Regioselective Ortho Lithiation of 3-Aryl and 3-Styryl Furans

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ABSTRACT

An unusual regioselectivity pattern for the ortho lithiation of 3-aryl and 3-styryl furans has been uncovered wherein lithiation occurs preferentially at the sterically encumbered 2-position. The results are attributed, at least in part, to stabilization of the intermediate furyl anion by through-space donation of \( \pi \) electron density from the substituent appended at the 3-position to the lithium cation. This ortho lithiation reaction may be applied as a useful synthetic tool for accessing 2,3-disubstituted furans.

The large number of natural and designed furans that constitute synthetic targets indicates that the ability to construct variously substituted furans at will is a highly sought after skill. In this paper, we report the results of a study investigating the selective ortho lithiation of 3-aryl and 3-styryl furans at the 2-position, and, thereby, we introduce a method that could assist those seeking to synthesize 2,3-substituted furans that are relatively difficult to access by other means.

Heteroatom-directed lithiations at the 2-position of 3-substituted furans (including 3-furoic acids, 3-arenesulfonyl furans, 3-furanmethanols, 3-furanmethanol derivatives and 3-bromofurans) are known in the literature. The intramolecular \([1,4]\) O\(\rightarrow\)C silyl migrations of 3-(silyloxy)methyl furans and trialkylsilyl esters of 3-furoic acids to provide 2-trialkylsilyl-3-(hydroxymethyl) furans and 2-trialkylsilyl-3-furoic acids, respectively, are also known.

On the other hand, the ortho lithiation of 3-alkylfurans is reported to afford a mixture of 2,3- and 2,4-disubstituted furans with the latter always being the major product, presumably for steric reasons. In most cases, the reported ratio of 2,4- vs 2,3-disubstituted furans varied between from 2:1 to 3:1.

During our studies toward the synthesis of a family of marine secondary metabolites, the prunolides, we attempted to silylate 3-(4-methoxyphenyl)furan \((3a)\) under standard ortho lithiation conditions (Scheme 1B). Despite our initial expectations for the predominant silylation occurring at the less sterically hindered 5-position, this reaction afforded...
mainly the 2-silylated product (4a:5a = 3:1). To investigate the generality of this surprising and interesting observation we decided to scrutinize the result further by examining a range of substrates bearing different substituents at the para position of the appended phenyl ring (Scheme 1).

Akin to 3a, substrates 3b and 3c were easily synthesized by employing a Suzuki coupling to unite 3-furanboronic acid (1) with the appropriate para-substituted bromobenzene (2b, c, Scheme 1A). Following the ortho lithiation/trimethylsilyl chloride quench sequence of these new substrates (3b and 3c), it quickly became obvious that the more electron-withdrawing the substituent on the phenyl ring, the greater the enhancement was in the observed regioselectivity (in favor of the 2,3-disubstituted product, Scheme 1).

In an attempt to deconvolute the role played by conjugation, between the furan and the phenyl moieties, in securing the unusual regioselectivity that we had been observing, substrates 7a and 7b were prepared using a Suzuki-coupling protocol (Scheme 2). When the benzylfurans 7a and 7b were subjected to the established ortho lithiation/silylation conditions, the 2,3- and 2,4-substituted furans 8a,b and 9a,b (respectively) were obtained in ratios of 8a:9a = 1:1.3 (for the reaction of 7a) and 8b:9b = 1.1:1 (for the reaction of 7b). These ratios, representing nearly equal substitution at the 2- and 5-positions of the furan substrate, not only differ significantly from those obtained for the previously tested conjugated substrates where the 2-position was favored but also differ slightly from the reported results for 3-alkylfurans9 where the 5-position was favored.

