

Synthesis of 3-Phenylpyrroles by Hydride Reduction of 4-Hydroxypyrrolidin-2-ones

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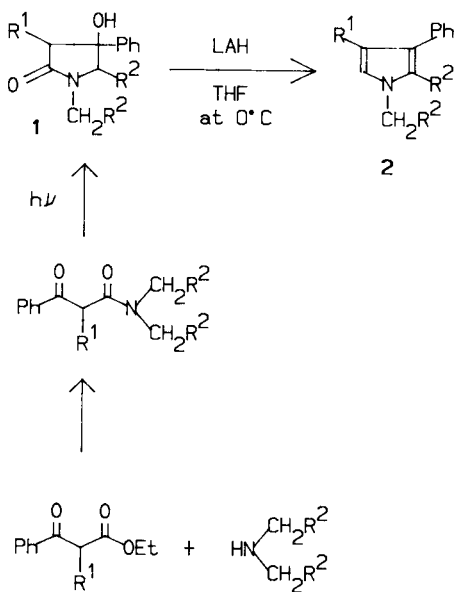
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Received August 18, 1986

3-Phenylpyrroles **2** were easily prepared in good yields by hydride reduction of 4-hydroxypyrrolidin-2-ones **1**, which have been prepared in high yields from the photoreaction of *N,N*-dialkylbenzoylacetylides, with lithium aluminum hydride.

J. Heterocyclic Chem., **24**, 829 (1987).

Pyrrole and its derivatives are the biologically important organic compounds [1]. The general and main methods for preparation of pyrroles are by the cyclization of a four-carbon chain with an appropriate nitrogen-containing group (Paal-Knorr Synthesis), and by the linking of carbon to carbon to give the 3,4-bond (Knorr Synthesis) [1,2]. However, there are some restrictions, such as those for positions of and types of substituents, in these methods. Numerous methods for syntheses of pyrroles have been reported [3]. We have already reported that 4-hydroxypyrrolidin-2-ones **1** are synthesized in high yields from photolyses of *N,N*-dialkylbenzoylacetylides prepared easily from ethyl benzoylacetate and the corresponding amines [4]. We report here that the reduction of the 4-hydroxypyrrolidin-2-ones **1** with lithium aluminum hydride gives 3-phenylpyrroles **2** easily and in good yields.



Reduction of 1-benzyl-4-hydroxy-4,5-diphenylpyrrolidin-2-one (**1a**) with an excess amount of lithium aluminum

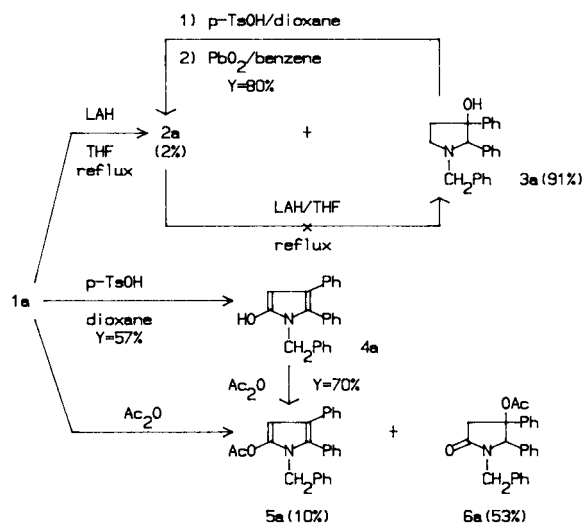
hydride in dry tetrahydrofuran at 0° gave 1-benzyl-2,3-diphenylpyrrole (**2a**) in 55% yield. The ¹H-nmr spectrum of **2a** showed the characteristic signals for the protons on the pyrrole ring at δ 6.45 (d) and 6.48 (d) attributable to protons on C-4 and C-5, respectively. Similarly, the hydride reduction of the 4-hydroxypyrrolidin-2-one **1b-d** gave the pyrrole **2b-d**, respectively in good yields. (Table 1).

