JOC Note

Regiospecific Metalation of Oligobromobenzenes

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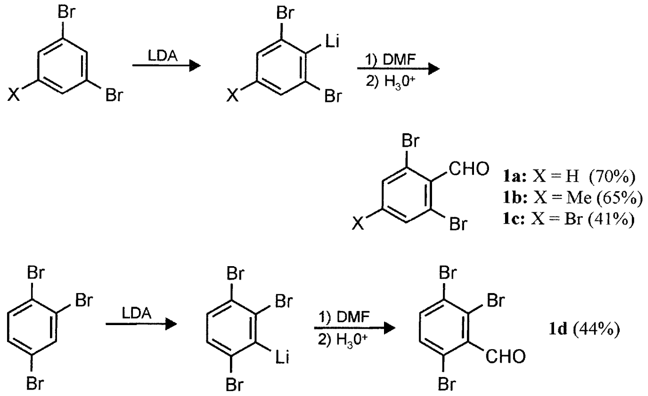
Abstract: The metalation of selected oligobromobenzenes with lithium diisopropylamide (LDA) was investigated. 1,3-Dibromo-substituted benzenes were metalated without special precautions since the resultant 2,6-dibromophenyllithium intermediates are relatively stable under reaction conditions: corresponding benzaldehydes were obtained in good or moderate yields after subsequent quench with *N*,*N*-dimethylformamide (DMF). Aryllithium compounds derived from 1,4- and 1,2-dibromobenzene are much less stable, but they could be trapped by the in situ use of chlorotrimethylsilane. The one-pot metalation/disilylation of 1,4-dibromo- and 1,2-dibromobenzene afforded 1,4-dibromo-2,5-bis(trimethylsilyl)benzene and 2,3-dibromo-1,4-bis(trimethylsilyl)benzene, respectively.

The ortho-directing ability of many common functional groups in the metalation of substituted benzenes has been extensively investigated and used for many years in organic synthesis.[1] Among halogens fluorine possesses the strongest ortho-directing ability therefore the metalation of fluorinated aromatics has received relatively much attention. In addition, ortho-fluorinated aryllithium intermediates are more thermally stable than their heavier halogen analogues which reveal a strong tendency to eliminate lithium halide due to the aryne formation.[2] The metalation of fluorobenzene with *n*-BuLi is rather slow in THF at −78 °C.[3] However, halogen substituted fluorobenzenes XC_6H_4F are lithiated without difficulty with *n*-BuLi ($X = F$,[4] Cl[5,6]) or LDA ($X = Br$,[5,6,7] I[5]) in the ortho position to the fluorine. The metalation of chlorobenzene can be accomplished with *sec*-BuLi in THF and the low temperature of ca −100 °C is crucial since the product, i.e., 2-chlorophenyllithium, decomposes at slightly higher temperature to form benzyne so it must be trapped at this temperature by appropriate electrophile.[8] However, dichlorobenzenes are metalated readily with ordinary butyllithium in THF at −75 °C. The products 2,3-dichlorophenyllithium,[9] 2,6-dichlorophenyllithium,[10] and 2,5-dichlorophenyllithium[9] obtained from *o*-, *m*-, and *p*-dichlorobenzene, respectively, are relatively stable at −78 °C. 2-Bromophenyllithium can be prepared from 1,2-dibromobenzene and *n*-BuLi, but it is even less stable than the 2-chloro derivative.[2,11] The reaction of 1,2-diiodobenzene with *n*-BuLi failed to yield 2-iodophenyllithium.[12]

SCHEME 1. Preparation of 2,6-Dibromobenzaldehydes 1a−d via Metalation of 1,3-Dibromobenzenes



