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Synthesis of a Thiophene-Based Nonlinear Optical Chromophore

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Abstract: This report details an eight-step synthesis of the thiophene-type nonlinear optical chromophore **1** in 38% overall yield. Only one early step required chromatography.

Keywords: Horner–Wadsworth–Emmons, Knoevenagel, nonlinear optical, thiophene, Vilsmeier–Haack

As part of a program to develop a nonlinear optical polymer for an optical modulator application, a consistent supply of the reported chromophore **1**[1,2] was needed (see Scheme 1). The chemistry started out similar to previous work on a CLD-type chromophore.[3] Protection of the hydroxyl group of **2** was found to proceed in neat acetic anhydride, and the acetylated product **3** could be purified by distillation directly from the reaction mixture.[4] The Vilsmeier–Haack formylation to give **4** was run at a molar scale. Although the reaction is exothermic, generated heat was controlled by dosing of the phosphorous oxychloride.[5,6] The product was purified by rapid filtration through a silica-gel plug. Acetate protection of **4** was easily removed by aqueous sodium hydroxide, and the alcohol **5** was isolated by precipitation. Using the previously prepared phosponate **6**,[7] the Horner–Wadsworth–Emmons condensation went smoothly to give the trans-stilbene **7**, and trace amounts of the regioisomer were removed by recystallization.

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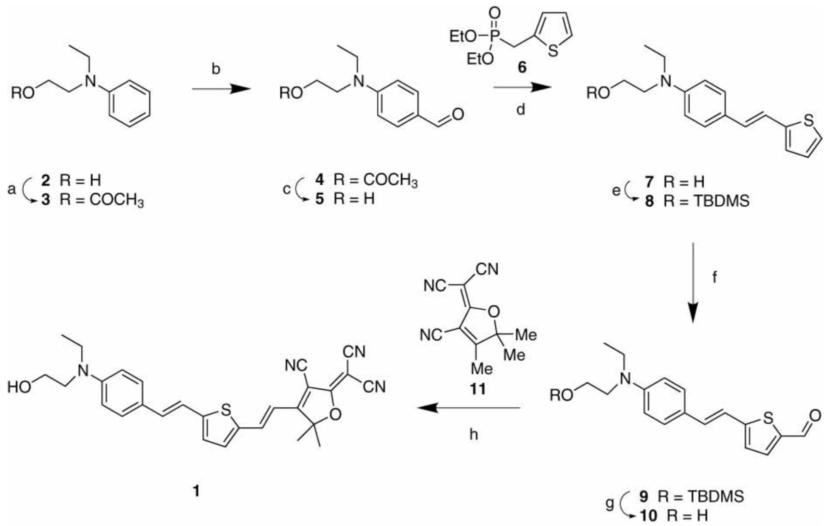

Scheme 1. Reagents and contions: a) Ac_2O, 99%; b) DCE, DMF, $POCl_3$, reflux, 93%; c) MeOH, H_2O, NaOH, 95%; d) KO*t*Bu, THF, 75%; e) TBDMSCl, imidazole, DMF, 100%; f) hexyllithium, DMF, THF, 0°C; g) acetone, H_2O, conc. HCl, 65% from 7; h) EtOH, piperidinium acetate, reflux, 89%.

In transforming **7** to **10**, attempts were made to avoid using the expensive *tertiary* butyldimethylsilyl chloride reagent as a protection strategy. We first tried to repeat the work of Hu et al.,[2] who were able to make **10** from **7** directly, without the use of any protection. The reaction was successful on a small scale (200 mg), but when scaling up, the formylation would not go to completion. The dilithium salt of **7** was found to precipitate under these conditions (−78°C, THF, hexyllithium in hexanes) and running the reaction at higher temperature (0°C) or more dilution did not help. Next, we tried trimethylsilyl protection similar to that of Alcaraz et al.[8] for lithiation of a thiophene containing a tertiary alcohol. The trimethylsilyl derivative of alcohol **7** was prepared in situ (trimethylsilyl chloride/hexyllithium) without isolation because of its labile nature. After silylation, 1 equiv of hexyllithium gave **10** along with some **7**, which was encouraging. However, in attempting to drive the formylation to completion with excess base, a new product was formed, which (by thin-layer chromatography) was probably the result of the lithiated thiophene attacking a trimethylsilyl ether and giving a trimethylsilylthiophene derivative. Because we could not find the correct ratio hexyllithium/trimethylsilyl chloride/*N*,*N*-dimethylformamide to give **10** cleanly on small scale, the idea was abandoned for scale up. Lastly, we acetylated the alcohol **7** and tried another Vilsmeier–Haack formylation with conditions used previously. The reaction gave the product but also polar impurities requiring chromatography.

