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Convenient Synthesis of 1-Alkyl -2, 5-bis(thiophenylmethylene)pyrroles using the Mannich reaction

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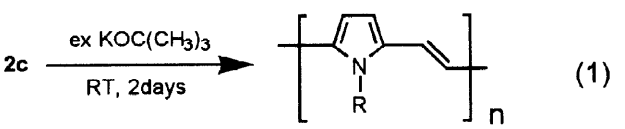
Abstract: Aminomethylation of 1-alkylpyrrole (alkyl: hydrogen, methyl, hexyl, dodecyl)by aqueous formaldehyde and dimethylamine hydrochloride, followed by reaction with iodomethane, affords the 1-alkyl-2,5-bis[(trimethylamino) methyl]pyrrole diiodide. These diiodide salt derivatives react with sodium thiophenoxide to give 1-alkyl-2,5-bis(thiophenyl methylene) pyrrole yielding monomers found to be useful for synthesizing new conducting polymers.

Attempts to synthesize new electrically conductive polymers has led to the synthesis of 1-hexyl-2,5-bis(thiophenylmethylene)pyrrole as the monomer (**2c**) used to prepare poly(1-hexylpyrrylene vinylene) (shown in eqn.1).[1] In addition, polymerization of pyrrole and 1-alkylpyrrole with oxidizing agents or by electrochemical methods has given highly conductive polypyrrole[2] and poly(1-alkyl pyrrole)(alkyl: methyl, propyl, etc).[3] In this paper, we report a detailed procedure and convenient synthesis of a wide range of 1-alkyl-2,5-disubstituted pyrroles in good yields (up to about 50-95%) as shown in Scheme 1 and Table 1.



(1)

1-Alkylpyrroles(alkyl: n-hexyl (**5a**), n-dodecyl (**5b**)) were synthesized by the condensation reaction of primary amines (n-hexyl, n-dodecyl) and 2,5-dimethoxy tetrahydrofuran with glacial acetic acid under reflux for 2hr. The final products(**5a-b**) were obtained after distillation of the dark residue. This method, largely developed by Clauson-kaas and associates,[4] has the advantages of simplicity, mild conditions, and generally excellent yields from readily available alkyl amine starting materials. Although many methods (e.g. condensation of primary amines with 2,5-diketones,[5] tetrabromobutanes,[6] 1,4-diaminobuta-1,3-dienes[7] and but-

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2-ene-1,4-diol [8]) have been used for the synthesis of 1-alkylsubstituted pyrroles, they require 2,5-diketones or their derivatives which are normally difficult to prepare and the yields are often low.

1-Alkyl-2,5-bis(dimethylaminomethyl)pyrroles (alkyl: hydrogen (**4a**), methyl (**4b**),hexyl (**4c**), dodecyl (**4d**)) were prepared by typical Mannich reactions [9] of dimethylaminehydrochloride in aqueous formaldehyde and **5a-b** at 0°C for 1hr and room temperature for 12hr (**4a-b**), 6days (**4c**), and 10days (**4d**). Reaction mixtures were neutralized with a 20% NaOH solution added dropwise and extracted with anhydrous ether. The final products (**4a-b**) were obtained after ether removal. Among the 2,5-disubstituted pyrroles(**4a-d**), **4c** was purified directly by aluminum oxide chromatography (typically, hexane as elution solvent) to afford pure **4c** in high yield (85%). **4d** was also purified by silica gel chromatography (acetone as elution solvent). Harry Heaney et al.[10] have reported that reactions of 1-methylpyrrole with aminals (e.g. bis(diethyl amino) methane, bis(dimethylamino) methane) are activated by chlorotrimethylsilane resulting in the rapid formation of the 1-methyl-2,5-bis (dimethylaminomethyl)pyrrole. In order to reduce reaction times, we ran reactions of **3c** and **3d** with aminals in the presence of a catalytic amount of chlorotrimethylsilane under reflux 24hr, but the products were not obtained.

