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Synthesis and photochromism of 1,2-bis(5-aryl-2-phenylethynylthien-3-yl)hexafluorocyclopentene derivatives

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ABSTRACT

Photochromic dithienylethenes that possess elements of lipid complementarity, and undergo large, photoinduced changes in molecular geometry have been prepared. Further, a regioselective approach has been developed for the preparation of dithienylethenes containing phenylethynyl and various aryl substituents at C2 and C5 of the thiophene moieties, respectively. The prepared photochromic compounds were observed to undergo reversible photoisomerization. Their absorption properties, reaction quantum yields, and photoconversions were determined in *n*-hexane.

1. Introduction

Photochromism is defined as a light-induced reversible transformation between two isomers having different absorption spectra [1]. Most photochromic compounds, such as azobenzenes and spirooxazines, undergo a thermally reversible isomerization as well. On the contrary, the majority of dithienylethenes are thermally irreversible and fatigue resistant [2]. As a result, these photoresponsive molecules have promising applications in photonic devices [3,4].

The photomodulation of liquid crystal properties has recently received considerable attention [5–10]. Notably, the photoisomerization of a dithienylethene dopant has been used to reversibly modulate the spontaneous polarization of ferroelectric smectic liquid crystals [11]. This dithienylethene derivative contained methyl substituents at the reactive carbons (i.e., C2) and 4-heptyloxyphenyl substituents at C5 of the thiophene moieties to improve its complementarity with the lamellar structure of the liquid crystals. In this study, we have designed a similar dithienylethene analog, **3a** (Scheme 1), with aspects of lipid complementarity by incorporating a 4-dodecylphenyl substituents at C5. However, **3a** contains bulky phenylethynyl substituents at C2 in place of the methyl substituents. As a result, the photoisomerization of **3a** will lead to a much larger change in molecular geometry as has been shown for **1a** [12]. Although the preparation of alkynyl derivatives such as **1a** have been reported [12–14], a synthetic strategy for dithienylethene derivatives of this general structure has not been well developed. Further, the synthetic protocol for **1a** is limited to the derivatization of 2,3-dibromo-5-phenylthiophene, which does not allow for the introduction of additional functionality at C5 of the thiophene ring. Consequently, we present a regioselective approach for the preparation of photochromic dithienylethenes, like **3a**, that possess elements of lipid complementarity, and undergo large, photoinduced changes in molecular geometry. Regioselective modification of thiophene heterocycles at three positions provides a versatile methodology for the incorporation of functional groups at C2 and C5 of the thiophene moieties of dithienylethenes. In addition, we have examined the absorption properties and photochromic reactivity of these molecules in solution. Compounds **1a**–**3a** may be used in the development of photoresponsive liposomes with reversible photocontrols over membrane stability, and **3a** may have interesting implications in the development of photonic devices based on liquid crystals.

2. Experimental

2.1. Instrumentation

^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded at 300.18, 282.46, and 75.48 MHz, respectively, on a Varian Mercury plus spectrometer (Palo Alto, CA, USA). Chemical shifts are referenced to solvent signals. High-resolution mass spectral analyses were carried out by the University of Saskatchewan on a VG 70SE mass spectrometer (Manchester, UK), which was operated in electron impact or electrospray ionization modes. X-ray data collection were carried out by the University of Alberta on a Bruker PLAT-

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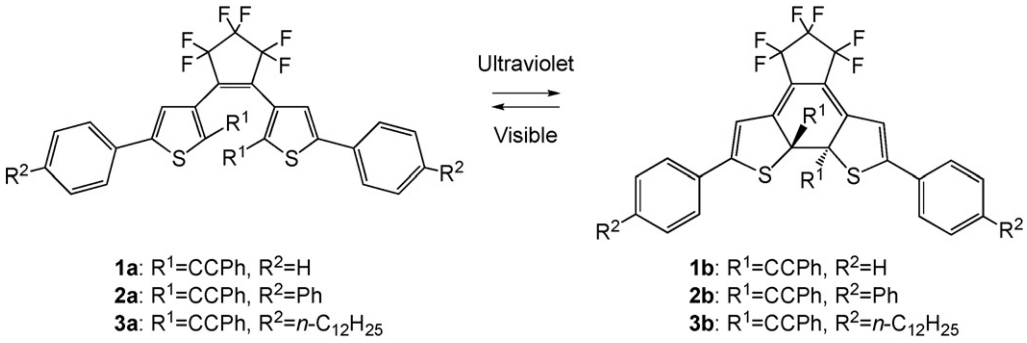


Scheme 1. The reversible photoisomerization of dithienylethenes, where **1a**–**3a** and **1b**–**3b** are the open-ring and closed-ring isomers, respectively.

FORM diffractometer/SMART 1000 CCD (Madison, WI, USA) using graphite-monochromated Mo Kα radiation at −80 °C. Elemental analyses were carried out by Guelph Chemical Laboratories on a Fisons/Carlo Erba CHNS-O EA 1108 elemental analyzer (Lakewood, NJ, USA) or by the University of Calgary on a PerkinElmer 2400 Series II CHNS/O elemental analyzer (Waltham, MA, USA). HPLC analyses were performed on a HP 1090 Series II liquid chromatograph (Santa Clara, CA, USA). A guard column containing SecurityGuard silica cartridges (4 mm × 3 mm i.d.) was connected to a Luna 5 μm Silica(2) analytical column (250 mm × 4.6 mm i.d.) from Phenomenex (Torrance, CA, USA). The mobile phase was 95:5 *n*-hexane/ethyl acetate for **1** and **2**, and *n*-hexane for **3** at a flow rate of 1 mL min^{-1}. The injection volume was 5 μL and signals were monitored at 254 nm. Steady-state absorption spectra were obtained at constant temperature (e.g., 21.0 ± 0.1 °C) on a Cary 300 Bio UV–vis spectrophotometer (Mississauga, ON, Canada) equipped with a dual cell Peltier circulator accessory. The absorption spectra were recorded at a scan rate, step size, and integration time of 300 nm min^{-1}, 0.5 nm, and 0.1 s, respectively. All samples were irradiated with a 300 W xenon light source from Luzchem (Ottawa, ON, Canada), measured in a 10 mm × 4 mm quartz Suprasil absorbance cell from Hellma (Concord, ON, Canada), and stirred. For ultraviolet irradiations, the xenon light source was filtered with a bandpass filter (Hoya U-340, $\lambda_c = 340 \pm 42$ nm) and an aqueous solution of potassium chromate ($\lambda_c = 313 \pm 7$ nm [15]) circulated through a 50 mm × 22 mm cylindrical cell from Hellma ($A_{313} = 0.040 \pm 0.005$). For visible irradiations, a bandpass filter (Throlabs FB530-10, $\lambda_c = 530 \pm 5$ nm) was used.

