A New Synthesis of Benzo[b]thiophenes and Benzo[c]thiophenes by Annulation of Disubstituted Thiophenes

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Nine newly prepared ortho-disubstituted thiophenes (1–5) react with Michael acceptors to form benzo[b]- and benzo[c]thiophenes. This novel annulation process is specifically suited to form benzothiophenes with substituents in the benzene moiety. Substitution patterns so obtained are uncommon and difficultly accessible otherwise; none of the 31 benzothiophenes described in this paper were reported previously. The synthesis of the precursor thiophenes 1–5 is described briefly.

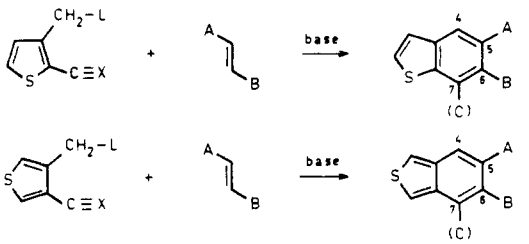
This paper deals with a newly developed approach to the synthesis of benzo[b]thiophenes and benzo[c]-thiophenes. It involves annulation of disubstituted thiophenes as indicated schematically in Schemes I and II.[1] This approach, in which the benzene part is constructed on to a thiophene ring, has received little attention until recently.[2-5]

Normally, benzo[b]thiophenes and benzo[c]thiophenes are prepared by building a thiophene ring on to a benzene nucleus.[6] In our converse process, thiophenes with two ortho substituents—one electrophilic and one potentially nucleophilic—react with Michael acceptors to form the benzene ring. This result is usually achieved in one operation by a series of consecutive reactions: a Michael addition followed by ring closure at the electrophilic center and subsequent aromatization. Thus the atoms C-4 and C-7 of the benzene ring derive from the thiophene substituents, and C-5 and C-6 from the Michael acceptor (Scheme II). A similar approach was developed previously by our group for the synthesis of naphthalenes from ortho-disubstituted benzenes.[7]

This approach provides an unique opportunity for introduction of substituents in the benzene moiety of benzothiophenes. In this regard we mention that electrophilic substitution is in general not a useful method to accomplish this task. Under electrophilic conditions substitution occurs predominantly at C-3 in benzo[b]thiophenes.[6,8] Certain substituents will enhance the reactivity at C-2, and strongly electron-donating groups sometimes direct electrophilic substitution into the benzene ring. Mixtures of products are usually the result of these approaches, however.[8]

Benzo[c]thiophenes normally are less stable and more difficult to prepare than benzo[b]thiophenes. This is mainly due to lower resonance stabilization[9] and to the highly reactive α-positions. Substituents, especially at C-1 and C-3, can stabilize these systems. Consequently, most benzo[c]thiophenes reported so far are of the 1,3-disubstituted type, prepared by construction of the thiophene ring. Even these 1,3-disubstituted benzo[c]thiophenes do not usually tolerate the conditions necessary for electrophilic substitutions.[9a] Benzo[c]thiophenes with substituents in the benzene ring have been prepared by dehydrogenation of the corresponding 1,3-dihydrobenzo[c]-thiophenes.[10]

Scheme I[a]



[a] L = leaving group; for A and B see text and Tables II-V. C≡X stands for CH=O, COOMe, and C≡N, and (C) for H, OH, or NH_2. (To avoid confusion the numbering of carbon atoms as given above is used throughout the entire paper).

Our new annulation reaction leads to benzo[b]-thiophenes and benzo[c]thiophenes that are functionalized in the benzene ring by a process that does not rely on electrophilic substitution. Therefore, it is not necessary to protect the α-positions of the precursor thiophenes. To substantiate this aspect in particular, we have worked out our synthesis for benzothiophenes that carry no substituents in the thiophene moiety.

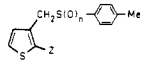
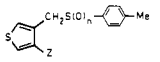
Results

As the electrophilic substituents in our precursor thiophenes (Table I), we have selected the carboxaldehyde, the carboxylate, and the cyano group.[11] For the potentially nucleophilic substituents the *p*-toluenesulfonylmethyl and *p*-toluenesulfinylmethyl groups were chosen. In the ultimate aromatization step *p*-toluenesulfinic or

(1) For a preliminary report see: van Leusen, A. M.; Terpstra, J. W. *Tetrahedron Lett.* **1981**, *22*, 5097.
(2) Loozen, H. J. J.; Godefroi, E. F. *J. Org. Chem.* **1973**, *38*, 1056.
(3) (a) Tominaga, Y.; Lee, M. L.; Castle, R. N. *J. Heterocycl. Chem.* **1981**, *18*, 967. (b) Pratap, R.; Tominaga, Y.; Lee, M. L.; Castle, R. N. *Ibid.* **1981**, *18*, 973. (c) Tominaga, Y.; Lee, M. L.; Castle, R. N. *Ibid.* **1981**, *18*, 977. (d) Thompson, R. D.; Iwao, M.; Lee, M. L.; Castle, R. N. *Ibid.* **1981**, *18*, 981. (e) Iwao, M.; Lee, M. L.; Castle, R. N. *Ibid.* **1980**, *17*, 1259.
(4) Reinecke, M. G. *Tetrahedron* **1982**, *38*, 427, and ref 134, 158, 159, and 165 cited therein.
(5) Dann, O.; Kokorudz, M.; Gropper, R. *Chem. Ber.* **1953**, *87*, 140.
(6) (a) Iddon, B.; Scrowston, R. M. In "Advances in Heterocyclic Chemistry"; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1970; Vol. 11, p 177. (b) Scrowston, R. M., ref 6a 1981; Vol. 29, p 172.
(7) Wildeman, J.; Borgen, P. C.; Pluim, H.; Rouwette, P. H. F. M.; van Leusen, A. M. *Tetrahedron Lett.* **1978**, 2213.
(8) Gronowitz, S. In "A Specialist Periodical Report: Heterocyclic Chemistry"; Suschitzky, H., Meth-Cohn, O., Senior Reporters: The Royal Society of Chemistry: London, 1980; Vol. 1, pp 67–109.
(9) (a) Iddon, B. In "Advances in Heterocyclic Chemistry"; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: London, 1972; Vol. 14, p 355. (b) Cook, M. J.; Katritzky, A. R.; Linda, P. "Advances in Heterocyclic Chemistry" 1974; Vol. 17, p 256.
(10) Mayer, R.; Kleinert, H.; Richter, S.; Gewald, K. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 115; *J. Prakt. Chem.* **1963**, *20*, 244.
(11) Work by other groups indicates that certain heteroatoms at the electrophilic and nucleophilic centers may be used also in related reactions: (a) Taylor, E. C.; Heindel, N. D. *J. Org. Chem.* **1967**, *32*, 1666 (cf. Hendrickson, J. B.; Rees, R.; Templeton, J. F. *J. Am. Chem. Soc.* **1964**, *86*, 107). (b) Sword, I. P. *J. Chem. Soc. C.* **1970**, 1916 (cf. London, J. P.; et al. *J. Chem. Soc.* **1960**, 3462, 3466, 3470).

0022-3263/86/1951-0230$01.50/0

Table I. Thiophenes[a] 1–5 Used in the Annulations of Tables II, III, IV, and V

	n	Z	mp (°C)
			
1a	2	CH=O	146–147
1b	1	CH=O	111.5–113
2a	2	COOMe	131–132
2b	1	COOMe	96–97
3a	2	C≡N	162–163
3b	1	C≡N	92–96
			
4a	2	COOMe	136–138
4b	1	COOMe	92–94
5	2	C≡N	157–159

[a] The thiophenes listed here are new compounds; for the syntheses see Schemes III and IV and accompanying text.

p-toluenesulfenic acid is eliminated.[12,13] Substituent C (Scheme I) in the final product varies from H to OH or NH_2 depending on the choice of the electrophilic substituent.

The disubstituted precursor thiophenes **1–5** (Table I) used in this investigation are new compounds.[14] They were prepared in good yields by essentially known chemistry, as is described below.

A. 5,6-Disubstituted Benzo[*b*]thiophenes. The thiophenecarboxaldehydes **1a** and **1b** react regiospecifically with Michael acceptors to form 5,6-disubstituted benzo[*b*]thiophene derivatives **7** (eq 1, Table II). We want to emphasize that in most cases all four reaction steps (i.e., Michael addition, cyclization, and elimination of H_2O and $C_7H_7S(O)_nH$) occur in one operation (entries 1–6, 8) and that Table II lists overall yields based on thiophenecarboxaldehydes **1a,b**.

All reactions were carried out with equimolar amounts of reactants and 2 to 4 equiv of base. Although details of the four reaction steps will be treated below (Discussion), we may already focus attention to the following. Under the conditions summarized in Table II, sulfone **1a** reacted with nearly all substrates to form fully aromatized products **7** (entries 1–6). However, with methyl crotonate, 4,5-dihydrobenzo[*b*]thiophene (**6a**) was formed rather than the desired benzo[*b*]thiophene **7f** (entry 7). Apparently, elimination of *p*-toluenesulfinic acid (TosH) from **6a** is prevented by the lower acidity of H-5 for A = methyl (as compared to A = carboxyl or benzoyl) and by the presence of an acidic proton at C-4.[12] Borderline behavior was observed for A = phenyl: aromatized product **7d** was formed with *t*-BuOK in DME (entries 4 and 5), whereas with weaker base (MeONa in Me_2SO)[15] no elimination of TosH took place, and the reaction stopped at the stage of dihydrobenzothiophenes **6** (entries 9 and 10).

The corresponding reaction with sulfoxide **1b** was investigated (entry 8) to circumvent the problems observed in the elimination of TosH with methyl crotonate (entry 7). In this case elimination of *p*-toluenesulfenic acid[13] (TolSOH) occurred smoothly, even at room temperature, to give the desired benzo[*b*]thiophene **7f** in 64% overall yield, without any indication of accumulation of the intermediate dihydrobenzothiophene.

No clear cut results were obtained with **1a** and methyl vinyl ketone (which may well polymerize under the conditions of the reaction) and with fumaronitrile (entries 11 and 12).

B. 7-Hydroxybenzo[*b*]thiophene Derivatives. Similar to the thiophenecarboxaldehydes **1a,b** (section A), thiophenecarboxylates **2a** and **2b** react with Michael acceptors to form 7-substituted benzo[*b*]thiophene derivatives. The products, 5,6,7-trisubstituted benzo[*b*]thiophenes **9** and 4,5-dihydrobenzo[*b*]thiophenes **8**, always carry an OH group at C-7. This OH obviously results from an addition–elimination reaction in the cyclization step (eq 2, Table III). This table gives the results of the annulations leading to **8** and **9**, in overall yields based on **2**.

