Lithiated Benzothiophenes and Benzofurans Require 2-Silyl Protection to Avoid Anion Migration

Marvin M. Hansen,*[a] Marcella T. Clayton,[a] Alexander G. Godfrey,[a] John L. Grutsch Jr.,[a] Sandra S. Keast,[a] Dan T. Kohlman,[b] Andreea R. McSpadden,[a] Steven W. Pedersen,[a] Jeffrey A. Ward,[a] Yao-Chang Xu[b]

[a] Chemical Product Research and Development, Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indiananapolis, IN 46285, USA

[b] Discovery Chemistry, Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indiananapolis, IN 46285, USA
Fax +1(317)2764507; E-mail: mmh@lilly.com

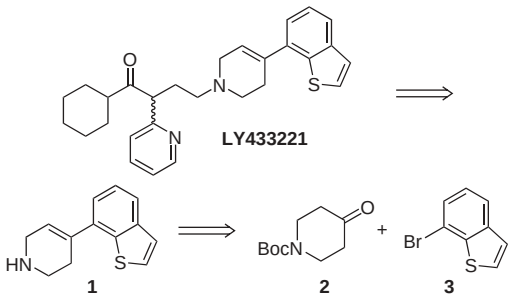
Received 5 February 2004

Dedicated to Professor Clayton H. Heathcock on the occasion of his retirement

Abstract: 2-Trimethylsilyl protection of benzothiophenes and benzofurans prevents anion migration to the 2-position when lithiated species are formed. These lithiated benzothiophenes and benzofurans provide superior results in additions to piperidones. Deprotection is conveniently achieved under acidic conditions. Direct C-7 metalation of benzothiophene is enabled by 2-triisopropylsilyl protection at C-2.

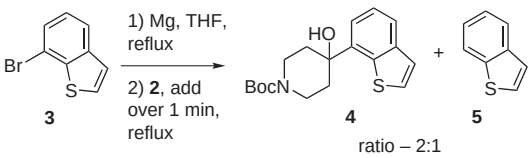
Key words: lithiation, metalation, benzothiophene, silyl protecting group, piperidone addition reactions

As key intermediates in the synthesis of the dual SSRI/5HT1A antagonist LY433221 and related compounds, we required an efficient large-scale synthesis of 4-benzothiophene substituted tetrahydropyridine derivatives such as **1** (Scheme 1).[1] Related 4-aryltetrahydropyridines are of general interest due to their wide range of biological activities.[2] An ideal approach to this class of compounds seemed to be addition of a Grignard reagent derived from 7-bromobenzothiophene (**3**) to 1-Boc-4-piperidone (**2**), followed by acid catalyzed elimination and deprotection (Scheme 1). We report herein that optimal implementation of the chemistry in Scheme 1 requires C-2 protection with a trimethylsilyl (TMS) group and formation of the 7-lithio anion. An extension of this protection strategy enables direct C-7 lithiation of 2-triisopropyl-silyl-benzothiophene. This novel strategy allows direct access to 7-substituted benzothiophenes.



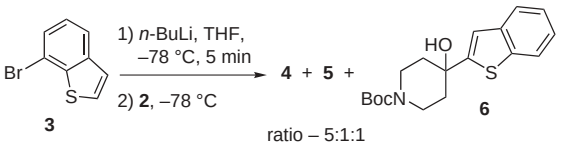
Scheme 1

Grignard addition to piperidone **2** has been reported to proceed in low yield due to competing attack of the Grignard reagent on the Boc group.[2a] In our hands, addition of piperidone **2** to the Grignard reagent of bromide **3**[3] in THF at reflux, afforded a 2:1 ratio of tertiary alcohol **4** and quenched benzothiophene (**5**), but no evidence for Boc removal (Scheme 2).[4] Enolization of piperidone **2** is the most likely explanation for these results.[5] Enolization by a Grignard reagent is normally a minor side reaction except for hindered or unusually acidic ketones.[6] Piperidone **2** may have increased acidity due to the inductive effect of the *N*-Boc group.[7,8]



