Rate Measurements of Certain Vilsmeier–Haack Reactions. Part 3.[1] The Reactivities of Various Pyrrole Substrates

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The rates of reaction of six pyrrole substrates with the Vilsmeier–Haack reagent derived from *NN*-dimethylbenzamide (and in some cases from *N*-benzoylmorpholine or *NN*-diethylbenzamide) and phosphoryl chloride were measured. The deactivating effect on substitution at the 5-position of a 3-ethoxycarbonyl group outweighed the activating effect of a 2-methyl group but not that of two methyl groups when present at the 2- and 4-position. This net activation of the substrate was lost when the bulkier Vilsmeier–Haack complex derived from *NN*-diethylbenzamide was used. The presence of a methyl or benzyl group at the 1-position of the pyrrole resulted in an unexpected and very marked deactivation of the substrate. A highly specific orientation of reagent and substrate in the transition state is suggested to account for this effect.

In view of the sensitivity of Vilsmeier–Haack aroylation to structural and other factors[2] an examination of the effect of substituents attached to the pyrrole nucleus on the rate of the reaction was in order. The effect was gauged by treating each of the six pyrroles (**3a**—**f**) with the Vilsmeier–Haack reagent derived from *NN*-dimethylbenzamide and phosphoryl chloride and measuring the rate of azafulvene formation by the method set out previously.[3] Certain steric factors were further examined by using reagents analogously prepared from *N*-benzoylmorpholine and *NN*-diethylbenzamide.

Results and Discussion

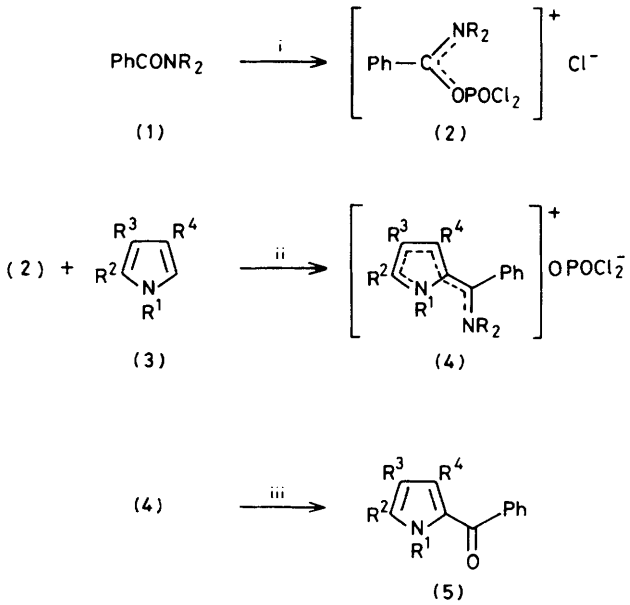
The reaction is set out in the Scheme, the results of the rate measurements appear in Table 1, and relative reaction rates are given in Table 2. All the reaction mixtures were worked up. With one exception, the resulting ketones were isolated in high yield as products of good quality.

The following inferences were drawn from the results in Table 2 (Case 1). (a) The activating effect of the two methyl groups of ethyl 2,4-dimethylpyrrole-3-carboxylate (**3b**) outweighed the deactivating effect of the ethoxycarbonyl group. (b) The steric effect due to the 4-methyl group was much smaller when *NN*-dimethylbenzamide or *N*-benzoylmorpholine were used to prepare the Vilsmeier–Haack reagent than when the bulkier *NN*-diethylbenzamide was employed. Use of the latter amide resulted in an approximately four-fold decrease in the relative reactivity of (**3b**) so that, in these circumstances, (**3b**) became less reactive than pyrrole (**3a**). (c) Little, if any, difference in the effective size of the Vilsmeier–Haack reagent resulted from the substitution of the morpholino- for the dimethylamino-group.

Having regard to these and previous results[1] it is difficult to find justification for the continued use of *NN*-diethylamides in preparative applications of the Vilsmeier–Haack reaction, especially in those involving pyrrole substrates substituted at the position adjacent to that under attack.

Examination of ethyl 2-methylpyrrole-3-carboxylate (**3c**) provided additional support for inference (a). The absence of the 4-methyl group resulted in a marked reduction of the reactivity of (**3c**) relative to (**3b**) and (**3a**) as illustrated in Table 2 (Cases 2 and 3). Neglecting steric effects, the 4-methyl group was responsible for a change in reactivity by a factor of *ca.* 14.5. Since it is reasonable to assume, however, that the decrease in reactivity of (**3c**) was partially offset by the removal of some steric hindrance due to the 4-methyl group, this factor is, no doubt, somewhat larger. The present observations are consistent, therefore, with the report by Clementi and Marino[4] that the reactivity of the pyrrole ring towards trifluoroacetylation is increased by a factor of *ca.* 24 on introduction of a methyl or other alkyl group.

