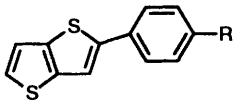
Synthesis of New 2-Arylthieno[3,2-*b*]thiophenes

Damian Prim and Gilbert Kirsch *
Laboratoire de Chimie Organique, Université de Metz, F-57045 Metz, France

2-Arylthieno[3,2-*b*]thiophenes **1** have been synthesized by palladium catalysed arylation reactions of thieno[3,2-*b*]thiophene **2** and intramolecular cyclisations of 2,3-substituted thiophenes **7**. A comparative study of the different methods is presented.

Condensed thiophene derivatives and polythiophenes have received much attention as potential conducting polymers,[1] electron acceptors,[2] hydrogen-poor heterocycles,[3] organic conductors or superconductors,[4] photosensitive receptors[5] and materials for non-linear optics.[6]

With a view to enhancing electron density and transmission effects for potential non-linear optical applications, we planned to use 2-arylthieno[3,2-*b*]thiophenes. We describe here the synthesis of compounds **1** by using either palladium catalysed



1a R = NO_2
b R = CN
c R = CO_2Me
d R = SO_2Me
e R = H

arylation reactions on thieno[3,2-*b*]thiophene **2** or cyclisation reactions of 2-formyl-3-(benzylsulfanyl)thiophenes **7**.

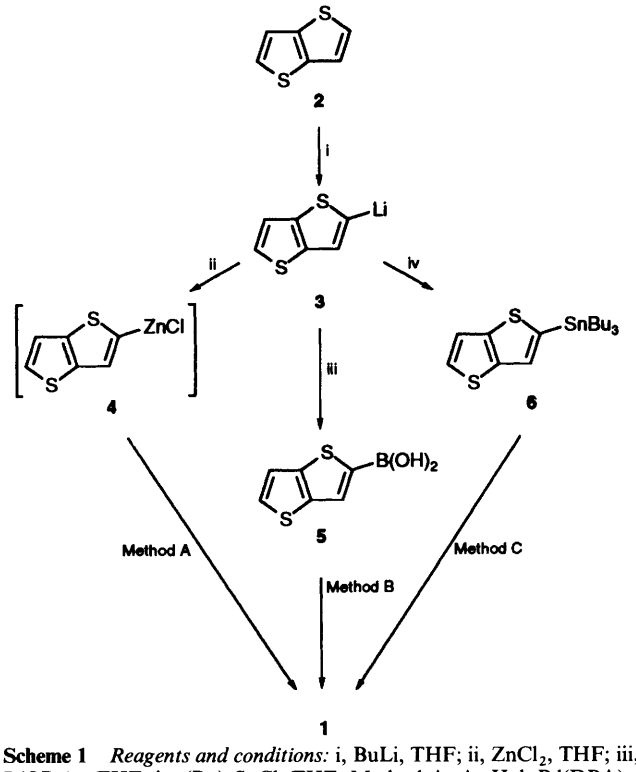
Results and Discussion

Thieno[3,2-*b*]thiophene **2** was prepared according to the method of Gol'dfarb and co-workers[7] in 30% overall yield from 3-bromothiophene. The lithio species **3** was prepared using Bugge's procedure.[8] Treatment of the thio species **3** with zinc chloride in THF gave the organometallic derivative **4** which was directly condensed with various aryl halides in the presence of Pd^0 (Scheme 1, Method A).[9] The condensation leads to compounds **1** (Table 1). Treatment of lithio species **3** with tributyl borate, followed by hydrolysis allows the preparation of the boronic acid **5**, which was isolated in a good yield. This acid was coupled with aryl halides to afford the derivatives **1** (Scheme 1, Method B).[10]

Compound **1d** could not be synthesized by either method A or B so we tried to prepare it by using method C[11] (Scheme 1). Treatment of compound **2** with tributylstannyl chloride gave the 2-tributylstannylthieno[3,2-*b*]thiophene **6** which was treated with methyl 4-bromobenzenesulfonate (Table 1) but this did not afford the desired compound **1d**. However, method C showed good efficiency for the preparation of **1c** and gave a high yield.

