A New Synthesis of Pyrroles

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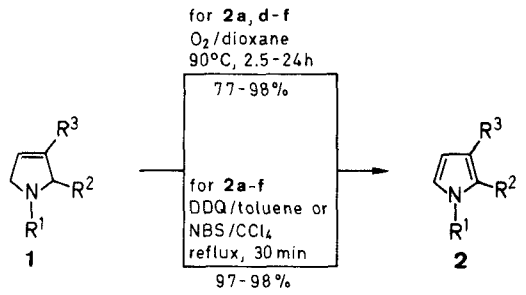
N-Protected 2,5-dihydro-1*H*-pyrrole derivatives are transformed into the corresponding pyrroles in high yield by a simple air oxidation or dehydrogenation reaction using tetrachloro-1,4-benzoquinone(*p*-chloranil), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or *N*-bromosuccinimide (NBS).

In the course of porphyrin syntheses[1] we found that β-unsubstituted pyrroles are easily obtained in very high yield from the corresponding pyrrolines by a simple air oxidation or dehydrogenation reaction, and we wish to report a new pathway for their synthesis.



1, 2	R^1	R^2	R^3
a	CO_2Et	H	CO_2Et
b	CO_2Et	Me	CO_2Et
c	CO_2Et	H	CH_2OH
d	Bn	H	CO_2Et
e	Bn	H	CH_2OH
f	CO_2Bn	H	CO_2Et

Several methods have been reported for the transformation of dihydroheterocyclic compounds into the corresponding heterocyclic aromatic compounds.[2] However, a simple air oxidation or dehydrogenation reaction of the dihydropyrrole system has not yet been reported.

These reactions turned out to be very simple and convenient. In the case of air oxidation, 1-benzyl-2,5-dihydro-1*H*-pyrroles **1d,e** which were obtained easily by a slight modification of the known procedure[3] were stirred in dioxane at 90 °C for a few hours to give the pyrroles in over 95% yield. To study the influence of solvent, dimethylformamide, diglyme, and dimethyl sulfoxide were used, but no significant change in the yield was found.

The corresponding carbamates **1a,f** did not react by simple air oxidation at room temperature in most solvents except for dioxane at 90 °C (Table). In diglyme, dimethylformamide, or dimethyl sulfoxide the reaction did not occur even at 90 °C for up to 48 hours. When an alkyl substituent was introduced at the 2-position, **1b**, of the dihydropyrrole carbamate or a hydroxymethyl group at

Table. Pyrrole Derivatives **2** Prepared

Product	Air Oxidation			Didehydrogenation			
	Reaction Time (h)	Yield (%) r.t.	90 °C	Reaction Time (h)	Yield (%) *p*-Chloranil	DDQ	NBS
2a	24	trace	77	0.5	[a]	97	98
2b	12	[a]	[b]	0.5	[a]	98	97
2c	12	[a]	[b]	0.5	[a]	97	98
2d	24	46	98[c]	0.5	98	97	98
2e	24	57	97[d]	0.5	98	98	97
2f	24	13	98[d]	0.5	[a]	98	97

[a] No reaction occured up to 48 h.
[b] Decomposition.
[c] Reaction time is 2.5 h.
[d] Reaction time is 12 h.

the 3-position, **1c**, instead of the ethoxycarbonyl group, only decomposition was observed in dimethylformamide, dimethyl sulfoxide, pyridine, or diglyme.

In the case of **1a**, the use of reagent grade dioxane at 90 °C without purification increased the yield of **2a** by ca. 20% (from 77% to 92%) presumably due to the peroxide impurity. When iron powder was added as an oxidation catalyst for the reaction of **1a** at 90 °C, the **2a** was obtained in a slightly higher yield (from 77% to 85%).

A similar air oxidation was published for 1,4-dihydropyridine.[4] We assume that the pyrrole was obtained via initial oxygenation on the nitrogen followed by dehydration to give the aromatic pyrrole ring.

The air oxidation discussed above is most convenient for 1-benzyl-2,5-dihydro-1*H*-pyrroles. In order to obtain pyrroles with other protecting groups various dehydrogenating agents such as tetrachloro-1,4-benzoquinone (*p*-chloranil), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone(DDQ) and *N*-bromosuccinimide (NBS) were investigated.

