A General Synthesis of Pyrroles from Aldehydes and Ketones

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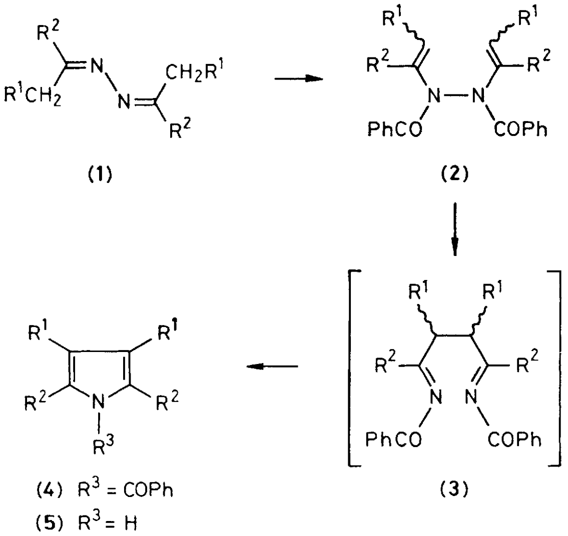
The azines of enolisable aldehydes and ketones are converted into pyrroles *via* thermal rearrangement of the derived benzoyl derivatives and subsequent hydrazinolysis of the resulting *N*-benzoylpyrroles.

The Piloty–Robinson Pyrrole synthesis[1] 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**) were relatively unstable and were directly utilised in the pyrrole synthesis, however the ^{1}H 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

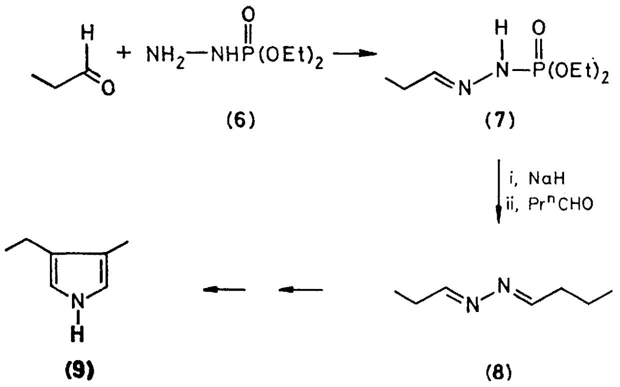


Scheme 1

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

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† 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}; ^{1}H 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}; ^{1}H 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}; ^{1}H 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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