The second approach to compound **1** is inspired by Litvinov's method of thieno[3,2-*b*]thiophene synthesis. Thiophene-3-thiolate, prepared from 3-bromothiophene by lithiation and sulfurisation,[12] was condensed with various benzyl bromides **8** to afford sulfides **9**. Formylation by the Vilsmeier–Haack reagent[13] of compounds **9** yielded exclusively the formyl derivatives **7** which were cyclised under basic conditions to compounds **1** (Scheme 2).

Most of the benzyl bromides are commercially available or



Scheme 1 *Reagents and conditions:* i, BuLi, THF; ii, $ZnCl_2$, THF; iii, $B(OBu)_3$, THF; iv, $(Bu)_3SnCl$, THF; Method A, Ar-Hal, $Pd(DBA)_2$, TPP, DMF; Method B, Ar-Hal, $Pd(TPP)_4$, $Ba(OH)_2$, DME; Method C, Ar-Hal, $Pd(TPP)_4$, dioxane

can be prepared by *N*-bromosuccinimide bromination of the *p*-substituted toluene derivatives.

A different method was used for the preparation of 2-phenylthieno[3,2-*b*]thiophene **1e**. In this case cyclisation using the poorly activated methylene group in structure **7e** ($R^1 = R^2$) is difficult. We chose a method that utilises the activation of the methine hydrogen in structure **9e**. Cyclisation occurs under basic conditions but aromatisation only takes place with decarboxylation at the acidification step.

3-Bromothiophene can be considered as the starting material for the two methods of synthesizing 2-arylthieno[3,2-*b*]thiophene. Table 2 presents the overall yields obtained using the arylation or the cyclisation method for preparing compounds **1**.

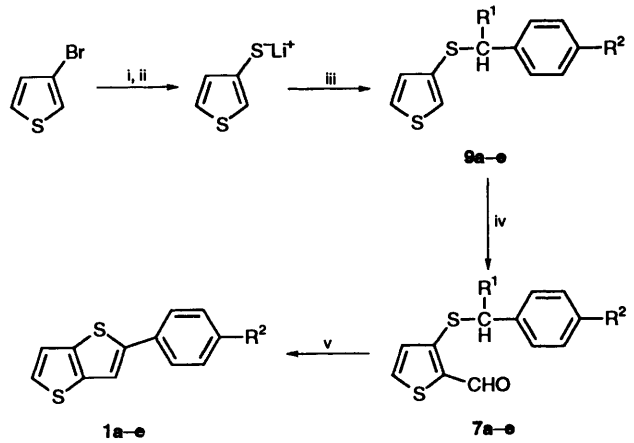
In general, the cyclisation route gave better yields of the desired final compound. The advantage of this method lies in the fact that the benzyl bromides are generally available making the condensation with lithium thiophene-3-thiolate possible. As formylation occurs preferably in the 2 position in structure **9**, the cyclisation step is obvious. The major problem in the synthesis using the palladium catalysed arylation is that the reaction does not work with all aryl halides or with all organometallic derivatives.

Table 1 Synthesis of thieno[3,2-*b*]thiophene **1** by coupling reaction

Compound	Aryl halide **8**	Reaction time (h) Method A	B	C	Mol% catalyst Method A	B	C	Yield **1** (%) Method A	B	C
1a	$IPhNO_2$	1	24		2	5		85	50	
1b	BrPhCN	1	16		2	5		30	55	
1c	$BrPhCO_2Me$	1	16	18	2	5	10	10	40	60
1d	$BrPhSO_2Me$	1	24	36	2	5	10	no reaction		
1e	IPh		20			5			65	
						5				

Table 2 Comparative yields of compounds **1** starting from 3-bromothiophene

Compound	R	**1** by coupling reaction (%)	**1** by cyclisation (%) **9**	**7**	overall
1a	NO_2	25	80	70	33
1b	CN	12	65	75	24
1c	CO_2Me	1	60	80	19
1d	SO_2Me	not obtained	70	65	27
1e	H	15	50	45	13