2.2. Materials

All reactants (99+%, Sigma–Aldrich, Oakville, ON, Canada), deuterated solvents (99.9 at.% D, Sigma–Aldrich), *trans*-dichlorobis(triphenylphosphine)palladium(II) ($[PdCl_2(PPh_3)_2]$) (99.9+% Pd, Strem Chemicals, Newburyport, MA, USA), isopropylidenesuccinic acid diethyl ester (TCI America, Portland, OR, USA), octafluorocyclopentene (99+%, SynQuest Laboratories, Alachua, FL, USA), and tetrakis(triphenylphosphine)palladium(0) ($[Pd(PPh_3)_4]$) (99.9+% Pd Strem Chemicals) were purchased and used as received. Carbon tetrachloride, copper iodide, diethyl ether, 1,4-dioxane, tetrahydrofuran, and triethylamine were purified following literature procedures [16]. Flash column chromatography was performed on silica gel (200–400 mesh, 60 Å, Sigma–Aldrich).

2.3. Procedures for the synthesis of photochromic compounds ***1a*–*3a***

2.3.1. 2,3,5-Tribromothiophene (***4***)

The bromination of thiophene was adapted from a previously published procedure [17]. A mixture of bromine (61.5 g, 0.385 mol) and 48% aqueous solution of hydrogen bromide (35 mL) was added dropwise to mixture of thiophene (9.57 g, 0.114 mol), 48% aqueous solution of hydrogen bromide (50 mL), and diethyl ether (35 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and refluxed for 2 h. The biphasic mixture was extracted with dichloromethane (3× 100 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was passed through a silica gel column (dichloromethane). Distillation of the liquid residue at 118–120 °C (ca. 5 Torr) gave pure **4** as a colorless solid (20 g, 57%). ^{1}H NMR ($CDCl_3$, δ): 6.90 (s, 1H, H4).

2.3.2. 2,4-Dibromothiophene (***5***)

Adapted from previously published procedures [18,19], *n*-butyllithium (25.0 mL of a 2.50 M solution in hexanes, 62.5 mmol) was added dropwise to a solution of **4** (20.0 g, 62.5 mmol) in diethyl ether (200 mL) at −78 °C and under an atmosphere of argon as shown (Scheme 2). After stirring for 10 min, the reaction mixture was poured into cold water (250 mL) to give a biphasic mixture. This mixture was extracted with diethyl ether (3× 60 mL), washed with water (100 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was passed through a silica gel column (1:12 chloroform/hexanes). Distillation of the liquid residue at 78–80 °C (ca. 5 Torr) gave pure **5** as a colorless liquid (7.9 g, 52%). ^{1}H NMR ($CDCl_3$, δ): 6.98 (d, J = 1.8 Hz, 1H, H3), 7.15 (d, J = 1.8 Hz, 1H, H5).

2.3.3. 4-Dodecylphenylboronic acid (***6c***)

The starting material, 1-bromo-4-dodecylbenzene, was synthesized following reported procedures [20,21]. Adapted from a previously published procedure [22], *n*-butyllithium (1.50 mL of a 2.50 M solution in hexanes, 3.75 mmol) was added dropwise to a solution of 1-bromo-4-dodecylbenzene (0.0400 g, 1.23 mmol) in tetrahydrofuran (10 mL) at −78 °C and under an atmosphere of argon. After stirring for 75 min, trimethoxyborane (0.418 mL, 3.75 mmol) was added dropwise to the mixture. The reaction mixture was allowed to warm to room temperature, stirred for 16.5 h, and poured into 2 M HCl (50 mL) to give a biphasic mixture. This mixture was washed with water (3× 30 mL), extracted with dichloromethane (4× 50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give **6c** as a pale yellow oil which was used for the next step without further purification.

2.3.4. 4-Bromo-2-phenylthiophene (***7a***)

Adapted from a previously published procedure [23], **5** (0.302 g, 1.25 mmol) and sodium carbonate (2.5 mL of a 2.0 M aqueous solution) were added dropwise to a stirred mixture of phenylboronic acid (0.165 g, 1.35 mmol), $Pd(PPh_3)_4$ (0.136 g, 0.118 mmol), and dioxane (15 mL) under an atmosphere of argon. After stirring at

100 °C for 4.5 h, the reaction mixture was allowed to cool to room temperature, diluted with diethyl ether (80 mL), poured into water (80 mL) to give a biphasic mixture, and extracted with diethyl ether (3× 80 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium chloride (3× 30 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification of the crude product by column chromatography (hexanes) gave pure **7a** as a colorless solid (0.2 g, 72%). ^{1}H NMR ($CDCl_3$, δ): 7.18 (d, J = 1.5 Hz, 1H, H3), 7.22 (d, J = 1.5 Hz, 1H, H5), 7.30–7.45 (m, 3H, Ar H), 7.54–7.61 (m, 2H, Ar H). ^{13}C NMR ($CDCl_3$, δ): 110.8, 122.2, 125.9, 126.0, 128.5, 129.3, 133.4, 145.7. HRMS-EI (m/z): $[M]^+$ calcd for $C_{10}H_7SBr$, 237.9452; found 237.9449.

