Liquid Crystals
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713926090

Regioselective synthesis of 2,4-disubstituted thiophenes

Eun Kyong Kim[a]; Kyung Uk Lee[a]; Bo Young Cho[a]; Yong Bae Kim[b]; Kyung-Tae Kang[a]
[a] Department of Chemistry and Chemistry Institute for Functional Materials, Pusan National University, Pusan 609-735, Korea, [b] Liquid Crystal Research Center and Department of Chemistry, Konkuk University, Seoul 143-701, Korea,

Online publication date: 06 August 2010

To cite this Article Kim, Eun Kyong , Lee, Kyung Uk , Cho, Bo Young , Kim, Yong Bae and Kang, Kyung-Tae(2001) 'Regioselective synthesis of 2,4-disubstituted thiophenes', Liquid Crystals, 28: 3, 339 — 345
To link to this Article: DOI: 10.1080/02678290010011599
URL: http://dx.doi.org/10.1080/02678290010011599

LIQUID CRYSTALS, 2001, VOL. 28, NO. 3, 339–345

Regioselective synthesis of 2,4-disubstituted thiophenes

EUN KYONG KIM, KYUNG UK LEE, BO YOUNG CHO,
YONG BAE KIM† and KYUNG-TAE KANG*

Department of Chemistry and Chemistry Institute for Functional Materials,
Pusan National University, Pusan 609-735, Korea
†Liquid Crystal Research Center and Department of Chemistry,
Konkuk University, Seoul 143-701, Korea

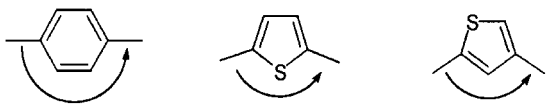
(*Received 4 May 2000; in final form 25 August 2000; accepted 30 August 2000*)

A highly regioselective route was established to 2-aryl-, 2-cyclohexyl-, and 2-(2-arylethyl)-4-alkylthiophenes, which are potential candidates as liquid crystalline compounds of low viscosity. The key synthetic intermediates, 2-substituted-4-(chloromethyl)thiophenes **6**, **14**, and **20** were prepared respectively from the reactions of β,γ-epoxycarbonyl compounds **5**, **13**, and **19** with Lawesson's reagent in the presence of a catalytic amount of *p*-toluenesulfonic acid. The epoxycarbonyl compounds were obtained from the $TiCl_4$-mediated reactions of 2-(chloromethyl)-3-(trimethylsliyl)propene (**10**) with acid chlorides followed by epoxidation with *m*-chloroperoxybenzoic acid, or from prior epoxidation followed by oxidation with pyridinium dichromate of homoallylic alcohols **3**. The homoallylic alcohols **3** were synthesized from the reactions of 2-(chloromethyl)-3-(trichlorosilyl)propene (**2**) with aldehydes in *N*,*N*-dimethylformamide. Copper(I) catalysed cross-coupling reactions of 2-substituted-4-(bromomethyl)thiophenes (which were prepared by transhalogenation of 2-substituted-4-(chloromethyl)thiophenes with NaBr in acetone) with Grignard reagents afforded 2,4-disubstituted thiophenes. Using this method, eleven 2,4-disubstituted thiophenes were synthesized and their potentials as liquid crystalline compound of low viscosity were examined. The synthesized 2-(4-cyanophenyl)-4-pentylthiophene was observed to have a lower melting point than the corresponding 2,5-disubstituted thiophene. This observation is consistent with the expectation from the basis of molecular linearity which can affect the viscosity and/or melting point of crystalline compounds.

1. Introduction

The influences of thiophene ring systems on mesomorphic behaviour have been studied in recent years [1]. The substitution of a 2,5-disubstituted thiophene ring in place of a 1,4-disubstituted phenyl ring in the rigid core of a molecule results in a lowering of the melting point and mesophase transition temperature [1*d*]. This is explained in terms of the geometric differences in linearity of 2,5-disubstituted thiophenes.

Being deviated more from linearity than 2,5-disubstituted thiophenes (core angle, 148°), the 2,4-disubstituted thiophenes (core angle, 141°) [2] are expected to have lower melting points and viscosity.



$\gamma = 180^\circ$ $\gamma = 148^\circ$ $\gamma = 141^\circ$

*Author for correspondence;
e-mail: kytkang@hyowon.cc.pusan.ac.kr

Recently, we found an efficient and regioselective method for the synthesis of various substituted thiophenes by using properly designed allylsilanes [3]; the strategy allowed the synthesis of variously substituted 2-aryl-4-alkylthiophenes. In order to produce liquid crystal materials with low melting points and low viscosities, we prepared new 2,4-disubstituted thiophenes having dimethylene or cyclohexyl linking groups between a thiophene and a phenyl ring. Furthermore, we prepared 2-(4-cyanophenyl)-4-alkylthiophenes and compared their properties with the properties of the corresponding 2,5-disubstituted derivatives.

2. Experimental

^{1}H NMR spectra were recorded on a Varian Gemini-200 (200 MHz) spectrometer using chloroform as an internal standard. ^{13}C NMR spectra were obtained on a Varian Gemini-200 spectrometer with $CDCl_3$ as the solvent and internal reference. High-resolution mass spectra were obtained with a JEOL JMX-SX 102 mass spectrometer employing perfluorokerosene as internal standard. All mass spectra were generated using a 70 eV

Liquid Crystals ISSN 0267-8292 print/ISSN 1366-5855 online © 2001 Taylor & Francis Ltd
http://www.tandf.co.uk/journals
DOI: 10.1080/02678290010011599

ionization potential. Phase transition temperatures were determined by differential scanning calorimetry (Setaram, TG/DTA 1600).

