Preparation of Pyrroles Having Long Alkyl Chains from Nitroalkenes

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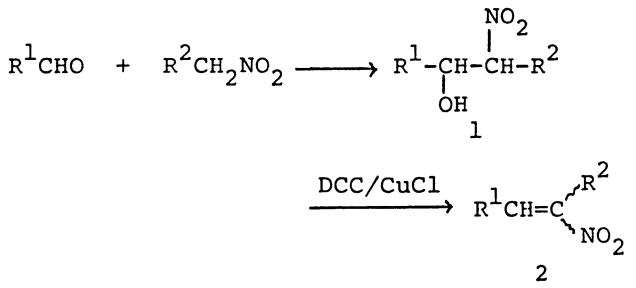
(Received June 16, 1988)

Synopsis. Pyrroles having long alkyl chains at the 3- and/or 4-positions are readily prepared by the reaction of ethyl isocyanoacetate with nitroalkenes having long alkyl chains.

As pyrroles having long alkyl chains at the 3- and/or 4-positions are important intermediates for the synthesis of lipophilic polypyrroles and porphyrins, synthesis of such pyrroles is becoming important in recent years.[1] Acylation of pyrroles followed by the reduction of the carbonyl group[2] or the Wittig type reaction of 3-formyl pyrroles followed by hydrogenation of the double bond has been used for the introduction of long chains at the 3-position.[3] However, they require tedious procedures and can not be applied to the synthesis of pyrroles having two long alkyl groups at the 3- and 4-positions. In connection with our study of porphyrin model systems, we need a more simple and effective method for the preparation of pyrroles having long alkyl chains. In this paper we wish to report the preparation of hitherto unfamiliar nitroalkenes having long alkyl chains and their conversion into the corresponding pyrroles by the reaction with isocyanides.[4]

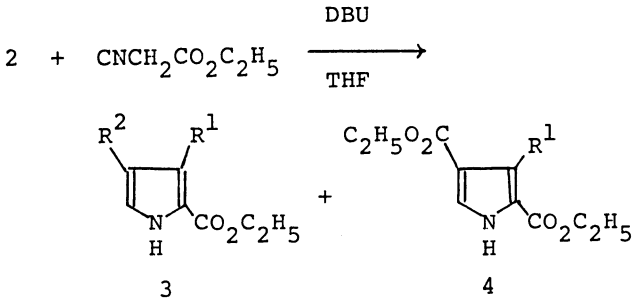
Results and Discussion

The requisite nitroalkenes were prepared by dehydration of the corresponding nitro alcohols (**1**) on treatment with dicyclohexylcarbodiimide (DCC) in the presence of copper(I) chlorid.[5] Nitro alcohols (**1**)



were prepared by the nitro aldol condensation of higher alkanals with higher nitroalkanes. A strong base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was required for this step.[6] Althogh many methods are available for the conversion of **1** into nitroalkenes (**2**)[7] the formation of nonconjugated nitroalkenes is a serious problem for higher nitroalkenes. In fact, the most widely used method consisted of methansulfonylation and the effecting elimination on treatment with a base[8] gave a mixture of **2** and the nonconjugated nitroalkenes whose ratio was about 7 : 3. Dehydration with DCC in the presence of copper(I) chloride gave **2** in good yields without formation of nonconjugated nitroalkenes. The results are summarized in Table 1.

Nitroalkenes **2** were converted into pyrroles on treatment with ethyl isocyanoacetate in the presence of a base.[4] The reaction was carried out by stirring a mixture of **2**, ethyl isocyanoacetate, and DBU in tetrahydrofuran (THF) at room temperature. 2-Ethoxycarbonyl-3,4-dialkylpyrroles (**3**) and 2,4-bis(ethoxycarbonyl)-3-alkylpyrroles (**4**) were obtained in 70—80% and 5—10% yields, respectively. They are readily separated by column chromatography (silica gel/benzene) to afford pure **3** and **4**. The results are summarized in Table 2. Formation of **4** has not been reported