We settled for the expensive but robust *tert*-butyldimethylsilyl protection strategy. The *tert*-butyldimethylsilyl group was put on easily by initially forming the *N*-silylimidazole intermediate and then adding alcohol **7**. The lithiation and formylation reactions were found to run cleanly at 0°C; no silylation of the thiophene was detected. The silyl-ether **9** could be telescoped into the deprotection reaction, and **10** precipitated during workup and purification by recrystallization.

The final Knoevenagel condensation between **10** and the tricyanodihydrofuran **11**[3] went very well, using a catalytic amount of piperidinium acetate in refluxing ethanol. (The final condensation conditions of refluxing ethanol were suggested by Dr. Philip A. Sullivan, University of Washington.) The best results came by using a slight excess of **10** to ensure complete consumption of **11**, which can contaminate the product. The chromophore **1** precipitated from the reaction mixture in a high-purity, crystalline form that only required a reslurry to become analytically pure.

In conclusion, we report an eight-step synthesis of the thiophene-type nonlinear optical chromophore **1**, in 38% overall yield. Conditions were found that gave the final product in high purity without chromatography.

EXPERIMENTAL

Melting points were collected on an electrothermal capillary melting-point apparatus and are not corrected. All NMR spectra were obtained on a Bruker AC-200 spectrometer (^{1}H at 200 MHz, ^{13}C at 50 MHz) in $CDCl_3$ and are referenced to solvent or tetramethylsilane. Silica gel (32–63 μm, 60 Å) was purchased from Scientific Adsorbents Inc. (Atlanta), (catalog no. 02826). For the silica gel, plug filtrations used to purify compounds **4**, a quick separation column/funnel from Chemglass (Vineland, NJ) (part no. 1412-27) was used. The bottom-drain 20L unjacketed reactor system (part no. 1966-620) was from Chemglass (Vineland, NJ). The following reagents were purchased from Aldrich Chemical Co. (Milwaukee) and used as received: **2** [-(*N*-ethyl-anilino)ethanol, 99%], acetic anhydride (ACS reagent, >98%), *tert*-butyldimethylsilyl chloride (97%), anhydrous *N*,*N*-dimethylformamide (99.8%), phosphorous(III) oxychloride (ReagentPlus™, 99%), 1,2-dichloroethane (ACS reagent, >99%), imidazole (ACS reagent, >99%), hexyllithium solution 2.3 M in hexanes, methylene chloride (ACS reagent, >99%, contains 50 ppm of amylene), anhydrous THF containing 250 ppm of BHT, and anhydrous THF, Darco® G-60. The piperidinium acetate was prepared by addition of 1 equiv of glacial HOAc to a cold, Et_2O solution of piperidine and suction filtration of the product. All other reagents were obtained commercially and used as received. Elemental analysis was performed by Atlantic Microlabs, Inc. (Norcross, GA).

