Halogen−Metal Exchange in 1,2-Dibromobenzene and the Possible Intermediacy of 1,2-Dilithiobenzene

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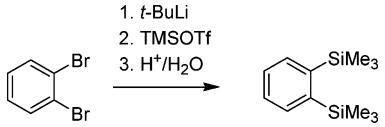

The one-step high-yield synthesis of 1,2-bis(trimethylsilyl)-benzene from 1,2-dibromobenzene using *tert*-butyllithium and trimethylsilyltriflate is reported. A mechanistic investigation shows that 1,2-dilithiobenzene is not an intermediate in this reaction; the coexistence of trimethylsilyltriflate and *tert*-butyllithium at very low temperatures allows a sequence of bromine−lithium exchange and subsequent derivatization reactions to operate.

Halogen−metal exchange in 1,2-dibromobenzenes **1** using organolithium reagents results in *ortho*-benzyne **2** due to the thermal instability of *ortho*-lithiobromobenzene **3**, and this has been exploited for the synthesis of biphenyls **4**.[1,2] However, **3** has a finite lifetime at temperatures below −90 °C as shown by Chen et al.[3] and can thus be trapped with suitable electrophiles to give *ortho*-substituted bromobenzenes **5**.

The question then arises whether a second lithiation step is possible at very low temperatures to give 1,2-dilithiobenzene **6**, provided a highly reactive organolithium reagent, like *tert*-butyl lithium (*t*-BuLi), is used. While **6** is known since the work of Wittig and his group dating back to the 1950s,[4−6] its synthesis requires an organomercury precursor.[7,8] It would thus be desirable to establish a more convenient and nontoxic access to this valuable reactive intermediate. We are not aware of a systematic investigation of this interesting problem but note that the other dilithiobenzene isomers[9] and 1,3,5-trilithiobenzene[10,11] have been prepared and even hexalithiobenzene[12] has been claimed.

TABLE 1. Yields (in %, from GC/MS Analysis) of the Products Obtained from Trapping the Reaction Mixture of 1,2-Dibromobenzene and *t*-BuLi in Et_2O/THF (1:1) at −120 °C with Various Electrophiles EX (See Experimental Section for Detailed Reaction Conditions)

entry	EX	condition	**7**	**9**	**5**	**5d**	**7d**
1	TMSOTf	A	89	6	0	0	<1
2	TMSCl	A	0	40	0	56	<1
3	ICl	A	0	0	91	7	<1
4	I_2	A	0	0	92	<3	<1
5	ICH_2CH_2I	A	0	0	68	28	<1
6	MeOTf	A	<1	<2	92	<2	<1
7	$SO_2(OMe)_2$	A	0	0	0	>90	5
8	MeI	A	0	11	0	77	4
9	DCl	A[a]	5	0	92	0	0
10	EtOD	A[a]	6	0	90	0	0
11	TMSOTf	B[b]	0	14	0	0	<1
12	EtOH/HCl	B[b]	0	0	0	0	<1

[a] Before addition of 1,2-dibromobenzene, the cooled reaction mixture is treated with 0.1 mL (0.148 mmol) of *t*-BuLi in pentane. [b]Various biphenyl and terphenyl products are obtained in varying amounts from the aryne route (see Supporting Information).

Reaction of **1** in Et_2O/THF (1:1) with 2 equiv of *t*-BuLi per bromine[13,14] at temperatures as low as −120 °C for a variable amount of time gives a yellow reaction mixture. Trapping of this mixture with an excess of trimethylsilyltriflate (TMSOTf), and subsequent quenching with HCl/EtOH, results in the formation of 1,2-bis(trimethylsilyl)benzene **7a** in up to >89% yield based on GC/MS. Under ideal conditions, we could easily isolate a >92% yield of **7a** in very high purity (see Supporting Information). This procedure allows for a high-yield synthesis of **7a**, avoiding the environmentally critical HMPTA of the standard protocol.[15]

Is the high yield of **7a** due to the intermediacy of **6**? It has been recognized over the past 20 years that difunctionalized products can arise from an alternating sequence of Li−Br exchange and derivatization reactions if electrophiles can coexist with lithium organyls at low temperatures to some extent.[9,10,16,17] In particular, the claimed preparation of 1,2-dilithiotetrafluorobenzene from the corresponding dibromo compound using *n*-butyl lithium (*n*-BuLi) at −78 °C by Tamborski and Soloski[18] has received skepticism in a critical review by Maercker.[17]

To establish the mechanism of formation of **7a**, via **6** or via an alternating sequence of Li−Br exchange and derivatizations involving **5**, we have treated the reaction mixture with a number of electrophiles under varying conditions (Table 1). With **6** as intermediate, we should obtain high combined yields of **7** plus **9** (low electrophile reactivity might impede formation of **7** for steric reasons in favor of **9**) but essentially no **5** (Scheme 1). Using electrophiles other than TMSOTf, however, does not give **7** in appreciable amounts. With trimethylsilylchloride the

