Selective Metalation of 4,6-Dibromoresorcinol Dimethyl Ether with LiTMP

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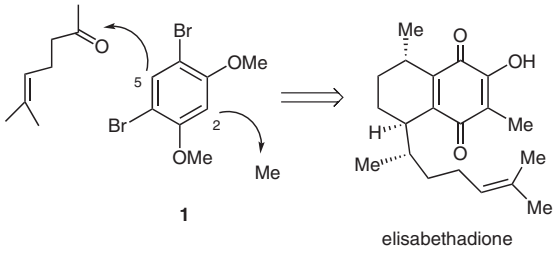
Abstract: 4,6-Dibromoresorcinol dimethyl ether was selectively metalated at C-5 with lithium tetramethylpiperidide (LiTMP). A rationale for the selective metalation is proposed.

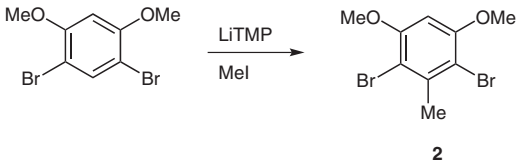
Key words: lithium tetramethylpiperidide, metalation, regioselectivity, theory, alkylation

As part of a synthetic approach to substituted quinones such as elisabethadione,[1] we planned a synthetic route from 4,6-dibromoresorcinol dimethyl ether (**1**), which is readily generated from commercially available 1,3-dimethoxybenzene (Scheme 1). Our plan was to introduce the methyl group and an eight-carbon alcohol through sequential metalation of **1**, and then use a palladium-mediated cyclization to generate the tetralin framework.[2]



Scheme 1

Previous studies had shown the facile metalation of 1,3-dimethoxybenzene using *n*-butyllithium.[3,4] In contrast, there have been only a few reports of the metalation of 1,3-dibromobenzenes.[5,6] Surprisingly, treatment of **1** with lithium tetramethylpiperidide (LiTMP) in tetrahydrofuran (THF) at –78 °C followed by methyl iodide, afforded the methylated derivative **2** in 96% yield as the *sole* product (Scheme 2). The structure of **2** was supported by a strong NOE correlation between the aromatic ring hydrogen and the O-methyl groups. As additional support for the assigned structure, the product obtained from dibromination of 2,6-dimethoxytoluene was found to generate a proton NMR spectrum that differed from that of compound **2**.

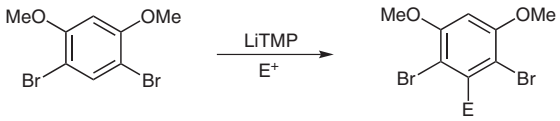


Scheme 2

The reason for the high selectivity of deprotonation *ortho* to the two bromines is not clear. In their key paper on the metalation of 2,5- and 3,5-dibromoanisole with lithium diisopropylamide at –85 °C, Serwatowski and co-workers showed that a mixture of metalation products was produced and that the ratio of the products formed was time dependent.[7] They observed benzyne formation at temperatures above –70 °C. Hickey and co-workers studied the metalation of 3-bromochlorobenzene on an industrial scale and also found that benzyne formation could be minimized by careful control of reaction temperature.[8]

Although the product was not what we had expected, the metalation was regioselective. We next examined the reaction of the anion of **1** with representative electrophiles. This work is described in Table 1.

Table 1 Reaction of Electrophiles with the Anion of **1**



Electrophile	Yield (%)	Compound
methyl iodide	96	**2**
allyl bromide	98	**3**
6-methyl-5-hepten-2-one	0	–
ethyl bromoacetate	0	–
benzaldehyde	72	**4**
2-bromobenzaldehyde	55	**5**
butanal	53	**6**
iodine	75	**7**

As the results from Table 1 illustrate, a number of compounds bearing acidic hydrogens, such as 6-methyl-5-hepten-2-one and ethyl bromoacetate, did not afford the desired products, presumably due to anion exchange. It is likely that this exchange takes place because of the steric hindrance that occurs between the electrophile and the bromine atoms of the anion of **1**. Fortunately, the anion of **1** reacts effectively with iodine, alkyl halides, and both aliphatic and aromatic aldehydes.

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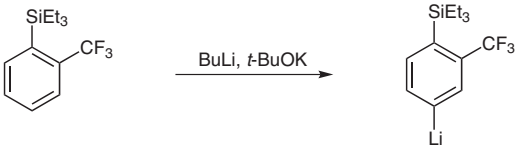
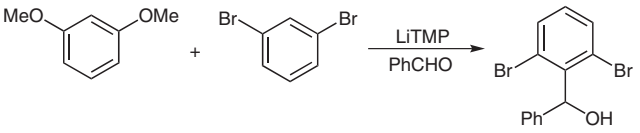
It had been shown by Trost and Saulnier that steric hindrance on the TBS protecting group can be used to direct metalation away from the positions *ortho* to the OTBS group.[9] A more subtle effect termed 'steric buttressing' has been invoked by Schlosser and co-workers to rationalize the novel metalation reaction shown in Scheme 3.[10] In the absence of the triethylsilyl group, metalation occurs *ortho* to the trifluoromethyl group.



