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SYNTHESIS OF 3-SUBSTITUTED PYRROLE DERIVATIVES WITH OLIGO(ETHYLENE GLYCOL) CHAINS

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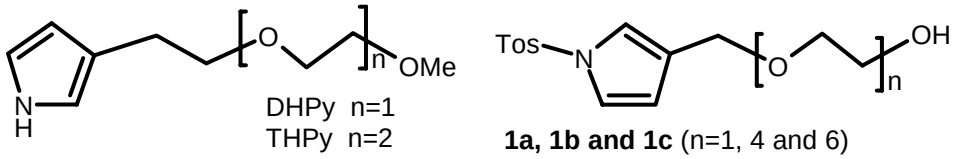
Abstract – An etherification method *via* alkoxymethyleniminium salt is described. Three pyrrole derivatives with oligo(ethylene glycol) chains at the 3-position were synthesized for the first time using the above method as the key step.

Polypyrrole (PPy), as one kind of the organic conducting materials, has been in research focus since its discovery.[1] Recently, new functional PPy's have been developed by using pyrrole derivatives as monomers.[2] These materials have many potential applications, such as for battery electrodes, electrobiosensors, and array technology.[3] In our endeavors to develop covalently modified electrochemical biosensors, a pyrrole monomer with oligo(ethylene glycol) chain on its 3-position was needed as a linker molecule. However, very few derivatives of PPy with an oligoether chain at the 3-position have been synthesized due to the difficult synthesis of the monomers.[4] Until now, only the synthesis of 3-(3,6-dioxaheptyl)pyrrole (DHPy) and 3-(3,6,9-trioxadecanyl)pyrrole (TDPy) has been reported.[4]

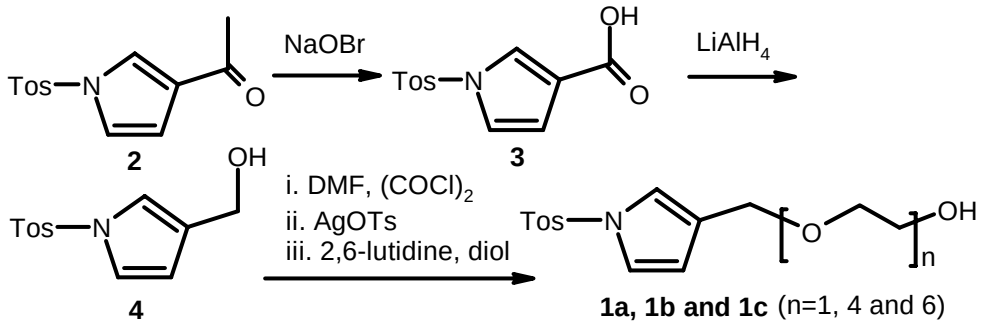
Target molecules (**1a**, **1b** and **1c**) in this study were a series of modified pyrroles with oligo(ethylene glycol) chains at the 3-position (chain length n=1, 4 and 6, respectively). A free hydroxyl group, which could serve as a connection site with a biological molecule, should be kept at the end of the long oligoether chain. Because of the presence of a free hydroxyl group and an *N*-protecting tosyl group, it is even more difficult to synthesize these molecules than to do DHPy or TDPy (as shown in Scheme 1).



Scheme 1 Comparison of target molecules (**1a**), (**1b**) and (**1c**) with DHPy/THPy.

RESULTS AND DISCUSSION

In the present study, a novel etherification method for pyrroles at the 3-position is developed. Three pyrrole derivatives with oligo(ethylene glycol) chains at the 3-position were synthesized for the first time using the new method as the key step. Scheme 2 summerizes the synthetic route of pyrroles carrying oligo(ethylene glycol) chains at the 3-position.



Scheme 2 Synthetic route of pyrroles with 3- oligo(ethylene glycol) substitution.

N-Tosyl-3-acetylpyrrole[5] (**2**) was oxidized with freshly prepared sodium hypobromite solution to the corresponding acid (**3**) quantitatively. The acid (**3**) was reduced by $LiAlH_4$ to give alcohol (**4**). The alcohol (**4**) was used immediately without further purification to react with *N*,*N*-dimethylchloromethyleniminium chloride (**5**), which was generated from dimethylformamide (DMF) and oxalyl chloride,[6, 7] to give the corresponding intermediate alkoxymethyleniminium chloride (**6**). Then AgOTs, 2,6-lutidine and an appropriate diol were added into the reaction mixture, and the reaction mixture was stirred at room temperature for 36 to 48 h, converting alcohol (**4**) to the oligo(ethylene glycol)-modified pyrroles (**1a**, **1b** and **1c**, respectively). Table 1 summerized the products and yields of pyrrole derivatives with oligo(ethylene glycol) chains at the 3-position.

