ISSN 1070-4280, Russian Journal of Organic Chemistry, 2015, Vol. 51, No. 3, pp. 335–340. © Pleiades Publishing, Ltd., 2015.
Original Russian Text © A.V. Lis, I.P. Tsyrendorzhieva, A.I. Albanov, B.A. Shainyan, V.I. Rakhlin, 2015, published in Zhurnal Organicheskoi Khimii, 2015, Vol. 51, No. 3, pp. 353–358.

Reaction of Sodium Bis(trimethylsilyl)amide with Bromotoluenes

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Received October 25, 2014

Abstract—Isomeric bromotoluenes react with sodium bis(trimethylsilyl)amide through intermediate methylbenzynes, yielding *N*,*N*-bis(trimethylsilyl)toluidines and rearrangement products, *N*,2-bis(trimethylsilyl)toluidines. The formation of the latter is a rare example of 1,3-migration of silyl group from nitrogen atom to aromatic carbon atom. The rearrangement is favored by increased solvent polarity and elevated temperature. The observed product ratio can be rationalized by DFT quantum chemical calculations.

DOI: 10.1134/S1070428015030082

The simplest aryne, 1,2-didehydrobenzene or benzyne, was proposed by Wittig as zwitterionic intermediate more than 70 years ago [1], and 11 years later its existence was proved by Roberts [2]. Since that time a number of methods for the generation of arynes have been developed [3]. However, despite unique reactivity and prospects of application in organic synthesis, arynes were mostly considered to be exotic intermediates. In 1980s Kobayashi proposed a convenient procedure for the generation of arynes from 2-trimethylsilylaryl trifluoromethanesulfonates [4], which opened wide possibilities for controlling their reactivity [5] and made them more attractive for practical purposes [6–8].

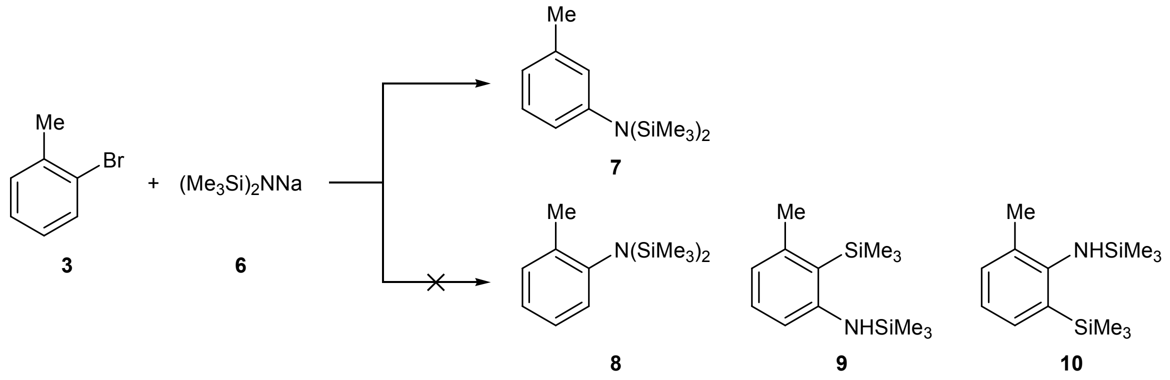
Nucleophilic substitution in non-activated aromatic compounds is the most widely used reaction involving arynes as intermediates; however, not only prediction but also explanation of the regioselectivity of nucleophilic addition to substituted arynes remain topical problems [9]. A rare example of high selectivity of nucleophilic addition is provided by reactions of arynes generated from disubstituted arenes containing alkoxy, alkylamino, or phenyl group or bulky substituents in addition to chlorine or fluorine atom. The formation of *meta*-substituted compounds was rationalized by the negative inductive effect and/or steric effect of substituents [10]. By contrast, the positive inductive effect of substituents is often leveled out by steric effects of substituent in the aromatic ring and nucleophile [11], which rules out formation of *ortho*-substituted arenes. Ikawa et al. [10] succeeded in increasing the reaction selectivity toward formation of *ortho*-substituted arenes by varying the conditions.

