Preparation of 2-Formyl-4-nitropyrroles

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The Vilsmeier reaction of 3-nitropyrroles which are prepared by the reaction of nitroalkenes with the sodium salt of tosylmethylisocyanide gives 2-formyl-4-nitropyrroles in good yields.

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Nitroazoles have been studied extensively due to their chemotherapeutic effectiveness. Especially nitropyrroles are important for pharmaceutical drugs, fungicides, and herbicides [1]. However, pyrrole is a π-excessive heteroaromatic that electrophiles substitute preferentially at the α position, making the synthesis of 3-nitropyrroles very difficult [2]. There are no good general methods to obtain 3-nitropyrroles with no substituents at the α positions. Recently Barton and his co-workers have reported that 3-nitropyrroles are prepared by the reaction of nitroalkenes with tosylmethylisocyanide [3]. However, the yield of 3-nitropyrroles prepared by this method is too low for practical use.

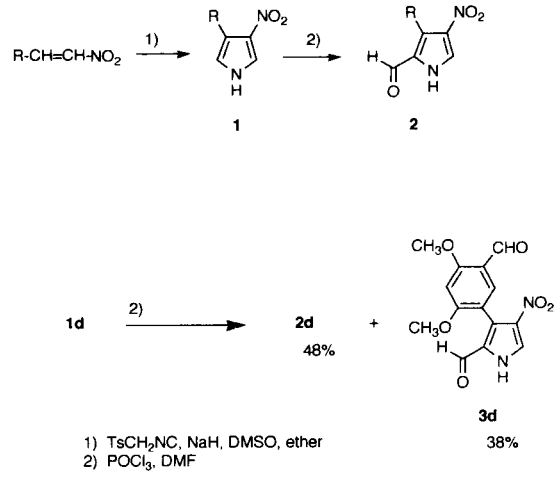
In this paper we report a modified procedure for the preparation of 3-nitropyrroles **1** and 2-formyl-3-nitropyrroles **2** by the formylation of 3-nitropyrroles *via* the Vilsmeier reaction. The reaction of nitroalkenes with the sodium salt of tosylmethylisocyanide was carried out under nitrogen atmosphere at 0-5° to give 3-nitropyrroles **1** in 30-60% yield. Thus, the yield of 3-nitropyrroles was greatly improved by this procedure (see Experimental) compared to the reported yield (10%). This provides a reliable method for the preparation of 3-nitropyrroles. As the requisite nitroalkenes are readily prepared from aldehydes and nitromethane, nitropyrroles having various substituents (R) are available by this method. The results are summarized in Table 1.

Table 1

Preparation of 3-Nitropyrroles 1 and 2-Formyl-4-nitropyrroles 2

R	1, yield %	2, yield %
Phenyl	**1a**, 55	**2a**, 76
p-Tolyl	**1b**, 44	**2b**, 90
p-Anisyl	**1c**, 58	**2c**, 82
2,4-Dimethoxyphenyl	**1d**, 40	**2d**, 90 [a]
2,4-Dichlorophenyl	**1e**, 38	**2e**, 12 [b]
2-Thienyl	**1f**, 43	**2f**, 82

Yields refer to pure isolated products. The Vilsmeier reaction was carried out by using two equivalents of the Vilsmeier complex except for **2d**. [a] Vilsmeier complex (1.1 equivalents) was used. When excess of the Vilsmeier complex was used, the yield of **2d** was reduced to 48% and bisformylated product **3d** was obtained in 38% yield. [b] Starting material **1e** was recovered in 60% yield.



Next, formylation *via* the Vilsmeier reaction was undertaken to get 2-formyl-4-nitropyrroles **2**, which are expected to be useful intermediates for the synthesis of various heterocycles. In general, the Vilsmeier reaction with dimethylformamide-phosphorus oxychloride complex is suitable only for electron-rich substrates [4]. Therefore, the formylation of **1** provides interesting questions; does the formylation take place even in the presence of the nitro group which is the strong electron-withdrawing group? If the formylation takes place, which positions are formylated? The results are summarized in Table 1. When R is phenyl, *p*-tolyl, *p*-anisyl, or 2-thienyl, the reaction of **1** with dimethylformamide-phosphorus oxychloride (2 equivalents) gives mono-formylated product **2** in good yield. Compound **1e** is less reactive than other pyrroles, for **1e** has two electron-withdrawing groups, nitro and dichlorophenyl groups. Therefore the reaction of **1e** under the same conditions gives **2e** only in 12% yield. On the other hand, one equivalent of dimethylformamide-phosphorus oxychloride complex is sufficient for the reaction of **1d** which is activated by 2,4-dimethoxyphenyl group. If excess of the complex is used, the product is further formylated at the phenyl ring to give bis-formylayed product **3d**.

Thus, pyrroles are reactive enough to attack the Vilsmeier complex even in the presence of the nitro group. The most reactive site of 3-nitropyrroles is the 5-position, which is more reactive than the 2,4-dimethoxyphenyl ring.

The 2-position is far less reactive than the other sites. These findings provide very useful information to introduce the functional groups into pyrroles in a regioselective manner.