The identities of reagents, intermediates and final products are indicated in the reaction schemes.

2.1. *Preparation of homoallylic alcohols **3** by the allylation of aldehydes with allyltrichlorosilane **2** in DMF*

A mixture of 4-fluorobenzaldehyde (**1a**, 3.7 g, 30 mmol) and 2-chloromethyl-3-(trichlorosilyl)propene (**2,** 8.0 g, 36 mmol) in *N*,*N*-dimethylformamide (DMF, 40 ml) was stirred at 0°C for 1 h. The reaction was quenched with 1N NaOH (100 ml) and the aqueous layer was extracted with ether (30 ml × 3). The ether layer was washed with brine, dried over Na_2SO_4, and concentrated to give 6.3 g (98%) of the crude homoallylic alcohol **3a**. ^{1}H NMR spectral data of **3a**: δ 1.88 (br s, 1H, OH), 2.55–2.61 (m, 2H, $C\underline{H_2}CHOH$), 4.07 (s, 2H, CH_2Cl), 4.88 (dd, 1H, J = 8.2, 5.0 Hz, $CH_2C\underline{H}OH$), 5.09 (s, 1H, vinyl), 5.28 (s, 1H, vinyl), 7.01–7.08, 7.30–7.39 (m, 4H, C_6H_4).

2.2. *Preparation of β,γ-epoxycarbonyl compounds **5** by the oxidation of homoallylic alcohols **3** with MCPBA and PDC*

m-Chloroperoxybenzoic acid (MCPBA, 50%, 15.5 g, 90 mmol) was added to a dichloromethane (50 ml) solution of crude **3a** (6.3 g, 29 mmol) and stirred for 20 h at room temperature. The mixture was washed with saturated aq $NaHCO_3$ solution, and the aqueous solution was extracted with dichloromethane (30 ml × 2). The organic extracts were dried (Na_2SO_4), evaporated to give the crude hydroxy epoxide **4a** (6.5 g, 96%). ^{1}H NMR spectral data of **4a**: δ 2.14–2.27 (m, 2H, $C\underline{H_2}CHOH$), 2.77 (d, 1H, J = 4.2 Hz, oxiran CH_2), 2.98 (d, 1H, J = 4.2 Hz, oxiran CH_2), 3.23 (br s, 1H, OH), 3.52 (d, 1H, J = 11.8 Hz, CH_2Cl), 3.65 (d, 1H, J = 11.8 Hz, CH_2Cl), 4.79 (dd, 1H, J = 9.8, 3.0 Hz, $CH_2C\underline{H}OH$), 6.96–7.10, 7.26–7.41 (m, 4H, C_6H_4).

Pyridinium dichromate (PDC, 17.0 g, 45 mmol) was added to a dichloromethane (50 ml) solution of the crude product **4a** (6.5 g, 28 mmol). The mixture was stirred at room temperature for 20 h, and then the solvent was evaporated. The residue was dissolved in ether and filtered. Evaporation of the filtrate afforded the crude β,γ-epoxycarbonyl compound **5a** (6.1 g, 95%). ^{1}H NMR spectral data of **5a**: δ 2.86 (d, 1H, J = 4.2 Hz, oxiran CH_2), 2.95 (d, 1H, J = 4.2 Hz, oxiran CH_2), 3.10 (d, 1H, J = 17.5 Hz, CH_2C=O), 3.61 (d, 1H, J = 11.7 Hz, CH_2Cl), 3.78 (d, 1H, J = 17.5 Hz, CH_2C=O), 3.98 (d, 1H, J = 11.7 Hz, CH_2Cl), 7.04–7.18, 7.94–8.06 (m, 4H, C_6H_4).

2.3. *Synthesis of 2-aryl-4-(chloromethyl)thiophenes **6***

Lawesson's reagent (5.6 g, 14 mmol) was added to a benzene (30 ml) solution of epoxycarbonyl compound **5a** (6.1 g, 27 mmol) and heated to boiling. After 30 min, *p*-toluenesulfonic acid (20 mg) was added, and the mixture heated at reflux for 1 h. The reaction mixture was partitioned between saturated aq $NaHCO_3$ and ether, and the aqueous layer was extracted with ether. The combined organic phases were washed with brine and dried over Na_2SO_4. Purification by chromatography on silica gel (hexanes) afforded 1.8 g (30%, overall yield based on the starting 4-fluorobenzaldehyde **1a**) of **6a**. Spectral data of **6a**: ^{1}H NMR δ 4.60 (s, 2H, CH_2Cl), 7.0–7.6 (m, 6H, aromatic); ^{13}C NMR δ 40.8 (CH_2Cl), 115.9 (d, $^2J_{CF}$ = 20.6 Hz, Ph−C_3, C_5), 123.1 (Th−C_5), 123.6 (Th−C_3), 127.7 (d, $^3J_{CF}$ = 7.8 Hz, Ph−C_2, C_6), 130.4 (Ph−C_1), 139.1 (Th−C_4), 144.7 (Th−C_2), 162.7 (d, $^1J_{CF}$ = 245.0 Hz, Ph−C_4).

