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A new and efficient synthetic route toward 3,4-alkylenedioxypyrrole (XDOP) derivatives via Mitsunobu chemistry

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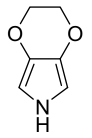
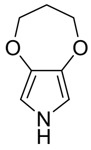
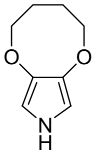
Abstract—A new and high yielding synthetic route toward 3,4-alkylenedioxy-functionalized pyrroles has been achieved by performing tandem Mitsunobu reactions on diethyl 1-benzyl-3,4-dihydroxypyrrole-2,5-dicarboxylate using a variety of 1,2-alkanediols or 1,3-alkanediols.

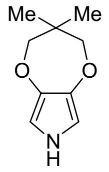
Heterocycle-based conjugated polymers, such as polypyrrole and polythiophene, have received significant attention due to their wide range of electrical, electrochemical, and optical properties that are controlled by the heteroatoms within the ring. This is due to their intrinsic electron-donating or electron-withdrawing capabilities and hydrogen-bonding and polarizability properties.[1] These polymers have been found to be useful in many applications including semiconductors for field-effect transistors[2,3] and LEDs,[3–5] conductors for electrostatic charge dissipation and EMI shielding, and redox active materials for energy storage (batteries and supercapacitors) and electrochromic devices.[6] As with 3,4-ethylenedioxythiophene (EDOT) and related derivatives, both the monomer and polymer oxidation potentials can be decreased by adding an alkylenedioxy bridge across the 3- and 4-positions of pyrroles which adds electron density to the aromatic ring resulting in ease of oxidative polymerization and the formation of highly stable conducting polymer.[7]

We have synthesized a series of 3,4-alkylenedioxypyrroles with varying ring sizes and substituents. Typical examples include 3,4-ethylenedioxypyrrole (1,4-dioxino[2,3-*c*]pyrrole, EDOP, **1**), 3,4-propylenedioxypyrrole (1,4-dioxepino[2,3-*c*]pyrrole, ProDOP, **2**), 3,4-butylenedioxypyrrole (BuDOP, **3**), and [3,4-(2,2-dimethyl-1,3-propylenedioxy)pyrrole] (ProDOP-Me_2, **4**). Our studies have demonstrated that the polymers prepared from these monomers have high conductivities, long-term stability, and exhibit unique electrochromic properties.[8–11] These promising results have encouraged us to expand our study to a set of 3,4-alkylenedioxypyrrole derivatives, which will provide a broad family of polymers having a range of properties.


1
EDOP


2
ProDOP


3
BuDOP


4
ProDOP-Me_2

To facilitate the successful production of these new derivatives, a mild and efficient route for monomer synthesis was needed. Currently, the typical route to produce these monomers (**1**, **2**, **3**, and **4**) involves Williamson etherification of diethyl 1-benzyl-3,4-dihydroxypyrrole-2,5-dicarboxylate with α–ω dihaloalkanes or alkanedisulfonates as a key step. This route is a straightforward synthesis for the parent monomers (**1** and **2**) or for those with relatively small substituents on the 3,4-alkylenedioxy bridge, but is limited when more sterically demanding alkyl substituents are added onto the bridge.

Keywords: 3,4-Alkylenedioxypyrroles; Mitsunobu reaction.

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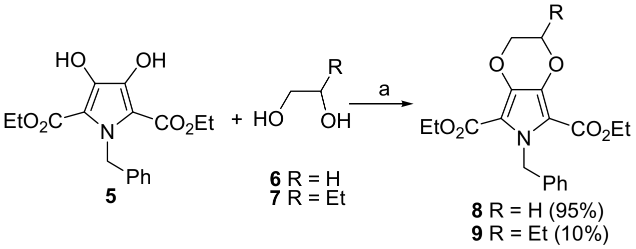
This is demonstrated by the low yields of **4**.[11] Here we report a new method for 3,4-alkylenedioxy cyclization by the reaction of diethyl 1-benzyl-3,4-dihydroxypyrrole-2,5-dicarboxylate with various 1,2-diols and 1,3-diols via double Mitsunobu reactions. This method produces high yields of the parent products and can be extended to a wide range of derivatives.