With tosyl-substituted thiophenecarboxylate **2a** only those Michael acceptors that carry strongly electron-withdrawing substituents A (necessary to increase H-5 acidity in **8**) led to fully aromatized products **9** (entries 1, 2, 3, and 7). All other substrates[16] gave 4,5-dihydrobenzothiophene derivatives **8** instead (with **2a** and *t*-BuOK in DME). For **2a** borderline behavior was found for A = COOMe: with *t*-BuOK in DME aromatized product **9a** was formed (entries 2 and 3), but with less strong base (MeONa, Me_2SO) 4,5-dihydrobenzothiophene **8a** was obtained (entry 5). However, with the sulfinyl analogue **2b** all substrates[16] reacted all the way to benzo[*b*]thiophenes **9** (entries 4, 6, 8, 10, 13, 14, 15, and 17).

The reaction of **2a** with chalcone (A = phenyl) was examined in greater detail. The highest yield (74%) of dihydrobenzothiophene **8c** was obtained with MeONa in Me_2SO at room temperature (entries 11 and 12). Several other base–solvent combinations were tried,[17] which gave lower yields of **8c**, but no fully aromatized **9d** was found. Elimination of TosH was not even observed after treating a sample of **8c** for 72 h with excess of *t*-BuOK in refluxing DME. Elmination of TosH from **8c** could only be effected after methylation of the acidic OH at C-7, as will be described in a separate paper.[18]

C. 7-Aminobenzo[*b*]thiophene Derivatives. Annulation of cyanothiophenes **3a** and **3b** with Michael acceptors gives 7-aminobenzo[*b*]thiophenes **10** and **11** (eq 3, Table IV).

We found these 7-aminobenzothiophenes rather unstable, and only a few examples were investigated. Table IV gives yields of crude products, since attempts to purify **10** and **11** by crystallization or chromatography were unsuccessful.

D. Benzo[*c*]thiophene Derivatives. 3,4-Disubstituted thiophenes **4a**, **4b**, and **5** react with Michael acceptors to form benzo[*c*]thiophene derivatives (eq. 4, Table V). Although this annulation to benzo[*c*]thiophenes was investigated in less detail, some remarkable differences

(12) Sulfones are known to give base-induced 1,2-eliminations in an E1cB or E2 fashion: (a) Magnus, P. D. *Tetrahedron* **1977**, *33*, 2019. (b) van Leusen, A. M. *Lect. Heterocycl. Chem.* **1980**, *5*, S-111. (c) Trost, B. M.; Schmuff, N. R.; Miller, M. J. *J. Am. Chem. Soc.* **1980**, *102*, 5979.

(13) Sulfoxides are known to give thermal syn eliminations: (a) Kingsbury, C. A.; Cram, D. J. *J. Am. Chem. Soc.* **1960**, *82*, 1810. (b) Culcough, T.; Cunneen, J. I. *Chem. Ind. (London)* **1960**, 626. (c) Ultee, W. J. *Ph.*D. Thesis, Leiden, Netherlands, 1979.

(14) In principle, the positions of the nucleophilic and the electrophilic substituents in our precursor thiophenes can be interchanged, leading to a reversal of positions of substituents in the product benzothiophenes. This, however, was not investigated.

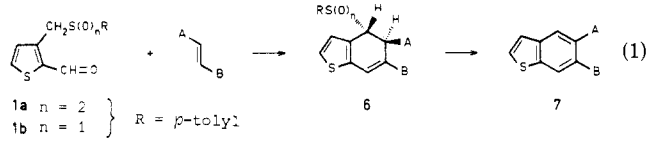
(15) Approximate pK_a values (relative to water) for R_3COH and CH_3OH are 19 and 16, respectively. March, J. In "Advanced Organic Chemistry: Reactions, Mechanism, and Structure"; McGraw-Hill: Tokyo, 1968; p 217. In the second edition (1977; p 253) the effect of solvation on the base strengths of simple alcohols is discussed. The influence of the cation on the base strength is described by Bowden (Bowden, K. *Chem. Rev.* **1966**, *66*, 119) and by Rochester (Rochester, C. H. *Q. Rev. Chem. Soc.* **1966**, *20*, 511).

(16) Fumaronitrile, crotonitrile, and methyl vinyl ketone did not give satisfactory results with **2a** or **2b** (compare Table II, entries 11 and 12).

(17) These base/solvent combinations, not listed in Table III, were as follows: *n*-BuLi/THF, LDA/THF, *t*-BuOK/DME, *t*-BuOK/THF, *t*-BuOK/HMPA, NaH/Me_2SO, and NaOH(50%)/$CHCl_3$/TEBAC.

(18) Terpstra, J. W.; van Leusen, A. M.; van Bolhuis, F., submitted for publication. Methylation, under various conditions, gave a mixture of two methyl ethers by reaction with both the C-7 and the benzoyl oxygens.

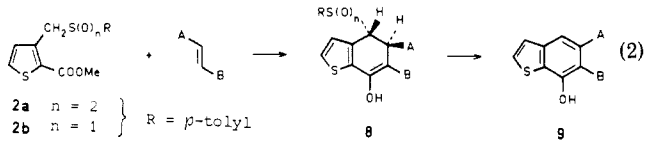
Table II. 5,6-Disubstituted Benzo[*b*]thiophenes 7 Synthesized by Annulation of Thiophenecarboxaldehyde 1a and 1b



entry		products A	B	mp (°C)	yield[a] (%)	precursor thiophene (1) and reactn conditns	base (equiv), solvent, time (h), temp (°C)
1	**7a**	COOH	COOH[b]	250 (d)	68	**1a**	*t*-BuOK (4), DME, 2, 60–70
2	**7b**	COOMe	COOMe	*c*	52	**1a**	*t*-BuOK (2), DME, 48, 20
3	**7c**	COPh	COPh	146–147	34	**1a**	*t*-BuOK (4), DME, 2, 60–70
4	**7d**	Ph	COPh	125–126	63	**1a**	*t*-BuOK (2.2), DME, 90, 20
5	**7d**	Ph	COPh	125–126	57	**1a**	*t*-BuOK (2), DME, 2, 75
6	**7e**	$CH_2CH_2CMe_2CO$		119–120	60	**1a**	*t*-BuOK (2.5), DME, 1, 20, + 3, 50
7	**6a**	Me	COOH[d]	140–150 (d)	55	**1a**	*t*-BuOK (2), DME, 48, 20
8	**7f**	Me	COOH[d]	180–181	64	**1b**	*t*-BuOK (2.5), DME, 24, 20
9	**6b**	Ph	COOMe	142–144	41	**1a**	MeONa (2.5), Me_2SO, 6, 20
10	**6c**	Ph	COPh	184–185	55	**1a**	MeONa (2.5), Me_2SO, 6, 20
11		H	COMe	*e*		**1a**	*t*-BuOK (2.5), DME, 48, 20
12		C≡N	C≡N	*e*		**1a**	*t*-BuOK (4), DME, 2, 60–70

[a] Overall yields of purified products, based on thiophenecarboxaldehydes **1**. [b] Prepared from dimethyl fumarate; diacid formed by hydrolysis during workup. [c] Crude diester was hydrolyzed to diacid **7a** during attempted crystallization. [d] Prepared from methyl crotonate; acid formed by hydrolysis during workup. [e] No products identified, see text.

Table III. 5,6,7-Trisubstituted Benzo[*b*]thiophenes 9 and Their 4,5-Dihydro Derivatives of 8 Synthesized by Annulation of Thiophenecarboxylates 2a and 2b



entry		products A	B	mp (°C)	yield[a] (%)	precursor thiophene (2) and reactn conditns	base (equiv), solvent, time (h), temp (°C)
1	**9a**	COOMe	COOMe	111–114	52	**2a**[b]	MeONa (4), DME, 24, 20 + 4, 60
2	**9a**	COOMe	COOMe	111–114	45	**2a**[b]	*t*-BuOK (4), DME, 2, 0 + 18, 60
3	**9a**	COOMe	COOMe	111–114	37	**2a**	*t*-BuOK (4), DME, 5, 20
4	**9a**	COOMe	COOMe	111–114	45	**2b**	*t*-BuOK (2.5), DME, 24, 20
5	**8a**	COOMe	COOMe	152–154	30	**2a**	MeONa (2.5), Me_2SO, 24, 20
6	**9a**	COOMe	COOMe	111–114	41	**2b**	MeONa (2.5), Me_2SO, 24, 20
7	**9b**	4-$PhNO_2$	COPh	180–182	32	**2a**	NaH (3), Me_2SO/Et_2O 4:1, 3, 20
8	**9b**	4-$PhNO_2$	COPh	180–182	13	**2b**	*t*-BuOK (2.5), DME, 64, 20
9	**8b**	Ph	COOMe	169–171	29	**2a**	*t*-BuOK (2.5), DME, 29, 20 + 1, 60
10	**9c**	Ph	COOMe	148–149	43	**2b**	*t*-BuOK (2.5), DME, 27, 20
11	**8c**	Ph	COPh	177–178	74	**2a**	MeONa (2.5), Me_2SO, 24, 20
12	**8c**	Ph	COPh	177–178	40	**2a**	*t*-BuOK (2), DME, 18, 20
13	**9d**	Ph	COPh	141–142	50	**2b**	MeONa (2.5), Me_2SO, 25, 20
14	**9d**	Ph	COPh	141–142	50	**2b**	NaH (2), Me_2SO, 72, 20
15	**9d**	Ph	COPh	141–142	21	**2b**	*t*-BuOK (2), DME, 48, 20 + 0.5, 70
16	**8d**	Me	COOMe	146–148	23	**2a**	*t*-BuOK (2.5), THF, 24, 20
17	**9e**	Me	COOMe	102–103	21	**2b**	*t*-BuOK (2.5), THF, 20, 20 + 4, 60

[a] Overall yields of purified products, based on thiophenecarboxylates **2**. [b] Entries 1 and 2 were carried out with dimethyl maleate, instead of dimethyl fumarate.

were found in comparison with benzo[*b*]thiophenes.

Generally, the annulation of 3,4-disubstituted thiophenes **4a**, **4b**, and **5** required more drastic conditions than their 2,3-disubstituted counterparts. Three examples may illustrate this point.