2.4. *Copper(I) catalysed cross-coupling reactions of the bromide 7 with alkylmagnesium bromides—synthesis of 2-aryl-4-alkylthiophenes **8***

A mixture of 10 ml of dry acetone, **6a** (1.2 g, 5.3 mmol) and NaBr (0.66 g, 6.4 mmol) was stirred for 18 h at room temperature. The reaction mixture was concentrated and treated with $Na_2S_2O_3$ aqueous solution. The mixture was extracted with ether (20 ml × 2). The organic phase was dried (Na_2SO_4) and concentrated to give 1.2 g (85%) of **7a**. ^{1}H NMR spectral data of **7a**: δ 4.49 (s, 2H), 7.0–7.6 (m, 6H).

The bromide **7a** (1.20 g, 4.4 mmol), *n*-butylmagnesium bromide (4.4 mmol, 2.2 ml of 2M solution) prepared from 1-bromobutane and magnesium in THF, and THF (10 ml) were added to a 25 ml round-bottom flask, which was previously flushed with nitrogen and sealed with a rubber septum. The solution was then cooled in an ice bath, and a THF solution of Li_2CuCl_3 (0.1M, 0.5 ml) was added. The reaction mixture was stirred for 5 h at room temperature. Work-up and purification by silica gel chromatography (hexanes) afforded 0.76 g (70%) of 2-(4-fluorophenyl)-4-pentylthiophene **8a**. The compounds **8b–8e** were similarly prepared. **8a**: ^{1}H NMR δ 0.90 (t, 3H, J = 5.7 Hz, $CH_2(CH_2)_3C\underline{H_3}$), 1.26–1.71 (m, 6H, $CH_2(C\underline{H_2})_3CH_3$), 2.60 (t, 2H, J = 7.7 Hz, $C\underline{H_2}(CH_2)_3CH_3$), 6.85 (s, 1H, Th−$H_5$), 7.00 (s, 1H, Th−$H_3$), 7.04–7.09, 7.50–7.57 (m, 4H, C_6H_4); ^{13}C NMR δ 14.0, 22.5, 30.0, 30.6, 31.5 (5C, aliphatic chain), 115.7 (d, $^2J_{CF}$ = 21.5 Hz, Ph−C_3, C_5), 119.4 (Th−C_5), 124.4 (Th−C_3), 127.3 (d, $^3J_{CF}$ = 8.2 Hz, Ph−C_2, C_6), 131.0 (Ph−C_1), 142.8 (Th−C_4), 144.3 (Th−C_2), 162.2 (d, $^1J_{CF}$ = 247.1 Hz, Ph−C_4); HRMS calcd for $C_{15}H_{17}FS$ 248.1035, found 248.1056. **8b**: ^{1}H NMR δ 0.86–0.89 (m, 3H, $CH_2(CH_2)_5C\underline{H_3}$), 1.31–1.64 (m, 10H, $CH_2(C\underline{H_2})_5CH_3$), 2.60 (t, 2H, J = 7.7 Hz, $C\underline{H_2}(CH_2)_5CH_3$), 6.85 (s, 1H, Th−$H_5$), 7.01 (s, 1H, Th−$H_3$), 7.06–7.08, 7.51–7.58 (m, 4H, C_6H_4); ^{13}C NMR δ 14.1, 22.7, 29.2, 29.3, 30.4, 30.6, 31.8 (7C, aliphatic chain), 115.6 (d, $^2J_{CF}$ = 22.0 Hz,

Ph–C_3, C_5), 119.3 (Th–C_5), 124.4 (Th–C_3), 127.2 (d, $^3J_{CF}$ = 7.8 Hz, Ph–C_2, C_6), 131.0 (Ph–C_1), 142.8 (Th–C_4), 144.2 (Th–C_2), 162.2 (d, $^1J_{CF}$ = 246.6 Hz, Ph–C_4); HRMS calcd for $C_{17}H_{21}FS$ 276.1348, found 276.1376. **8c**: ^{1}H NMR δ 0.84–0.91 (m, 3H, $CH_2(CH_2)_7C\underline{H_3}$), 1.26–1.67 (m, 14H, $CH_2(C\underline{H_2})_7CH_3$), 2.60 (t, 2H, J = 7.7 Hz, $C\underline{H_2}(CH_2)_7CH_3$), 6.85 (s, 1H, Th–$H_5$), 7.00 (s, 1H, Th–$H_3$), 7.04–7.09, 7.50–7.57 (m, 4H, C_6H_4); ^{13}C NMR δ 14.1, 22.7, 29.4, 29.5, 29.6, 29.7, 30.5, 30.6, 32.0 (9C, aliphatic chain), 115.7 (d, $^2J_{CF}$ = 22.0 Hz, Ph–C_3, C_5), 119.4 (Th–C_5), 124.4 (Th–C_3), 127.3 (d, $^3J_{CF}$ = 7.8 Hz, Ph–C_2, C_6), 131.0 (Ph–C_1), 142.9 (Th–C_4), 144.3 (Th–C_2), 162.2 (d, $^1J_{CF}$ = 247.1 Hz, Ph–C_4); HRMS calcd for $C_{19}H_{25}FS$ 304.1661, found 304.1650. **8d**: ^{1}H NMR δ 0.85–0.88 (m, 3H, $CH_2(CH_2)_5C\underline{H_3}$), 1.28–1.63 (m, 10H, $CH_2(C\underline{H_2})_5CH_3$), 2.60 (t, 2H, J = 7.5 Hz, $C\underline{H_2}(CH_2)_5CH_3$), 6.91 (s, 1H, Th–$H_5$), 7.14 (s, 1H, Th–$H_3$), 7.39–7.43 (m, 2H, Ph–$H_5$, H_6), 7.66 (s, 1H, Ph–H_2); ^{13}C NMR δ 14.1, 22.7, 29.1, 29.3, 30.4, 30.5, 31.8 (7C, aliphatic chain), 120.5 (Th–C_5), 124.7 (Th–C_3), 125.4 (Ph–C_6), 127.1 (Ph–C_2), 130.6 (Ph–C_5), 130.8 (Ph–C_1), 132.8 (Ph–C_4), 134.6 (Ph–C_3), 141.1 (Th–C_4), 144.5 (Th–C_2); HRMS calcd for $C_{17}H_{20}Cl_2S$ 326.0663, found 326.0662. **8e**: ^{1}H NMR δ 0.88–1.00 (m, 3H, $CH_2CH_2C\underline{H_3}$), 1.54–1.72 (m, 2H, $CH_2C\underline{H_2}CH_3$), 2.58 (t, 2H, J = 7.7 Hz, $C\underline{H_2}CH_2CH_3$), 6.87 (s, 1H, Th–H_5), 7.12–7.45 (m, 5H, C_6H_4 and Th–H_3). **8f**: ^{1}H NMR δ 0.91–0.94 (m, 3H, $CH_2(CH_2)_3C\underline{H_3}$), 1.26–1.69 (m, 6H, $CH_2(C\underline{H_2})_3CH_3$), 2.61 (t, 2H, J = 7.5 Hz, $C\underline{H_2}(CH_2)_3CH_3$), 6.86 (s, 1H, Th–$H_5$), 7.15 (s, 1H, Th–$H_3$), 7.28–7.40, 7.57–7.61 (m, 4H, C_6H_4).

