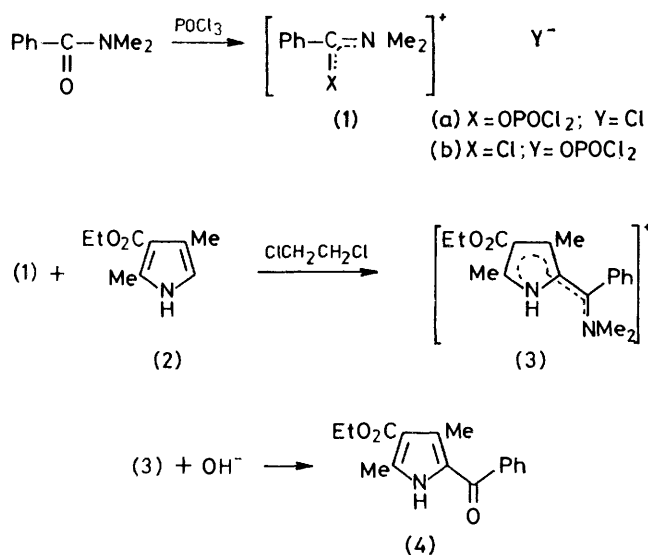# Rate Measurements of Certain Vilsmeier–Haack Reactions. Part 1. The Benzoylation of a Trisubstituted Pyrrole

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Rate measurements on the reaction between the NN-dimethylbenzamide–$POCl_3$ complex (1) and ethyl 2,4-dimethylpyrrole-3-carboxylate (2) in 1,2-dichloroethane show that the reaction follows second-order kinetics, first order in each of (1) and (2), for reactions taken to at least 90% of completion. The rate constant remained unchanged for reactions in which an excess of $POCl_3$ was present, or where the concentration of the pyrrole (2) was varied, but became inconsistent when the concentration of the complex (1) was varied. The Arrhenius activation energy was determined and the low value obtained is consistent with a very early transition state. The presence of traces of water was found to have a marked effect on both the rate of the reaction and the yield obtained.

IN the course of developing the Vilsmeier–Haack reaction as a useful method for the aroylation of pyrroles[1] it became apparent that certain important features of the reaction could be studied only by way of rate measurements. No established method of measuring the rate of Vilsmeier–Haack aroylation had been published when the present investigation was undertaken and it proved necessary to develop our own method. The present paper will deal with the method developed and show

some of the results obtained thereby. During our investigation, rate measurements for certain electrophilic substitution reactions of pyrroles[2] and for the acetylation[3] of pyrrole and other heterocycles taken by other procedures were reported.

The reagents used for rate measurements are shown in Scheme 1. The choice of amide-activating species was restricted to phosphoryl chloride which, while being only one of a number[4] available, is that most commonly used[5] and the only one to have enjoyed success in previous aroylations of pyrroles.[6]

Ethyl 2,4-dimethylpyrrole-3-carboxylate (2) was selected as the substrate because it reacted at a reasonable rate with no ambiguity as to the site of attack and is a

stable, easily purified solid. The use of 1,2-dichloroethane (DCE) as an effective solvent in Vilsmeier–Haack reactions is well established [5,6b,c,7] and relatively concentrated solutions (0.2M) were used for the rate measurements to obtain results applicable to reactions carried out on preparative scale.[1] The ketone (4) was in each case isolated after the rate measurements had been taken thereby providing accurate information as to yield and product quality.

RESULTS AND DISCUSSION

Preliminary investigations confirmed that it was necessary for the NN-dimethylbenzamide–phosphoryl chloride (DMB–$POCl_3$) complex (1) to be formed prior to the introduction of the pyrrolic substrate.[6] The structure of this complex is uncertain, both (1a and b) having been proposed, but for the complex generated *in situ* we favour (1a).[8]

Formation of the DMB–$POCl_3$ *Complex* (1).—Formation of the complex in an excess of $POCl_3$ was monitored by n.m.r. spectrometry.[1] The reaction, using 2.16 mol. equiv. of $POCl_3$, was invariably complete in *ca.* 5 min at 35 °C which observation is in conflict with a recent report[9] of a much longer reaction time. The reason for this discrepancy is not clear. As in the case of dimethylformamide–$POCl_3$,[3,10,11] complex formation was incomplete in solution in DCE. Dissolving the preformed complex in

DCE resulted in the formation of an equilibrium mixture containing *ca.* 65% of the complex. However, the dissociation reaction was slow (see Table 1) relative to the Vilsmeier–Haack reaction and did not interfere with the rate measurements discussed below.