An aryne distortion model [9, 12, 13] was employed to explain the observed regioselectivity of nucleophilic addition to arynes. Numerous structural and mechanistic studies of the transformations of 2-haloaryllithium derivatives revealed a considerable joint effect of the solvent nature and departing halogen on the regioselectivity of these reactions [14].

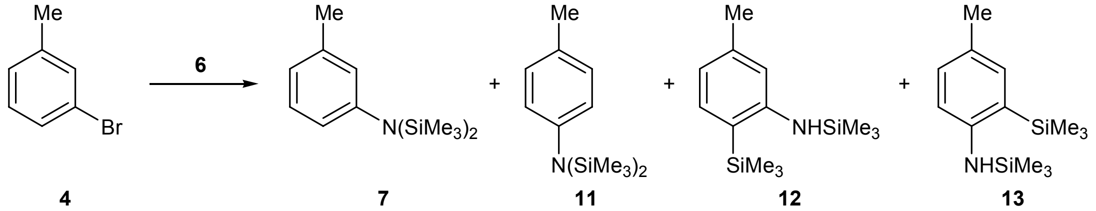
We have recently found that sodium bis(trimethylsilyl)amide reacts with bromobenzene to give *N*,*N*-bis(trimethylsilyl)aniline (**1**) as a result of replacement of the bromine atom and an unexpected product resulting from rearrangement with 1,3-migration of one trimethylsilyl group from the nitrogen atom to the *ortho*-carbon atom, *N*,2-bis(trimethylsilyl)aniline (**2**) [15]. The product ratio **1**:**2** changed from 4:1 in toluene to 1:4 in THF. The formation of *N*,*N*-diethylaniline in the reaction of bromobenzene with sodium bis(trimethylsilyl)amide in triethylamine is a direct proof for intermediate formation of benzyne [16]. The observed silyl group migration is a fairly rare rearrangement in the aromatic series. We have found only one published example of analogous rearrangement, the formation of 2-silylanilines in the reactions of silylamines with arynes generated from 2-(trimethylsilyl)aryl trifluoromethanesulfonates in the presence of potassium fluoride and 18-crown-6 [17].

In the present work we studied the reaction of isomeric bromotoluenes **3**–**5** with sodium bis(trimethyl-

Scheme 1.



Scheme 2.



silyl)amide (**6**) under different conditions. The reaction of *o*-bromotoluene (**3**) with sodium amide **6** gave only one product, 3-methyl-*N*,*N*-bis(trimethylsilyl)aniline (**7**); the yield of **7** ranged from 33 to 76%, depending on the conditions (Table 1). Neither isomeric 2-methyl-*N*,*N*-bis(trimethylsilyl)aniline (**8**) nor rearrangement products, 3-methyl-*N*,2-bis(trimethylsilyl)aniline (**9**) and 2-methyl-*N*,6-bis(trimethylsilyl)aniline (**10**), were detected (Scheme 1). The effect of steric factor in this reaction is reflected in the absence of compound **9** among the products, as well as in the formation of **7** as the only product; furthermore, no aryne adduct with Me_3SiNEt_2 was obtained even when the reaction was carried out using the latter as solvent.

