Sulfur Derivatives of 1-Methylpyrrole

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Metalation of 1-methylpyrrole using *n*-butyllithium and tetramethylethylenediamine (TMEDA) in ether furnished 1-methyl-2-pyrrolyllithium, which in turn was converted to 1-methyl-2-methylthiopyrrole upon treatment with dimethyldisulfide. Further formylation with dimethylformamide, phosphorus oxychloride in dichloroethane led to the corresponding pyrrole-2-carboxaldehyde, which was then condensed with malononitrile and methylcyanoacetate under Knoevenagel reaction conditions to give 2-cyano-3-(1-methyl-5-methylthio-2-pyrrolyl)acrylonitrile and 2-cyano-3-(1-methyl-5-methylthio-2-pyrrolyl)acrylic acid methyl ester, respectively. Their oxidation by hydrogen peroxide furnished the corresponding sulfones. Analogously, 5-phenylthio derivatives were prepared.

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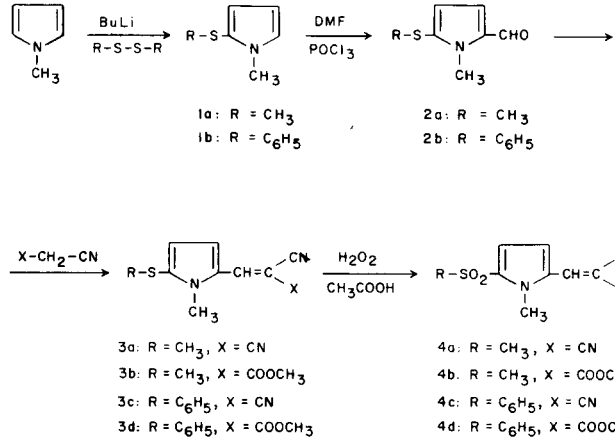
In the scope of our study of nucleophilic reactions of 5-membered heterocycles, we reported the nucleophilic substitution of arylthio, heteroarylthio and arylsulfonyl group in a series of 2-cyano-3-(5-X-2-furyl)acrylonitriles, as well as 2-cyano-3-(5-X-2-furyl)acrylic acid methyl esters [3-4], (X = arylthio-, heteroarylthio-, arylsulfonyl-). In the case of 5-X-2-substituted furan derivatives these reactions proceed at room temperature, and saturated cyclic secondary amines in ethanol or other solvents served as nucleophiles. Easy substitution under mild condition contrasts with the reactions of 5-phenylsulfonyl-2-furaldehyde. In this case, nucleophilic displacement of the phenylsulfonyl groups cannot be accomplished, even under drastic conditions.

Similar reactions on thiophene analogues showed, that although secondary amines were not able to displace the arylsulfonyl group the substitution proceeded well with arylthio anions [5].

This paper describes the synthesis of 2-cyano-3-(1-methyl-5-methylthio-2-pyrrolyl)acrylonitrile (**3a**), 2-cyano-3-(1-methyl-5-methylthio-2-pyrrolyl)acrylic acid methyl ester (**3b**) as well as the corresponding sulfones **4a, 4b**. The goal of these syntheses was the preparation of suitable substrates for nucleophilic displacement reactions. The starting compound in both syntheses was 1-methylpyrrole (Scheme 1). First, it was subjected to metalation with *n*-butyllithium, catalyzed by TMEDA in ether, and then reacted with dimethyldisulfide to give 1-methyl-2-methylthiopyrrole (**1a**). Compound **1a** was then formylated (DMF, phosphorus oxychloride) at position 5, and the resulting aldehyde **2a** was condensed with malononitrile or methyl cyano acetate in absolute ethanol with a catalytic amount of sodium methanolate to form **3a** and **3b**, respectively (see Scheme 1). Sulfones **4a, 4b** were prepared by oxidation with hydrogen peroxide in acetic acid. An analogous set of reactions was utilized to prepare the corresponding 5-phenylthio and 5-phenylsulfonyl derivatives of pyrrole. This sequence of reactions is a simple and easily accessible synthetic route to some sulfur-containing derivatives of pyrrole. The yields in all steps are fairly high, and the starting compound is commercially available. Alternative synthetic procedure, *e.g.*, starting from 1-methyl-5-halogenpyrrole-2-carbaldehyde, followed by halogen exchange with thiolate anions or alkyl (aryl) sulfinic acid anions, are much less convenient due to laboratory preparation of the starting aldehyde.