SCHEME 1

TABLE 1

Dissociation of the DMB–$POCl_3$ complex [a] in DCE [b]

t/h	Complex (%) [c]
0	100
7.5	80
25.5	70
48	68
120	65
>120	65

[a] Pre-generated using a $POCl_3$: DMB ratio of 2.16 : 1. [b] Using a 0.20M solution at 35 °C. [c] Determined from the integrals of the n.m.r. signals of the aromatic protons.

Kinetics of the Vilsmeier–Haack Reaction.—The rate of the reaction was determined by measuring the formation of the azafulvene (3) spectrophotometrically. All reactions were allowed to proceed to at least 90% of completion and in each case the completeness of reaction was confirmed by hydrolysis of the azafulvene to the ketone (4) and isolation thereof.
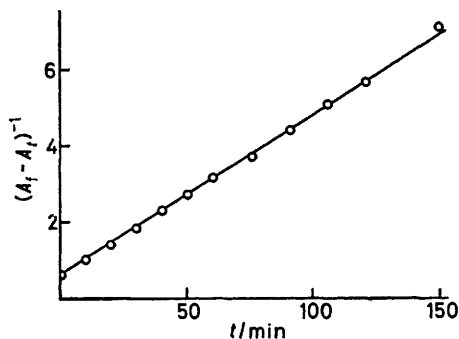
Linear plots such as that shown in Figure 1 were

FIGURE 1   Second-order plot for the formation of (3) at 35 °C in DCE. $[(1)] = [(2)] = 0.20\text{M}$

obtained on substitution of the spectrophotometric data for reactions proceeding to at least 90% of completion in the integrated rate expression for a second-order reaction. It was found that the reaction was first-order in each of (1) and (2), *i.e.* rate $= k[(1)][(2)]$. This suggests that the reaction follows a pathway such as that outlined in Scheme 2.

$$(1) + (2) \xrightarrow{\text{slow}} \text{Transition State} \xrightarrow[\text{–HCl}]{\text{fast}} (3)$$

SCHEME 2

For the reagents shown in Scheme 1 at 35 °C in 0.2M solution in 1,2-dichloroethane it was found that $k = 5.70 \times 10^{-3}$ l mol^{-1} s^{-1} and the half-reaction time $= 14.6$ min.

Further confirmation of second-order kinetics was provided by observation of the expected 1 : 3 relationship between the half-reaction time $(t_{0.5})$ and three-quarter-reaction time $(t_{0.75})$ derived from the absorbance–time curves such as Figure 2 $(t_{0.5}$ 14.8 min; $t_{0.75}$ 44.8 min).

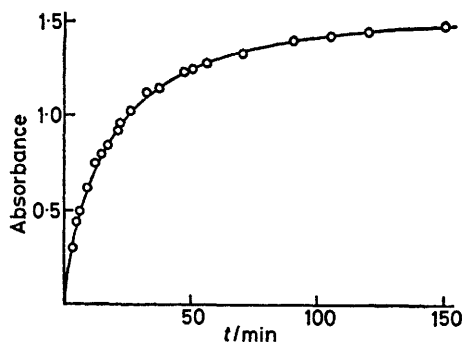The present observation of second-order kinetics is

FIGURE 2   Absorbance of (3) *versus* time

consistent with those reported for the formylation of thiophen [11] and acetylation of pyrrole.[3]   The preservation of linearity of the second-order plot shows that no protonation of the pyrrole (2) by hydrogen chloride liberated on formation of the azafulvene (3) occurred and also that dissociation of the complex (1) in DCE during the reaction was negligible.   Further confirmation of the latter inference was provided by rate measurements using complex (1) that had been allowed to dissociate for 48 h at 35 °C in DCE.   A linear plot could not be obtained until a second-order rate expression appropriate to the equilibrium concentration of complex (1) in DCE (*ca.* 65% of the original) was applied.

