Synthesis of 3,4-Dihydroxythiophene-2-carboxylate and Uses as Building Block for Efficient Synthesis of 3,4-Alkylenedioxythiophene (ADOT) Derivatives

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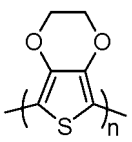
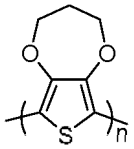
Heterocycle-based on conjugated polymers, such as polypyrrole, polythiophene, polyfuran, and others, have received significant attention due to the wide range of electrical, electrochemical, and optical properties they display. The heteroatoms within ring play an important role in controlling the properties of the polymers due to their intrinsic electron-donating or electron-withdrawing capabilities, along with other properties which include hydrogen-bonding and polarizability.[1] These polymers have been utilized in the applications as semiconductors for field-effect transistors[2] and OLEDs,[3] as conductors for electrostatic charge dissipation and EMI shielding, and redox active materials for energy storage (batteries and supercapacitors) and electrochromic devices.[4] As one of many polyheterocycles investigated, poly(3,4-ethylenedioxythiophene) (PEDOT, **1**) stands out for its vastly improved redox and conductivity stability properties when compared to its parent, polythiophene.[5] Appending an alkylenedioxy bridge across the 3- and 4-positions of the heterocycle adds electron density to aromatic ring, reducing both the monomer and polymer oxidation potentials, which results in the formation of highly stable conducting polymers. Its analogs, poly(3,4-propylenedioxythiophene) (PProDOT, **2**) and its derivatives, have recently emerged as important materials for potential use in stable and fast switching organic electrochromic devices.[5]



1

PEDOT

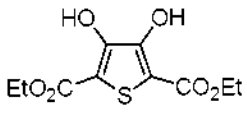


2

PProDOT

Along with rapid expansion of PXDOT chemistry, PXDOT hybridized conjugated polymers has also been intensively studied as a potential use of organic light emitting materials.[6]

Commercially available monomer, 3,4-ethylenedioxythiophene (EDOT), has been synthesized from diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate (**3**) as a key intermediate. The commercial production of EDOT has still been known to involve the reaction of **3** with 1,2-dihaloethane in the step of dioxine ring formation even if the use of dihalo compound in the production has been increasingly restricted due to its environmental hazard. In view of industrial or academic importance of EDOT, it is necessary to develop new synthetic routes that are convenient and environmentally friendly. We recently reported a highly efficient synthesis of a key EDOT intermediate and other EDOT derivatives *via* Mitsunobu chemistry.[7] We also reported the synthesis of pyrrole-analogs of EDOT through Pd-catalyzed dioxane ring formation.[8] This method turned out efficient and useful because of mild reaction condition, high yielding, and no use of halo-compounds. However, the extension of Pd-catalyzed dioxane ring formation route toward the synthesis of EDOT derivatives has not been successful possibly due to electronic or steric hindrance arising from the 2,5-dicarboxylate groups of **3**. Here we wish to report the synthesis of 3,4-dihydroxythiophene-2-carboxylate (**5**) and its use as a useful compound for the synthesis of EDOT derivatives *via* various synthetic routes.



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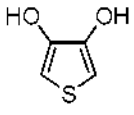

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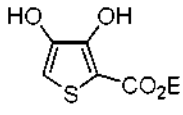
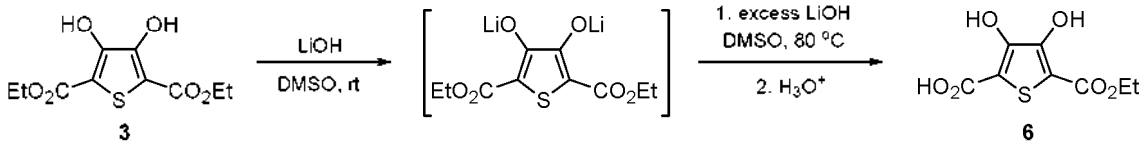