The structures of all prepared compounds were confirmed by elemental analysis, uv and ^{1}H-nmr spectra.

Scheme 1



EXPERIMENTAL

Electron absorption spectra were measured with a Specord ultraviolet VIS (Zeiss, Jena) spectrometer in the 200-800 nm region. Measured were methanolic solutions at a $1\text{-}5\cdot10^{-5}$ *M* concentration in 1 cm-cells. The ^{1}H-nmr spectra were measured on a Jeol MH-100 instrument using tetramethylsilane as an internal standard and solvents as specified.

1-Methyl-2-methylthiopyrrole (**1a**).

To a stirred solution of 16.2 g (0.2 mole) of *N*-methylpyrrole in 150 ml of dry ether under a nitrogen atmosphere at room temperature, a mixture of 26.4 g (0.22 mole) of TMEDA and 220 ml of a 1.53 *N* solution of *n*-butyllithium in hexane was added dropwise. After completed addition, the reaction mixture was refluxed for 30 minutes, and subsequently cool-

ed to −70°. Then an ethereal solution of 18.9 g of dimethyldisulfide (0.2 mole) was slowly introduced. The reaction mixture was then allowed to warm up, stirred for an additional 2 hours at room temperature and treated with water. The combined ethereal extracts were washed with a cold solution of potassium hydroxide, then with water, filtered, and dried with calcium chloride. Vacuum distillation afforded 17 g (68%) of 1-methyl-2-methylthiopyrrole, bp 75-76°; uv spectrum (methanol): λ max (log ε) 223 nm (4.41), 248-249 nm (4.47); ^{1}H-nmr spectrum (deuteriochloroform): δ (ppm) 3.61 (s, 3H, N-CH_3), 2.19 (s, 3H, S-CH_3), 6.30 (dd, 1H, H_3), 6.05 (dd, 1H, H_4), 6.68 (dd, 1H, H_5), $J_{H_3\text{-}H_4}$ = 3.7 Hz, $J_{H_3\text{-}H_5}$ = 2.8 Hz, $J_{H_3\text{-}H_5}$ = 1.8 Hz.

Anal. Calcd. for C_6H_9S: C, 56.60; H, 7.07; N, 11.00; S, 25.62. Found: C, 56.39; H, 7.07; N, 10.88: S, 25.46.

1-Methyl-2-phenylthiopyrrole (**1b**).

This compound was prepared as described above for **1a** from 16.2 g (0.2 mole) *N*-methylpyrrole, 26.4 g (0.22 mole) TMEDA, 177 ml 1.46 *N* solution of *n*-butyllithium in hexane and 43.6 g (0.2 mole) diphenylsulfide in 200 ml of dry ether. After distillation, the yield of **1b** was 25 g (66%), bp 144-145° at 12 torr; uv spectrum (methanol): λ max (log ε) 207 nm (4.32), 246-250 nm (4.25); ^{1}H-nmr spectrum (deuteriochloroform): δ (ppm) 3.51 (s, 3H, CH_3), 6.20 (dd, 1H, H_4), 6.55 (dd, 1H, H_3), 6.78-7.22 (m, 6H, H_5 + C_6H_5), $J_{H_3\text{-}H_4}$ = 3.7 Hz, $J_{H_4\text{-}H_5}$ = 3.0 Hz.

Anal. Calcd. for $C_{11}H_{11}NS$: C, 69.80; H, 5.85; N, 7.39; S, 16.93. Found: C, 69.66; H, 5.80; N, 7.26; S, 16.79.

1-Methyl-5-methylthio-2-pyrrolecarboxaldehyde (**2a**).

