Synthesis of Pyrroles under Mild Conditions using PCl_3, Ketones, and Alkylhydrazines

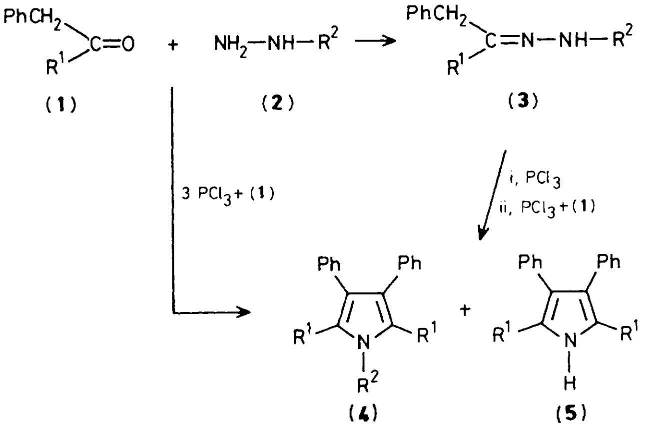
Graziano Baccolini* and Claudio Sandali

Istituto di Chimica Organica, Università, Viale Risorgimento 4, 40136 Bologna, Italy

A one-pot synthesis of symmetrical pyrroles was obtained by reaction of alkylhydrazones of enolizable ketones, PCl_3, and subsequent addition of the same ketone.

Pyrroles represent an important major class of heterocycles[1] and their prominent role in organic synthesis leads to continuing development of new methods of preparing pyrroles. Symmetrically substituted pyrroles are usually prepared through variations of the Piloty–Robinson synthesis using the respective ketoazine as intermediate.[2] However, this reaction needs drastic conditions and often the yields are very poor.[3] In the last few years we have found[4] that reaction at room temperature between ketone phenylhydrazones and PCl_3 gives indoles. We now describe a reaction using PCl_3 in the synthesis of pyrroles from ketone alkylhydrazones.

We have found that treatment of hydrazone (**3**) (1 equiv.) with PCl_3 (2 equiv.) and with the same enolizable ketone (**1**) (1 equiv.) gives a mixture of symmetrical pyrroles (**4**) and (**5**). The yields and the ratios of pyrroles are highly dependent on the reactants and on the reaction conditions. Table 1 shows the results obtained and the corrresponding reaction conditions. A typical procedure, giving the best yields, is as follows. A dry dichloromethane or benzene solution of hydrazone (**3**) is treated, at room temperature, with 1 equiv. of PCl_3. After about 2 h, ketone (**1**) (1 equiv.) and another equivalent of PCl_3



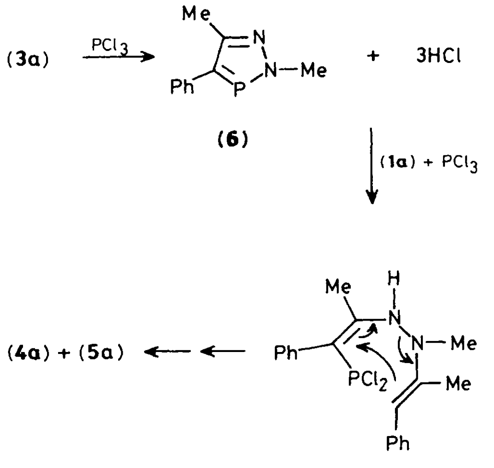
a; $R^1 = R^2 = Me$
b; $R^1 = Me$, $R^2 = PhCH_2$
c; $R^1 = PhCH_2$, $R^2 = Me$

Scheme 1

Table 1. Conversion of hydrazone (**3**) into pyrroles (**4**)[a,b] and (**5**)[c] by reaction with PCl_3 and ketone.

Hydrazone	Solvent	Conditions	% Overall yield[d]	Ratio (**4**):(**5**)
(**3a**)	CH_2Cl_2	Room temp. (3 d)	40	5:1
	C_6H_6	Reflux (3 h)	46	2:1
(**3b**)	CH_2Cl_2	Room temp. (6 d)	35	3:1
	C_6H_6	Reflux (4 h)	40	2:1
(**3c**)	CH_2Cl_2	Room temp. (8 d)	30	3:1
	C_6H_6	Reflux (12 h)	28	1:1

[a] For data of (**4a**), (**4c**) see: J. P. Chapelle, J. Elguero, R. Jaquier, and G. Tanago, *Bull. Soc. Chim.*, 1971, 280. [b] For data of (**4b**) see: H. Meyer, *Liebigs Ann. Chem.*, 1981, 1534. [c] For data of (**5a**) see: J. Hambrecht, *Synthesis*, 1977, **4**, 280. [d] Yields were calculated with respect to ketone (**1**) on isolated product.



Scheme 2

are added to the mixture and the reaction is allowed to stand for some days at room temperature or for a few hours at reflux. The reaction mixture is then quenched with aqueous sodium bicarbonate and extracted with dichloromethane. The pyrroles are isolated by column chromatography and structures are assigned essentially by ^1H n.m.r. and mass spectroscopy and confirmed by comparison with authentic samples. From the reaction mixture about 20% of the starting ketone is recovered. Surprisingly pyrroles were also obtained when the reaction was carried out at room temperature directly on a mixture of ketone (**1**) (2 equiv.), hydrazine (**2**) (1 equiv.), and PCl_3 (3 equiv.). In this case, however, the yields were lower (~30%), the reaction time was longer, and the ratio between (**4**) and (**5**) was about 1 : 1. It should be noted that PCl_3 is being used here as a water scavenger and as an activator of hydrazone and pyrrole formation.

N-substituted (**4**) and N-unsubstituted (**5**) pyrroles arise from the fact that presumably at the stage of heterocyclic ring-closure and subsequent elimination, either the imino or amino nitrogen atom of hydrazone may be retained. However, when the reaction was carried out at room temperature the almost exclusive or predominant formation of (**4**) was observed. In contrast, when the reaction was carried out in refluxing benzene or with an excess of PCl_3, a relative increase of (**5**) was detected.

In order to study the possibility of obtaining unsymmetrical pyrroles we have carried out the reaction between (**3a**), dimethyl acetylenedicarboxylate, and PCl_3. After 2 days at room temperature we obtained 1,2-dimethyl-3-phenyl-4,5-dimethoxycarbonylpyrrole[5] in 28% yield.

Preliminary results show that diazaphosphole derivatives such as (**6**) may be intermediates in the above reactions. It is known[6] that reaction of methylhydrazones with PCl_3 leads to diazaphospholes. In particular, we have followed the reaction of 1 equiv. of (**3a**) with 1 equiv. of PCl_3 by g.l.c.–mass spectrometric analysis and observed the disappearance of the peak of (**3a**) and the formation of the corresponding diazaphosphole (**6**) [m/z 190 (M^+)]. Subsequently, after addition of another equivalent of ketone (**1a**) and PCl_3 (1 equiv.), we have detected the gradual disappearance of (**6**) and the concomitant formation of pyrroles (**4a**) and (**5a**). Therefore (**6**) or its hydrochloride is actually formed in the first stage of our reaction and it presumably undergoes cleavage of the P–N bond under acid conditions.

The hypothetical dienehydrazine formed after condensation with ketone (**1a**) (see Scheme 2) might give pyrroles (**4a**) and (**5a**) by a series of steps analogous to the Piloty mechanism.[2a,5] In our case the phosphorus moiety could have an important role in promoting the loss of nitrogen atom in the last stage of this pyrrole synthesis.

Finally our results provide further evidence[7] that diazaphosphole derivates may be intermediates in the synthesis of aza-heterocycles.

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