Table 1 Products and yields of pyrrole derivatives with oligo(ethylene glycol) chains at the 3-position

Entry	Product	Number of ethylene glycol units	Equivalents of diol	t (h)	Yield (%)[a]
1	**1a**	1	4	48	42.0
2	**1b**	4	4	36	37.1
3	**1c**	6	4	48	14.7

[a] Two steps from acid **(3)**.

Etherification is a common practice in organic chemistry. Up to now, the most well-known etherification method is the Williamson method and its many variations, for example, the application of phase transfer catalysts. However, Williamson synthesis of ether usually requires a basic condition, which is not applicable in the conversion of **4** to **1**, because of the sensibility of the tosyl protective group.

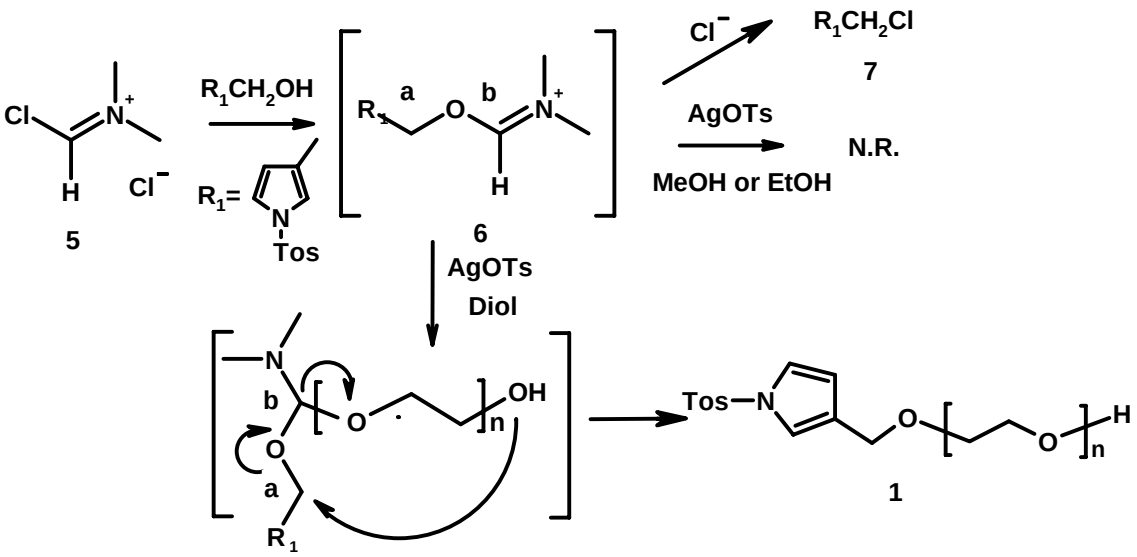
In Moon's procedure,[4] DHPy (or TDPy) were synthesized by the nucleophilic substitution of 3-chloroacetyl-*N*-tosylpyrrole with 2-methoxyethanol (or 3,6-dioxaheptanol), followed by deprotection and then reduction of the carbonyl group. The substitution requires a high temperature (145 °C), and the deprotection step is necessary before the reduction of carbonyl group. When a diol without any protective group was used, Moon's procedure failed to give the desired product.

N,*N*-Dimethylchloromethyleniminium chloride is known to react with carboxylic acid to produce carboxymethyleniminium salt which reacts with various nucleophiles such as alcohol, amine, azide and hydride to give ester, amide, acyl azide and alcohol, respectively.[8, 9] It can also react with alcohol to produce alkoxymethyleniminium chloride. The alkoxymethyleniminium species could react with potassium benzoate or potassium phthalimide to give the products of S_N2 substitution in excellent yields.[6] Moreover, the cyclization of hydroxy-phenols to provide dihydrobenzodioxans *via* alkoxymethyl- eniminium salts and intramolecular displacement by phenoxide was reported by Procopiou et al.[7]

Therefore, attempts were made to convert alcohol (**4**) to **1**, adopting a similar procedure as Procopiou described. Unfortunately, our first attempt turned out to be a failure: the reaction led to chloride (**7**) exclusively. And various attempts to convert the chloride (**7**) to monoether (**1**) *via* Williamson etherification also resulted in vain, due to the reasons described above. Unlike the synthesis of dihydrobenzodioxans, our reaction was intermolecular and the nucleophile (the diol) was less nucleophilic than phenols. In order to effect the etherification smoothly, it was essential to remove Cl^- from the reaction system.