2.5. *Preparation of 2-(4-cyanophenyl)-4-alkylthiophenes* ***9***

A suspension of 2-(4-bromophenyl)-4-propylthiophene (**8e**, 2.0 g, 7.1 mmol) and copper(I) cyanide (0.95 g, 10.6 mmol) in DMF (4 ml) was stirred at 200°C (bath temperature) for 8 h. The hot solution was poured into a solution of iron(III) chloride (3.6 g) and 10M hydrochloric acid (1.4 ml) in water (5.5 ml) and stirred at 60–70°C for 20 min. The hot mixture was then shaken with toluene (30 ml × 2). The combined extracts were washed with 6M hydrochloric acid (25 ml) and water, dried and evaporated. The crude product was purified by silica gel column chromatography (hexanes : dichloromethane = 4 : 1) to give **9a** (940 mg, 58%). **9a**: ^{1}H NMR δ 0.97 (t, 3H, J = 7.1 Hz, $CH_2CH_2C\underline{H_3}$), 1.60–1.70 (m, 2H, $CH_2C\underline{H_2}CH_3$), 2.58 (t, 2H, J = 7.5 Hz, $C\underline{H_2}CH_2CH_3$), 6.96 (s, 1H, Th–H_5), 7.17 (s, 1H, Th–H_3), 7.5–7.7 (m, 4H, C_6H_4); ^{13}C NMR δ 13.6, 23.3, 32.3 (3C, aliphatic chain), 110.0 (Ph–C_4), 118.6 (CN), 121.7 (Th–C_5), 125.4 (Th–C_3), 126.2 (Ph–C_2, C_6), 132.3 (Ph–C_3, C_5), 138.5 (Th–C_4), 141.3 (Ph–C_1), 144.4 (Th–C_2); HRMS calcd for $C_{14}H_{13}NS$ 227.0769, found 227.0766. **9b**: ^{1}H NMR δ 0.87–0.94 (m, 3H, $CH_2(CH_2)_3C\underline{H_3}$), 1.25–1.72 (m, 6H, $CH_2(C\underline{H_2})_3CH_3$), 2.61 (t, 2H, J = 7.5 Hz, $C\underline{H_2}(CH_2)_3CH_3$), 6.98 (s, 1H, Th–$H_5$), 7.26 (s, 1H, Th–$H_3$), 7.5–7.7 (m, 4H, C_6H_4); ^{13}C NMR δ 14.0, 22.4, 30.5, 31.5, 34.1 (5C, aliphatic chain), 110.3 (Ph–C_4), 118.8 (CN), 121.8 (Th–C_5), 125.8 (Th–C_3), 126.4 (Ph–C_2, C_6), 132.6 (Ph–C_3, C_5), 138.9 (Th–C_4), 141.6 (Ph–C_1), 144.9 (Th–C_2); HRMS calcd for $C_{16}H_{17}NS$ 255.1082, found 255.1082.