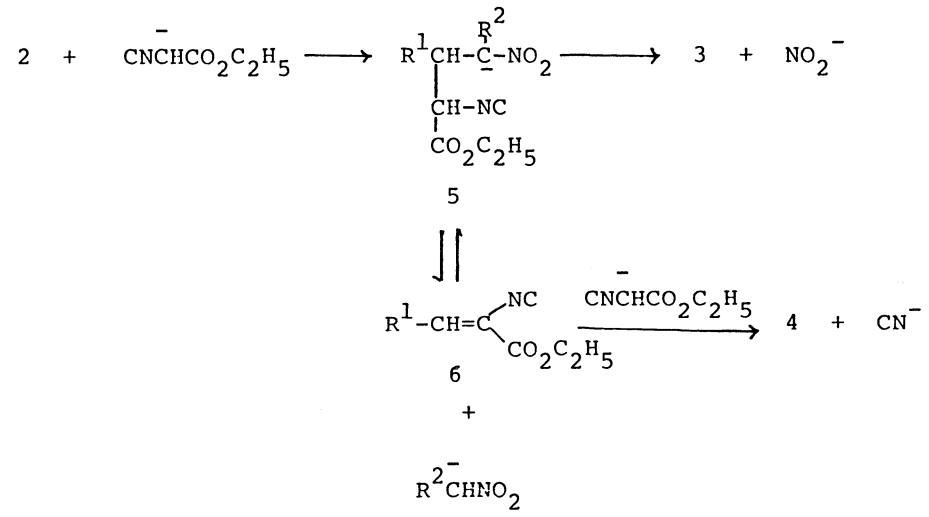


in the literature,[4] but it is unavoidable in the preparation of pyrroles using nitroalkenes. The possible route for the formation of **3** and **4** is shown in Scheme 1. The intermediate **5** undergoes either cyclization to give **3** or elimination of the anion of nitro compounds to give **6** which reacts with ethyl isocyanoacrtate to give **4**.[9]

Table 1. Preparation of Nitro Alcohols (**1**) and Nitroalkenes (**2**) Having Long Alkyl Chains

R^1	R^2	Base (equiv)	Method[a]	**1**, Yield/%	**2**, Yield/% (*E*/*Z*)[b]
n-C_6H_{13}	CH_3	DBU (0.1)	A	**1a**, 90	**2a**, 85 (63/37)
n-C_9H_{19}	CH_3	DBU (0.1)	A	**1b**, 95	**2b**, 80 (65/35)
n-C_5H_{11}	*n*-C_7H_{15}	DBU (0.3)	B	**1c**, 98	**2c**, 88 (60/40)
n-C_7H_{15}	*n*-C_7H_{15}	DBU (0.3)	B	**1d**, 95	**2d**, 80 (57/43)
n-C_8H_{17}	*n*-C_8H_{17}	DBU (0.3)	B	**1e**, 90	**2e**, 85 (57/43)
n-C_5H_{11}	$CH_2CH_2CO_2CH_3$	DBU (0.3)	B	**1f**, 94	**2f**, 76 (55/45)

a) Method A: The reaction was carried out in acetonitrile at room temperature. Method B: the reaction was carried out without solvents at room temperature. b) The *E*/*Z* ratio was determined by NMR and HPLC.



Scheme 1.

Table 2. Preparation of Pyrroles **3** and **4**[a)]

R^1	R^2	Time h	**3**, yield %	**4**, yield %
n-C_6H_{13}	CH_3	15	**3a**, 78	**4a**, 8
n-C_9H_{19}	CH_3	20	**3b**, 80	**4b**, 5
n-C_5H_{11}	n-C_7H_{15}	20	**3c**, 80	**4c**, 8
n-C_7H_{15}	n-C_7H_{15}	20	**3d**, 77	**4d**, 6
n-C_8H_{17}	n-C_8H_{17}	20	**3e**, 85	**4e**, 5
n-C_5H_{11}	$CH_2CH_2CO_2CH_3$	20	**3f**, 70	**4c**, 5

(a) The reaction was carried out by stirring amixture of **2** (10 mmol), ethyl isocyanoacetate (10 mmol), and DBU (10 mmol) in THF (20 ml). The separation of **3** was carried out by column chromatography (silica gel/benzene).