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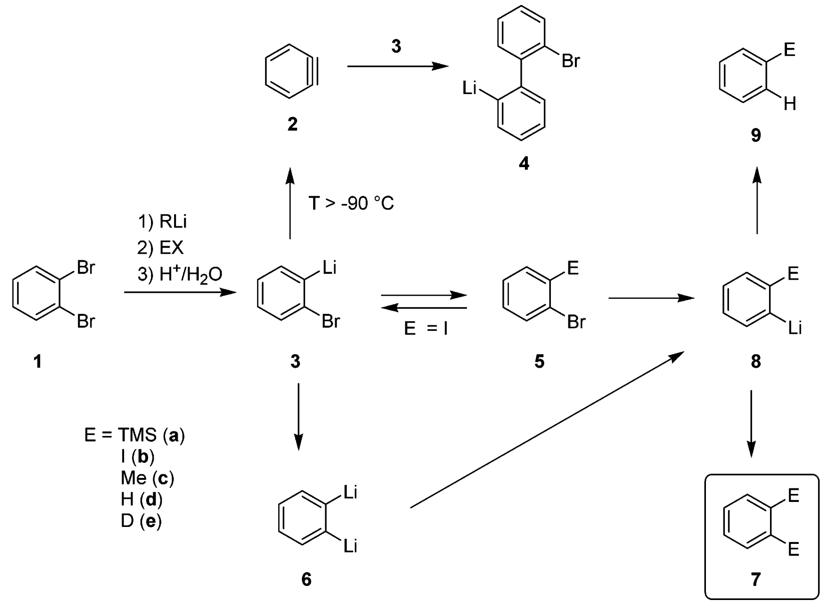
SCHEME 1



combined yield of derivatization products is similar to that obtained with TMSOTf, but the relative yields differ dramatically: **7a** cannot be detected at all, while the yield of **5d** increases from 0 to 56%. Also the production of **9a** is significantly increased. This qualitative change in product composition with electrophile reactivity is incompatible with the intermediacy of **6** and is best rationalized by a consecutive mechanism. The different outcome may reflect the higher reactivity of TMSOTf toward phenyllithium nucleophiles having bulky *ortho*-substituents.[19]

Reaction products obtained from trapping with iodine containing electrophiles (I_2, ICl, 1,2-diiodoethane) are also incompatible with the intermediacy of **6**. Formation of the major product, 1-bromo-2-iodobenzene **5b**, can be rationalized with a consecutive halogen−lithium exchange reaction mechanism. Here, excess *t*-BuLi preferentially abstracts iodine from **5** thus excluding formation of **9b** and **7b**. The products obtained using carbon electrophiles (MeOTf, dimethylsulfate, and methyliodide) are also compatible with a sequential bromine−lithium exchange−derivatization mechanism. With MeOTf high yields of **5c** and only trace amounts of *o*-xylene **7c** and toluene **9c** are obtained. Compared with TMSOTf, the less sterically protected MeOTf should have an increased reactivity toward *t*-BuLi. Dimethylsulfate, on the other hand, does not react with *o*-bromolithiobenzene **3** under our conditions, as bromobenzene **5d** is observed as the major reaction product. Trapping with iodomethane, on the other hand, gives bromobenzene **5d** as the major product along with some 11% toluene **9c**. This result is somewhat unexpected but might indicate a decreased reactivity of MeI compared to MeOTf toward *o*-bromolithiobenzene **3**.

In all experiments mentioned so far, trace amounts of benzene **7d** can be detected in the product mixture by GC/MS, but these are due to residual traces of water and can be eliminated by treating the solvent with a small amount of *t*-BuLi before adding the reactants. Only when electrophiles of low reactivity, iodomethane and dimethylsulfate, are used does the benzene yield increases slightly. Likewise, trapping of the lithium organic compounds with DCl or EtOD in Et_2O yields *ortho*-deuterobromobenzene **5e** in ≥90% yield but also 5−6% of 1,2-[D_2]-benzene **7e**.

To establish that the observed formation of 1,2-[D_2]-benzene **7e** is due to the coexistence of DCl or EtOD with *t*-BuLi at −120 °C, another set of experiments was performed at slightly elevated temperatures. After the *t*-BuLi had reacted with **1** for 30 min, the cooling bath was removed, and the reaction mixture was allowed to warm for 10 min. The color of the mixture changed from yellow to orange before it was cooled down to −120 °C and treated with the electrophile. Dilithiobenzene **6** should be stable thermally under these conditions as Wittig and co-workers generate it in diethylether at room temperature.[5,6] Only when thermally labile **3** is the major reactive intermediate, biphenyl products should be formed *via* the aryne route. Such reaction products are indeed observed: after briefly warming the reaction mixture and trapping the lithium organic species with TMSOTf, no more **7a** is found by GC/MS. The major products are silylated biphenyls and terphenyls along with some dibenzosilol derivatives.[20] Similarly, biphenyl and terphenyl derivatives in varying amounts were obtained from trapping of the reaction mixture with HCl rather than TMSOTf after briefly warming.[20] Benzene is no longer observed, indicating that DCl or EtOD and *t*-BuLi can coexist at very low temperatures.