Scheme 3

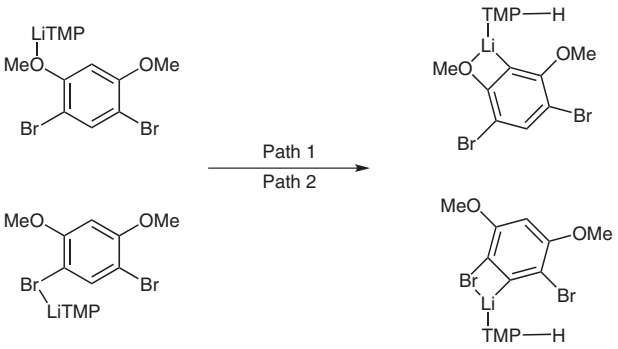
Since we found no reports of the reaction of 1,3-dimethoxybenzene with LiTMP, a possible explanation for the observed result is that LiTMP does not readily deprotonate 1,3-dimethoxybenzene at low temperatures. Treatment of 1,3-dimethoxybenzene with LiTMP under the conditions used to deprotonate **1**, followed by addition of benzaldehyde, afforded a 40% yield of the benzhydrol. Significantly, a competition experiment using one equivalent of 1,3-dimethoxybenzene and one equivalent of 1,3-dibromobenzene with one equivalent of LiTMP, using conditions employed to deprotonate **1** followed by quenching with benzaldehyde, produced *only* the adduct with 1,3-dibromobenzene (Scheme 4). In view of this experiment, it is unlikely that steric buttressing plays a large role in the observed selectivity with **1**.



Scheme 4

Theoretical analysis was used to further understand how deprotonation competition occurs with respect to the reactions of LiTMP with 1,3-dibromobenzene, 1,3-dimethoxybenzene, and 1,3-dibromo-4,6-dimethoxy benzene prior to electrophilic substitution. All stationary structures (including transition states), energies, and frequencies were calculated using the 6-311G(d,p) basis set for H, C, N, Li and O and the Hay–Wadt LANL2DZdp ECP for the Br at the HF and B3LYP levels of theory.[11] The zero point energies (ZPE) were calculated at –78 °C. B3LYP calculations using NWChem were performed to obtain structures including correlation and to improve the energetics and frequencies.[12] Finally, in order to incorporate some of the solvent effects, single point energies were performed with the B3LYP-COSGMS method as implemented in GAMESS.[13–15] For the COSGMS runs, an extrapolation based on experimental data was used to obtain a dielectric constant for the THF solvent at –78 °C of 12.02 Debyes.[16] Geometries for all minima and transition states, as well as absolute and relative energetics, are included in the Supporting Information.

In the computational work, the B3LYP calculations produced intermediates that were complexes of LiTMP with the various substituted benzenes species. The two bromine atoms *ortho* to the hydrogen being abstracted would have strong non-bonded interactions with any base. Dissociation of the TMP dimer into the monomer may precede deprotonation.[17] Optimizations of any separated species at less than ~10 Å led to these complexes. For the 1,3-dibromo-4,6-dimethoxybenzene reactions, the initial barrier of path 2 is 4.6 (5.7) kcal/mol lower than the initial barrier of path 1 at the DFT (COSGMS) level without ZPE (Scheme 5). With ZPE, the initial barrier of path 2 is 5.3 kcal/mol lower than the initial barrier of path 1. Furthermore, both path 1 and path 2 are exothermic; however, path 2 is exothermic by –13.4 kcal/mol whereas path 1 is exothermic by –3.8 at the DFT level with ZPE. The COSGMS calculations also produced similar results for the exothermicity (e.g., –15.5 and –3.8 kcal/mol).



Scheme 5

For the 1,3-dibromobenzene and 1,3-dimethoxybenzene reactions, calculations identified similar trends. Comparison of the initial barriers in both reactions favored deprotonation between the substituents (as opposed to the hydrogens *meta* to the substituents) by ~6–10 kcal/mol. Comparisons of the overall complex energetics in both reactions favored deprotonation between substituents by ~3–6 kcal/mol. In the 1,3-dimethoxybenzene reactions, both DFT and COSGMS calculations identified endothermic reactions for both *meta* and *ortho* deprotonation. In the 1,3-dibromobenzene reactions, COSGMS showed a further increase in the exothermicity already present at the DFT level for both deprotonations. These results support those obtained in the competition experiment.