2.3.5. 2-Biphenyl-4-bromothiophene (**7b**)

Prepared by a method similar to that used for **7a**, **7b** was obtained as a colorless solid (79%). ^{1}H NMR ($CDCl_3$, δ): 7.19 (d, J = 1.5 Hz, 1H, H3), 7.25 (d, J = 1.5 Hz, 1H, H5), 7.33–7.41 (m, 1H, Ar H), 7.42–7.50 (m, 2H, Ar H), 7.58–7.66 (m, 6H, Ar H). ^{13}C NMR ($CDCl_3$, δ): 110.6, 121.9, 125.6, 126.1, 126.9, 127.6, 127.6, 128.9, 132.1, 140.2, 141.0, 145.0. HRMS-ESI (m/z): $[M]^+$ calcd for $C_{16}H_{11}SBr$, 315.9744; found 315.9750. Anal. Calcd for $C_{16}H_{11}SBr$: C, 60.96; H, 3.52. Found: C, 60.25; H, 3.84. All values are given as percentages.

2.3.6. 4-Bromo-2-(4-dodecylphenyl)thiophene (**7c**)

Prepared by a method similar to that used for **7a**, **7c** was obtained as a colorless solid (60%). ^{1}H NMR ($CDCl_3$, δ): 0.89 (m, 3H, CH_3), 1.27 (m br, 18H, CH_2), 1.62 (m br, 2H, CH_2), 2.62 (m, 2H, CH_2), 7.13 (d, J = 1.5 Hz, 1H, H3), 7.15 (d, J = 1.5 Hz, 1H, H5), 7.17–7.23 (m, 2H, Ar H), 7.42–7.50 (m, 2H, Ar H). ^{13}C NMR ($CDCl_3$, δ): 14.3, 22.9, 29.5, 29.6, 29.7, 29.8, 29.9, 31.6, 32.2, 35.9, 110.6, 121.6, 125.4, 125.9, 129.3, 130.9, 143.6, 145.6. HRMS-EI (m/z): $[M]^+$ calcd for $C_{22}H_{31}SBr$, 406.1330; found 406.1332. Anal. Calcd for $C_{22}H_{31}SBr$: C, 64.85; H, 7.67. Found: C, 65.41; H, 7.71. All values are given as percentages.

2.3.7. 2,3-Dibromo-5-phenylthiophene (***8a***)

Adapted from a previously published procedure [24], **7a** (1.34 g, 5.60 mmol) and 70% aqueous solution of perchloric acid (100 μL, 1.16 mmol) were added to a stirred mixture of *N*-bromosuccinimide (1.27 g, 7.14 mmol) and carbon tetrachloride (8 mL) under an atmosphere of argon. After stirring at room temperature for 36 h, the reaction mixture diluted with chloroform (70 mL) and sodium carbonate (30 mL of a 2.0 M aqueous solution) to give a biphasic mixture. This mixture was extracted with chloroform (3× 70 mL), washed with water (2× 50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification of the crude product by column chromatography (pentane) gave pure **8a** as a colorless solid (1.5 g, 83%, mp 81 °C). ^{1}H NMR ($CDCl_3$, δ): 7.10 (s, 1H, H4), 7.30–7.43 (m, 3H, Ar H), 7.45–7.51 (m, 2H, Ar H). ^{13}C NMR ($CDCl_3$, δ): 110.1, 114.6, 125.5, 125.6, 128.6, 129.1, 132.7, 145.4. HRMS-EI (m/z): $[M]^+$ calcd for $C_{10}H_6SBr_2$, 315.8557; found 315.8556.

2.3.8. 5-Biphenyl-2,3-dibromothiophene (***8b***)

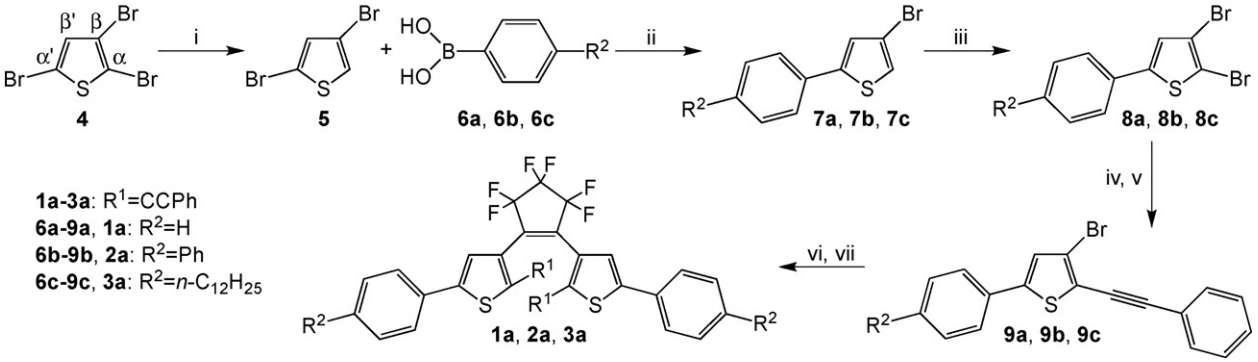
Prepared by a method similar to that used for **8a**, **8b** was obtained as a colorless solid (76%). ^{1}H NMR ($CDCl_3$, δ): 7.14 (s, 1H, H4), 7.33–7.41 (m, 1H, Ar H), 7.42–7.50 (m, 2H, Ar H), 7.52–7.66 (m, 6H, Ar H). ^{13}C NMR ($CDCl_3$, δ): 110.3, 114.8, 125.7, 126.0, 127.1, 127.9, 127.9, 129.1, 131.8, 140.3, 141.6, 145.2. HRMS-ESI (m/z): $[M]^+$ calcd for $C_{16}H_{10}SBr_2$, 393.8849; found 393.8854. Anal. Calcd for $C_{16}H_{10}SBr_2$: C, 48.76; H, 2.56. Found: C, 48.79; H, 2.84. All values are given as percentages.

