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Facile and Scalable Synthesis of the Fused-Ring Heterocycles Thieno[3,2-*b*]-thiophene and Thieno[3,2-*b*]furan

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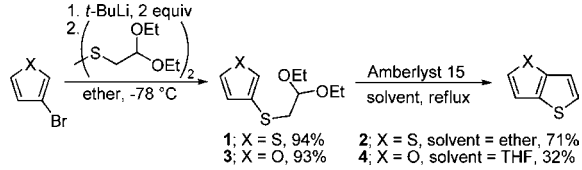
ABSTRACT



An optimized synthetic methodology which allows for efficient and scalable access to the important fused-ring heterocycle thieno[3,2-*b*]thiophene and the first reported isolation of thieno[3,2-*b*]furan is presented. The properties of thieno[3,2-*b*]furan were assessed through a detailed analysis of the NMR data and an investigation of the chemical reactivity. Thieno[3,2-*b*]furan is chemically robust and offers good selectivity toward functionalization at the 2-position via bromination and the 5-position via deprotonation.

Incorporation of fused-ring five-membered heterocycles in place of traditionally α-linked segments has increasingly been utilized as a powerful means of tuning properties of conjugated oligomers and polymers.[1,2] Thieno[3,2-*b*]-thiophene, a structure with two fused thiophene rings, a heterocyclic analog of naphthalene, has been employed as a key component in a wide range of molecular architectures including high performance materials such as porous hydrogen storage hosts[3] and conjugated oligomers and polymers.[2] The established utility of this fused-ring moiety and its potential for incorporation into the design of novel materials makes the route to produce thieno[3,2-*b*]thiophene an important target for synthetic optimization.

The fusion of a thiophene ring with a different five-membered heterocycle has also been an area of synthetic

(1) Selected examples include:(a) Fong, H. H.; Pozdin, V. A.; Amassian, A.; Malliaras, G. G.; Smilgies, D. M.; He, M. Q.; Gasper, S.; Zhang, F.; Sorensen, M. *J. Am. Chem. Soc.* **2008**, *130*, 13202–13203. (b) Okamoto, T.; Kudoh, K.; Wakamiya, A.; Yamaguchi, S. *Chem.—Eur. J.* **2007**, *13*, 548–556. (c) Miguel, L. S.; Matzger, A. J. *Macromolecules* **2007**, *40*, 9233–9237. (d) He, M. Q.; Zhang, F. X. *J. Org. Chem.* **2007**, *72*, 442–451. (e) Zhang, X. N.; Johnson, J. P.; Kampf, J. W.; Matzger, A. J. *Chem. Mater.* **2006**, *18*, 3470–3476. (f) Zhang, X. N.; Cote, A. P.; Matzger, A. J. *J. Am. Chem. Soc.* **2005**, *127*, 10502–10503. (g) Lim, E.; Jung, B. J.; Lee, J.; Shim, H. K.; Lee, J. I.; Yang, Y. S.; Do, L. M. *Macromolecules* **2005**, *38*, 4531–4535. (h) Zhang, X. N.; Kohler, M.; Matzger, A. J. *Macromolecules* **2004**, *37*, 6306–6315. (i) Zhang, X. N.; Matzger, A. J. *J. Org. Chem.* **2003**, *68*, 9813–9815. (j) Yamamoto, T.; Takimiya, K. *J. Am. Chem. Soc.* **2007**, *129*, 2224–2225. (k) Okamoto, T.; Kudoh, K.; Wakamiya, A.; Yamaguchi, S. *Org. Lett.* **2005**, *7*, 5301–5304. (l) Nakayama, J.; Dong, H. B.; Sawada, K.; Ishii, A.; Kumakura, S. *Tetrahedron* **1996**, *52*, 471–488. (m) Liu, J. Y.; Zhang, R.; Sauve, G.; Kowalewski, T.; McCullough, R. D. *J. Am. Chem. Soc.* **2008**, *130*, 13167–13176. (n) Ogawa, K.; Rasmussen, S. C. *Macromolecules* **2006**, *39*, 1771–1778. (o) Radke, K. R.; Ogawa, K.; Rasmussen, S. C. *Org. Lett.* **2005**, *7*, 5253–5256. (p) Murphy, A. R.; Frechet, J. M. J. *Chem. Rev.* **2007**, *107*, 1066–1096. (q) Litvinov, V. P. *Usp. Khim.* **2005**, *74*, 235–267.