The Mitsunobu reaction is an important synthetic tool for accomplishing reactions under mild, essentially neutral conditions[12–17] and has been used by our group,[18] and others,[19] in 3,4-alkylenedioxythiophene syntheses. The reaction of a relatively acidic diol (**5**) as a nucleophile with an 1,2-alkanediol (**6**) or 1,3-alkanediol (**10**) under standard Mitsunobu conditions is illustrated in reactions (1) and (2), respectively. The synthesis of the key intermediate, diethyl 1-benzyl-3,4-dihydroxypyrrole-2,5-dicarboxylate (**5**), is well documented in the literature from the reaction of *N*-benzyl iminodiacetic acid diethyl ester with diethyl oxalate in the presence of sodium ethoxide, followed by acidification to produce **5** in excellent yield.[11] With this key intermediate on hand, subjecting **5** to standard Mitsunobu conditions [diethyl azodicarboxylate (DEAD), PPh_3, THF, room temperature] using ethylene glycol was sluggish and gave the desired product only in low yield (<10%), even with an extended reaction time of three days. However, when the reaction was heated to reflux, the desired cyclized product was produced via tandem Mitsunobu reactions in excellent yield (95%).[18]

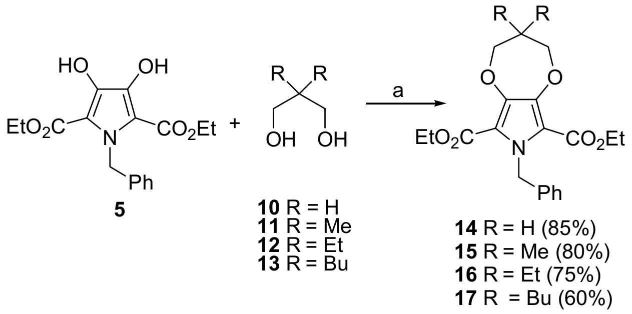


Reaction conditions; (a) DEAD, PPh3, THF, reflux, 48 h.

(1)

In order to define the scope and limitations of this new method, a more sterically hindered diol, 1,2-butanediol (**7**), was attempted. Under various conditions, including using different azo compounds and phosphines, the reaction led to only a low yield (5–10%) of product **9**. Subsequently, 2,3-butanediol underwent these reaction conditions and the desired product was not produced. It is our opinion that the reaction is highly sensitive to the degree of steric congestion of the diols employed, and the secondary hydroxyl group seems to be impractical with this application.

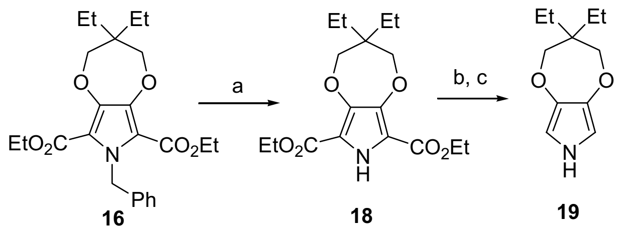
The reaction was further explored by employing 1,3-alkanediols where the 7-membered ring is obtained by reaction (2). The reaction of **5** with 1,3-propanediol (**10**), under THF reflux, gave the cyclized product **14** in excellent yield. A systematic study was conducted by increasing the steric environment around the 1,3-diol employed. The reaction of 2,2-dimethyl-1,3-propanediol (**11**) led to the product in high yield (80%). Similarly, when 2,2-diethyl-1,3-propanediol (**12**) and 2,2-dibutyl-1,3-propanediol (**13**) were employed, the reaction gave rise to the desired products in good yield. As with many examples of Mitsunobu type reactions, it should be noted that primary alcohols are more reactive than secondary.



Reaction conditions; (a) DEAD, PPh3, THF, reflux, 48 h.