Since a methyl group attached to the 4-position of the pyrrole nucleus exerted a powerful activating effect on the 5-position with relatively little adverse steric effect, it was astonishing to observe that the presence of a methyl group attached to the adjacent nitrogen atom led to very strong deactivation of the pyrrole ring so substituted (Table 2, Cases 4 and 5). The reduction in reactivity occasioned by the 1-methyl group, to an extent of two orders of magnitude or more, indicated that a very



a; $R^1 = R^2 = R^3 = R^4 = H$
b; $R^1 = H$, $R^2 = R^4 = Me$, $R^3 = CO_2Et$
c; $R^1 = R^4 = H$, $R^2 = Me$, $R^3 = CO_2Et$
d; $R^1 = Me$, $R^2 = R^3 = R^4 = H$
e; $R^1 = R^2 = R^4 = Me$, $R^3 = CO_2Et$
f; $R^1 = CH_2Ph$, $R^2 = R^4 = Me$, $R^3 = CO_2Et$

Scheme. *Reagents:* i, $POCl_3$; ii, $-HCl$; iii, aqueous Na_2CO_3

Table 1.

(3) $\xrightarrow[(2)\ Na_2CO_3,\ H_2O]{(1)\ PhCOA–POCl_3}$ (5)

Substrate	A	10^3k/[a] l mol^{-1} s^{-1}	$t_{0.5}$[a]	% Yield[b]
(**3a**)	NMe_2	2.82	29.5 min	88 (84)
(**3b**)	NMe_2	5.71	14.6 min	>99 (92)
(**3c**)	NMe_2	0.39	212 min	98 (91)
(**3d**)	NMe_2	*ca.* 0.03	*ca.* 48 h	86 (72)[c]
(**3e**)	NMe_2	*ca.* 0.01	*ca.* 121 h	78 (76)[d]
(**3f**)	NMe_2	?	?	−(−)[e]
(**3a**)	NEt_2	1.47	56.6 min	92 (64)[f]
(**3b**)	NEt_2	0.81	103 min	98 (92)
(**3a**)	$N(CH_2CH_2)_2O$	21.6	3.85 min	88 (86)
(**3b**)	$N(CH_2CH_2)_2O$	45.0	1.85 min	>99 (92)
(**3c**)	$N(CH_2CH_2)_2O$	3.11	26.8 min	90 (88)

[a] For the formation of (**4**) at 35 °C in a 0.2M solution in 1,2-dichloroethane, precision 1 in 200. [b] Yield of (**5**) determined by u.v. assay (isolation, first crop only from hexane except 1-methyl-2-benzoylpyrrole which was purified by distillation) and corrected for sample withdrawal. [c] Reaction quenched after 17 days at the 88% reaction stage. [d] Reaction quenched after 20 days at the 81% reaction stage. [e] After 23 days an estimated 20% of the azafulvene was present. Owing to dissociation of (**2**) no meaningful rate measurements could be taken. [f] Use of improperly distilled hexane led to loss of product.

Table 2. Relative reactivities of pyrrole substrates

Case	Substrates	Relative reactivities[a]	Carboxamide used[b]
1	(**3b**), (**3a**)	2.02:1	DMB
		2.08:1	NBM
		0.549:1	DEB
2	(**3b**), (**3c**)	14.5:1	DMB
		14.5:1	NBM
3	(**3a**), (**3c**)	7.18:1	DMB
		6.96:1	NBM
4	(**3a**), (**3d**)	*ca.* 100:1	DMB
5	(**3b**), (**3e**)	*ca.* 500:1	DMB

[a] Ratios calculated from the reaction rates reported in Table 1. [b] DMB = *NN*-dimethylbenzamide, NBM = *N*-benzoylmorpholine, DEB = *NN*-diethylbenzamide.

powerful steric effect was involved. Indeed, taking the expected electronic activation factor as *ca.* 20, the reduction in reactivity due to steric factors may be estimated as 2 000-fold for 1-methylpyrrole (**3d**) *versus* pyrrole (**3a**) and 10 000-fold for ethyl 1,2,4-trimethylpyrrole-3-carboxylate (**3e**) *versus* ethyl 2,4-dimethylpyrrole-3-carboxylate (**3b**). The five-fold difference in reactivity between the two sets may reasonably be ascribed to the steric effect of the 4-methyl group present in (**3b**) and (**3e**). It is apparent, therefore that the Vilsmeier–Haack reaction at the 2-position of a 1,3-disubstituted pyrrole is rather severely hindered with the greater part of such hindrance arising from the presence of the 1-substituent.