Scheme 2

Utilization of the more reactive lithium anion should allow operation at low temperature where enolization side reactions are normally suppressed. The 7-lithio anion was prepared by treatment of bromide **3** in THF with *n*-BuLi in hexanes at –78 °C for five minutes. Addition of piperidone **2** afforded the expected products **4** and **5** along with by-product **6** in a ratio of 5:1:1 (Scheme 3). By-product **6** is derived from proton transfer from the more acidic 2-position. Formation of the 2-isomer was eliminated by adding *n*-BuLi last to a mixture of bromide **3** and ketone **2** in THF at –78 °C, but complete conversion of bromide **3** required 1.5 equivalents of *n*-BuLi due to competing reaction with the ketone.

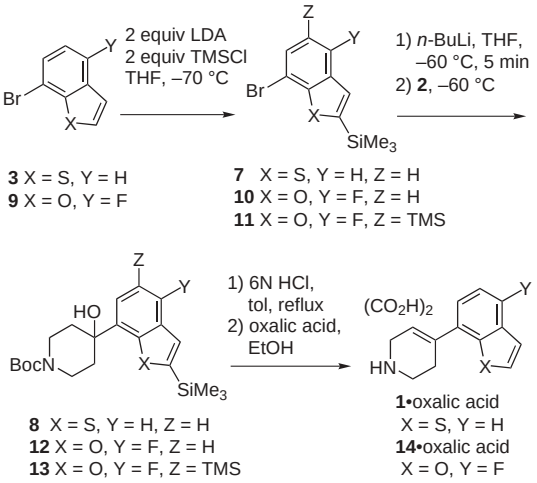


Scheme 3

SYNLETT 2004, No. 8, pp 1351–1354
Advanced online publication: 04.06.2004
DOI: 10.1055/s-2004-825609; Art ID: Y00404ST

The rearrangement of benzothiophene anions to the thermodynamically favored 2-position is known.[9] Although proton transfer may be suppressed by use of a less polar solvent, metal-halogen exchange rates are slowed and anion solubility issues became problematic with bromide **3**.[10] Blocking the 2-position with a silyl group is commonly used to solve this problem in metalation of aryl,[11] or thiophene rings,[12] but has been rarely applied to benzothiophene chemistry.[13] This strategy was successfully applied to 7-bromobenzothiophene (**3**) and related molecules as described below.

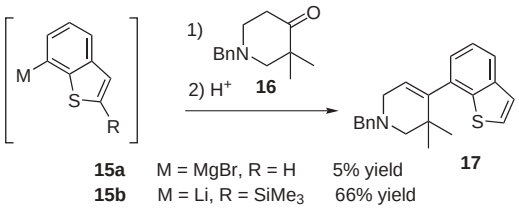
Treatment of bromide **3** with two equivalents of lithium diisopropylamide (LDA) and two equivalents of commercial trimethylsilyl chloride (TMSCl) afforded the silyl-protected bromide **7** in quantitative yield (Scheme 4). Use of excess reagents allowed the reaction to be driven to completion without use of purified TMSCl. Metal-halogen exchange of protected bromide **7** in THF at –60 °C afforded a stable organolithium species. Addition of piperidone **2** as a solution in THF at –60 °C afforded the desired addition product **8** in 92% yield. This is a dramatic improvement over the 40–60% yields that were typical using the Grignard chemistry. Silyl deprotection can be achieved under basic or acidic conditions.[14] As shown in Scheme 4, deprotection occurred readily in 91% yield with 6 N HCl and toluene at reflux, the standard conditions used for Boc deprotection and alcohol dehydration. The overall process from 7-bromobenzothiophene (**3**) proceeded in 84% yield and required only one step for the silyl protection strategy, since protiodesilylation occurred during Boc removal/dehydration.[15,16] Conversion of tetrahydropyridine **1** to **LY433221** will be described in due course.



