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Sterically facilitated *meta*-lithiation of arenes, containing electron-donating groups

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ABSTRACT: The influence of the bulky trimethylsilyl substituent on the selectivity of metallation of dimethylaniline, anisole and 1-dimethylaminonaphthalene is studied. The neighboring SiMe₃ group forces dimethylamino and methoxy groups to occupy a conformation with an unshared electron pair turned towards silicon atom. This forced conformation prevents NMe₂ and OMe groups from providing the DOM-effect, thus facilitating *meta*-metallation with the use of bulky LiCKOR. While the inverted NMe₂ group completely suppresses *ortho*-metallation, the less bulky and more electron withdrawing OMe group demonstrates more rotation freedom allowing selective *ortho*-metallation with smaller reagents such as *n*-BuLi or *tert*-BuLi.

INTRODUCTION

It is widely known that arenes containing electron donating groups with unshared electron pairs undergo selective *ortho*-metallation due to the so-called Direct *Ortho*-Metallation (DOM) effect.[1] Thus *N*,*N*-dimethylaniline **1**, anisole **2** and fluorobensene **3** are selectively metallated to the *ortho*-position upon treatment with *n*-butyllithium in ethers in the presence of *N*,*N*,*N*,*N*-tetramethylethylenediamine (TMEDA), which gives corresponding aryllithiums **4-6** with good to high yields (scheme 1).[2–4]



The situation dramatically changes in the case of related naphthalene derivatives **7-9**. The lithiation of 1-dimethylaminonaphthalene **7** leads to the formation of a *peri*-lithio derivative **12** with high yield, while fluoronaphthalene **9** undergoes exclusively *ortho*-lithiation.[4,5] Methoxynaphthalene **8** occupies an intermediate position: depending on the conditions, it can be lithiated to either the *ortho*- or *peri*-position, thus demonstrating competition between the higher CH-acidity of the H-2 atom and the higher stability of the five-membered metallocycle (scheme 2).[6]



Scheme 2.

The metallation of 1,8-bis(dimethylamino)naphthalene (DMAN, proton sponge) **14** is especially surprising because it leads to the formation of a *meta*-lithioderivative **15** as the main product in all cases (scheme 3).[7,8] It has been proven that the preferable *in/in* conformation of NMe₂ groups is responsible for this issue: it prevents the realization of the DOM-effect and sterically hinders the C2(7)-H bond from deprotonation by bulky reagents.[8]



The above-mentioned phenomenon raises the question on whether or not the direct selective *meta*functionalisation of arenes containing electrondonating groups can be achieved by the sterical hindering of the DOM-effect. This is especially desirable since reactions of such substrates with electrophiles yield mostly *ortho*- and *para*-substituted products.[9] Here we present our experimental and theoretical study on the influence of bulky trimethylsilyl groups in the *ortho*- or *peri*-position on the metallation of methoxy and dimethylamino benzenes and naphthalenes.

RESULTS AND DISCUSSION

We started our experiments with the preparation of thrimethylsilyllated arenes **16-18** through the treatment of lithioarenes **4**, **5** and **12** with trimethychlorosilane (scheme 4). It was expected that the sterical pressure of the bulky substituent will force the methoxy and especially the dimethylamino group to occupy the conformation with unshared electron pairs turned to the silicon atom (*in*-conformation), and thus being unable to provide the DOM-effect.



Journal Pre-proof Scheme 4.

Since all obtained trimethylsilylarenes are liquids, their X-Ray study was not possible. Instead, we performed gas phase quantum chemical calculations in order to confirm our expectation on the structure of the studied substrates (Figure 1). Indeed, the maps of the electron localization function maxima (ELF) demonstrate the expected *in*-conformation with lone pairs turned towards the silicon atom for all cases. One can assume that this conformation is stabilized by the interaction of nitrogen or oxygen lone pairs with the silicon empty d-orbital. However, the performed NBO analysis [10] revealed that there is no such interaction and the silicon d-orbitals remain empty even in the case of amine **18** (see Figure S2 in Supplementary materials). Thus, the mentioned *in*-conformation is forced and stabilized only by sterical pressure of the bulky SiMe₃ group. We also calculated an optimized geometry and proton affinities for all possible monoanions of compounds **16-18** in order to compare their CH acidities (Figure 2, see also Figure S3 in Supplementary materials). One can see that the PA of anions with a negative charge in the *ortho*-position to a nitrogen or oxygen atom is 5-10 kcal/mole lower than for any other isomer.