Scheme 2 *Reagents and conditions:* i, BuLi, −78 °C, THF; ii, S_8; iii, *p*-substituted benzyl bromides **8** [in case of **9e** $PhCH(Br)CO_2Et$], THF; iv, DMF–$POCl_3$; v, EtONa, EtOH (for **7e**: NaOH, H_2O, EtOH), reflux 2 h then acidification

Experimental

M.p.s were determined on a Kofler Bench and are uncorrected. ^1H NMR spectra were recorded on a Bruker 250 MHz spectrometer and elemental analyses performed on a Carlo Erba elemental analyser. DBA represents dibenzylideneacetone. Thieno[3,2-*b*]thiophene was prepared according to the method of Gol'dfarb *et al.*[7]

(Thieno[3,2-b]*thiophen-2-yl)boronic Acid* **5**.—A solution of butyllithium (2.5 mol dm^{-3} in hexanes; 40 cm^3, 0.1 mol) was added to a stirred solution of thieno[3.2-*b*]thiophene **2** (14 g, 0.1 mol) in anhydrous THF (100 cm^3) at 0 °C under nitrogen. The solution was stirred at 0 °C for 30 min and then at room temperature for an additional 0.5 h. Tributyl borate (24 g, 0.1 mol) dissolved in THF (20 cm^3) was added to it and the mixture was left to stand 1 h at room temperature. It was then poured into water and extracted twice with diethyl ether. The organic phases were combined and extracted with a 20% aqueous sodium hydroxide. The basic aqueous phase was separated, acidified with 20% aqueous HCl and then extracted with diethyl ether. The organic layer was dried over sodium sulfate and then the solvent was removed under reduced pressure. The crude boronic acid **5** (13.8 g, 75%) was used as such in the coupling reactions; m.p. 158 °C; δ(250 MHz; $CDCl_3$) 6.0 (2 H, br s, OH), 7.2 (1 H, d, *J* 5.2), 7.4 (1 H, d, *J* 5.2) and 7.55 (1 H, s, Ar-H).

2-*(Tributylstannyl)thieno*[3,2-b]*thiophene* **6**.—To the 2-thieno[3,2-*b*]thienyllithium **3**, prepared as previously reported,[8] was added tributylstannyl chloride (32.5 g, 0.1 mol). After 1 h at room temperature, the mixture was poured into water and extracted with diethyl ether. The organic layer was washed twice with water and dried and then the solvent removed under reduced pressure. The oily residue was purified by chromatography on silica gel using diethyl ether–cyclohexane (1:1) to give the title compound **6** (25.5 g, 60%); δ(250 MHz; $CDCl_3$) 1.0 (9 H, m, CH_3), 1.2 (6 H, m, CH_3CH_2), 1.35 (6 H, m, $CH_2CH_2CH_2$), 1.6 (6 H, m, $SnCH_2$), 7.3 (1 H, d, *J* 5.1), 7.4 (1 H, d, *J* 5.1) and 7.45 (1 H, s, Ar-H).

Coupling of Aryl Halides and 2-*Thieno*[3,2-b]*thienylzinc Chloride* **4**. *Method A*.—The intermediate **4** was obtained by the addition of zinc chloride (13.5 g, 0.1 mol) to lithium compound **3**. After 30 min, the THF was removed under reduced pressure and freshly distilled DMF (100 cm^3) was added to the residue.[14] The mixture was stirred for 15 min and then a mixture of aryl halide **8** (0.1 mol) in DMF (50 cm^3), $Pd(DBA)_2$ (1.05 g, 0.002 mol) and triphenylphosphine (1.05 g, 0.004 mol) was added. The reaction mixture was heated at 80 °C for 1 h and then poured into ice–water. The solid was collected by filtration and recrystallised.

