Preparation of 2,3-Disubstituted-4,5-dihydrothiophenes and Thiophenes Using the Intramolecular Non-classical Wittig Reaction of Thiolcarboxylates

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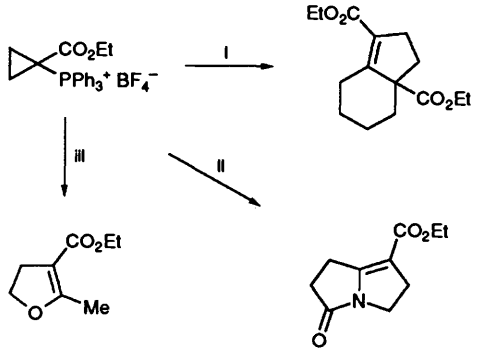
2-Ethoxycarbonylcyclopropyl(triphenyl)phosphonium fluoroborate **1** reacts with alkali-metal thiolates to give 2,3-disubstituted 4,5-dihydrothiophenes **3** which can be aromatised to the corresponding thiophenes **5**.

2-Ethoxycarbonylcyclopropyl(triphenyl)phosphonium fluoroborate **1** has previously been shown to be a useful reagent for intramolecular cyclisations with ketones,[1] esters[2] and imides;[3] the reactions proceed *via* nucleophilic opening of the cyclopropane ring to generate a stabilised phosphorane intermediate which then undergoes Wittig cyclisation (Scheme 1). In

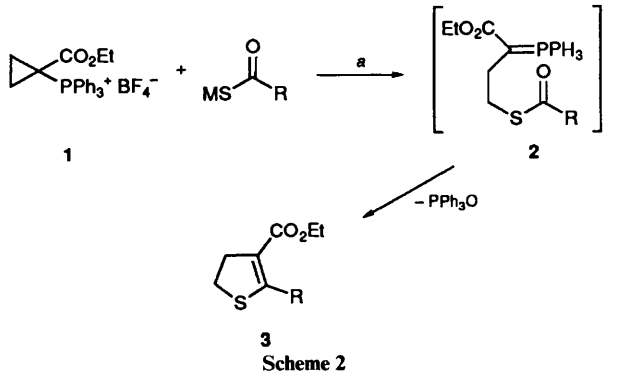


Scheme 1 i, Ethyl 2-oxocyclohexanecarboxylate NaH; ii, sodium succinimide; iii, sodium acetate

connection with work on approaches to thiospiroketals and synthetic applications of the non-classical Wittig reaction,[4] we were interested in this methodology as a potential route for the preparation of dihydrothiophenes; we report our preliminary findings herein.

Reaction of the phosphonium salt **1** with the alkali-metal salts of several *O*-thio-acids resulted in the formation of the intermediate phosphoranes **2a–i**, which cyclised under the conditions of the reaction to give dihydrothiophenes **3a–i** (Table 1) (Scheme 2). Several differing conditions were employed for the cyclisations, the choice being dictated by the availability of *O*-thioacids or their salts from commercial sources. Where they were available (entries 1 and 5, potassium *O*-thioacetate and potassium ethyl xanthate, respectively) it sufficed to merely heat **1** under reflux with an excess of the commercial material in THF to obtain a satisfactory yield of the dihydrothiophene **3**. When the *O*-thioacid is available the salt can be generated by treatment with potassium *tert*-butoxide and cyclisation takes the same course (entry 3). Where the *O*-thioacid is not available, a more convenient and higher yielding route is to generate the thiolate and the intermediate phosphorane *in situ* by simply combining equimolar amounts of the phosphonium salt **1**, sodium sulfide and the required acid chloride in a suitable solvent. This mixture under reflux generates the required product in good yield in the majority of cases.