5

In the course of our study of synthesizing 3,4-dihydroxythiophene (**4**) in order that it might be used as a intermediate for synthesis of EDOT derivatives, we found that diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate (**3**) was very difficult to be hydrolyzed under several conditions. We investigated several bases such as sodium hydroxide, potassium hydroxide, sodium methoxide, sodium *tert*-butoxide in aqueous and/or using alcoholic solvent as co-solvent but failed to hydrolyze it in any meaningful yield. When the base was added, di-metal salt was immediately precipitated out, and then won't be dissolved into solution again at various conditions such as changing reaction temperature (resulted in decomposition upon too high temperature), changing bases and solvents. Gogte and coworkers reported they hydrolyzed **3** in aqueous sodium hydroxide solution with ethanol as a co-solvent at elevated temperature but they commented that the consistent reproducibility could not be achieved.[9] We attempted to reproduce their method but was not successful. Now we turned our attention to small and soft metal cation such as lithium and polar organic solvent such as dimethylsulfoxide (DMSO). Indeed, DMSO turned out much helpful to dissolve initially formed metal salt. Especially when LiOH was employed as a base in DMSO at elevated temperature

Table 1. Bases and reaction conditions used in hydrolysis of **3**

Entry	Solvent	Reaction Temp. (°C)	Reaction time (h)	Hydrolyzed yield (%)
NaOH	H_2O	80-85 °C	12	0
NaOH	H_2O/EtOH (1:1)	reflux	12	< 10
NaOH	DMSO	80-85 °C	12	10-20
t-BuOK	THF/H_2O (98:2)	reflux	12	0
LiOH	H_2O	80-85 °C	12	0
LiOH	DMSO	80-85 °C	12	90



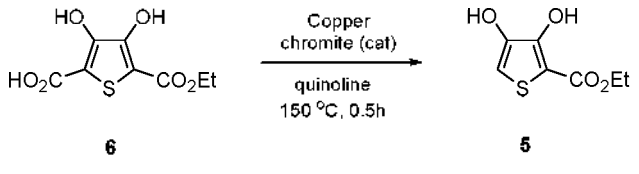
Scheme 1

(80-85 °C), nicely homogenized solution was obtained. All bases and reaction conditions used in hydrolysis of **3** is summarized in Table 1. After workup and isolation, the product was proven to be only mono-hydrolyzed compound (**6**) in 90 % yield (Scheme 1). However, further hydrolysis toward another ester group was not successful in spite of extended reaction time and at even higher temperature.

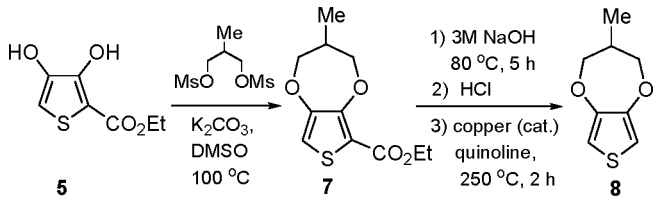
Decarboxylation of **6** in the presence of copper chromite in quinoline was easily proceeded at 150 °C for 0.5 h to give **5** as pale yellow crystals in 70% isolated yield (Scheme 2). It should be noteworthy that the decarboxylation was quickly finished under mild condition as compared with that happened in most thiophene-carboxylic acid derivatives (190-250 °C, 2-20 h). It might be explained that decarboxylation of **6** took place in similar fashion of that often seen in malonic acid derivatives. It has been observed that the diol **5** could be stored for several months without any significant decomposition.

In order to compare with **3** in reactivity, the diol **5** was subjected to dioxane ring closure with 2-methylpropane-1,3-dimethanesulfonate under standard Williamson etherification condition and the cyclized product **7** was obtained in 85% yield. This route showed that the diol **5** also be comparable with the diol **3** in performing Williams etherification. Sequential hydrolysis and decarboxylation of **7** gave Pro-DOT-Me (**8**) in 68% yield (Scheme 3).