2.3.9. 2,3-Dibromo-5-(4-dodecylphenyl)thiophene (***8c***)

Prepared by a method similar to that used for **8a**, **8c** was obtained as a colorless solid (71%). ^{1}H NMR ($CDCl_3$, δ): 0.88 (m, 3H, CH_3), 1.25 (m br, 18H, CH_2), 1.61 (m, 2H, CH_2), 2.60 (m, 2H, CH_2), 7.05 (s, 1H, H3), 7.15–7.22 (m, 2H, Ar H), 7.36–7.42 (m, 2H, Ar H). ^{13}C NMR ($CDCl_3$, δ): 14.1, 22.7, 29.2–29.7, 31.3, 31.9, 35.7, 109.4, 114.4, 125.0, 125.4, 129.1, 130.2, 143.8, 145.6. HRMS-EI (m/z): $[M]^+$ calcd for $C_{22}H_{30}SBr_2$, 484.0435; found 484.0426. Anal. Calcd for $C_{22}H_{30}SBr_2$: C, 54.33; H, 6.22. Found: C, 55.12; H, 6.21. All values are given as percentages.

2.3.10. 3-Bromo-5-phenyl-2-phenylethynylthiophene (***9a***)

Adapted from a previously published procedure [23], ethynylbenzene (0.067 g, 0.66 mmol) in triethylamine (1 mL), $PdCl_2(PPh_3)_2$ (2.3 mg, 3.3 μmol), and triphenylphosphine (1.1 mg, 4.2 μmol) were added dropwise to a stirred mixture of **8a** (0.207 g, 0.651 mmol) in triethylamine (1 mL) under an atmosphere of argon. After stirring at 35 °C for 15 min, copper iodide (2.0 mg, 10 μmol) was added to the reaction mixture and was stirred at 60 °C for 3.5 h. After allowing the reaction mixture to cool to room temperature, it was diluted with ethyl acetate (25 mL) and poured into water (25 mL) to give a biphasic mixture. This mixture was extracted with ethyl acetate (3× 25 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification of the crude product by column chromatography (1:9 chloroform/hexanes) gave pure **9a** as a colorless solid (0.14 g, 63%, mp 110.0–110.6 °C). ^{1}H NMR ($CDCl_3$, δ): 7.21 (s, 1H, H4), 7.31–7.45 (m, 6H, Ar H), 7.52–7.62 (m, 4H, Ar H). ^{13}C NMR ($CDCl_3$, δ): 81.6, 98.0, 117.0, 120.2, 122.9, 125.9, 126.0, 128.7, 128.9, 129.0, 129.4, 131.8, 133.0, 145.4. HRMS-EI (m/z): $[M]^+$ calcd for $C_{18}H_{11}SBr$, 337.9765; found 337.9755.



Scheme 2. Synthesis of dithienylethenes **1a**–**3a**. Reagents and conditions: (i) *n*-BuLi, Et_2O, Ar, −78 °C, 10 min, H_2O; (ii) $[Pd^0(PPh_3)_4]$, 6:1 dioxane/2 M Na_2CO_3, Ar, 100 °C, 4.5 h; (iii) NBS, 10 mol% $HClO_4$ (70% in H_2O), CCl_4, rt, 36 h; (iv) ethynylbenzene, $[Pd^{II}(PPh_3)_2]Cl_2$, PPh_3, Et_3N, Ar, 35 °C, 15 min; (v) CuI, Ar, 60 °C, 3.5 h; (vi) *n*-BuLi, THF, Ar, −78 °C, 30 min; (vii) octafluorocyclopentene, Ar, −78 °C, 4 h. Assignment of C^{α}, $C^{\alpha'}$, C^{β}, and $C^{\beta'}$ is shown for **4**, and used consistently for other thiophene derivatives.

*2.3.11. 5-Biphenyl-3-bromo-2-phenylethynylthiophene (**9b**)*

Prepared by a method similar to that used for **9a**, **9b** was obtained as a colorless solid (79%). ^{1}H NMR ($CDCl_3$, δ): 7.25 (s, 1H, H4), 7.33–7.41 (m, 4H, Ar H), 7.43–7.50 (m, 2H, Ar H), 7.55–7.66 (m, 8H, Ar H). ^{13}C NMR ($CDCl_3$, δ): 81.6, 98.0, 117.0, 120.0, 122.8, 126.0, 126.3, 127.2, 127.9, 128.0, 128.7, 129.0, 129.1, 131.8, 131.9, 140.4, 141.8, 145.0. HRMS-ESI (m/z): $[M]^+$ calcd for $C_{24}H_{15}SBr$, 416.0057; found, 416.0069. Anal. Calcd for $C_{24}H_{15}SBr$: C, 69.40; H, 3.64. Found: C, 68.73; H, 3.75.

*2.3.12. 3-Bromo-5-(4-dodecylphenyl)-2-phenylethynylthiophene (**9c**)*

Prepared by a method similar to that used for **9a**, **9c** was obtained as a colorless solid (67%, mp 63.1–63.7 °C). ^{1}H NMR ($CDCl_3$, δ): 0.88 (m, 3H, CH_3), 1.26 (m br, 18H, CH_2), 1.61 (m, 2H, CH_2), 2.61 (m, 2H, CH_2), 7.15 (s, 1H, H4), 7.16–7.22 (m, 2H, Ar H), 7.32–7.38 (m, 3H, Ar H), 7.42–7.48 (m, 2H, Ar H), 7.51–7.59 (m, 2H, Ar H). ^{13}C NMR ($CDCl_3$, δ): 14.4, 22.9, 29.5, 29.6, 29.7, 29.8, 29.9, 31.6, 32.2, 35.9, 81.7, 97.7, 116.8, 119.4, 122.9, 125.5, 125.8, 128.6, 128.9, 129.4, 130.4, 131.8, 144.1, 145.7. HRMS-EI (m/z): $[M]^+$ calcd for $C_{30}H_{35}SBr$, 506.1643; found 506.1623. Anal. Calcd for $C_{30}H_{35}SBr$: C, 70.99; H, 6.95. Found: C, 71.41; H, 6.65. All values are given as percentages.

