Efficient Syntheses of 2-Functionalized Thiophenes, Cyclopent[*b*]thiophenes, and Polysubstituted Benzo[*b*]thiophenes from 2-(Benzotriazol-1-ylmethyl)thiophenes

Alan R. Katritzky,* Larisa Serdyuk, Linghong Xie, and Ion Ghiviriga

Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, Florida 32611-7200

Received April 15, 1997[⊗]

Diverse 2-(functionalized-alkyl)- and 2-alkenylthiophenes **2a**,**b**, **4a**,**b**, and **6a**−**d** are prepared *via* the side chain elaboration of 2-(benzotriazol-1-ylmethyl)thiophenes **3a**,**b**, themselves readily available from the condensation of 1-(hydroxymethyl)benzotriazole with thiophenes **1a**,**b**. Treatment of 2-(benzotriazol-1-ylmethyl)thiophenes **3b** and **5g**,**j** with styrenes in the presence of zinc bromide results in formal [3 + 2] cycloaddition to give in good yields substituted cyclopent[*b*]thiophenes **16a**/**17a**, **16b**/**17b**, and **18**. Lithiation and 1,4-addition to a variety of α,β-unsaturated ketones and aldehydes, and subsequent acid-catalyzed intramolecular cyclization followed by debenzotriazolylation−dehydration converts **3** and **5** to a range of polysubstituted benzo[*b*]thiophenes **19a**−**d** and **25a**−**e** in moderate to excellent yields. NOE difference spectroscopy and NMR $^1H-^{13}C$ long-range correlation support structures of types **19** and **25** and exclude those of type **26**, thus confirming the cyclization pathway.

Introduction

2-Substituted thiophenes are useful, *inter alia* as dyestuffs, flavor agents, drugs, and inhibitors.[1] Cyclopent[*b*]thiophenes are of special interest as they constitute heteroaromatic analogues of many biologically active bicyclic compounds such as prostacyclin (PGI_2)[2] and 1-(dimethylamino)-3-phenylindane.[3] Benzothiophenes have attracted interest as potential biologically active agents and as bioisosters of indoles; for example, numerous benzo[*b*]thiophene analogs of biologically active indoles are agonists or antagonists of their indole congeners.[4]

Previous work has demonstrated the versatility of benzotriazole as a synthetic auxiliary in many transformations.[5] We have recently described the benzotriazole-assisted side-chain elaborations of indoles,[6] pyrroles,[7] and benzenes.[8] We have now extended this strategy to provide facile and efficient routes to 2-(functionalized-alkyl)- and 2-alkenylthiophenes, cyclopent[*b*]thiophenes, and polysubstituted benzo[*b*]thiophenes all starting from readily available 2-(benzotriazol-1-ylmethyl)thiophenes **3a**,**b**.

Results and Discussion

Preparation of 2-(Benzotriazol-2-ylmethyl)thiophenes (3a,b and 5a−j). 2-(Benzotriazol-1-ylmethyl)-thiophenes **3a**,**b** were prepared according to our previously reported procedure from thiophenes and 1-(hydroxymethyl)benzotriazole in refluxing acetic acid[9] (Scheme 1). Novel compound **3a** was characterized by NMR and CHN analyses.

Side-chain metalation of thiophene derivatives is normally difficult to achieve because ring metalation is predominant.[10] However, due to the electron-withdrawing ability of the benzotriazolyl group,[5b] compounds **3** can easily be deprotonated exclusively at the side-chain CH_2 α to the benzotriazolyl group. Accordingly, treatment of **3a**,**b** with *n*-butyllithium at −78 °C under argon in tetrahydrofuran furnished deep green solutions of the lithio derivatives. Reactions of these anions with phenyl isocyanate, phenyl isothiocyanate, various alkyl halides, or cyclohexanone gave the corresponding products **5a**,**b**,**d**,**f**−**j** in good yields. Reaction of the anion of **3b** with benzaldehyde, followed by the addition of methyl iodide, provided methyl ether derivative **5c** in 87% yield. Compounds **5a**−**d**,**f**−**j** were previously unknown and were characterized by NMR spectroscopy and elemental analyses. Compound **5e** was prepared according to a literature procedure[11] from 2-methylthiophene and *N*-(1-benzotriazolylalkyl)carbamate.

Syntheses of 2-(Functionalized-alkyl)thiophenes 6a−d and 2-Alkenylthiophenes (2a,b and 4a,b). The C-2 side chain of thiophenes **5** should be capable of further elaboration by the displacement of the benzotriazolyl moiety with nucleophiles (for reviews of benzotriazole as a leaving group, see ref 5). Indeed, treatment of **5a**,**b** and **5d** with zinc in refluxing acetic acid afforded, as expected, the corresponding amides **6a**,**d** and thioa-

[⊗] Abstract published in *Advance ACS Abstracts,* August 1, 1997.

(1) Campaigne, E. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984, p 910.

(2) (a) Cook, S.; Henderson, D.; Richardson, K. A.; Taylor, R. J. K.; Saunders, J.; Strange, P. G. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1825. (b) Richardson, K. A.; Saunders, J.; Taylor, R. J. K. *Tetrahedron Lett.* **1985**, *26*, 1171.

(3) Acheson, R. M.; MacPhee, K. E.; Philpott, P. G.; Barltrop, J. A. *J. Chem. Soc.* **1956**, 698.

(4) Campaigne, E. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984, p 911.

(5) (a) Katritzky, A. R.; Rachwal, S.; Hitchings, G. J. *Tetrahedron* **1991**, *47*, 2683. (b) Katritzky, A. R.; Yang, Z.; Cundy, D. J. *Aldrichimica Acta* **1994**, *27*, 31. (c) Katritzky, A. R.; Lan, X. *Chem. Soc. Rev.* **1994**, 363. (d) Katritzky, A. R.; Lan, X.; Fan, W.-Q. *Synthesis* **1994**, 445.

(6) (a) Katritzky, A. R.; Li, J.; Stevens, C. V. *J. Org. Chem.* **1995**, *60*, 3401. (b) Katritzky, A. R.; Xie, L.; Cundy, D. *Synth. Commun.* **1995**, *25*, 539. (c) Katritzky, A. R.; Zhang, G.; Xie, L.; Ghiviriga, I. *J. Org. Chem.* **1996**, *61*, 7558.

(7) (a) Katritzky, A. R.; Li, J. *J. Org. Chem.* **1996**, *61*, 1624. (b) Katritzky, A. R.; Levell, J. R.; Li, J. *Tetrahedron Lett.* **1996**, *37*, 5641.

(8) Katritzky, A. R.; Zhang, G.; Xie, L. *J. Org. Chem.* **1997**, *62*, 721.

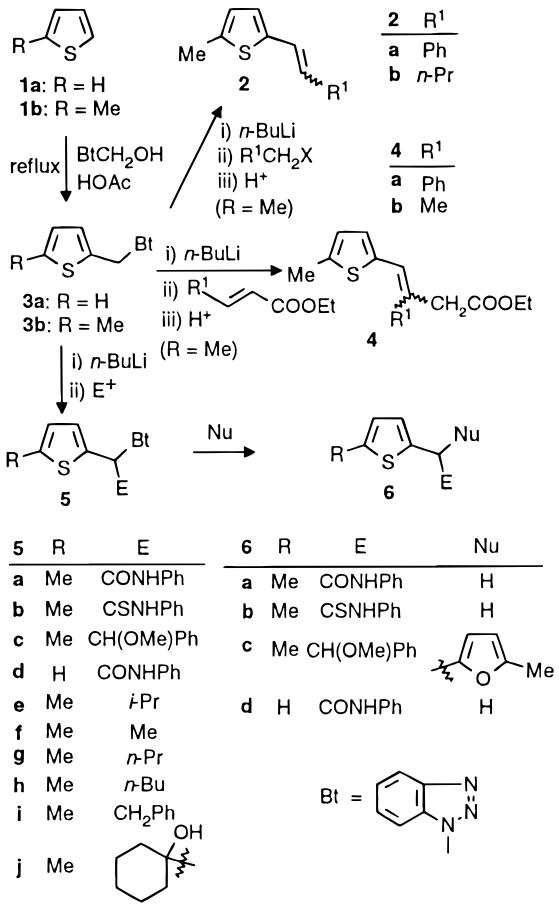
(9) Katritzky, A. R.; Toader, D.; Xie, L. *J. Org. Chem.* **1996**, *61*, 7571.

(10) Clarke, A. J.; McNamara, S.; Meth-Cohn, O. *Tetrahedron Lett.* **1974**, 2373.

(11) Katritzky, A. R.; Xie, L.; Fan, W.-Q. *J. Org. Chem.* **1993**, *58*, 4376.