It was clear from the observations made that the aroylation of 1-methylpyrroles by the Vilsmeier–Haack reaction is sluggish and that, from a preparative point of view, introduction of the 1-methyl group after aroylation would offer a more efficient route. This was, in fact, shown to be the case.[5]

Attempts to determine whether the deactivating effect of the pyrrole 1-methyl group applied in the case of Vilsmeier–Haack formylation as well were frustrated by the rapidity of that reaction. Both pyrrole (**3a**) and 1-methylpyrrole (**3d**) underwent complete reaction in < 1 min at 35 °C and the absence of a steric effect evident from the results of Clementi *et al.*,[6] while reasonably inferred, could not be established by the use of available facilities. Acetylation, however, was almost certainly subject to this steric factor although quantitative data were lacking. This conclusion was based on the fact that the reaction of both (**3a**) and (**3b**) with the *NN*-dimethylacetamide–phosphoryl chloride complex was rapid ($t_{0.5}$ < 15 s) and essentially quantitative at 25 °C whereas that of the 1-methylated analogues (**3d**) and (**3e**) with the same reagent proceeded at a rate which was much lower than that of the self-condensation[7] of the Vilsmeier–Haack reagent. Satisfactory rate measurements could not, therefore, be taken. Moreover, the absorbance values obtained suggested that by the time self-condensation was nearly complete (*ca.* 14 days at 25 °C) very little of the expected azafulvenes had formed.

That the unforeseen effect of 1-methyl (and presumably other 1-alkyl) groups on the reactivity of pyrrole substrates was a result of steric factors is partially supported by results reported by Candy *et al.*[8] who found that, on Vilsmeier–Haack formylation of a series of 1-alkylated pyrroles, the degree of 3-substitution increased from zero to *ca.* 90% as the 1-alkyl group was changed from methyl to t-butyl. The fact that exclusive 2-attack on 1-methylpyrrole was reported by these workers showed that steric effects due to the methyl group were negligible in formylation in contrast to the present case in which larger groups are involved. It may be mentioned, however, that the experimental conditions used by Candy *et al.* were far harsher than those here employed so that the conclusions arrived at on the basis of α:β substitution ratios are not necessarily applicable to the present study.

Insofar as the use of Vilsmeier–Haack reagents prepared from benzamides and phosphoryl chloride is concerned, it would appear from the marked difference between the steric effects due to 1- and 3-substitution that a highly specific orientation of the transition state components is involved. The orientations illustrated in Figures 1 and 2 offer a reasonable explanation for the behaviour observed and are consistent not only with the data obtained in the present study but also with the suggestion that the formation of the π-complex may be rate determining.[9] The reasoning which led to the suggestion that the transition state orientations may be as illustrated is as follows.

(a) The retardation of the reactions of 1-methylated pyrroles when dimethylamides or morpholides were used to generate the Vilsmeier–Haack reagent appeared to be governed solely by the size of the aroyl or other group attached to the carboxamido moiety. If so, the steric effect arose from the repulsion between the aroyl or other group and the 1-methyl group as illustrated in Figure 2.

(b) The relatively insignificant steric effect of a 3-methyl group suggested that, during the formation of the transition state, the aroyl or other group adopted a highly specific orientation such that little or no interaction between the pyrrole 3-methyl and the aroyl or other groups was involved.

(c) The dipole moments of pyrrole and its derivatives show these molecules to be in the permanent ground-state polarized form consistent with a π-excessive aromatic system such that, unlike the cases of thiophene and furan, the positive end of the dipole lies in the direction of the heteroatom.[10] Interaction with a highly dipolar species such as a Vilsmeier–Haack reagent to form a π-complex may therefore be expected to lead to an alignment of this reagent with the pyrrolic substrate which represents the most favourable electrostatic situation. Consideration of the dipolar species involved showed such an orientation to be one in which the aroyl or other group was situated above the relative positively charged pyrrole nitrogen atom and the positively charged activated carboxamido group of the Vilsmeier–Haack reagent to be above the centre of the pyrrole ring.

(d) The use of Dreiding models of (**3a**) and (**3b**) showed that

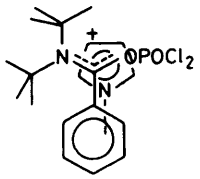


Figure 1. *NN*-Dimethylbenzamide–$POCl_3$, pyrrole

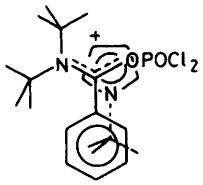


Figure 2. *NN*-Dimethylbenzamide–$POCl_3$, *N*-methylpyrrole

such an orientation was feasible. In the 1-methyl analogues, however, severe interference between the 1-methyl and the aroyl or other group was immediately apparent except where the other group was hydrogen. In this case the hydrogen of the formylation species was sufficiently small to avoid severe repulsion by the 1-methyl group.

The present hypothesis would also account for the extreme sluggishness of the reaction in which ethyl 1-benzyl-2,4-dimethylpyrrole-3-carboxylate (**3f**) was used as the substrate if it is accepted that the orientation of the benzyl group is such that the phenyl group incorporated therein tends to adopt a position remote from the 2-methyl group thereby blocking the vacant position of the ring. This orientation would serve to augment the steric effect of the benzyl methyl group so that the approach of the Vilsmeier–Haack reagent and formation of the π-complex would be hindered to a considerable extent.

Experimental

Amide–phosphoryl chloride complexes were preformed at 35 °C using 2.16 mol. equiv. phosphoryl chloride. Rate measurements (taken at 35 °C in 0.2M solution in 1,2-dichloroethane), half-reaction time and rate-constant determination used as a description of one set of operations, azafulvene hydrolysis, and yield determination were carried out as previously described.[2,3]

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