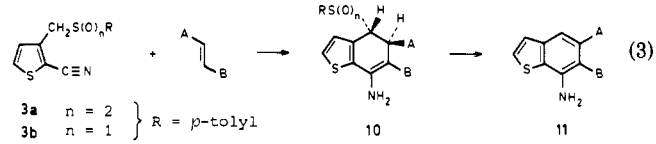
(1) Thiophene esters **4a** and **4b** gave no reaction with dimethyl fumarate and MeONa in DME at room temperature in contrast to the thiophene esters **2a,b** (compare Table III, entries 1, 5, and 6).

(2) Reaction of the sulfinyl ester **4b** with chalcone (*t*-BuOK, DME) gave at room temperature dihydrobenzo[*c*]thiophene **12b** as the main product (ca. 72% yield of crude material), which was converted almost quantitatively to benzo[*c*]thiophene **14b** on heating for 1 h at 70–80 °C (Table V, entries 4 and 5). Dihydrobenzothiophene **12b** is the only example of a dihydro intermediate with a *sulfinyl* substituent that we were able to identify as such (although it was not obtained in analytically pure form). In the reaction of **2b** (i.e., a regioisomer of **4b**) with chalcone, the corresponding sulfinyl-substituted dihydrobenzo[*b*]thiophene was not detected; apparently aromatization to benzo[*b*]thiophene **9d** took place even at temperatures as low as −40 °C (section B).

(3) Sulfinyl ester **4b** gave no annulation with methyl cinnamate or with methyl crotonate; only the acids formed by hydrolysis of the starting esters were found. In contrast to this failure with **4b**, sulfonyl ester **4a** reacted smoothly with methyl cinnamate to the expected dihydrobenzo[*c*]thiophene **12c** (Table V, entry 6).

The 4-aminobenzo[*c*]thiophene derivatives **13** and **15** gave problems with isolation and purification, as did the benzo[*b*]thiophene isomers **10** and **11** discussed in section

Table IV. Annulation of Cyanothiophenes 3a and 3b



(3)

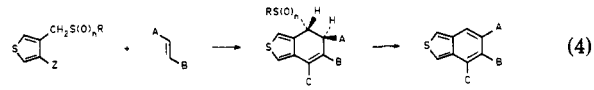
3a n = 2
3b n = 1
} R = p-tolyl

10 11

entry	products					precursor thiophene (3) and reactn conditns	
		A	B	mp (°C)	yield[a] (%)		base (equiv), solvent, time (h), temp (°C)
1	11	COOMe	COOMe	*b*	30	**3a**	*t*-BuOK (2), DME, 4, 20
2	11	COOMe	COOMe	*b*	28	**3b**	NaH (2), Me_2SO, 72, 20
3	10	Ph	COPh	116–118	84	**3a**	*t*-BuOK (2), DME, 47, 20

[a] Overall yields of crude products, reasonably pure according to ^1H NMR; no satisfactory elemental analyses due to instability. Both compounds **10** and **11** gave correct exact mass analyses. Compound **10**: ^1H NMR ($CDCl_3$) δ 2.32 (s, 3, Me of tosyl), 4.31 and 4.74 (two d, 1 + 1, J = 1 Hz, H-4 and H-5), 6.56–7.73 (m, 18, Ar and NH_2 protons); exact mass M^+ calcd for $C_{28}H_{23}NO_3S_2$ at m/e 485.112, found at m/e 485.113. Compound **11**: ^1H NMR ($CDCl_3$) δ 3.81 and 3.84 (two s, 3 both, two MeO groups), 5.65 (br s, 2, NH_2), 7.19 and 7.45 (AB q, 2, J = 5 Hz, H-2 and H-3), 7.33 (s, 1, H-4); exact mass M^+ calcd for $C_{12}H_{11}NO_4S$ at m/e 265.041, found at m/e 265.042. [b] Brownish yellow oil.

Table V. 5,6,7-Trisubstituted Benzo[c]thiophenes 14 and 15 and Their 4,5-Dihydro Derivatives 12 and 13 Synthesized by Annulation of Methyl Thiophenecarboxylates 4 and Cyanothiophene 5



(4)

4a Z = COOMe, n = 2
4b Z = COOMe, n = 1
5 Z = C≡N, n = 2
} R = p-tolyl

12 C = OH 13 C = NH_2 14 C = OH 15 C = NH_2

entry	products					precursor thiophene (4, 5) and reactn conditns	
		A	B	mp (°C)	yield[a] (%)		base (equiv), solvent, time (h), temp (°C)
1	**14a**	COOMe	COOMe	114–116	70	**4a**[b]	*t*-BuOK (2.5), DME, 5, 60–70
2	**14a**	COOMe	COOMe	114–116	48	**4b**[b]	*t*-BuOK (2.5), DME, 5, 60–70
3	**12a**	Ph	COPh	198–201	49	**4a**	MeONa (2.5), Me_2SO, 24, 20
4	**12b**	Ph	COPh	*c*		**4b**	*t*-BuOK (2.5), DME, 40, 20
5	**14b**	Ph	COPh	124–126	62	**4b**	*t*-BuOK (2.5), DME, 6, 70–80
6	**12c**	Ph	COOMe	149–151	53	**4a**	*t*-BuOK (2.5), DME, 24, 20 + 3, 60
7	**14c**	Ph	COOMe			**4b**	*t*-BuOK (2.5), DME, 6, 80
8	**14d**	Me	COOMe			**4b**	*t*-BuOK (2.5), DME, 6, 80
9	**15**[d]	COOMe	COOMe	64–66	47	**5**	*t*-BuOK (2.5), DME, 6, 80
10	**13**[d]	Ph	COPh	dec	81	**5**	*t*-BuOK (2), DME, 48, 20

[a] Isolated yields based on thiophenes **4** and **5**. [b] Entries 1 and 2 were carried out with dimethyl maleate instead of dimethyl fumarate as indicated by eq 4. [c] Not purified; converted to **14b**, see text. [d] Compound **13**: ^1H NMR ($CDCl_3$) δ 2.35 (s, 3, Tos), 4.29 and 4.75 (d, 1, J = 1 Hz, both H-6 and H-7), 6.80 (s, 2, NH_2), 6.9–8.0 (m, 16, Ar protons); exact mass M^+ calcd for $C_{28}H_{23}NO_3S_2$ at m/e 485.112, found at m/e 485.113. Compound **15**: ^1H NMR ($CDCl_3$) δ 3.75 and 3.80 (two s, 3 both, two MeO groups), 6.34 (br s, 2, NH_2), 7.07 (s, 1, H-7), 7.50 and 7.68 (two d, 1 + 1, J = 2.8 Hz, H-1 and H-3); exact mass M^+ calcd for $C_{12}H_{11}NO_4S$ at m/e 265.041, found m/e 265.043.

C. Compounds **13** and **15** were obtained as crude products only.

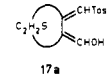
No ring closure occurred in the reaction of **5** with dimethyl fumarate (*t*-BuOK, DME) at room temperature. Instead, TosH was eliminated from the initially formed Michael adduct to give 3-cyano-4-[2,3-(dicarbomethoxy)-1-propenyl]thiophene (**16**). However, **16** did ring close thermally (80 °C) to the desired benzo[c]thiophene **15**, which by the way provides an alternative route (see further under Discussion).

Discussion

A reasonable, generalized rationale of the annulation process is given in Scheme II. A Michael addition of **17** to **18** followed by an aldol condensation (for Z = CHO) leads to dihydrobenzothiophenes **19** (C = H), which in a number of cases were identified as intermediates or as end products.[19,20] For Z = COOR and C≡N ring closures related to the Dieckmann and Thorpe–Ziegler reactions lead to **19** with C = OH or NH_2, respectively. Aromatization to the benzene ring of **20**[21] by elimination of RS-$(O)_nH$ from **19** appears to be the final step in the majority of the reactions. In one case, however, we have observed elimination of TosH prior to ring closure (compound **15**, Table V, entry 9). This may well be a reflection of more difficult ring closure to form benzo[c]thiophenes, combined with lower electrophilicity of C≡N.

Occasionally, the formation of the double bond at C-4 and C-5 in **19**, by base-induced elimination of *p*-toluenesulfonic acid (TosH),[12] has given problems, even though the driving force of aromatization was expected to facilitate

(19) An alternative one-step formation of **19** by a [2 + 4]-cycloaddition of tautomeric *o*-dimethylenethiophenes like **17a** seems less likely, inter alia, because complete regiospecificity was observed with unsymmetrical Michael acceptors: Terpstra, J. W. Ph.D. Thesis, Groningen, Netherlands, 1982.

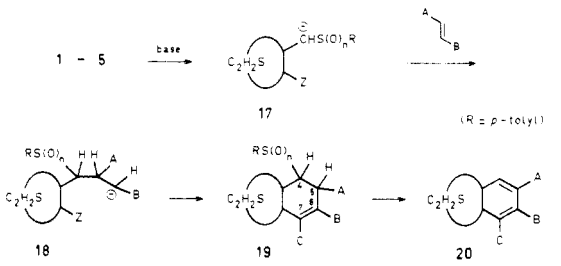


17a

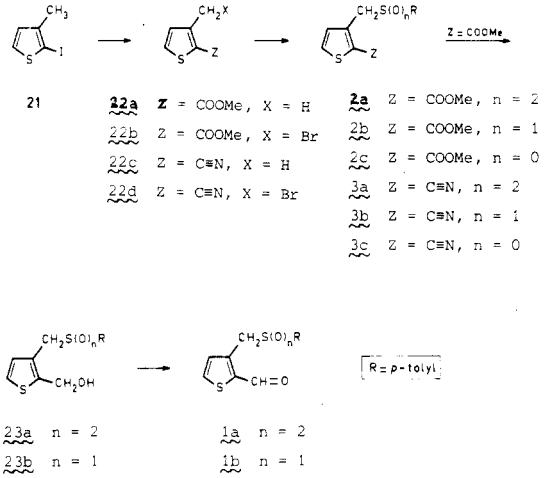
(20) Formula **19** is the generalized form of compounds **6** (Table II), **8** (Table III), **10** (Table IV), and **12** and **13** (Table V).

(21) Formular **20** is the generalized form of compounds **7** (Table II), **9** (Table III), **11** (Table IV), and **14** and **15** (Table V).