S0022-3263(97)00672-5 CCC: $14.00

Scheme 1



5	R	E
a	Me	CONHPh
b	Me	CSNHPh
c	Me	CH(OMe)Ph
d	H	CONHPh
e	Me	*i*-Pr
f	Me	Me
g	Me	*n*-Pr
h	Me	*n*-Bu
i	Me	CH_2Ph
j	Me	

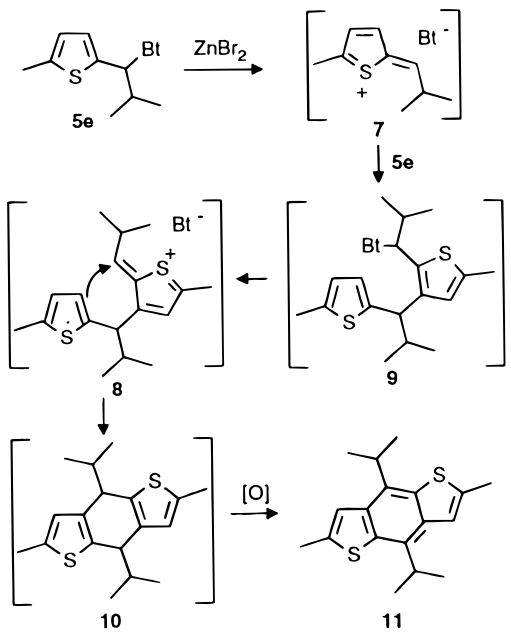
6	R	E	Nu
a	Me	CONHPh	H
b	Me	CSNHPh	H
c	Me	CH(OMe)Ph	
d	H	CONHPh	H

mide **6b** in 59−76% yields *via* the displacement of the benzotriazolyl group with hydride. Again, when **5c** was treated with 2-methylfuran in the presence of zinc bromide, the thienylfuryl compound **6c** was produced as a mixture of two diastereomers in 59% yield.

Importantly, if protons are present in side-chain E at the β-position of the benzotriazolyl group in compounds of type **5**, debenzotriazolylation can occur upon heating in the absence of nucleophiles to provide a variety of 2-alkenylthiophenes. Such reactions were accomplished without the isolation of **5** as intermediates. Thus, the anion of **3b** underwent alkylation with alkyl halides to give the alkylated intermediates, which without separation, upon refluxing in 1,4-dioxane in the presence of Amberlyst-15 acidic resin, provided 2-alkenylthiophenes **2a**,**b** in good yields. Similar reactions of the 1,4-addition products of the anion of **3b** with α,β-unsaturated esters gave **4a**,**b**. In the cases of **2a**,**b**, only *trans* isomers were produced, while **4a**,**b** were each obtained as an inseparable mixture of *trans* and *cis* isomers.

Previous preparations of 2-alkenylthiophenes have included (i) reactions of 2-thiophenecarboxaldehydes[12] and esters[13] with phosphorus ylides, (ii) palladium-catalyzed cross-coupling of 2-iodothiophene with diisopropyl (1-alkyl-1-alkenyl)boronates,[14] and (iii) addition of thiophene to acetylenes in the presence of $Rh_4(CO)_{12}$.[15] The present one-pot approach, which is capable of leading to functionalized 2-alkenylthiophenes directly from thiophenes, complements the existing methods.

Scheme 2

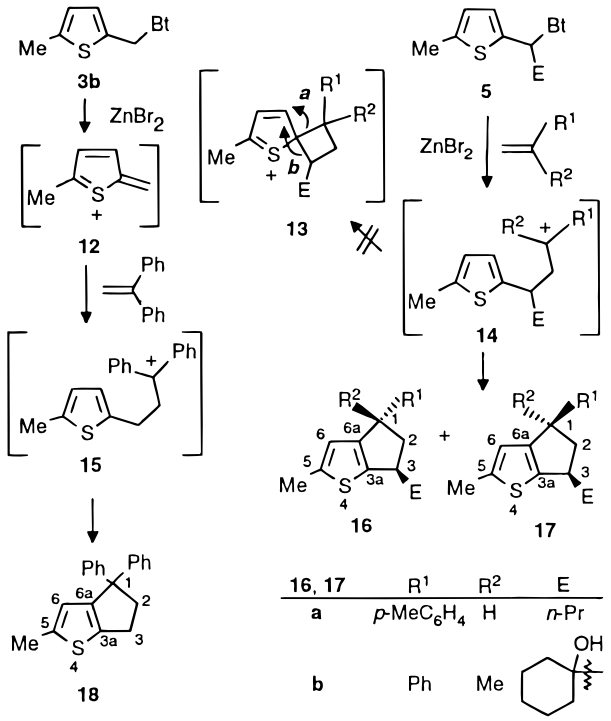


Synthesis of 2,6-Dimethyl-4,8-diisopropylbenzo[1,2-*b*:4,5-*b*′]dithiophene (11). Interestingly, when **5e** was refluxed in methylene chloride in the presence of zinc bromide, the benzo[1,2-*b*:4,5-*b*′]dithiophene **11** was obtained in 40% yield. This transformation is envisioned to proceed *via* two successive nucleophilic substitutions between two molecules of **5e** to intermediate **10**, which then aromatized to give compound **11** (Scheme 2). However, in the cases of **5f**−**i**, after similar refluxing in methylene chloride with zinc bromide, although GC−MS analyses showed the existence in the crude reaction mixtures of the corresponding benzo[1,2-*b*:4,5-*b*′]dithiophenes, they could not be separated from oligomers of similar polarity. Benzo[1,2-*b*:4,5-*b*′]dithiophenes have previously been prepared *via* the reaction of dithienylmethanes with dichloromethyl alkyl ethers in the presence of tin(IV) chloride[16] and also *via* a four-step sequence starting from 3-bromo-2-thiophenecarboxaldehyde and 3-bromothiophene.[17]

Synthesis of Cyclopent[*b*]thiophenes 16a/17a, 16b/17b, and 18. Our previous work has included the facile synthesis of 1-functionalized cyclopent[*b*]indoles from 3-(benzotriazol-1-ylmethyl)indole.[6c] Following a similar protocol, we found that alkenes could function as nucleophiles to induce formal [2 + 3] cycloadditions with 2-(benzotriazol-1-ylmethyl)thiophenes **3b** and **5g**,**j** to provide cyclopent[*b*]thiophenes. Thus, treatment of **3b** with zinc bromide, followed by the addition of 1,1-diphenylethylene, afforded 1,1-diphenyl-5-methylcyclopent[*b*]thiophene (**18**) in 52% yield *via* the addition of cation **12** to 1,1-diphenylethylene and subsequent ring closure of the intermediate benzylic cation **15** (Scheme 3). Similarly, 3-functionalized cyclopent[*b*]thiophenes (**16a**/**17a** and **16b**/**17b**) were prepared from $ZnBr_2$-catalyzed reactions of **5** with styrenes. While **5g** (derived from **3b** and *n*-propyl iodide) reacted with 4-methylstyrene to give a mixture of two diastereoisomeric cyclopent[*b*]thiophenes (**16a** and **17a**) in yields of 85%, reaction of **5j** (prepared from **3b** and cyclohexanone) with α-methylstyrene provided a mixture of **16b** and **17b** in

(12) Dopper, J. H.; Oudman, D.; Wynberg, H. *J. Am. Chem. Soc.* **1973**, *95*, 3692.
(13) Uijttewaal, A. P.; Jonkers, F. L.; van der Gen, A. *Tetrahedron Lett.* **1975**, 1439.
(14) Satoh, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1986**, 1329.
(15) Hong, P.; Cho, B.-R.; Yamazaki, H. *Chem. Lett.* **1980**, 507.
(16) Ahmed, M.; Ashby, J.; Ayad, M.; Meth-Cohn, O. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1099.
(17) Beimling, P.; Koβmehl, G. *Chem. Ber.* **1986**, 119, 3198.

Scheme 3



83% yield. In both cases, the *E* isomers **16** are slightly predominant (14:9 for **16a**/**17a**, and 2:1 for **16b**/**17b**). In these reactions, zinc bromide is essential to the ionization of 2-(benzotriazol-1-ylmethyl)thiophenes by coordinating with the nitrogen atom on the benzotriazole ring.

Novel compounds **16**−**18** were characterized by elemental (C, H, N) analyses and NMR spectroscopy. Since the thiophene 2-position is more nucleophilic than the thiophene 3-position, the cyclization of cations **14** and **15** could possibly occur either at the 3-position or first at the 2-position (*ipso* attack) to give spiro intermediates of type **13** (Scheme 3), followed by the migration of one of the two alkyl groups. Although the later pathway seems unlikely, as only single regioisomers were obtained, the regiochemistries of **16a**/**17a** and **18** were examined by NOE difference spectroscopy to confirm structures **16**−**18**. In the case of **18**, irradiation of the signal at 6.52 ppm (position 6) produced a positive NOE on the methyl group at 2.44 ppm (position 5) and on the phenyl signals at 7.20 ppm, which confirmed the regiochemistry assigned. The NOE difference experiments for compounds **16a** and **17a** were run on the mixture (**16a**/**17a**). The regiochemistry was demonstrated by positive NOE's on the singlet in position 6 (6.34 and 6.29 ppm correspondingly) and on the *ortho* protons on the phenyl group (7.01 and 7.10 ppm correspondingly) when the protons in position 1 at 4.21 ppm (**16a**) or 4.12 ppm (**17a**) were selectively irradiated.