The metalation of arenes containing bromine as the ortho-activating substituent was performed very recently, showing that the presence of two bromine atoms in the meta position gives best results as far as regioselectivity and stability of organolithium intermediates are concerned.[13,14] The only earlier report describes the lithiation of related compound, namely 2,5-dibromothiophene, as a useful method for the synthesis of several 3-substituted 2,5-dibromothiophenes.[15] Our results confirm that selected meta-dibromosubstituted benzenes can be easily and regioselectively metalated using LDA at the position between bromine atoms as demonstrated by the preparation of corresponding 2,6-dibromobenzaldehydes (Scheme 1). This is in accord with the behavior of 1,3-difluoro- and 1,3-dichlorobenzene which are also metalated exclusively at the ortho position adjacent to both halogen atoms. Quite obviously, the hydrogen atom located between two electronegative halogen atoms reveals stronger activity (or acidity) than the hydrogen atoms neighboring to only one halogen atom.[16] 2,6-Dibromophenyllithium was ob-

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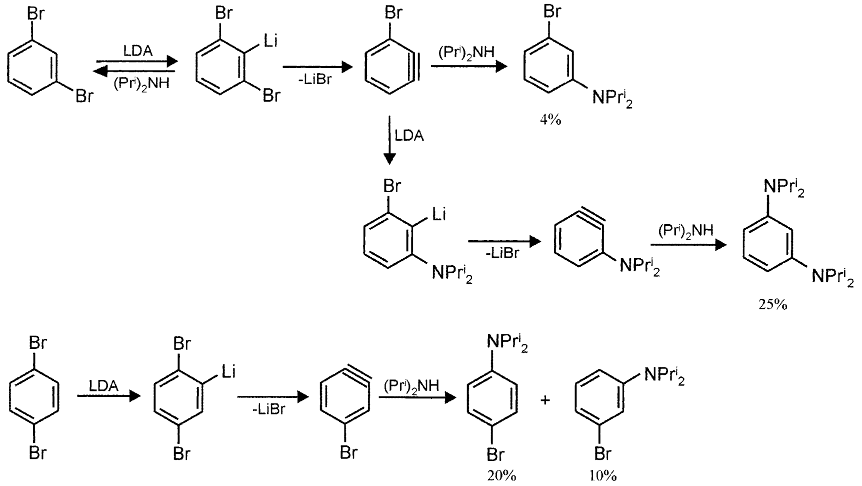
SCHEME 2. Addition of Nitrogen Nucleophiles to Arynes Generated from 1,3- and 1,4-Dibromobenzene



tained as an orange suspension in THF. On the contrary to 2-bromophenyllithium, this species was found to be reasonably stable below −50 °C. Thus, it can be conveniently prepared under standard conditions (cooling with dry ice/acetone) and used for consecutive reactions with electrophiles. Very similar behavior was observed for the metalation of 3,5-dibromotoluene showing that the presence of the methyl group does not influence the regioselectivity of the reaction and the stability of the organolithium intermediate; the comparable yields of benzaldehydes **1a** and **1b** (70 and 65%, respectively) were obtained. A slight difference was found in the case of 1,3,5-tribromobenzene and 1,2,4-tribromobenzene since the lower yields of the products 2,4,6-tribromobenzaldehyde (**1c**, 41%) and 2,3,6-tribromobenzaldehyde (**1d**, 44%), respectively, were isolated. The isolation of pure **1d** provides further evidence for the higher activity of the hydrogen atom flanked by two bromine atoms with respect to remaining hydrogen atoms.

We investigated the thermal stability of 2,6-dibromophenyllithium. A rapid and highly exothermic decomposition of this species was observed to start above −40 °C to give a complex mixture which was not analyzed in detail. However, it should be noted that a significant amount of 1,3-bis(diisopropylamino)benzene (25%) together with a small amount of 3-bromo-*N*,*N*-diisopropylaniline (4%) was isolated.[17] The latter is formed by the simple addition of Pr^i_2NH to 3-bromobenzyne generated directly from 2,6-dibromophenyllithium. The formation of the former must involve the addition of LDA to 3-bromobenzyne, elimination of LiBr, and finally trapping 3-aminobenzyne with Pr^i_2NH (Scheme 2). The availability of LDA is not obvious, but it can be rationalized assuming the equilibrium between substrates and products of the metalation reaction. In fact, a significant amount of 1,3-dibromobenzene (ca 15% of the starting material) was recovered which lends a strong support to the view that this compound is not converted quantitatively into 2,6-dibromophenyllithium.