To a stirring solution of 1-alkyl-2,5-bis(dimethylaminomethyl)pyrroles (**4a-d**) in dried THF was added three equivalents of iodomethane. After stirring the solution for 5hr at room temperature and filtration, the 1-alkyl-2,5-bis[(trimethylamino)methyl]pyrrole diiodide (**3a-c**) was obtained. Lumma, Jr and coworkers[11] made **3a** as an intermediate used to synthesize a novel, potent, and selective histamine H2 antagonist. But they could not further purify **3a**. However, we report that bisquaternary salts(**3b-d**) can be purified by recrystallization with methanol as solvent. **3a** was purified by stirring with acetone overnight. This appears to be the first report affording such pure bis quaternary salts which are valuable intermediates for the synthesis of a wide variety of 2,5-disubstituted pyrroles.

Mixtures of **3a-c** and thiophenoxide derivatives in tetrahydrofuran as solvent were stirred under reflux overnight. After removing solvent, the residues were stirred with anhydrous ethyl ether for 4hr and precipitate filtered. Crude products were obtained formed after ether removal. The crude products (light yellow oils) were purified by column chromatography (silica gel, elution solvent; hexane to dichloromethane (8:2)) to afford pure **2a-c**. The oxidation of **2a** and **2b** was performed by mCPBA at -10°C for 6hr. After removing solvent, products(**1-a,b**) were purified by column chromatography (silica gel, elution solvent; acetone to dichloromethane (7:3)) to afford the pure sulfoxides.

In summary, this convenient route gives a number of 1-alkyl-2,5-disubstituted pyrroles(alkyl: hydrogen, methyl, hexyl, dodecyl) starting with the parent heterocycles. The representative data of new each compound are listed in note 12.

Scheme 1. Synthesis of 1-alkyl-2,5-disubstituted pyrroles

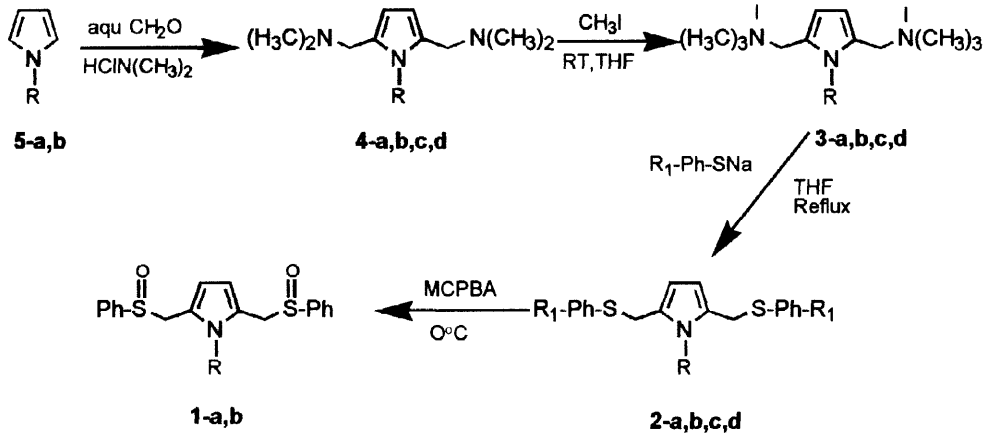

Table 1. Products of each reactions

Entry	Material	R and R_1	Yield(%)
1	5a	R= $-(CH_2)_5CH_3$	69
2	5b	R= $-(CH_2)_{11}CH_3$	62
3	4a	R= -H	82
4	4b	R= $-CH_3$	87
5	4c	R= $-(CH_3)_5CH_3$	85
6	4d	R= $-(CH_3)_{11}CH_3$	74
7	3a	R= -H	92
8	3b	R= $-CH_3$	95
9	3c	R= $-(CH_3)_5CH_3$	81
10	3d	R= $-(CH_3)_{11}CH_3$	75
11	2a	R= -H R_1= -H	74
12	2b	R= $-CH_3$ R_1= -H	78
13	2c	R= $-CH_3$ R_1= -F	74
14	2d	R= $-(CH_3)_5CH_3$	57
15	1a	R= -H	62
16	1b	R= $-CH_3$	65