The products were generally formed in high yield (65–95%), the best being those that were derived from simple n-alkyl or aryl *O*-thioacid salts (entries 1–4, 6, 7, 10). When an acid



Scheme 2

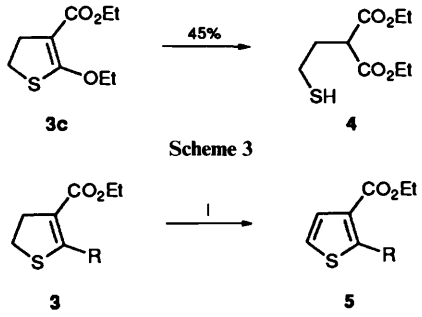
Table 1

Entry	Product	R	M	Method[a]	Time (h)	Yield (%)
1	**3a**	Me	K	A	72	65
2	**3a**	Me	Na	C	48	80
3	**3b**	Ph	K	B	72	88
4	**3b**	Ph	Na	C	48	98
5	**3c**	OEt	K	A	72	*b*
6	**3d**	Pr	Na	C	48	98
7	**3e**	Pr^i	Na	C	48[c]	82
8	**3f**	Bu^t	Na	C	48[d]	—
9	**3g**	2-Furyl	Na	C	48	74
10	**3h**	EtO_2C	Na	C	48	30

[a] Method A; **1** and potassium thiolate (1:3 ratio), THF, reflux. Method B; RCOSH, KOBu^t, then **1**, THF, reflux. Method C; **1**, Na_2S, RCOCl (1:1:1 ratio), THF, reflux. [b] See text. [c] Solvent exchanged for toluene. [d] Solvent exchanged for xylene.

chloride with a branched chain was used, for example isobutyryl chloride, used in the preparation of **3e** (entry 7), the reaction does not proceed in refluxing THF but required forcing conditions (toluene reflux). The use of trimethylacetyl chloride (entry 8) introduced further branching which had a detrimental effect on the outcome of the reaction since refluxing the intermediate phosphorane **3f** in toluene or xylene failed to effect cyclisation. A rationale for this result can obviously be made on steric grounds. It was further observed that when potassium ethyl xanthate (entry 5) was used it was obvious from ^1H NMR analysis of the crude reaction product that the reaction had proceeded in high yield. However, on attempted silica gel chromatography the product **3c** had hydrolysed to the acyclic malonate derivative **4** (Scheme 3). Although the reaction of ethyl oxalyl chloride was also problematic since extensive decomposition occurred under the reaction conditions, a 30% yield of **3h** was obtained.

These products have potential as intermediates in organic synthesis and one obvious transformation was to effect an



Scheme 4 *Reagent*: i, DDQ (see Table 2)

Table 2

Entry	Starting material	Product	R	Conditions[a] T/°C	Time(h)	Yield (%)
1	**3a**	**5a**	Me	40	2	58
2	**3b**	**5b**	Ph	40	5	62
3	**3d**	**5d**	Pr	40	8	68
4	**3e**	**5e**	Pr^i	40	2	67
5	**3g**	**5g**	2-Furyl	Room temp.	10 min	93

[a] CH_2Cl_2–DDQ (1.5–2.0 equiv.).

aromatisation of the dihydrothiophene ring to generate the corresponding thiophene **5** in high yield on treatment with an excess of DDQ in dichloromethane (Scheme 4, Table 2).

We have demonstrated a new and versatile preparation of 4,5-disubstituted dihydrothiophenes and thiophenes utilising the non-classical Wittig reaction and further applications of this reaction to the synthesis of thiospiroketals will be reported in due course.

Experimental

Column chromatography was carried out on Kieselgel (230–400 mesh) with the eluent specified in each case; all substances are oils unless otherwise stated. TLC was conducted on pre-coated Kieselgel 60 F254 (Art. 5554; Merck) glass plates. All reactions were conducted in oven-dried apparatus under a static atmosphere of argon. Light petroleum refers to the fraction boiling in the range 35–60 °C. Diethyl ether and THF were dried and distilled using standard methods. Chemical shifts are reported as δ values relative to tetramethylsilane as an internal standard; J values are given in Hz. ^1H and ^{13}C NMR spectra were recorded in deuteriochloroform on a Bruker AC250 spectrometer. IR were recorded as thin films (oils) or as a chloroform solution on a Perkin-Elmer 1600 series instrument. Mass spectra were recorded on a VG Masslab Model 12/253 spectrometer using CI (with ammonia as the reagent gas) or EI.

Method A.—2-Ethoxycarbonylcyclopropyl(triphenyl)phosphonium fluoroborate **1** (500 mg, 1.08 mmol) and the corresponding potassium thiolate (3 equiv.) were suspended in THF (5 cm^3) and the mixture heated at reflux in an inert atmosphere for the stated time (Table 1). The resulting suspension was evaporated to dryness, triturated with light petroleum–diethyl ether (4:1, 5 × 5 cm^3) and each triturate filtered through a short silica pad (2 cm). Evaporation and chromatography (solvent and R_f given) of the residue gave the required product.