Thus, pyrroles having long alkyl chains are conveniently prepared from nitroalkenes. Pyrroles **3** are useful for the synthesis of lipophilic porphyrins.[1)]

Experimental

Nitroalkanes were prepared by the reaction of the corresponding alkyl bromides with sodium nitrite in dimethyl sulfoxide,[10)] or the Michael addition of nitrometane to methyl acrylate.[11)] Aldehydes were used after distillation of commercially available materials. Ethyl isocyanoacetate was prepared according to the literature.[12)]

Preparation of β-Nitro Alcohols. Method A: A mixture of nitroethane (8.3 g, 0.11 mol), heptanal (11.4 g, 0.10 mol), and DBU (0.15 g, 0.01 mol) in acetonitrile (10 ml) was stirred at room temperature for 24 h and then diluted with water (50 ml) containing 1 M HCl (10 ml; 1 M=1 mol dm^{-3}), and extracted with ethyl acetate. The extracts were washed with water and dried with anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was distilled to give 2-nitro-3-nonanol (**1a**), 16 g (90%), bp 100—105 °C/1 mmHg (1 mmHg=133.32 Pa); lit.,[11)] 110 °C/1.5 mmHg. 2-Nitro-3-dodecanol (**1b**): bp 110—115 °C/1 mmHg.

Method B: A mixture of 1-nitrooctane (3.2 g, 20 mmol), hexanal (2.0 g, 20 mmol), and DBU (0.45 g, 2 mmol) was stirred at room temperature for 24 h and then diluted with ethyl acetate (20 ml). The resulting solution was poured into 1 M HCl (100 ml) and extracted with ethyl acetate. The extracts were washed with water and the solvent was removed to give 7-nitro-6-tetradecanol (**1c**), which was pure enough to use for the next step; 4.9 g (98%).

Preparation of Nitroalkenes (2). A mixture of **1c** (3.68 g, 14.2 mmol), copper(I) chloride (34 mg, 3.4 mmol), and DCC (3.50 g, 17.1 mmol) in dioxane (40 ml) was stirred at room temperature for 48 h. The precipitated solid was removed by filtration and washed with hexane. The filtrate and washings were combined, and washed with 1 M HCl and water. The solvent was removed after drying with anhydrous magnesium sulfate. The residue was subjected to column chromatography (silica gel/ benzene-hexane) to give **2c**, 3.01 g (88%). ^{1}H NMR ($CDCl_3$) δ=0.87 (t, 6 H, J=7 Hz), 1.00—1.60 (m, 16 H), 1.64—1.98 (m, 2 H), 2.04—2.68 (m, 2 H), 5.63 (t, Z-CH=C), and 6.98 (t, E-CH=C). IR (neat) 1360, 1530, and 1670 cm^{-1}. Found: m/z 241.2064. Calcd for $C_{14}H_{27}NO_2$: M, 241.2042.

Following nitroalkenes were prepared by this procedure.

2a: ^{1}H NMR ($CDCl_3$) δ=0.90 (t, 3 H, J= 7 Hz), 1.10—1.70 (m, 8 H), 2.10 (s, 3 H), 2.28—2.45 (m, 2 H), 5.83 (t, Z-CH=C), and 7.07 (t, E-CH=C). IR (neat) 1360, 1530, and 1650 cm^{-1}. Found: m/z 171.1138. Calcd for $C_9H_{17}NO_2$: M, 171.1145.

2b: ^{1}H NMR ($CDCl_3$) δ=0.90 (t, 3 H, J= 7 Hz), 1.05—1.75 (m, 14 H), 2.08 (s, 3 H), 2.20—2.50 (m, 2 H), 5.83 (t, Z-CH=C), and 7.02 (t, E-CH=C). IR (neat) 1360, 1530, and 1650 cm^{-1}. Found: m/z 230.1932. Calcd for $C_{12}H_{23}NO_2$: M, 230.1934.

2d: ^{1}H NMR ($CDCl_3$) δ=0.85 (t, 6 H, J=7 Hz), 1.04—1.78 (m, 20 H), 2.05—2.74 (m, 4 H), 5.64 (t, Z-CH=C), and 7.00 (t, E-CH=C). IR (neat) 1360, 1530, and 1650 cm^{-1}. Found: m/z 269.2348. Calcd for $C_{16}H_{31}NO_2$: M, 269.2354.