Effect of an Excess of POCl$_3$ *on the Vilsmeier–Haack Reaction.*—By custom, the amide–POCl$_3$ complex required for the Vilsmeier–Haack reaction is prepared using one equivalent of POCl$_3$, or an excess which is removed prior to the introduction of the pyrrole substrate.[5,6]   As the inference that the presence of an excess of POCl$_3$ is harmful was unsupported by published data the effect of an excess of this reagent was examined.   In all cases excellent linearity of the second order plots was obtained and the results are given in Table 2.   From these results

TABLE 2

The effect of an excess of phosphoryl chloride

$\dfrac{[\text{POCl}_3]}{[\text{DMB}]}$ [a]	$10^3 k/$ l mol^{-1} s^{-1} [b]	Yield (%) [c]
1.08	5.63	>99 (92)
2.16	5.71	99 (92)
3.24	5.71	>99 (91)
4.32	5.52	>99 (94)
6.48	5.63	96 (88)
8.64	5.56	97 (87)
10.80	5.59	90 (82)

[a] 1.0 ml POCl$_3$ (10.8 mmol) was more accurately measurable than 0.926 ml (10.0 mmol).   [b] For formation of (3) at 35 °C in 0.20M solution in DCE.   [c] Yield of (4), determined by u.v. assay and isolation; corrected for sample withdrawal.

it can be seen that, within experimental error, the rate of the reaction is unaffected by the presence of excess POCl$_3$.   This also shows that small changes in dielectric constant of the solvent system have little effect on the rate of reaction.

Because of the advantages of having an excess of POCl$_3$ present during complex formation,[1] the use during rate measurements of 2.16 mol. equiv. of POCl$_3$ was adopted as a standard procedure.

Effect of Reagent Concentration on the Vilsmeier–Haack Reaction.—The results obtained using different reagent concentrations are shown in Table 3.

In all cases, application of the appropriate integrated rate equation resulted in excellent linearity of the second-order plots up to at least 90% of reaction.   In those cases (Table 3, entries 1—3) where the concentration of the pyrrole substrate (2) was varied but that of the DMB–POCl$_3$ complex (1) was not, the rate constants obtained were consistent and showed that the reaction is first order in each of reagents (1) and (2).   However, when the concentration of the complex (1) was varied marked inconsistencies in the value of the rate constant

TABLE 3

The effect of reagent concentration

Entry	$[(1)]/$ mol l^{-1}	$[(2)]/$ mol l^{-1}	$10^3 k/l$ mol^{-1} s^{-1} [a]	Yield (%) [b]
1	0.20	0.20	5.71	99 (92)
2	0.20	0.40	5.71	93 (—) [c]
3	0.20	0.10	5.65	95 (89)
4	0.40	0.20	3.85	95 (90)
5	0.05	0.05	12.58	93 (84) [d]
6	0.10	0.10	8.47	96 (88)
7	0.40	0.40	3.15	89 (81) [e]

[a] For formation of (3) at 35 °C in DCE. [b] Yield of (4) determined by u.v. assay (isolation) and corrected for sample withdrawal. [c] Quenched at 95% of completion; product not isolated due to presence of unchanged (2). [d] Quenched at 96% of completion. [e] Quenched at 93% of completion.

(Table 3, entries 4—7) became apparent. Both the reduction in rate on lowering the concentration of the complex and the increase in rate when the concentration was raised were less than was to be expected. The inconsistency of the rate constant cannot be ascribed to a
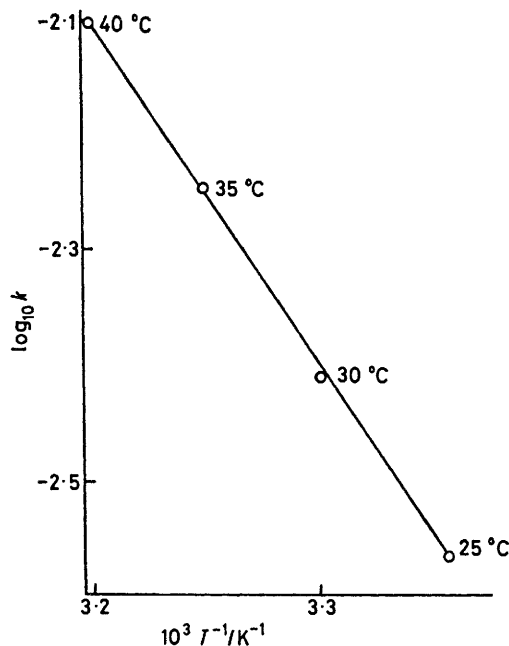

FIGURE 3 Arrhenius plot for the formation of (3) in DCE. $[(1)] = [(2)] = 0.20M$

simple solvent–polarity effect inasmuch as the use of a variable excess of POCl$_3$ would then have led to similar deviations. Moreover, the observed deviations are opposite to that in which an increase in ionic strength results in an enhanced rate for reactions between positive ions and dipolar molecules.[12]