The *cis*−*trans* stereochemistries of **16a** and **17a** were also determined by NOE. The *cis* relationship of the protons in positions 1 and 3 in **17a** was evidenced by their positive NOE's upon irradiation of the proton at 2.98 ppm (position 2). However, attempts to prove the regiochemistry and stereochemistry by NMR for **16b**/**17b** failed due to the overlap of the OH proton with the thiophene CH.

The most preparatively efficient previous syntheses of cyclopent[*b*]thiophenes include (i) the cyclization of acetylenic cyclic ketones,[2] (ii) palladium-catalyzed cycloaddition of 2-iodothiophene, carbon monoxide and an olefin,[18] and (iii) the ring-closure of 3-thienylpropionic acids.[3,19] However, routes i and ii are not general and the strongly acidic conditions required for method iii, such as heating in PPA, may limit its applicability.

Synthesis of Polysubstituted Benzo[*b*]thiophenes (19a−d and 25a−e). We have previously reported benzotriazole-mediated aromatic annulations to polysubstituted carbazoles[6c] and naphthalenes.[8] Following a similar protocol, polysubstituted benzo[*b*]thiophenes were readily accessible. Thus, additions of the lithio derivatives of **3** and **5** to α,*β*-unsaturated ketones or aldehydes, followed by refluxing in 1,4-dioxane in the presence of an acidic resin (Amberlyst-15), formed a variety of polysubstituted benzo[*b*]thiophenes **25a**−**e** and **19a**−**d** in moderate to excellent yields (Scheme 4). As exemplified by the transformation sequence of **3** to **25** shown in Scheme 4, the process is envisioned to proceed *via* Michael addition, acid-catalyzed cyclization, and dehydrobenzotriazolylation.

The conditions required for the cyclizations **5** → **19** and **3** → **25** reflect that the reactivity of the thiophene ring is intermediate between those of benzene and pyrrole. Thus, while strong acidic conditions such as HBr + HOAc or PPA were required for the cyclization in the case of a benzene system,[8] cyclization of 2-(benzotriazol-1-ylmethyl)pyrroles was effected by refluxing in THF in the presence of Amberlyst-15 acidic resin.[7b] In the case of the present thiophenes, cyclization required refluxing in the higher boiling 1,4-dioxane in the presence of Amberlyst-15 acidic resin.

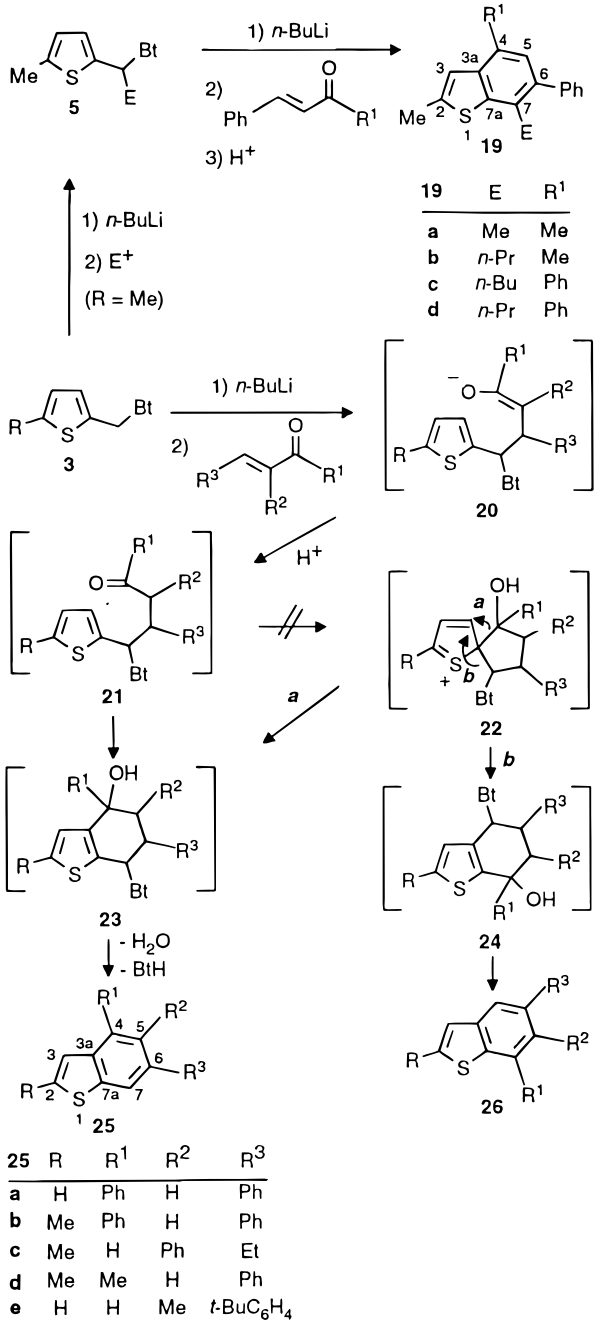
Benzo[*b*]thiophenes **19a**−**d** and **25a**−**e** were all novel and their structures were fully supported by elemental analyses and NMR spectroscopy. As discussed above for the ring closure of **14** and **15** in the synthesis of cyclopent[*b*]thiophenes (Scheme 3), the *ipso* attack in the cyclization of **21** was also taken into consideration. While direct cyclization of **21** would give only the single regioisomers **25**, possibly pathways *via* spiro intermediates **22** could furnish, in each case, two regioisomers **25** and **26** (Scheme 4). However, in all cases, single isomers **25a**−**e** and **19a**−**d** were obtained, suggesting that the direct C−3 ring closure is operative under our reaction conditions. However, structures of types **19** and **25** were supported, and that of type **26** excluded, by NOE difference experiments together with $^{1}H-^{13}C$ long-range correlations.

In the case of **19a**, irradiation of the singlet at 6.93 ppm produced positive NOE's on two methyl signals (2.42 and 2.44 ppm), identifying the proton on the thiophene moiety and the methyl groups in positions 2 and 4. Irradiation of the other deshielded singlet at 7.01 ppm (on the benzene moiety) produced a positive NOE to the same methyl group at 2.44 ppm (position 4) and not at 2.38 ppm (position 7). Structure **19b** showed, as expected, positive NOE's on both deshielded singlets at 6.97 and 7.04 ppm when the methyl group at 2.50 ppm was irradiated. Irradiation of the other methyl signal (2.60 ppm) led to a positive NOE at 7.04 ppm. This allows the assignment of the signals at 2.60, 7.04, 2.50, and 6.97 ppm to positions 2, 3, 4, and 5, respectively. Irradiation of the methyl group in **19c** (2.57 ppm) produced a positive NOE on the singlet at 7.12 ppm, which was thus assigned to position 3. Irradiation of the proton in position 3 led

(18) Grigg, R.; Khalil, H.; Levett, P.; Virica, J.; Sridharan, V. *Tetrahedron Lett.* **1994**, *35*, 3197.

(19) (a) Dallemagne, P.; Rault, S.; Cugnon de Sevricourt, M.; Hassan, Kh. M.; Robba, M. *Tetrahedron Lett.* **1986**, *27*, 2607. (b) Stanetty, P. *J. Chem. Res. (S)* **1981**, 99. (c) Frejd, T.; Karlsson, O. *Tetrahedron* **1979**, *35*, 2155. (d) Schneller, S. W.; Moore, D. R. *J. Org. Chem.* **1975**, *40*, 1840. (e) Meth-Cohn, O.; Gronowitz, S. *Acta Chem. Scand.* **1966**, *20*, 1577.

Scheme 4



19	E	R^1
a	Me	Me
b	*n*-Pr	Me
c	*n*-Bu	Ph
d	*n*-Pr	Ph

25	R	R^1	R^2	R^3
a	H	Ph	H	Ph
b	Me	Ph	H	Ph
c	Me	H	Ph	Et
d	Me	Me	H	Ph
e	H	H	Me	*t*-BuC_6H_4

to a positive NOE on the doublet at 7.55 ppm, demonstrating that position 4 is a phenyl ring.

Compound **19d** displays ^{1}H chemical shifts very similar to those in **19c**. When the doublet at 7.55 ppm was irradiated, both singlets at 7.21 and 7.11 ppm showed a positive NOE, thus discarding a structure of type **26**. The later signal was assigned to position 3, based on its positive NOE upon irradiation of the methyl group in position 2 (2.52 ppm).