Scheme 4

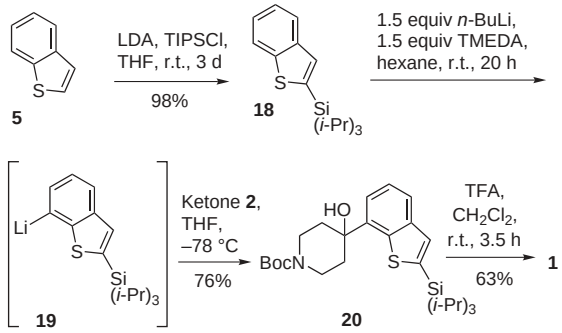
The benzothiophene silyl protection strategy was applied to the preparation of the related benzofuran **14** (Scheme 4).[17] The 4-fluoro group complicated the robust and simple silylation conditions described above, due to the *ortho* directing ability of the fluorine.[18] Treatment of 7-bromo-4-fluorobenzofuran (**9**)[19] with excess LDA and excess TMSCl afforded a 1:1 mixture of mono-silylated product **10** and the bis-silylated product **11**. These compounds could be separated by chromatography, but it was more convenient to carry the mixture directly into the metal-halogen exchange/addition step to afford a mixture of mono- and bis-silylated products **12** and **13** in 72% yield. Both products were conveniently deprotected under acidic conditions to afford the 4-substituted tetrahydropyridine oxalate salt **14** in 75% yield.[20] Subsequently it was shown that the mono-silylated benzofuran **10** could be obtained with <1% of bis-silylated **11** by silylation with 1.3 equivalents of LDA and 1.3 equivalents of TMSCl in THF/chlorobenzene at –78 °C.

Additions to hindered *N*-benzylpiperidone **16**[21] highlighted the benefit of lithio anion **15b** relative to the Grignard reagent **15a** (Scheme 5). Due to steric hindrance, enolization by the Grignard reagent was now the major reaction. Simple substitution of the lithium reagent **15a** in this sequence led to a dramatically improved 66% yield of **17** over the same two steps.[22]



Scheme 5

After demonstrating that 2-silyl protection of benzothiophenes allowed generation of a stable 7-lithio anion by metal-halogen exchange, it was of interest to see if directed *ortho* lithiation of a 2-silyl protected benzothiophene could give access to the same species. Although metalation of related dibenzothiophenes has been achieved, the C-7 directed metalation of benzothiophenes has not been reported.[23] Initially benzothiophene (**5**) was converted to the 2-TMS derivative and treated with *n*-BuLi in THF at room temperature. After addition of piperidone **2**, a mixture of 7-substituted and 2-susbstituted products was obtained, indicating competition between deprotonation at C-7 and nucleophilic silyl removal at C-2. In order to prevent attack at silicon, the triisopropylsilyl (TIPS) derivative **18** was prepared (Scheme 6).[24] Complete metalation of TIPS protected **18** could not be achieved using *n*-BuLi in THF without competing reaction with THF.[25] Metalation using 1.5 equivalents of *n*-BuLi and 1.5 equivalents of TMEDA in hexane at room temperature, followed by addition of ketone **2** in THF at –78 °C afforded a 76% yield of the desired 7-substituted benzothiophene **20**.[26] Tandem alcohol dehydration and deprotection using TFA occurred analogously to the TMS derivative to provide tetrahydropyridine **1**. This novel approach to 7-substituted benzothiophenes avoids dealing with the odiferous bromo thiophenol precursors that lead to the bromo substituted benzothiophenes used above. This strategy should find further application in benzothiophene synthesis.



Scheme 6

In conclusion we have shown that 2-TMS protected benzothiophene and benzofuran substrates enable metal-halogen exchange to provide useful lithiated intermediates. These lithiated intermediates provide superior results in additions to ketones relative to the corresponding Grignard reagents. 2-TIPS protection of benzothiophene allows directed metalation at C-7, providing an expedient route to 7-susbstituted benzothiophenes.