The metalation of 1,4-dibromobenzene was accomplished using lithium 2,2,6,6-tetramethylpiperidide (LTMP) as reported recently, but no details were given.[13] We observed that the treatment of 1,4-dibromobenzene with LDA leads to the highly exothermic decomposition starting already at −70 °C. Clearly 2,5-dibromophenyllithium, whose formation in the first step should be assumed, is much less stable than the 2,6-isomer and does not survive under these conditions. Distillation of the reaction mixture afforded substantial amounts of 3- and 4-bromo-*N*,*N*-diisopropylaniline in ca. 10% and 20% yields, respectively, which points to some regioselectivity of the addition of amine to the aryne species (Scheme 2).

The instability of 2,5-dibromophenyllithium precludes its use for subsequent reactions with electrophiles, e.g., with DMF. However, this difficulty was overcome by the improved approach based on the in situ use of the appropriate electrophile, namely chlorotrimethylsilane (TMSCl), which allowed us to trap 2,5-dibromophenyllithium. Apparently, LDA deprotonates 1,4-dibromobenzene much more rapidly than it attacks TMSCl to give diisopropyl(trimethylsilyl)amine. On the other hand, TMSCl is able to trap aryllithium with a sufficient rate, precluding undesired aryne formation. When the metalation was carried out in the presence of 1 equiv of LDA and 1 equiv of TMSCl, the mixture of unreacted 1,4-dibromobenzene (20%) and 1,4-dibromo-2-trimethylsilylbenzene (**2a**, 60%) as well as 1,4-dibromo-2,5-bis(trimethylsilyl)benzene (**2b**, 20%) was obtained. The latter was isolated as the sole product in a high yield (84%) when 2 equiv of LDA and 2 equiv of TMSCl were used (Scheme 3). These results point that the introduction of one TMS group does not decrease the reactivity. The high regioselectivity of the second metalation/silylation leading to the exclusive formation of **2b** without traces of 1,4-dibromo-2,6-bis(trimethylsilyl)benzene should be noted.

The metalation of 1,2-dibromobenzene was reported recently as resulting in the formation of the relatively stable 2,6-dibromophenyllithium via the rearrangement of the unstable 2,3-dibromophenyllithium.[13] Nevertheless, the in situ use of 1 equiv of TMSCl resulted again in successful trapping the primary metalation product to give the mixture of 1,2-dibromobenzene (30%), 1,2-dibromo-3-trimethylsilylbenzene (**3a**, 55%), and 2,3-dibromo-1,4-bis(trimethylsilyl)benzene (**3b**, 15%). When 2 equiv of TMSCl was taken, the mixture of **3a** (48%) and

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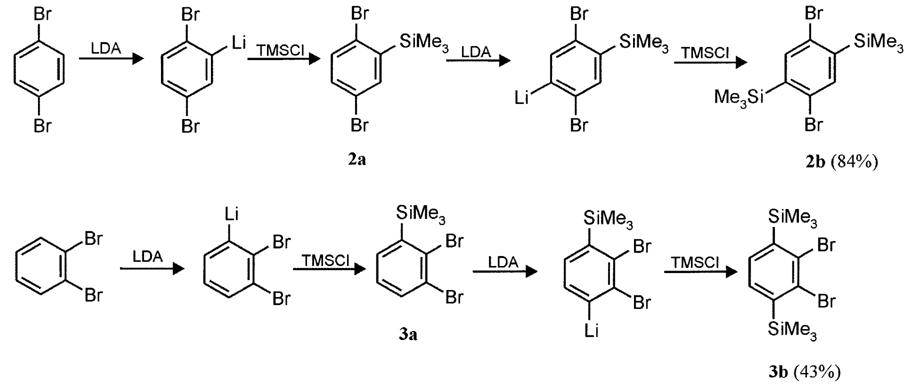
(17) For the up-to-date information concerning reactivity of arynes towards amines and other nucleophiles, see: Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701, and references therein.