(2)

To prove the usefulness of these benzylic intermediates, compound **16** was further manipulated to isolate the corresponding monomer as shown in reaction (3).[19,20] Debenzylation of **16** via catalytic hydrogenolysis afforded the unsubstituted pyrrole **18** in excellent yield (95%). Hydrolysis and decarboxylation of the resulting dicarboxylic acid, under standard conditions, gave the diethyl substituted ProDOP (**19**) in good yield (70% over both steps).[21]



(3)

Reaction conditions; (a) H_2 (Pd/C), AcOH, 90 °C,12 h, 95%. (b) 3M NaOH, 70 °C, 6 h.
(c) triethanolamine, 180 °C, 10 min, 70% in two steps.

In conclusion, we have demonstrated that **5** undergoes double Mitsunobu alkylation using 1,2- and 1,3-diols to afford the corresponding dioxypyrrole derivatives in good yields. The corresponding unprotected 3,4-alkylenedioxypyrroles, being promising monomers for conducting and/or electroactive polymers, can subsequently be isolated in good yields via deprotection/decarboxylation steps.

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20. *General procedure for cyclization via double Mitsunobu reactions*: To a solution of diethyl *N*-benzyl-3,4-dihydroxypyrrole-2,5-dicarboxylate (**5**) (2.00 g. 6 mmol), ethylene glycol (**6**) (0.37 g, 6 mmol), and PPh$_3$ (3.14 g, 12 mmol) in dry THF, was dropwise added diethyl azodicarboxylate (2.09 g, 12 mmol), under argon at room temperature. The reaction mixture was stirred for 1 h and stirred at reflux for 48 h. The reaction was cooled to room temperature and the THF was removed by a rotary evaporator. The residue was diluted with ether and stood for crystallization of triphenylphosphine oxide for 12 h, which was filtered off and the filtrate was concentrated again. Purification of the residue by chromatography on silica gel using hexane/ethyl acetate (3:1) as an eluent gave the desired product **8**. For compounds **8**, **9**, **14**, and **15**, refer to Refs. 10 and 11. The yield of compound **18** is for crude but the compound was quite pure enough to be used for next step by judging proton NMR.
    Diethyl N-benzyl-3,4-(2,2-dibutyl-1,3-propylenedioxy)pyrrole-2,5-dicarboxylate **17**. A colorless oil; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.20 (m, 3H), 6.95 (m, 2H), 5.90 (s, 2H), 4.25 (q, $J = 7.0$ Hz, 4H), 3.94 (s, 4H), 1.50–1.18 (m, 18H), 0.95 (t, $J = 7.3$ Hz, 6H); HRMS (FAB) calcd for $C_{28}H_{39}NO_6$ (MH$^+$) 486.2853, found 486.2853; Anal. Calcd for $C_{28}H_{39}NO_6$: C, 69.25; H, 8.09; N, 2.88. Found: C, 69.20; H, 8.12; N, 2.85.
    Diethyl N-benzyl-3,4-(2,2-diethyl-1,3-propylenedioxy)pyrrole-2,5-dicarboxylate **16**. A colorless oil; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.20 (m, 3H), 6.85 (m, 2H), 5.79 (s, 2H), 4.23 (q, $J = 7.0$ Hz, 4H), 3.91 (s, 4H), 1.48 (q, $J = 7.5$ Hz, 4H), 1.22 (t, $J = 7.0$ Hz, 6H), 0.90 (t, $J = 7.3$ Hz, 6H); HRMS (FAB) calcd for $C_{24}H_{32}NO_6$ (MH$^+$) 430.2230, found 430.2230; Anal. Calcd for $C_{24}H_{31}NO_6$: C, 67.11; H, 7.27; N, 3.26. Found: C, 67.08; H, 7.30; N, 3.20.
21. *3,4-(2,2-Diethyl-1,3-propylenedioxy)pyrrole* **19**. For experimental detail of the reaction, see Refs. 10 and 11; a pale yellow solid; mp 86 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.15 (br, 1H), 6.26 (d, $J = 3.4$ Hz, 2H), 3.78 (s, 4H), 1.45 (q, $J = 7.5$ Hz, 4H), 0.88 (t, $J = 7.5$ Hz, 6H); HRMS (FAB) calcd for $C_{11}H_{17}NO_2$ (M$^+$) 195.1295, found 195.1295; Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.70; H, 8.80; N, 7.15.