In compound **25a**, extensive overlapping of the proton signals required ^{1}H−^{13}C direct and long-range correlation for the identification of the chemical shifts of the protons on the benzothiophene moiety. A HETCOR experiment was run preserving the ^{1}H−^{1}H couplings in the proton dimension. Singlets at 7.57 and 8.04 ppm correspond to positions 5 and 7. The doublets at 7.31 and 7.41 ppm are directly correlated to carbon signals of half the intensity of those corresponding to positions *ortho* and *meta* on the phenyl rings, thus they were assigned to positions 2 and 3. The singlet at 8.04 ppm was the only signal which could be selectively irradiated, and this irradiation produced a positive NOE on the signal at 7.65 ppm, corresponding to an *ortho* position on a phenyl ring. No positive NOE at 7.31 or 7.41 ppm, as expected for a structure of type **26**, was observed.

Irradiation of the methyl signal in **25b** (2.58 ppm) produced a positive NOE on the singlet at 7.05 ppm, which identified this signal as the one for the proton in position 3. The regiochemistry of this compound was proven by a positive NOE on a doublet at 7.60 ppm and not a singlet as expected for a structure of type **26**. In **25c**, irradiation of the signal at 6.87 ppm produced positive NOE's on the methyl signal at 2.54 ppm (position 2) and on the singlet at 7.40 ppm, which is thus in position 4. Irradiation of the methylene protons of the ethyl group (2.59 ppm) produced a positive NOE on a different singlet at 7.60 ppm, demonstrating that the ethyl group is in position 6. The regiochemistry of **25d** was demonstrated by the positive NOE's on the singlets at 7.27 and 6.77 ppm upon irradiation of the methyl group at 2.39. The proton *ortho* to the methyl group in **25e** was identified as the one at 7.64 ppm by a positive NOE upon irradiation at 2.37 ppm. Irradiation at 7.64 ppm produced a positive NOE on the doublet at 7.27 ppm, which evidenced a structure of type **25**.

Substituted benzo[*b*]thiophenes have previously usually been constructed by building a thiophene ring onto a benzene nucleus[20] and, less frequently, by the annulation of a benzene ring onto a thiophene moiety.[21] However, the latter approach is of special importance for the preparation of benzothiophenes multisubstituted in the benzene moiety. Building a benzene ring onto a thiophene has been accomplished (i) from thiophenes bearing two *ortho* substituents (one electrophilic and one potentially nucleophilic) and Michael acceptors, followed by intramolecular cyclization;[21e] this approach is useful for the preparation of benzothiophenes with electron-withdrawing substituents; (ii) Diels−Alder reactions of thieno[2,3-*c*]furans with dienophiles,[21c,d] however, in many cases the dienophile must be symmetrical in order to control the regiochemistry; (iii) palladium-catalyzed cyclocarbonylation of 3-(thienyl)allyl acetates,[21a,b] which is restricted to the synthesis of benzothiophenes with an acetoxy group; and (iv) condensations of β-metallo derivatives of protected propanals [$MCH_2CH_2CH(OR)_2$] with 2-thiophenecarboxaldehyde, followed by cyclization effected by dilute sulfuric acid,[21f] which are limited by the availability of annulating reagents with suitable substitution patterns.

Conclusion

In conclusion, general and efficient approaches to 2-substituted thiophenes, cyclopent[*b*]thiophenes, and

(20) (a) Buchwald, S. L.; Fang, Q. *J. Org. Chem.* **1989**, *54*, 2793. (b) Johnson, F.; Subramanian, R. *J. Org. Chem.* **1986**, *51*, 5040. (c) de Groot, A.; Jansen, B. J. M. *Synthesis* **1985**, 434. (d) Kitamura, T.; Kawasato, H.; Kobayashi, S.; Taniguchi, H. *Chem. Lett.* **1986**, 839. (e) Kitamura, T.; Kobayashi, S.; Taniguchi, H. *Chem. Lett.* **1988**, 1637. (f) Bridges, A. J.; Lee, A.; Maduakor, E. C.; Schwartz, C. E. *Tetrahedron Lett.* **1992**, *33*, 7499. (g) Russavskaya, N. V.; Korchevin, N. A.; Sukhomazova, E. N.; Turchaninova, L. P.; Deryagina, E. N.; Voronkov, M. G. *J. Org. Chem. (USSR)* **1991**, 305. (h) Leardini, R.; Pedulli, G. F.; Tundo, A.; Zanardi, G. *J. Chem. Soc., Chem. Commun.* **1985**, 1390. (i) Arnoldi, A.; Carughi, M. *Synthesis* **1988**, 155.

(21) (a) Iwasaki, M.; Kobayashi, Y.; Li, J.-P.; Matsuzaka, H.; Ishii, Y.; Hidai, M. *J. Org. Chem.* **1991**, *56*, 1922. (b) Iwasaki, M.; Li, J.-P.; Kobayashi, Y.; Matsuzaka, H.; Ishii, Y.; Hidai, M. *Tetrahedron Lett.* **1989**, *30*, 95. (c) Schîning, A.; Friedrichsen, W. *Tetrahedron Lett.* **1988**, *29*, 1137. (d) Kuroda, T.; Takahashi, M.; Ogiku, T.; Ohmizu, H.; Kondo, K.; Iwasaki, T. *J. Chem. Soc., Chem. Commun.* **1991**, 1635. (e) Terpstra, J. W.; van Leusen, A. M. *J. Org. Chem.* **1986**, *51*, 230. (f) Loozen, H. J. J.; Godefroi, E. F. *J. Org. Chem.* **1973**, *38*, 1056.

polysubstituted benzothiophenes have been developed, all starting from readily available 2-(benzotriazol-1-ylmethyl)thiophenes **3**. While the cyclopent[*b*]thiophene construction takes advantage of the ready introduction of functionality into the 4-position of cyclopent[*b*]thiophenes, the benzothiophene synthesis provides special opportunities for the introduction of substituents into the benzene moiety of benzothiophenes. The main limitation of these synthetic reactions is the acidic conditions required: thus acid-sensitive substituents would not be tolerated.

Experimental Section

General. Melting points were determined with a hot-stage apparatus and are uncorrected. NMR spectra were taken in $CDCl_3$ or DMSO-d_6 with tetramethylsilane as the internal standard for ^{1}H (300 MHz) or solvent as the internal standard for ^{13}C (75 MHz). Tetrahydrofuran (THF) was distilled under nitrogen immediately prior to use from sodium/benzophenone. All reactions with air-sensitive compounds were carried out under an argon atmosphere. Column chromatography was conducted with silica gel 230−400 mesh. 2-(Benzotriazol-1-ylmethyl)-5-methylthiophene (**3b**)[9] and 2-(1-benzotriazol-1-yl-2-methylpropyl)-5-methylthiophene (**5e**)[11] were prepared according to our previously reported procedure.

Preparation of 2-(Benzotriazol-1-ylmethyl)thiophene (3a). A mixture of 1-(hydroxymethyl)benzotriazole (30 mmol, 4.5 g), thiophene (180 mmol, 15.1 g), and *p*-toluenesulfonic acid (0.1 g) in dioxane (20 mL) was refluxed for 3 days. The solvent and an excess amount of thiophene were evaporated under vacuum. To the oil residue was added sodium hydroxide (5% aqueous, 10 mL) and chloroform (50 mL). The organic layer was separated, washed with water (2 × 50 mL) and dried (Na_2SO_4). Evaporation of the solvent gave the crude product which was recrystallized from CH_2Cl_2/hexane to afford the pure product as a colorless solid: yield 35% (2.23 g); mp 103−104 °C; ^{1}H NMR ($CDCl_3$) δ 5.99 (s, 2H), 6.95 (dd, J = 5.2 and 3.5 Hz, 1H), 7.10 (d, J = 3.5 Hz, 1H), 7.24 (dd, J = 5.2 and 1.3 Hz, 1H), 7.34 (t, J = 7.4 Hz, 1H), 7.41−7.49 (m, 2H), 8.03 (d, J = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 46.8, 109.5, 120.0, 124.0, 126.4, 127.1, 127.4, 127.5, 132.4, 136.6, 146.1. Anal. Calcd for $C_{11}H_9N_3S$: C, 61.37; H, 4.21; N, 19.52. Found: C, 61.38; H, 4.26; N, 19.40.

General Procedure for the Preparation of 2-(1-Benzotriazol-1-ylalkyl)thiophenes 5a−j. To a solution of 2-(benzotriazol-1-ylmethyl)thiophene **3** (5 mmol) in dry THF (50 mL) at −78 °C under argon was added *n*-BuLi (2 M, 2.8 mL, 5.5 mmol). After 1.5 h, the appropriate electrophile (5.5 mmol) (phenyl isocyanate for **5a**, phenyl isothiocyanate for **5b**, benzaldehyde for **5c**, phenyl isocyanate for **5d**, methyl iodide for **5f**, *n*-propyl iodide for **5g**, *n*-butyl iodide for **5h**, benzyl bromide for **5i**, and cyclohexanone for **5j**) in THF (7 mL) was added. The mixture was stirred at −78 °C for an additional 4 h and then at rt overnight. After being quenched with water (50 mL), the mixture was extracted with Et_2O (3 × 50 mL) and the combined organic layer was dried ($MgSO_4$). The solvent was evaporated under vacuum and the residue purified either by recrystallization or by column chromatography to give the corresponding pure product **5**. In the case of **5c**, after 4 h of stirring at −78 °C, methyl iodide (0.7 g, 5 mmol) in HMPA (10 mL) was added to protect the oxygen anion. The mixture was stirred at this temperature for an additional 2 h and then at rt overnight before workup.