Acknowledgment

We thank Dr. Vincent Rocco and Dr. Jean Takeuchi for helpful advice and the Lilly Research Laboratories Physical Chemistry group for characterization data. We thank Eli Lilly and Company for a Summer Intern Fellowship for A. R. McSpadden.

References

(1) Hertel, L. W.; Kohlman, D. T.; Liang, S. X.; Wong, D. T.; Xu, Y. PCT Int. Appl., WO 00/000198, **2000**.

(2) (a) Wustrow, D. J.; Wise, L. D. *Synthesis* **1991**, 993. (b) Eastwood, P. R. *Tetrahedron Lett.* **2000**, *41*, 3705. (c) Glase, S. A.; Akunne, H. C.; Heffner, T. G.; Jaen, J. C.; MacKenzie, R. G.; Meltzer, L. T.; Pugsley, T. A.; Smith, S. J.; Wise, L. D. *J. Med. Chem.* **1996**, *39*, 3179. (d) Zimmerman, D. M.; Cantrell, B. E.; Reel, J. K.; Hemrick-Luecke, S. K.; Fuller, R. W. *J. Med. Chem.* **1986**, *29*, 1517.

(3) Prepared by alkylation of 2-bromothiophenol with bromoacetaldehyde diethyl acetal, followed by Amberlyst-15 catalyzed Friedel–Crafts cyclization, see: Zhang, T. Y.; Allen, M. J.; Godfrey, A. G.; Vicenzi, J. T., 215th National Meeting of the American Chemical Society, Dallas, TX, **1998**, Poster ORGN 242.

(4) Product ratios assigned by reverse phase high-pressure liquid chromatography (HPLC). No other products observed by HPLC.

(5) For reports of moderate yields where enolization is likely, see: (a) Merschaert, A.; Delhaye, L.; Kestemont, J.; Brione, W.; Delbeke, P.; Mancuso, V.; Napora, F.; Diker, K.; Giraud, D.; Vanmarsenille, M. *Tetrahedron Lett.* **2003**, *44*, 4531. (b) Annoura, H.; Nakanishi, K.; Uesugi, M.; Fukunaga, A.; Imajo, S.; Miyajima, A.; Tamura-Horikawa, Y.; Tamura, S. *Bioorg. Med. Chem. Lett.* **2002**, *10*, 371. (c) Sui, Z.; De Voss, J. J.; DeCamp, D. L.; Li, J.; Craik, C. S.; Ortiz de Montellano, P. R. *Synthesis* **1993**, 803.

(6) March, J. *Advanced Organic Chemistry, Reactions Mechanisms and Structure*, 4th ed.; John Wiley and Sons: New York, **1992**, 926–927.

(7) Changes in solvent, addition rate or reaction temperature had little impact on the product to benzothiophene ratio. However, inverse addition of the Grignard reagent to the ketone in THF at reflux significantly increased the amount of enolization (0.3:1 ratio of **4**:**5**).

(8) (a) Due to cost and waste disposal issues, the classical approach using $CeCl_3$ was not investigated, see: Liu, H.; Shia, K.; Shang, X.; Zhu, B. *Tetrahedron* **1999**, *55*, 3803. (b) The organotitanium reagent made from $ClTi(Oi\text{-}Pr)_3$ was unreactive, see: Hutton, J.; Jones, A. D.; Lee, S. A.; Martin, D. M. G.; Meyrick, B. R.; Patel, I.; Peardon, R. F.; Powell, L. *Org. Process Res. Dev.* **1997**, *1*, 61. (c) TMEDA as an additive was not investigated, but has been reported to suppress enolization in a related case, see: Herrinton, P. M.; Owen, C. E.; Gage, J. R. *Org. Process Res. Dev.* **2001**, *5*, 80.