*2.3.13. 1,2-Bis(5-phenyl-2-phenylethynylthien-3-yl) hexafluorocyclopentene (**1a**)*

Adapted from previously published procedures [3,25], *n*-butyllithium (0.17 mL of a 2.5 M solution in hexanes, 0.42 mmol) was added dropwise to a solution of **9a** (0.139 g, 0.410 mmol) in tetrahydrofuran (10 mL) at −78 °C and under an atmosphere of argon. After stirring for 30 min, octafluorocyclopentene (0.0275 mL, 0.205 mmol) was added dropwise to the reaction mixture at −78 °C. The mixture was stirred for another 4 h at −78 °C and then allowed to warm to room temperature. After 2 h, hydrochloric acid (50 mL of a 1.2 M aqueous solution) was added. Following vigorous stirring, tetrahydrofuran was removed under reduced pressure. After neutralization of the acid with saturated aqueous solution of sodium bicarbonate, the mixture was extracted with chloroform (3 × 20 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification of the crude product by column chromatography (1:3 toluene/hexanes) and recrystallization (*n*-hexane) gave pure **1a** as yellow crystals (0.077 g, 54%). ^{1}H NMR (CD_3COCD_3, δ): 7.18–7.25 (m, 4H, Ar H), 7.27–7.41 (m, 16H, Ar H), 7.50 (s, 2H, H4). ^{13}C NMR (CD_3COCD_3, δ): 80.5, 100.5, 121.9, 123.0, 123.9, 128.8, 129.0, 129.3, 131.5, 132.3, 132.5, 146.4. ^{19}F NMR (CD_3COCD_3, δ): −110.5 (t, J = 5.2 Hz, 4F), −132.7 (m, J = 5.2 Hz, 2F). HRMS-ESI (m/z): $[M]^+$ calcd for $C_{41}H_{22}S_2F_6$, 692.1067; found, 692.1066. Anal. Calcd for $C_{41}H_{22}S_2F_6$: C, 71.09; H, 3.20. Found: C, 71.32; H, 2.97. All values are given as percentages. UV–vis (*n*-hexane) λ_{max}, nm (log ε): 308 (4.63), 574 (4.07).

*2.3.14. 1,2-Bis(5-biphenyl-2-phenylethynylthien-3-yl) hexafluorocyclopentene (**2a**)*

Prepared by a method similar to that used for **1a**, **2a** was obtained as yellow crystals (46%). ^{1}H NMR (CD_3COCD_3, δ): 7.20–7.54 (m, 20H, Ar H), 7.57 (s, 2H, H4), 7.60–7.75 (m, 8H, Ar H). ^{13}C NMR ($CDCl_3$, δ): 81.2, 100.3, 122.5, 123.0, 124.0, 126.4, 127.1, 127.6, 127.9, 128.6, 129.1, 131.6, 131.9, 132.8, 140.5, 141.3, 145.5. ^{19}F NMR (CD_3COCD_3, δ): −110.5 (t, J = 5.2 Hz, 4F), −132.7 (m, J = 5.2 Hz, 2F). HRMS-ESI (m/z): $[M]^+$ calcd for $C_{53}H_{30}S_2F_6$, 844.1693; found 844.1729. Anal. Calcd for $C_{53}H_{30}S_2F_6$: C, 75.34; H, 3.58. Found: C, 75.50; H, 3.28. All values are given as percentages. UV–vis (*n*-hexane) λ_{max}, nm (log ε): 326 (4.90), 591 (4.43).

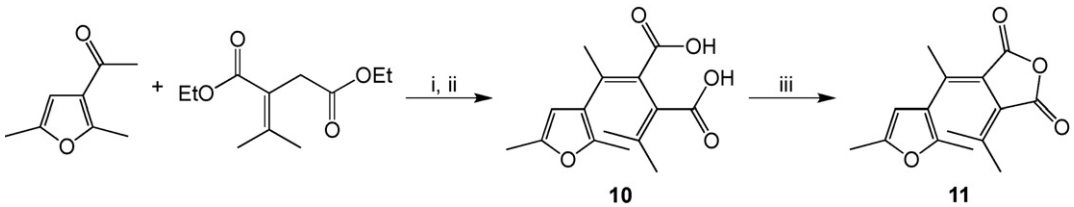
*2.3.15. 1,2-Bis(5-(4-dodecylphenyl)-2-phenylethynylthien-3-yl) hexafluorocyclopentene (**3a**)*

Prepared by a method similar to that used for **1a**, **3a** was obtained as a yellow solid (51%). ^{1}H NMR (CD_3COCD_3, δ): 0.88 (m, 6H, CH_3), 1.29 (m br, 36H, CH_2), 1.64 (m br, 4H, CH_2), 2.63 (m, 4H, CH_2), 7.13–7.24 (m, 8H, Ar H), 7.25–7.35 (m, 10H, Ar H), 7.44 (s, 2H, H4). ^{13}C NMR (CD_3COCD_3, δ): 13.7, 22.7, 29.2, 29.6, 29.7–29.8, 31.5, 32.0, 35.5, 80.6, 100.3, 122.0, 122.4, 123.4, 125.9, 128.8, 129.2, 129.3, 130.0, 131.5, 132.3, 144.1, 146.7. ^{19}F NMR (CD_3COCD_3, δ): −110.4 (t, J = 5.2 Hz, 4F), −132.7 (m, J = 5.2 Hz, 2F). HRMS-ESI (m/z): $[M]^+$ calcd for $C_{65}H_{70}S_2F_6$, 1028.4823; found 1028.4808. Anal. Calcd for $C_{65}H_{70}S_2F_6$: C, 75.84; H, 6.85. Found: C, 76.08; H, 7.05. All values are given as percentages. UV–vis (*n*-hexane) λ_{max}, nm (log ε): 312 (4.76), 580 (4.59).