N-Ethyl-*N*-(2-acetoxyethyl)aniline, 3

A 3-L, two-neck, round-bottomed flask was equipped with a thermometer for internal temperature and magnetic stirbar. The flask was charged with 400 g of **2** (2.42 mol), and the other neck of the flask was equipped with a reflux condenser with a 500-mL addition funnel on top. The addition funnel was charged with 271.5 g of acetic anhydride (251.4 mL, 1.1 equiv). The reaction was run open to the atmosphere. A heating mantle was equipped, and the alcohol was heated to 75°C. The anhydride was added over 30 min, and the internal temperature gradually rose to 130°C. At the halfway point, a liquid can be seen refluxing, which presumably is acetic acid. The reaction was complete (measured by thin-layer chromatography) after the addition. The mixture was allowed to cool to rt. The by-product acetic acid and excess acetic anhydride were distilled (60–70°C, 5 torr) and collected. Stronger vacuum was applied, and the product was distilled from the pot (120–130°C, 1.5 torr). The colorless liquid obtained weighed 499 g (99%). δ_H: 7.29 (t, $J = 8.3$ Hz, 2H), 6.85–6.69 (m, 3H), 4.28 (t, $J = 6.5$ Hz, 2H), 3.59 (t, $J = 6.5$ Hz, 2H), 3.46 (q, $J = 7.1$ Hz, 2H), 2.09 (s, 3H), 1.23 (t, $J = 6.9$ Hz, 3H); δ_C: 147.56, 129.28, 116.18, 111.95, 61.64, 48.75, 45.13, 20.76, 12.18.

4-(*N*-Ethyl-*N*-(2-acetoxyethyl)amino)benzaldehyde, 4

To a 3-L reactor, 207 g of **3** (1 mol), 128 g of anhydrous DMF (1.75 mol, 1.75 equiv), and 800 mL of 1,2-dichloroethane were added. The mixture was vigorously stirred with a magnetic stirbar while a steady stream of 162.3 mL of $POCl_3$ (1.75 mol, 1.75 equiv) was added by addition funnel over 25 min. The temperature within the reaction rose to 78°C. The mixture was then heated to 82°C for 6 h. The reaction was cooled to rt and poured onto 2.5 kg of ice and H_2O in a 20-L bottom-drain pilot reactor. The mixture was neutralized (pH 8–9) with 500 g of anhydrous Na_2CO_3 dissolved in 2 L of H_2O. The mixture was extracted four times with 1-L portions of CH_2Cl_2. The combined organic layers were washed with 1 L of H_2O followed by 1 L of brine. The organic layer was then evaporated, leaving a brown oil. The oil was dissolved in 1 L of Et_2O and filtered through 100 g of SiO_2 to remove some of the color. The combined filtrates were evaporated to leave the title compound as a light brown liquid (218.2 g, 93%). ^1H NMR showed that the material was >97%. δ_H: 9.78 (s, 1H), 7.76 (d, $J = 9.3$ Hz, 2H), 6.78 (d, $J = 9.3$ Hz, 2H), 4.29 (t, $J = 6.4$ Hz, 2H), 3.67 (t, $J = 6.4$ Hz, 2H), 3.52 (q, $J = 7.1$ Hz, 2H), 2.07 (s, 3H), 1.25 (t, $J = 7.1$ Hz, 3H).

4-(*N*-Ethyl-*N*-(2-hydroxyethyl)amino)benzaldehyde, 5

In a 2-L reaction flask, 218.2 g of **4** (0.93 mol) followed by 1 L of MeOH were added. The solution was magnetically stirred while 10% aqueous NaOH

[37.2 g of NaOH (0.93 mol)/H_2O (370 mL)] was added over 10 min. The mixture becomes warm to the touch, and TLC showed hydrolysis was complete after the addition was complete. The solvent was rotary evaporated, leaving a pale orange oil. The oil was partitioned between 500 mL of CH_2Cl_2 and 500 mL of H_2O. The aqueous phase was further extracted twice with 100-mL portions of CH_2Cl_2. The combined organic phases were rotary evaporated, leaving an oil. The oil was stirred with 200 mL of hexanes/Et_2O (2 : 1) while cooling in an ice bath to cause the product to precipitate. The light tan powder was collected on a medium-porosity glass frit and air-dried overnight (171.4 g, 95%). We were unable to obtain crystals of the low-melting solid for melting-point determination. δ_H: 9.59 (s, 1H), 7.64 (d, $J = 9.2$ Hz, 2H), 6.72 (d, $J = 8.9$ Hz, 2H), 3.83 (q, $J = 5.8$ Hz, 2H), 3.62–3.39 (m, 4H), 1.20 (t, $J = 7.2$ Hz, 3H); δ_C: 190.45, 152.99, 132.42, 124.67, 111.03, 59.73, 52.28, 45.74, 11.98.