EXPERIMENTAL

Melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. The ^{1}H nmr spectra were recorded on a JEOL JNM-JSX-270 spectrometer, chemical shifts (in deuteriochloroform) being reported in the data scale (ppm) relative to tetramethylsilane. The ir spectra were recorded on Hitachi 215 spectrometer.

General Procedure for the Preparation of 3-Nitropyrroles **1**.

A solution of tosylmethylisocyanide (50 mmoles) in dry dimethyl sulfoxide (20 ml) was added to a suspension of sodium hydride (55 mmoles) in dry diethyl ether which was cooled at 0-5° under nitrogen atmosphere. The mixture was stirred for 5 minutes at 0-5° and to it a solution of nitroalkene (50 mmoles) in dimethyl sulfoxide (50 ml) was added. The resulting mixture was stirred at 0-5° for additional 2 hours. The reaction mixture was then poured into saturated aqueous ammonium chloride solution, and extracted with diethyl ether. The combined extracts were washed with saturated sodium chloride aqueous solution, and dried with anhydrous magnesium sulfate, the solvents were removed, and the remaining solid was recrystallized from ethanol to give pure 3-nitropyrrole **1**.

3-Nitro-4-phenylpyrrole (**1a**).

Compound **1a** was obtained in 55% yield, mp 157-159°; ir (potassium bromide): 3140, 1480, 1340 cm^{-1}; ^{1}H nmr: 6.78 (1H, d, 2-H), 7.27-7.41 (5H, m, phenyl), 7.78 (1H, d, 5-H), 8.65 (1H, s, NH).

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.83; H, 4.28; N, 14.88. Found: C, 63.74; H, 4.29; N, 14.81.

3-Nitro-4-*p*-tolylpyrrole (**1b**).

Compound **1b** was obtained in 44% yield, mp 144-146°; ir (potassium bromide): 3170, 1480, 1350 cm^{-1}; ^{1}H nmr: 2.34 (3H, s, CH_3), 6.71 (1H, d, 2-H), 7.21-7.42 (4H, m, tolyl), 7.73 (1H, d, 5-H), 8.60 (1H, s, NH).

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.85. Found: C, 65.03; H, 5.23; N, 14.04.

3-*p*-Anisyl-4-nitropyrrole (**1c**).

Compound **1c** was obtained in 58% yield, mp 159-162°; ir (potassium bromide): 3260, 1485, 1345 cm^{-1}; ^{1}H nmr: 3.82 (3H, s, OCH_3), 6.71 (1H, d, 2-H), 6.93 (2H, d, anisyl), 7.38 (2H, d, anisyl), 7.75 (1H, d, 5-H), 8.60 (1H, s, NH).

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.43; H, 4.56; N, 12.78.

3-(2,4-Dimethoxyphenyl)-4-nitropyrrole (**1d**).

Compound **1d** was obtained in 40% yield, mp 181-183°; ir (potassium bromide): 3260, 1480, 1350 cm^{-1}; ^{1}H nmr: 3.75 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 6.52 (1H, d, 2-H), 6.68 (1H, s, Ar), 7.16 (2H, d, Ar), 7.35 (1H, d, 5-H), 8.65 (1H, s, NH).

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28. Found: C, 57.89; H, 4.68; N, 11.34.

3-(2,4-Dichlorophenyl)-4-nitropyrrole (**1e**).

Compound **1e** was obtained in 38% yield, mp 187-189°; ir (potassium bromide): 3150, 1485, 1350 cm^{-1}; ^{1}H nmr: 6.73 (1H, d, 2-H), 7.4 (3H, m, Ar), 7.80 (1H, d, 5-H), 8.60 (s, 1H, NH).

Anal. Calcd. for $C_{10}H_6N_2O_2Cl_2$: C, 46.72; H, 2.35; N, 10.89. Found: C, 45.89; H, 2.56; N, 10.78.

3-Nitro-4-(2-thienyl)pyrrole (**1f**).

Compound **1f** was obtained in 43% yield, mp 132-134°; ir (potassium bromide): 3335, 1480, 1330 cm^{-1}; ^{1}H nmr: 6.90 (d, 1H, 5-H), 7.20 (3H, m, thienyl), 7.76 (1H, d, 2-H), 8.60 (1H, s, NH).

Anal. Calcd. for $C_8H_6N_2O_2S$: C, 49.47; H, 3.11; N, 14.43. Found: C, 49.48; H, 2.84; N, 14.13.

General Procedure for the Preparation of 2-Formyl-4-nitropyrrole **2**.

In a flask fitted with a dropping funnel and a reflux condenser was placed dimethylformamide (4 ml). The flask was immersed in an ice bath and the internal temperature was maintained at 10-20° while phosphorus oxychloride (4 ml) was added over 15 minutes. The ice bath was removed and 10 ml of ethylene dichloride was added to the mixture. A solution of 3-nitropyrrole **2** (20 mmoles) in ethylene dichloride (15 ml) was added to the stirred, cooled mixture over a period of 1 hour. Then the ice bath replaced with a heating mantle, and the mixture was stirred at the reflux temperature for 1 hour. The mixture was then cooled to 20-25° and to it was added dropwise a solution of sodium acetate trihydrate (35 g) in about 70 ml of water. The reaction mixture was again refluxed for 15 minutes vigorous stirring being maintained all the while. After the ethylene dichloride layer was separated, the aqueous solution was extracted with methylene dichloride. The methylene dichloride and ethylene dichloride solutions were combined and washed with three 10 ml portions of saturated aqueous sodium carbonate solution. The organic layer was dried with anhydrous magnesium sulfate, the solvents were removed and the remaining solid was recrystallized from ethanol to give pure **2**.