Method B.—*O*-Thiobenzoic acid (239 mg, 0.23 cm^3, 1.73 mmol, 3.2 equiv.) and potassium *tert*-butoxide (198 mg, 1.62 mmol, 3 equiv.) were dissolved in THF (5 cm^3) and the solution stirred at room temperature for 30 min under nitrogen. 2-Ethoxycarbonylcyclopropyl(triphenyl)phosphonium fluoroborate **1** (250 mg, 0.541 mmol, 1 equiv.) was added to the resulting mixture which was then stirred at reflux for 24 h. The resulting suspension was filtered through a silica pad, which was washed with diethyl ether and the combined filtrates were rotary evaporated to dryness. The residue was triturated with light petroleum–diethyl ether (4:1; 5 × 5 cm^3) and each triturate filtered through a short silica pad (2 cm); evaporation of these and subsequent chromatography gave **3b** (111.7 mg, 88%) as an oil.

Method C.—2-Ethoxycarbonylcyclopropyl(triphenyl)phosphonium fluoroborate **1** (500 mg, 1.08 mmol) and sodium sulfide (84.3 mg, 1.08 mmol) were suspended in cooled (0 °C) THF (5 cm^3) and the mixture stirred for 30 min. The corresponding acid chloride (1.08 mmol) was then added dropwise to the reaction mixture over 5 min (microlitre syringe). After warming to room temperature (*ca.* 30 min) the mixture was heated at reflux under an inert atmosphere for the stated time (Table 1). The resulting suspension was evaporated to dryness and triturated with light petroleum–diethyl ether (4:1, 5 × 5 cm^3), each triturate being filtered through a short silica pad (2 cm). Evaporation and chromatography (solvent and R_f given) of the residue gave the required product.

Ethyl 2-methyl-4,5-dihydrothiophene-3-carboxylate **3a**. Chromatography in 10% diethyl ether in light petroleum, R_f 0.26; δ_H 1.27 (3 H, t, CH_3, J 7.0), 2.31 (3 H, t, CH_3, J 1.6), 3.13 (4 H, m, 2 × CH_2) and 4.17 (2 H, t, J 7.0, CH_2); δ_C 14.21 (CH_3), 16.27 (CH_3), 30.43 (CH_2), 36.76 (CH_2), 59.60 (CH_2), 120.03 (C), 156.68 (C) and 164.02 (C); ν_{max}/cm^{-1} 1698 (C=O) and 1604 (C=C); m/z (EI) 172 (M^+, 63%), 143 (M^+ − Et, 55%) and 127 (M^+ − EtO, 100%); m/z (CI) 173 (M^+ + H, 100%) [Found: m/z (HRMS) 172.0558. $C_8H_{12}O_2S$ (M^+) requires 172.0558].

Ethyl 2-phenyl-4,5-dihydrothiophene-3-carboxylate **3b**. Chromatography in 10% diethyl ether in light petroleum, R_f 0.32; δ_H 0.93 (3 H, t, CH_3, J 7.0), 3.20 (4 H, m, 2 × CH_2), 3.93 (2 H, q, J 7.0, CH_2) and 7.2–7.4 (5 H, m, Ph); δ_C 14.07 (CH_3), 32.13 (CH_2), 38.58 (CH_2), 60.09 (CH_2), 121.15 (C), 127.78 (2 × CH), 128.53 (2 × CH), 128.62 (CH), 134.27 (C), 156.98 (C) and 163.88 (C); ν_{max}/cm^{-1} 2728 (C–H), 1707 (C=O) and 1586 (C=C); m/z (EI) 234 (M^+, 27%), 189 (M^+ − OEt, 25%) and 160 (M^+ − HCO_2Et, 100%); m/z (CI) 235 (M^+ + H, 100%) [Found: m/z (HRMS) 234.0715. $C_{13}H_{14}O_2S$ (M^+) requires 234.0715].