The successful etherification was carried out at room temperature. Immediately after the formation of the alkoxymethyleniminium salt, AgOTs (2 eq.) was added into the reaction in order to scavenge free Cl^-, which might otherwise give rise to the chloride (**7**) as a byproduct (as shown in Scheme 3). Then 2,6-lutidine and an appropriate diol (n=1, 4 and 6) were added. The resulting suspension was stirred for 36-48 h, to allow the complete conversion of alcohol (**4**) to products (**1a**, **1b** and **1c**).

Possible mechanism of the etherification could be that an alkoxymethyleniminium intermediate (**6**) was formed from *N*,*N*-dimethylchloromethyleniminium chloride (**5**) and a molecule of DMF was substituted by the diol. Nevertheless, the substitution might be undergoing in several possible pathways: 1) The intermediate (**6**) could form a carbocation which might led to an S_N1 type substitution; 2) The intermediate (**6**) might be transformed into R_1CH_2OTs, which then underwent substitution; 3) The alcohol attacked the sp^3 carbon (a) directly or 4) The substitution might occur in a stepwise manner (as shown in Scheme 3). We found that monoalchohols, such as methanol or ethanol, could not yield the corresponding methyl or ethyl ether with the procedure described above, which suggested that none of the pathways 1), 2) and 3) was suitable for the mechanism of the reaction.



Scheme 3 Possible mechanism of the substitution.

In the proposed stepwise mechanism of the substitution, one hydroxyl group of the diol attacked the sp^2 carbon (b) in the first place, and then attack of the terminal free hydroxyl intramolecularly at the sp^3 carbon (a) resulted in formation of products (**1a**, **1b** and **1c**).

In conclusion, we have provided a procedure for etherification. Our method can serve as an alternative choice for etherification, apart from the Williamson's method. Many biological active molecules or intermediates are sensitive under strong basic conditions; in these cases, the method described in this paper might be a practical mild synthetic procedure. Because of the mildness of the reaction, some pyrrole derivatives with an oligo(ethylene glycol) chain at the 3-position were synthesized successfully in 14% to 42% yields.

EXPERIMENTAL

General: All reactions were conducted under an argon atmosphere. Melting points were uncorrected. IR spectra were recorded on a Perkin-Elmer 983 spectrometer with absorptions in cm^{-1}. ^1H NMR spectra were recorded on a Mercury 300 spectrometer (Varian) using $CDCl_3$ as solvent. Chemical shifts are downfield from internal tetramethylsilane. MS spectra were recorded on an HP 5989A spectrometer. HRMS spectra were recorded on a Finnian MAT spectrometer. DMF and CH_2Cl_2 were freshly distilled from CaH_2. Ether and THF were freshly distilled from Na. 3-Acetyl-*N*-tosylpyrrole [5] and AgOTs [10] were prepared according to literature. Oxalyl chloride, $LiAlH_4$, tetra(ethylene glycol) and hexa(ethylene glycol) were purchased from Aldrich Chemical Co. and were used without further purification. Pyrrole was purchased from Fluka and was freshly redistilled under vacuum.

1-(*p*-Methylphenylsufonyl)pyrrole-3-carboxylic acid (3). A solution of sodium hydroxide (9.0 g, 225 mmol) in water (77 mL) was cooled to 0 °C. Bromine (9.0 g, 55 mmol) is then added carefully. Dioxane (51 mL) was added too. The resulting hypobromite solution was kept at 0 °C before use.

3-Acetyl-*N*-tosylpyrrole (4.46 g, 17.0 mmol) in dioxane (234 mL) and water (68 mL) was cooled to 0 °C, and then the above precooled hypobromite solution was added dropwisely with stirring. The temperature was kept below 10 °C throughout the reaction. A white precipitate began to form after 10 min and the solution became colorless after 0.5 h. The reaction was quenched with Na_2SO_3 (2.2 g, 17.5 mmol) in water (20 mL), and the mixture was acidified with concentrated HCl until pH 1. The product was extracted with dichloromethane. The extracts were washed with brine, dried over Na_2SO_4, and concentrated at reduced pressure. Flash chromatography (silica gel, petroleum ether: ethyl acetate = 1:1) gave compound (**3**) (4.5 g, quantitative). mp 205-206 ^oC. ^1H NMR ($CDCl_3$, 300 MHz, δ/ppm): 7.82 (m, 3H), 7.34 (d, 2H, J = 8.4 Hz), 7.14 (s, 1H), 6.68 (s, 1H), 2.43 (s, 3H); IR (KBr, cm^{-1}): 3137, 2921, 1680, 1558, 1488, 1286, 1188, 1091, 958, 702; MS (EI, 70 eV, m/z): 91 (100.00), 155 (26.91), 65 (25.97), 93 (24.73), 265 (M^+, 20.49), 92 (8.30), 89 (5.74), 63 (5.58).