(2) Selected examples include: (a) McCulloch, I.; Heeney, M.; Chabinyc, M. L.; DeLongchamp, D.; Kline, R. J.; Coelle, M.; Duffy, W.; Fischer, D.; Cundloch, D.; Hamadani, B.; Hamilton, R.; Richter, L.; Salleo, A.; Shkunov, M.; Sporrowe, D.; Tierney, S.; Zhong, W. *Adv. Mater.* **2009**, *21*, 1091–1109. (b) Liu, Y.; Wang, Y.; Wu, W. P.; Liu, Y. Q.; Xi, H. X.; Wang, L. M.; Qiu, W. F.; Lu, K.; Du, C. Y.; Yu, G. *Adv. Funct. Mater.* **2009**, *19*, 772–778. (c) Parmer, J. E.; Mayer, A. C.; Hardin, B. E.; Scully, S. R.; McGehee, M. D.; Heeney, M.; McCulloch, I. *Appl. Phys. Lett.* **2008**, *92*, 1133090–1133093. (d) Tang, W. H.; Ke, L.; Tan, L. W.; Lin, T. T.; Kietzke, T.; Chen, Z. K. *Macromolecules* **2007**, *40*, 6164–6171. (e) Li, Y. N.; Wu, Y. L.; Liu, P.; Birau, M.; Pan, H. L.; Ong, B. S. *Adv. Mater.* **2006**, *18*, 3029–3032. (f) Xiao, K.; Liu, Y. Q.; Qi, T.; Zhang, W.; Wang, F.; Gao, J. H.; Qiu, W. F.; Ma, Y. Q.; Cui, G. L.; Chen, S. Y.; Zhan, X. W.; Yu, G.; Qin, J. G.; Hu, W. P.; Zhu, D. B. *J. Am. Chem. Soc.* **2005**, *127*, 13281–13286.

(3) (a) Koh, K.; Wong-Foy, A. G.; Matzger, A. J. *J. Am. Chem. Soc.* **2009**, *131*, 4184–4185. (b) Wong-Foy, A. G.; Matzger, A. J.; Yaghi, O. M. *J. Am. Chem. Soc.* **2006**, *128*, 3494–3495.

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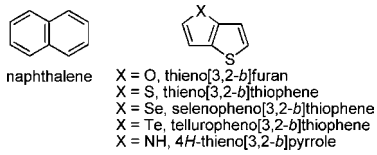
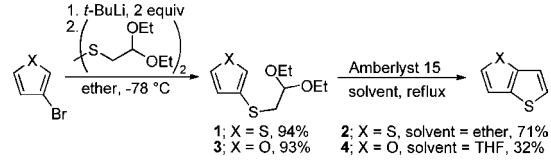


Figure 1. Selected π-conjugated fused-ring molecules.

interest for decades. For example, 4H-thieno[3,2-*b*]pyrrole,[4] selenopheno[3,2-*b*]thiophene,[5] and telluropheno[3,2-*b*]-thiophene[6] have all been synthesized and their properties have been studied through experimental and computational methods.[7] However, one combination that has presented a particular challenge for synthetic chemists is that of a thiophene and a furan ring, as in thieno[3,2-*b*]furan.[8] Two effective methods of altering the physical and electronic properties, as well as the solid-state packing of conjugated molecules, include (1) substituting furan rings in place of thiophene rings[9] and (2) introducing ring fusion to α-linked heterocyclic oligomers.[1,2] Thieno[3,2-*b*]furan has the potential to leverage both of these strategies. Although data from a crude ^{1}H NMR spectrum of thieno[3,2-*b*]furan has been reported, isolation of the parent compound has not been demonstrated.[10] Here we disclose an optimized synthetic methodology that allows for efficient access to the important heterocycle thieno[3,2-*b*]thiophene and the first reported isolation of thieno[3,2-*b*]furan. The reactivity of thieno[3,2-*b*]-furan was also investigated to shed light on the properties of this new building block.

