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Citation

Published Version
doi:10.1021/ol502348y

Accessed
June 18, 2017 7:07:34 AM EDT

Citable Link
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Preferential Geminal Bis-silylation of 3,4-Benzothiophene Is Caused by the Dominance of Electron Withdrawal by R₃Si over Steric Shielding Effects

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Supporting Information

ABSTRACT: Benzylic C—H lithiation of 3,4-benzothiophene and subsequent treatment with triphenyl- or trimethylchlorosilane under a variety of conditions leads to α,α- rather than α,α'-bis-silylation products as a consequence of anion stabilization by R₃Si and very fast deprotonation of the intermediate monosilylated product, even with a sterically bulky base such as lithium diisopropylamide.

The origin of the research reported herein was the question of whether chiral cyclic sulfi des of general structure 1 (or enantiomers) might be useful for catalytic enantioselective methylene transfer to C=C or C=O from methylene precursors such as Et₂Zn/ICH₂Cl or Zn/CH₂I₂, following a process in which 1 serves as a carrier to provide chiral ylide 2. Initial studies were directed toward the synthesis of α,α'-bis-silyl ethers such as 1, R = Me₃Si, Ph₃Si, and t-BuMe₂Si, from the readily available starting material 3 (Figure 1). It seemed reasonable that rapid access to the series of silyl ligands 1 might be secured simply by sequential, one-flask silylation of monoanions derived from 3 or by one-step bis-silylation of the α,α'-dianion of 3, a 12-π-electron (non-Hückel stabilized) system. Surprisingly, however, access to the desired 2,5-bis-silylated 3,4-benzothiophene structure proved to be difficult because the behavior of anions desired from 3 was strongly influenced by the electronic and steric effects of silyl substituents.

Reaction of 3 in THF at −78 °C with 1.0 equiv of n-BuLi (2.5 M in hexanes) for 3 h followed by slow addition of Ph₃SiCl (in THF at −78 °C) afforded as major product (along with unreacted 3) the crystalline gem-bis-silane 4 in 31% yield. The structure of 4 was established by X-ray crystallographic analysis (Figure 2).

The formation of 4 likely occurs via the C(2)-monosilylation product 5 by further deprotonation at C(2) (either by monolithiated 3 or residual BuLi) followed by a second silylation (Scheme 1). The putative intermediate 5 could be obtained by the gradual addition of a cold (−78 °C) solution of lithium diisopropyl amide (LDA) in THF to a mixture of 3 and Ph₃SiCl in THF at −78 °C, which gave 5 in 42% yield along with recovered 3 (40%). Consistent with these observations was the finding that the addition of 1.0 equiv of LDA in THF at −78 °C to a solution of 5 and Ph₃SiCl in THF at −78 °C afforded 4 (76%) as major product, without the formation of a detectable amount of the α,α'-silylated product 1, R = Ph (Scheme 2). Evidently even with the use of the very bulky base LDA, the acidifying effect of an C(2) Ph₃Si group is sufficiently great to override its steric shielding of the geminal C(2)-H proton. An α-triphenylsilyl group has been found to increase the acidity of the C(9)-proton of fluorene by about 10⁴ in previous work. Despite

Received: August 7, 2014
Published: August 26, 2014
extensive experimentation, no conditions could be found to convert 3 to the α,α′-bis-silylated derivative 1, R = Ph.

The same preference for the formation of gem-bis-silylated product was demonstrated using Me₃SiCl as the silylation reagent. Thus, the addition of 3 to a mixture of 2.0 equiv of LDA and 6.0 equiv of TMSCl at −78 °C produced the gem-bis-silylation product 7 in 64% yield with no measurable amount of the isomeric α,α′-bis-TMS compound (Figure 3).

At this point, it should be mentioned that all of the above silylation reactions must be carried out at low temperatures because the intermediate 6 is unstable above −60 °C. There is considerable precedent for decomposition via the cyclo-elimination pathway shown in Scheme 3.

Although the reaction of monolithium intermediate 6 with triphenylchlorosilane occurs readily at −78 °C to form 5, NMR studies showed that proton transfer from 5 to 6 is even faster to form the silyl stabilized lithio-anion 9. Further, NMR measurements also revealed that the reaction of 9 with Ph₃SiCl (Scheme 4) is slower than expected and requires several hours at −78 °C. The slower rate of the silylation 9 to 4 appears to be a consequence of the anion-stabilizing effect (electron withdrawal) of Ph₃Si combined with the steric shielding by Ph₃Si in both 9 and Ph₃SiCl.

The research described above has revealed significant nuances in the behavior of lithiation products derived from 3,4-benzothiophene involving surprising rates of C–H lithiation and C–Li silylation.

ASSOCIATED CONTENT

5 Supporting Information

Experimental procedures and characterization data for all reactions and products, including copies of ¹H NMR and ¹³C NMR spectra and single-crystal X-ray diffraction analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Y.H. was a visiting scholar of the Science Council of China. We thank Dr. S.-L. Zhang of Harvard University for the X-ray crystallographic analysis. Financial support of Pfizer, Inc., and Gilead Sciences is gratefully acknowledged by E.J.C. This work was also supported by National Institutes of Health grants (GM 39764 and NIGMS GM077167) to D.B.C. We thank Dr. Karavadi Surendra of Harvard University for helpful advice.

REFERENCES

(3) All organolithium reactions reported herein were carried out under an atmosphere of N₂ at −78 °C.
(4) See the Supporting Information for details.

Scheme 2. Preferential Geminal Triphenylsilylation

\[
\begin{align*}
\text{Ph}_3\text{Si} + \text{Ph}_3\text{SiCl} & \xrightarrow{\text{LDA, THF, -78 °C}} \text{Ph}_3\text{SiSiPh}_3 \\
\text{Ph}_3\text{SiSiPh}_3 & \xrightarrow{\text{MeOD}} \text{Ph}_3\text{SiSiPh}_3
\end{align*}
\]

Scheme 3. Possible Pathway for Anion Decomposition

\[
\begin{align*}
\text{Ph}_3\text{Si} & \xrightarrow{\text{LDA, 6.0 equiv of TMSCl, -78 °C}} \text{Ph}_3\text{SiSiPh}_3 \\
\text{Ph}_3\text{SiSiPh}_3 & \xrightarrow{\text{MeOD}} \text{Ph}_3\text{SiSiPh}_3
\end{align*}
\]

Scheme 4. NMR Rate Studies