A New and Simple Route to 3-Arylthiophenes[1)]

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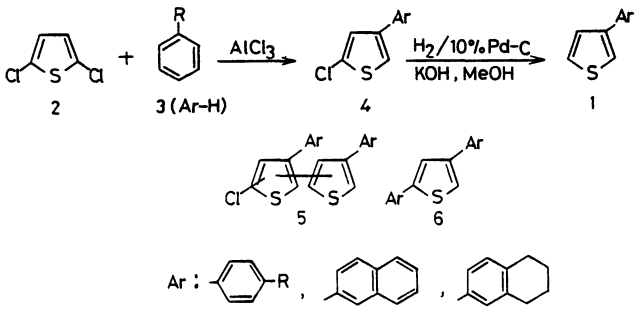
Synopsis. 3-Arylthiophenes were prepared from 2,5-dichlorothiophene in two steps. 2,5-Dichlorothiophene reacted regioselectively with various aromatic compounds in the presence of $AlCl_3$ under mild conditions to give 4-aryl-2-chlorothiophenes. The latter compounds were easily converted to the corresponding 3-arylthiophenes by catalytic dechlorination in good yields.

Electrophilic substitutions of thiophene occur predominantly at the 2-position, making access to 3-substituted thiophenes rather troublesome.[2)] This is also the case with 3-arylthiophenes (**1**), one of the thiophene analogues of biphenyls; thus, it has been desired to find a general method for the preparation of **1**.[3)] Certain 3-substituted thiophenes,[3,4)] including **1** as well as the parent thiophene, have recently attracted attention in connection with the potential electric conductivity and their electrochromic property of their electrochemically prepared polymers. We wish to report here on a new and simple route to **1**.

It has been assumed that the chlorine atom(s) of chlorothiophenes is generally unreactive under Friedel-Crafts conditions, as is true for those of aryl chlorides. However, Ramsey et al. have reported that chlorothiophenes undergo polymerization by $AlCl_3$-$CuCl_2$ through a nuclear coupling with the elimination of HCl.[5)] Recently, we have also reported that, in the presence of $AlCl_3$, 2-chlorothiophene reacts with active aromatic compounds, giving the corresponding 2-arylthiophenes.[6)] Furthermore, we have observed an unusual $AlCl_3$-catalyzed Friedel-Crafts reaction of 2,5-dichloro-3-chloromethylthiophene with benzene and its simple alkyl derivatives, which yield 4-aryl-3-arylmethyl-2-chlorothiophenes, exclusively.[7)] In an extension of our studies, we found that under similar conditions 2,5-dichlorothiophene (**2**) reacted regioselectively with various aromatic compounds (**3**) to afford the unusual products, 4-aryl-2-chlorothiophenes (**4**). Early studies suggest that chlorine atom(s) in chlorothiophenes can be removed only with difficulty.[8,9)] However, contrary to expectation, **4** were found to be successfully dechlorinated by catalytic hydrogenation. Thus, the $AlCl_3$-catalyzed reaction provides a two-step synthesis (three-step from thiophene) of **1** from readily available **2** (Scheme 1).



Scheme 1.

The procedure of the $AlCl_3$-catalyzed reaction is simple: one mole equiv of $AlCl_3$ was added to an equimolar mixture of **2** and **3** in CH_2Cl_2 under ice-cooling, and the mixture stirred below 40 °C for a total of 2 h. The results are summarized in Table 1. As shown in the Table, the reaction yielded the corresponding **4** as the major products in good yield, except for a reaction with chlorobenzene (**3f**), which yielded an inseparable mixture of 2,5-dichlorothiophene oligomers. In many cases, the presence of isomers due to the position of the substituent(s) on the aromatic ring, diarylthiophenes (**6**), and self-condensation products (**5**) which were derived from two moles of **4** with the elimination of HCl, were also suggested in the products (MS, UV, NMR). The corresponding 2-

Table 1. $AlCl_3$-Catalyzed Reaction of 2,5-Dichlorothiophene (**2**) with Aromatic Compounds (**3**)