trans-2-[4-(*N*-Ethyl-*N*-(2-hydroxyethyl)amino)styryl]thiophene, 7

A 1-L, two-neck flask equipped with magnetic stirbar and reflux condenser was charged with 47.4 g of **5** (0.245 mol), 53.54 g of **6**[7] (0.245 mol, 1 equiv), and 500 mL of anhydrous THF (inhibitor free). The mixture was stirred until dissolution. Within 15 min, 32.89 g of KO*t*Bu (0.29 mol, 1.2 equiv) were added in 5-g portions to the reaction mixture. The mixture becomes red in color and reaches reflux temperature. The mixture was stirred 1 h, slowly cooling to rt, whereby TLC showed the reaction was complete. The solvent was rotary evaporated, leaving a red oil. Saturated aqueous $NaHCO_3$ (500 mL) was added to the flask, and the mixture became a green color. A yellow-green solid precipitated. The mixture was stirred for 1 h and filtered through a medium-porosity glass frit. The filter cake was washed four times with 300-mL portions of H_2O on the frit and air-dried on the frit overnight. The mass of the crude product was 50.16 g (75%). The aqueous washes were not extracted. The crude product was dissolved in 400 mL of CH_2Cl_2 to give a green solution and washed with 200 mL of saturated aqueous $NaHCO_3$, 200 mL of H_2O, and finally 200 mL of brine. The organic phase was dried over $MgSO_4$ and filtered. The filtrate was treated with 5 g of Darco® G-60 for 1 h and filtered through diatomaceous earth. The yellow filtrate was rotary evaporated to a yellow-orange solid. The solid was more than 95% by NMR. The title compound can be recrystallized from toluene to give slightly orange, chunky crystals. Mp 93–95°C. δ_H: 7.36 (d, $J = 8.9$ Hz, 2H), 7.1–7.11 (m, 1H), 7.05 (d, $J_{ab} = 16.2$ Hz, 1H), 7.01–6.95 (m, 2H), 6.86 (d, $J_{ab} = 16.2$ Hz, 1H), 6.75 (d, $J = 8.9$ Hz, 2H), 3.81 (t, $J = 5.7$ Hz, 2H), 3.54–3.38 (m, 4H), 1.76 (bs, OH), 1.19 (t, $J = 7.0$ Hz, 3H); δ_C: 147.84, 143.97, 128.61, 127.73, 127.61, 125.41, 124.72, 123.16, 117.77, 112.62, 60.22, 52.45, 45.68, 12.08. $C_{16}H_{19}NOS$: C, 70.29; H, 7.00; N, 5.12.

trans-2-[4-(*N*-Ethyl-*N*-(2-*tert*-butyldimethylsiloxyethyl)amino)styryl]thiophene, 8

To a magnetically stirred solution of 5.72 g of imidazole (0.084 mol, 1.1 equiv) in 50 mL of anhydrous DMF, 12.68 g TBDMSCl (0.084 mol, 1.1 equiv) were added in one portion. After stirring at rt for 20 min, all the solids had dissolved, and 20.87 g of **7** (0.076 mol, 1 equiv) were added portionwise over 15 min. The temperature rose to 35°C. The reaction was allowed to stir until rt, whereupon TLC indicated complete reaction. The mixture was poured into 500 mL of H_2O and extracted with 250 mL of $CHCl_3$. The aqueous was extracted twice more with 100-mL portions of $CHCl_3$. The organic extracts were combined and washed twice with 200-mL portions of H_2O. The organic extracts were washed with 200 mL of saturated $NaHCO_3$ and then 200 mL of brine and then dried over $MgSO_4$. The solvent was rotary evaporated, and volatiles were removed under high vacuum (60°C, 1 torr). The yellow-orange oil (29.6 g, 100%) was more than 98% by NMR, and no further purification performed. δ_H: 7.29 (d, $J = 9.2$ Hz, 2H), 7.1–7.01 (m, 1H), 6.97–6.9 (m, 3H), 6.82 (d, $J_{ab} = 15.9$ Hz, 1H), 6.62 (d, $J = 9.0$ Hz, 2H), 3.74 (t, $J = 6.1$ Hz, 2H), 3.47–3.31 (m, 4H), 1.14 (t, $J = 7.2$ Hz, 3H), 0.88 (s, 9H), 0.02 (s, 6H); δ_C: 147.69, 144.27, 128.95, 127.82, 127.64, 124.69, 124.54, 123.04, 117.36, 111.83, 60.86, 52.69, 45.70, 26.14, 18.51, 12.45, −5.13.

