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A study on the metalation of alkoxydibromobenzenes

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Abstract—The metalation of (quasi)alkoxy-substituted dibromobenzenes $C_6H_3(OR)Br_2$ with lithium diisopropylamide (LDA) has been investigated. For 1-(quasi)alkoxy-3,5-dibromobenzenes (R = Me, TMS), different selectivities were observed depending on reaction conditions and the size of the alkoxy group. The methoxy group was an effective *ortho*-director whereas this was not the case for the bulky trimethylsilyloxy group. The metalation of related 2,5-dibromoanisole was also examined showing a significant *meta*-directing effect by the methoxy group. The thermal stability of aryllithium intermediates is significantly lower when lithium is flanked by a bromine and a methoxy group, whereas 4-(quasi)alkoxy-2,6-dibromoaryllithiums are less labile.

1. Introduction

Directed *ortho*-metalation of substituted arenes has been thoroughly investigated for many years and nowadays it is a powerful method for the diverse functionalization of aromatic systems.[1] However, bromine has been ranked as a relatively weakly *ortho*-directing group and hence metalation of bromoarenes has not been the subject of many studies. To effect *ortho*-directed deprotonation, nonnucleophilic strong bases such as LDA must be used as bromine–lithium exchange predominates when alkyllithium bases are employed. The aryllithium intermediates thus generated are usually very labile and may readily isomerize[2] or release the corresponding arynes.[3] This latter reaction has found numerous synthetic applications,[4] for example, in the synthesis of polycyclic systems.[5,6] Due to the limited stability of *ortho*-bromoaryllithium species, their subsequent trapping is frequently difficult. An internal quench with an appropriate electrophile may often be the only alternative.[7] The metalation of simple bromoanisoles was investigated showing 2- and 4-bromoanisole to be resistant to LDA-mediated deprotonation under cryogenic conditions.[8] However, the metalation of 3-bromoanisole proceeded readily between the two substituents reflecting their enhanced activating effect, but the resultant aryllithium decomposed instantaneously to form 3-methoxybenzyne, which was trapped with furan as a Diels–Alder adduct.[9] Our study focused on the reactivity of related alkoxydibromobenzenes and is an extension of our recent investigations on the metalation and functionalization of various bromobenzenes.[10] We attempted to use an internal TMSCl quench to trap the labile 2-bromo-6-methoxyphenyllithium at −70 and −90 °C, however, we obtained only a low yield (ca. 10%) of impure 3-bromo-2-(trimethylsilyl)anisole. 3-Methoxy-*N*,*N*-diisopropylaniline derived from the addition of diisopropylamine to 3-methoxybenzyne was formed as the main product. Recently, Schlosser and Castagnetti demonstrated that 2-bromo-6-(trifluoromethoxy)phenyllithium generated from 1-bromo-3-(trifluoromethoxy)benzene is stable at −78 °C.[11]

2. Results and discussion

We investigated the metalation of other compounds related to the parent 3-bromoanisole, namely, 1-alkoxy-3,5-dibromo- and 1-alkoxy-2,5-dibromobenzenes. The metalation of 3,5-dibromoanisole was thoroughly examined (Scheme 1). It is known that the position between two bromine atoms can be readily deprotonated with LDA due to their cooperating acidifying effect.[12] However, we observed that the position flanked by bromine and the methoxy group was deprotonated rather than that between the two bromines, thus resembling the *s*-BuLi promoted lithiation of 3,5-dichloroanisole.[13] The resultant aryllithium species was not stable on the macroscopic time scale at around −70 °C and decomposed

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Keywords: *ortho*-Metalation; Dibromobenzenes; Silylation.

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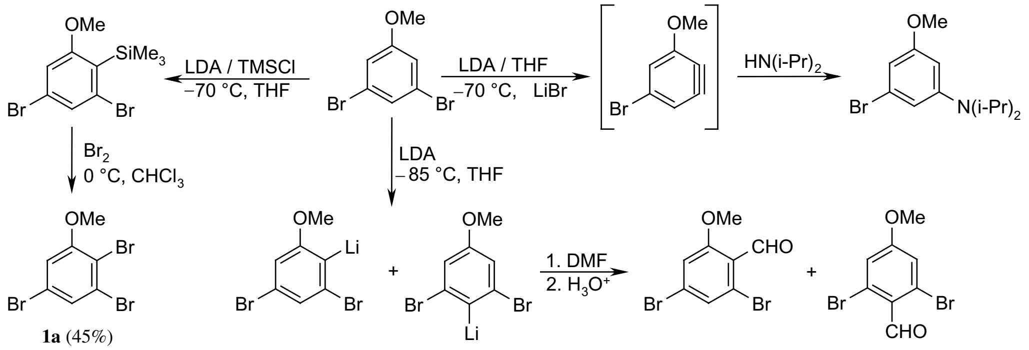