SCHEME 3. The One-Pot Double Metalation/Silylation of 1,4- and 1,2-Dibromobenzene



3b (52%) was obtained (Scheme 3). Hence, the general reactivity pattern observed in the one-pot metalation/disilylation of 1,4-dibromobenzene was confirmed. However, it is clear that the metalation of the monosilylated derivative **3a** is rather sluggish since its conversion into the final product **3b** is not complete.

In conclusion, oligobromobenzenes undergo metalation easily using LDA in THF at −70 °C. However, the stability of the resultant aryllithium intermediates varies significantly depending on the kind of the substrate employed. Those bearing two bromine atoms adjacent to lithium are quite stable and can be subjected to reactions with appropriate electrophile, e.g., with DMF to give aldehydes. 2,5-Dibromo- and 2,3-dibromophenyllithium undergo rapid decomposition under metalation conditions, but it was possible to trap these unstable species by the in situ action of TMSCl. This approach seems to be an interesting synthetic tool for the synthesis of arylsilanes which cannot be prepared by the standard two-step route. Our research in this area is now in progress.

Experimental Section

All reactions were carried out under an argon atmosphere. Solvents were stored over sodium wire before use. Commercially available bromobenzenes as well as anhydrous *N*,*N*-dimethylformamide (DMF) and chlorotrimethylsilane (TMSCl) were used. Lithium diisopropylamide (LDA) was used as a 2 M solution in THF/heptane/ethylbenzene. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer using $CDCl_3$ as the solvent. All compounds gave satisfactory elemental analyses.

2,6-Dibromobenzaldehyde (1a). LDA (30 mL, 60 mmol) was added dropwise to the solution of 1,3-dibromobenzene (11.8 g, 50 mmol) in THF (100 mL) at −70 °C. An orange precipitate was formed. The mixture was stirred 30 min at −75 °C, and then DMF (4.4 g, 60 mmol) was added dropwise while maintaining the temperature at −70 °C. A purple solution was stirred for 30 min at −70 °C and hydrolyzed with dilute aq H_2SO_4. The yellow organic phase was separated. The water phase was extracted with ether (50 mL), and the extract was added to the organic phase. Solvents were evaporated to leave the crude product as a yellow-brown solid residue. It was washed with water and petroleum ether. Finally, it was recrystallized from cyclohexane (50 mL) to give **1a** as pale yellow needles, mp 89−91 °C.[18] Yield: 9.2 g (70%). ^{1}H NMR δ 10.24 (s, 1H), 7.63 (d, 2H), 7.20 (t, 1H). ^{13}C {^{1}H} NMR δ 191.30, 134.12, 133.80, 132.94, 124.94. Anal. Calcd for $C_7H_4Br_2O$: C, 31.86; H, 1.53. Found C, 31.71; H, 1.24.

2,6-Dibromo-4-methylbenzaldehyde (1b). This compound was prepared as described for **1a** starting from 3,5-dibromotoluene (12.5 g, 50 mmol). The crude product was obtained as a yellow solid which was washed with water and purified by recrystallization from cyclohexane (80 mL) to give **1b** as pale yellow needles, mp 95−97 °C. Yield: 9.0 g (65%). ^{1}H NMR δ 10.23 (d, 1H), 7.46 (q, 2H), 2.36 (t, 3H). ^{13}C {^{1}H} NMR δ 191.14, 145.90, 134.62, 129.84, 125.30, 21.14. Anal. Calcd for $C_8H_6Br_2O$: C, 34.57; H, 2.18. Found C, 34.80; H, 2.15.