*2.4. Procedures for the synthesis of photochromic actinometer **11***

*2.4.1. (E)-2-(1-(2,5-Dimethylfur-3-yl)ethylidene)-3-isopropylidenesuccinic acid (**10**)*

Adapted from a previously published procedure [26], a mixture of diethyl isopropylidenesuccinate (3.69 g, 17.2 mmol) and 3-acetyl-2,5-dimethylfuran (2.38 g, 17.2 mmol) was added to a stirred suspension of sodium hydride (1.38 g of a 60% dispersion in oil, 34.2 mmol) in toluene (35 mL) at 60 °C and under an atmosphere of argon as shown (Scheme 3). A drop of ethanol was added to initiate the reaction. After 1.5 h, the brownish reaction mixture was allowed to cool to room temperature and poured onto crushed ice (60 g) to give a biphasic mixture. The mixture was extracted with water (2× 50 mL) and the combined aqueous layers were acidified to a pH of 2 with hydrochloric acid (6.0 M aqueous solution) to liberate an oil. The organic phase was washed with water, extracted with ethyl acetate (3× 80 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The (*E*)- and (*Z*)-half-esters were obtained as a red gum (5.0 g, 96%). A 6% ethanolic solution of potassium hydroxide (50 mL) was added to the half-esters, refluxed for 15 h, and concentrated under reduced pressure. Water (60 mL) was added to the mixture and washed with diethyl ether (2× 40 mL). The aqueous layer was acidified to a pH of 2 with hydrochloric acid (6.0 M aqueous solution), extracted with ethyl acetate (3× 60 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The brownish oil was recrystallized (ethyl acetate/hexane) and an off-white solid, the (*Z*)-diacid, was removed by filtration (1.3 g). The remaining mother liquor was concentrated under reduced pressure and gave 10 as a brownish oil (3.4 g, 74%). This crude product was used for the next step without further purification.



Scheme 3. Synthesis of **11**. Reagents and conditions: (i) NaH, toluene, Ar, 60 °C, 1.5 h; (ii) KOH (6% in EtOH), 15 h; (iii) Ac_2O, 70 °C, 30 min.

2.4.2. (E)-2-(1-(2,5-Dimethyfurl-3-yl)ethylidene)-3-isopropylidenesuccinic anhydride (**11**)

Compound **11**, commonly known as Aberchrome 540, was synthesized since it is no longer commercially available. Adapted from a previously published procedure [26], a solution of **10** (3.30 g, 11.8 mmol) in acetic anhydride (34.2 mL, 362 mmol) was stirred at 70 °C for 30 min and concentrated under reduced pressure. Purification of the crude product by column chromatography (1:8 ethyl acetate/hexanes) and recrystallization (ethyl acetate/hexane) gave pure **11** as orange crystals (1.0 g, 33%, mp 124.0–124.5 °C). ^{1}H NMR ($CDCl_3$, δ): 1.35 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 5.92 (d, J = 0.6 Hz, 1H, Ar H).

2.5. Quantum yield and photoconversion studies

The cyclization and cycloreversion quantum yields of **1–3** in *n*-hexane were determined using **11** in *n*-hexane as a chemical actinometer. The procedures used to measure the photon rate or moles of photons absorbed by the irradiated solution per unit time have been well described [26–28]. Briefly, the absorbance of the solution containing **11** was matched to a solution containing the dithienylethene (i.e., **1–3**). The absorbances were matched at 313 and 530 nm for the cyclization and cycloreversion quantum yields, respectively. The matched solutions were irradiated with either UV or visible light for a known period of time under identical experimental conditions. After irradiation, the absorbance of each solution was measured immediately. From the change in absorbance for the solution containing **11**, the photon rate ($N_A h\nu/t$) was calculated using Eq. (1) when not all the incident light is absorbed [29],

$$\frac{N_A h\nu}{t} = \left[\frac{\log T_0}{(1-T_0)} - \frac{\log T_t}{(1-T_t)}\right] \times \frac{V}{\Phi_{\mathbf{11}} \times \varepsilon_{473} \times l \times t} \quad (1)$$

where $T = 10^{-A}$, A is the absorbance at 473 nm before irradiation, A_t is the absorbance at 473 nm after irradiation, V is the irradiated volume (L), $\Phi_{\mathbf{11}}$ is the quantum yield for the cyclization of **11** at the irradiation wavelength used ($\Phi_{\mathbf{11}} = 0.21$ [30]), ε_{473} is the molar absorptivity of **11** at 473 nm ($\varepsilon_{473} = 8189\ M^{-1}\ cm^{-1}$ [30]), l is the optical pathlength of the quartz cell, and t is the irradiation time.

To determine the cyclization quantum yield, the change in absorbance for the dithienylethene solution before and after irradiation with UV light was measured at the wavelength of maximum absorption (λ_{max}) in the visible region. From this change in absorbance and rearranging Eq. (1), the quantum yield (Φ) was calculated using Eq. (2),

$$\Phi = \left[\frac{\log T_0}{(1-T_0)} - \frac{\log T_t}{(1-T_t)}\right] \times \frac{V}{(N_A h\nu/t) \times \varepsilon_{max} \times l \times t} \quad (2)$$

where T_0 is the transmittance at λ_{max} before irradiation, T_t is the transmittance at λ_{max} after irradiation, ε_{max} is the molar absorptivity at λ_{max} in the visible region. The cycloreversion quantum yield was determined in a similar manner. Before the solutions containing **11** and the dithienylethene were matched, they were irradiated with UV light (ca. 10–30 min) to their photostationary state. The absorbance of each solution was measured following irradiation with visible light and the photon rate was calculated using $\Phi_{\mathbf{11}} = 0.10$ [29]. In order to determine ε_{max} for the closed-ring isomer of the dithienylethene, the concentration of the closed-ring isomer at the photostationary state required calculation. This was achieved by multiplying the photoconversion (see below) by the concentration of the dithienylethene solution prior to irradiation with UV light.

The photoconversion from the open-ring to the closed-ring isomers at the photostationary state after irradiation with UV light was determined for **1–3** from HPLC studies. The integrated area for the peak representing the closed-ring isomer was divided by the sum of the integrated areas for the peaks representing both isomers and was calculated as a percentage. Note that irradiation of **1a** with UV light near the photostationary state did produce an unidentified photoproduct which was not reversible upon exposure to visible light. Irreversible photoproducts resulting from the diatropic rearrangement of the closed-ring isomer of other dithienylethenes have been reported [31,32]. The observed differences between the UV–vis spectra obtained by HPLC for **1b** and the photoproduct are consistent with these previous reports. As a result, prolonged irradiation with UV light should be avoided. The photoproduct was not observed during irradiation times used for quantum yield determinations. The integrated area for the photoproduct was included in our sum and was <5% of the total integrated area. The retention times for the unidentified photoproduct, **1a**, **1b**, **2a**, **2b**, **3a**, and **3b** were 7.0, 7.4, 12.1, 7.7, 11.0, 20.9, and 27.0 min, respectively.