Scheme II



Scheme III



this process considerably. These problems are associated above all with the presence, in **19**, of protons of higher acidity than H-5. In all cases investigated this problem was circumvented by elimination of *p*-toluenesulfenic acid, TolSOH, instead of TosH. The elimination of TolSOH, known to be a thermal syn elimination,[13] was so fast at room temperature (and below) that we have been able in one case only to identify a dihydro intermediate **19** for $n = 1$: compound **12b** (Table V, entries 4 and 5).

For Z = CHO, the only other acidic proton in **19** that can interfere with the elimination of TosH is H-4.[12c] Elimination of TosH was achieved in all cases, except for A = Me (Table II). In the latter case, H-5 apparently is activated insufficiently to compete successfully with H-4 in the base-induced elimination process. The desired compound **7f** was obtained, however, through the sulfoxide approach (Table II, entries 7 and 8).

For Z = COOMe the OH proton at C-7 in **19** (C = OH) gave greater problems, and one has to rely more often on the sulfoxide approach to obtain fully aromatized products (Tables III and V). We have shown, however, that base-induced elimination of TosH can be effected after O methylation.[18] The results for Z = C≡N display similar characteristics, although this type of reaction was investigated in less detail (Tables IV and V).

Comparison of the results of Tables III and V for Z = COOMe shows that more drastic conditions are needed in the ring closure to benzo[*c*]thiophenes as compared with benzo[*b*]thiophenes. We propose that this is related partially to lower electrophilicity of COOMe in thiophene at C-3 than at C-2, as appears, for example, from the decrease in rate of hydrolysis of the following ethyl esters: 2-thiophenecarboxylate > benzoate > 3-thiophenecarboxylate.[22] Lower resonance stabilization in benzo[*c*]thiophenes than in the [*b*]isomers may be another factor.[9]

In conclusion, we feel that our method for annulation of thiophenes is reliable and useful. It serves a purpose, in particular, when benzo[*b*]thiophenes or benzo[*c*]thiophenes are desired with substituents in the benzene ring. Extrapolation from the many examples of Tables III–V indicates for which substituents A and C the sulfone approach may be used or when the sulfoxide route should be preferred. When both methods are possible, the sulfone approach is to be preferred because it provides cleaner reaction mixtures that are more easy to handle.

Synthesis of Precursor Thiophenes 1–5. None of the starting materials **1–5** (Table I) were previously reported. Compounds **1a,b**, **2a,b**, and **3a,b** were all prepared in acceptable yields from commercially available 3-methylthiophene, which was converted in 81% yield to the 2-iodo derivative[23] **21**. Grignard reaction of **21** with dimethyl carbonate gave **22a**[24] (in 74%, Scheme III), bromination (NBS) gave **22b**[24] (in 81%), and reaction with sodium *p*-toluenesulfinate (TosNa) gave **2a** (in 74%, 44% overall yield based on 3-methylthiophene). Sulfoxide **2b** was prepared in 61% yield from **22b** with sodium thiocresolate followed by oxidation with $NaIO_4$.

Reduction of **2a** and **2b** with $LiEt_3BH$ gave hydroxy compounds **23a** and **23b**, which upon oxidation with pyridinium dichromate (PDC) gave the aldehydes **1a** and **1b** (in 71% and 68% yield based on **2a** and **2b**, respectively).

Reaction of **21** with $Cu^IC{\equiv}N$ gave **22c**[23] which was converted to the nitriles **3a** and **3b** (45% and 22% yield, respectively), analogously to the esters **2a** and **2b**.

3,4-Disubstituted thiophenes **4a,b** and **5** were prepared from 3-cyano-4-methylthiophene[25] (**25a**), which was obtained in 94% yield by reaction of **24**[26] with $Cu^IC{\equiv}N$ (Scheme IV). Methanolysis of **25a** gave carboxylate **25c** (in 75% yield), from which **4a** and **4b** were prepared analogously to **2a** and **2b** (58% and 46% yield, respectively). Similarly, nitrile **5** was prepared via **25a** by NBS bromination and reaction with TosNa.

Structure Elucidation. None of the benzothiophenes and their dihydro derivatives listed in Tables II–V have been reported previously. The structure assignments are based mainly on ^1H and ^{13}C NMR data,[27a] in combination with X-ray analysis of a derivative of **8c**. Methylation of **8c** gave the C-7 methoxy derivative **26** (Table VI) of which the crystal structure was determined.[18] Elimination of TosH from **26** gave **27**, which in fact is the *O*-methyl ether of **9d**. The crystal structure of **26** established both the benzo[*b*]thiophene skeleton as well as the positions of the substituents at C-4 to C-7 (and the trans relation between the substituents at C-4 and C-5).[27b] By extrapolation the benzo[*b*]thiophene structure of **27** can be deduced.

NMR data (^1H and ^{13}C shifts and coupling constants) of the benzothiophene derivatives **6**, **7**, **8**, **9**, **12**, and **14**, together with **26** and **27** are collected in Table VI, which is available as supplementary material. The internal

(22) (a) Price, C. C.; Mertz, E. C.; Wilson, J. *J. Am. Chem. Soc.* **1954**, *76*, 5131. (b) Oae, S.; Price, C. C. *J. Am. Chem. Soc.* **1957**, *79*, 2547. (c) Gronowitz, S. *Arkiv. Kemi* **1958**, *13*, 295.

(23) Suzuki, H.; Iwao, T.; Sugiyama, T. *Bull. Inst. Chem. Res., Kyoto Univ.* **1974**, *52*, 561; *Chem. Abstr.* **1975**, *82*, 170554a.

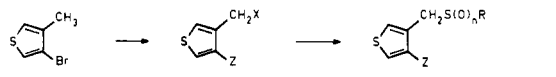
(24) Scrowston, R. M.; Shaw, D. C. *J. Chem. Soc., Perkin Trans. 1* **1976**, 749.

(25) Toland, W. G. *J. Org. Chem.* **1962**, *27*, 869.

(26) 3-Bromo-4-methylthiophene (**24**) was prepared from 3-methylthiophene analogously to the procedure described for 3-bromothiophene. Gronowitz, S.; Raznikiewicz, T. In "Organic Syntheses"; Baumgarten, H. E., Ed.,; Wiley and Sons, Inc.: New York, 1973; Collect Vol. V, p 149.

(27) Terpstra, J. W. Ph.D. Thesis, Groningen, Netherlands, 1982. (a) Attempts to correlate **9a** by hydrolysis and decarboxylation to the known 7-hydroxybenzo[*b*]thiophene were unsuccessful. (b) In all annulations leading to 4,5-dihydrobenzothiophenes, we found spectroscopic indications for only one isomer with respect to the configuration at carbons 4 and 5.

Scheme IV



24

25a Z = C≡N, X = H
25b Z = C≡N, X = Br
25c Z = COOMe, X = H
25d Z = COOMe, X = Br

4a Z = COOMe, n = 2
4b Z = COOMe, n = 1
4c Z = COOMe, n = 0
5 Z = C≡N, n = 2

consistency of the data of compounds **6–9**, together with the correlation with **26**, **27**, and literature data of other benzothiophenes,[28] provides unambiguous evidence for our assignments.

The following characteristic trends are observed in Table VI.[29] (1) Benzo[*b*]thiophene derivatives **6–9**, **26**, and **27** show an AB system for H^2 and H^3 with $J_{2,3}$ of ca. 5 Hz.[30] (2) Benzo[*c*]thiophene derivatives **12** and **14** show H^1 and H^3 as an aromatic AB system with $J_{1,3}$ ca. 2.8 Hz.[30] (3) The vicinal coupling constant $J_{4,5}$ for H^4 and H^5 in compounds **6**, **8**, **12**, and **26** is ca. 1 Hz. (4) Singlets are found for H^4 and H^7 in compound **7** (δ 7.0–8.2) and for H^4 in compounds **9** and **14** (ca. δ 7.2). (5) In the ^{13}C NMR spectra of the benzo[*b*]thiophene derivatives doublets are found for C^2 and C^3 with $J(2)$ between 185 and 190 Hz and $J(3)$ between 170 and 174 Hz.[31] (6) Benzo[*c*]thiophene derivatives show doublets for C^1 and C^3 with $J(1)$ and $J(3)$ between 185 and 190 Hz. (7) The doublets for C^4 and C^5 in the dihydrobenzothiophenes have a coupling constant $J(4)$ of ca. 145 Hz and $J(5)$ of ca. 135 Hz. (8) 7-Hydroxybenzothiophenes show a low-field signal for C^7.

Experimental Section

All reactions were carried out at room temperature under nitrogen, unless indicated otherwise.

Melting points were determined on a Mettler FP 1 melting point apparatus provided with a Mettler FP 52 microscope. Infrared spectra were recorded on a Unicam SP 200 spectrophotometer, neat or in Nujol. ^1H NMR spectra were recorded on a 60-MHz Hitachi-Perkin-Elmer R-24B apparatus. The chemical shifts are given in δ units (ppm) downfield of internal Me_4Si. ^{13}C NMR spectra were recorded at 25.2 MHz on a Varian XL-100 or 50.3 MHz on a Nicolet NT-200 spectrophotometer. The chemical shifts were obtained in δ units (ppm) downfield of the solvent and converted to δ values related to Me_4Si, by using δ ($CDCl_3$) 76.91 and δ (Me_2SO-d_6) 39.56. Coupling constants (J) are given in hertz. IR and NMR data for the tosyl substituents were within the range given in ref 29 and are omitted in the experimental results, as are those data already mentioned in Table VI. Elemental microanalyses were performed in the Analytical Department of Groningen University. Mass spectra were obtained on a AEI MS-902 spectrometer.

1,2-Dimethoxyethane (DME) and tetrahydrofuran (THF) were purified by distillation from $LiAlH_4$. Dimethyl sulfoxide (Me_2SO, from Hopkins and Williams) and hexamethylphosphoramide (HMPA, from Aldrich) were dried over molecular sieves (4 Å). Potassium *tert*-butoxide (*t*-BuOK) and sodium methoxide (MeONa) were purchased from Merck-Schuchardt. Sodium hydride (50% in mineral oil) was purchased from Fluka.