Ethyl 2-ethoxy-4,5-dihydrothiophene-3-carboxylate **3c**. δ_H 1.25 (3 H, t, CH_3, J 7.1), 1.38 (3 H, t, CH_3, J 7.0), 2.98 (2 H, dt, J 8, 1.6, CH_2) 3.17 (2 H, dt, 8, 1.6, CH_2) and 4.16 (4 H, m, 2 × CH_2). This compound was unstable to chromatography and decomposed to give diethyl 2-sulfanylethylmalonate **4** (45% yield), R_f 0.23 (20% diethyl ether in light petroleum); δ_H 1.27 (6 H, t, 2 × CH_3, J 7.1), 1.40 (1 H, t, SH, J 8.4), 2.19 (2 H, app q, J 7.2, CH_2), 2.58 (2 H, app q, 7.9, CH_2), 3.60 (1 H, t, J 7.3, CH) and 4.21 (4 H, q, J 7.1, CH_2); δ_C 13.82 (CH_3), 20.08 (CH_2), 32.54 (CH_2), 50.13 (CH), 61.31 (CH_2) and 168.74 (C); ν_{max}/cm^{-1} 2980, 2936, 2872 (CH), 2574, (SH, weak) and 1735 (C=O); m/z (CI) 238 (M^+ + NH_4, 100%) and 221 (M^+ + H, 45%) [Found: m/z (HRMS): 221.0848. $C_9H_{17}O_4S$ (M^+ + H) requires 221.0848].

Ethyl 2-propyl-4,5-dihydrothiophene-3-carboxylate **3d**. Chromatography in 5% diethyl ether in light petroleum, R_f 0.25; δ_H 0.96 (3 H, t, CH_3, J 7.3), 1.28 (3 H, t, CH_3, J 7.1), 1.58 (2 H, app. septet, CH_2, J 7.7), 2.76 (2 H, t, CH_2, J 7.7), 3.12 (4 H, m, 2 × CH_2) and 4.17 (2 H, q, J 7.1, CH_2); δ_C 13.93 (CH_3), 14.37 (CH_3), 22.79 (CH_2), 30.40 (CH_2), 32.24 (CH_2), 37.15 (CH_2), 59.77 (CH_2), 119.86 (C), 162.48 (C) and 164.06 (C); ν_{max}/cm^{-1}

2960 (CH), 1698 (C=O) and 1595 (C=C); *m/z* (EI) 200 (M^+, 33%), 127 ($M^+ - CO_2Et$, 18%) and 71 (100%); *m/z* (CI) 201 ($M^+ + H$, 100%) [Found: *m/z* (HRMS) 200.0870. $C_{10}H_{16}O_2S$ (M^+) requires 200.0871].

Ethyl 2-isopropyl-4,5-dihydrothiophene-3-carboxylate **3e**. Chromatography in 5% diethyl ether in light petroleum R_f 0.35; δ_H 1.16 (3 H, d, CH_3, *J* 6.7), 1.30 (3 H, t, CH_3, *J* 7.1), 3.10 (4 H, 2 × CH_2), 3.92 (1 H, septet, *J* 6.7, CH) and 4.18 (2 H, q, *J* 7.1, CH_2); δ_C 14.32 (CH_3), 22.42 (2 × CH_3), 29.24 (CH), 29.78 (CH_2), 37.08 (CH_2), 59.70 (CH_2), 118.50 (C), 163.93 (C) and 169.97 (C); ν_{max}/cm^{-1} 2970 (C–H), 1699 (C=O) and 1587 (C=C); *m/z* (EI) 200 (M^+, 90%) and 171 ($M^+ - Et$, 25%); *m/z* (CI) 201 ($M^+ + H$, 100%) [Found: *m/z* (HRMS) 200.0871. $C_{10}H_{16}O_2S$ (M^+) requires 200.0871].