Although the exact nature of this concentration dependent effect is obscure it is conceivable that, in the more polar medium resulting from a higher DMB–POCl$_3$ complex concentration, the relatively localized charge of the complex experiences greater dispersion than does the diffused charge of the transition state thereby increasing the activation energy of the reaction. This charge-dispersal effect would be the opposite of the usual positive salt effect which leads to an increased rate of

reaction when the transition state is more polar than the species preceding it.[13]

The present inconsistencies could no doubt have been avoided by following the standard practice of using very dilute solutions for rate measurements. This would, however, have run counter to the aim of the present investigation.[1]

Temperature Effects in the Vilsmeier–Haack Reaction.— The results of rate measurements taken during reactions carried out at 25, 30, 35, and 40 °C are reflected in Figure 3 from which the values of 55.2 kJ mol^{-1} for the Arrhenius activation energy and 1.25×10^7 l mol^{-1} s^{-1} for the frequency factor were obtained. This low activation energy is consistent with a transition state lying nearer to starting materials than the Wheland intermediate [14] and provides support for the suggestion [15,16] that it is the formation of the π-complex that is rate determining in electrophilic substitution reactions of pyrroles.

It is apparent from the linearity of the Arrhenius plot (Figure 3) that the mechanism of the reaction remained unchanged over the temperature range examined. This is in conflict with the contention [4] that amide–POCl$_3$ complexes of the type (1a) rearrange to type (1b) at temperatures above 30 °C.

In the reaction at 40 °C, a slight drop in both the yield and product quality was observed. This confirmed preliminary observations that heating of the reaction mixture was undesirable.

Effect of Traces of Water on the Vilsmeier–Haack Reaction.—Both the rate of reaction and the yield of product were markedly reduced by the presence of traces of water in the reaction mixture and these results are summarized in Table 4. The observed order of the re-

TABLE 4

The effect of traces of water

% H$_2$O mass/ vol	$\dfrac{[H_2O]}{[(2)]}$	$t_{0.5}/$ min [a]	Yield (%) [b]	Product quality [c]
0 [d]	0	14.6	99 (92)	Very good
0.05	0.139	23.0	87 (78)	Good
0.10	0.278	37.0	76 (73)	Fair
0.20	0.556	117.0	55 (51)	Poor
0.36 [e]	1.000		14	

[a] For formation of (3) at 35 °C in 0.20M solution in DCE. [b] Yield of (4), determined by u.v. assay (isolation) and corrected for sample withdrawal. [c] Based on m.p. and colour. [d] DCE twice redistilled from P$_4$O$_{10}$ under dry argon. [e] 0.36% exceeds the solubility of water in DCE at 35 °C.

action remained unchanged, however, and satisfactorily linear second-order plots were obtained. This unexpected result showed that stringent measures were necessary to ensure anhydrous conditions without which the accuracy of rate measurements would have been suspect.

The observation that the linearity of the second-order plots for equimolecular quantities remained undisturbed while the rate of reaction decreased is consistent with a reduction, to precisely the same extent, of the concentrations of both (1) and (2). Support for this view was provided by the observation that the decrease in both

the rate and yield of product was directly proportional to the amount of water present. It is conceivable that the presence of water led to partial hydrolysis of complex (1) and generation of an equivalent quantity of some highly acidic species such as $HOPOCl_2$ which in its turn removed the equivalent quantity of the pyrrole (2) by way of protonation. This hypothesis would serve also to account for the progressive increase in dirtiness of the reaction mixture as the water content increased.

EXPERIMENTAL

Reagents and solvents were purified and the complex generated as previously described.[1] Temperatures of mixtures were maintained to within 0.05 °C. U.v. spectra were recorded on a Unicam SP 800 spectrophotometer.

General Procedure.—Typically, a solution of the pyrrole (2) (10 mmol) in the entire volume of DCE required was brought to water-bath temperature and added swiftly, with vigorous magnetic stirring, to the syrupy complex (1) [DMB (10 mmol) in $POCl_3$ (2.0 ml)] which had been allowed to stand at the bath temperature for at least 1 h after generation. A period of at least 2 min was allowed for thorough mixing before the first sample was drawn and magnetic stirring was continued throughout the reaction.

Because of the high molar absorptivity of the developing azafulvene, sequential dilution to $10^{-4}M$ of samples drawn was necessary for accurate u.v. absorbance measurements. Inasmuch as the viscosity of the reaction mixture increased with time a blood pipette (calibrated for rinsing) was used for sampling. Because of the relatively small temperature range (25—40 °C) involved, no calibration corrections were applied to the pipette used in the first stage of dilution. Composite spectra using a recording spectrophotometer scanning over the region 225—450 nm were drawn so that the presence of an isosbestic point could be used to confirm sampling precision. This revealed that certain absorbance peaks (other than that for the azafulvene) were fugitive. Accordingly, all sampling and dilution operations were performed in a timed sequence to ensure consistency of measurement.