Ar-H **3**	**4**	
	% Yield[a)]	Mp(θ_m/°C)
a R=H	62	74—75
b R=Me	54 (72)	117—118
c R=Et	66 (71)	97—98
d R=1,3-Me_2	63[b)]	bp 95—97/2 mmHg
e R=OMe	34[c)] (40)	126—127
f R=Cl	(5)	
g tetralin	63[d)]	49—50
h naphthalene	52[e)] (60)	114—15

a) Yields of the purified products based on **2** used; figures in parentheses are those of the crude products which contain the positional isomers. b) 2-Chloro-4-(2,4-dimethylphenyl)thiophene. c) Chlorobis(*p*-methoxyphenyl)bithienyl (**5e**; mp 103—104 °C, 17%) and 2,4-bis(*p*-methoxyphenyl)thiophene (**6e**; 4%) were also isolated. d) 2-Chloro-4-(5,6,7,8-tetrahydro-2-naphthyl)thiophene. e) 2-Chloro-4-(2-naphthyl)-thiophene.

Table 2. Catalytic Dechlorination of 4-Aryl-2-chlorothiophenes (**4**)

4 Ar	**1**	
	% Yield[a)]	Mp(θ_m/°C) (lit)
a R=H	85	93—94 (91—92,[17)] 89—91[15)])
b R=Me	83	112—113 (111—112,[17)] 113—113.5[15)])
c R=Et	80	96—97
d R=2,4-Me_2	68	bp 78—80/2 mmHg
e R=OMe	86	126—127 (129,[17)] 127[3)])
h 2-Naph[b)]	70	145—146 (145.5—146.5[15)])

a) Yields of the purified products based on **4** used. b) Naph: naphthyl.

arylthiophene derivatives, such as 2-aryl-5-chlorothiophenes, which might be expected, were not detected in the products. Interestingly, while naphthalene (**3h**) produced a mixture of the 1- and 2-naphthyl derivatives (**4h**; main product), tetralin (**3g**) yielded 2-chloro-4-(5,6,7,8-tetrahydro-2-naphthyl)thiophene (**4g**).

The structures of **4** were assigned on the basis of their elemental analyses and spectral data. The UV spectra excluded the presence of the 2-arylthiophene unit in the structures; instead, it suggested the presence of the 3-arylthiophene unit.[10] The NMR spectra showed, in addition to the absorption due to the aromatic ring protons, an AB quartet with a coupling of 1.25—1.70 Hz, characteristic for 2,4-disubstituted thiophenes[11] in the ring proton region. Further, the structure assignment of **4** was confirmed by chemical evidence. The reductive desulfurization of **4e** by Raney nickel, for example, gave *p-s*-butylanisole. Treatment of **4g** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave **4h**, which afforded 3-(2-naphthyl)-thiophene (**1h**) by dechlorination; this indicates that 2-naphthyl and the tetrahydro-2-naphthyl moieties are included in the molecules of **4h** and **4g**, respectively. When the reaction was conducted at −50 °C between **3** and the protonated **2**[12] which was prepared at the same temperature in advance, **4** were produced in somewhat higher yield. The reaction using $SnCl_4$ instead of $AlCl_3$ gave no products under the conditions studied.

The catalytic hydrogenation of **4** under atmospheric pressure using 10% Pd-C as a catalyst gave the corresponding **1** in satisfactory yield, as shown in Table 2.

The obtained results indicate that protonated **2** serves as electrophilic species in the $AlCl_3$-catalyzed reaction. An NMR spectroscopic method revealed that, in an $AlCl_3$-HCl-CH_2Cl_2 system at low temperature, **2** produced 2*H*-2,5-dichlorothiophenium ion.[12] However, the entire reaction pathway still remains unclear.