To stirred and ice-cooled dimethylformamide, 25.6 g (0.35 mole) phosphorus oxychloride, 53.9 g (0.35 mole), was added within 5 minutes. The cooling bath was then removed and the mixture stirred for 15 minutes at room temperature. Subsequently, 80 ml of dichloroethane was added, the mixture again cooled to 5° and a solution of 38.1 g (0.3 mole) of 1-methyl-2-methylthiopyrrole in 80 ml of dichloroethane was slowly added. The addition should be completed within one hour. The reaction mixture was thereupon refluxed for 15 minutes, then cooled to room temperature. After portion-wise addition of 142 g of sodium acetate in 300 ml of water the mixture was again refluxed for 15 minutes, cooled, the organic layer separated, and the aqueous layer extracted 3 times with ether. The combined organic extracts were washed with sodium carbonate solution, dried with sodium carbonate and distilled. Compound **2a** was obtained in 78% yield (36 g), bp_{14} = 129-131°; uv spectrum (methanol): λ max (log ε) 213 nm (3.88), 246 nm (3.53), 320 nm (4.31); ^{1}H-nmr spectrum (deuteriochloroform): δ (ppm) 2.43 (s, 3H, S-CH_3), 3.94 (s, 3H, N-CH_3), 6.22 (d, 1H, H_4), 6.88 (d, 1H, H_3), 9.43 (s, 1H, CH=O), $J_{H_3\text{-}H_4}$ = 4.2 Hz.

Anal. Calcd. for C_7H_9NOS: C, 54.17; H, 5.81; N, 9.02; S, 20.66. Found: C, 54.22; H, 5.87; N, 9.08; S, 20.55.

1-Methyl-5-phenylthio-2-pyrrolecarboxaldehyde (**2b**).

This compound was prepared as described above for **2a** from 8 g (0.11 mole) of dimethylformamide, 16.9 g (0.11 mole) of phosphorus oxychloride, 18.9 g (0.1 mole) of 1-methyl-2-phenylthiopyrrole in 50 ml of dichloroethane. After vacuum distillation 17 g (78%) of **2b** was obtained, bp 130°/0.7 torr; uv spectrum (methanol): λ max (log ε) 206 nm (4.62), 244 (4.34), 304 (4.47); ^{1}H-nmr spectrum (deuteriochloroform): δ (ppm) 3.91 (s, 3H, CH_3), 6.52 (d, 1H, H_4), 6.94 (d, 1H, H_3), 7.00-7.40 (m, 5H, C_6H_5), 9.55 (s, 1H, CH=O), $J_{H_3\text{-}H_4}$ = 4.2 Hz.

Anal. Calcd. for $C_{12}H_{11}NOS$: C, 66.35; H, 5.10; N, 6.44; S, 14.76. Found: C, 66.27; H, 5.04; N, 6.37; S, 14.58.

2-Cyano-3-(1-methyl-5-methylthio-2-pyrrolyl)acrylonitrile (**3a**).

To a solution of 0.77 g (0.005 mole) of **2a** in 10 ml of dry ethanol, 0.33 g (0.005 mole) of malonitrile dissolved in 10 ml of absolute ether was added. Then 5 drops of a 10% solution of sodium ethoxide was added to the stirred reaction mixture. Soon after addition of ethoxide, condensation product started to precipitate. The stirring was continued for another hour, and the separated crystals were filtered off and dried. The filtrate, upon dilution with water, furnished another portion of product. The overall yield was almost quantitative, mp 204-205°, crystallized from ethanol; uv spectrum (methanol): λ max (log ε) 210 nm (3.90), 432 nm (4.54); ^{1}H-nmr spectrum (DMSO-d_6): δ (ppm) 2.56 (s, 3H, S-CH_3), 3.67 (s, 1H, N-CH_3), 6.54 (dd, 1H, H_4), 7.53 (d, 1H, H_3), 8.08 (s, 1H, CH=), $J_{H_3\text{-}H_4}$ = 4.6 Hz, $J_{H_4\text{-}H_\alpha}$ = 0.6 Hz.

Anal. Calcd. for $C_{10}H_9N_3S$: C, 59.08; H, 4.46; N, 20.67; S, 15.77. Found: C, 58.87; H, 4.40; N, 20.55; S, 15.69.

2-Cyano-3-(1-methyl-5-methylthio-2-pyrrolyl)acrylic Acid Methyl Ester (**3b**).