2.6. *Preparation of 2-[2-(4-fluorophenyl)ethyl]-4-alkylthiophenes* ***16***

3-(4-Fluorophenyl)propanoyl chloride (**11**, 2.4 g, 13 mmol) and **10** (2.0 g, 12 mmol) in dichloromethane (5 ml) at − 78°C were slowly added to a dichloromethane (15 ml) solution of $TiCl_4$ (1.5 ml, 2.7 g, 14 mmol). After stirring the solution at − 78°C for 1 h, the reaction was quenched with 20 ml of 1N HCl aqueous solution. The aqueous layer was extracted with dichloromethane (20 ml × 2). The combined organic extracts were washed with saturated aq $NaHCO_3$ solution (20 ml × 2) and brine, dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give the crude β,γ-unsaturated ketone **12**. A dichloromethane (1 ml) solution of **12** (2.0 g, 9.4 mmol) was added at 0°C to a dichloromethane (30 ml) solution of MCPBA (50%, 5.2 g, 30.0 mmol), and allowed to react further for 20 h at room temperature. The reaction mixture was stirred with a saturated aq $NaHCO_3$ solution (30 ml) for 2 h. The aqueous layer was extracted with dichloromethane (20 ml × 2). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to give the crude β,γ-epoxycarbonyl compound **13** (3.1 g). The crude product **13** was added to a benzene (15 ml) solution of Lawesson's reagent (2.4 g, 6.0 mmol), and the solution was heated to boiling. After 30 min, *p*-toluenesulfonic acid (10 mg) was added and the mixture heated at reflux for 1 h. The reaction mixture was partitioned between saturated aq $NaHCO_3$ and ether, and the aqueous layer was extracted with ether. The combined organic phases were washed with brine and dried over Na_2SO_4. Purification by chromatography on silica gel (hexanes) gave 0.7 g (23%, overall yield based on the allylsilane **10**) of **14**. *Trans*-halogenation of the chloride **14** to the bromide **15,** and a cross-coupling reaction of the bromide **15** with *n*-butylmagnesium bromide in the presence of the Kochi catalyst were performed similarly to the processes described above. After the usual work-up and purification with chromatography (silica gel, hexanes), 2-[2-(4-fluorophenyl)ethyl]-4-pentylthiophene (**16a,** 270 mg, 49%) was obtained. **16a**: ^{1}H NMR δ 0.93–1.00 (m, 3H, $CH_2(CH_2)_3C\underline{H_3}$), 1.34–1.72 (m, 6H, $CH_2(C\underline{H_2})_3CH_3$), 2.58 (t, 2H, J = 7.3 Hz, $C\underline{H_2}(CH_2)_3CH_3$), 2.94–3.15

(m, 4H, PhC$\underline{H_2}$C$\underline{H_2}$Th), 6.62 (s, 1H, Th−H_5), 6.73 (s, 1H, Th−H_3), 6.9–7.2 (m, 4H, C_6H_4); ^{13}C NMR δ 14.0, 22.5, 30.1, 30.5, 31.5 (5C, aliphatic chain), 32.1, 37.1 (PhC$\underline{H_2}$C$\underline{H_2}$Th), 115.0 (d, $^2J_{CF}$ = 21.0 Hz, Ph−C_3, C_5), 117.5 (Th−C_5), 126.0 (Th−C_3), 129.8 (d, $^3J_{CF}$ = 7.8 Hz, Ph−C_2, C_6), 136.8 (Th−C_4), 142.9 (Ph−C_1), 143.7 (Th−C_2), 161.4 (d, $^1J_{CF}$ = 244.3 Hz, Ph−C_4); HRMS calcd for $C_{17}H_{21}FS$ 276.1348, found 276.1342. **16b**: ^{1}H NMR δ 0.87–0.94 (m, 3H, $CH_2(CH_2)_5C\underline{H_3}$), 1.30–1.62 (m, 10H, $CH_2(C\underline{H_2})_5CH_3$), 2.54 (t, 2H, J = 7.7 Hz, $C\underline{H_2}(CH_2)_5CH_3$), 2.89–3.12 (m, 4H, PhC$\underline{H_2}C\underline{H_2}$Th), 6.59 (s, 1H, Th−$H_5$), 6.71 (s, 1H, Th−$H_3$), 6.9–7.2 (m, 4H, C_6H_4); ^{13}C NMR δ 14.1, 22.6, 29.1, 29.3, 30.4, 30.5, 31.8 (7C, aliphatic chain), 32.2, 37.1 (PhC$\underline{H_2}$C$\underline{H_2}$Th), 115.0 (d, $^2J_{CF}$ = 21.0 Hz, Ph−C_3, C_5), 117.5 (Th−C_5), 126.0 (Th−C_3), 129.8 (d, $^3J_{CF}$ = 7.8 Hz, Ph−C_2, C_6), 136.8 (Th−C_4), 142.9 (Ph−C_1), 143.7 (Th−C_2), 161.4 (d, $^1J_{CF}$ = 243.9 Hz, Ph−C_4); HRMS calcd for $C_{19}H_{25}FS$ 304.1661, found 304.1674.

2.7. *Preparation of trans-2-[4-(4-fluorophenyl)-cyclohexyl]-4-heptylthiophene* ***22***

Chloromethylthiophene **20** (200 mg, 32% overall yield) was prepared using the procedures described above, starting with *trans*-4-(4-fluorophenyl)cyclohexanecarbonyl chloride (**17**, 0.53 g, 2.2 mmol) and allylsilane **10** (360 mg, 2.2 mmol). Compound **22** (116 mg, 58%) was prepared from the *trans*-halogenation of **20** (200 mg, 0.56 mmol) with sodium bromide and followed a cross-coupling reaction with *n*-hexylmagnesium bromide (1.1 mmol) in the presence of the Kochi catalyst. **22**: ^{1}H NMR δ 0.76–0.88 (m, 3H, $CH_2(CH_2)_5C\underline{H_3}$), 1.26–1.73, 1.97–2.23 (m, 20H, $CH_2(C\underline{H_2})_5CH_3$ and cyclohexyl), 2.55 (t, 2H, J = 7.7 Hz, $C\underline{H_2}(CH_2)_5CH_3$), 6.67 (s, 1H, Th−$H_5$), 6.71 (s, 1H, Th−$H_3$), 6.94–7.02, 7.13–7.22 (m, 4H, C_6H_4); ^{13}C NMR δ 14.1, 22.7, 29.2, 29.4, 30.4, 30.7, 31.8, 34.4, 35.4, 39.0, 43.1 (11C, aliphatic chain and cyclohexyl), 115.0 (d, $^2J_{CF}$ = 20.6 Hz, Ph−C_3, C_5), 116.7 (Th−C_5), 123.5 (Th−C_3), 128.1 (d, $^3J_{CF}$ = 7.8 Hz, Ph−C_2, C_6), 137.1 (Th−C_4), 142.8 (Th−C_2), 151.1 (Ph−C_1), 161.2 (d, $^1J_{CF}$ = 245.7 Hz, Ph−C_4); HRMS calcd for $C_{23}H_{31}FS$ 358.2131, found 358.2128.

