

A General Synthesis of Pyrroles from Aldehydes and Ketones

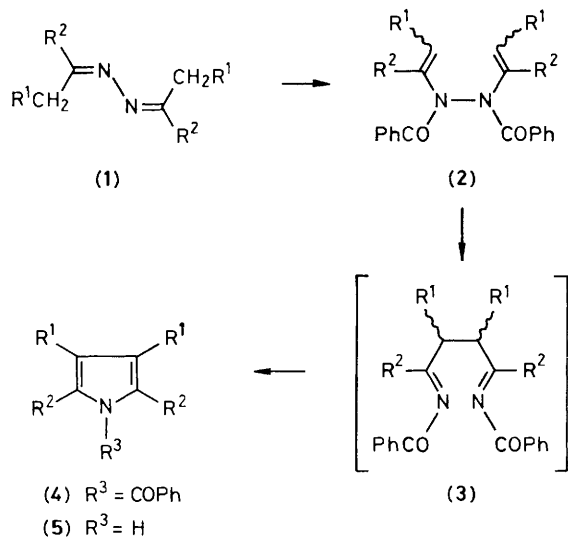
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The azines of enolisable aldehydes and ketones are converted into pyrroles *via* thermal rearrangement of the derived benzoyl derivatives and subsequent hydrazinolysis of the resulting *N*-benzoylpyrroles.

The Piloty–Robinson Pyrrole synthesis¹ has been used in the conversion of ketone azines into pyrroles.² However, this reaction suffers from a number of drawbacks. Thus, the yields are often poor owing to the strongly acidic conditions of the reaction (180 °C, HCl gas) and also, the conversion of aldehyde azines into pyrroles by this reaction has not been possible.³ Finally, the synthesis of unsymmetrical pyrroles by this method has never been achieved. We report a related and general pyrrole synthesis which, starting with either aldehydes or ketones, gives pyrroles of any substitution pattern in fair to excellent yield.

The procedure is as follows. The azines (1) of enolisable aldehydes and ketones are first converted into the *N,N'*-dibenzoyl-*N,N'*-bis(enyl)hydrazines (2) by treatment with benzoyl chloride and pyridine in benzene solution. These intermediates are refluxed in xylene (140 °C) to yield the *N*-benzoylpyrroles (4), presumably by way of compounds (3). Hydrazinolysis in isopropyl alcohol (80 °C, 1–3 days) cleanly liberates the pyrrole (5), Scheme 1. The bis(enyl)hydrazines (2)



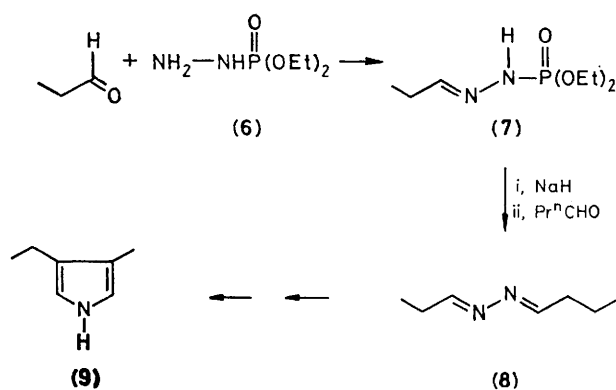
Scheme 1

were relatively unstable and were directly utilised in the pyrrole synthesis, however the ¹H n.m.r. spectra of the benzoylation product supported the structural assignment. The symmetrical pyrroles made by this method which were completely characterised are listed in Table 1 along with the overall yields, which were not optimised. In order to extend this method to unsymmetrical pyrroles we investigated the reaction of propanal with diethyl phosphorohydrazidate (6);⁴ which gave the hydrazone (7).[†] Further reaction of the sodium salt of

Table 1

Starting azine	Product ^a	Overall yield (%)
Cyclohexanone	1,2,3,4,5,6,7,8-octahydrocarbazole	90
Acetone	2,5-dimethylpyrrole	30
Propanal	3,4-dimethylpyrrole	20
Butanal	3,4-diethylpyrrole	35

^a W. H. Perkin and S. G. P. Plant, *J. Chem. Soc.*, 1924, 1503; K. Schofield, 'Hetero-Aromatic Nitrogen Compounds,' Butterworths, London, 1967, pp. 52 and 54.



Scheme 2

[†] All new compounds have given satisfactory analytical and spectral data.

(7) with another aldehyde provided a convenient synthesis of the unsymmetrical azine (8) which was converted into opsopyrrole (9), as above, Scheme 2. The detailed procedure was as follows: propanal (0.2 mol) was condensed with (6) (0.15 mol) in methylene chloride (25 °C, 100 ml) in the presence of acetic acid (0.5 ml), to provide hydrazone (7) (75%), as a mixture of stereoisomers, i.r. (neat) 3150, 1480, 1235, and 1030 cm^{-1} ; ^1H n.m.r. (CDCl_3), δ 7.9 (1H, d, J 27 Hz), 7.2 (1H, t, J 5 Hz), 4.2 (4H, m), 2.25 (2H, m), and 1.4 (6H, m). This product (7) (0.1 mol) in ether (200 ml) was treated sequentially with NaH (0.1 mol, 25 °C) and butanal (0.13 mol, slow addition). The azine (8), as a mixture of stereoisomers [i.r. (neat) 1690 and 1650 cm^{-1} ; ^1H n.m.r. (CDCl_3), δ 0.90 (3H, t, J 10 Hz), 1.1 (3H, t, J 8 Hz), 1.5 (4H, m), 2.3 (4H, m), and 7.8 (2H, m)] isolated by distillation (70%), was converted into opsopyrrole (9) by treatment of (8) (0.07 mol) with benzoyl chloride (0.15 mol) in benzene (100 ml) with pyridine (20 ml, 75 °C,

6 h). The filtered solution was evaporated and refluxed in xylene (100 ml, 50 h) with 1 ml of pyridine. Hydrazinolysis of the product was achieved by refluxing in isopropyl alcohol (50 ml) with hydrazine (6 ml, 24 h) to give after distillation, opsopyrrole (9) (2.8 g, 33%),⁵ i.r. (neat) 3400 cm^{-1} ; ^1H n.m.r. (CDCl_3), δ 1.1 (3H, t, J 6 Hz), 2.0 (3H, s), 2.35 (2H, quart., J 6 Hz), 6.3 (2H, d, J 3 Hz), and 7.4 (1H, d, J 3 Hz).

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