(9) (a) Dickinson, R. P.; Iddon, B. *J. Chem. Soc. C* **1968**, 2733. (b) Dickinson, R. P.; Iddon, B. *J. Chem. Soc. C* **1971**, 3447. (c) Scrowston, R. M. *Recent Advances in the Chemistry of Benzo[b]thiophenes*, In *Advances in Heterocyclic Chemistry*, Vol 29; Katritzky, A. R., Ed.; Academic Press: London, **1981**, 171–249. (d) Rajappa, S.; Natekar, M. V. *Thiophenes and their Benzo Derivatives: Reactivity*, In *Comprehensive Heterocyclic Chemistry II*, Vol 2; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon: Oxford, **1996**, 419–606. (e) See ref.[8b]

(10) Wu, X.; Chen, T.; Zhu, L.; Rieke, R. D. *Tetrahedron Lett.* **1994**, *35*, 3673.

(11) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(12) (a) Samanta, S. S.; Ghosh, S. C.; De, A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2683. (b) Sakamoto, Y.; Komatsu, S.; Suzuki, T. *J. Am. Chem. Soc.* **2001**, *123*, 4643.

(13) In these cases silicon directs the initial metalation, rather than preventing a subsequent proton transfer: (a) Kamila, S.; Mukherjee, C.; Mondal, S. S.; De, A. *Tetrahedron* **2003**, *59*, 1339. (b) Ghosh, S. C.; De, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3705. (c) Mandal, S. S.; Samanta, S. S.; Deb, C.; De, A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2559.

(14) See ref.[11]

(15) Tetrahydropyridine **1** was isolated as the oxalate salt to aid in purification and to provide a stable solid for storage.

(16) **Procedures for Scheme 4: Compound 7:** To 7-bromo-benzothiophene (**3**, 34.6 g, 0.16 mmol) in THF (346 mL) at –78 °C was added TMSCl (41.1 mL, 0.32 mmol) followed by LDA (Aldrich, 162 mL, 2 M, 0.32 mmol). After 1 h, workup with 1 N HCl and MTBE followed by plug filtration through silica gel with hexanes afforded 52.8 g (ethylbenzene corrected = 47.5 g, 100%) of 7-bromo-2-trimethylsilyl-benzothiophene(**7**) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76 (dd, 1 H, *J* = 7.7, 0.8 Hz), 7.56 (s, 1 H), 7.47 (dd, 1 H, *J* = 7.7, 0.8 Hz), 7.22 (t, 1 H, *J* = 7.7 Hz), 0.40 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.0, 143.5, 141.95, 131.5, 126.9, 125.4, 122.3, 115.6, –0.4). MS: *m/z* = 284 [M^+]. Anal. Calcd for $C_{11}H_{13}BrSSi$: C, 46.31; H, 4.59. Found: C, 46.07; H, 4.65. **Compound 8:** To **7** (2.67 g, 9.36 mmol) in THF (15 mL) at –78 °C was added *n*-BuLi (2.5 M in hexanes, 4.5 mL, 11.3 mmol, 1.2 equiv). After 10 min, a solution of piperidone **2** (2.25 g, 11.3 mmol, 1.2 equiv) in THF (12 mL) was added. After 1 h, workup with 1 N HCl and toluene afforded 5.62 g of crude **8**. Reslurry in 20% EtOAc/hexane afforded 2.63 g (69%) of **8** as a solid. The filtrate was chromatographed on flash silica gel to afford 0.84 g (yield = 3.47 g, 92%): mp 153–158 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74 (dd, 1 H, *J* = 7.7, 1.1 Hz), 7.48 (s, 1 H), 7.32 (t, 1 H, *J* = 7.7, 7.4 Hz), 7.23 (dd, 1 H, *J* = 7.4, 1.1 Hz), 4.04 (br s, 2 H), 3.30 (br t, 2 H), 2.16 (br t, 2 H), 2.09 (s, 1 H), 1.99 (d, 2 H, *J* = 12.9 Hz), 1.48 (s, 9 H), 0.38 (t, 9 H, *J* = 3.6 Hz). ^{13}C NMR (75 MHz, DMSO): δ = 154.0, 143.5,