3. Results and discussion

The allylsilane, 2-(chloromethyl)-3-(trichlorosilyl)-propene (**2**) [4] reacts with aldehydes **1** in DMF at 0°C without a catalyst to afford the corresponding homoallylic alcohols **3** in high yield [5]. The β,γ-epoxycarbonyl compounds **5** were conveniently prepared from the homoallylic alcohols **3** by first epoxidation with MCPBA, followed by oxidation with PDC in a dichloromethane solution [6]. The reactions of crude β,γ-epoxycarbonyl compounds **5** with Lawesson's reagent in the presence of a catalytic amount of *p*-toluenesulfonic acid in refluxing benzene afforded 2-aryl-4-(chloromethyl)-thiophenes **6** [3]. The order of addition of Lawesson's reagent and *p*-toluenesulfonic acid was important for the successful reactions; when *p*-toluenesulfonic acid was added prior to the Lawesson's reagent, a certain amount of furans were formed along with the corresponding thiophenes [7].

The following four procedures—alkylation reaction of aldehydes with trichloroallylsilane **2**, epoxidation of homoallylic alcohols, oxidation to β,γ-epoxycarbonyl compounds, and cyclization process to thiophenes—were performed successively without isolation of the intermediate products. The yields of thiophenes **6** listed in scheme 1 are overall yields based on the starting aldehydes.

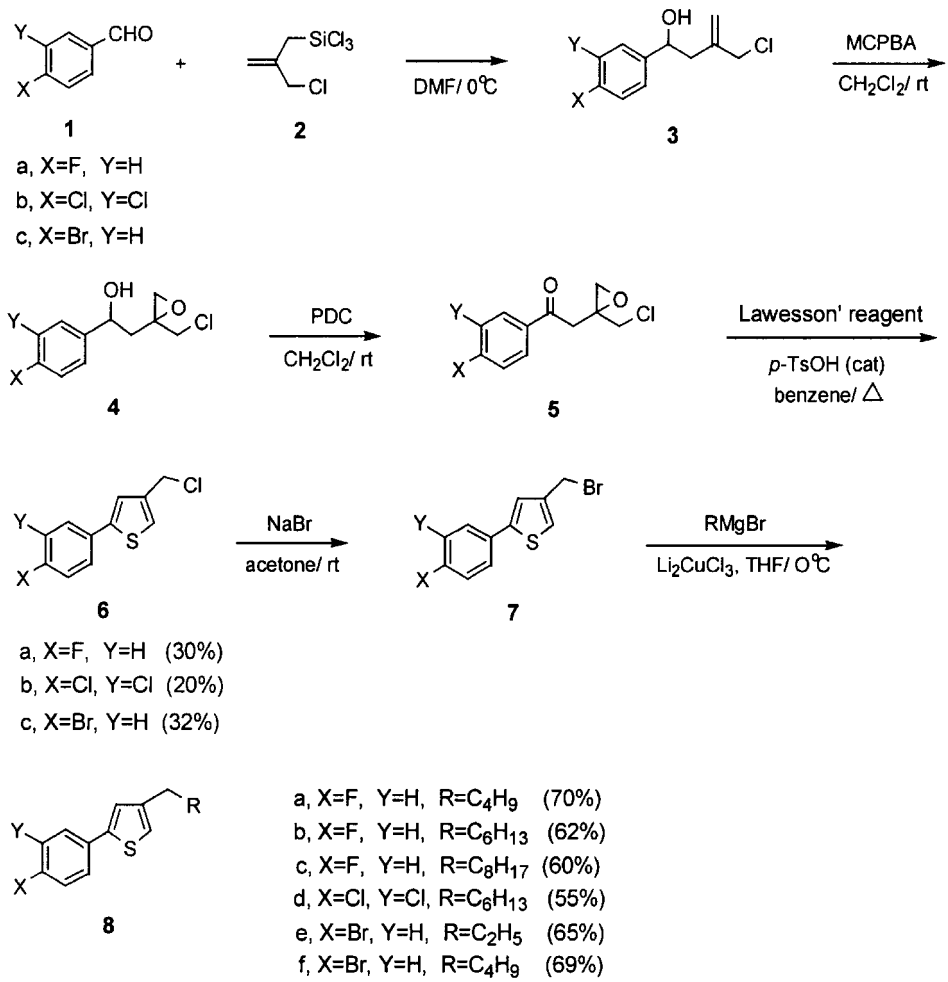
The bromides **7** were obtained from the *trans*-halogenation of the chlorides **6** with NaBr in acetone. Alkylation reactions of the bromides **7** with Grignard reagents in the presence of a catalytic amount of the Kochi catalyst (Li_2CuCl_3) [8] produced a good yield of 2-aryl-4-alkylthiophenes **8**. When the coupling reactions of the Grignard reagents with the iodides, instead of the bromides **7**, were performed, the reduced products 2-aryl-4-methylthiophenes were formed as byproducts; the yields of the alkylation products **8** were decreased.