Coupling of Aryl Halides and Boronic Acid **5**. *Method B*.—Tetrakis(triphenylphosphine)palladium (0.58 g, 0.5 mmol) was added to a stirred mixture of the aryl halide **8** (10 mmol), the crude boronic acid **5** (1.85 g, 10 mmol), barium hydroxide (4.32 g, 20 mmol) in DME (50 cm^3) and water (2 cm^3). The

mixture was heated at reflux for the time indicated in Table 1. It was then poured into ice–water and the solid collected and recrystallised.

Coupling of Aryl Halides and Tin Compound **6**. *Method C.*—Tetrakas(triphenylphosphine)palladium (1.15 g, 1 mmol) was added to a stirred solution of tin compound **6** (4.28 g, 10 mmol) and the aryl halide **8** (10 mmol) in dioxane (50 cm^3) and the mixture heated at reflux for the time indicated in Table 1. The reaction mixture was poured into cold water and the solid collected and recrystallised.

Sulfides **9**.—3-Bromothiophene (16.4 g, 0.1 mol) was added to a stirred solution of butyllithium (2.5 mol dm^{-3} solution in hexanes; 40 cm^3, 0.1 mol) in THF (70 cm^3) at −78 °C under nitrogen. After 45 min sulfur (3.2 g, 0.1 mol) was added in portions and the mixture was stirred for 30 min at −78 °C. Benyl bromide (0.1 mol) in THF (100 cm^3) was added dropwise to the mixture and the reaction was left to reach room temperature. The reaction was then refluxed for 3 h and then left to stand at room temperature overnight and then poured into water. The phases were separated and the aqueous phase was extracted with diethyl ether. The organic phases were combined, dried and then evaporated. The residue was chromatographed on silica gel (cyclohexane–diethyl ether, 1:1) to elute derivatives **9**.

3-*Thienyl*-4-*nitrobenzyl sulfide* **9a**. (80%); m.p. 55 °C (Found: C, 52.4; H, 3.5; N, 5.7. $C_{11}H_9NO_2S_2$ requires C, 52.6; H, 3.6; N, 5.6%); δ(250 MHz; $CDCl_3$) 4.05 (2 H, s, SCH_2), 7.0 (1 H, m, Ar-H), 7.1 (2 H, m, Ar-H), 7.3 (2 H, d, *J* 8.6) and 8.1 (2 H, d, *J* 8.6).

3-*Thienyl*-4-*cyanobenzylsulfide* **9b**. (65%); m.p. 43 °C (Found: C, 62.1; H, 3.8; N, 6.0. $C_{12}H_9NS_2$ requires C, 62.3; H, 3.9; N, 6.1%); δ(250 MHz; $CDCl_3$) 4.0 (2 H, s, SCH_2), 6.95 (1 H, m, Ar-H), 7.2 (2 H, m, Ar-H), 7.3 (2 H, d, *J* 8.7), 7.6 (2 H, d, *J* 8.7).

3-*Thienyl*-4-*methoxycarbonylbenzyl sulfide* **9c**. (70%); m.p. 92 °C (Found: C, 59.3; H, 4.5. $C_{13}H_{12}O_2S_2$ requires C, 59.1; H, 4.5%); δ(250 MHz; $CDCl_3$) 3.95 (3 H, s, CH_3), 4.0 (2 H, s, SCH_2), 7.0 (1 H, m, Ar-H), 7.15 (2 H, m, Ar-H), 7.4 (2 H, d, *J* 8.4) and 8.0 (2 H, d, *J* 8.4).

3-*Thienyl* 4-*methylsulfonylbenzyl sulfide* **9d**. (60%); m.p. 104°C (Found: C, 50.9; H, 4.5. $C_{12}H_{12}O_2S_3$ requires C, 50.7; H, 4.3%); δ(250 MHz; $CDCl_3$) 3.05 (3 H, s, CH_3), 4.05 (2 H, s, SCH_2), 7.0 (1 H, m, Ar-H), 7.15 (2 H, m, Ar-H), 7.45 (2 H, d, *J* 8.5) and 7.90 (2 H, d, *J* 8.5).

