *63*, 4199. (d) Kawakami, T.; Suzuki, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1259.

(17) Pentacoordinated and other hypervalent states of silicon are well-known, see: Holmes, R. R. *Chem. Rev.* **1996**, *96*, 927. Chuit, C.; Corriu, J. P.; Reye, C.; Colin Young, J. *Chem. Rev.* **1993**, *93*, 1371. Anglada, J. M.; Bo, C.; Bofill, J. M.; Crehuet, R.; Poblet, J. M. *Organometallics* **1999**, *18*, 5584 and references therein.

(18) Bunnett, J. F. *Acc. Chem. Res.* **1978**, *11*, 413.

(19) By semiempirical methods (AM1) the energy of the pentacoordinate complex is much lower than that of the $\sigma$ adduct (for PhF and PhI). The intermediate $\sigma$ adduct does not exist (AM1) for PhCl and PhBr. Calculations at a higher level of theory are in progress for all the compounds in this system.