Reactions of 2-(4-bromophenyl)-4-pentylthiophenes **8e** with copper(I) cyanide in DMF at 200°C for 8 h gave the desired cyano compounds **9** (scheme 2). Purification of **9** was performed by warming it with iron(III) chloride/hydrochloric acid, followed by extraction into warm toluene and column chromatography (silica gel, hexanes : dichloromethane = 4 : 1) [1*c*].

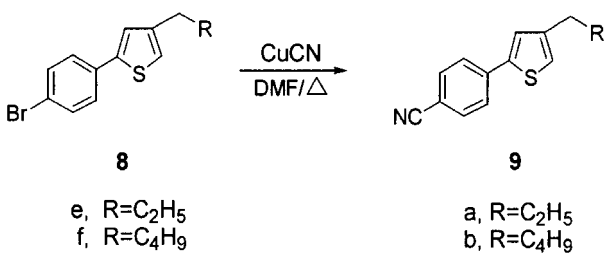
The $TiCl_4$-promoted reaction of the allylsilane, 2-(chloromethyl)-3-(trimethylsilyl)propene (**10**) [5] with 3-(4-fluorophenyl)propanoyl chloride (**11**) afforded β,γ-unsaturated ketone **12**. Epoxidation of **12** with 2 equiv of MCPBA in dichloromethane at 0°C-room temperature produced β,γ-epoxycarbonyl compound **13**. The *p*-toluenesulfonic acid-catalyzed reaction of **13** with Lawesson's reagent afforded chloromethylthiophene **14**. The overall yield of **14** was 23%, based on the starting allylsilane **10** (scheme 3). When the alkylation reactions of the chlorides **14** were performed similarly to those described above, 2-[2-(4-fluorophenyl)ethyl]-4-alkylthiophenes **16** were obtained.

2-[4-(4-Fluorophenyl)cyclohexyl]-4-heptylthiophene (**22**) was also prepared from allylsilane **10** and 4-(4-fluorophenyl)cyclohexanecarbonyl chloride (**17**) in 19% overall yield (scheme 4).

Compounds **8b**, **8d**, **16**, and **22** are liquid at room temperature, and compounds **8a** and **9a** melt directly to the isotrophic phase. The compounds **8c** and **9b** show a



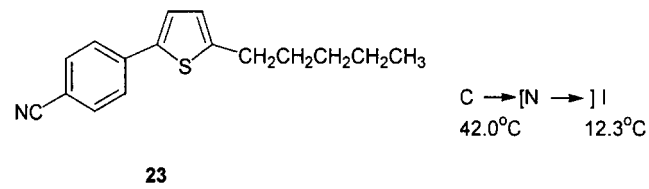
Scheme 1.



Scheme 2.

narrow nematic phase (see the table). The compound **9b** was observed to have a lower melting point than the corresponding 2,5-disubstituted thiophene **23**. (The phase transition temperatures were determined by polarizing microscopy.)

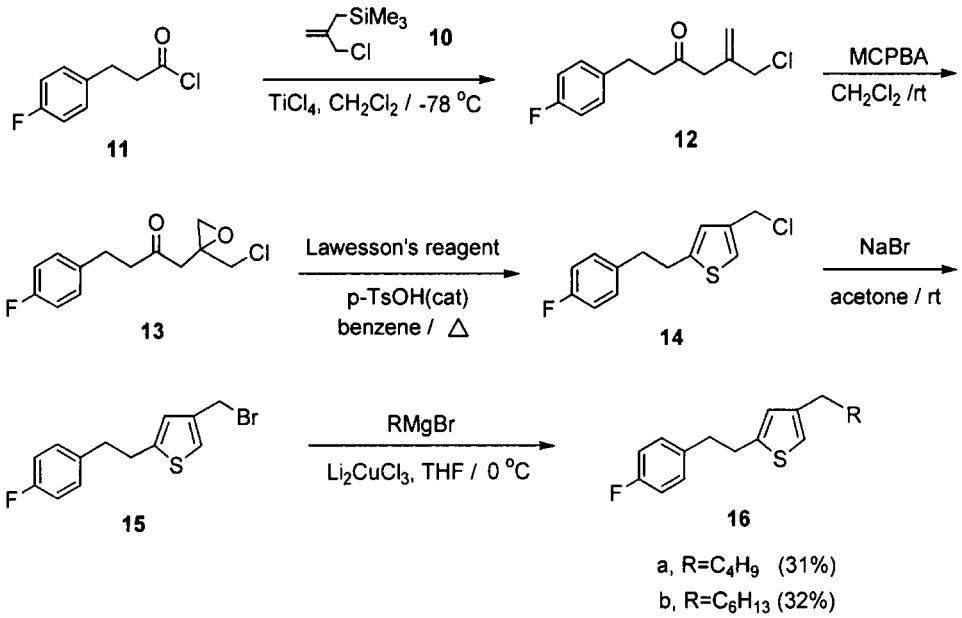
The decrease in the thermal stabilities and melting points of 2,4-disubstituted thiophenes, compared with the isomeric 2,5-disubstituted derivatives, are due to the larger deviation from linearity for the 2,4-disubstituted thiophenes.