3-*Thienyl ethoxycarbonyl*(*phenyl*)*methyl sulfide* **9e**. (50%); oil (Found: C, 60.4; H, 5.1. $C_{14}H_{14}O_2S_2$ requires C, 60.4; H, 5.1%); δ(250 MHz; $CDCl_3$) 1.3 (3 H, t, CH_3), 4.15 (2 H, q, CH_2), 4.75 (1 H, s, SCH), 7.0 (1 H, m, Ar-H), 7.25 (2 H, m, Ar-H) and 7.35 (5 H, m, Ar-H).

Formyl Derivatives **7**.—DMF (11 cm^3) was added dropwise to an ice cold solution of phosphoryl chloride (11 cm^3) and the mixture was stirred for 10 min. To the Vilsmeier–Haack reagent, compound **7** (0.1 mol) in DMF (30 cm^3) was added dropwise and the mixture was stirred for 3 h at 95 °C. The reaction was poured into water and extracted with diethyl ether. The organic phase was dried and then evaporated to give the crude product. The product was purified by chromatography on silica gel (diethyl ether–cyclohexane, 1:2) to give the formyl derivatives **7**.

3-(4-*Nitrobenzylsulfanyl*)*thiophene*-2-*carbaldehyde* **7a**. (70%); m.p. 156 °C (Found: C, 51.6; H, 3.4; N, 5.1. $C_{12}H_9NO_3S_2$ requires C, 51.6; H, 3.2; N, 5.0%); δ(250 MHz; $CDCl_3$) 4.2 (2 H, s, SCH_2), 7.05 (1 H, d, *J* 5.2), 7.4 (2 H, d, *J* 8.6), 7.75 (1 H, d, *J* 5.2), 8.1 (2 H, d, *J* 8.6) and 9.95 (1 H, s, CHO).

3-(4-*Cyanobenzylsulfanyl*)*thiophene*-2-*carbaldehyde* **7b**. (75%); m.p. 170 °C (Found: C, 60.3; H, 3.4; N, 5.3. $C_{13}H_9NOS_2$ requires C, 60.2; H, 3.5; N, 5.4%); δ(250 MHz; $CDCl_3$) 4.15 (2 H, s, SCH_2), 7.05 (1 H, d, *J* 5.3), 7.25 (2 H, d, *J* 8.7), 7.7 (1 H, d, *J* 5.3), 7.95 (2 H, d, *J* 8.7) and 9.95 (1 H, s, CHO).

3-[(4-*Methoxycarbonyl*)*benzylsulfanyl*]*thiophene*-2-*carbaldehyde* **7c**. (60%); m.p. 117 °C (Found: C, 57.6; H, 4.3. $C_{14}H_{12}O_3S_2$ requires C, 57.5; H, 4.1%); δ(250 MHz; $CDCl_3$) 3.95 (3 H, s, CH_3), 4.2 (2 H, s, SCH_2), 7.1 (1 H, d, *J* 6), 7.35 (2 H, d, *J* 8.4), 7.7 (1 H, d, *J* 6), 8.05 (2 H, d, *J* 8.4) and 9.95 (1 H, s, CHO).

3-[(4-*Methylsulfonyl*)*benzylsulfanyl*]*thiophene*-2-*carbaldehyde* **7d**. (80%); m.p. 108 °C (Found: C, 49.8; H, 3.8. $C_{13}H_{12}O_3S_3$ requires C, 50.0; H, 3.8%); δ(250 MHz; $CDCl_3$) 3.05 (3 H, s, CH_3), 4.15 (2 H, s, SCH_2), 7.15 (1 H, d, *J* 5.2), 7.35 (2 H, d, *J* 8.5), 7.75 (1 H, d, *J* 5.2), 7.90 (2 H, d, *J* 8.5) and 10.0 (1 H, s, CHO).

3-[*Ethoxycarbonyl*(*phenyl*)*methyl*]*thiophene*-2-*carbaldehyde* **7e**. (45%); m.p. 86 °C (Found: C, 59.0; H, 4.7. $C_{15}H_{14}O_3S_2$ requires C, 58.8; H, 4.6%); δ(250 MHz; $CDCl_3$) 1.3 (3 H, t, CH_3), 4.15 (2 H, q, CH_2), 4.85 (1 H, s, SCH), 7.1 (1 H, d, *J* 5.1), 7.35 (5 H, m, Ar-H), 7.6 (1 H, d, *J* 5.1) and 9.90 (1 H, s, CHO).