Table 1

Pyrroles **2** from 4-Hydroxypyrrolidin-2-ones **1**

	R ¹	R ²	Yield of 2 (%)
a	H	Ph	55
b	Me	Ph	51
c	H	Me	37
d	H	H	47

The efficiency of the hydride reduction of the hydroxypyrrolidin-2-ones to the pyrroles depended on the reaction temperature. Yields of the pyrrole were decreased with increase of the reaction temperature [5] (Figure 1). The



hydride reduction of the 4-hydroxypyrrolidin-2-one **1a** under heating at reflux in tetrahydrofuran gave 1-benzyl-3-hydroxy-2,3-diphenylpyrrolidine **3a** and the pyrrole **2a** in 91 and 2% yield, respectively. The pyrrole **2a** did not produce the pyrrolidine **3a** under the reductive conditions. When the pyrrole **2a** was refluxed with lithium aluminum hydride in tetrahydrofuran, 93% of **2a** was recovered. Therefore, the formation of the pyrrole **2** and that of the pyrrolidine **3** are the competing reactions.

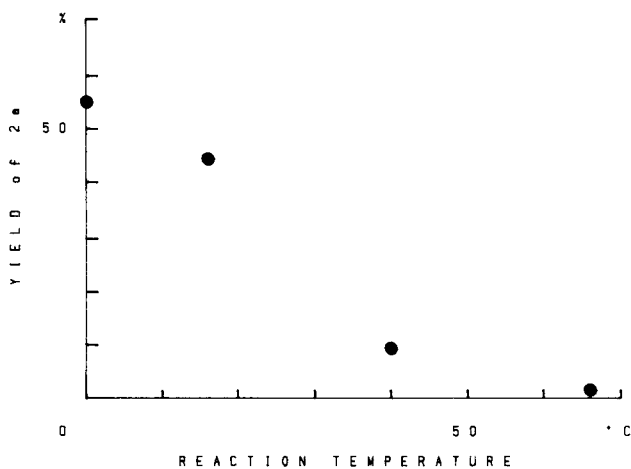


Figure 1. Reaction of **1a** at Various Temperature.

The alcohol **3a** could be converted to the pyrrole **2a** by dehydration under heating at reflux in dioxane in the presence of *p*-toluenesulfonic acid followed by oxidation with lead dioxide.

Hydroxypyrroles could be obtained by dehydration of the 4-hydroxypyrrolidin-2-ones **1**. When a dioxane solution of **1a** was heated at reflux in the presence of *p*-toluenesulfonic acid, the hydroxypyrrole **4a** was obtained in 57% yield. Reaction of **1a** with acetic anhydride gave the acetyloxypyrrole **5a** and the acetyloxypyrrolidin-2-one **6a** in 10 and 53% yield, respectively.

EXPERIMENTAL

All melting points were uncorrected. The ir spectra were recorded on a JASCO A-3 spectrometer. The ¹H and ¹³C-nmr spectra were taken on a JEOL FX90Q spectrometer in deuteriochloroform using tetramethylsilane as internal standard.

Materials.

The 4-hydroxypyrrolidin-2-ones **1a-d** were prepared according to the method in our previous paper [4].

General Procedure for Hydride Reduction of 4-Hydroxypyrrolidin-2-ones **1**.

To a suspended mixture of an excess amount (ca. 0.5 g) of lithium aluminum hydride in 25 ml of dry tetrahydrofuran at 0°, a 4-hydroxypyrrolidin-2-one **1** (ca. 0.5 g, 1-3 mmoles) in 2 ml of dry tetrahydrofuran was added dropwise. The mixture was allowed to stir for 2 hours at the

temperature, and then poured onto a mixture of ice-water. Benzene (100 ml) was added to the mixture. This mixture was stirred for 15 minutes at room temperature. After separation of unsolved material by filtration using sellalite, the benzene solution was separated and dried over anhydrous sodium sulfate for 10 minutes. After filtration, the benzene was removed under reduced pressure. The residue was chromatographed on silica gel using benzene as an eluent to give a 3-phenylpyrrole **2**. Yields of **2a-d** are collected in Table 1.

1-Benzyl-2,3-diphenylpyrrole (**2a**).

This compound had mp 118-119°; ir (potassium bromide): 1600 cm⁻¹; ¹H-nmr (deuteriochloroform): δ 4.95 (s, 2H, CH₂Ph), 6.45 (d, J = 4.1 Hz, H-4), 6.48 (d, J = 4.1 Hz, H-5), and 6.7-7.3 (m, 15H, aromatic).

Anal. Calcd. for C₂₃H₁₉N: C, 89.28; H, 6.19; N, 4.53. Found: C, 88.43; H, 6.12; N, 4.48.

1-Benzyl-4-methyl-2,3-diphenylpyrrole (**2b**).

This compound had mp 97-98°; ir (potassium bromide): 1600 cm⁻¹; ¹H-nmr (deuteriochloroform): δ 2.12 (s, 3H, CH₃), 4.95 (s, 2H, CH₂Ph), 6.56 (s, 1H, H-5), and 6.9-7.4 (m, 15H, aromatic).