Synthesis of Precursor Thiophenes 1–5 (Table I, Schemes III and IV). Methyl 3-Methylthiophene-2-carboxylate[24] (22a). 2-Iodo-3-methylthiophene[23] (**21**, 113 g, 0.50 mol) was added dropwise to magnesium chips (12.7 g, 0.52 mol) and stirred in Et_2O (250 mL) while cooling in an ice–water bath. After the addition was complete (15 min), stirring was continued without cooling for 2 h, then the mixture was cooled again in ice, and dimethyl carbonate (65 g, 0.72 mol) was added (in 1 min). The mixture was stirred without further cooling for another 30 min and then hydrolyzed with 5 N HCl (250 mL). The organic layer was dried (Na_2CO_3) and concentrated in vacuum. The residue was distilled to yield **22a** (57.6 g, 74%): bp 98–102 °C (12–13 mmHg) [lit.[24] bp 66–68 °C (0.5 mmHg)]; IR (neat) 1705 cm^{-1}; ^1H NMR (CCl_4) δ 2.52 (s, 3), 3.80 (s, 3), 6.77 and 7.23 (AB q, 2, J = 5 Hz).

Methyl 3-(Bromomethyl)thiophene-2-carboxylate[24] (22b). A mixture of NBS[32] (39.2 g, 0.22 mmol) and dibenzoyl peroxide (0.5 g) was added over a period of 1.5 h to a refluxing mixture of **22a** (31.2 g, 0.20 mmol) and dibenzoyl peroxide (0.5 g) in CCl_4 (250 mL). After having been refluxed for 2 h, the mixture was cooled, filtered, concentrated, and distilled to give **22b** (38.5 g, 81%) as an oil, which solidified on standing: bp 106–108 °C (0.035 mmHg); mp 34–35 °C [lit.[24] bp 118–120 °C (0.5 mmHg); mp 32–33 °C]; ^1H NMR (CCl_4) δ 3.83 (s, 3), 4.83 (s, 2), 7.09 and 7.37 (AB q, 2, J = 5 Hz).

Methyl 3-(Tosylmethyl)thiophene-2-carboxylate (2a). A mixture of **22b** (35.4 g, 150 mmol) and sodium *p*-toluenesulfinate (27.6 g, 155 mmol) in Me_2SO (150 mL) was stirred for 17 h and then poured in ice–water (250 mL). The white precipitate was collected, washed with water (4 × 100 mL), dissolved in CH_2Cl_2 (100 mL), and dried (Na_2SO_4). After removal of the solvent, washing the residue with ethyl acetate/pentane (100 mL, 1:1), and drying, **2a** (34.2 g, 74%) was obtained: mp 131–132.5 °C; IR (Nujol) 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.61 (s, 3), 4.89 (s, 2), 7.0–7.6 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 51.8 (q, J = 139 Hz, CH_3O), 55.3 (t, J = 142 Hz, CH_2), 130.4 (d, J = 190 Hz, C-5), 130.7 (s, C-2), 131.5 (d, J = 173 Hz, C-4), 134.7 and 135.0 (s, CSO_2 and s, C-3), 161.7 (s, CO_2). Anal. Calcd for $C_{14}H_{14}O_4S_2$: C, 54.17; H, 4.55; S, 20.66. Found: C, 53.99; H, 4.59; S, 20.65.

Methyl 3-(*p*-Toluenesulfenylmethyl)thiophene-2-carboxylate (2c). A 1 M solution of sodium *p*-thiocresolate in MeOH[33] (100 mL, 0.10 mol) was added to a stirred solution of **22b** (23.7 g, 0.10 mol) in MeOH (50 mL). The mixture was refluxed for 3.5 h, cooled, and poured in water (500 mL). Extraction with ether (2 × 75 mL), washing the extract with brine, drying (Na_2SO_4), and removal of the solvent gave **2c** (27.4 g, 98%) as a yellow oil. This material was sufficiently pure (^1H NMR) to be used as such for the preparation of **2b**. Analytically pure **2c** was obtained by two distillations: bp 166 °C (0.5 mmHg); mp 53.5–55.5 °C; IR (Nujol) 1705 cm^{-1}; ^1H NMR (CCl_4) δ 2.27 (s, 3), 3.75 (s, 3), 4.37 (s, 2), 6.74–7.35 (m, 6); ^{13}C NMR ($CDCl_3$) δ 20.7 (q, J = 127 Hz, Ar CH_3), 32.4 (t, J = 145 Hz, CH_2), 51.4 (q, J = 148 Hz, CH_3O), 127.1 (s, C–S), 129.2 and 131.0 (d, J = 160 Hz and d, J = 162 Hz, Ar CH of tolyl), 129.9 (d, J = 186 Hz, C-5), 130.3 (d, J = 170 Hz, C-4), 131.5 (s, C-2), 136.4 (s, C-3), 145.8 (s, CCH_3), 162.2 (s, CO_2). Anal. Calcd for $C_{14}H_{14}O_2S_2$: C, 60.43; H, 5.03; S, 23.02. Found: C, 60.61; H, 5.06; S, 23.06.

Methyl 3-(*p*-Toluenesulfinylmethyl)thiophene-2-carboxylate (2b). A solution of **2c** (13.45 g, ca. 48 mmol) in MeOH (150 mL) was stirred with $NaIO_4$[34] (11.0 g, 51 mmol). Water was added until the mixture just became turbid. After having been stirred for 18 h, most of the methanol was removed under vacuum, and the residue was treated with CH_2Cl_2 (100 mL)

(28) Clark, P. D.; Ewing, D. F.; Scrowston, R. M. *Org. Magn. Reson.* **1976**, *8*, 252; Kellogg, R. M. in "Comprehensive Heterocyclic Chemistry; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 3, p 713.

(29) (a) Not listed in Table VI, although highly informative, were the signals of the enolic and phenolic protons and those of the tosyl substituents. (b) The spectra of all products containing a tosyl substituent showed the following characteristic signals: IR (Nujol) 1120–1160 and 1290–1350 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 2.3–2.4 (s, 3), 6.9–7.6 (Ar protons, AA'BB', J = 7–9 Hz); ^{13}C NMR ($CDCl_3$) δ 21.3–21.6 (q, J = 127–129 Hz), 128.2–128.6 and 129.0–129.9 (d, J = 164–170 Hz and d, J = 160–166 Hz, respectively), 133.2–134.7 (s, CSO_2), 144.5–145.5 (s, CMe). cf., for example: van Leusen, A. M.; Schaart, F. J.; van Leusen, D. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 258.

(30) Günther, H. In "NMR-Spektroskopie"; Georg Thieme Verlag: Stuttgart, 1973; p 376.

(31) (a) Mooney, E. F.; Winson, P. H. In "Annual Review of NMR Spectroscopy"; Mooney, E. F., Ed.; Academic Press: London, 1969; Vol. 2, p 153. (b) Wehrli, F. W.; Wirthlin, T. In "Interpretation of Carbon-13 NMR Spectra"; Heyden: London, 1976; p 47.

(32) *N*-Bromosuccinimide (NBS) was prepared as described in "Practical Organic Chemistry", 3rd Ed; Vogel, A. I., Ed.; Longmans: London, 1962; p 927, and was stored in air or under vacuum (cf. Chapmans, N. B.; Williams, J. F. A. *J. Chem. Soc.* **1952**, 5044).

(33) This solution was freshly prepared from *p*-thiocresol (12.42 g, 0.1 mol) and sodium (2.30 g, 0.1 mol) in MeOH (80 mL), after which the solution was diluted to 100 mL.

(34) Johnson, C. R.; Keiser, J. E. In "Organic Syntheses"; Baumgarten, H. E., Ed.; Wiley and Sons, Inc.: New York, 1973; Collect Vol. V, p 791.

and water (100 mL). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated to yield crude **2b** (12.9 g). Crystallization from CCl_4 gave **2b** (9.0 g, 62%)[35] as a slightly yellow solid: mp 96–97 °C; IR (Nujol) 1700, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.40 (s, 3), 3.78 (s, 3), 4.53 (d, 2, J = 2 Hz), 6.9–7.5 (m, 6); ^{13}C NMR ($CDCl_3$) δ 21.3 (q, J = 128 Hz, Ar CH_3), 51.8 (q, J = 148 Hz, CH_3O), 57.0 (t, J = 143 Hz, CH_2), 124.2 and 129.4 (d, J = 163 Hz and d, J = 161 Hz, respectively, Ar CH of tolyl), 130.2 (d, J = 184 Hz, C-5), 131.6 (d, J = 170 Hz, C-4), 137.3 and 137.4 (s, C-2 and s, CSO), 140.2 (s, C-3), 141.4 (s, CCH_3), 162.3 (s, CO_2). Anal. Calcd for $C_{14}H_{14}O_3S_2$: C, 57.14; H, 4.76; S, 21.77. Found: C, 56.53; H, 4.76; S, 21.61.

2-(Hydroxymethyl)-3-(tosylmethyl)thiophene (23a). A 1 M solution of lithium triethylborohydride in THF (32.5 mL, 32.5 mmol)[36] was added dropwise to a solution of **2a** (4.65 g, 15 mmol) in THF (30 mL). After stirring for 2.5 h, additional $LiEt_3BH$ solution (3 mL, 3 mmol) was added, and stirring was continued for 1.5 h. After addition of 5 N HCl to pH 6, the mixture was poured on ice (ca. 100 g). The separated oil was combined with an Et_2O extract (2 × 30 mL) of the water layer, washed with brine, and dried (Na_2SO_4). Concentration in vacuum gave an oil, which crystallized on addition of a little Et_2O and MeOH. The solid was washed with pentane and dried to give **23a** (4.0 g, 95%, mp 85–90 °C).[37] Analytically pure **23a** was obtained by one crystallization from CCl_4: mp 89–91 °C; IR (Nujol) 3425 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.05 (t, 1, J = 6.6 Hz), 4.37 (s, 2), 4.60 (d, 2, J = 6.6 Hz), 6.48 and 7.09 (AB q, 2, J = 6 Hz); ^{13}C NMR ($CDCl_3$) δ 55.5 (t, J = 139 Hz, $TosCH_2$), 56.7 (t, 145, CH_2OH), 121.4 (s, C-2), 124.4 (d, J = 185 Hz, C-5), 129.7 (d, J = 170 Hz, C-4), 143.8 (s, C-3). Anal. Calcd for $C_{13}H_{14}O_3S_2$: C, 55.32; H, 4.96; S, 22.70. Found: C, 55.20; H, 5.03; S, 22.61.

