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Efficient synthesis of 3,4-ethylenedioxythiophenes (EDOT) by Mitsunobu reaction

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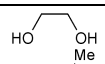
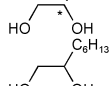
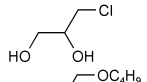
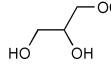
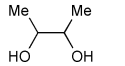
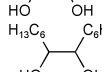
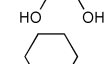
Using the Mitsunobu reaction as a key step, a general and efficient method for the synthesis of EDOT monomers has been developed. Novel substituted EDOTs and the first chiral derivatives were generated in high yields.

Due to its unique combination of high environmental stability, high conductivity and transparency in the oxidized state, poly(3,4-ethylenedioxythiophene) (PEDOT) is widely used as antistatic coatings in photographic films, as electrode materials for solid electrolyte capacitors, and in several other applications.[1] Oxidative polymerization of monomeric 3,4-ethylenedioxythiophene (EDOT) results in an insoluble and structurally undefined polymer which in the presence of polyelectrolyte anions can only be processed from aqueous suspensions (BAYTRON P®).[2] Therefore, we explore the development of novel EDOT derivatives as a basis for soluble and self-organizing PEDOTs as well as of structurally defined model oligomers.

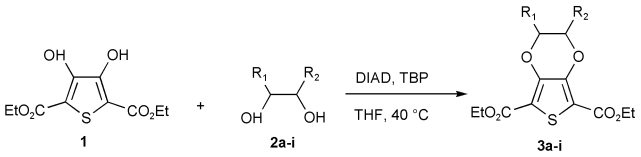
The most common and industrially applied route for the synthesis of EDOTs is the double Williamson etherification of 3,4-dihydroxy-2,5-thiophenedicarboxylic acid diethyl ester **1**, which is readily available by Hinsberg reaction of thiodiacetic acid diethyl ester and glyoxal,[3] with 1,2-dihaloethanes under basic conditions as the key step.[1,4] EDOT is formed efficiently, whereas monosubstituted EDOTs are typically obtained in medium to moderate yields. The ring closure reaction, however, completely fails when either sterically hindered or higher substituted dihaloethanes are used. Recently, acid-catalyzed transetherification of 3,4-dialkoxythiophenes with 1,3-propanediols using widely available reagents was successfully employed for the synthesis of some 3,4-propylenedioxythiophene (ProDOT) derivatives.[1,5] Herein, we report a novel and general procedure for the synthesis of EDOT derivatives. In particular, a number of these are not accessible by the Williamson ether synthesis and, for the first time, chiral EDOTs become available.

The key step of our synthesis is the Mitsunobu reaction between 3,4-dihydroxy-2,5-thiophenedicarboxylic acid diethyl ester **1** and 1,*n*-alkanediols by means of dialkylazodicarboxylates and trialkylphosphines. This condensation reaction occurs under mild and neutral reaction conditions and tolerates a variety of functional groups. The general synthetic applicability of this method is demonstrated by reacting thiophene **1** with a number of differently substituted glycols **2a**–**i** resulting in EDOTs **3a**–**i** (Table 1). Derivatives **3a**–**d** which also have previously been prepared by Williamson ether synthesis are obtained in higher yields (entries 1, 2, 5, 6) throughout. In particular, novel mono and disubstituted derivatives **3e**–**i** which were not available with the traditional syntheses are formed in good yields (entries 7–11). From these derivatives, chloromethylated EDOTs **3e** can be used as precursors for higher functionalized EDOTs due to the versatility of the halide functionality. Furthermore, the first disubstituted EDOTs **3g**–**i** represent promising precursors for soluble PEDOTs. The reaction is not operative when sterically demanding diols, such as 3-methylbutane-1,2-diol, 3,3-dimethylbutane-1,2-diol, 1,2-diphenylethane-1,2-diol and tertiary alcohols, such as 2,3-dimethylbutane-2,3-diol are used. Sterically crowded reactants represent a rather general problem in Mitsunobu reactions.[6,7]