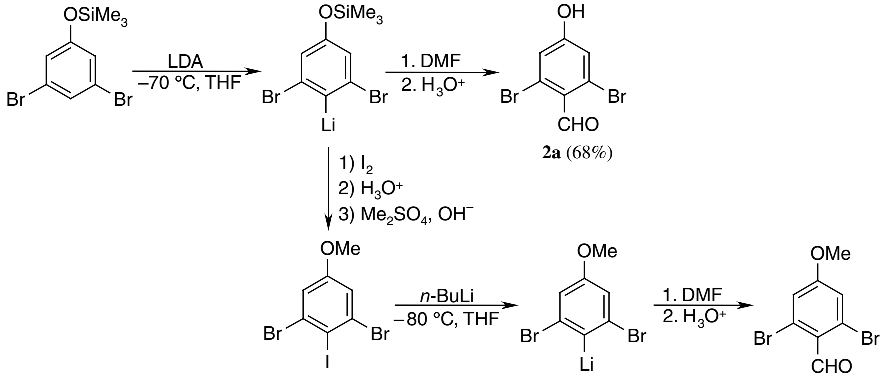
1a (45%)

1b (31%) **1c**

Scheme 1. LDA-mediated metalation of 3,5-dibromoanisole.

via the corresponding aryne to form 3-bromo-5-methoxy-*N*,*N*-diisopropylaniline as the major product in ca. 50% yield. On the other hand, it could be effectively trapped in situ with TMSCl to give 3,5-dibromo-2-(trimethylsilyl)anisole, contaminated with some impurities but not with its regioisomeric analogue. This compound was resistant to subsequent metalation/silylation and underwent easy desilylation with bromine to produce 2,3,5-tribromoanisole **1a**.[14] We found that it was possible to generate 2,4-dibromo-6-methoxyphenyllithium in the absence of the trapping electrophile at a temperature around −85 °C without instantaneous decomposition. Thus, the slight structural modification of placing a bromine at the 4-position had a remarkable positive effect on the thermal stability of the 2-bromo-6-methoxyphenyllithium system. However, under these conditions the lithiation was not regioselective as a mixture of 3,5-dibromo-2-(trimethylsilyl)anisole and 3,5-dibromo-4-(trimethylsilyl)anisole in a ratio of 85:15 was formed after subsequent TMSCl quench, and a substantial amount of 3,5-dibromoanisole was recovered. Similarly, 2,4-dibromo-6-methoxybenzaldehyde **1b** and the isomeric 2,6-dibromo-4-methoxybenzaldehyde **1c** were obtained in 55% overall yield and in a comparable ratio with DMF as the electrophile, the major product **1b** being isolated in 31% yield. DMF is known to react reversibly with some aryllithiums and the composition of the reaction mixture might not reflect the real proportion of aryllithium isomers before trapping.[15] However, the self-consistency with in situ silylation suggests that this is not the case here. The selectivity of the reaction is time dependent: when the lithiation was carried out for 2 h prior to the DMF quench, the mixture of **1b** and **1c** was formed in a ratio of 70:30. These results suggest that the lithiation of 3,5-dibromoanisole at the 2-position is kinetically favored but the resultant aryllithium isomerizes slowly to form 2,6-dibromo-4-methoxyphenyllithium.

In the case of 1,3-dibromo-5-(trimethylsilyloxy)benzene the bulky substituent completely protects the neighboring hydrogen atoms against attack by LDA. Thus, the position between the two bromine atoms is selectively deprotonated as shown in Scheme 2. The resultant aryllithium species is stable at a temperature around −70 °C. Apparently, the stabilization by the second bromine is better than that provided by the methoxy group. The trimethylsilyloxy group was readily cleaved during aqueous workup to liberate the hydroxyl group, which offers synthetic potential for subsequent transformations. For example, treatment with DMF afforded 2,6-dibromo-4-hydroxybenzaldehyde **2a** in good yield. Similarly, an iodine quench followed by hydrolysis gave 3,5-dibromo-4-iodophenol and subsequent Williamson methylation afforded 3,5-dibromo-4-iodoanisole **2b**. This compound was subjected to iodine–lithium ex-



2a (68%)

2b (57%)

1c (78%)

Scheme 2. LDA-mediated metalation of 1,3-dibromo-5-(trimethylsilyloxy)benzene.