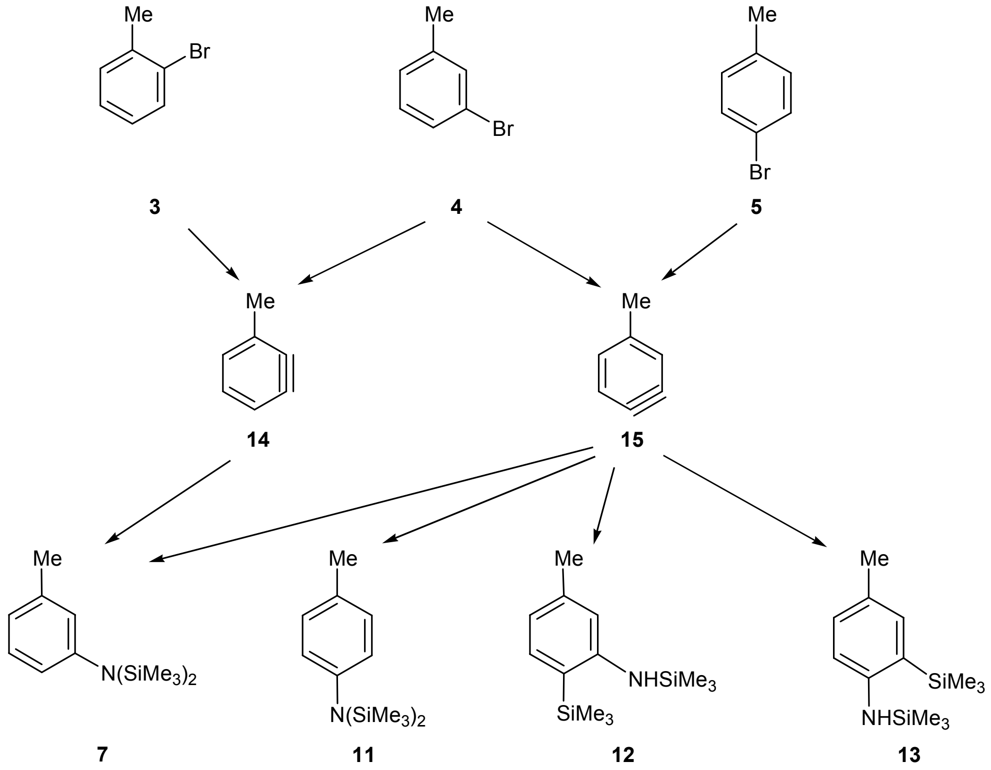
The products of the reaction of **6** with *m*-bromotoluene (**4**) were compounds **7** and **11**–**13** whose ratio depended on the conditions (Scheme 2, Table 1). The same compounds but at a different ratio were also formed in the reaction of **6** with *p*-bromotoluene (**5**) (Table 1). Thus, the general scheme of transformations of isomeric bromotoluenes in the reaction with sodium bis(trimethylsilyl)amide (**6**) may be illustrated by Scheme 3 which implies intermediacy of two arynes: 1- and 2-methylcyclohexa-1,3-dien-5-ynes **14** and **15**.

As follows from the data in Table 1, the overall yield in a moderately polar basic solvent, THF ($\varepsilon = 7.5$, Gutmann donor number $DN = 20$), is somewhat higher than in nonpolar neutral toluene ($\varepsilon = 2.4$, $DN = 0.1$)

Table 1. Overall yields and product ratios in the reactions of isomeric bromotoluenes **3**–**5** with sodium bis(trimethylsilyl)amide (**6**)

Compound no.	Solvent, temperature, °C	Overall yield, %	Ratio **7**:**11**:**12**:**13**
3	Toluene, 130	37	100:0:0:0
	THF, 100	56	100:0:0:0
	THF, 70	76	100:0:0:0
4	Toluene, 130	40	32:49:12:7
	THF, 100	42	13:20:31:36
	THF, 70	52	18:20:33:29
5	Toluene, 130	48	20:47:20:13
	THF, 100	70	8:16:38:38
	THF, 70	61	15:31:30:24

Scheme 3.



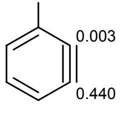
[18]. Presumably, this is related to higher reactivity of the base [bis(trimethylsilyl)amide ion] in THF due to solvation of the counterion (sodium cation). For instance, basic solvents like THF favor dissociation of lithium bis(trimethylsilyl)amide dimers into ion pairs, thus enhancing its reactivity [19].

The solvent also affects the rearrangement process. The change of the **1**/**2** product ratio in the reaction of bromobenzene with **6** from 4:1 to 1:4 in going from toluene to THF [15] (see above) is consistent with the calculated dipole moment of **1**, which is close to zero (0.06 D) against μ = 1.49 D for polar rearrangement product **2**. However, solvent effect on the ratio of the corresponding products in the reactions with isomeric bromotoluenes is less pronounced (Table 1).