1-(*p*-Methylphenylsufonyl)-3-pyrrolylmethanol (4). To a solution of compound (**3**) (1.0 g, 3.7 mmol) in anhydrous ether (20 mL) at rt was added cautiously with $LiAlH_4$ (173 mg, 4.5 mmol). The resulting suspension was stirred at rt over night. The reaction was quenched with 2 N H_2SO_4, and the product was extracted with dichloromethane. The extracts were washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated at reduced pressure. The resulting crude product (**4**) was used immediately without further purification.

4-[1-(*p*-Methylphenylsufonyl)-3-pyrrolyl]-3-oxabutanol (1a) (Typical procedure). Oxalyl chloride (312 μL, 4 mmol) was added dropwisely with stirring into a solution of DMF (312 μL, 4 mmol) and CH_2Cl_2 (3.4 mL). A large amount of white precipitate was formed soon after the addition. The precipitate was resuspended in THF (5 mL). Compound (**4**) from the above procedure dissolved in THF (10 mL) was added dropwisely. Then AgOTs (2.52 g, 8 mmol) was added immediately. Finally, 2,6-lutidine (933 μL, 8 mmol), and ethylene glycol (0.93 g, 15 mmol) was added. The mixture was stirred at rt for 36 h. The resulting suspension was filtered and concentrated. Flash chromatography (silica gel, petroleum ether: ethyl acetate= 1:1) gave compound (**1a**) [458 mg, yield 42.0 % (2 steps)] as yellow oil. ^1H NMR ($CDCl_3$, 300 MHz, δ/ppm): 7.53 (d, 2H, J = 8.1 Hz), 7.30 (d, 2H, J = 7.8 Hz), 7.13 (m, 2H), 6.29 (m, 1H), 4.38 (s, 2H), 3.72 (t, 2H, J = 4.5 Hz), 3.54 (t, 2H, J = 4.5 Hz), 2.41 (s, 3H); IR (KBr, cm^{-1}): 3357(br), 2926, 1664, 1337, 1160, 1080, 1065, 952, 815, 701; MS (EI, 70 eV, m/z): 91 (100.00), 155 (75.70), 235 (62.14), 250 (32.84), 80 (22.79), 65 (18.63), 79 (11.68), 92 (10.70), 295 (M^+, 5.05); HRMS calcd for $C_{14}H_{17}NO_4S$: 295.0878, Found 295.0886.

13-[1-(*p*-Methylphenylsufonyl)-3-pyrrolyl]-12,9,6,3-tetraoxatridecanol (1b). As the procedure described above, tetra(ethylene glycol) (2.90 g, 15 mmol) was used instead of ethylene glycol to yield product (**1b**) (37.1 %, 2 steps) as yellow oil from flash chromatography (silica gel, ethyl acetate). ^{1}H NMR ($CDCl_3$, 300 MHz, δ/ppm): 7.75 (d, 2H, J = 8.4 Hz), 7.29 (d, 2H, J = 8.7 Hz), 7.11 (m, 2H), 6.30 (m, 1H), 4.38 (s, 2H), 3.56-3.74 (m, 16H), 2.41 (s, 3H); MS (EI, 70 eV, m/z): 234 (100.00), 155 (67.36), 45 (63.46), 91 (59.27), 89 (52.75), 235 (23.22), 80 (15.37), 79 (13.15), 427 (M^+, 6.62); HRMS calcd For $C_{20}H_{29}NO_7NaS$: 450.1555, Found 450.1557.

19-[1-(*p*-Methylphenylsufonyl)-3-pyrrolyl]-18,15,12,9,6,3-hexaoxanonadecanol (1c). As the procedure for preparation of **1a,** hexa(ethylene glycol) (4.2g, 15 mmol) was used instead of ethylene glycol to yield product (**1c**) (14.7 %, 2 steps) as yellow oil from flash chromatography (silica gel, ethyl acetate). ^{1}H NMR ($CDCl_3$, 300 MHz, δ/ppm): 7.75 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.11 (m, 2H), 6.30 (m, 1H), 4.38 (s, 2H), 3.56-3.74 (m, 24H), 2.41 (s, 3H); MS (MALDI, m/z): 538.2 (M^++Na); HRMS calcd For $C_{24}H_{37}NO_9NaS$: 538.2087, Found 538.2099.

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