Figure 1. Optimized molecular structure for compounds **16–18** in vacuo (B3LYP/6-311++G(d,p)). The electron localization function (ELF) level is shown.



Figure 2. Calculated proton affinities (kcal/mole) for anions of compounds **16–18** (B3LYP/6-311++G(d,p)).

We performed metallation of compounds **16-18** with a mixture of potassium *tert*-butylate, *n*-butyllithium (aka LiCKOR [11]) and TMEDA – a bulky and extremely strong metallation agent, as well as with *n*-BuLi-TMEDA and *tert*-BuLi-TMEDA mixtures. We expected that forced *in*-conformation would prevent *ortho*-to NMe₂ group positions from metallation by bulky reagents. In all cases, no evidences of

CH bond *ortho* to the SiMe₃ group deprotonation were detected. This corresponds to the experiments performed by Schlosser and Knochel, who both attributed this phenomenon to the sterical hindrance of the *ortho*-CH proton by the bulky SiAlk₃ group.[11,12] This statement seems reasonable and to some extent obvious, however we performed the visualisation of electron density isosurfaces mapped by electrostatic potential (see Figure S4 in Supplementary materials), which clearly demonstrates that the CH proton *ortho* to the SiMe₃ group holds the least (among other aromatic CH protons) positive potential. As a result, this position becomes less favorable for the interaction with the negatively charged deprotonating agent (carbanionic center of organometallic reagent). Moreover, from the PA values (Figure 2) one can see that the deprotonation of mentioned CH bonds leads to the formation of less stable carbanions. Thus, the bulkiness of the SiMe₃ group is not the only feature preventing metalation of the neighbouring CH bonds, and the electron donating nature of this substituent is also to be considered. Keeping all this in mind, it was expected to observe somewhat selective lithiation of the CH-bond *meta* to the NMe₂ (or OMe) group, since these protons bear the second most positive charge and their deprotonation leads to the formation of the second most stable carbanion.

We found that compound **16** yields only products of H-4 and H-5 hydrogens deprotonation upon treatment with LiCKOR-TMEDA, despite a noticeably higher acidity of the C6-H bond (Scheme 5, Figure 3a). In contrast, *N*,*N*-dimethylaniline **1** gives a mixture of all possible products (Scheme 5, Figure 3b)[8] under same conditions. Switching to the *tert*-BuLi-TMEDA mixture gives the similar result, however some unreacted started material remains. The treatment of the amine **16** with an *n*-BuLi-TMEDA mixture in Et₂O or hexane leads to no metallation even at an elevated temperature. Thus, our expectations were confirmed: 1) the sterical pressure of the bulky SiMe₃ group prevents the NMe₂ group of **16** to occupy an *out*-conformation, requested for the DOM-effect realization, and 2) the *in*-conformated NMe₂ group sterically hinders the H-6 atom from deprotonation.



Scheme 5.



Figure 3. Fragments of ¹H NMR spectra (CDCl₃) for the reaction mixture after the metallation of compounds **16** (a, 500 MHz) and **1** (b, 250 MHz) with *tert*-BuOK, *n*-BuLi, TMEDA mixture.

Treating of **18**, the calculated molecular structure of which is very reminiscent of a proton sponge **14**, with LiCKOR-TMEDA unexpectedly leads to the formation of a complicated mixture of products, which is very unlikely for **14** but typical for naphthalene [11]. We believe that the higher inertness of the proton sponge originates from a strong +*M*-effect provided by two NMe₂ groups, which noticeably overcome their -*I*-effect. In the case of **18**, one NMe₂ group obviously provides a less strong +*M*-effect, thus facilitating polymetallation. Indeed, switching to the *tert*-BuLi-TMEDA mixture (less basic than LiCKOR but also quite bulky) leads to a significant simplification of the reaction mixture and formation of four aldehydes (after treatment with DMF) **23a-d** (Scheme 6, Figure 4). The result of this experiment leads to two main conclusions: 1) expectedly, the sterical hindrance prevents the deprotonation of H-7 or H-2 hydrogens, 2) the formation of the aldehydes **23a-d** originates from the proximity of PA values for the related anions (Figure 2).