Ethyl 2-(2-furyl)-4,5-dihydrothiophene-3-carboxylate **3g**. Chromatography in 5% diethyl ether in light petroleum, R_f 0.20; δ_H 1.30 (3 H, t, *J* 7.1, CH_3), 3.27 (4 H, second order m, 2 × CH_2), 4.23 (2 H, q, *J* 7.1, CH_2), 6.50 (1 H, dd, *J* 1.7, 3.7, CH), 7.44 (1 H, d, *J* 3.7, CH) and 7.47 (1 H, d, *J* 1.7, CH); δ_C 14.29 (CH_3), 29.96 (CH_2), 38.76 (CH_2), 60.16 (CH_2), 112.01 (CH), 115.20 (CH), 118.54 (C), 143.39 (CH), 143.81 (C), 147.33 (C) and 163.61 (C); ν_{max}/cm^{-1} 1693 (C=O) and 1575 (C=C); *m/z* (EI) 224 (M^+, 100%), 179 ($M^+ - OEt$, 80%) and 151 ($M^+ - CO_2Et$, 70%) [Found: *m/z* (HRMS) 224.0507. $C_{11}H_{12}O_3S$ (M^+) requires 224.0507).

Diethyl 4,5-dihydrothiophene-2,3-dicarboxylate **3h**. Chromatography in 10% diethyl ether in light petroleum, R_f 0.23; δ_H 1.24 (3 H, t, CH_3, *J* 7.2), 1.31 (3 H, t, CH_3, *J* 7.2), 3.14 (2 H, app. dt, CH_2, *J* 1.0, 8.5), 3.35 (2 H, app. dt, CH_2, *J* 1.0, 8.5), 4.15 (2 H, q, CH_2, *J* 7.2) and 4.26 (2 H, q, *J* 7.2, CH_2); δ_C 13.97 (CH_3), 14.10 (CH_3), 32.62 (CH_2), 36.33 (CH_2), 60.88 (CH_2), 62.32 (CH_2), 127.23 (C), 144.91 (C), 162.39 (C) and 163.76 (C); ν_{max}/cm^{-1} 2983 (C–H), 1737 (C=O), 1706 (C=O) and 1604 (C=C); *m/z* (EI) 230 (M^+, 50%), 156 ($M^+ - HCO_2Et$, 90%) and 46 (100%); *m/z* (CI) 231 ($M^+ + H$, 100%) [Found: *m/z* (HRMS) 230.0613. $C_{10}H_{14}O_4S$ (M^+), requires 230.0613).

General Conditions for Aromatisation of 4,5-Dihydrothiophenes.—The dihydrothiophene **3** (0.5–1 mmol) was dissolved in dichloromethane (5 cm^3) and an excess (1.5–2.0 equiv.) of 2,3-dichloro-4,5-dicyanoquinone (DDQ) was added in one portion to the solution. The reaction mixture was stirred at the required temperature for the time given (see Table 2), whereupon silica (1–2 g), was added to it. The reaction mixture was then evaporated to dryness under reduced pressure and chromatography (diethyl ether–light petroleum, dry loading of column) of the residue gave the thiophenes **5**.

Ethyl 2-methylthiophene-3-carboxylate **5a**. Chromatography in 10% diethyl ether in light petroleum, R_f 0.7; δ_H 1.34 (3 H, t, *J* 7.1, CH_3), 2.71 (3 H, s, CH_3), 4.28 (2 H, q, *J* 7.1, CH_2), 6.94 (1 H, d, *J* 5.4, CH) and 7.36 (1 H, d, *J* 5.4, CH); δ_C 14.35 (CH_3), 15.38 (CH_3), 60.17 (CH_2), 120.82 (CH), 128.42 (C), 129.25 (CH), 149.11 (C) and 163.68 (C); ν_{max}/cm^{-1} 2780 (CH) and 1713 (C=O); *m/z* (EI) 170 (M^+, 45%), 142 ($M^+ - C_2H_4$, 70%) and 126 (100%); *m/z* (CI) 188 ($M^+ + NH_4$, 40%) and 171 ($M^+ + H$, 100%) [Found: *m/z* (HRMS) 170.0400. $C_8H_{10}O_2S$ (M^+) requires 170.0402].

Ethyl 2-phenylthiophene-3-carboxylate **5b**. Chromatography in 5% diethyl ether in light petroleum, R_f 0.4; δ_H 1.22 (3 H, t, *J* 7.1, CH_3), 4.23 (2 H, q, *J* 7.1, CH_2), 7.27 (1 H, d, *J* 4.5, CH) and 7.28–7.57 (6 H, m, 6 × CH); δ_C 13.97 (CH_3), 60.43 (CH_2), 123.97 (CH), 127.84 (2 × CH), 128.36 (C), 128.45 (CH), 129.83 (2 × CH), 129.92 (CH), 138.44 (C), 150.76 (C) and 163.32 (C); ν_{max}/cm^{-1} 1718 (C=O); *m/z* (EI) 232 (M^+, 53%) and 187 ($M^+ - OC_2H_5$, 100%); *m/z* (CI) 250 ($M^+ + NH_4$, 45%) and 233 ($M^+ + H$, 100%) [Found: *m/z* (HRMS) 232.0558. $C_{13}H_{12}O_2S$ (M^+) requires 232.0558].