2.6. X-ray crystallography

Structure solution was carried out using the SHELX97 suite of programs [33] and the WinGX graphical interface [34]. Initial solutions were obtained by direct methods and refined by successive least-squares cycles. The fluorinated cyclopentene ring in the structure of **2a** was disordered.

3. Results and discussion

Dithienylethenes **1a–3a** all contain rigid phenylethynyl substituents at the C2 position (C^{α}) of both thiophene rings, the reactive carbons that participate in electrocyclic ring-closing and ring-opening reactions. The presence of potentially reactive alkyne substituents does present some limitations to the relative substitution order on thiophene. For this reason, our regioselective approach introduces functional groups at $C^{\alpha'}$ of thiophene prior to the introduction of alkynyl substituents at C^{α}. The synthetic methodology presented here is based on the conversion of 2,3,5-tribromothiophene (**4**) to 2,4-dibromothiophene (**5**) (Scheme 2). Palladium-catalyzed Suzuki cross-coupling reactions were used for the regioselective substitution at C2 of the α′-halogenated thiophene ring systems [23]. The availability of boronic acid derivatives is dependent on the conversion of halogenated reagents to the corresponding borates. We explored the possibility of forming a borate at C2 of **5**, however, reaction with an additional equivalent of *n*-BuLi followed by quenching with water showed no evidence for lithiation at C2 ($C^{\alpha'}$). Further, we observed the formation of a 2-lithio-3,5-dibromothiophene intermediate, primarily due to bromine rearrangements accompanied by hydrogen abstraction. This base-catalyzed halogen dance reaction has been reported for other α-halothiophene ring systems [35,36]. Therefore, phenylboronic acid (**6a**), biphenylboronic acid (**6b**), and 4-dodecylphenylboronic acid (**6c**) [22] were employed in palladium-catalyzed Suzuki cross-coupling reactions with **5**. We observed regioselective coupling of **5** at C2 ($C^{\alpha'}$) to produce compounds **7a**, **7b**, and **7c** in modest yields (72, 79, and 60%, respectively). A two-phase catalytic method was utilized for further bromination of **7a–7c**. It has been shown that 0.1–10 mol% of 70% perchloric acid can act as a phase-transfer catalyst in the electrophilic substitution of heterocycles such as thiophene [24]. The electrophilic bromination of **7a–7c** was achieved in high yields (>70%) and regioselectively at C^{α} to produce **8a–8c**. The regioselective conversion of the 2,4-disubstituted thiophene to the 2,3,5-trisubstituted analog is illustrated in Fig. 1 by comparing the aromatic regions of the ^{1}H NMR spectra of **7c** (a) and **8c** (b). It is important to note that no side-products were found at either $C^{\beta'}$ of thiophene, or the benzylic carbon of **7c**. Conditions for the well-known palladium-catalyzed Sonogashira cross-coupling were used

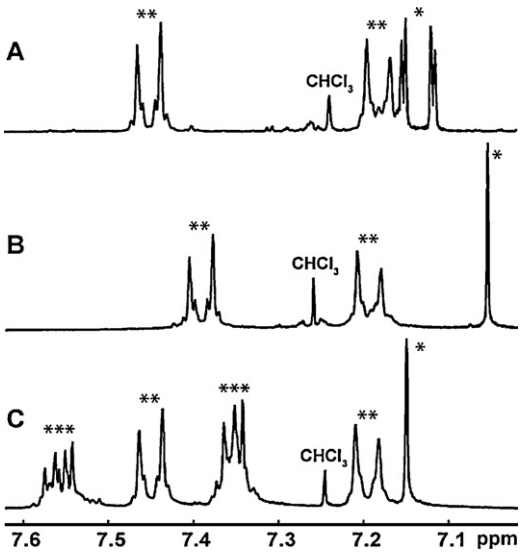


Fig. 1. ^{1}H NMR spectra showing regioselective substitutions on thiophene (aromatic regions only) for **7c** (a), **8c** (b), and **9c** (c). The peaks labeled with asterisks represent the following proton environments: *thiophene, **2-dodecylphenyl, and ***2-phenylethynyl.

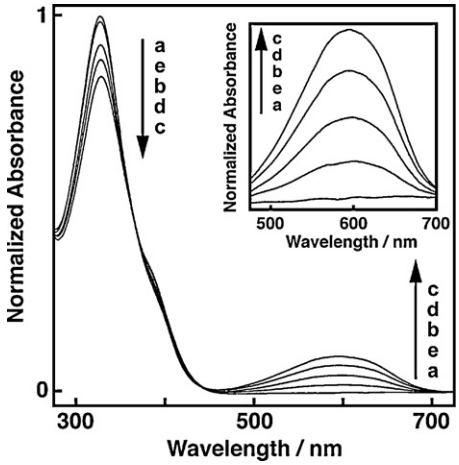


Fig. 2. Normalized absorption spectra of 2 in *n*-hexane prior to irradiation (a) and after irradiation with UV or visible light in the following sequence: (b) 6 min of UV, (c) 21 min of UV, (d) 15 s of visible, and (e) 80 s of visible. The inset is an expansion of the 475–700 nm region. The absorption spectra recorded after irradiation were normalized to the absorption spectrum prior to irradiation with light by dividing the absorbance values of the former by the absorbance value of the latter at λ_{max} (i.e., 326 nm).

to conjugate phenylacetylene to the bromo-substituted C2 position (C^{α}) of **8a**–**8c** [23]. Regioselective modification at C2 (C^{α}) was clearly observed by ^{1}H NMR (Fig. 1(c)). The final coupling of **9a**–**9c** with octafluorocyclopentene gave compounds **1a**–**3a** in moderate yields.