Finally, considering that the electrophilic substitutions of **1** occur in the 5-position as well as in the 2-position,[13] **4** could also be versatile intermediates for the selective syntheses of certain isomer-free 2-substituted 3-arylthiophenes. Namely, the introduction of an appropriate group into the vacant α-position of **4**, followed by a subsequent dechlorination would yield 2-substituted 3-arylthiophenes, the chlorine atom of **4** serving as a blocking group.

Experimental

All the melting and boiling points are uncorrected. The ^1H NMR (90 MHz, TMS as an internal reference), UV (in MeOH, unless otherwise noted), IR, and MS (70 eV) spectra were obtained on Hitachi R-22, Hitachi EPU-2A, Hitachi EPI-S2, and Hitachi RMU spectrometers, respectively.

2,5-Dichlorothiophene (**2**) was prepared by a method described in the literature.[14] Commercial $AlCl_3$ was used without special precautions against moisture.

$AlCl_3$-Catalyzed Reaction of 2,5-Dichlorothiophene (2) with Aromatic Compounds (3) (General Procedure). Pulverized $AlCl_3$ (20 mmol) was added in portions over ca. 5-min period to a mixture of **2** (20 mmol) and the substrate (**3**, 60 mmol) in CH_2Cl_2 (10 ml; 20 ml in the case of naphthalene) under ice-cooling. Exothermic reactions occurred with the appearance of a coloration and the rise of the temperature of the reaction mixture. The mixture was stirred at ca. 5 °C for 30 min, then at ambient temperature for 1 h, and at the reflux temperature of the solvent for an additional 30 min. The reaction mixture was poured into ice-water (ca. 70 ml) and extracted with $CHCl_3$ (10 ml×3). The extracts were combined, washed successively with water, 5% $NaHCO_3$ solution, and water, and dried. After removal of the solvent and the starting substances by distillation, the residue was sublimed under reduced pressure (2—3 mmHg (1 mmHg= 133.322 Pa)) yielding crude 4-aryl-2-chlorothiophene (**4**) which was contaminated with a small amount of the positional isomer. Chromatography (silica gel/hexane) of the residue of the sublimation gave another crop of **4**. The crude **4** was purified by recrystallization (hexane) or distillation. In the case of naphthalene (**3h**), the reaction mixture, after removal of the solvent, was sublimed under reduced pressure (7 mmHg) to recover **3h**, and the residue was directly chromatographed.

The minor products were not investigated further, except for those produced in the reaction of **2** with anisole (**3e**).

4a: MS *m/z* 194 (M^+, 100). UV λ_{max} 232 (4.25), 261 (3.95). ^1H NMR ($CDCl_3$) δ=7.1—7.6 (m, Ph+Th (thiophene; 3-H, 5-H)). Anal. ($C_{10}H_7ClS$) C, H.

4b: MS *m/z* 208 (M^+, 100). UV λ_{max} 235 (4.27), 267 (3.90). ^1H NMR (acetone-d_6) δ=2.29 (3H, s, CH_3), 7.17 and 7.26 (2H, AA'BB'm, *p*-Ph (*p*-substituted phenyl)), 7.41 and 7.51 (1H, d, $J_{3,5}$=1.6 Hz each, Th (3-H, 5-H)), 7.50 and 7.59 (2H, AA'BB'm, *p*-Ph). Anal. ($C_{11}H_9ClS$) C, H.

4c: MS *m/z* 222 (M^+, 100). UV λ_{max} 235 (4.36), 265 (4.06). ^1H NMR (acetone-d_6) δ=1.16 (3H, t, $J_{CH_2\text{-}CH_3}$=7.1 Hz, $CH_2\underline{CH_3}$), 2.62 (2H, q, $J_{CH_2\text{-}CH_3}$=7.1 Hz, $C\underline{H_2}CH_3$), 7.18 and 7.27 (2H, AA'BB'm, *p*-Ph), 7.39 and 7.49 (1H, d, $J_{3,5}$=1.6 Hz each, Th (3-H, 5-H)), 7.50 and 7.59 (2H, AA'BB'm, *p*-Ph). Anal. ($C_{12}H_{11}ClS$) C, H.