The next task we identified for our investigation was an examination of furan substrates where conjugation was achieved not by an aromatic substituent at the 3-position but by an olefin appended at this site instead. To this end, furan substrates 11 and 13 were synthesized, as shown in Scheme 3, using a combination of Wittig olefinations and a Suzuki coupling. For substrates 11 and 13 the selectivity obtained in the ortho lithiation reaction was lower (ranging between 1.1 and 2.0:1) than we had previously observed with 3-arylfurans; however, once again, the more sterically hindered 2-position was favored (Scheme 3). Furthermore, and, once again, electron-donating groups decreased the selectivity (see (E)-11 vs (Z)-11, (E)-13 vs (Z)-13). (E)-Substrates must be compared when we are talking about this electronic effect because, in the case of the (Z)-substrates, other factors come into play. On going from (E)-11 to (Z)-11, the observed selectivity for the reaction at the 2-position dropped from 2.0:1 to 1.4:1 for steric reasons; however, on going from (E)-13 to (Z)-13, the selectivity increased possibly due to the stabilizing influence of coordination of the methoxy group to the lithium cation (II, Figure 2).
Bearing all the results obtained thus far in mind, we decided next to examine the effect of extended conjugation at the 3-position of the furan ring. For this purpose, we targeted the 3-styrylfurans \(17a-c\) (both the \((E)\)- and \((Z)\)-isomers). These new substrates were easily prepared using standard Wittig protocols (Scheme 4). Crucially, careful chromatographic separation of the mixture of geometrical isomers obtained from the Wittig reactions allowed us access to pure samples of each isomer. Separate ortho lithiation, under our established conditions, of each of the \((E)\)- or \((Z)\)-configured isomers of \(17a-c\) afforded a set of interesting new results in which the selectivity in favor of the 2,3-disubstituted product was universally higher than had been recorded for any of our previously tested substrates (Scheme 4).

Within this latest set of results, a similar increase in the observed regioselectivity was recorded in the cases of the unsubstituted and \(p\)-CF\(_3\)-substituted substrate when compared to the \(p\)-OMe-substituted substrate ((\((E)\)-\(17a\) vs \((E)\)-\(17c\)) and \((Z)\)-\(17c\)). The most impressive feature for this batch of results, however, was the high selectivity (for the 2,3-disubstituted product) obtained for the \((Z)\)-substrates ((\((Z)\)-\(17a-c\)) in which the 2-position was severely sterically encumbered by the proximal phenyl ring (Scheme 4).

To investigate the postulate that conjugation of the 3-substituent (aryl, alkenyl, or styryl) with the furan is pivotal to the unexpected regioselectivity (of the ortho lithiation reaction of these substrates), two more unconjugated substrates were prepared (20 and 21, Figure 1). In 3-prenylfuran (20), the olefin was included as a potential through-space \(\pi\)-donor for the lithium cation in order to test whether an alternative interaction of this sort was important in producing the observed regioselectivity. Likewise, in 3-(2-phenyl)ethyl furan (21), the aryl group was included to act similar to a potential \(\pi\)-donor.

3-Prenylfuran (20; Figure 1) was synthesized by lithium halogen exchange (between 3-bromofuran and \(n\)-BuLi) followed by alkylation of the resulting furyl anion with prenyl-Br. 3-(2-Pheny1)ethyl furan (21), on the other hand, was easily prepared by hydrogenation (H\(_2\), Pd/C) of 17b (a mixture containing both geometrical isomers was used). In both cases, the standard ortho lithiation reaction (\(n\)-BuLi, TMSCl, \(-25 \to 25^\circ C\)) resulted in formation of the less sterically hindered 2,4-disubstituted furan in stark contrast to the results for the previously examined conjugated substrates. It had, therefore, become obvious that simple hydrogenation of the double bond of \(17b\) to furnish 21 produced a change in the regioselectivity in the subsequent ortho lithiation reaction by a factor of approximately 11 and led to the preferential formation of the opposite regioisomer.

At this point we should note that TMSCl was used as the quenching electrophile in all the ortho lithiation reactions for the purpose of directly comparing the results obtained. However, numerous other electrophiles may be employed to give access to a broad range of synthetically useful 2,3-disubstituted furans (starting from 3-aryl and 3-styryl furans). Further elaboration in the case of 2-substituted 3-styrylfurans might readily be achieved by functionalization (i.e., oxidative cleavage) of the double bond.