Rise in temperature leads to increased fraction of rearrangement products **12** and **13** relative to substitution products **7** and **11**. Their ratio changes from 1.6 to 2.0 for *m*-bromotoluene and from 1.2 to 3.2 for *p*-bromotoluene in THF as the reaction temperature increased from 70 to 100°C (Table 1).

In order to gain a deeper insight into the mechanism of the described reactions, quantum chemical calculations of all substrates, intermediates, and products were performed with full geometry optimization at the DFT B3LYP/6-311+G(*d*,*p*) level of theory using Gaussian 09 software package [20]. The calculated benzyne and zwitterionic structures and Mulliken charges on the atoms are given below, and the total energies of all species are presented in Table 2.

A probable mechanism involving intermediate formation of zwitterionic structures **16**–**18** is shown in Scheme 4. Taking into account that the reactants [bromotoluenes and $(Me_3Si)_2NNa$] were taken in equimolar amounts, we presume that intermediate arynes react with hexamethyldisilazane rather than with its sodium salt **6** to give zwitterionic intermediates; otherwise, aryl anions would be formed.



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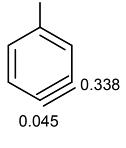

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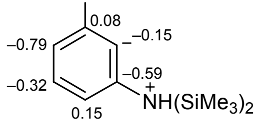

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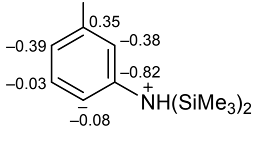

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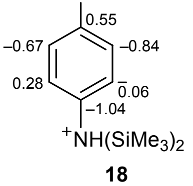

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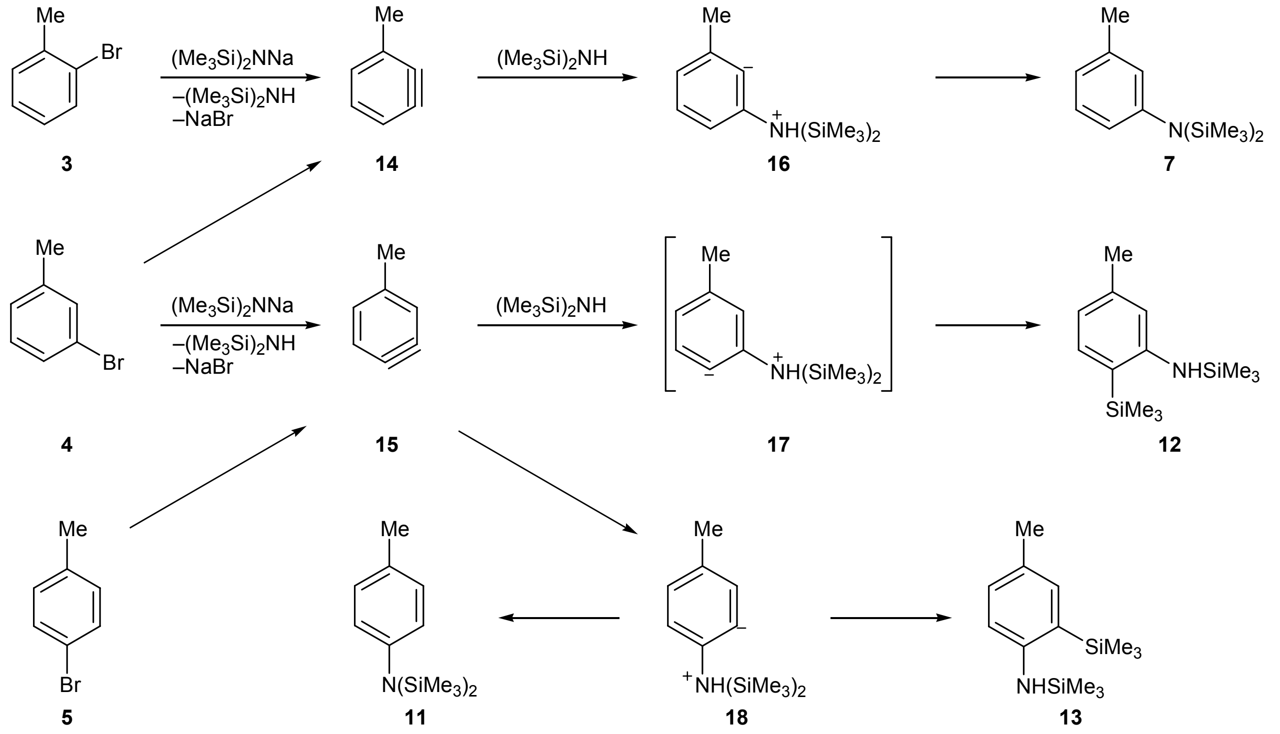
Scheme 4.