At present, thieno[3,2-*b*]thiophene is most commonly accessed using a literature procedure that involves a four-step route with a total linear yield of 51%.[11] To improve synthetic efficiency, a more direct approach developed by Ghaisas and Tilak was revisited.[12] In this route, a key step is the treatment of 3-(2,2-diethoxy-ethylsulfanyl)thiophene, **1**, with phosphorus pentoxide in refluxing benzene. This step generates thieno[3,2-*b*]thiophene in 18% yield, but perhaps

Scheme 1. Synthetic Route to Thieno[3,2-*b*]thiophene (**2**) and Thieno[3,2-*b*]furan (**4**)



due to the low yield, the route has not been widely employed. With optimization of the acid source, solvent, temperature, reaction time, and isolation method, we have achieved significant improvement in the yield of this step. Altering the cyclization conditions by exposing **1** to a sulfonic acid resin in refluxing ether produces the desired thieno[3,2-*b*]-thiophene product, **2**, in 71% yield (Scheme 1), on greater than 10 g scale. Ghaisas and Tilak prepared the cyclization precursor, **1**, in 66% yield from thiophene-3-thiol, sodium, and 2-bromo-1,1-diethoxyethane in ethanol.[12] Our strategy begins with Li−Br exchange of 3-bromothiophene with *t*-BuLi followed by quenching with 1,2-bis(2,2-diethoxyeth-yl)disulfide[13] to afford **1** in 94% yield (Scheme 1) which is carried on to the final ring closing step described above. This scalable approach to high purity thieno[3,2-*b*]thiophene offers improved overall yield in fewer synthetic steps as compared to all published methods to date.[14]

Thieno[3,2-*b*]furan, **4**, is generated in 32% yield on greater than 5 g scale (Scheme 1) utilizing the general method presented for the synthesis of **2**. The modest yield of **4** relative to **2** may be ascribed to a greater instability of **4** in the presence of strong acid; yield further decreases upon extended exposure to the sulfonic acid resin and therefore the reaction time was chosen to balance starting material conversion with product decomposition. Although ether is used as the reaction solvent to produce **2**, the yield of **4** is significantly higher when the reaction is carried out in THF. Recovery of compounds **2** and **4** from the reaction mixture poses a significant challenge due to their high volatility. This is especially true for **4** which is more volatile than **2** and is prepared with a higher boiling point reaction solvent. To address this issue, the crude reaction mixture is diluted with petroleum ether and washed with water. Careful evaporation of solvent is then critical for recovery of **4** (see Supporting Information for details).[15]

A detailed analysis of the NMR data and an investigation of chemical reactivity were performed for **4**. The optimized geometry of **4** was determined using density functional theory (DFT) at the B3LYP/6-31G* level and predictions of the ^{1}H and ^{13}C NMR chemical shifts were calculated by the gauge included atomic orbitals (GIAO) method within the

(4) First report see: Snyder, H. R.; Carpino, L. A.; Zack, J. F.; Mills, J. F. *J. Am. Chem. Soc.* **1957**, *79*, 2556–2559.

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(6) First report see: Yasuike, S.; Kurita, J.; Tsuchiya, T. *Heterocycles* **1997**, *45*, 1891–1894.

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(8) Perhaps even more surprisingly, furano[3,2-*b*]furan is unknown.

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(10) Paulmier, C.; Morel, J.; D., S.; Pastour, P. *Bull. Soc. Chim. Fr.* **1973**, *243*, 4–2441.