The reaction of dihydropyrrole carbamate derivatives with *p*-chloranil did not give the corresponding pyrroles, but with DDQ or NBS the transformations were very smooth to give pyrroles in quantitative yield (Table). For a reaction with DDQ the 2,5-dihydro-1*H*-pyrroles **1a–f** were dissolved in dry toluene and refluxed for 30 minutes with equimolar amount of DDQ. After cooling the hydroquinone was filtered off and the reaction mixture was column chromatographed on silica gel with dichloromethane to give the desired product.

For the reaction with NBS, the dihydropyrrole derivative was dissolved in carbon tetrachloride and refluxed for 30 minutes. After cooling, the succinimide was filtered off and the reaction mixture was column chromatographed on silica gel with dichloromethane to give the desired product.

When 1-benzyl 3-ethyl 1,3-pyrroledicarboxylate **2f** was hydrogenated at room temperature with palladium on carbon (Pd-C) in tetrahydrofuran, the corresponding *N*-unsubstituted pyrrole was obtained in quantitative yield. This new, simple, and efficient procedure constitutes a general preparation of 2-unsubstituted pyrroles, which can be used in porphyrin synthesis,[5] or for othe pyrrolic compounds.

All reagents used were purchased from Aldrich Chemical Co. Silica gel for flash column chromatography (silica gel 60, 230 ~ 400 mesh ASTM) were purchased from Merck Co. Melting point was obtained using a Thomas Hoover melting point apparatus and is uncorrected. ^{1}H-NMR spectra were obtained on Varian EM-360A. IR spectra were obtained using a Shimadzu IR-435 spectrophotometer. Mass spectra were obtained using a Jeol model JMS-DX 303 spectrometer with El ionization.

Ethyl 1-Benzylpyrrole-3-carboxylate (2d); Typical Procedure:
Ethyl 1-benzyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**1d**; 48 mg, 0.21 mmol), which is obtained according to literature procedure[3] is dissolved in dioxane (10 mL) and is heated for 2.5 h with stirring in an oil bath at 90 °C under O_2 atmosphere using O_2 balloon. The solvent is evaporated under reduced pressure and the product is separated by flash column chromatography on silica gel with hexane/EtOAc (3:1) to give the oily product **2d**; yield: 47.7 mg (98%).

MS (EI): m/z = 229 (M^+, 61), 69 (100).

IR (KBr): ν = 1701 cm^{-1} ($CO_2CH_2CH_3$).

^{1}H-NMR (300 MHz, $CDCl_3$/TMS): δ = 1.32 (t, 3H, CH_3), 4.27 (q, 2H, CH_2), 5.05 (s, 2H, CH_2Ph), 6.61, 6.62 (2s, H each, $H_{pyrrole}$), 7.24 (m, 6H, 1 $H_{pyrrole}$ + 5 H_{arom}).

Diethyl 1,3-Pyrroledicarboxylate (2a); Typical Procedure:
Diethyl 2,5-Dihydro-1,*H*-pyrrole-1,3-dicarboxylate[3] (48 mg, 0.21 mmol) is dissolved in toluene (10 mL) and is refluxed for 30 min with DDQ (47.7 mg, 0.21 mmol). The hydroquinone is filtered off at. r.t. The filtrate is concentrated under vacuum and the product is separated by flash column chromatography on silica gel with CH_2Cl_2. After solvent evaporation the solid **2a** is obtained; yield: 43.5 mg (98); mp 40–41 °C.

MS (EI). m/z = 211 (M^+, 36), 94 (100).

IR (KBr): ν = 1742, 1696 cm^{-1} ($CO_2CH_2CH_3$).

^{1}H-NMR (300 MHz, $CDCl_3$/TMS): δ = 1.35 (t, 3H, CH_3), 1.43 (t, 3H, CH_3), 4.30 (q, 2H, CH_2), 4.46 (q, 2H, CH_2), 6.64, 7.26, 7.89 (m each, 3 $H_{pyrrole}$).

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