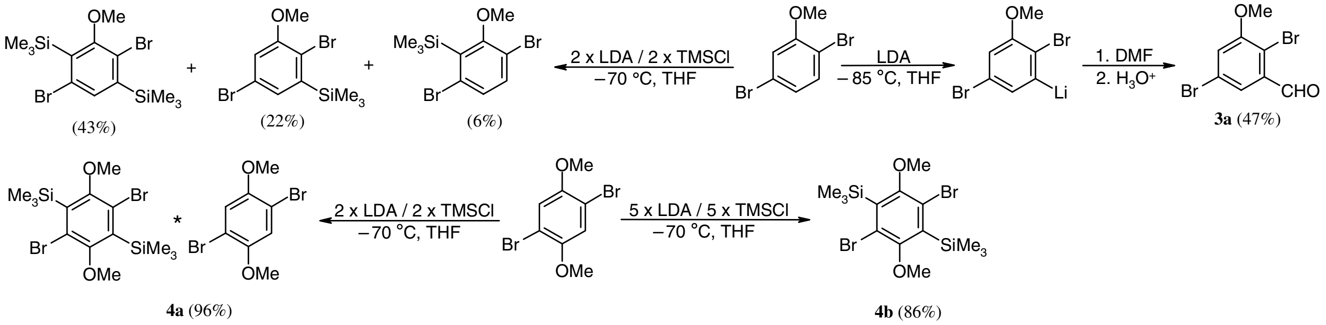
change producing an aryllithium that was stable at temperatures around −80 °C and could be successfully trapped with DMF as shown in Scheme 2 to give a good yield of **1c**—the by-product of the direct lithiation of 3,5-dibromoanisole. It should be noted that attempted isomerization of this aryllithium by the addition of diisopropylamine prior to addition of DMF failed and again pure **1c** was isolated. To summarize, a selective and diverse functionalization of 3,5-dibromophenol at the 4-position can be achieved using an *O*-silylation/metalation sequence.

The metalation of 2,5-dibromoanisole was performed using 2 equiv of LDA followed by an internal TMSCl quench (Scheme 3). According to GC/MS analysis, 2,5-dibromo-3,6-bis(trimethylsilyl)anisole was the major product (43%), accompanied by substantial amounts of 2,5-dibromo-3-(trimethylsilyl)anisole (22%) and 3,6-dibromo-2-(trimethylsilyl)anisole (6%) as well as unreacted starting material (14%). Thus, in contrast to 3,5-dibromoanisole, the metalation is not preferentially *ortho*-directed by the methoxy group. In another experiment, lithiation at around −85 °C followed by a DMF quench afforded 2,5-dibromo-3-methoxybenzaldehyde **3a** in moderate yield. The regiochemistry of metalation is clearly controlled primarily by the bromine. Deprotonation at the 3-position suggests that the long-range inductive effect of the methoxy group is responsible for the preferred orientation. We believe that the relatively weak susceptibility of the angular position (the position between two substituents) to undergo metalation can be rationalized in terms of steric interactions between the bromine and the methoxy group. Due to these interactions, the methoxy group becomes *anti*-oriented with respect to the neighboring bromine, and this conformation provides, in turn, significant steric hindrance in the vicinity of the neighboring hydrogen, which results in its decreased reactivity.