2-Formyl-3-phenyl-4-nitropyrrole **2a**.

Compound **2a** was obtained in 76% yield, mp 172-175°; ir (potassium bromide): 3232, 1640, 1500, 1360 cm^{-1}; ^{1}H nmr: 7.40 (5H, m, Ph), 8.02 (1H, d, 5-H), 9.31 (1H, s, CHO), 10.35 (1H, NH).

Anal. Calcd. for $C_{11}H_8N_2O_3$: C, 61.11; H, 3.73; N, 12.96. Found: C, 61.30; H, 3.57; N, 12.70.

2-Formyl-4-nitro-3-(*p*-tolyl)pyrrole **2b**.

Compound **2b** was obtained in 90% yield, mp 161-162°; ir (potassium bromide): 3230, 1640, 1500, 1360 cm^{-1}; ^{1}H nmr: 2.40 (3H, s, CH_3), 7.28, 7.32 (4H, m, tolyl), 7.91 (1H, d, 5-H), 9.39 (1H, s, CHO), 10.46 (1H, NH).

Anal. Calcd. for $C_{12}H_{10}N_2O_3$: C, 62.60; H, 4.38; N, 12.10. Found: C, 62.38; H, 4.44; N, 12.10.

2-Formyl-3-(*p*-anisyl)-4-nitropyrrole **2c**.

Compound **2c** was obtained in 78% yield, mp 215-218°; ir (potassium bromide): 3175, 1645, 1500, 1370 cm^{-1}; ^{1}H nmr: 3.84 (3H, s, OCH_3), 6.99 (2H, d, Ar), 7.41 (2H, d, Ar), 8.10 (1H, d, 5-H), 9.31 (1H, s, CHO), 10.40 (1H, NH).

Anal. Calcd. for $C_{12}H_{10}N_2O_4$: C, 58.53; H, 4.09; N, 11.47. Found: C, 58.62; H, 4.12; N, 11.26.

2-Formyl-3-(2,4-dimethoxyphenyl)-4-nitropyrrole **2d**.

Compound **2d** was obtained in 90% yield, mp 220-222°; ir (potassium bromide): 3170, 1640, 1500, 1370 cm^{-1}; ^1H nmr: 3.75 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 6.57, 6.58, 7.24 (3H, Ar), 7.96 (1H, d, 5-H), 9.37 (1H, s, CHO), 10.46 (1H, NH).

Anal. Calcd. for $C_{12}H_{12}N_2O_5$: C, 54.54; H, 4.58; N, 10.60. Found: C, 54.36; H, 4.62; N, 10.56.

2-Formyl-3-(2,4-dichlorophenyl)-4-nitropyrrole **2e**.

Compound **2e** was obtained in 12% yield, mp 198-199°; ir (potassium bromide): 3170, 1640, 1500, 1370 cm^{-1}; ^1H nmr: 7.22-7.40 (3H, Ar), 7.96 (1H, d, 5-H), 9.16 (1H, s, CHO), 10.46 (1H, NH).

Anal. Calcd. for $C_{11}H_6N_2O_3Cl_2$: C, 46.34; H, 2.12; N, 9.83. Found: C, 46.32; H, 2.16; N, 9.81.

2-Formyl-3-(2-thienyl)-4-nitropyrrole **2f**.

Compound **2f** was obtained in 82% yield, mp 112-114°; ir (potassium bromide): 3220, 1660, 1445, 1385 cm^{-1}; ^1H nmr: 7.98-8.20 (4H, thienyl and 5-H), 9.37 (1H, s, CHO), 10.30 (1H, NH).

Anal. Calcd. for $C_9H_6N_2O_3S$: C, 48.65; H, 2.27; N, 12.60. Found: C, 48.70; H, 2.18; N, 12.57.

2-Formyl-3-(3-formyl-4,6-dimethoxyphenyl)-4-nitropyrrole **3d**.

Compound **3d** was obtained in 38% yield as a side product in the preparation of **2d** using excess of the Vilsmeier complex, mp 224-226°; ir (potassium bromide): 3300, 1660, 1600, 1500, 1350 cm^{-1}; ^1H nmr: 3.90 (3H, s, OCH_3), 4.09 (3H, s, OCH_3), 6.90 (1H, s), 7.73 (1H, s, phenyl), 8.13 (1H, d, 5-H), 9.36 (1H, s, CHO), 10.31 (1H, s, CHO), 10.40 (1H, s, NH).

Anal. Calcd. for $C_{13}H_{10}N_2O_5$: C, 56.94; H, 3.68; N, 10.21. Found: C, 56.87; H, 3.62; N, 10.28.

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