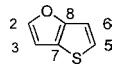
(11) Fuller, L. S.; Iddon, B.; Smith, K. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, *22*, 3465–3470.

(12) Ghaisas, V. V.; Tilak, B. D. *Proc. Ind. Acad. Sci.* **1954**, *39A*, 14–19. This method utilizes thiophene-3-thiol, which is not commercially available.

(13) Although 1,2-bis(2,2-diethoxyethyl)disulfide is commercially available, we have adapted a literature procedure to generate the disulfide (Supporting Information): Parham, W. E.; Wynberg, H. *Org. Syn.* **1955**, *35*, 51–52.

(14) The general method used to generate **2** can also be used to make other derivatives and we demonstrate this utility with the production of 3-bromothieno[3,2-*b*]thiophene in fewer steps and higher yield than the best literature procedure (Supporting Information).

Table 1. Peak Assignments and Chemical Shifts (ppm) in ^{1}H and ^{13}C NMR Spectra of **4** Based on Experimental and Computational Data (GIAO/DFT B3LYP/6-31++G** level) from the B3LYP/6-31G* Optimized Structure



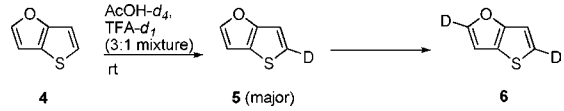
atom	experimental	calculated	Δ
C8	158	160	2
C2	146	151	5
C5	126	132	6
C7	123	131	8
C6	111	115	4
C3	106	110	4
H2	7.56	7.76	0.20
H5	7.21	7.24	0.03
H6	7.07	7.11	0.04
H3	6.74	6.89	0.15

experimental coupling constants:

$J_{2-3} = 2.1$ Hz $J_{5-6} = 5.3$ Hz

$J_{2-5} = 1.4$ Hz $J_{3-6} = 0.6$ Hz

Scheme 2. Hydrogen-Deuterium Isotopic Exchange in Thieno[3,2-*b*]furan

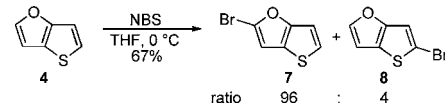


DFT approach at the B3LYP/6-31++G** level of theory (Table 1). A one-bond proton-carbon correlation experiment (HMQC) was used to verify the accuracy of the computationally predicted direct proton-carbon connectivity.

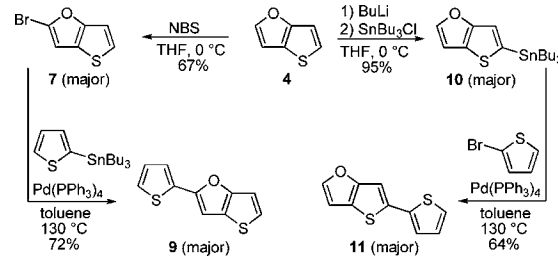
Hydrogen−deuterium isotopic exchange was carried out in order to investigate electrophilic aromatic substitution (EAS)[16] on **4**, as well as the relative reactivity compared to structurally similar furan, thiophene, and thieno[3,2-*b*]-thiophene. Each compound was diluted in a 3:1 v/v mixture of acetic acid-d_4 (AcOH-d_4)/trifluoroacetic acid-d_1 (TFA-d_1) at 25 °C (Scheme 2) and conversion was monitored by ^{1}H NMR spectroscopy. Exchange is most rapid on the thiophene ring at the 5-position of **4** (>95% after 24 h). Under these conditions the relative reactivity at each position for this set of molecules is: **4** (5-position) ≫ **4** (2-position) ≫ **2** (α) > furan (α) > thiophene (α).