Table 1 Mitsunobu reaction of thiophene **1** and 1,*n*-alkanediols **2**,**4** to EDOTs **3** and ProDOTs **5**

Entry	Diol		Product	Yield (%)[a]
1		**2a**[b]	**3a**	80
2		**2b**[b]	**3b**	74
3		(***R***)**2b**[c]	(***S***)**3b**[f]	74
4		(***S***)**2b**[c]	(***R***)**3b**[f]	70
5		**2c**[b]	**3c**	70
6		**2d**[b]	**3d**	47
7		**2e**[b]	**3e**[h]	65
8		**2f**[d]	**3f**[i]	70
9		**2g**[be]	**3g**[h]	67
10		**2h**[df]	**3h**[h]	40
11		**2i**[bg]	**3i**[h]	20
12		**4a**[b]	**5a**	60
13		**4b**[b]	**5b**	40

[a] Isolated yields. [b] Commercially available diol. [c] (*R*)-(−)-1,2-propanediol (***R***)**2b** (ee >97%) and (*S*)-(+)-1,2-propanediol (***S***)**2b** (ee >99%) were purchased from Aldrich. [d] Diols **2f** and **2h** are new and were prepared following literature procedures (3-butoxypropane-1,2-diol **2f** in 65% yield according to ref. 11 and 7,8-tetradecanediol **2h** in 72% yield according to ref. 12). [e] *Meso*/*trans*-mixture, 93/7. [f] *Meso*/*trans*-mixture, 87/13. [g] *Meso*/*trans*-mixture, 30/70. [h] New EDOT derivative. [i] Analogous derivatives have been synthesized using Chevrot's method.[13]



In order to widen the scope of the new method, we reacted 1,3-propanediols **4a**,**b** with thiophene **1** under Mitsunobu conditions. ProDOTs **5a**,**b** were efficiently obtained in good to

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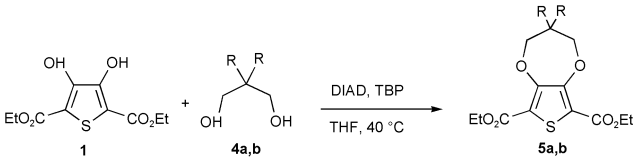
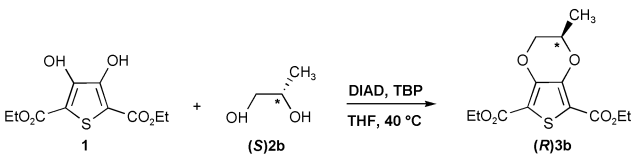
medium yields (entries 12, 13).† Due to the need to form an unfavorable 8-membered ring, the next higher homologue 1,4-butanediol, however, showed no reaction.

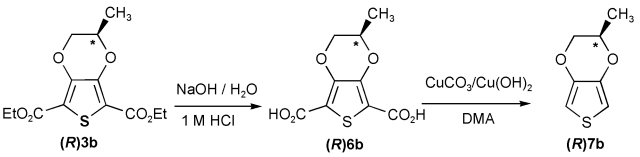


In recent years, the scope of the Mitsunobu reaction in natural products syntheses has been extensively discussed and reviewed. Since a clean S_N2 process is generally observed, this reaction is found to be particularly effective at inverting the configuration of chiral secondary alcohols.[7] If no racemisation occurs, the use of chiral glycols in the reaction with thiophene **1** could lead to chiral EDOT derivatives. In this respect, we reacted **1** with (*R*)-(+)-1,2-propanediol (***R***)**2b** and (*S*)-(−)-1,2-propanediol (***S***)**2b**, respectively, under Mitsunobu conditions (entries 3, 4). The resulting chiral 5-methyl-EDOTs (***S***)**3b** and (***R***)**3b** were obtained in good yields comparable to that of racemic 5-methyl-EDOT **3b** (entry 2). The enantiomeric purity of the chiral compounds (***S***)**3b** and (***R***)**3b** was determined to be >97% by ^{1}H-NMR in the presence of chiral europium complex [Eu(tfc)$_3$].[8]



These results clearly confirm that the Mitsunobu reaction of thiophene **1** with chiral diols takes place without any racemisation resulting in enantiomers of high optical purity. The absolute configuration at C-5 of EDOTs (***S***)**3b** and (***R***)**3b** can not be established by this method.