142.1, 141.8, 139.2, 130.8, 124.2, 122.3, 120.0, 78.5, 70.9, 35.7, 28.1, 0.38. MS: *m/z* = 406 (M^+). **Compound 1**: A solution of alcohol **8** (1.09 g, 2.68 mmol), toluene (10 mL) and 6 N HCl (10 mL) was heated at reflux for 5 h. The layers were separated and the acid layer was washed with toluene. The acid layer was made basic with 5 N NaOH (pH = 12–13) and extracted with EtOAc. The extracts were concentrated to afford 0.52 g of **1**. To **1** (7.73 g, 35.9 mmol) in EtOH (65 mL) at reflux was added a solution of oxalic acid (3.23 g, 35.9 mmol) in EtOH (15 mL). The mixture was allowed to cool and product was collected and dried to afford 8.93 g (87%) of **1**·oxalic acid: mp 192–193 °C (dec). ^{1}H NMR (300 MHz, DMSO): δ = 8.48 (br s, 3 H), 7.84 (d, 1 H, *J* = 7.9 Hz), 7.79 (d, 1 H, *J* = 5.5 Hz); 7.51 (d, 1 H, *J* = 5.8 Hz), 7.42 (t, 1 H, *J* = 7.6 Hz), 7.32 (d, 1 H, *J* = 7.3 Hz), 6.29 (s, 1 H), 3.83 (s, 2 H), 3.35 (t, 2 H, *J* = 5.8 Hz), 2.76 (s, 2 H). ^{13}C NMR (62.5 MHz, DMSO): δ = 164.9, 140.4, 136.6, 135.3, 135.2, 127.5, 124.7, 124.6, 123.3, 122.2, 120.0, 41.23, 40.13, 24.8. MS: *m/z* = 216 [MH^+]. Anal. Calcd for $C_{13}H_{13}BrNS{\cdot}C_2H_2O_4$: C, 59.00; H, 4.95; N, 4.59. Found: C, 59.04; H, 4.65; N, 4.33.

(17) 2-Silyl benzofurans: (a) Hart, D. J.; Mannino, A. *Tetrahedron* **1996**, *52*, 3841. (b) Mohamadi, F.; Spees, M. US 5,169,860, **1992**. (c) 2-Silyl furans: Keay, G. *Chem. Soc. Rev.* **1999**, *28*, 209.

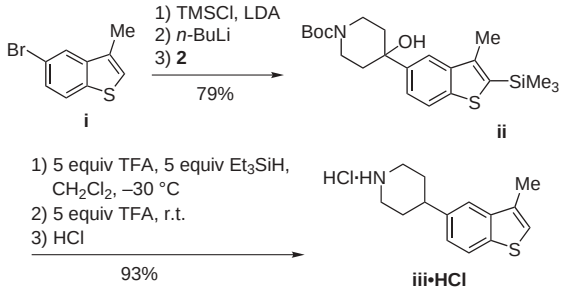
(18) (a) Black, W. C.; Guay, G.; Scheuermeyer, F. *J. Org. Chem.* **1997**, *62*, 758. (b) Moyroud, J.; Guesnet, J.; Bennetau, B.; Mortier, J. *Tetrahedron Lett.* **1995**, *36*, 881.