3-(Tosylmethyl)thiophene-2-carboxaldehyde (1a). A mixture of **23a** (6.58 g, 23.5 mmol) and pyridium dichromate[38] (PDC, 15 g, 41 mmol) in CH_2Cl_2 (100 mL) was stirred for 60 h and filtered over a layer of $MgSO_4$ (thickness 3 cm, diameter 3 cm). The residue on the $MgSO_4$ layer was extracted with additional CH_2Cl_2 (50 mL). The filtrate was concentrated, and the crude solid was extracted with Et_2O in a Soxhlet apparatus to yield **1a** (4.87 g, 75%): mp 144–147 °C; IR (Nujol) 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.75 (s, 2), 7.0–7.8 (m, 6), 9.55 (s, 1); ^{13}C NMR ($CDCl_3$) δ 55.1 (t, J = 140 Hz, CH_2), 132.1 (d, J = 170 Hz, C-4), 133.9 (d, J = 187 Hz, C-5), 134.2 or 134.7 (s, C-3), 140.8 (s, C-2), 181.0 (d, J = 181 Hz, CHO). Anal. Calcd for $C_{13}H_{12}O_3S_2$: C, 55.71; H, 4.29; S, 22.86. Found: C, 55.77; H, 4.34; S, 22.76.

2-(Hydroxymethyl)-3-(*p*-toluenesulfinylmethyl)thiophene (23b). A solution of **2b** (1.0 g, 3.4 mmol) in THF (20 mL) and $LiEt_3BH$[36] (1 M in THF, 7.5 mmol) was stirred for 24 h, then poured on ice, acidified carefully (0.5 N HCl), and extracted with Et_2O (3 × 30 mL). The extract was washed with water and brine and dried ($MgSO_4$). Concentration gave crude **23b** (656 mg, 72%): mp 90–95 °C.[37] Analytically pure **23b** was obtained by one crystallization from $CHCl_3/Et_2O$: mp 95.5–96.5 °C; IR (Nujol) 3350, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.38 (s, 3), 3.84 and 4.23 (AB q, 2, J = 14 Hz), 4.5–4.7 (m, 3), 6.20 (d, 1, J = 5 Hz), 6.9–7.5 (m, 5); ^{13}C NMR ($CDCl_3$) δ 21.3 (q, J = 128 Hz, CH_3), 55.3 (t, J = 138 Hz, CH_2SO), 55.9 (t, J = 145 Hz, CH_2OH), 124.0 (d, J = 188 Hz, C-5), 124.1 and 129.7 (d, J = 163 Hz and d, J = 161 Hz, respectively, Ar CH of tolyl), 125.5 (s, C-2), 129.2 (d, J = 168 Hz, C-4), 137.9 (s, CSO), 141.8 (s, CCH_3), 144.7 (s, C-3). Anal. Calcd for $C_{13}H_{14}O_2S_2$: C, 58.61; H, 5.30; S, 24.08. Found: C, 58.50; H, 5.28; S, 23.97.

3-(*p*-Toluenesulfinylmethyl)thiophene-2-carboxaldehyde (1b). A solution of **23b** (300 mg, 1.13 mmol) in CH_2Cl_2 (10 mL) was stirred with PDC[38] (635 mg, 1.7 mmol) for 24 h. Filtration over $MgSO_4$ and concentration of the solution followed by chromatography (SiO_2, i.d. = 2.5 cm, l = 7 cm, Et_2O) gave **1b** (276 mg, 95%): mp 111.5–113 °C; IR (Nujol) 1045, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.33 (s, 3), 4.24 and 4.52 (AB q, 2, J = 15 Hz), 6.7 (d, 1, J = 5 Hz), 7.12 (s, 4), 7.53 (d, 1, J = 5 Hz), 9.46 (s, 1); ^{13}C NMR ($CDCl_3$) δ 21.3 (q, J = 127 Hz, CH_3), 55.1 (t, J = 142 Hz, CH_2), 123.8 and 129.6 (d, J = 164 Hz and d, J = 162 Hz, Ar CH of tolyl), 131.8 (d, J = 170 Hz, C-4), 133.3 (d, J = 185 Hz, C-5), 136.1 and 138.6 (s, CSO and s, C-3), 140.8 (s, C-2), 142.0 (s, CCH_3), 181.3 (d, J = 183 Hz, CHO). Anal. Calcd for $C_{13}H_{12}O_2S_2$: C, 59.06; H, 4.58; S, 24.26. Found: C, 58.76; H, 4.62; S, 24.07.

2-Cyano-3-methylthiophene[39] (22c). A mixture of **21**[23] (27.5 g, 125 mmol) and $Cu^I C{\equiv}N$ (22.4 g, 250 mmol) in HMPA (25 mL) was stirred at 70–75 °C for 2 h and then at 130 °C for 1 h and was subsequently allowed to cool. It was poured in a saturated solution of sodium cyanide in water (100 mL) and stirred for 2 h. The aqueous layer was extracted with CH_2Cl_2 (100 mL). The combined extract and organic layer were washed with water (50 mL) and with brine (50 mL), dried (Na_2SO_4), and concentrated. Distillation gave **22c** (12.8 g, 85%): bp 84–88 °C (12 mmHg); IR (neat) 2255 cm^{-1}; ^1H NMR (CCl_4) δ 2.37 (s, 3), 6.88 (d, 1, J = 5 Hz), 7.41 (d, 1, J = 5 Hz); [lit.[23] bp 90–91 °C (16 mm Hg); IR 2225 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.42 (s, 3), 6.92 (d, 1, J = 6 Hz), 7.43 (d, 1, J = 6 Hz)].

3-(Bromomethyl)-2-cyanothiophene (22d) was prepared similarly to **22b**. NBS was added in portions, together with catalytic amounts of dibenzoyl peroxide, to the refluxing mixture of **22c** (12.3 g, 0.10 mol) in CCl_4 (100 mL) until ^1H NMR showed the completion of the reaction. The mixture was cooled, filtered, concentrated, and distilled to yield **22d** (13.4 g, 66%) as a lachrymatory oil:[40] bp 134–154 °C (13 mmHg); ^1H NMR (CCl_4) δ 4.53 (s, 2), 7.17 and 7.54 (AB q, 2, J = 5 Hz).

2-Cyano-3-(tosylmethyl)thiophene (3a). A mixture of **22d** (7.2 g, 35 mmol), sodium *p*-toluenesulfinate (7.0 g, 39 mmol), and tetrabutylammonium bromide[41] (0.59 g, 5 mol %) in Me_2SO (30 mL) was stirred for 6 days. Water (70 mL) was added, and the mixture was stirred for 30 min. The precipitate was collected and washed with water and with Et_2O/pentane (1:1, 10 mL). After drying this gave **3a** (7.73 g, 80%): mp 162–163 °C; IR (Nujol) 2250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.46 (s, 2), 7.1–7.7 (m, 6); ^{13}C NMR ($CDCl_3$) 56.3 (t, J = 144 Hz, CH_2), 110.6 (s, C≡N), 112.1 (s, C-2), 129.7 (d, J = 175 Hz, C-4), 132.1 (d, J = 190 Hz, C-5), 138.9 (s, C-3). Anal. Calcd for $C_{13}H_{11}NO_2S_2$: C, 56.30; H, 4.00; N, 5.05; S, 23.12. Found: C, 55.89; H, 3.98; N, 5.06; S, 23.13.

2-Cyano-3-(*p*-toluenesulfenylmethyl)thiophene (3c) was prepared analogously to **2c** from **22d** at room temperature for 7 days and gave crude **3c** in 96% yield (yellow oil). HPLC (toluene, SiO_2) and two crystallizations (Et_2O/pentane) gave **3c**: mp 42.9–43 °C; IR (neat) 2270 cm^{-1}; ^1H NMR (CCl_4) δ 2.30 (s, 3), 4.03 (s, 2), 6.8–7.4 (m, 6). Anal. Calcd for $C_{13}H_{11}NS_2$: C, 63.64; H, 4.52; N, 5.71; S, 26.14. Found: C, 63.19; H, 4.50; N, 5.88; S, 25.80.

2-Cyano-3-(*p*-toluenesulfinylmethyl)thiophene (3b). *m*-Chloroperbenzoic acid (MCPBA, 1.80 g, 10.5 mmol) was added to a solution of crude **3c** (2.45 g, 10 mmol) in MeOH (10 mL) and stirred for 20 h. Filtration and concentration gave 3.15 g of crude product, which was dissolved (CH_2Cl_2, 20 mL), washed with a saturated sodium bicarbonate solution and with water, and dried. After concentration and crystallization of the residue from CH_2Cl_2/pentane, **3b** (1.01 g, 40%)[35] was obtained: mp 92–96 °C; IR (Nujol) 1050, 2245 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.38 (s, 3), 4.15 (d, 2, J = 3 Hz), 7.03 and 7.47 (AB q, 2, J = 6 Hz), 7.25 (s, 4). Anal. Calcd for $C_{13}H_{11}NS_2O$: C, 59.78; H, 4.21; N, 5.36; S, 24.52. Found: C, 58.91; H, 4.27; N, 5.22; S, 23.42.

3-Cyano-4-methylthiophene[25] (25a). A mixture of 3-bromo-4-methylthiophene[26] (**24**, 53.1 g, 0.30 mol) and $Cu^I C{\equiv}N$ (60 g, 0.67 mol) in HMPA (75 mL) was stirred at 130–140 °C for 18 h. The cooled mixture was poured in a solution of sodium cyanide (100 g, 2 mol) in water (150 mL) and was stirred until the layers were almost clear. The oily layer and the Et_2O extract (2 × 75 mL) of the aqueous layer were combined, washed with water and with brine, and dried (Na_2SO_4). Evaporation of the

(35) This product was contaminated with traces of the corresponding sulfone and gave a somewhat low percentage of carbon in the elemental microanalysis.

(36) $LiEt_3BH$ was obtained as 1 M solution in THF under the trade name Super-Hydride from Aldrich.

(37) This product was used without further purification for the preparation of the aldehyde.

(38) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

(39) We found only partial (50–60%) conversion of **21** to cyanide **22c** under the conditions (80–90 °C, 2 h) of Suzuki et al.[23] The use of a twofold excess of Cu(I)C≡N and additional heating (130 °C, 1 h) gave a more complete conversion.

(40) Although this product was contaminated with traces of 2-cyano-3-(dibromomethyl)thiophene according to ^1H NMR ($CDCl_3$), which showed a signal at δ 6.78 (s, 1), it was used as such for the preparation of **3a** and **3c**.