As follows from the data in Table 2, the formation of only one sterically determined isomer **7** as substitution product in the reaction with *o*-bromotoluene is advantageous from both kinetic (high positive charge on C^5 against almost zero charge on C^6 in **14**) and thermodynamic viewpoints (the energy difference ΔE between isomers **7** and **8** is 1.4 kcal/mol). The absence of rearrangement product may be rationalized by the high endothermicity of the transformation of **7** into **9** (ΔE = 15.4 kcal/mol), which is likely to be determined by steric hindrances intrinsic to the latter.

The aryne distortion model [12, 13] is inappropriate for arynes **14** and **15** because of small distortion angle. Unlike 3-methoxy- and 3-(trialkylsilyl)benzynes characterized by considerable and oppositely directed distortions of the aryne triple bond, the structure of 3-methylbenzyne (**14**) is essentially similar to the structure of 3-*tert*-butylbenzyne [9]. The angles in both structures coincide within ~0.5°, and the degrees of flattening of the triple-bonded C^1 and C^2 atoms are very similar (127.4 and 128.1°). Analogous pattern is observed for 4-methylbenzyne (**15**) (126.4 and 127.6°).

Table 2. Total energies of the substrates, intermediates, and products in the reactions of isomeric bromotoluenes **3**–**5** with sodium bis(trimethylsilyl)amide (**6**)

Comp. no.	E_{tot}, a.u.	Comp. no.	E_{tot}, a.u.
1	–1105.192558	**12**	–1144.507044
2	–1105.179278	**13**	–1144.505731
7	–1144.519966	**14**	–270.302927
8	–1144.517741	**15**	–270.299026
9	–1144.495354	**16**	–1144.408858
10	–1144.497578	**17**	–1144.406079
11	–1144.519327	**18**	–1144.407533

The proposed mechanism is also supported by the different behaviors of isomeric *meta*-substituted zwitterionic intermediates **16** and **17** (Scheme 4). Intermediate **16** corresponds to a minimum on the potential energy surface, whereas structure **17** is not an energy minimum and is transformed into rearrangement product **12** in the course of optimization. The N→C^4 migration of the trimethylsilyl group is preceded by rotation of the benzene ring initially lying in one plane with the N–H bond (the dihedral angle HNC^5C^4 is equal to zero) and bisecting the SiNSi angle; this rotation makes the benzene ring coplanar to the N–Si bond with the migrating trimethylsilyl group. Insofar as structure **17** does not correspond to a minimum on the potential energy surface, its total energy (Table 2) and charge distribution therein are given only for the sake of comparison and were calculated on the basis of incompletely optimized geometric parameters (variations in energy were less than 0.1 kcal/mol). These parameters characterized the structure in which the Me_3Si group has just started to move toward C^4. Like *meta*-substituted analog **17**, *para*-substituted zwitterionic intermediate **18** was converted during geometry optimization process into a structure in which the benzene ring lies in one plane with the NH bond (dihedral angle HNC^5C^4 is equal to 0°).