Polymerizable EDOT monomers are typically obtained by saponification[9] and decarboxylation[10] of the diesters. As an example, chiral derivative (***R***)**3b** was transformed to the corresponding diacid (***R***)**6b** and subsequently to the 5-methyl-EDOT (***R***)**7b** in yields of 92 and 64%, respectively. Since the reactions do not break any of the four bonds to the chiral center of the starting diester (***R***)**3b**, it is obvious that the relative positions of the groups bonded to the chiral center will not change.



In summary, we have demonstrated that the Mitsunobu reaction is a useful and efficient method for the synthesis of mono- and disubstituted EDOT and ProDOT derivatives. Moreover, this method allows, for the first time, the preparation of chiral EDOT monomers in high enantiomeric excess. Studies to further examine the scope and limitations of this novel method are now in progress as well as the polymerization of the various monomers to the corresponding substituted PEDOTs. In particular, polymerization of enantiomerically pure EDOT **7b** should lead to the corresponding chiral polymer.

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Notes and references

† *General procedure for the Mitsunobu reaction of thiophene **1** and 1,n-alkanediols **2**, **4***: Under argon and exclusion of light, to a solution of 3,4-dihydroxy-2,5-thiophenedicarboxylic acid diethyl ester **1** (1.72 g, 6.6 mmol), diol **2**, **4** (6.6 mmol) and tributylphosphine (TBP) (4.3 mL, 16.5 mmol) in THF (abs., 12 mL) at 20 °C, was slowly added diisopropylazodicarboxylate (DIAD) (3.4 mL, 16.5 mmol) *via* cannula and without dilution over 20 minutes. After the addition, the reaction mixture was warmed to 40 °C for 48 h. The solvent was then removed under reduced pressure. The resulting yellow–red oil was diluted in hexane (15 mL) and stirred vigorously to produce a precipitation of the product and hydrazine dicarboxylic acid. Final purification by flash chromatography (SiO_2–dichloromethane) yielded the pure compounds **3**,**5** as white solids.

Representative data: *Disubstituted EDOT* **3g**: mp 132–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.45 (m, 2H), 4.33 (q, ^3J = 7.1 Hz, 4H), 1.37 (dd, ^3J = 6.7 Hz, ^4J = 2.4 Hz, 6 H), 1.36 (t, ^3J = 7.1 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 160.78, 144.68, 111.17, 73.24, 61.03, 14.26, 14.18; Anal. calc. for $C_{14}H_{18}O_6S$: C 53.49, H 5.77, S 10.20; found: C 53.20, H 5.74, S 10.08%.

Representative data: *Chiral EDOT* (***R***)**-(+)-3b:** mp 126–128 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.46–4.30 (m, 6H), 3.99 (dd, ^3J = 11.6 Hz, ^4J = 7.9 Hz 1H), 1.46 (d, 3H), 1.36 (t, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 160.84, 145.46, 144.77, 111.52, 111.46, 70.58, 69.32, 61.24, 61.18, 16.17, 14.28, 14.26; $[\alpha]_D^{20}$ +51 (*c*1.0, $CHCl_3$); Anal. calc. for $C_{13}H_{16}O_6S$: C 51.99, H 5.37, S 10.68; found: C 51.96, H 5.28, S 10.71%.

Representative data: *Chiral EDOT* (***R***)**-(+)-7b:** bp 90–100 °C/1 × 10^{-2} mbar; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.30 (AB system, J_{AB} = 3.74 Hz, 2H), 4.29–3.79 (m, 3H), 1.33 (d, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 142.22, 141.48, 99.32, 70.03, 69.47, 16.25; $[\alpha]_D^{20}$ + 34.3 (*c*1.0, $CHCl_3$); Anal. calc. for $C_7H_8O_2S$: C 53.83, H 5.16, S 20.53; found: C 53.65, H 5.37, S 20.66%.

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