(41) Cf. Wildeman, J.; van Leusen, A. M. *Synthesis* **1979**, 733.

solvent and distillation of the residual oil gave **25a** (21.3 g, 57%): bp 56–61 °C (0.1 mmHg); mp 31–34 °C. A second portion of **25a**, slightly less pure, but useful for most purposes, was obtained by redistillation of the forerun [46–56 °C (0.1 mmHg)] of the first distillation. This gave **25a** (13.8 g, 37%): bp 96–99 °C (30 mmHg); IR (neat) 2265 cm^{-1}; ^1H NMR (CCl_4) δ 2.40 (s, 3), 7.00 (m, 1), 7.80 (d, 1, J = 3 Hz); [lit.[25] bp 87 °C (10 mmHg), mp 34.7–35.1 °C].

3-Cyano-4-(tosylmethyl)thiophene (5). A mixture of *N*-bromosuccinimide[32] (8.8 g, 50 mmol) and dibenzoyl peroxide (0.15 g) was added to a refluxing solution of 3-cyano-4-methylthiophene (**25a**, 6.15 g, 50 mmol) and dibenzoyl peroxide (0.1 g) in CCl_4 (35 mL). The mixture was refluxed for 2 h, after which the NBS had disappeared. The ^1H NMR spectrum of a sample, however, showed that not all starting material was converted; therefore, another portion of *N*-bromosuccinimide (4.4 g, 25 mmol) and dibenzoyl peroxide (0.1 g) were added and refluxing was continued for 1 h. After having been cooled, the mixture was filtered and concentrated. This gave crude 3-(bromomethyl)-4-cyanothiophene (**25b**, 9.98 g, 98%), which was used without purification. A mixture of this crude product, sodium *p*-toluenesulfinate (10 g, 56 mmol), and tetrabutylammonium bromide (0.85 g, 6 mol %) in DME[41] (40 mL) was stirred for 72 h and was then filtered. The filter cake was washed with $CHCl_3$ (100 mL). The combined organic layer was washed with water and dried (Na_2SO_4). Concentration gave an oil, which partly crystallized. The product was washed with Et_2O/ethyl acetate (1:1) and with Et_2O, respectively, to yield **5** (5.0 g, 37%): mp 153–155 °C. Analytically pure **5** was obtained by two crystallizations from ethyl acetate: mp 157–159 °C; IR (Nujol) 2265 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.45 (s, 2), 7.1–8.0 (m, 6); ^{13}C NMR ($CDCl_3$) δ 55.3 (t, J = 140 Hz, CH_2), 112.8 (s, C≡N), 113.2 (s, C-3), 128.5 (d, J = 191 Hz, C-5), 129.5 (s, C-4), 135.4 (d, J = 188 Hz, C-2). Anal. Calcd for $C_{13}H_{11}NO_2S_2$: C, 56.30; H, 4.00; N, 5.05; S, 23.12. Found: C, 56.19; H, 3.99; N, 4.99; S, 23.02.

Methyl 4-Methylthiophene-3-carboxylate (25c). Nitrile **25a** (21.2 g, 172 mmol) was refluxed for 72 h with MeOH (100 mL), concentrated HCl (6 mL) and concentrated H_2SO_4 (6 mL). After cooling, the mixture was concentrated partially under reduced pressure. The residue was treated with Et_2O (100 mL) and water (100 mL). The water layer was extracted with Et_2O (50 mL). The combined Et_2O solutions were washed with a saturated $NaHCO_3$ solution and with brine and dried (Na_2SO_4). Distillation gave **25c** (19.9 g, 75%) as an oil: bp 87–88 °C (11 mmHg); IR (neat) 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.44 (s, 3), 3.79 (s, 3), 6.81 (m, 1), 7.97 (d, 1, J = 3 Hz); [lit.[42] bp 50 °C (0.001 mmHg); IR (CCl_4 or $CHCl_3$) 1730 cm^{-1}].

Methyl 4-(bromomethyl)thiophene-3-carboxylate (25d) was obtained by NBS bromination of **25c** similarly to **22b** and **22d**. This gave **25d** (79% yield) as an oil, which partly solidified in the condensor, and which was used as such for the preparation of **4a** and **4b**: bp 95–112 °C (0.1 mmHg); ^1H NMR ($CDCl_3$) δ 3.82 (s, 3), 4.75 (s, 2), 7.23 (d, 1, J = 4 Hz), 7.99 (d, 1, J = 4 Hz).

Methyl 4-(Tosylmethyl)thiophene-3-carboxylate (4a). A mixture of crude **25d** (5.20 g, 22 mmol) and sodium *p*-toluenesulfinate (3.90 g, 22 mmol) in Me_2SO (25 mL) was stirred for 24 h and then poured into water (150 mL). The white solid was collected, washed with water (150 mL) and Et_2O (50 mL), and dried under vacuum. The crude product was crystallized (MeOH) to yield **4a** (4.97 g, 73%): mp 121–131 °C. One crystallization from EtOAc gave **4a** (3.57 g, 52%): mp 131–134 °C; IR (Nujol) 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.61 (s, 3), 4.83 (s, 2), 7.0–7.6 (m, 5), 7.95 (d, 1, J = 4 Hz); ^{13}C NMR ($CDCl_3$) 51.2 (q, J = 148 Hz, CH_3O), 55.0 (t, J = 139 Hz, CH_2), 128.5 and 131.0 (s, C-3 and s, C-4), 128.7 (d, J = 193 Hz, C-2), 133.8 (d, J = 190 Hz, C-5), 162.4 (s, *C*OOMe). Anal. Calcd for $C_{14}H_{14}O_4S$: C, 54.17; H, 4.55; S, 20.66. Found: C, 54.26; H, 4.53; S, 20.82.

Methyl 4-(*p*-Toluenesulfinylmethyl)thiophene-3-carboxylate (4b). A solution of sodium *p*-thiocresolate (1 M) in MeOH[33] (57 mL, 57 mmol) was added to crude **25d** (13.4 g, 56 mmol) in MeOH (50 mL). The mixture was stirred for 40 h, then diluted with Et_2O (100 mL), and filtered. The filter cake was washed with Et_2O (50 mL), and the combined Et_2O solutions were concentrated. The residual oil was dissolved in Et_2O again, washed with water and with brine, and dried ($MgSO_4$). Evaporation of the solvent gave methyl 4-(*p*-toluenesulfenylmethyl)-thiophene-3-carboxylate **4c** (14.4 g, 92%) as an oil: ^1H NMR ($CDCl_3$) δ 2.26 (s, 3), 3.78 (s, 3), 4.29 (s, 2), 6.8–7.5 (m, 5), 7.96 (d, 1, J = 3 Hz). This product was used as such in the oxidation to **4b**. A mixture of **4c** (14.4 g, 51.8 mmol) and $NaIO_4$ (11.5 g, 53.7 mmol) in MeOH (100 mL) and water (25 mL) was stirred at 0 °C for 23 h. The mixture was then filtered, the filter cake was washed with methanol, and the combined filtrates were concentrated. The residue was dissolved in CH_2Cl_2 (100 mL), washed with water and with brine, and dried ($MgSO_4$). Concentration of this solution gave **4b** as an oil. Addition of Et_2O (10 mL) and pentane (5 mL) resulted in crystallization, after which the product was washed with Et_2O and dried to yield **4b** (9.84 g, 63%): mp 92–94 °C, IR (Nujol) 1045, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.36 (s, 3), 3.76 (s, 3), 4.38 (d, 2, J = 5 Hz), 7.1–7.5 (m, 5), 8.02 (d, 1, J = 4 Hz); ^{13}C NMR ($CDCl_3$) δ 21.3 (q, J = 128 Hz, CH_3 of tolyl), 5.15 (q, J = 148 Hz, CH_3O), 57.8 (t, J = 143 Hz, CH_2), 124.1 and 129.4 (d, J = 163 Hz and d, J = 162 Hz, Ar CH of tolyl), 127.6 (d, J = 187 Hz, C-2), 130.6 and 130.8 (s, CSO and s, C-3), 134.4 (d, J = 190 Hz, C-5), 140.1 (s, C-4), 141.2 (s, CCH_3), 162.9 (s, CO_2CH_3). Anal. Calcd for $C_{14}H_{14}O_3S_2$: C, 57.14; H, 4.76; S, 21.77. Found: C, 56.87; H, 4.83; S, 21.69.

Since the annulation reactions were carried out by essentially the same method, a general procedure is given for all reactions described in sections A–D. The general procedure is followed by a number of typical examples, which are worked out in full detail.[29,43]

General Procedure for the Annulations of Precursor Thiophenes 1–5 with Michael Acceptors. To a stirred solution of precursor thiophene (**1–5**, 2 mmol) and Michael acceptor substrate (2–2.5 mmol) in a solvent (DME, Me_2SO, or THF, 10 mL) 2–4 equiv of base (see Tables II–V) is added. The mixture is stirred under nitrogen for the time specified in Tables II–V and is then poured in water. Acidification with 0.5 N HCl (neutral to slightly acidic) causes precipitation of the product in most cases (If no precipitate forms on acidification, the aqueous layer is extracted with CH_2Cl_2 or $CHCl_3$. The extract is washed with water and with brine, dried (Na_2SO_4 or $MgSO_4$), and concentrated. The crude product is further purified as indicated.). The product is collected, washed with water, and, still wet, dissolved in CH_2Cl_2 or $CHCl_3$. The solution is dried over Na_2SO_4 or $MgSO_4$ and concentrated. The crude product is purified by chromatography or flash chromatography,[44] or by crystallization.

Benzo[*b*]thiophene-5,6-dicarboxylic Acid (7a). (Typical Example of the Annulation of Thiophenecarboxaldehydes 1 (Section A, Table II)). To a stirred solution of **1a** (280 mg, 1.0 mmol) and dimethyl fumarate (150 mg, 1.04 mmol) in DME (5 mL) was added *t*-BuOK (448 mg, 4 mmol). The mixture was stirred at 60–70 °C for 2 h, then poured in water (100 mL, and acidified (0.5 N HCl) to about pH 5. The mixture became turbid and crystallized upon standing overnight. The product was collected, washed (H_2O), and dried to yield **7a** (150 mg, 68%): mp 250 °C dec; IR (Me_2SO) 1650, 1700, 3300, and 3450 cm^{-1}; ^1H NMR ($CDCl_3$ + ca. 10% $(CD_3)_2SO$) δ 10.87 (br s, 2, COOH's); ^{13}C NMR ($(CD_3)_2SO$) δ 168.6 and 168.8 (both s, COOH's); MS, M^+ calcd at m/e 222, found m/e 222. Anal. Calcd for $C_{10}H_6O_4S$: C, 54.05; H, 2.72; S, 14.43. Found: C, 53.86; H, 2.85; S, 14.55.