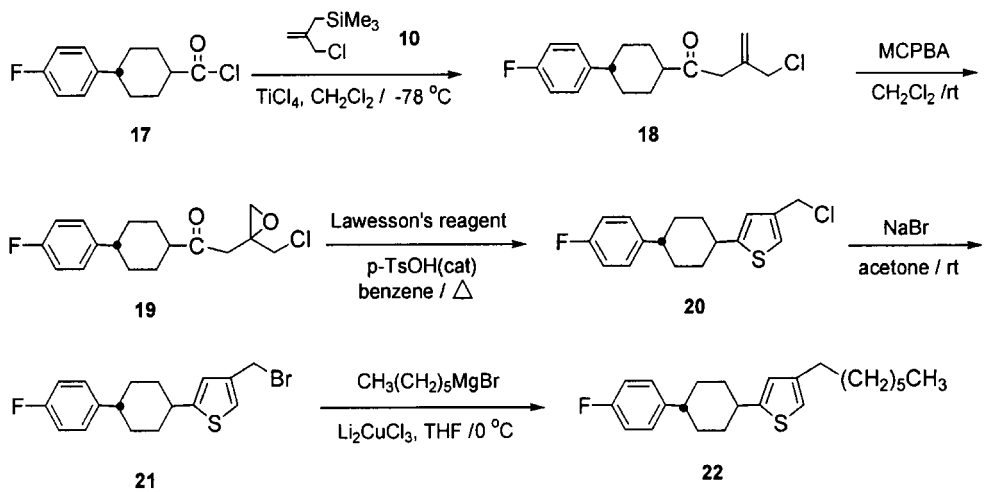
23

4. Conclusion

We have successfully developed an efficient and regioselective route to the variously substituted 2-aryl-, 2-cyclohexyl-, and 2-(2-arylethyl)-4-alkylthiophenes, which are difficult to prepare via other routes [9]. The following points enhance the value of the present method: first, starting materials such as allylsilanes **2** and **10**, substituted benzaldehydes and benzoyl chlorides, are easily



Scheme 3.



Scheme 4.

Table. Transition temperature for the 2-aryl-4-alkyl-thiophenes.

Compound	Transition	T_{DSC}/°C
8a	Cr → I	34.2
8c	Cr → N	40.5
	N → I	41.3
9a	Cr → I	39.6
9b	Cr → N	35.1
	N → I	44.4
	(I → N)	38.3
	(N → Cr)	31.0

available; second, an alkyl substituent at the 4-position can be easily introduced by the copper(I) catalysed cross-coupling reactions to the bromides **7**, **15** or **21** with Grignard reagents.

Thiophenes with substituents at the 2- and 4-positions show lower melting points and thermal stabilities than the corresponding 2,5-disubstituted thiophenes. This observation is consistent with the expectation from the basis of molecular linearity, which can affect the melting points and the viscosities of crystalline compounds. In order to aquire a liquid crystalline mixture with low viscosity which might have practical utility,

blending studies using the 2,4-disubstituted thiophenes are under investigation.

This work was financially surpported by the Ministry of Commerce, Industry and Energy, and the Ministry of Science and Technology as part of the G7-Project. We thank Professor K. Goto, University of Tokyo, for providing high-resolution mass spectra.

References

[1] (*a*) Koßmehl, G., Hoppe, F. D., and Hirsch, B. Z., 1993, *Naturforsch*, **486,** 826; (*b*) Gallardo, H., and Favarin, I., 1993, *Liq. Cryst*., **13,** 115; (*c*) Koßmehl, G., and Hoppe, F. D., 1993, *Liq. Cryst*., **15,** 383; (*d*) Brettle, R., Dunmur, D. A., Marson, C. M., Pinol, M., and Toriyama, K., 1993, *Liq. Cryst*., **13,** 515; (*e*) Cai, R., Preston, J., and Samulski, E. T., 1992, *Macromolecules*, **25,** 563; (*f*) Brettle, R., Dunmur, D. A., Marson, C. M., and Pinol, M., 1992, Japanese Patent Application No. 3-139 998.

[2] Meth-Cohn, O., 1979, in *Comprehensive Organic Chemistry*, Vol. 4, edited by D. Barton and W. D. Ollis (Oxford: Pergamon Press), pp. 789–838.

[3] Kang, K.-T., and U, J. S., 1995, *Synth. Commun*., **25,** 2647.

[4] Kang, K.-T., U, J. S., Park, D. K., Kim, J. G., and Kim, W. J., 1995, *Bull. Korean chem. Soc*., **16,** 464.

[5] Kobayashi, S., and Nishio, K., 1993, *Tetrahedron Lett*., **34,** 3453.

[6] Cormier, R. A., Grosshans, C. A., and Skibbe, S. L., 1988, *Synth. Commun*., **18,** 677.

[7] (*a*) U, J. S., and Kang, K.-T., 1994, *Bull. Korean chem. Soc*., **15,** 1019; (*b*) Kang, K,-T., U, J. S., Hwang, S. S., and Jyung, K. K., 1994, *Synth. Commun*., **24,** 2915.

[8] Tamura, M., and Kochi, J., 1971, *Synthesis*, 303.

[9] Nakayama, J., 1996, in *Comprehensive Heterocyclic Chemistry*, edited by A. R. Katritzky, C. W. Rees, and E. F. V. Scriven (Oxford: Pergamon Press), pp. 607–678.