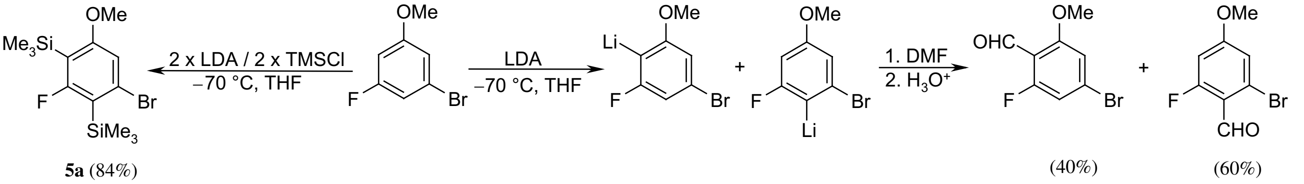
Attempted in situ disilylation of 1,4-dibromo-2,5-dimethoxybenzene using stoichiometric amounts of LDA and TMSCl gave a product, which X-ray analysis revealed to be an intermolecular 1:1 compound **4a** consisting of the starting material and the disilylation product **4b**. Conformational restrictions imposed by methoxy groups did not prevent subsequent metalation/silylation but significantly decreased the reactivity: 1,4-bis(trimethylsilyl)-2,5-dibromo-3,6-dimethoxybenzene **4b** was isolated in good yield when a 2.5-fold excess (i.e., 5:1) of LDA and TMSCl was used (Scheme 3).

In addition, the metalation of 3-bromo-5-fluoroanisole with LDA was investigated to probe the relative *ortho*-directing ability by bromine versus methoxy in the presence of strongly acidifying fluorine.[16,17] According to our earlier findings,[10] disilylation was efficient at both positions adjacent to fluorine, to give 2,4-bis(trimethylsilyl)-5-bromo-3-fluoroanisole **5** in 84% yield (Scheme 4). The introduction of a third TMS group was not possible, presumably reflecting a strong buttressing effect of the two TMS groups in **5**. Lithiation followed by a DMF quench afforded a mixture of 4-bromo-2-fluoro-6-methoxybenzaldehyde and 2-bromo-6-fluoro-4-methoxybenzaldehyde (40:60). Hence, in this case bromine revealed a slightly stronger *ortho*-directing power in comparison with a methoxy group.

In conclusion, metalation of alkoxydibromobenzenes with LDA proceeds with varying regioselectivity. Bromine is able to compete with methoxy as the effective *ortho*-director to a significant extent. Bulky trimethylsilyloxy groups prevent *ortho*-lithiation and this property facilitates regioselective functionalization of alkoxydibromobenzenes. In addition, the regioselectivity of the metalation is strongly influenced by a combination of steric (conformational) factors with distinct long-range



Scheme 3. LDA-mediated metalation of 2,5-dibromoanisole and 1,4-dibromo-2,5-dimethoxybenzene.



Scheme 4. LDA-mediated metalation of 3-bromo-5-fluoroanisole.

interactions as demonstrated by the behavior of 2,5-dibromoanisole.

3. A typical procedure for metalation of alkoxydibromobenzenes

In a typical lithiation, LDA freshly prepared from diisopropylamine (2.42 g, 24 mmol) and *n*-BuLi (10 M solution in hexanes, 2.4 mL, 24 mmol) in THF (15 mL) at −70 °C was added dropwise (ca. 15 min) to a solution of 3,5-dibromoanisole (6.48 g, 20 mmol) in THF (30 mL) at −85 °C. The resultant solution was stirred for 15 min followed by slow addition of DMF (1.80 g, 24 mmol). The mixture was stirred for 15 min and then hydrolyzed with dilute aq H_2SO_4. The organic phase was separated and the water phase was extracted with ether (10 mL). Evaporation of the combined organic solutions left a solid that was washed with water and recrystallized from toluene (5 mL) to give **1b** as colorless crystals, mp 128–130 °C. Yield: 1.8 g (31%). Evaporation of the mother liquor followed by washing of the residue with hexane (5 mL) afforded a mixture of **1b** and the isomeric by-product **1c** (1.0 g, ca. 70:30). Characterization of **1b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.33 (1H, s, C*H*O), 7.43 (1H, d, *J* 1.5 Hz, Ph), 7.11 (1H, d, *J* 1.5 Hz, Ph), 3.93 (3H, s, O*Me*); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 189.5, 162.1, 129.3, 129.0, 125.6, 122.4, 115.0, 56.7. Anal. Calcd for $C_8H_6Br_2O_2$: C, 32.69; H, 2.06. Found C, 32.55; H, 2.16.

Acknowledgements

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Supplementary data

Selected synthetic experimental data, copies of the ^{13}C NMR spectra of all new compounds and X-ray experimental data of compound **4a** are included. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 264395. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk]. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tetlet.2005.04.065.

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