***N*-Phenyl-2-benzotriazol-1-yl-2-(5-methylthien-2-yl)acetamide (5a)** was purified by recrystallization from EtOAc/hexane to give a colorless solid: yield 80% (1.39 g); mp 173−175 °C; ^{1}H NMR (DMSO-d_6) δ 2.44 (s, 3H), 6.81 (d, J = 3.5 Hz, 1H), 7.13 (t, J = 7.4 Hz, 1H), 7.19 (d, J = 3.5 Hz, 1H), 7.28−7.45 (m, 4H), 7.52 (t, J = 8.2 Hz, 1H), 7.57−7.65 (m, 3H), 8.08 (d, J = 8.2 Hz, 1H), 10.82 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 14.1, 61.4, 111.2, 118.2, 118.7, 122.7, 123.2, 123.8, 126.2, 127.6, 131.6, 131.7, 136.9, 141.1, 145.0, 163.5; HRMS calcd for $C_{19}H_{16}N_4OS$ 349.1123 (M + 1), found 349.1118.

***N*-Phenyl-2-benzotriazol-1-yl-2-(5-methylthien-2-yl)-thioacetamide (5b)** was purified by recrystallization from EtOAc/hexane to give a colorless solid: yield 78% (1.41 g); mp 109−110 °C; ^{1}H NMR (DMSO-d_6) δ 2.49 (s, 3H), 6.86 (d, J = 3.5 Hz, 1H), 7.27−7.52 (m, 7H), 7.64 (s, 1H), 7.85 (d, J = 7.8 Hz, 2H), 8.07 (d, J = 8.4 Hz, 1H), 12.39 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 15.0, 67.4, 111.5, 119.3, 123.2, 124.0, 125.1, 126.7, 127.4, 128.8, 129.9, 133.0, 133.1, 138.8, 142.4, 145.5, 194.9. Anal. Calcd for $C_{19}H_{16}N_4S_2$: C, 62.61; H, 4.42. Found: C, 62.82; H, 4.77.

1-Benzotriazol-1-yl-1-(5-methylthien-2-yl)-2-methoxy-2-phenylethane (5c) was purified by recrystallization from Et_2O to give a mixture of two diastereoisomers as an oil: yield 87% (1.52 g); one of the isomers was obtained as a colorless solid in a pure state by washing the mixture with Et_2O: mp 120−122 °C; ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3H), 3.19 (s, 3H), 5.35 (d, J = 8.2 Hz, 1H), 6.13 (d, J = 8.2 Hz, 1H), 6.42 (d, J = 3.6 Hz, 1H), 6.63 (d, J = 3.6 Hz, 1H), 7.20−7.39 (m, 6H), 7.45 (t, J = 7.2 Hz, 1H), 7.67 (d, J = 8.3 Hz, 1H), 8.06 (d, J = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.1, 57.0, 64.6, 85.4, 110.5, 119.8, 123.7, 124.5, 127.0, 127.4, 127.5, 128.4, 128.5, 133.3, 135.2, 137.6, 140.9, 145.9. Anal. Calcd for $C_{20}H_{19}N_3OS$: C, 68.74; H, 5.48; N, 12.02. Found: C, 69.00; H, 5.57; N, 12.19.

***N*-Phenyl-2-benzotriazol-1-yl-2-thien-2-ylacetamide (5d)** was purified by recrystallization from EtOAc/hexane to give a colorless solid: yield 64% (1.1 g); mp 164−165 °C; ^{1}H NMR (DMSO-d_6) δ 7.11−7.19 (m, 2H), 7.34−7.72 (m, 10H), 8.11 (d, J = 8.3 Hz, 1H), 10.82 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 61.6, 111.7, 119.4, 119.7, 124.1, 124.3, 127.0, 127.6, 128.7, 128.9, 129.3, 132.5, 135.1, 138.0, 145.6, 164.4. Anal. Calcd for $C_{18}H_{14}N_4OS$: C, 64.65; H, 4.22; N, 16.75. Found: C, 64.46; H, 4.28; N, 16.64.

2-(1-Benzotriazol-1-ylethyl)-5-methylthiophene (5f) was purified by column chromatography (hexane/EtOAc = 10:1) to give a colorless oil: yield 68% (0.82 g); ^{1}H NMR ($CDCl_3$) δ 2.15 (d, J = 6.9 Hz, 3H), 2.39 (s, 3H), 6.33 (q, J = 6.9 Hz, 1H), 6.60 (d, J = 3.5 Hz, 1H), 6.85 (d, J = 3.5 Hz, 1H), 7.29−7.42 (m, 3H), 8.06 (d, J = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.0, 21.1, 54.8, 110.1, 119.7, 123.7, 124.6, 125.2, 126.9, 131.7, 140.1, 140.2, 146.2. Anal. Calcd for $C_{13}H_{13}N_3S$: C, 64.17; H, 5.39; N, 17.27. Found: C, 63.80; H, 5.31; N, 17.31.

2-(1-Benzotriazol-1-ylbutyl)-5-methylthiophene (5g) was purified by column chromatography (hexane/EtOAc = 2:1) to give a colorless oil: yield 92% (1.29 g); ^{1}H NMR ($CDCl_3$) δ 0.95 (t, J = 7.2 Hz, 3H), 1.18−1.44 (m, 2H), 2.39 (s, 3H), 2.40−2.52 (m, 1H), 2.59−2.72 (m, 1H), 6.11 (dd, J = 9.3 and 6.3 Hz, 1H), 6.57 (d, J = 3.5 Hz, 1H), 6.85 (d, J = 3.5 Hz, 1H), 7.32 (t, J = 8.0 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 8.05 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.4, 15.2, 19.6, 37.0, 59.2, 110.1, 120.0, 123.8, 124.7, 125.7, 127.0, 132.0, 139.5, 140.3, 146.3. Anal. Calcd for $C_{15}H_{17}N_3S$: C, 66.39; H, 6.31; N, 15.48. Found: C, 65.97; H, 6.39; N, 15.53.

2-(1-Benzotriazol-1-ylpentyl)-5-methylthiophene (5h) was purified by column chromatography (hexane/EtOAc = 2:1) to give a colorless oil: yield 93% (1.32 g); ^{1}H NMR ($CDCl_3$) δ 0.84 (t, J = 7.0 Hz, 3H), 1.11−1.25 (m, 1H), 1.25−1.90 (m, 3H), 2.38 (s, 3H), 2.41−2.56 (m, 1H), 2.58−2.72 (m, 1H), 6.07 (dd, J = 9.1 and 6.3 Hz, 1H), 6.56 (d, J = 3.5 Hz, 1H), 6.84 (d, J = 3.5 Hz, 1H), 7.31 (t, J = 8.0 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 8.04 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 15.2, 22.0, 28.5, 34.8, 59.6, 110.1, 120.0, 123.8, 124.7, 125.7, 127.0, 132.1, 139.5, 140.3, 146.3. Anal. Calcd for $C_{16}H_{19}N_3S$: N, 14.72. Found: N, 14.88.

2-[(1-Benzotriazol-1-yl-2-phenyl)methyl]-5-methylthiophene (5i) was purified by recrystallization from EtOAc/hexane to give a colorless solid: yield 87% (1.4 g); mp 118−119 °C; ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H), 3.78 (dd, J = 13.9 and 6.4 Hz, 1H), 3.98 (dd, J = 13.9 and 9.3 Hz, 1H), 6.24 (dd, J = 9.3 and 6.4 Hz, 1H), 6.56 (d, J = 3.4 Hz, 1H), 6.84 (d, J = 3.4 Hz, 1H), 7.01−7.03 (m, 2H), 7.03−7.15 (m, 3H), 7.25−7.37 (m, 3H), 8.01 (d, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.2, 41.7, 60.8, 109.7, 119.9, 123.7, 124.7, 125.9, 126.9, 127.1, 128.4, 128.8, 132.4, 136.5, 138.8, 140.6, 146.0. Anal. Calcd for $C_{19}H_{17}N_3S$: C, 71.44; H, 5.36; N, 13.15. Found: C, 71.34; H, 5.39; N, 13.19.