Treatment of **4** with one equivalent of NBS in either AcOH or THF results in bromination at the 2-position as the major product. The most selective bromination toward a single position is achieved in THF at 0 °C (Scheme 3). The reaction yields 67% of monobrominated **4** with substitution at the 2 vs 5-position in a ratio of 96:4 (NMR spectroscopy). To unambiguously assign the position of bromination in the major product, the mixture of isomers **7** and **8** was derivatized in order to generate a crystalline material for structure determination by X-ray crystallography. Under Stille coupling conditions the isomer mixture was coupled to tributyl(thiophen-2-yl)stannane in 72% yield to provide **9** as the major product (Scheme 4). The crystal structure of **9** confirms the assignment of bromination at the α-position on the furan ring of **4**. This change in substitution position in comparison to the isotopic exchange experiment strongly suggests that EAS is not the dominant mechanistic pathway for the monobromination of **4**. The result can be explained by considering **4** to be analogous to 3-vinylthiophene where the 2−3 bond in the furan ring is subject to electrophilic substitution via an addition−elimination mechanism. Similar observations have been reported for benzo[*b*]furan[17] and benzothieno[3,2-*b*]furan.[18]

Scheme 3. Bromination of Thieno[3,2-*b*]furan in THF with NBS



Scheme 4. Synthetic Route to 2-(Thiophen-2-yl)thieno[3,2-*b*]furan (**9**) and 5-(Thiophen-2-yl)thieno[3,2-*b*]furan (**11**)



Experimental assignment of the H2 peak location in the ^{1}H NMR spectrum of **4** was made by Li−Br exchange of **7** and quenching the resulting anion with D_2O. The ^{1}H NMR spectrum of the deuterated product does not contain a peak at 7.56 ppm, which matches the computed peak assignment for the α-position on the furan ring. Further, the 1.4 and 2.1 Hz splitting are absent from the peaks at 7.21 and 6.74 ppm, respectively.

To determine the position of deprotonation in **4**, one equivalent of BuLi was added to a solution of **4** in THF at 0 °C and the resulting anion was quenched with Bu_3SnCl to form **10** in 95% crude yield (Scheme 4). Stannyl compound

(15) Slight modifications to the conditions used to obtain **4** were empolyed to generate an isomer, thieno[2,3-*b*]furan, which has not been previously reported (Supporting Information). Thieno[2,3-*b*]furan is an analog of cross conjugated thieno[2,3-*b*]thiophene, which has been utilized in band gap controlled conjugated copolymers that display among the highest charge carrier mobilities to date for polymer organic thin film transistors: Heeney, M.; Bailey, C.; Genevicius, K.; Shkunov, M.; Sparrowe, D.; Tierney, S.; McCulloch, I. *J. Am. Chem. Soc.* **2005**, *127*, 1078–1079.

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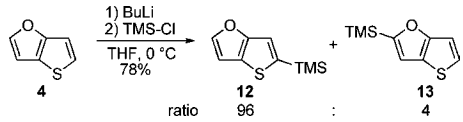
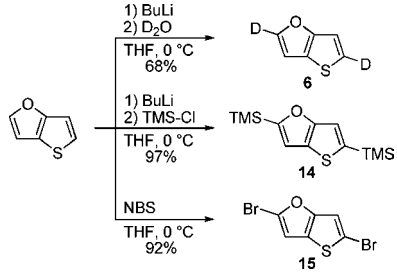
(17) (a) Okuyama, T.; Kunugiza, K.; Fueno, T. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1267–1270. (b) Baciocchi, E.; Clementi, S.; Sebastiani, G. V. *J. Heterocycl. Chem.* **1977**, *14*, 359–360.

Scheme 5. Deprotonation of Thieno[3,2-*b*]furan and Substitution with TMS



Scheme 6. Synthesis of 2,5-Dideuterothieno[3,2-*b*]furan (**6**), 2,5-Bis(trimethylsilanyl)thieno[3,2-*b*]furan (**14**), and 2,5-Dibromothieno[3,2-*b*]furan (**15**)



10 was then coupled to 2-bromothiophene under Stille conditions in 64% yield to give **11** as the major product (Scheme 4). As evidenced by NMR data (Supporting Information), oligomer **11** is the regioisomer of **9** where the thiophene ring is coupled to **4** at the 5-position. Therefore, the 5-position was the site of deprotonation and subsequent stannylation to form the precursor **10**.