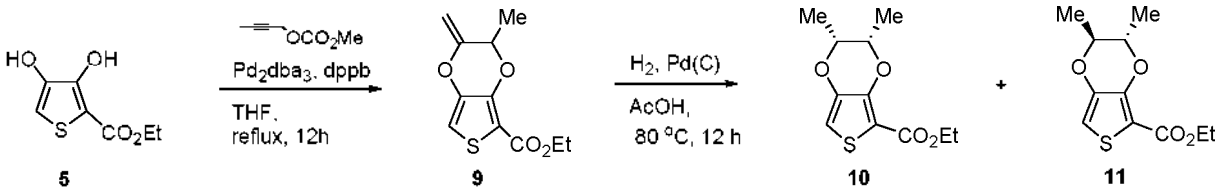
Then we explored whether **5** may undergo palladium catalyzed cyclization with propargylic carbonates. It has been considered highly valuable to install a variety of substituants on the dioxane ring of EDOT in order to control electronic or chemical property of PEDOT but the routes toward them are pretty limited yet. We demonstrated in our previous work that dioxine ring formation of EDOT could be achieved by palladium catalyzed cyclization using propargylic carbonates.[8] However, our initial attempts by employing **3** was not successful possibly due to steric or electronic effects arising from the substrate. We assumed that two hydroxyl groups of **3** might not be nucleophilic enough to react with palladium-propargylic carbonate complex due to two electron-withdrawing ester groups. To our delight, the diol **5** smoothly reacted with a propargylic carbonate in the presence of palladium catalyst to give the cyclized product (**9**) in 92% yield. It should be noted that the removal of one ester group



Scheme 2



Scheme 3



Scheme 4

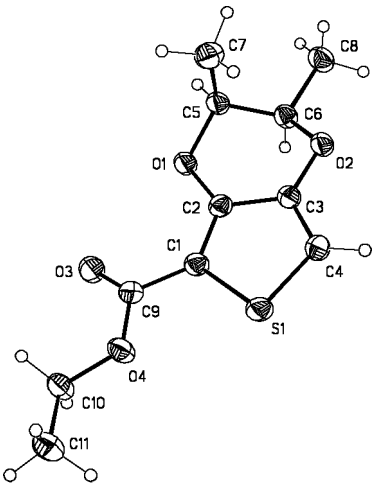
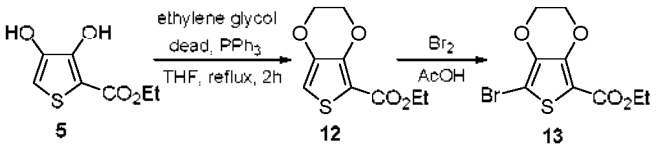


Figure 1. X-ray crystal structure of **10**.



Scheme 5

from **3** brought much higher acceleration in the reaction which made **5** as a useful compound for further explorations with it. The reaction also showed high degree of regioselectivity to provide the compound **9** predominantly as have seen in the literatures.[10,11] This method generally performs under mild condition and showed a great potential for reacting with other propargylic carbonates to afford a wide range of EDOT pre-monomers. In addition, the vinyl group of **9** provides additional advantage for functionalization by simple chemical manipulations such as hydrogenation, halogenation, hydroboration, and others. Hydrogenation of **7** in the presence of palladium catalyst gave *cis*-**10** and *trans*-**11** in 4:1 ratio in quantitative yield (Scheme 4). X-ray crystal structure of **10** showed that hydrogenation on less hindered side of *exo*-vinyl group took place dominantly to give *cis*-**10** (Figure 1).

We also compared **5** with **3** by performing the dioxane ring formation under Mitsunobu reaction condition. The compound **5** as well as **3** well reacted with ethylene glycol under Mitsunobu condition to give **12** in 95% yield and upon bromination on it led to **13** in 95% yield (Scheme 5).