2-[Benzotriazol-1-yl(1-hydroxy-1-cyclohexyl)methyl]-5-methylthiophene (5j) was purified by column chromatography (hexane/EtOAc = 2:1) to give a colorless solid: yield 79% (1.42 g); mp 145−146 °C; ^{1}H NMR ($CDCl_3$) δ 1.21−1.89 (m, 10H), 2.40 (s, 3H), 3.81 (s, 1H), 5.90 (s, 1H), 6.57 (d, J = 3.3

Hz, 1H), 7.02 (d, J = 3.3 Hz, 1H), 7.36 (t, J = 8.0 Hz, 1H), 7.50 (t, J = 8.0 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 8.06 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.1, 21.6, 21.8, 25.4, 35.1, 35.6, 66.5, 74.2, 109.9, 120.1, 124.0, 124.2, 127.7, 128.4, 133.3, 134.2, 141.7, 145.2. Anal. Calcd for $C_{18}H_{21}N_3OS$: N, 12.83. Found: N, 12.67.

General Procedure for the Preparation of 2-Functionalized Thiophenes 7a,b,d. A mixture of the corresponding compound **5** (**5a** for **7a**, **5b** for **7b**, and **5d** for **7d**) (2 mmol), zinc metal (2.6 g, 40 mmol) in acetic acid (10 mL), and dry THF (20 mL) was refluxed for 3 days. On cooling the excess amount of zinc metal was filtered off. To the solution was added diethyl ether (50 mL) and the mixture was then washed with water (3 × 50 mL) and dried (Na_2SO_4). The solvent was removed under vacuum to give an oil which was separated by column chromatography to give the pure product.

***N*-Phenyl-2-(5-methylthien-2-yl)acetamide (6a).** Chloroform was used as the eluent to give a colorless solid: yield 76% (0.35 g); mp 104−105 °C; ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 3H), 3.87 (s, 2H), 6.69 (d, J = 3.4 Hz, 1H), 6.82 (d, J = 3.4 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 7.31 (t, J = 7.5 Hz, 2H), 7.38 (br s, 1H), 7.45 (d, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 15.0, 38.2, 119.8, 123.9, 124.8, 126.6, 128.5, 133.6, 137.9, 139.4, 168.4. Anal. Calcd for $C_{13}H_{13}NOS$: C, 67.50; H, 5.66; N, 6.06. Found: C, 67.57; H, 5.61; N, 5.92.

***N*-Phenyl-2-(5-methylthien-2-yl)thioacetamide (6b).** Et_2O/hexane (1:2) was used as the eluent to give a colorless oil: yield 67% (0.31 g); ^{1}H NMR ($CDCl_3$) δ 2.51 (s, 3H), 4.40 (s, 2H), 6.72 (d, J = 3.0 Hz, 1H), 6.86 (d, J = 3.0 Hz, 1H), 7.27 (t, J = 7.7 Hz, 1H), 7.38 (t, J = 7.7 Hz, 2H), 7.62 (d, J = 7.7 Hz, 2H), 8.87 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.3, 48.6, 123.5, 125.6, 127.0, 128.4, 128.8, 133.4, 138.3, 141.4, 199.7. Anal. Calcd for $C_{13}H_{12}NS_2$: C, 63.12; H, 5.30; N, 5.66. Found: C, 63.16; H, 5.55; N, 5.68.

***N*-Phenyl-2-thien-2-ylacetamide (6d).** Chloroform was used as the eluent to give a colorless solid: yield 59% (0.26 g); mp 116−117 °C; ^{1}H NMR ($CDCl_3$) δ 3.89 (s, 2H), 6.90−7.01 (m, 2H), 7.06 (t, J = 7.1 Hz, 1H), 7.21 (d, J = 4.6 Hz, 1H), 7.27 (t, J = 7.7 Hz, 2H), 7.58 (d, J = 7.7 Hz, 2H), 9.39 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 37.6, 119.4, 123.3, 124.3, 126.0, 126.3, 128.2, 136.2, 138.1, 167.9. Anal. Calcd for $C_{12}H_{11}NOS$: C, 66.33; H, 5.10; N, 6.45. Found: C, 66.23; H, 5.18; N, 6.38.

Preparation of 1-(5-Methylthien-2-yl)-1-(5-methylfuran-2-yl)-2-methoxy-2-phenylethane (6c). A mixture of 1-benzotriazol-1-yl-1-(5-methylthien-2-yl)-2-methoxy-2-phenylethane (**5c**) (1.6 g, 4.6 mmol), 2-methylfuran (0.41 g, 5 mmol), and $ZnBr_2$ (2.5 g, 11 mmol) in methylene chloride (40 mL) was stirred at rt for 5 days. The solid was filtered and water (50 mL) was added to the solution. After separation, the aqueous layer was extracted with Et_2O (2 × 50 mL) and dried (Na_2SO_4). The solvent was removed under vacuum to give an oil which was purified by column chromatography (hexane/EtOAc = 4:1) to give the pure product as a mixture of two disteroisomers: colorless oil; 59% (0.84 g); ^{1}H NMR ($CDCl_3$) (signals for the minor isomer are in square brackets) δ 2.19 (s, 3H) [2.27 (s, 3H)], 2.45 (s, 3H) [2.34 (s, 3H)], 3.24 (s, 3H) [3.21 (s, 3H)], 4.35 (d, J = 7.7 Hz, 1H) [4.41 (d, J = 8.3 Hz, 1H)], 4.66 (d, J = 7.7 Hz, 1H) [4.60 (d, J = 8.3 Hz, 1H)], 5.71 (d, J = 3.5 Hz, 1H) [5.79 (d, J = 3.0 Hz, 1H)], 5.90 (d, J = 3.0 Hz, 1H) [6.10 (d, J = 3.5 Hz, 1H)], 6.33 (d, J = 3.3 Hz, 1H) [6.39 (d, J = 3.0 Hz, 1H)], 6.55 (d, J = 3.5 Hz, 1H) [6.60 (d, J = 3.3 Hz, 1H)], 7.11−7.27 (m, 5H); ^{13}C NMR ($CDCl_3$) (signals for the minor isomer are in square brackets) δ 13.5 [13.6], 15.3 [15.2], 48.5 [48.3], 57.2, 86.0 [86.3], 105.9 [106.2], 107.9 [107.4], 124.1 [124.3], 125.7 [125.5], 127.1, 127.5, 127.6, 127.9 [128.0], 138.7 [138.5], 140.1 [139.9], 150.6, 152.1 [152.5]. Anal. Calcd for $C_{19}H_{20}O_2S$: C, 73.04; H, 6.45. Found: C, 72.89; H, 6.35.

Preparation of 2,6-Dimethyl-4,8-bis(1-methylethyl)-benzo[1,2-*b*:4,5-*b*′]dithiophene (11). A mixture of 2-(1-benzotriazol-1-yl-2-methylpropyl)-5-methylthiophene (**5e**) (1.3 g, 5 mmol) and $ZnCl_2$ (0.7 g, 5 mmol) in methylene chloride (50 mL) was refluxed overnight and then ice water (50 mL) was added. After separation, the aqueous layer was extracted with chloroform (2 × 30 mL) and the combined organic extracts were washed with NaOH (aqueous 3%, 40 mL) and water (50 mL). On drying ($NaSO_4$), the solvent was evaporated to give an oil which was washed with a mixture of Et_2O and hexane (1:1) to give a colorless solid: 40% (0.60 g); mp 288−289 °C; ^{1}H NMR ($CDCl_3$) δ 1.53 (d, J = 7.1 Hz, 12 H), 2.60 (s, 6H), 3.58 (m, 2H), 7.22 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 16.5, 21.3, 33.9, 120.0, 120.1, 132.8, 134.9, 138.7. Anal. Calcd for $C_{18}H_{22}S_2$: C, 71.47; H, 7.33. Found: C, 71.60; H, 7.37.

General Procedure for the Preparation of 2-Alkenylthiophenes 2a,b and 4a,b. To a stirred solution of 2-(benzotriazol-1-ylmethyl)-5-methylthiophene (**3b**) (1.2 g, 5 mmol) in THF (45 mL) was added *n*-BuLi (2.0 M, 2.5 mL, 5.5 mmol) under argon at −78 °C. After 1 h, an appropriate electrophile (benzyl bromide for **2a**, *n*-butyl bromide for **2b**, ethyl cinnamate for **4a**, and ethyl crotonate for **4b**) (5.5 mmol) in THF (10 mL) was added. The mixture was stirred at −78 °C for an additional 3 h and was allowed to warm to rt overnight. *(i) In the cases of **2a** and **2b**, Amberlyst-15 resin (10 g) was added and the mixture was refluxed under argon for 5 h. (ii) In the cases of **4a** and **4b**, THF was distilled off, and Amberlyst-15 resin (15 g) and 1,4-dioxane (50 mL) were added. The mixture was refluxed under argon for 3 days.* Upon cooling, the resin was filtered off and the solvent evaporated. Methylene chloride (50 mL) was added to the residue and the solution was washed with NaOH (2 N, 30 mL) and water (30 mL). The organic layer was separated and dried ($NaSO_4$). After the solvent was removed, the crude product was purified by column chromatography to give the pure product.