(19) Prepared by alkylation of 2-bromo-5-fluorophenol with bromoacetaldehyde diethylacetal, followed by Amberlyst-15 catalyzed cyclization, see ref.[3] **Compound 9:** ^{1}H NMR (300 MHz, DMSO): δ = 8.18 (d, 1 H, *J* = 2 Hz), 7.56 (dd, 1 H, *J* = 9, 5 Hz), 7.21 (d, 1 H, *J* = 2 Hz), 7.10 (dd, 1 H, *J* = 9, 9 Hz). ^{13}C NMR (75 MHz, DMSO): δ = 156.3, 153.0, 147.3, 127.6, 127.5, 117.5, 117.2, 110.4, 110.2, 103.8, 98.4, 98.3. MS: *m/z* = 214, 216 (M^+ for two Br isotopes).

(20) *p*-TsOH in toluene at reflux provided higher yields than aq HCl in the deprotection of this substrate.

(21) Rizzo, J. R.; Staszak, M. A.; Zhang, T. Y. PCT Int. Appl., WO 01/00577, **2001**.

(22) The silyl protection strategy was also applied to the synthesis of reduced piperidine **iii** shown below (Scheme 7). The ionic reduction conditions were optimized to avoid elimination to the alkene or premature removal of the Boc group: To alcohol **ii** (458 g, 1.09 mol) and Et_3SiH (871 mL, 5.46 mol, 5 equiv), in CH_2Cl_2 (4.6 L) at –30 °C was added TFA (420 mL, 5.45 mol, 5 equiv) over 35 min. After warming to 13 °C over 2.5 h, 420 mL of TFA was added. After 3.5 h at r.t., a mixture of ice (6 L), H_2O (5 L), and 12 M NaOH (628 mL) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The organic layers were dried (Na_2SO_4) and concentrated. The oil was dissolved in 4 L of Et_2O and HCl/EtOAc was added until the pH measured 2–3. The solid was collected and dried to afford 271 g (93%) of **iii**·HCl: ^{1}H NMR (500 MHz, DMSO): δ = 2.10–2.20 (m, 2 H), 2.30 (m, 2 H), 2.42 (s, 3 H), 2.93 (m, 1 H), 3.00–3.10 (m, 2 H), 3.69 (m, 2 H), 7.09 (s, 1 H), 7.25 (d, 1 H, *J* = 6 Hz), 7.57 (s, 1 H), 7.80 (d, 1 H, *J* = 6 Hz), 9.62 (br s, 1 H), 9.88 (br s, 1 H). ^{13}C NMR (62.5 MHz, DMSO): δ = 13.5, 29.6, 38.9, 43.4, 119.3, 122.7, 12.9, 123.2, 131.5, 137.7, 139.6, 140.9. MS: *m/z* = 231 [M^+]. Anal. Calcd for $C_{14}H_{18}ClNS$: C, 62.79; H, 6.77; N, 5.23. Found: C, 62.66; H, 6.65; N, 5.24.



Scheme 7

(23) (a) Kuehm-Caubere, C.; Adach-Becker, S.; Fort, Y.; Caubere, P. *Tetrahedron* **1996**, *52*, 9087. (b) Partial conversion to a 2,7-dianion has been reported: Chadwick, D. J.; Willbe, C. *J. Chem. Soc., Perkin Trans. 1* **1977**, 887.

(24) Compound **18** is the first reported 2-TIPS benzothiophene. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.22 (d, 18 H, *J* = 7 Hz), 1.49 (septet, 3 H, *J* = 7 Hz), 7.39 (m, 2 H), 7.57 (m, 1 H), 7.90 (m, 1 H), 7.96 (d, 1 H, *J* = 12 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.6, 141.0, 136.7, 132.6, 124.0, 123.8, 123.4, 122.0, 18.7, 11.9. MS: *m/z* = 290 [M^+]. Anal. Calcd for $C_{17}H_{26}SSi$: C, 70.28; H, 9.02. Found: C, 70.06; H, 9.16.

(25) Bates, R. B.; Kroposki, L. M.; Potter, D. E. *J. Org. Chem.* **1972**, *37*, 560.

(26) Alcohol **20** was isolated as a 10:1 mixture containing an inseparable impurity tentatively identified as the isomeric 4-substituted benzothiophene.