In conclusion, we demonstrated an efficient mono- hydrolysis of diethyl 3,4-dihydroyxythiophene-2,5-dicarboxylate (**3**), the synthesis of ethyl 3,4-dihydroyxythiophene-2-carboxylate (**5**) from decarboxylation of **3**, and useful chemical manipulations of **5**. Especially, transition metal mediated 1,4-dioxine ring formation of **5** with a propargylic carbonate and subsequent hydrogenation opened a new route for synthesis of 1,2-disubstituted EDOT derivatives otherwise difficult to be achieved.

Experimental Section

5-Ethoxycabonyl-3,4-dihydroxythiophene-2-carboxylic acid (6). The solution of **3** (1.0 eq.) and LiOH (5.0 eq.) in DMSO was stirred at 80-85 °C for 12 h. After cooled to room temperature, the reaction was acidified by adding carefully 5 M HCl solution to precipitate the product out. The product was filtered, washed with water several times and dried in vacuum to give **6** as an off-white powder.: ^{1}H NMR (300 MHz, DMSO-d_6) δ 10. 80- 9.50 (br, 3H), 4.21 (q, J = 7.0 Hz, 2H), 1.22 (t, J = 7.0 Hz, 3H).

Ethyl 3,4-dihydroxythiophene-2-carboxylate (5). The reaction mixture of copper chromite (0.2 g) in quinoline was heated to 150 °C and then **6** (5.0 g, 0.022 mol) was added in one portion under nitrogen atmosphene. After the evolution of carbon dioxide on decarboxylation was stopped in 0.5 h, the reaction was cooled to room temperature, diluted with ether (50 mL), and washed with 1 M HCl until most of quinoline was washed out. The organic layer was then dried over $MgSO_4$ and the residue after concentrated was recrystallized in methanol to give pale yellow crystals (70%), a pale yellow crystal; mp 71 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.80-9.30 (br, 1H), 6.55 (s, 1H), 5.80-5.30 (br, 1H), 4.37 (q, J = 7.0 Hz, 2H), 1.39 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 152.7, 142.6, 107.3, 103.1, 61.5, 14.5 ; HRMS (FAB) calcd for $C_7H_8O_4S$ (M^+) 188.0143, found 188.0143; Anal. Calcd for $C_7H_8O_4S$: C, 44.67; H, 4.28; S, 17.04. Found: C, 44.70; H, 4.25; S, 17.00.

Ethyl 3-methyl-3,4-dihydro-2*H*-thieno[3,4-*b*][1,4]dioxepine-6-carboxylate (7). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65 (s, 1H), 4.33 (dd, J = 4.2, 12.2 Hz, 1H), 4.28 (q, J = 7.0 Hz, 2H), 4.18 (dd, J = 4.4, 12.0 Hz, 1H), 3.96 (dd, J = 7.3, 12.0 Hz, 1H), 3.76 (dd, J = 6.6, 12.0 Hz, 1H), 2.45 (m, 1H), 1.32 (t, J = 7.0 Hz, 3H), 1.02 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4, 153.8, 150.1, 111.4, 75.9, 75.8, 60.8, 36.9, 14.5, 13.8; HRMS (FAB) calcd for $C_{11}H_{14}O_4S$ (M^-) 242.0613, found 242.0612; Anal. Calcd for $C_{11}H_{14}O_4S$: C, 54.53; H, 5.82; S, 13.23. Found: C, 54.50; H, 5.87; S, 13.30.