***trans*-1-(5-Methylthien-2-yl)-2-phenylethene (2a).** EtOAc/hexane (1:4) was used as the eluent to give a colorless solid: 92% (0.91 g); mp 79−80 °C (lit.[22] mp 85 °C); ^{1}H NMR ($CDCl_3$) δ 2.49 (s, 3H), 6.64−6.66 (m, 1H), 6.80 (d, J = 16.0 Hz, 1H), 6.85 (d, J = 3.3 Hz, 1H), 7.15 (d, J = 16.0 Hz, 1H), 7.23 (t, J = 8.0 Hz, 1H), 7.33 (t, J = 8.0 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 15.6, 122.2, 125.8, 126.2, 126.3, 127.1, 127.3, 128.6, 137.2, 139.3, 140.9.

***trans*-1-(5-Methylthien-2-yl)pentene (2b).** EtOAc/hexane (1:8) was used as the eluent to give a colorless oil: 90% (0.74 g); ^{1}H NMR ($CDCl_3$) δ 0.94 (t, J = 7.4 Hz, 3H), 1.42−1.56 (m, 2H), 2.09−2.17 (m, 2H), 2.44 (s, 3H), 5.84 (dt, J = 15.7 and 6.9 Hz, 1H), 6.41 (d, J = 15.7 Hz, 1H), 6.51−6.58 (m, 1H), 6.64 (d, J = 3.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 15.4, 22.5, 34.9, 123.5, 124.1, 125.2, 129.7, 137.6, 141.1. Anal. Calcd for $C_{10}H_{14}S$: C, 72.25; H, 8.50. Found: C, 72.47; H, 8.55.

Ethyl 4-(5-Methylthien-2-yl)-3-phenyl-3-butenate (4a). EtOAc/hexane (1:8) was used as the eluent to give a colorless oil as a mixture of *cis* and *trans* isomers: 71% (1.02 g); ^{1}H NMR ($CDCl_3$) (signals for the minor isomer are in square brackets) δ 1.17 (t, J = 7.1 Hz, 3H) [1.19 (t, J = 7.2 Hz, 3H)], 2.26 (s, 3H) [2.49 (s, 3H)], 3.40 (s, 2H) [3.87 (s, 2H)], 4.08 (q, J = 7.1 Hz, 2H) [4.14 (q, J = 7.2 Hz, 2H)], 6.47 (d, J = 3.5 Hz, 1H) [6.70 (d, J = 3.5 Hz, 1H)], 6.62 (d, J = 3.5 Hz, 1H) [6.94 (d, J = 3.5 Hz, 1H)], 6.65 (s, 1H) [6.99 (s, 1H)], 7.23−7.47 (m, 5H); ^{13}C NMR ($CDCl_3$) (signals for minor isomers are in square brackets) δ 14.1, 15.2 [15.3], 45.9 [37.5], 60.7 [60.9], 124.3 [124.2], 124.3 [125.5], 126.1, 127.9 [127.3], 128.4, 129.0 [128.9], 131.9, 138.0 [138.1], 139.8, 140.4 [140.6], 170.9. Anal. Calcd for $C_{17}H_{18}SO_2$: C, 71.30; H, 6.34. Found: C, 71.64; H, 6.35.

Ethyl 4-(5-Methylthien-2-yl)-3-methyl-3-butenate (4b). EtOAc/hexane (1:8) was used as the eluent to give a colorless oil as a mixture of *cis* and *trans* isomers: 62% (0.69 g); ^{1}H NMR ($CDCl_3$) (signals for the minor isomer are in square brackets) δ 1.28 (t, J = 7.1 Hz, 3H), 2.05 (s, 3H) [1.97 (s, 3H)], 2.48 (s, 3H) [2.46 (s, 3H)], 3.16 (s, 2H) [3.39 (s, 2H)], 4.18 (q, J = 7.1 Hz, 2H), 6.43 (s, 1H) [6.51 (s, 1H)], 6.63−6.69 (m, 1H), 6.76−6.81 (m, 1H); ^{13}C NMR ($CDCl_3$) (signals for minor isomers are in square brackets) δ 14.1, 15.1, 18.5, 46.1 [39.1], 60.5, 122.5 [121.9], 124.8 [125.1], 126.9 [126.4], 128.5, 138.4, 139.3, 171.3; HRMS calcd for $C_{12}H_{16}O_2S$ 224.0871 (M^+), found 224.0907.

General Procedure for the Preparation of Cyclopent-[*b*]thiophenes 16−18. To a solution of 2-(benzotriazol-1-ylmethyl)thiophene **3** or **5** (**3b** for **18**, **5g** for **16**/**17a**, and **5j** for **16**/**17b**) (4 mmol) in methylene chloride (50 mL) was added $ZnBr_2$ (2.7 g, 12 mmol) at rt under nitrogen. After 15 min, an appropriate styrene (1,1-diphenylethylene for **18**, 4-methylstyrene for **16**/**17a**, and α-methylstyrene for **16**/**17b**) (4.4 mmol)

(22) Tominaga, Y.; Tedjamulia, M. L.; Castle, R. N.; Lee, M. L. *J. Heterocycl. Chem.* **1983**, *20*, 487.

in methylene chloride (5 mL) was added. On cooling, $ZnBr_2$ was filtered off and NaOH (1 N, 20 mL) was added. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 40 mL). The combined organic extracts were washed with water (60 mL) and dried (Na_2SO_4). After the solvent was evaporated under vacuum, the residue was separated by column chromatography to give the pure product.

1,1-Diphenyl-5-methylcyclopent[*b*]thiophene (18). Hexane/EtOAc (30:1) was used as the eluent to give a colorless solid: 52% (0.76 g); mp 109−110 °C; ^{1}H NMR ($CDCl_3$) δ 2.48 (s, 3H), 2.90−2.96 (m, 2H), 3.04−3.09 (m, 2H), 6.55 (s, 1H), 7.15−7.30 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 16.3, 28.1, 46.6, 59.0, 120.9, 125.9, 127.6, 128.0, 139.4, 142.6, 148.1, 150.6. Anal. Calcd for $C_{20}H_{18}S$: C, 82.71; H, 6.25. Found: C, 83.11; H, 6.62.

1-(4-Methylphenyl)-3-propyl-5-methylcyclopent[*b*]thiophene (16/17a). Hexane/EtOAc (40:1) was used as the eluent to give a colorless oil as a mixture of two disteroisomers (*trans:cis* = 14:9 based on GC−MS of crude product, *trans:cis* = 1:1 after column): 83% (0.89 g); ^{1}H NMR ($CDCl_3$) (signals for *cis* isomer are in square brackets) δ 0.91−0.99 (m, 3H), 1.36−1.72 (m, 4H), 1.77−1.86 (m, 1H) [2.92−3.02 (m, 1H)], 2.30 (s, 3H) [2.32 (s, 3H)], 2.41 (s, 3H), 2.43−2.55 (m, 1H), 3.12−3.22 (m, 1H) [3.22−3.35 (m, 1H)], 4.11 (t, J = 8.3 Hz, 1H) [4.21 (t, J = 6.1 Hz, 1H)], 6.29 (s, 1H) [6.33 (s, 1H)], 6.95−7.11 (m, 4H); ^{3}C NMR ($CDCl_3$) δ 14.2, 16.2, 21.0, 21.1 [21.3], 38.9 [39.3], 41.6 [42.3], 46.2 [47.1], 47.1 [47.6], 120.2, 127.1 [127.4], 129.1, 135.5 [135.6], 142.2 [142.5], 142.7 [143.0], 144.7 [145.0], 147.4. Anal. Calcd for $C_{18}H_{22}S$: C, 79.95; H, 8.20. Found: C, 79.74; H, 8.39.

1,5-Dimethyl-1-phenyl-3-(1-hydroxycyclohexyl)cyclopent[*b*]thiophene (16/17b). Hexane/EtOAc (20:1) was used as the eluent to give a colorless oil as a mixture of two disteroisomers (*trans:cis* = 2:1 based on GC−MS of crude product, *trans:cis* = 2:1 after column): 85% (1.3 g); ^{1}H NMR ($CDCl_3$) (signals for *cis* isomer are in square brackets) δ 0.75−1.50 (m, 5H), 1.54 (s, 3H) [1.62 (s, 3H)], 1.62−1.82 (m, 6H), 2.44 (s, 3H), 2.53−2.59 (m, 2H), 3.50 (t, J = 9.9 Hz, 1H) [3.06 (dd, J = 13 and 6.3 Hz, 1H)], 6.61 (s, 1H) [6.57 (s, 1H)], 7.18−7.26 (m, 1H), 7.29−7.38 (m, 2H), 7.52 (d, J = 7.5 Hz, 2H); ^{3}C NMR ($CDCl_3$) δ 15.2, 22.0 [21.7], 23.4 [23.3], 25.8, 31.9 [33.8], 32.4 [32.5], 38.2 [37.0], 45.3 [45.8], 50.7 [49.7], 81.6 [82.1], 84.1 [83.8], 124.5 [124.3], 124.5 [124.6], 124.7 [124.9], 126.2 [126.3], 128.0 [127.9], 137.8 [137.7], 140.0, 150.6 [149.5]. Anal. Calcd for $C_{21}H_{26}OS$: C, 77.25; H, 8.03. Found: C, 77.33; H, 8.29.