4d: MS *m/z* 222 (M^+, 100). UV λ_{max} 233 (4.28), 256sh (3.91). ^1H NMR (CCl_4) δ=2.22 and 2.25 (3H, s each, Me), 6.78 and 6.85 (d, $J_{3,5}$=1.3 Hz each, Th (3-H, 5-H)), 6.7—7.4 (5H, m, Ph+Th (3-H, 5-H)). Anal. ($C_{12}H_{11}ClS$) C, H.

4f: MS *m/z* 232 (M^++4, 14), 230 (M^++2, 69), 228 (M^+, 100).

4g: MS *m/z* 248 (M^+, 100). UV λ_{max} 236 (4.37), 267 (4.04). ^1H NMR ($CDCl_3$) δ=1.6—1.9 (4H, m, $PhCH_2\text{-}C\underline{H_2}\text{-}$), 2.78 (4H, br s, $Ph\text{-}C\underline{H_2}\text{-}CH_2\text{-}$), 6.9—7.3 (5H, m, Ph+Th (3-H, 5-H)). Anal. ($C_{14}H_{13}ClS$) C, H.

4h: MS *m/z* 244 (M^+, 100). UV λ_{max} 230 sh (4.63), 238 (4.75), 247 sh (4.66), 257sh (4.43), 265 sh (4.30), 281 (4.06), 290 (4.14), 302 (4.08). ^1H NMR ($CDCl_3$) δ= 7.1—8.0 (m, Naph+Th (3-H, 5-H; two doublets at 7.27 and 7.33 ($J_{3,5}$=1.7 Hz each)). Anal. ($C_{14}H_9ClS$) C, H.

Reaction with Anisole (3e). Chromatography (silica gel/hexane-benzene (1 : 1)) of the residue of the sublimation afforded the second crop of **4e** and the self-condensation product (**5e**; 0.7 g, mp 103—104 °C after crystallization from MeOH-acetone). The combined **4e** was recrystallized from EtOH. When the reaction mixture was poured into ice-water, a small amount of precipitate was separated out, which was recrystallized from *N,N*-dimethylformamide to give 2,4-bis(*p*-methoxyphenyl)thiophene (**6e**; 0.2 g, mp 220—221 °C (lit,[6] 219—221 °C).

4e: MS *m/z* 224 (M^+, 100). UV λ_{max} 242 (4.31), 273 (4.15). ^1H NMR ($CDCl_3$) δ= 3.81 (3H, s, OMe), 6.85 and 6.95 (2H, AA'BB'm, *p*-Ph), 7.05 and 7.15 (1H, d, $J_{3,5}$=1.6 Hz each, Th (3-H, 5-H)), 7.38 and 7.47 (2H, AA'BB'm, *p*-Ph). Anal. ($C_{11}H_9ClOS$) C, H.

5e: MS *m/z* 412 (M^+, 100). UV λ_{max} 245sh (4.40), 254 (4.43), 273 (4.42), 318—331 (3.89). ^1H NMR (acetone-d_6) δ= 3.79 (6H, s, OMe), 6.89 and 6.98 (4H, AA'BB'm, *p*-Ph), 7.05 (1H, s, Th), 7.2—7.7 (6H, m, *p*-Ph+Th). Anal. ($C_{22}H_{17}ClO_2S_2$) C, H.

Catalytic Dechlorination of 4-Aryl-2-chlorothiophenes (4). The procedure is a modification of the one used by Zwanenberg et al.[9] Hydrogenation was conducted by stirring a mixture of **4** (5 mmol), KOH (1.5 g), 10% Pd-C (0.7 g), and MeOH (100 ml) at room temperature in an atmospheric pressure hydrogenation apparatus filled with H_2. Within 1 h one equivalent of H_2 was consumed. After removal of the catalyst the solution was concentrated to ca. 30 ml. Water was added to the residue and the resulting crystalline mass was purified by sublimation under reduce pressure and/or recrystallization.