EXPERIMENTAL

The NMR spectra were recorded on a Bruker DPX-400 spectrometer at 400.13, 100.58, and 79.46 MHz for ^1H, 13C, and ^{29}Si, respectively; $CDCl_3$ was used as solvent, and tetramethylsilane, as reference. The mass spectra were obtained on a Shimadzu GCMS-QP2010 instrument (HP-1MS column, 30000 × 0.25 mm; quadrupole mass analyzer, electron impact ionization, 70 eV; ion source temperature 250°C; a.m.u. range 35–500). The reaction mixtures were analyzed by GLC on a Tsvet-500 chromatograph equipped with a thermal conductivity detector (glass column, 3 m × 4 mm, packed with 10% of PSM-1000 on Inerton Super, 0.125–0.150 mm; carrier gas helium).

Initial sodium bis(trimethylsilyl)amide was prepared according to the procedure described in [21].

Reaction of bromotoluenes 3–5 with sodium bis(trimethylsilyl)amide (6) (*general procedure*). An equimolar amount of bromotoluene **3–5** was added dropwise at room temperature to a solution of sodium salt **6** in the corresponding organic solvent. The mixture was stirred for 4 h on heating under reflux. While heating to the boiling point, a solid precipitated. When the reaction was complete, the solvent was distilled off, and the residue was distilled under reduced pressure.

Reaction with *o*-bromotoluene (3). *a.* From 12.0 g (65 mmol) of **6** and 11.2 g (65 mmol) of **3** in 70 mL of toluene we obtained 5.4 g (33%) of 3-methyl-*N*,*N*-bis(trimethylsilyl)aniline (**7**), bp 72–73°C (1 mm), n_D^{20} = 1.4893. ^1H NMR spectrum, δ, ppm: 0.05 s (18H, Me_3Si), 2.88 s (3H, CH_3), 6.68 d (1H, 6-H, ^3J = 7.5 Hz), 6.69 br.s (1H, 2-H), 6.85 d (1H, 4-H, ^3J = 7.5 Hz), 7.06 t (1H, 5-H, ^3J = 7.5 Hz). ^{13}C NMR spectrum, δ_C, ppm: 2.1 (Me_3Si), 124.3 (C^6), 127.20 (C^2), 128.1 (C^4), 130.9 (C^5), 138.0 (C^3), 147.8 (C^1). ^{29}Si NMR spectrum: δ_{Si} 4.2 ppm. Found, %: C 62.20; H 9.94; N 5.61. $C_{13}H_{25}N_2Si$. Calculated, %: C 62.08; H 10.02; N 5.57.

b. From 13.0 g (71 mmol) of **6** and 12.1 g (71 mmol) of **3** in 50 mL of THF we obtained 5.1 g (29%) of **7**, bp 70–74°C (1 mm).

Reaction with *m*-bromotoluene (4). *a.* From 12.6 g (69 mmol) of **6** and 11.75 g (69 mmol) of **4** in 70 mL of toluene we obtained 5.3 g (31%) of a mixture of compounds **7** and **11–13** at a ratio of 8 : 7.5 : 2.1 : 1 (according to the ^1H NMR data), bp 68–79°C (1 mm).

Compound **7**. Mass spectrum, *m*/*z* (I_{rel}, %): 251 (20) $[M]^+$, 236 (100) $[M - Me]^+$, 220 (14) $[M - 2Me]^+$, 73 (30) $[Me_3Si]^+$.

4-Methyl-*N*,*N*-bis(trimethylsilyl)aniline (11). ^1H NMR spectrum, δ, ppm: 0.04 s (18H, Me_3Si), 2.28 s (3H, CH_3), 6.75 d (2H, 2-H, 6-H, ^3J = 8.1 Hz), 6.98 d (2H, 3-H, 5-H, ^3J = 8.1 Hz). ^{29}Si NMR spectrum: δ_{Si} 4.19 ppm. Mass spectrum, *m*/*z* (I_{rel}, %): 251 (18) $[M]^+$, 236 (100) $[M - Me]^+$, 220 (13) $[M - 2Me]^+$, 73 (33) $[Me_3Si]^+$.