Scheme 6



Figure 4. Fragment of ¹H NMR spectra for the reaction mixture after the metallation of compound **18** with a *tert*-BuLi, TMEDA mixture (CDCl₃, 400 MHz).

Noticeably, the metallation of ether **17** with an *n*-BuLi-TMEDA mixture in hexane leads to selective H-6 hydrogen deprotonation with 57% conversion over 24 hours (Scheme 7). Switching to a *tert*-BuLi-TMEDA mixture gives the same *ortho*-selectivity, however with 100% conversion. One can assume that the sterical pressure of the SiMe₃ group on the OMe group does not fully hinder the H-6 proton and leaves an opportunity for the OMe group to coordinate the organometallic reagent, thus providing the DOM-effect. Indeed, scanning the potential energy surface for the complex of **17** with the LiMe molecule using the ModRedundant method revealed the possibility for the coordination of an oxygen atom to lithium when the distance between these atoms reaches ~1.9 Å (Figure 5, see also Figure S5 in Supplementary materials). However, optimization of molecular geometry of the *ortho*-lithiated complexes **26-28** demonstrate that neither OMe nor NMe₂ groups undergo rotation/inversion to coordinate the neighboring lithium atom (Figure 6). Altogether, this data leads to the conclusion that the selective *ortho*-metallation of **17** with *n*-BuLi or *tert*-Bull originates not from a DOM-effect provided by the OMe group, but from the highest acidity of the C6-H bond (magnified by the strong *-I*-effect of oxygen) which is only moderately hindered by the OMe group and thus accessible for the interaction with relatively small organometallic reagents.



Scheme 7.



Figure 5. Optimized molecular structure for the complex of **17** with MeLi (B3LYP/6-311++G(d,p)). Optimal O-Li distance (Å) is shown.



Figure 6. Optimized molecular structure for the complex of **26-28** with TMEDA (B3LYP/6-311++G(d,p)). Total energies are shown.

As it was expected, the treatment of **17** with the LiCKOR-TMEDA mixture results in significant *meta*lithiation. Due to relatively high CH-acidity (compared to benzene, or *N*,*N*-dimethylaniline) of the substrate, the resulting mixture is quite complicated. However, through the use of NOESY NMR spectroscopy, it becomes clear that the main reaction products are *ortho*-aldehyde **25a** and *meta*aldehyde **25b** (Scheme 8).





CONCLUSIONS

In summary, it has been proven that the insertion of bulky SiMe₃ groups into *ortho-* or *peri*-positions to NMe₂ or OMe groups prevents the realization of the DOM-effect. Firstly, the bulky SiMe₃ group forces dimethylamino and methoxy groups to occupy a stable conformation with lone electron pairs oriented towards the silicon atom, which prevents the effective coordination with lithium. Secondly, methyl groups of immobilized NMe₂ or OMe groups sterically hinder the C2(7)-H bonds from deprotonation by bulky bases. Thirdly, while *ortho*-CH-bonds are blocked, the noticeably high acidity of *meta*-CH bonds facilitates *meta*-lithiation.

ASSOCIATED CONTENT

Experimental details, quantum-chemical calculations, ¹H, ¹³C, NOESY and COSY NMR spectra for all obtained compounds are available in Supplementary Information.

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- 1) Bulky SiMe₃ groups in *ortho* or *peri*-positions to NMe₂ or OMe groups prevent realization of the DOM-effect.
- 2) Methyl fragments of immobilized NMe₂ or OMe groups sterically hinder *ortho*-CH-bonds from deprotonation by bulky bases.
- 3) While *ortho*-CH-bonds are blocked, noticeably high acidity of *meta*-CH bonds facilitates meta-lithiation.

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