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12. **5a** : ^{1}H NMR: δ 6.60(s, 2H), 6.10(s, 2H), 3.83-3.78(t, 3H), 2.64-1.27(m, 8H), 0.89-0.85(t, 3H). ^{13}C NMR: δ 120.31, 107.68, 49.52, 31.49, 31.34, 26.37, 22.46, 13.91. Anal. Cald for $C_{10}H_{17}N$: C, 79.38; H, 11.30; N, 9.26. Found: C, 79.18; H, 11.00; N, 9.21. **4c**: ^{1}H NMR: δ 5.87(s, 2H), 4.03-3.98(t, 2H), 3.30(s, 4H), 2.20-2.17(s.12H), 1.72-1.31(m.8H), 0.91-0.87(t,3H); ^{13}C NMR: δ 129.79, 107.60, 56.00, 44.98, 43.75, 31.28, 31.18, 26.70, 22.43,13.92; Anal. Cald for $C_{16}H_{31}N_3$: C, 72.45; H, 11.80; N, 15.84. Found: C, 72.19; H,11.61; N,15.69. **3a**: mp 140-142°C (dec): ^{1}H NMR: δ 11.59(s, 1H), 6.47(s, 2H), 4.55(s,4H), 3.16(s, 18H); ^{13}C NMR: δ 121.44, 114.77, 61.09, 51.71; Anal. Cald for $C_{12}H_{22}N_3I_2$: C, 30.96; H, 5.37; N, 9.07; I, 54.62. Found: C, 30.95; H, 5.34; N, 8.96; I, 54.40. **2b**: mp 70-71°C: ^{1}H NMR: δ 7.27-7.24 (m,10H), 5.80 (s, 2H), 4.06 (s,4H), 3.57(s,3H); ^{13}C NMR: δ 135.68, 130.76, 128.72, 128.01, 126.62, 108.28, 31.53, 30.48; Anal. Calcd for $C_{19}H_{19}NS_2$: C, 70.11; H, 5.88; N, 4.30; S, 19.70. Found: C, 70.20; H, 5.97; N, 4.23; S, 19.80. **2c**: mp 68-69°C : ^{1}H NMR: δ 7.20-6.96(m, 8H), 5.42(s, 2H), 4.00(s, 4H), 3.59(S, 3H); ^{13}C NMR: δ 159.22, 133.97, 127.93, 125.61, 114.45, 107.96, 55.22, 33.68; Anal. Calcd for $C_{19}H_{17}NS_2F_2$: C, 63.12; H, 4.74; N, 3.87; S, 17.75; F,10.49. Found: C, 62.83; H, 4.63; N, 3.74; S, 17.94; F, 10.38.**1a**: mp 137-138°C: ^{1}H NMR: δ 11.00(s, 1H), 7.63(s, 10H), 5.76-5.67(d, 2H), 4.24-4.09(m, 4H).^{13}C NMR: δ 143.95, 130.85, 128.96, 124.18, 121.54, 121.40, 109.98, 109.92, 55.95, 55.77.Anal. Cald for $C_{18}H_{17}NS_2O_2$: C, 62.97; H, 4.95; N, 4.08; S, 18.65. Found: C, 62.70; H, 4.81; N, 3.96; S, 18.46.**1b**: mp 148-150°C: ^{1}H NMR: δ 7.50-7.40(m, 10H), 5.73-5.70(d, 2H), 4.43-3.87(m, 4H), 3.14-3.00(d, 3H). ^{13}C NMR: δ 143.00, 131.31, 128.94, 124.32, 122.48, 111.58, 111.45, 55.65, 30.77. Anal. Cald for $C_{19}H_{19}NS_2O_2$: C, 63.83; H, 5.35; N, 3.91; S, 17.90. Found: C, 63.70; H, 5.35; N, 3.81; S, 18.00.