The metalation of **1** is remarkably regioselective. The anion is sufficiently stable at –78 °C to react with a variety of electrophiles. Regardless of the origin of the regioselectivity, this selective deprotonation will likely find a number of applications in the synthesis of resorcinol-based natural products.[19]

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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(19) **Representative experimental procedure**. To a solution of tetramethylpiperidine (326 mg, 0.392 mL, 2.3 mmol) in THF (5 mL) at 0 °C was added *n*-BuLi (2.5 M in hexane, 0.843 mL, 2.1 mmol). After stirring for 20 min, the flask was cooled to –78 °C and opened quickly, solid 4,6-dibromoresorcinol dimethyl ether (**1**; 297 mg, 1.0 mmol) was added all at once, and the flask was immediately sealed. Compound **1** dissolved to give a homogeneous mixture, which became a white slurry about 30 min after the addition. After stirring at –78 °C for a total time of 3 h, a solution of allyl bromide (607 mg, 0.424 mL, 5.0 mmol) in THF (1 mL) was added over 1 min. The resulting mixture was stirred at –78 °C for 30 min, and then the ice bath was removed. After warming to r.t., the reaction mixture was poured into saturated NH_4Cl solution and the aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo and the residue was purified by silica gel column chromatography (EtOAc–hexane, 1:99) to give **3** (329 mg, 98%) as a white solid.
1,3-Dibromo-2-methyl-4,6-dimethoxybenzene (2): Purification by column chromatography on silica gel (EtOAc–hexane, 1:20) gave the title compound **2** in 96% yield, which crystallized from benzene–hexane (3:1) as white needles; mp 168–169 °C (Lit.[18] 168–169 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.42 (s, 1 H), 3.91 (s, 6 H), 2.62 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.7, 139.2, 105.7, 94.8, 56.5, 24.2. HRMS (EI): *m*/*z* calcd for $C_9H_{10}Br_2O_2$: 309.9027; found: 309.9032. Anal. Calcd for $C_9H_{10}Br_2O_2$: C, 34.87; H, 3.25. Found: C, 34.85; H, 3.20.
2-Allyl-1,3-dibromo-4,6-dimethoxybenzene (3): Purification by column chromatography on silica gel (EtOAc–hexane, 1:99) gave the title compound **3** in 98% yield, which crystallized from hexane as white plates; mp 67–68 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.45 (s, 1 H), 5.96–5.86 (m, 1 H), 5.12–5.07 (m, 2 H), 3.92 (s, 6 H), 3.87 (d, *J* = 8.00 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.9, 140.2, 133.1, 116.5, 105.8, 95.3, 56.5, 40.9. HRMS (EI): *m*/*z* calcd for $C_{11}H_{12}Br_2O_2$: 335.9184; found: 335.9189.
(2,6-Dibromo-3,5-dimethoxyphenyl)(phenyl)methanol (4): Purification by column chromatography on silica gel (EtOAc–hexane, 1:9) gave the title compound **4** in 72% yield, which crystallized from benzene–hexane (1:3) as white prisms; mp 147–148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.25 (m, 5 H), 6.80 (d, *J* = 11.2 Hz, 1 H), 6.55 (s, 1 H), 3.94 (s, 6 H), 3.87 (d, *J* = 11.2 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.2, 141.5, 141.4, 128.1, 126.9, 125.4, 96.3, 96.3, 76.5, 56.6. HRMS (EI): *m*/*z* calcd $C_{15}H_{14}Br_2O_3$: 401.9289; found: 401.9294.
(2-Bromophenyl)(2,6-dibromo-3,5-dimethoxyphenyl)methanol (5): Purification by column chromatography on silica gel (EtOAc–hexane, 1:9) gave the title compound **5** in 55% yield, which crystallized from benzene–hexanes (3:1) as a white powder; mp 190–191 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 8.0 Hz, 1 H), 7.37 (d, *J* = 8.0 Hz, 1 H), 7.22 (t, *J* = 8.0 Hz, 1 H), 7.14 (t, *J* = 8.0 Hz, 1 H), 6.75 (d, *J* = 8.0 Hz, 1 H), 6.54 (s, 1 H), 3.93 (s, 6 H), 3.50 (d, *J* = 8.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.2, 139.8, 139.2, 133.4, 129.8, 129.3, 126.8, 123.7, 105.8, 96.5, 77.2, 56.7. HRMS (EI): *m*/*z* calcd for $C_{15}H_{13}Br_3O_3$: 367.9446; found: 367.9450.

1-(2,6-Dibromo-3,5-dimethoxyphenyl)butan-1-ol (6): Purification by column chromatography on silica gel (EtOAc–hexane, 1:9) gave the title compound **6** in 53% yield as a pale-yellow viscous liquid which solidified upon drying in vacuo; mp 73–74 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.44 (s, 1 H), 5.54–5.48 (m, 1 H), 3.89 (s, 6 H), 3.27 (d, *J* = 8.0 Hz, 1 H), 2.12–2.03 (m, 1 H), 1.87–1.78 (m, 1 H), 1.65–1.53 (m, 1 H), 1.41–1.28 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.9, 141.9, 95.7, 75.9, 56.6, 37.2, 19.2, 13.9. HRMS (EI): *m*/*z* calcd for $C_{12}H_{16}Br_2O_3$: 367.9446; found: 367.9450.

2,6-Dibromo-1-iodo-3,5-dimethoxybenzene (7): Purification by column chromatography on silica gel (EtOAc–hexane, 1:9) gave the title compound **7** in 75% yield, which crystallized from hexanes as white needles; mp 181–182 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.57 (s, 1 H), 3.91 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.3, 112.2, 111.5, 96.9, 56.9. HRMS (EI): *m*/*z* calcd for $C_8H_7Br_2IO_2$: 421.7837; found: 421.7845.