Compounds **1a**–**3a** were observed to undergo reversible photoisomerization in *n*-hexane. Upon irradiation with UV light, a pale yellow solution of **2a** turned blue and an increase in absorbance was observed at 591 nm with a concomitant decrease at 326 nm, as shown in Fig. 2(b). This new absorption band in the visible region represents the formation of the closed-ring isomer **2b**. The wavelengths of maximum absorption for **2** were ca. 18 nm larger than **1** due to the extended conjugation length of the biphenyl derivative (Table 1). Further irradiation with UV light brought the system to a photostationary state of the open-ring and closed-ring isomers (Fig. 2(c)). In fact, the isosbestic point observed at 439 nm is a strong indication that only two interconverting species are present in solution [37]. The photoisomerization of **2b** was completely reversible following irradiation with visible light (Fig. 2(d and e)). Similar reversibility was also observed for **1b** and **3b**. In addition, no thermal discoloration of **1b**–**3b** was observed even after 24 h in the dark at room temperature.

The cyclization and cycloreversion quantum yields of **1–3** were also determined in *n*-hexane. An equilibrium mixture of two conformers exists for dithienylethenes in solution. The thienyl rings have either mirror symmetry (parallel conformation) or C_2 symmetry (antiparallel conformation). The conrotatory photocyclization reaction can proceed only from the antiparallel conformation [3]. In general, the ratio of the two conformers is 1:1, therefore, the cyclization quantum yield cannot exceed 0.5. Consequently, the cyclization quantum yield is dependent on the ratio of the conformations. When the ratio of the non-photoreactive parallel conformation is increased, the quantum yield is expected to decrease. Consistent with a previous report [12], the photoconversion from **1a** to **1b** was 56% and the cyclization quantum yield was 0.14. The cyclization quantum yield for **2a** and **3a** were 2-fold and ca. 4-fold lower than **1a**, respectively. The large decreases in the cyclization quantum yields strongly correlate with the lower conversions for **2a** and **3a** of 40 and 21%, respectively. The decrease in conversion efficiencies is most likely due to an increased concentration of the parallel conformation prior to photoirradiation. In particular, we suggest that intramolecular interactions between the long alkyl chains of **3a** will favor the parallel conformation, thus lowering the cyclization quantum yield.

The introduction of phenylethynyl substituents at the reactive carbons has been shown to enhance the efficiency of the cycloreversion reaction relative to the cyclization reaction [12]. We observed similar enhancements, in which cycloreversion quantum yields for **1b**–**3b** were at least 3-fold larger than the cyclization quantum yields.

X-ray crystallographic analysis was performed for **2a**. As shown in Fig. 3, **2a** is packed in the crystal as the antiparallel conformer. The distance between the reactive carbon atoms in **2a** was determined to be 355 pm, which is short enough for photocyclization to occur within the crystal [38]. However, given the large change in molecular geometry upon isomerization, **2a** was not expected to undergo a crystal-to-crystal transformation. A similar finding was observed for **1a** where the distance between reactive carbon

Table 1
Absorption properties and photochromic reactivity of dithienylethenes (DTE) in *n*-hexane.[a]

DTE	λ_{max} (nm)[b]	ε_{max} (10^4 M^{-1} cm^{-1})	$\Phi_{o\rightarrow c}$[c]	DTE	λ_{max} (nm)[b]	ε_{max} (10^4 M^{-1} cm^{-1})	$\Phi_{c\rightarrow o}$[d]	Conversion (%)[e]
1a	308	4.27 ± 0.14	0.14 ± 0.01	**1b**	574	1.17 ± 0.04	0.44 ± 0.02	56
2a	326	8.01 ± 0.35	0.070 ± 0.002	**2b**	591	2.67 ± 0.12	0.23 ± 0.03	40
3a	312	5.76 ± 0.23	0.036 ± 0.002	**3b**	580	3.86 ± 0.09	0.13 ± 0.01	21

[a] The error is the standard deviation for the mean taken from a minimum of three independent measurements.
[b] The error is ± 1 nm.
[c] Cyclization quantum yield.
[d] Cycloreversion quantum yield.
[e] The error is ± 2%.

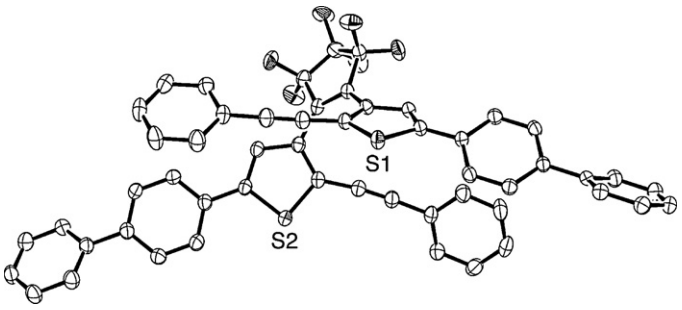


Fig. 3. ORTEP diagram showing the molecular structure of **2a**. Hydrogen atoms have been omitted for clarity.

atoms was 344 pm [12]. In addition, we suggest that intramolecular π–π interactions between the biphenyl and phenylethynyl substituents in the crystalline state may also suppress this reactivity.

4. Conclusions

This work provides a regioselective approach for the preparation of dithienylethenes containing phenylethynyl substituents at the reactive carbons, and various functional groups at the periphery. The prepared dithienylethenes undergo reversible photoisomerization in solution and the closed-ring isomers are thermally stable. Compound **3a** has been specifically designed to improve the lipid complementarity of these photochromic molecules in liposomes, through the integration of long alkyl chains. Given the large changes in molecular geometry expected for **3a**, this molecule may be used in the development of photoresponsive liposomes with reversible photocontrols over membrane stability. In fact, preliminary results suggest that the photoisomerization of **1a**–**3a** in liposomes is reversible. While these results are encouraging, further studies are currently underway to fully characterize the photoisomerization and inclusion of these photochromic molecules in liposomes, and to evaluate the effect of their photoisomerization on membrane stability.

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