Ethyl 2-propylthiophene-3-carboxylate **5d**. Chromatography in 7% diethyl ether in light petroleum, R_f 0.7; δ_H 1.03 (3 H, t, *J* 7.4, CH_3), 1.39 (3 H, t, *J* 7.1, CH_3) 1.75 (2 H, app. hextet, *J* 7.4, CH_2), 3.19 (2 H, t, *J* 7.4, CH_2), 4.33 (2 H, q, *J* 7.1, CH_2), 7.03 (1 H, d, *J* 5.3, CH) and 7.42 (1 H, d, *J* 5.3, CH); δ_C 13.65 (CH_3), 14.12 (CH_3), 24.62 (CH_2), 31.20 (CH_3), 59.97 (CH_2), 120.83 (CH), 127.62 (C), 129.08 (CH), 154.85 (C) and 163.36 (C) ν_{max}/cm^{-1} (IR) 2963 (CH) and 1713 (C=O); *m/z* (EI); 198 (M^+, 80%), 169 ($M^+ - C_2H_5$, 65%) and 141 (100%); *m/z* (CI) 216 ($M^+ + NH_4$, 35%) and 199 ($M^+ + H$, 100%) [Found: *m/z* (HRMS) 198.0715. $C_{10}H_{14}O_2S$ (M^+) requires 198.0715].

Ethyl 2-isopropylthiophene-3-carboxylate **5e**. Chromatography in 5% diethyl ether in light petroleum, R_f 0.67; δ_H 1.36 (9 H, m, 3 × CH_3), 4.16 (1 H, septet, *J* 6.8, CH_2), 4.33 (2 H, q, *J* 7.1, CH_2), 7.05 (1 H, d, *J* 5.4, CH) and 7.41 (1 H, d, *J* 5.4, CH); δ_C 14.31 (CH_3), 24.81 (2 × CH_3), 29.01 (CH_2), 60.16 (CH_2), 120.67 (CH), 126.88 (C), 129.18 (CH), 163.27 (C) and 163.45 (C); ν_{max}/cm^{-1} 2968, 2869 (CH) and 1712 (C=O); *m/z* (EI) 198 (M^+, 30%), 169 ($M^+ - C_2H_5$, 20%) and 153 ($M^+ - OC_2H_5$, 100%); *m/z* (CI) 216 ($M^+ + NH_4$, 50%) and 199 ($M^+ + H$, 100%) [Found: *m/z* (HRMS) 198.0715. $C_{10}H_{14}O_2S$ (M^+) requires 198.0715].

Ethyl 2-(2-furyl)thiophene-3-carboxylate **5g**. Chromatography in 2% diethyl ether in light petroleum, R_f 0.44; δ_H 1.38 (3 H, t, *J* 7.1, CH_3), 4.36 (2 H, q, *J* 7.1, CH_2), 6.54 (1 H, dd, *J* 1.8, 3.5, CH), 7.19 (1 H, d, *J* 5.4, CH), 7.40 (1 H, dd, *J* 0.5, 3.5, CH) and 7.48 (2 H, m, 2 × CH); δ_C 14.33 (CH_3), 60.67 (CH_2), 111.96 (CH), 112.24 (CH), 123.20 (CH), 126.19 (C), 130.29 (CH), 139.81 (C), 142.66 (CH), 147.58 (C) and 163.05 (C); ν_{max}/cm^{-1} 2980, 2933 (CH) and 1714 (C=O); *m/z* (EI) 222 (M^+, 100%) and 177 ($M^+ - OC_2H_5$, 70%); *m/z* (CI) 223 ($M^+ + H$, 100%) [Found: *m/z* (HRMS) 222.0351. $C_{11}H_{10}O_3S$ (M^+) requires 222.0351].

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