6-Benzoyl-7-hydroxy-5-phenyl-4-tosyl-4,5-dihydrobenzo[*b*]thiophene (8c). (Typical Example of Formation of Dihydrobenzo[*b*]thiophenes from Thiophenecarboxylate 2a (Section B, Table III)). A mixture of **2a** (3.10 g, 10 mmol) and chalcone (2.10 g, 10 mmol) in Me_2SO (50 mL) was stirred with MeONa (1.40 g, 25 mmol) at room temperature for 24 h. The mixture was poured in water (300 mL), acidified (0.5 N HCl) to about pH 6, and stirred for 15 min. The precipitate was collected, washed (H_2O), and dissolved in CH_2Cl_2. The solution was washed with brine, dried (Na_2SO_4), and concentrated. The crude yellow product was crystallized (EtOH) to give **8c** (3.57 g, 74%): mp

(42) Bohlmann, F.; Bresinsky, E. *Chem. Ber.* **1964**, *97*, 2109 (cf. Steinkopf, W.; Hanske, W. *Liebigs Ann. Chem.* **1937**, *532*, 236).

(43) Correct elemental microanalysis data and/or exact mass data of all other compounds listed in Tables II–V, together with additional spectroscopic data not listed in Table VI, are described in the Ph.D. Thesis of J. W. Terpstra, Groningen, 1982. The values obtained for the elemental microanalysis on carbon for compounds **6b** and **6c** were too low. No elemental microanalysis or exact mass analyses were available for compounds **7b** and **7c**. However, **7b** was correlated to **7a** by hydrolysis.

(44) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

177–178 °C; IR (Nujol) 1595, 1605, 1705, and 3150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.0–7.5 (m, protons of benzoyl, phenyl, tolyl, and H-3), 16.19 (s, 1, OH); ^{13}C NMR ($CDCl_3$) δ 127.0–130.0 (complex spectrum of 7 closely spaced doublets,[45] J = 160–165 Hz), 138.8 and 142.3 (both s, benzoyl and phenyl), 180.1 and 181.5 (both s, CO of benzoyl and C-7); MS, M^+ calcd at m/e 486, found m/e 331 (M^+ – tosyl). Anal. Calcd for $C_{28}H_{22}O_4S_2$: C, 69.11; H, 4.56; S, 13.18. Found: C, 68.95; H, 4.51; S, 13.22.

6-Benzoyl-7-hydroxy-5-phenylbenzo[*b*]thiophene (9d). (Typical Example of Formation of Benzo[*b*]thiophenes from Thiophenecarboxylate 2b (Section B, Table III)). To a mixture of **2b** (588 mg, 2 mmol) and chalcone (417 mg, 2 mmol) in Me_2SO (10 mL) was added MeONa (300 mg, 5.5 mmol), and the mxiture was stirred for 25 h at room temperature, poured out in water, and acidified (0.5 N HCl) to about pH 6. The yellow precipitate was washed (H_2O), dissolved in CH_2Cl_2, and combined with a CH_2Cl_2 extract of the filtrate. The CH_2Cl_2 solution was washed (H_2O), dried (Na_2SO_4), and concentrated to give crude **9d**. Crystallization (EtOH/Et_2O) afforded **9d** (334 mg, 50%): mp 141–142 °C; IR (Nujol) 1590, 1600, and 3050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.0–7.5 (m, protons of benzoyl, phenyl, and half AB q of thiophene), 11.15 (s, 1, OH); ^{13}C NMR ($CDCl_3$) δ 126.7, 127.2, 127.8, 129.1, 129.6, 131.5 (six d, J = 160–161 Hz, CH of benzoyl and phenyl), 139.5 (s, CCO of benzoyl), 141.1 (s, phenyl), 201.4 (s, CO). Anal. Calcd for $C_{21}H_{14}O_2S$: C, 76.36; H, 4.24; S, 9.70. Found: C, 76.20; H, 4.27; S, 9.48.

Methyl 7-Hydroxy-5-phenyl-4-tosyl-4,5-dihydrobenzo-[*c*]thiophene-6-carboxylate (12c). (Typical Example of Formation of a Dihydrobenzo[*c*]thiophene (Section D, Table V)). A mixture of **4a** (310 mg, 1.0 mmol) and methyl cinnamate (165 mg, 1.0 mmol) in DME (5 mL) was stirred with *t*-BuOK (280 mg, 2.5 mmol) for 24 h at 20 °C and then for 3 h at 60 °C. The mixture was cooled and poured in a mixture of 60 mL of water plus 10 mL of 0.5 N HCl. The precipitate was collected, washed with water (200 mL), and dissolved in Et_2O, and this solution was washed with brine and dried ($MgSO_4$). Concentration gave crude **12c** which was washed with Et_2O/pentane to give **12c** (231 mg, 53%): mp 149–151 °C; IR (Nujol) 1620, 1640, and 3115 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.62 (s, 3, MeO), 6.75–7.50 (m, 10, Ar protons), 12.03 (s, 1, OH); ^{13}C NMR ($CDCl_3$) δ 51.9 (q, J = 149 Hz, MeO), 124.7, 127.0, and 127.1 (all d, J = 160–168 Hz, CH of phenyl), 132.3 (s, phenyl), 162.0 (s, C-7), 171.8 (s, CO_2R). Anal. Calcd for $C_{23}H_{20}O_5S_2$: C, 62.70; H, 4.58; S, 14.56. Found: C, 62.72; H, 4.70; S, 14.56.

Dimethyl 4-Hydroxybenzo[*c*]thiophene-5,6-dicarboxylate (14a). (Typical Example of Annulations of 3,4-Disubstituted Thiophene 4a (Section D, Table V)). To a solution of **4a** (310 mg, 1 mmol) and dimethyl maleate (212 mg, 1.5 mmol) in DME (5 mL) was added *t*-BuOK (280 mg, 2.5 mmol). The mixture was stirred for 5 h at 60–70 °C, then kept at 20 °C overnight, and subsequently poured in water. Acidification (0.5 N HCl) to about pH 6 gave a precipitate that was collected, washed (H_2O), and dissolved in Et_2O. The solution was dried ($MgSO_4$) and concentrated to give crude **14a** as a brown-yellow solid. This crude product was filtered with Et_2O over a layer (1 cm) of silica gel and crystallized (CH_2Cl_2, heptane, Et_2O) to yield **14a** (185 mg, 70%): mp 114–116 °C; IR (Nujol) 1655, 1725, 3095, and 3115 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.83 and 3.87 (two s, 3, MeO), 12.04 (s, 1, OH); ^{13}C NMR ($CDCl_3$) δ 52.3 (q, J = 147 Hz, MeO), 52.5 (q, J = 148 Hz, MeO), 169.6 and 170.6 (s, and s, two ester carbonyls). Anal. Calcd for $C_{12}H_{10}O_5S$: C, 54.13; H, 3.79; S, 12.04. Found: C, 53.86; H, 3.89; S, 11.90.

Registry No. **1a**, 99708-86-8; **1b**, 99708-87-9; **2a**, 81452-50-8; **2b**, 81458-99-3; **2c**, 99708-82-4; **3a**, 99708-83-5; **3b**, 99708-84-6; **3c**, 99708-85-7; **4a**, 99708-93-7; **4b**, 99708-94-8; **4c**, 99708-95-9; **5**, 99708-96-0; **6a**, 81459-01-0; **6b**, 99708-98-2; **6c**, 99708-99-3; **7a**, 81452-61-1; **7b**, 98449-83-3; **7c**, 81452-62-2; **7d**, 81452-53-1; **7e**, 81452-63-3; **7f**, 99708-97-1; **8a**, 81452-64-4; **8b**, 81452-65-5; **8c**, 81452-51-9; **8d**, 99709-01-0; **9a**, 81452-59-7; **9b**, 81452-49-5; **9c**, 99709-00-9; **9d**, 81452-46-2; **9e**, 99709-02-1; **10**, 99709-04-3; **11**, 99709-03-2; **12a**, 99709-06-5; **12b**, 99709-07-6; **12c**, 99709-09-8; **13**, 99709-13-4; **14a**, 99709-05-4; **14b**, 99709-08-7; **14c**, 99709-10-1; **14d**, 99709-11-2; **15**, 99709-12-3; **21**, 16494-40-9; **22a**, 81452-54-2; **22b**, 59961-15-8; **22c**, 55406-13-8; **22d**, 99708-88-0; **23a**, 99708-89-1; **23b**, 99708-90-4; **24**, 30318-99-1; **25a**, 73229-39-7; **25b**, 99708-91-5; **25c**, 61755-84-8; **25d**, 99708-92-6; (E)-4-$O_2NC_6H_4CH$=CHCOPh, 2960-55-6; (E)-PhCOCH=CHCOPh, 959-28-4; (E)-PhCOCH=CHPh, 614-47-1; (E)-PhCH=CHCOOMe, 1754-62-7; dimethyl fumarate, 624-49-7; methyl crotonate, 18707-60-3; 6,6-dimethylcyclohex-2-enone, 6553-64-6; sodium *p*-toluenesulfinate, 824-79-3; sodium *p*-thiocresolate, 10486-08-5.

Supplementary Material Available: Table VI with NMR data (^1H and ^{13}C chemical shifts and coupling constants) of the benzothiophene skeleton of compounds **6–9**, **12**, **14**, **26**, and **27** (3 pages). Ordering information is given on any current masthead page.

(45) Two lines probably fall together in this spectrum. However, the coupled spectrum is too complex to decide which ones.

Notes

Interfacial Superbase Chemistry. The Catalyzed Reaction of Potassium Hydride with Trisiamylborane. A New Convenient Synthesis of Potassium Trisiamylborohydride[1a]

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Potassium hydride is a highly reactive reagent for the metalation of highly hindered alcohols, amines, phenols, ketones, sulfoxides, etc.[2] The reactivity exhibited by this hydride is far superior to the other, more commonly used, alkali metal hydrides. In addition, potassium hydride is exceptionally reactive toward weak Lewis acids, such as trialkylboranes and trialkoxyboranes.[3] Unlike lithium and sodium hydrides, potassium hydride reacts with hindered organoboranes, such as tri-*sec*-butylborane, rapidly and quantitatively, even at room temperature. The corre-

(1) (a) Quaternary Boron. 8. Part 7; Brown, C. A.; Desai, M. C.; Jadhav, P. K. submitted for publication. Part 6, see ref 5b. (b) Joint Study Fellow at IBM, Spring 1977.

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