trans-[4-(*N*-Ethyl-*N*-(2-*tert*-butyldimethylsiloxyethyl)amino)styryl]thiophene-5-carboxaldehyde, 9

A two-neck, 2-L, round-bottomed flask was charged with a magnetic stirbar and equipped with a 100-mL pressure-equalizing addition funnel. The flask was adapted to a N_2 bubbler. The flask was charged with 500 mL of anhydrous THF (containing 250 ppm of BHT) and 29.7 g of **7** (0.077 mol). The solution was cooled to 0°C with an ice bath. To the addition funnel, 56.5 mL of 2.3 M hexyllithium in hexanes (0.13 mol, 1.7 equiv) were added, and the base was added dropwise over 20 min. The mixture became green in color and was stirred a further 15 min. A new pressure-equalizing addition funnel was equipped and filled with a solution of 11.2 g of anhydrous DMF (0.15 mol, 2 equiv) in 50 mL of anhydrous THF (containing 250 ppm of BHT), which was added over 10 min. The internal temperature increased to 6°C during the addition. The cooling bath was removed, and the mixture stirred at rt for 2 h. The addition funnel was charged with 14.9 g of glacial HOAc (0.26 mol, 2 equiv relative to base) dissolved in 100 mL of H_2O and was added over 15 min. The internal temperature rose to 29°C, and the mixture became bright orange in color. The mixture was rotary evaporated, and the red residue was partitioned between 250 mL of $CHCl_3$ and 200 mL of H_2O. The organic phase was washed again with

200 mL of H_2O and rotary evaporated. The red oil was placed under vacuum (rt, 1 torr) to remove residual solvent. NMR showed the crude product was more than 95% pure and was used in the next step without further purification. δ_H: 9.76 (s, 1H), 7.56 (d, $J = 4.1$ Hz, 1H), 7.30 (d, $J = 8.9$ Hz, 2H), 7.03 (d, $J_{ab} = 15.9$ Hz, 1H), 6.98 (d, $J = 4.1$ Hz, 1H), 6.90 (d, $J_{ab} = 16.3$ Hz, 1H), 6.60 (d, $J = 8.9$ Hz, 2H), 3.71 (t, $J = 5.9$ Hz, 2H), 3.47–3.30 (m, 4H), 1.12 (t, $J = 7.4$ Hz, 3H), 0.83 (s, 9H), −0.02 (s, 6H).