Anal. Calcd. for C₂₄H₂₁N: C, 89.12; H, 6.54; N, 4.33. Found: C, 88.84; H, 6.64; N, 4.19.

1-Ethyl-2-methyl-3-phenylpyrrole (**2c**).

This compound had bp 165-175° (4 mm Hg); ir (neat): 1600 cm⁻¹; ¹H-nmr (deuteriochloroform): δ 1.37 (t, J = 7.3 Hz, 3H, CH₃), 2.32 (s, 3H, CH₃), 3.86 (q, J = 7.3 Hz, 2H, CH₂), 6.23 (d, J = 2.9 Hz, 1H, H-4), 6.60 (d, J = 2.9 Hz, 1H, H-5), and 7.1-7.4 (m, 5H, aromatic).

Anal. Calcd. for C₁₃H₁₅N: C, 84.28; H, 8.16; N, 7.56. Found: C, 83.95; H, 8.13; N, 7.47.

1-Methyl-3-phenylpyrrole (**2d**).

The structure of this compound was determined by comparison with an authentic sample [6]; ir (potassium bromide): 1600 cm⁻¹; ¹H-nmr (deuteriochloroform): δ 3.59 (s, 3H, CH₃), 6.38 (t, 1H, J = 2.5 Hz, H-4), 6.55 (t, 1H, J = 2.5 Hz, H-2), 6.83 (t, 1H, J = 2.5 Hz), and 7.0-7.5 (m, 5H, aromatic).

Hydride Reduction of **1a** under Heating at Reflux. 1-Benzyl-3-hydroxy-2,3-diphenylpyrrolidine (**3a**).

A mixture of 0.2 g of lithium aluminum hydride and 100 mg (0.3 mmole) of **1a** in 25 ml of dry tetrahydrofuran was refluxed for 2 hours. The reaction mixture was then worked up as described above. Elution with a mixture of benzene-ethyl acetate (4/1 (v/v)) gave 2 mg (2%) of the pyrrole **2a**, 12 mg of the unreacted starting lactam **1a**, and 77 mg (91%) of **3a**.

The compound **3a** is a paste-like material and could not be fully purified because it changed slowly and gradually to the pyrrole **2a** even at room temperature: ir (neat): 3400 cm⁻¹; ¹H-nmr (deuteriochloroform): δ 1.1-1.4 (m, 1H, CH₂), 2.0 (s, 1H, OH), 2.0-2.4 (m, 1H, CH₂), 2.4-3.0 (m, 1H, N-CH₂), 3.0-3.4 (m, 1H, N-CH₂), 3.22 (d, J = 11.3 Hz, 1H, CH₂Ph), 3.94 (d, J = 11.3 Hz, 1H, CH₂Ph), and 6.6-7.5 (m, 15H, aromatic); ¹³C-nmr (deuteriochloroform): δ 39.6 (t), 51.8 (t), 58.1 (t), 80.5 (d), 84.4 (s), 126.2 (d), 126.6 (d), 126.9 (d), 127.2 (d), 127.4 (d), 128.2 (d), 128.5 (2C, d), 128.7 (d), 138.4 (s), 138.9 (s), and 144.2 (s).

Conversion of the Pyrrolidine **3a** to the Pyrrole **2a**.

A mixture of **3a** (71 mg, 0.2 mmole) and *p*-toluenesulfonic acid (200 mg, 0.1 mmole) in 50 ml of dioxane was refluxed for 10 hours. After removal of the solvent, dilute sodium hydroxide solution was added to the mixture. The mixture was extracted with benzene. The extract was washed with water and dried over anhydrous sodium sulfate. After filtration and evaporation of the solvent, the residue was chromatographed on silica gel. Elution with benzene gave a trace of the pyrrole **2a**, unreacted **3a** (33 mg), and 1-benzyl-4,5-dihydro-2,3-diphenylpyrrole (**7a**). The compound **7a** could not be purified because it changed slowly to the pyrrole **2a**. The crude **7a** showed the ir absorption at 2800 cm⁻¹. The crude **7a** was dissolved in 10 ml of benzene and then lead dioxide (0.1 g) was added

ed. The mixture was stirred overnight at room temperature. The oxide was filtered off and the benzene was removed under reduced pressure. The residue was chromatographed on silica gel. Elution with benzene gave 29 mg of the pyrrole **2a** (80% conversion yield based on the starting pyrrolidine **3a**).