2,4,6-Tribromobenzaldehyde (1c). This compound was prepared as described for **1a** starting from 1,3,5-tribromobenzene (15.7 g, 50 mmol). The crude product was obtained as a brown solid residue which was washed with water and petroleum ether and recrystallized from cyclohexane (50 mL) to give **1c** as pale brown crystals, mp 101−103 °C.[19] Yield: 7.0 g (41%). ^{1}H NMR δ 10.17 (s, 1H), 7.81 (s, 2H). ^{13}C {^{1}H} NMR δ 190.40, 136.46, 131.57, 127.81, 125.55. Anal. Calcd for $C_7H_3Br_3O$: C, 24.53; H, 0.88. Found C, 24.75; H, 0.78.

2,3,6-Tribromobenzaldehyde (1d). This compound was prepared as described for **1a** starting from 1,2,4-tribromobenzene (15.7 g, 50 mmol). The crude product was obtained as a brown solid residue which was washed with water and petroleum ether and recrystallized from cyclohexane (50 mL) to give **1d** as pale brown crystals, mp 114−116 °C, yield: 7.5 g (44%). ^{1}H NMR δ 10.11 (d, 1H), 7.62 (d, 1H), 7.50 (dd, 1H). ^{13}C {^{1}H} NMR δ 190.94, 137.22, 136.49, 134.33, 126.86, 126.82, 122.18. Anal. Calcd for $C_7H_3Br_3O$: C, 24.53; H, 0.88. Found C, 25.39; H, 0.82.

1,4-Dibromo-2,5-bis(trimethylsilyl)benzene (2b). LDA (2 M, 55 mL, 110 mmol) was added dropwise to the suspension of 1,4-dibromobenzene (11.8 g, 50 mmol) in THF (70 mL) containing TMSCl (12.0 g, 14 mL) at −70 °C. The resultant orange solution was stirred 30 min at −75 °C and hydrolyzed with dilute aq H_2SO_4. The yellow organic phase was separated, and the water phase was extracted with ether. Evaporation of the combined organic solutions left the crude product as a pale yellow solid residue. It was filtered, washed with cold methanol (3 × 10 mL), and dried to give **2b** as a white crystalline material, mp 98−100 °C. Yield: 16.0 g (84%). ^{1}H NMR δ 7.51 (s, 2H), 0.39 (s, 18H). ^{13}C {^{1}H} NMR δ 144.88, 140.07, 129.60, −0.65. Anal. Calcd for $C_{12}H_{20}Br_2Si_2$: C, 37.90; H, 5.30. Found C, 37.65; H, 4.91.

2,3-Dibromo-1,4-bis(trimethylsilyl)benzene (3b). This compound was prepared as described for **2b** starting from 1,2-dibromobenzene (11.8 g, 50 mmol). The residue obtained upon workup the reaction mixture was distilled in vacuo. A pale yellow oil, being the mixture of **3a** (48%) and **3b** (52%), was collected (bp 70−115 °C, 1 mmHg) and dissolved in the acetone/methanol mixture (10 mL, 1:1). Colorless crystals, which were separated from this solution while standing in a −70 °C freezer, were filtered, washed with cold methanol (2 × 10 mL), and dried to

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(19) Lock, G. *Chem. Ber.* **1939**, *72*, 511.

give **3b**, mp 71−73 °C. Yield: 8.2 g (43%). ^{1}H NMR δ 7.34 (s, 2H), 0.40 (s, 18H). ^{13}C {^{1}H} NMR δ 145.97, 134.15, 133.58, −0.18. Anal. Calcd for $C_{12}H_{20}Br_2Si_2$: C, 37.90; H, 5.30. Found C, 38.06; H, 4.94.

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Supporting Information Available: Copies of the ^{13}C NMR spectra of compounds **1a**−**d**, **2b**, **3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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