1a: MS *m/z* 160 (M^+, 100). UV λ_{max} 227 (4.15), 258 (4.14) (lit,[15] (96% EtOH) 227 (4.11), 259 (4.08)). ^{1}H NMR ($CDCl_3$) δ=7.1—7.8 (m, Ph+Th).

1b: MS *m/z* 174 (M^+, 100). UV λ_{max} 227 (4.27), 260 (4.23) (lit,[15] (96% EtOH) 228 (4.17), 261 (4.17)). ^{1}H NMR ($CDCl_3$) δ=2.35 (3H, s, Me), 7.13 and 7.22 (2H, AA'BB'm, *p*-Ph), 7.35 (3H, s, Th), 7.43—7.52 (2H, AA'BB'm, *p*-Ph).

1c: MS *m/z* 188 (M^+, 100). UV λ_{max} 228 (4.20), 262 (4.21). ^{1}H NMR ($CDCl_3$) δ=1.24 (3H, t, $J_{CH_2\text{-}CH_3}$=7.6 Hz, CH_2-$C\underline{H}_3$), 2.66 (2H, q, $J_{CH_2\text{-}CH_3}$=7.6 Hz, $C\underline{H}_2$-CH_3), 7.16 and 7.24 (2H, AA'BB'm, *p*-Ph), 7.35 (3H, s, Th), 7.45 and 7.54 (2H, AA'BB'm, *p*-Ph). Anal. ($C_{12}H_{12}S$) C, H.

1d: MS *m/z* 188 (M^+, 100). UV λ_{max} 227 sh (4.17), 248 (4.01). ^{1}H NMR ($CDCl_3$) δ=2.29 and 2.33 (3H, s each, Me), 6.9—7.4 (6H, m, Ph+Th). Anal. ($C_{12}H_{12}S$) C, H.

1e: MS *m/z* 190 (M^+, 100). UV λ_{max} 230 (4.11), 269 (4.21). ^{1}H NMR ($CDCl_3$) δ=3.81 (3H, s, -OMe), 6.85 and 6.95 (2H, AA'BB'm, *p*-Ph), 7.2—7.35 (3H, m, Th), 7.45 and 7.54 (2H, AA'BB'm, *p*-Ph).

1h: MS *m/z* 210 (M^+, 100). UV λ_{max} 226 (4.58), 244 (4.51), 252 (4.53), 280 (4.05), 290 (4.13), 301 (4.05) (lit,[15] (96% EtOH) 228 (4.59), 254 (4.57), 279 (4.11), 290 (4.16), 301 (4.08)). ^{1}H NMR ($CDCl_3$) δ=7.15—8.1 (m, Naph+Th).

Dehydrogenation of 4g. A mixture of **4g** (1.24 g, 5 mmol) and DDQ (2.27 g, 10 mmol) in benzene (30 ml) was stirred for 8 h at the reflux temperature of the solvent. After removal of the solvent by distillation, the residue was chromatographed (silica gel/hexane) to afford **4h** (mp 114—115 °C, 1.1 g, 90%).

Reductive Desulfurization of 4e with Raney Nickel. A mixture of 2-chloro-4-(*p*-methoxyphenyl)thiophene (**4e**; 1 g, 4.5 mmol) and W-7 Raney nickel (prepared from 10 g of the alloy) in benzene (100 ml) was stirred at the reflux temperature of the solvent for 20 h. The reaction mixture was filtered and the nickel was extracted with hot benzene for several hours in a Soxhlet extractor. The filtrate and the extract were combined and evaporated. The residue (0.6 g) were chromatographed (silica gel/hexane-chloroform (4:1) to give *p-s*-butylanisole (oil; 0.12 g, 17%) and 3-(*p*-methoxyphenyl)thiophene (**1e**; mp 123—125 °C; 0.09 g, 10%). The IR and NMR spectra of the oily product was identical with those of the authentic sample (bp 109—112 °C (16 mmHg); lit,[16] 106—108 °C (16 mmHg)) which was obtained by the methylation of *p-s*-butylphenol with dimethyl sulfate in basic solution.

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