In summary, we conclude that the high-yield one-step synthesis of 1,2-bis(trimethylsilyl)benzene **7a** from 1,2-dibromobenzene **1**, *t*-BuLi, and trimethylsilyltriflate proceeds through a sequence of lithiation−derivatization steps and does not involve 1,2-dilithiobenzene **6** as reactive intermediate in significant amounts. Note that extension of the reaction time or activation of the organolithium reagent by addition of TMEDA or glyme does not give indication for the formation of **6** either. The high yield of difunctionalized benzene **7a** arises from the fortuitous coexistence of TMSOTf and *t*-BuLi in our ethereal solvent system at −120 °C: TMSOTf shows sufficient stability toward *t*-BuLi but undergoes reactions with both **3** and the

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(19) Very recently, Kawachi et al. showed that the related *o*-(fluorodimethylsilyl)phenyllithium does not react with TMSCl at −78 °C. Kawachi, A.; Tani, A.; Machida, K.; Yamamoto, Y. *Organometallics* **2007**, *26*, 4697.

(20) As the temperature increase cannot be controlled precisely under our conditions, the yields of the individual species vary appreciably.

sterically more demanding **8**. Other electrophiles investigated here do not show this property and are thus not suited for twofold derivatization under the conditions described here. In view of our results, the reported synthesis of hexalithiobenzene from hexachlorobenzene and an excess of *t*-BuLi in 1,4-dioxane/pentane at very low temperatures is very remarkable.[12]

Experimental Section

General Procedure (Reaction Conditions A). A solution of 1,2-dibromobenzene **1** (0.1 mL, 0.829 mmol) in 60 mL of Et_2O/THF (1:1) was cooled to −120 °C with a nitrogen/ethanol cooling bath, and a cold (−78 °C) pentane solution of *t*-BuLi (2.3 mL, 3.4 mmol, 4.15 equiv) was added very rapidly. The yellow reaction mixture was stirred for 30 min at −120 °C, and the reaction was treated with an excess (10 equiv) of a cold solution (−78 °C) of the electrophile EX in 15 mL of Et_2O and stirred for 30 min at −120 to −110 °C. The solution was cooled down again to −120 °C and quenched by addition of 3 mL of cold (−78 °C) EtOH/concd HCl (8:2), stirred for 30 min, and warmed slowly to room temperature. Then hexamethylbenzene (0.134 g, 0.829 mmol) in 100 mL of Et_2O and 50 mL of water (or a half-concd solution of Na_2SO_3 in the case of iodine containing electrophiles) were added and stirred for 15 min. The organic layer was separated and washed with a half-concd aqueous solution of NaCl, $NaHCO_3$, and water (25 mL) and dried over $MgSO_4$. The products and their yields were identified by GC/MS.

Modification to Reaction Conditions A. In case of deutero-electrophiles the solvent was treated with a small amount of *t*-BuLi (0.1 mL, 0.148 mmol) before adding the reactants.

Reaction Conditions B. After the *t*-BuLi has reacted with **1** for 30 min, the cooling bath was removed and the reaction mixture was allowed to warm for 10 min before it was cooled down to −120 °C and treated with the electrophile as described above.

Preparation of 1,2-Bis(trimethylsilyl)benzene (7a). Compound **7a** was prepared according to the general procedure (reaction conditions A) by adding *t*-BuLi in pentane (36 mL, 53.28 mmol, 4.15 equiv) to 1,2-dibromobenzene **1** (1.5 mL, 12.44 mmol) in 160 mL THF/Et_2O (1:1). The reaction mixture was quenched by TMSOTf (12.5 mL, 69.06 mmol) in 15 mL Et_2O, then treated with EtOH/concd HCl (8:2) (5 mL). Then 100 mL of Et_2O and 50 mL of water were added. The organic layer was separated and washed with a half-concd aqueous solution of NaCl, $NaHCO_3$, and water (30 mL) and dried. The solvent was evaporated, and the colorless residue was dried in vacuo to remove trimethylsilyl benzene **9a**. The product **7a** was obtained in >92% yield (2.56 g, 11.51 mmol) with a purity of >99% based on GC analysis.

^{1}H NMR ($CDCl_3$) δ 0.36 (s, 6 H), 7.29−7.32 (dd, 2 H), 7.65−7.67 (dd, 2 H); ^{13}C NMR ($CDCl_3$) δ 1.9, 127.7, 135.2, 146.0; MS (EI): *m*/*z* (%): 222 (12) [$M^{+\bullet}$], 207 (100), 191 (98), 175 (39), 135 (6), 119 (13), 88 (8), 73 (91), 60 (21), 45 (57). Anal. Calcd for $C_{12}H_{22}Si_2$: C, 64.78, H, 9.97. Found: C, 64.63, H, 9.92. HRMS calcd: 222.12654. Found: 222.12659.

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Supporting Information Available: Analytical data for 1,2-bis(trimethylsilyl)benzene and GC/MS analyses of the reaction products obtained under reaction conditions B. This material is available free of charge via the Internet at http://pubs.acs.org.

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