Dehydration of the 4-Hydroxypyrrolidin-2-one (**1a**). 1-Benzyl-2-hydroxy-4,5-diphenylpyrrole (**4a**).

A mixture of 190 mg (0.6 mmole) of **1a** and 10 mg (0.06 mmole) of *p*-toluenesulfonic acid in 30 ml of dioxane was refluxed overnight. The reaction mixture was concentrated under reduced pressure and then 30 ml of benzene was added. The benzene solution was washed with dilute sodium hydroxide solution and then with water. After drying over anhydrous sodium sulfate, the mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with a mixture of benzene-ethyl acetate (2/1 (v/v)) gave 107 mg (59%) of 1-benzyl-2-hydroxy-4,5-diphenylpyrrole (**4a**).

Compound **4a** had mp 114-118°; ir (potassium bromide): 3350 and 1680 cm^{-1} ; $^1\text{H-nmr}$ (deuteriochloroform): δ 3.50 (d, $J = 8.1$ Hz, 1H, CH_2Ph), 5.19 (d, $J = 8.1$ Hz, 1H, CH_2Ph), 5.20 (s, 1H, OH), 6.59 (s, 1H, H-3), and 7.0-7.6 (m, 15H, aromatic).

Anal. Calcd. for $\text{C}_{23}\text{H}_{19}\text{NO}$: C, 84.89; H, 5.89; N, 4.30. Found: C, 85.10; H, 6.04; N, 3.99.

A mixture of **4a** (10 mg, 0.03 mmole) and 1 ml of acetic anhydride was refluxed for 3 hours. The reaction mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with a mixture of benzene-ethyl acetate (4/1 (v/v)) gave 2-acetyloxy-1-benzyl-4,5-diphenylpyrrole (**5a**) in 70% yield.

Compound **5a** had mp 176-178°; ir (potassium bromide): 1750 and 1700 cm^{-1} ; $^1\text{H-nmr}$ (deuteriochloroform): δ 2.08 (s, 3H, CH_3), 4.88 (s, 2H, CH_2Ph), 6.25 (s, 1H, H-3), and 6.8-7.3 (m, 15H, aromatic).

Anal. Calcd. for $\text{C}_{25}\text{H}_{21}\text{NO}_2$: C, 81.72; H, 5.76; N, 3.81. Found: C, 81.41; H, 5.84; N, 3.62.

Reaction of **1a** with Acetic Anhydride. 4-Acetyl-1-benzyl-4,5-diphenylpyrrolidine (**6a**).

A mixture of 80 mg (0.2 mmole) of **1a** and 10 ml of acetic anhydride was refluxed for 3 hours. After concentration of the mixture, the residue

was chromatographed on silica gel. Elution with a mixture of benzene-ethyl acetate (4/1 (v/v)) gave 6 mg (10%) of **5a**, 32 mg (53%) of **6a**, and 22 mg of the unreacted 4-hydroxypyrrolidin-2-one **1a**.

Compound **10a** had mp 114-115°; ir (potassium bromide): 1750 and 1700 cm^{-1} ; $^1\text{H-nmr}$ (deuteriochloroform): δ 2.01 (s, 3H, CH_3), 3.48 (q, 2H, $J = 18.0$ Hz, CH_2), 3.56 (d, $J = 15.0$ Hz, 1H, N- CH_2), 4.72 (s, 1H, CH), 5.36 (d, $J = 15.0$ Hz, 1H, N- CH_2) and 6.6-7.4 (m, 15H, aromatic).

Anal. Calcd. for $\text{C}_{25}\text{H}_{23}\text{NO}_3$: C, 77.90; H, 6.01; N, 3.63. Found: C, 77.83; H, 5.50; N, 3.65.

Reaction of **1a** at Various Temperature.

All reactions were performed using 50 mg (0.015 mmole) of **1a**, 10 ml of tetrahydrofuran and 0.1 g of lithium aluminum hydride. After the reaction at different temperature, 0.5 ml of water was added to the reaction mixture, and then a known amount of phenanthrene was added as calibrant. Analyses were performed using a Gasukuro Kogyo 570B high pressure liquid chromatograph with a Model 511 single wave uv detector (254 nm). Employing a Unishil QC18 column (4 x 250 mm) with a mixture of acetonitril-water (3/2 (v/v)) as the moving phase at a flow rate of 0.7 ml/minute phenanthrene and the pyrrole **2a** eluted in 11.2 and 20.8 minutes, respectively.

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