This compound was prepared as described above for **3a** from 0.77 g (0.005 mole) of **2a**, and 0.49 g (0.005 mole) of ethyl cyanoacetate in 20 ml of absolute ethanol. Crystallization from ethanol yielded 0.85 g (73%) of **3b**, mp 162-163°; uv spectrum (methanol): λ max (log ε) 213 nm (3.95), 422 nm (4.50); ^{1}H-nmr spectrum (DMSO-d_6): δ (ppm) 2.53 (s, 3H, S-CH_3), 3.70 (s, 3H, N-CH_3), 3.80 (s, 3H, O-CH_3), 6.55 (dd, 1H, H_4), 7.58 (s, 1H, H_3), 8.03 (bs, 1H, CH=); $J_{H_3\text{-}H_4}$ = 4.5 Hz, $J_{H_\alpha\text{-}H_\alpha}$ = 0.7 Hz.

Anal. Calcd. for $C_{11}H_{12}N_2O_2S$: C, 55.91; H, 5.11; N, 11.85; S, 13.57. Found: C, 55.83; H, 5.05; N, 11.88; S, 13.52.

2-Cyano-3-(1-methyl-5-phenylthio-2-pyrrolyl)acrylonitrile (**3c**).

This compound was prepared as described above for **3a** from 6.5 g (0.03 mole) of **2b**, 1.98 g (0.03 mole) of malononitrile in 50 ml of absolute ethanol. By crystallization from ethanol 7.5 g (95%) of **3c** was obtained, mp 117-118°; uv spectrum (methanol): λ max (log ε) 206 nm (4.33), 246 (4.04), 399 nm (4.40); ^{1}H-nmr spectrum (DMSO-d_6): δ (ppm) 3.73 (s, 3H, CH_3), 6.66 (dd, 1H, H_4), 7.51 (d, 1H, H_3), 7.00-7.40 (m, 5H, C_6H_5), 8.28 (bs, 1H, CH=), $J_{H_3\text{-}H_4}$ = 4.6 Hz, $J_{H_4\text{-}H_\alpha}$ = 0.6 Hz.

Anal. Calcd. for $C_{15}H_9N_3S$: C, 67.89; H, 4.17; N, 15.83; S, 12.08. Found: C, 67.65; H, 4.12; N, 15.87; S, 11.95.

2-Cyano-3-(1-methyl-5-phenylthio-2-pyrrolyl)acrylic Acid Methyl Ester (**3a**).

This compound was prepared as desribed above for **3a** from 6.5 g (0.03 mole) of **2b**, 2.97 g (0.03 mole) of methyl cyanoacetate in 50 ml of absolute ethanol. By crystallization there was obtained from ethanol 7.2 g (81%) of **3d**, mp 126-127°; uv spectrum (methanol): λ max (log ε) 204 nm (4.44), 245 nm (4.10), 394 nm (4.39); ^{1}H-nmr spectrum (DMSO-d_6): δ (ppm) 3.75 (s, 3H, N-CH_3), 3.83 (s, 3H, O-CH_3), 6.71 (d, 1H, H_4), 7.00-7.40 (m, 5H, C_6H_5), 7.06 (d, 1H, H_3), 8.14 (bs, 1H, CH=), $J_{H_3\text{-}H_4}$ = 4.4 Hz.

Anal. Calcd. for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.72; N, 9.38; S, 10.74. Found: C, 64.32; H, 4.65; N, 9.27; S, 10.69.

2-Cyano-3-(1-methyl-5-methylsulfonyl-2-pyrrolyl)acrylonitrile (**4a**).

A mixture of 0.5 g (0.005 mole) of **3a** and 1.5 ml of 30% hydrogen peroxide in 50 ml of glacial acetic acid was stirred for 5 days at room temperature. The separated sulfone **4a** was then filtered off, the filtrate concentrated to 1/6 of its original volume and diluted with water (1:4) to give 0.5 g (81%) of **4a**, mp 214-215° (acetone); uv spectrum (methanol): λ max (log ε) 223 nm (3.94), 360 nm (4.58); ^{1}H-nmr spectrum (DMSO-d_6): δ (ppm) 3.34 (s, 3H, SO_2CH_3), 4.00 (s, 3H, N-CH_3), 7.00 (dd, 1H, H_4), 7.40 (d, 1H, H_3), 89.47 (bs, 1H, CH=), $J_{H_3\text{-}H_4}$ = 4.8 Hz, $J_{H_4\text{-}H_\alpha}$ = 0.6 Hz.