In an effort to further explain our ortho lithiation results, the \(\textit{J}^{(13C\text{--}H)}\) coupling constants for both ortho positions of some representative substrates were measured. It is well-known that this coupling constant can be associated with the kinetic acidity of the corresponding hydrogens.\(^{13}\) It is important to note here that the full assignment of the relevant \(^{13C}\) NMR peaks was accomplished using HMOC experiments. The results obtained from this NMR study are summarized in Table 1.

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**Table 1.** \(\textit{J}^{(13C\text{--}H)}\) for C-2 and C-5 of Selected Substrates

<table>
<thead>
<tr>
<th>Substrate</th>
<th>(\textit{J}^{(13C2\text{--}H)})</th>
<th>(\textit{J}^{(13C5\text{--}H)})</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>200.1</td>
<td>202.1</td>
</tr>
<tr>
<td>3b</td>
<td>201.0</td>
<td>203.4</td>
</tr>
<tr>
<td>7a</td>
<td>199.5</td>
<td>201.3</td>
</tr>
<tr>
<td>((E))-17b</td>
<td>201.2</td>
<td>202.2</td>
</tr>
<tr>
<td>((Z))-17b</td>
<td>201.2</td>
<td>202.2</td>
</tr>
</tbody>
</table>

The \(\textit{J}^{(13C\text{--}H)}\) coupling constants measured reveal that for substrates 3a, 3b, and 7a, the 5-position hydrogen would

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\(^{12}\) All product ratios reported in Schemes 1–4 were measured by \(^1H\) NMR of the crude reaction mixtures, while yields refer to isolated yields after chromatographic purification.

appear to be more acidic than the other ortho hydrogen at the 2-position (the C-5 coupling constant is higher by ∼2 Hz than the corresponding C-2 coupling constant). Despite this fact, the deprotonation of 3a and 3b occurs predominantly at the 2-position. In cases where the kinetic acidity of the two ortho protons is closer (such as substrates (E)-17b and (Z)-17b with ∼1 Hz difference) the observed regioselectivity in favor of the 2-position hydrogen is even higher. The kinetic acidity of the ortho hydrogens is not, therefore, by itself sufficient to explain the observed regioselectivity. However, an increase in the acidity of the 2-position proton compared to the position-5 proton (on going from conjugated substrates 3a and 3b to (E)-17b and (Z)-17b) is in accord with higher regioselectivity in favor of the 2-position. While the data also make it obvious (Table 1) that having conjugated substituents at the 3-position increases the kinetic acidity of the ortho furan protons (see 7a vs 3a, 3b, and 17b), electron-donating groups appended to the conjugated 3-substituent decrease the kinetic acidity (3a vs 3b). The latter effect can easily be rationalized as being the result of destabilization of the furyl anion by the electron-donating substituent.

A plausible mechanistic explanation for how this complicated situation arises has to do with the presence of a stabilizing interaction between the π-electronic system of the conjugated 3-aryl, 3-alkenyl, and 3-styryl substituents (I, III, and IV, Figure 2) and the lithium cation. These through-space interactions, known as π-stacking interactions,14 are not included in the measured kinetic acidity. The stabilization of a late transition state in the deprotonation step, due to interactions of this nature, may be of key importance. For this hypothesis to be correct, we need to assume that the π-donating group of 21 is positioned at too great a distance to participate strongly in such a stabilizing coordination. Likewise, the 3-benzyl furans (7a and 7b) and 3-prenylfuran (20) readily adopt different conformations (due to their extra degrees of rotational freedom) many of which do not facilitate the stabilizing coordination between the π-system and the lithium cation; thus, overall, the stabilization in these substrates is of reduced strength.

In summary, we have revealed an unusual regioselectivity pattern in the ortho lithiation of 3-aryl and 3-styryl furans (lithiation at the sterically encumbered 2-position is favored over lithiation at the 5-position) that may be attributed to stabilization of the intermediate furyl anion by through-space donation of π-electron density from the substituent appended at the 3-position to the lithium cation. The means by which to access sterically encumbered 2,3-disubstituted furans in preference to the alternative 2,4-disubstituted furans that we have uncovered is a useful synthetic tool.

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Supporting Information Available: Experimental procedures and 1H, 13C, and GC-MS spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.