5-Methyl-*N*,2-bis(trimethylsilyl)aniline (12). ^1H NMR spectrum, δ ppm: 0.27 s (9H, Me_3SiN), 0.30 s (9H, Me_3SiC), 2.27 s (3H, CH_3), 3.56 br.s (1H, NH), 6.54 s (1H, 6-H), 6.58 d (1H, 4-H, ^3J = 7.5 Hz), 7.17 d (1H, 3-H, ^3J = 7.5 Hz). ^{29}Si NMR spectrum, δ_{Si}, ppm: –6.6 ($CSiMe_3$), 2.4 ($NSiMe_3$). Mass spectrum, *m*/*z* (I_{rel}, %): 251 (57) $[M]^+$, 236 (40) $[M - Me]^+$, 220 (36) $[M - 2Me]^+$, 162 (29), 148 (22), 73 (100) $[Me_3Si]^+$.

4-Methyl-*N*,2-bis(trimethylsilyl)aniline (13). *a.* ^1H NMR spectrum, δ ppm: 0.25 s (9H, Me_3SiN), 0.31 s (9H, Me_3SiC), 2.23 s (3H, CH_3), 3.47 br.s (1H, NH), 6.64 d (1H, 6-H, ^3J = 8.2 Hz), 7.00 d.d (1H, 5-H, ^3J = 8.2, ^4J = 2.0 Hz), 7.08 br.s (1H, 3-H). ^{29}Si NMR spectrum, δ_{Si}, ppm: –6.4 ($CSiMe_3$), 2.3 ($NSiMe_3$). Mass spectrum, *m*/*z* (I_{rel}, %): 251 (40) $[M]^+$, 236 (33) $[M - Me]^+$, 220 (30) $[M - 2Me]^+$, 178 (25), 148 (27), 73 (100) $[Me_3Si]^+$.

b. From 14.5 g (79 mmol) of **6** and 13.5 g (79 mmol) of **4** in 80 mL of THF we obtained 7.0 g (35%) of a mixture of compounds **7** and **11–13** at a ratio of 1.3 : 1.6 : 1 : 1 (^1H NMR), bp 80–90°C (2 mm).

Reaction with *p*-bromotoluene (5). *a.* From 18.1 g (99 mmol) of **6** and 16.9 g (99 mmol) of **5** in 100 mL of toluene we obtained 7.3 g (29%) of a mixture of compounds **7** and **11–13** at a ratio of 17 : 23 : 3 : 1 (^1H NMR), bp 75–86°C (1–2 mm).

b. From 15.2 g (83 mmol) of **6** and 14.2 g (83 mmol) of **5** in 70 mL of THF we obtained 5.80 g (28%) of a mixture of compounds **7** and **11–13** at a ratio of 1.5 : 2.0 : 1.2 : 1 (^1H NMR), bp 78–89°C (2 mm).

Reaction of sodium bis(trimethylsilyl)amide (6) with *o*-bromotoluene (3) in *N*-(trimethylsilyl)diethylamine. A dry ampule was charged with 3.4 g (18.5 mmol) of sodium bis(trimethylsilyl)amide (**6**), 15 mL of *N*-(trimethylsilyl)diethylamine and 3.2 g (18.5 mmol) of *o*-bromotoluene (**3**) were added, and the mixture was frozen and evacuated (freeze–pump–thaw technique). The ampule was sealed, heated for 4 h on a water bath, cooled, and opened. After removal of volatile components, vacuum distillation gave 1.5 g (32%) of compound **7**, bp 53°C (0.5 mm).

General procedure for the determination of product yield and ratio. A dry ampule was purged with dry argon, charged with an equimolar mixture of sodium bis(trimethylsilyl)amide, bromotoluene, and cyclohexane (as standard) in the corresponding solvent, degassed by the freeze–pump–thaw technique, and sealed. The ampule was heated for 3 h at 130°C (toluene) or 100°C (THF) or for 4 h at 70°C (THF). The yield and product ratio were determined by ^{1}H NMR spectroscopy.

This study was performed under financial support by the Council for Grants at the President of the Russian Federation (project no. NSh-3649.2014.3) and by the Russian Foundation for Basic Research (project no. 13-03-01198).

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