2-*Arylthieno*[3,2-b]*thiophene* **1**.—Compound **7** (0.1 mol) was added to sodium ethoxide (0.1 mol) in ethanol and the mixtures refluxed for 1 h. The solvent was removed by distillation and the residue poured into water. The mixture was acidified and the precipitated solid was collected by filtration and purified by recrystallization.

2-(4-*Nitrophenyl*)*thieno*[3,2-b]*thiophene* **1a**. (60%); m.p. 218 °C (from MeOH) (Found: C, 55.4; H, 2.7; N, 5.1. $C_{12}H_7NO_2S_2$ requires C, 55.4; H, 2.7; N, 5.3%); δ(250 MHz; $CDCl_3$) 7.2 (1 H, d, *J* 5.2), 7.45 (1 H, d, *J* 5.2), 7.65 (1 H, s, Ar-H), 7.85 (2 H, d, *J* 8.6) and 8.25 (2 H, d, *J* 8.6).

2-(4-*Cyanophenyl*)*thieno*[3,2-b]*thiophene* **1b**. (50%); m.p. 208 °C (from MeOH) (Found: C, 64.85; H, 2.9; N, 5.7. $C_{13}H_7NS_2$ requires C, 64.7; H, 2.9; N, 5.8%); δ(250 MHz; $CDCl_3$) 7.25 (1 H, d, *J* 5.3), 7.45 (1 H, d, *J* 5.3), 7.6 (1 H, s, Ar-H), 7.65 (2 H, d, *J* 8.7) and 7.75 (2 H, d, *J* 8.7).

2-(4-*Methoxycarbonylphenyl*)*thieno*[3,2-b]*thiophene* **1c**. (40%); m.p. 212 °C (from MeOH) (Found: C, 61.5; H, 3.5. $C_{14}H_{10}O_2S_2$ requires C, 61.3; H, 3.6%); δ(250 MHz; $CDCl_3$) 3.95 (3 H, t, CH_3), 7.25 (1 H, d, *J* 6), 7.4 (1 H, d, *J* 6), 7.6 (1 H, s, Ar-H), 7.7 (2 H, d, *J* 8.4) and 8.05 (2 H, d, *J* 8.4).

2-(4-*Methylsulfonylphenyl*)*thieno*[3,2-b]*thiophene* **1d**. (59%); m.p. 232 °C (MeOH) (Found: C, 53.4; H, 3.4. $C_{13}H_{10}O_2S_3$ requires C, 53.2; H, 3.4%); δ(250 MHz; $CDCl_3$) 3.05 (3 H, s, CH_3), 7.25 (1 H, d, *J* 5.2), 7.45 (1 H, d, *J* 5.2), 7.65 (1 H, s, Ar-H), 7.8 (2 H, d, *J* 8.5) and 7.95 (2 H, d, *J* 8.5).

2-*Phenylthieno*[3,2-b]*thiophene* **1e**. Compound **1e** was synthesized by cyclisation and saponification of compound **7e** (0.1 mol) with aqueous sodium hydroxide (0.25 mol) in ethanol (200 cm^3). The mixture was refluxed for 2 h and then the solvent was removed and the residue was poured into water. The resulting mixture was acidified and extracted with diethyl ether. The organic extract was dried and the solvent was evaporated to leave a residue which was purified by chromatography on silica gel (cyclohexane) to give the title compound **1e** (57%); m.p. 168 °C (lit.,[15] 166 °C) (Found: C, 66.8; H, 3.8. $C_{12}H_8S_2$ requires C, 66.7; H, 3.7%); δ(250 MHz; $CDCl_3$) 7.25 (2 H, m, Ar-H), 7.4 (3 H, m, Ar-H), 7.5 (1 H, s, Ar-H) and 7.65 (2 H, m, Ar-H).

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