Anal. Calcd. for $C_{10}H_9N_3O_2S$: C, 51.06; H, 3.85; N, 17.86; S, 13.63. Found: C, 50.88; H, 3.82; N, 17.77; S, 13.58.

2-Cyano-3-(1-methyl-5-methylsulfonyl-2-pyrrolyl)acrylic Acid Methyl Ester (**4b**).

This compound was prepared as described above for **4a** from 0.6 g (0.0025 mole) of **3b** and 1.5 ml of 30% hydrogen peroxide in 50 ml of glacial acetic acid. After crystallization from ethanol, 0.5 g (74%) of **4b** was obtained, mp 187°; uv spectrum (methanol): λ max (log ε) 224 nm (3.86), 355 nm (4.51); ^{1}H-nmr spectrum (DMSO-d_6): δ (ppm) 3.36 (s, 3H, SO_2CH_3), 3.86 (s, 3H, N-CH_3), 4.00 (s, 3H, OCH_3), 7.01 (dd, 1H, H_4), 7.42 (dd, 1H, H_3), 8.22 (bs, 1H, CH=), $J_{H_3\text{-}H_4}$ = 4.6 Hz, $J_{H_4\text{-}H_\alpha}$ = 0.6 Hz.

Anal. Calcd. for $C_{11}H_{12}N_2O_4S$: C, 49.24; H, 4.50; N, 10.44; S, 11.95. Found: C, 49.04; H, 4.48; N, 10.40; S, 11.81.

2-Cyano-3-(1-methyl-5-phenylsulfonyl-2-pyrrolyl)acrylonitrile (**4c**).

This compound was prepared as described for **4a** from 2.65 g (0.01 mole) **3c** and 6 ml of 30% hydrogen peroxide in 100 ml of glacial acetic acid. After crystallization 2.3 g (78%) of **4c** was obtained from ethanol, mp 185-186°; uv spectrum (methanol): λ max (log ε) 208-212 nm (4.12), 252 nm (3.90), 367 nm (4.59); ^{1}H-nmr spectrum (DMSO-d_6): δ (ppm) 3.85 (s, 3H, CH_3), 7.14 (dd, 1H, H_4), 7.42 (dd, 1H, H_3), 7.60-8.00 (m, 5H, C_6H_5), 8.40 (t, 1H, CH=), $J_{H_3-H_4}$ = 4.5 Hz, $J_{H_4-H_\alpha}$ = 0.6 Hz, $J_{H_3-H_\alpha}$ = 0.6 Hz.

Anal. Calcd. for $C_{15}H_{11}N_3O_2S$: C, 60.59; H, 3.72; N, 14.13; S, 10.78. Found: C, 60.45; H, 3.68; N, 14.04; S, 10.70.

2-Cyano-3-(1-methyl-5-phenylsulfonyl-2-pyrrolyl)acrylic Acid Methyl Ester (**4d**).

This compound was prepared as descriobed above for **4a** from 2.98 g (0.01 mole) of **3d**, and 6 ml of 30% hydrogen peroxide in 100 ml of glacial acetic acid. After crystallization from ethanol, 2.4 g (73%) of **4d** was obtained, mp 153-154°; uv spectrum (methanol): λ max (log ε) 210 nm (4.19), 252 nm (3.88), 361 nm (4.57); ^{1}H-nmr spectrum (DMSO-d_6): δ 3.85 (m, 6H, N-CH_3, O-CH_3), 7.16 (d, 1H, H_4), 7.46 (d, 1H, H_3), 7.60-8.10 (m, 5H, C_6H_5), 8.16 (bs, 1H, CH=), $J_{H_3-H_4}$ = 4.5 Hz.

Anal. Calcd. for $C_{16}H_{14}N_2O_4S$: C, 58.17; H, 4.27; N, 8.48; S, 9.70. Found: C, 58.06; H, 4.19; N, 8.41; S, 9.62.

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