2e: ^{1}H NMR ($CDCl_3$) δ=0.85 (t, 6 H, J=7 Hz), 1.02—1.78 (m, 24 H), 2.10—2.65 (m, 4 H), 5.62 (t, Z-CH=C), 7.02 (t, E-CH=C). IR (neat) 1360, 1530, and 1650 cm^{-1}. Found: m/z 297.2876. Calcd for $C_{18}H_{35}NO_2$: M, 297.2886.

2f: ^{1}H NMR ($CDCl_3$) δ=0.89 (t, 3 H, J=7 Hz), 1.10—1.80 (m, 6 H), 2.12—2.82 (m, 4 H), 2.85 (q, 2 H, J=8 Hz), 3.64 (s, 3 H), 5.91 (t, Z-CH=C), and 7.13 (t, E-CH=C). IR (neat) 1360, 1530, 1650, and 1730 cm^{-1}. Found: m/z 229.1314. Calcd for $C_{11}H_{19}NO_4$: M, 229.1314.

Preparation of Pyrroles. Typical Procedure: A mixture of **2a** (1.71 g, 10 mmol), ethyl isocyanoacetate, and DBU (1.52 g, 10 mmol) in THF (20 ml) was stirred at room temperature for 15 h. The reaction mixture was poured into water (100 ml) containing 1 M HCl (10 ml) and extracted with ethyl acetate (3×50 ml). The extracts were washed with water and dried with anhydrous magnesium sulfate, The solvent was

removed under reduced pressure, and the reside was subjected to column chromatography (silica gel/benzene) to give **3a** (1.85 g, 78%) and **4a** (0.24 g, 8%). **3a**: mp 55—56 °C. IR (KBr) 3340 and 1680 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.95 (t, 3 H, J=7 Hz), 1.2—1.8 (m, 11 H), 2.02 (s, 3 H), 2.70 (q, 2 H, J=7 Hz), 4.25 (q, 2 H, J=7 Hz), 6.70 (d, 1 H, J=3 Hz), and 9.45 (br s, 1 H). Found: C, 70.76; H, 9.87; N, 5.93%. Calcd for $C_{14}H_{23}NO_2$: C, 70.84; H, 9.77; N, 5.90%. **4a**: oil. IR (neat) 3340, 1620, and 1680 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.95 (t, 3 H, J=7 Hz), 1.2—1.7 (m, 14 H), 3.10 (q, 2 H, J=7 Hz), 4.28 (q, 2 H, J=7 Hz), 4.35 (q, 2 H, J=7 Hz), 7.45 (d, 1 H, J=2 Hz), and 9.28 (br s, 1 H). Found: C, 65.14; H, 8.39; N, 4.68%. Calcd for $C_{16}H_{25}NO_4$: C, 65.06; H, 8.53; N, 4.74%. Following pyrroles were prepared by this procedure.

3b: Oil. IR (neat) 3340 and 1685 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.90 (t, 3 H, J=7 Hz), 1.1—1.8 (m, 17 H), 2.0 (s, 3 H), 2.69 (q, 2 H, J=7 Hz), 4.25 (q, 2 H, J=7 Hz), 6.68 (d, 1 H, J=3 Hz), and 9.40 (br s, 1 H). Found: C, 75.51; H, 10.78; N, 5.13%. Calcd for $C_{17}H_{29}NO_2$: C, 75.79; H, 10.85; N, 5.20%.

3c: Oil. IR (neat) 3340 and 1680 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.90 (t, 6 H, J=7 Hz), 1.1—1.8 (m, 19 H), 2.36 (q, 2 H, J=7 Hz), 2.70 (q, 2 H, J=7 Hz), 4.25 (d, 2 H, J=7 Hz), 6.66 (d, 1 H, J=3 Hz), and 9.20 (br s, 1 H). Found: C, 74.38; H, 10.78; N, 4.79%. Calcd for $C_{19}H_{33}NO_2$: C, 74.22; H, 10.82; N, 4.56%.