To quantify the selectivity of deprotonation, **4** was treated with one equivalent of BuLi as previously described and quenched with TMS-Cl (Scheme 5). The ratio of substitution at the 2 vs 5-positions is 4:96 (NMR spectroscopy). This result is well correlated with data from similar studies on the α-linked 2-(thiophen-2-yl)furan[19] and from competition studies between thiophene and furan.[20]

The H5 peak in the ^{1}H NMR spectrum was experimentally identified by quenching the anion of **4** with D_2O. The resulting ^{1}H NMR spectrum does not contain a peak at 7.21 ppm and the 1.4 and 5.3 Hz splitting are absent from the peaks at 7.56 and 7.07 ppm, respectively, thus confirming the computationally determined peak assignment of H5 as the α-position on the thiophene ring. It is worth pointing out that upon deuteration of **4** by EAS, this is the same peak that most rapidly decreased in the ^{1}H NMR spectrum, experimentally reaffirming the aforementioned substitution assignment.

The dianion of **4** can be generated at the 2 and 5-positions by treatment with two equivalents of BuLi in THF at 0 °C. Quenching the dianion with D_2O (Scheme 6) leaves only the peaks at 6.74 and 7.07 ppm in the ^{1}H NMR spectrum, corresponding to the H3 and H6 protons. The coupling constant is 0.6 Hz. As a means of comparison, the long-range coupling constants were measured between the α−α protons and β−β protons in **2**. Because each of these two sets of protons are chemically equivalent, the coupling constants can not be measured from the major peaks directly. Instead a concentrated NMR sample was analyzed so that measurements could be made from the ^{13}C satellites. The coupling constants in **4** between the α−α protons (1.4 Hz) and the β−β protons (0.6 Hz) are quite similar to those observed for **2** (1.5 and 0.7 Hz, respectively).

To quantify the efficiency of bis-substitution via metalation, the dianion was generated with BuLi and quenched with TMS-Cl under lithiation conditions analogous to those previously described, producing **14** in 97% yield (Scheme 6). Dibromination is also easily achieved at the α-positions upon addition of two equivalents of NBS to a solution of **4** in THF, yielding **15** in 92% yield.

Replacement of a thiophene ring with furan in **2** results in markedly different spectroscopic and physical properties. For example, the absorption profile of **4** is blue-shifted as compared to **2**, reflected in a 22 nm shift in the longest wavelength absorption maximum from 269 to 247 nm. As evidenced by the boiling and melting points, the intermolecular interactions are weaker for **4** than for **2**. Boiling points of 177 and 228 °C were measured for **4** and **2**, respectively. Furthermore, a 90 °C depression in the melting point was observed when comparing **4** (−35 °C) to **2** (55 °C). With regards to general stability, like **2**, compound **4** and all derivatives presented in this report are stable for more than a month upon storage in neat form (−10 °C) under air and show no signs of degradation upon general handling in ambient conditions over several hours.

In summary, we report an optimized synthetic route to thieno[3,2-*b*]thiophene and the first route which allows for the isolation of thieno[3,2-*b*]furan. This general approach is also useful in producing other derivatives of these fused-ring heterocycles.[14] The fundamental reactivity of thieno[3,2-*b*]-furan with regards to selectivity involving EAS, addition−elimination, deprotonation, and Stille coupling were evaluated. Thieno[3,2-*b*]furan is chemically robust and offers good selectivity toward functionalization at either the 2 or 5-position under appropriate reaction conditions. Substitution of thieno[3,2-*b*]thiophene with thieno[3,2-*b*]furan will serve as an additional means of tailoring the molecular and bulk properties of conjugated oligomers and polymers. Incorporation of thieno[3,2-*b*]furan into conjugated materials is currently being investigated in our laboratory.

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Supporting Information Available: Experimental procedures, UV-vis spectra for **2** and **4**, NMR spectra, computational details and a CIF file for **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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