Ethyl 3-methyl-2-methylene-2,3-dihydrothieno[3,4-*b*][1,4-dioxine-5-carboxylate (9). A mixture of 5 (0.28 g, 1.5 mmol) and propargylic carbonate (0.2 g, 1.65 mmol) in THF was deoxygenated by bubbling with argon for 15 min. The solution prepared above was then added to a deoxygenated solution of $Pd(PPh_3)_4$ (47 mg, 0.04 mmol) and dppb (71 mg, 0.16 mmol) in THF under argon. The reaction mixture was stirred at reflux for 12 h. After cooling to room temperature, the solvent was removed by rotary evaporator and the residue was purified by column chromatography on silica gel using hexane/ethyl acetate (3:1) as eluent to give **9** (92%) as clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.62 (s, 1H), 4.79 (d, J = 2.2 Hz, 1H), 4.72 (q, J = 6.6Hz, 1H), 4.52 (dd, J = 0.8, 2.2 Hz, 1H), 4.31 (q, J = 7.1 Hz, 3H), 1.60 (d, J = 6.6 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H).

Ethyl 2,3-dimethyl-2,3-dihydrothieno[3,4-*b*][1,4-]dioxine-5-carboxylate (10). A colorless crystal; mp 109 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.52 (s, 1H), 4.43 (q, J = 6.5Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 4.30 (q, J = 6.5 Hz, 1H), 1.36 (t, J = 7.1 Hz, 3H), 1.35 (d, J = 6.6 Hz, 3H), 1.34 (d, J = 6.6 Hz, 3H); HRMS (FAB) calcd for $C_{11}H_{14}O_4S$ (MH^-) 243.0691, found 243.0691; Anal. Calcd for $C_{11}H_{14}O_4S$: C, 54.53; H, 5.82; S, 13.23. Found: C, 54.58; H, 5.80; S, 13.30. Crystal data and structure refinement for **9**. Empirical formula, $C_{11}H_{14}O_4S$;

Formula weight, 242.28; Temperature, 193(2) K; Wavelength, 0.71073 Å; Crystal system, Triclinic; Space group, P-1; Unit cell dimensions, a = 8.3260(4) Å α = 100.506(2)°, b = 8.5039(4) Å β = 112.737(2)°, c = 9.8367(5) Å γ = 109.632(2)°; Volume, 564.59(5) Å^3; Z, 2; Density (calculated), 1.425 Mg/m^3; Absorption coefficient, 0.282 mm^{-1}; F(000), 256; Crystal size, 0.25 × 0.19 × 0.15 mm^3; Theta range for data collection, 2.41 to 27.50°; Index ranges, -10 ≤ h ≤ 10, -11 ≤ k ≤ 10, -12 ≤ l ≤ 12; Reflections collected, 4910; Independent reflections, 2479 [R(int) = 0.0771]; Completeness to theta = 27.50°, 95.6%; Absorption correction, Integration; Max. and min. transmission, 0.9619 and 0.9346; Refinement method, Full-matrix least-squares on F^2; Data / restraints / parameters, 2479 / 0 / 149; Goodness-of-fit on F^2, 1.062; Final R indices, [I > 2 sigma(I)] R1 = 0.0325, wR2 = 0.0862 [2307]; R indices (all data), R1 = 0.0349, wR2 = 0.0894; Extinction coefficient, 0.021(5); Largest diff. peak and hole, 0.342 and -0.217 e.Å^{-3}.

Ethyl 2,3-dimethyl-2,3-dihydrothieno[3,4-*b*][1,4-]dioxine-5-carboxylate (11). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.51 (s, 1H), 4.30 (q, J = 7.1 Hz, 2H), 4.00 (p, J = 6.5Hz, 1H), 3.90 (p, J = 6.5Hz, 1H), 1.43 (d, J = 6.3 Hz, 3H), 1.35 (d, J = 6.3 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 146.8, 142.2, 105.6, 98.4, 75.9, 74.9, 60.7, 17.2, 17.1, 14.5; HRMS (FAB) calcd for $C_{11}H_{14}O_4S$ (MH^+) 243.0691, found 243.0691; Anal. Calcd for $C_{11}H_{14}O_4S$: C, 54.53; H, 5.82; S, 13.23. Found: C, 54.50; H, 5.90; S, 13.18.

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