3d: Oil. IR (neat) 3320 and 1680 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.90 (t, 6 H, J=7 Hz), 1.1—1.8 (m, 23 H), 2.38 (q, 2 H, J=7 Hz), 2.70 (q, 2 H, J=7 Hz), 4.25 (q, 2 H, J=2 H), 6.62 (d, 1 H, J=3 Hz), and 8.98 (br s, 1 H). Found: C, 75.25; H, 11.28; N, 4.28%. Calcd for $C_{21}H_{37}NO_2$: C, 75.17; H, 11.12; N, 4.18%.

3e: Oil. IR (neat) 3320 and 1680 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.90 (t, 6 H, J=7 Hz), 1.1—1.8 (m, 27 H), 2.40 (q, 2 H, J=7 Hz), 2.72 (q, 2 H, J= 7 Hz), 4.26 (q, 2 H, J=7 Hz), 6.62 (d, 1 H, J=3 Hz), and 9.90 (br s, 1 H). Found: C, 75.89; H, 12.57; N, 3.74%. Calcd for $C_{23}H_{41}NO_2$: C, 75.98; H, 12.32; N, 3.85%.

3f: Oil. IR (neat) 1680, 1730, and 3340 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.97 (t, 3 H, J=7 Hz), 1.2—2.0 (m, 11 H), 2.64 (q, 2 H, J=7 Hz), 2.86 (q, 2 H, J=7 Hz), 3.64 (s, 3 H), 4.28 (q, 2 H, J=7 Hz), 6.78 (d, 1 H, J=3 Hz), and 9.90 (br s, 1 H). Found: C, 65.28; H, 8.38; N, 4.57%. Calcd for $C_{16}H_{25}NO_4$: C, 65.06; H, 8.53; N, 4.74%.

4b: Oil. IR (neat) 3340, 1640, and 1680 cm^{-1}. H NMR ($CDCl_3$) δ=0.95 (t, 3 H, J=7 Hz), 1.2—1.8 (m, 20 H), 3.12 (q, 2 H), J=7 Hz), 4.26 (q, 2 H, J=7 Hz), 4.36 (q, 2 H, J=7 Hz), 7.35 (d, 1 H, J= 2 Hz), and 9.26 (br s, 1 H). Found: C, 67.73; H, 9.12; N, 4.27%. Calcd for $C_{19}H_{31}NO_4$: C, 67.62; H, 9.26; N, 4.15%.

4c: Oil. IR (neat) 3340, 1640, and 1680 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.95 (t, 3 H, J=7 Hz), 1.2—1.8 (m, 12 H), 3.20 (q, 2 H, J=7 Hz), 4.25 (q, 2 H, J=7 Hz), 4.36 (q, 2 H, J=7 Hz), 7.40 (d, 1 H, J=2 Hz), and 9.30 (br s, 1 H). Found: C, 64.17; H, 8.13; N, 4.78%. Calcd for $C_{15}H_{23}NO_4$: C, 64.04; H, 8.24; N, 4.92%.

4d: Oil. IR (neat) 3340, 1640, and 1680 cm^{-1}. ^1H NMR ($CDCl_3$) δ= 0.95 (t, 3 H, J=7 Hz), 1.2—1.8 (m, 16 H), 3.12 (q, 2 H, J=7 Hz), 4.25 (q, 2 H, J=7 Hz), 4.36 (q, 2 H, J=7 Hz), 7.32 (d, 1 H, J= 2 Hz), and 9.25 (br s, 1 H). Found: C, 66.17; H, 8.89; N, 4.40%. Calcd for $C_{17}H_{27}NO_4$: C, 65.99; H, 8.80; N, 4.53%.

4e: Oil. IR (neat) 3340, and 1680 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.95 (t, 3 H, J=7 Hz), 1.2—1.8 (m, 18 H), 3.12 (q, 2 H, J=7 Hz), 4.25 (q, 2 H, J=7 Hz), 4.36 (q, 2 H, J=7 Hz), 7.37 (d, 1 H, J=2 Hz), and 9.25 (br s, 1 H). Found: C, 66.79; H, 9.23; N, 4.15%. Calcd for $C_{18}H_{29}NO_4$: C, 66.84; H, 9.04; N, 4.33%.

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