***trans*-2-[4-(*N*-Ethyl-*N*-(2-hydroxyethyl)amino)styryl]thiophene-5-carboxaldehyde, 10**

A 1-L round-bottomed flask containing 32 g of **9** (0.077 mol) was charged with a magnetic stirbar and 500 mL of acetone. The mixture was stirred until dissolution, and a solution of 7 mL of conc. HCl (0.085 mol, 1.1 equiv) in 20 mL of H_2O was added in a steady stream over 10 min. The mixture was stirred at 35°C for 3 h, after which time no **9** remained by TLC. The solvent was rotary evaporated to leave thick red oil. Water (500 mL) was added to the flask, and the mixture was magnetically stirred and slowly basified (pH 8) with saturated aqueous Na_2CO_3. A brick-red solid precipitated. After stirring 30 min, the mixture was filtered on a coarse-porosity glass frit. The filter cake was washed on the frit twice with 250-mL portions of H_2O and then air dried on the frit 1 h. The brick-red, granular solid was transferred to a 1-L Erlenmeyer flask and partitioned between 500 mL of CH_2Cl_2 and 500 mL of H_2O. The phases were split, and the organic phase was washed again with 500 mL of H_2O. The organic layer was separated, dried over $MgSO_4$, and rotary evaporated to a brick-red solid. The crude was slurried with 100 mL of EtOAc for 1 h and filtered. The product was recrystallized from toluene to give 15.0 g of title compound as clear, garnet-colored crystals (65% from **8**). The mother liquor from the EtOAc slurry carried the remainder of the product. Mp 95–97°C (lit.[1] 106.2°C). δ_H: 9.76 (s, 1H), 7.59 (d, $J = 3.9$ Hz, 1H), 7.34 (d, $J = 8.6$ Hz, 2H), 7.07 (d, $J_{ab} = 14$ Hz, 1H), 7.02 (d, $J = 3.9$ Hz, 1H), 6.95 (d, $J_{ab} = 16$ Hz, 1H), 6.7 (d, $J = 8.6$ Hz, 2H), 3.8 (t, $J = 5.9$ Hz, 2H), 3.56–3.36 (m, 4H), 2.22 (bs, OH), 1.17 (t, $J = 7.1$ Hz, 3H); δ_C: 182.59, 154.49, 148.83, 140.16, 137.93, 133.61, 128.72, 125.19, 123.91, 116.19, 112.29, 60.28, 52.42, 45.65, 12.15. Elemental analysis calculated for $C_{17}H_{19}NO_2S$: C, 67.8; H, 6.3; N, 4.65. Found: C, 67.74; H, 6.35; N, 4.65.

***E*,*E*-[3-Cyano-4-[2-[5-[2-[4-[ethyl(2-hydroxyethyl)amino]phenyl]ethenyl]-2-thienyl]-ethenyl]-5,5-dimethyl-2(5*H*)-furanylidene]-propanedinitrile, 1**

A 500-mL round-bottomed flask equipped with magnetic stirbar was charged with 5.0 g of **10** (0.017 mol, 1.1 equiv), 2.9 g of **11** (0.015 mol, 1.0 equiv), 200 mg of piperidinium acetate (0.001 mol, 0.06 equiv), and 200 mL of EtOH, and the mixture was refluxed under an N_2 atmosphere protected from light. After 12 h, the mixture was dark maroon, and TLC (SiO_2; EtOAc) showed all **10** and **11** were consumed. The mixture was cooled in an ice bath and filtered through a medium-porosity glass frit. The rust-colored, microcrystalline powder was washed twice with 50-mL portions of EtOH and air dried on the frit for 1 h. Residual solvent was removed (60°C, 10 torr) to give 6.45 g of the title compound in 89% yield. NMR showed the material to be more than 97%, and no further purification was performed. Mp 225–227°C (lit.[1] 239°C). δ_H (DMSO-d_6): 8.10 (d, $J = 15.9$ Hz, 1H), 7.74 (d, $J = 3.9$ Hz, 1H), 7.46 (d, $J = 8.7$ Hz, 2H), 7.32–7.11 (m, 3H), 6.70 (d, $J = 9.6$ Hz, 2H), 6.64 (d, $J = 16.9$ Hz, 1H), 4.74 (t, $J = 4.8$ Hz, OH), 3.54 (pent, $J = 5.3$ Hz, 2H), 3.48–3.34 (m, 2H), 1.79 (s, 6H), 1.10 (t, $J = 6.7$ Hz, 3H); δ_C (DMSO-d_6): 176.81, 174.37, 153.60, 148.60, 140.39, 139.00, 137.51, 134.37, 129.03, 127.48, 122.75, 115.65, 113.03, 112.25, 111.64, 111.43, 111.23, 98.46, 96.14, 58.34, 52.63, 51.96, 44.71, 25.55, 12.00. Elemental analysis calculated for $C_{28}H_{26}N_4O_2S$: C, 69.69; H, 5.43; N, 11.61. Found: C, 69.80; H, 5.31; N, 11.55.

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