General Procedure for the Preparation of Polysubstituted Benzothiophenes 19a−d and 25a−e. To a stirred solution of an appropriate 2-(1-benzotriazol-1-ylalkyl)thiophene **3** or **5** (5 mmol) in THF (45 mL) was added *n*-BuLi (1.6 M, 3.2 mL, 5.5 mmol) at −78 °C under argon. After 1 h, an appropriate α,β-unsaturated aldehyde or ketone (5.5 mmol) in THF (10 mL) was added. The mixture was stirred at −78 °C for an additional 3 h and then allowed to warm to rt overnight. The THF was distilled off, and Amberlyst-15 acidic resin (13 g) and 1,4-dioxane (50 mL) were added. The mixture was refluxed for 3 h under argon. After the resin was filtered off, the solvent was evaporated, and water (50 mL) and methylene chloride (50 mL) were added to the residue. After separation, the aqueous layer was extracted with Et_2O (2 × 40 mL). The combined organic extracts were washed with NaOH (2 N, 30 mL) and water (50 mL). On drying ($NaSO_4$), the solvent was evaporated and the crude product was purified by column chromatography to give the pure compound.

2,4,7-Trimethyl-6-phenylbenzo[*b*]thiophene (19a). Hexane was used as the eluent to give the pure product as a colorless solid: 81% (1.01 g); mp 61−62 °C; ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3H), 2.54 (s, 3H), 2.61 (s, 3H), 7.06 (s, 1H), 7.07 (s, 1H), 7.29−7.43 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 16.3, 18.3, 19.2, 120.5, 125.8, 126.5, 127.4, 127.9, 128.9, 129.7, 136.7, 138.7, 140.2, 141.0, 141.8. Anal. Calcd for $C_{17}H_{16}S$: C, 80.91; H, 6.39. Found: C, 80.63; H, 6.83.

2,4-Dimethyl-6-phenyl-7-propylbenzo[*b*]thiophene (19b). Hexane/EtOAc (40:1) was used as the eluent to give the pure product as a colorless solid: 64% (0.89 g); mp 72−73 °C; ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 7.5 Hz, 3H), 1.57−1.70 (m, 2H), 2.54 (s, 3H), 2.62 (s, 3H), 2.75 (t, J = 7.9 Hz, 2H), 7.01 (s, 1H), 7.06 (s, 1H), 7.30−7.43 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.4, 16.3, 19.2, 22.8, 34.5, 120.3, 126.6, 127.8, 127.9, 128.9, 129.5, 131.1, 136.8, 139.2, 140.1, 140.3, 142.2. Anal. Calcd for $C_{19}H_{20}S$: C, 81.38; H, 7.19. Found: C, 81.34; H, 7.41.

2-Methyl-4,6-diphenyl-7-butylbenzo[*b*]thiophene (19c). Hexane/EtOAc (40:1) was used as the eluent to give the pure product as a colorless oil: 42% (0.73 g); ^{1}H NMR ($CDCl_3$) δ 0.84 (t, J = 7.3 Hz, 3H), 1.27−1.39 (m, 2H), 1.63−1.73 (m, 2H), 2.58 (s, 3H), 2.87 (t, J = 8.2 Hz, 2H), 7.15 (s, 1H), 7.23 (s, 1H), 7.32−7.47 (m, 8H), 7.57 (d, J = 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.7, 16.3, 22.9, 31.5, 32.2, 121.5, 126.7, 127.1, 127.7, 128.0, 128.4, 129.1, 129.6, 133.0, 134.2, 136.9, 137.8, 140.6, 141.0, 141.1, 141.9. Anal. Calcd for $C_{25}H_{24}S$: C, 84.22; H, 6.79. Found: C, 83.97; H, 7.08.

2-Methyl-4,6-diphenyl-7-propylbenzo[*b*]thiophene (19d). Hexane was used as the eluent to give the pure product as a colorless oil: 36% (0.62 g); ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7.3 Hz, 3H), 1.64−1.77 (m, 2H), 2.57 (s, 3H), 2.81−2.86 (m, 2H), 7.16 (s, 1H), 7.24 (s, 1H), 7.32−7.47 (m, 8H), 7.58 (t, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.4, 16.2, 22.7, 34.7, 121.5, 126.7, 127.0, 127.7, 128.0, 128.4, 129.1, 129.6, 132.8, 134.2, 137.0, 137.8, 140.5, 141.0, 141.1, 141.9. Anal. Calcd for $C_{24}H_{22}S$: C, 84.16; H, 6.47. Found: C, 83.91; H, 6.88.

4,6-Diphenylbenzo[*b*]thiophene (25a). Hexane/EtOAc (4:1) was used as the eluent to give the pure product as a colorless solid: 90% (1.35 g); ^{1}H NMR ($CDCl_3$) δ 7.31−7.54 (m, 8H), 7.58−7.71 (m, 3H), 7.69 (d, J = 7.5 Hz, 2H), 8.08 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 119.8, 123.1, 124.5, 126.6, 127.3, 127.4, 127.5, 128.5, 128.8, 129.1, 137.1, 137.8, 138.0, 140.9, 141.2. Anal. Calcd for $C_{20}H_{14}S$: C, 83.88; H, 4.93. Found: C, 83.61; H, 4.89.

2-Methyl-4,6-diphenylbenzo[*b*]thiophene (25b). Hexane/EtOAc (30:1) was used as the eluent to give the pure product as a colorless solid: 45% (0.67 g); mp 86−87 °C; ^{1}H NMR ($CDCl_3$) δ 2.56 (s, 3H), 7.10 (s, 1H), 7.31−7.52 (m, 6H), 7.55 (s, 1H), 7.60 (d, J = 7.5 Hz, 2H), 7.67 (d, J = 7.5 Hz, 2H), 7.95 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 16.3, 119.4, 120.8, 124.3, 127.1, 127.3, 128.5, 128.8, 129.0, 136.9, 137.0, 137.8, 141.1, 141.2, 141.3. Anal. Calcd for $C_{21}H_{16}S$: C, 83.96; H, 5.37. Found: C, 83.94; H, 5.45.

2-Methyl-5-phenyl-6-ethylbenzo[*b*]thiophene (25c). Hexane/EtOAc (40:1) was used as the eluent to give the pure product as a colorless oil: 69% (0.87 g); ^{1}H NMR ($CDCl_3$) δ 1.11 (t, J = 7.5 Hz, 3H), 2.55 (s, 3H), 2.66 (q, J = 7.5 Hz, 2H), 6.89 (s, 1H), 7.30−7.43 (m, 5H), 7.46 (s, 1H), 7.65 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.6, 16.1, 26.4, 121.2, 121.3, 123.6, 126.7, 128.0, 129.5, 137.5, 138.5, 138.6, 139.2, 140.4, 142.2. Anal. Calcd for $C_{17}H_{16}S$: C, 80.91; H, 6.39. Found: C, 80.96; H, 6.43.

2,4-Dimethyl-6-phenylbenzo[*b*]thiophene (25d). Hexane/EtOAc (20:1) was used as the eluent to give the pure product as a colorless oil: 74% (0.88 g); ^{1}H NMR ($CDCl_3$) δ 2.60 (s, 6H), 7.02 (s, 1H), 7.28−7.34 (m, 2H), 7.42 (t, J = 7.6 Hz, 2H), 7.62 (d, J = 7.6 Hz, 2H), 7.79 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 16.3, 19.7, 118.0, 119.7, 124.4, 126.9, 127.2, 128.7, 131.9, 136.8, 139.1, 140.4, 140.7, 141.4; HRMS calcd for $C_{16}H_{14}S$ 238.0816 (M^+), found 238.0800.

5-Methyl-6-(4-*tert*-butylphenyl)benzo[*b*]thiophene (25e). Hexane/EtOAc (40:1) was used as the eluent to give the pure product as a colorless solid: 77% (1.08 g); mp 99−100 °C; ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 9H), 2.39 (s, 3H), 7.26−7.35 (m, 3H), 7.39−7.48 (m, 3H), 7.73 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 20.9, 31.4, 34.6, 123.3, 124.5, 125.0, 126.4, 129.0, 132.1, 137.4, 138.9, 139.1, 149.7. Anal. Calcd for $C_{19}H_{20}S$: C, 81.38; H, 7.19. Found: C, 81.32; H, 7.30.

Supporting Information Available: ^{1}H and ^{13}C spectra for compounds **5a**, **4b**, and **25d** (6 pages). This material is contained in libraries on microfiche, immediately followed this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO970672G