By carrying out reactions in triplicate at different times an even spread of sampling times was possible and the difficulty of examining samples at <2 min intervals (the time taken for quenching and dilution and also to record a full spectrum) was overcome.

After hydrolysis of the azafulvene with aqueous sodium carbonate[1] the DCE solution containing the ketone was spectrophotometrically assayed. The yields so determined were confirmed by isolation and purification of the product. Although in most cases only a first crop was taken the yields obtained were substantially in agreement with those determined instrumentally.

Determination of Half-reaction Times ($t_{0.5}$) *and Reaction Constants.*—The absorbance values of $10^{-4}M$ solutions at

372 nm for samples drawn at different times from each of the (triplicate) reaction mixtures were plotted on a single sheet and the smoothest curve selected (Figure 2). The $t_{0.5}$ value could be determined directly from this curve but was obtained more accurately as follows.

The average absorbance values at convenient times (A_t) were taken from the curve and used to plot the value of $(A_f - A_t)^{-1}$ against time for equimolecular mixtures (Figure 1) or the value of $\log_{10}[(2A_f - A_t)/(A_f - A_t)]$ against time in those cases where the reagents were present in a 2:1 ratio. A_f represents the absorbance value corresponding to 100% reaction and had previously been determined indirectly as 1.610 by correlating absorbance values and yields on quenched reaction mixtures as well as by selection of that value of A_f which gave rise to inflection from positive to negative curvature of the plot of $(A_f - A_t)^{-1}$ against time.[17] The value obtained was confirmed by measuring the molar absorptivity of the azafulvene (3) isolated as the perchlorate.[18]

REFERENCES

[1] J. White and G. McGillivray, *J. Org. Chem.*, 1977, **42**, 4248.
[2] R. S. Alexander and A. R. Butler, *J.C.S. Perkin II*, 1976, 696; A. R. Butler, P. Pogorzelec, and P. T. Shepherd, *ibid.*, 1977, 1452.
[3] A. Cipiciani, S. Clementi, P. Linda, G. Marino, and G. Savelli, *J.C.S. Perkin II*, 1977, 1284.
[4] S. Seshadri, *J. Sci. Indian Res.*, 1973, **32**, 128.
[5] R. M. Silverstein, E. E. Ryskiewicz, and C. Willard, *Org. Synth.*, 1967, Coll. Vol. IV, p. 831.
[6] See for example (a) G. G. Kleinspehn and A. E. Briod, *J. Org. Chem.*, 1961, **26**, 1652; (b) J. A. Balantine, A. H. Jackson, G. W. Kenner, and G. McGillivray, *Tetrahedron*, 1966, suppl. 7, 241 and other papers in the series; (c) L. J. Dolby, S. J. Nelson, and D. Senkovich, *J. Org. Chem.*, 1972, **37**, 3691.
[7] P. Linda, A. Lucarelli, G. Marino, and G. Savelli, *J.C.S. Perkin II*, 1974, 1610.
[8] W. Scheuermann, G. McGillivray, and J. White, *J. Raman Spectroscopy*, 1977, **6**, 204 and references cited therein.
[9] M. E. Kuehne and P. J. Shannon, *J. Org. Chem.*, 1977, **42**, 2082.
[10] G. J. Martin and S. Poignant, *J.C.S. Perkin II*, 1972, 1964.
[11] S. Alunni, P. Linda, G. Marino, S. Santini, and G. Savelli, *J.C.S. Perkin II*, 1972, 2070.
[12] E. S. Amis, G. Jaffé, and R. T. Overman, *J. Amer. Chem. Soc.*, 1944, **66**, 1823.
[13] P. Sykes, ' The Search for Organic Reaction Pathways,' Longman, London, 1972, p. 31.
[14] G. S. Hammond, *J. Amer. Chem. Soc.*, 1955, **77**, 334.
[15] G. A. Olah, S. J. Kuhn, and S. H. Flood, *J. Amer. Chem. Soc.*, 1961, **83**, 4571.
[16] G. Marino, *Pr. Nauk. Inst. Chem. Technol. Nafty. Wegla Politech. Wroclaw*, 1973, 89 (*Chem. Abs.*, 1973, **79**, 77564).
[17] L. P. Hammett, ' Physical Organic Chemistry,' McGraw-Hill, New York, 1940, p. 100.
[18] C. F. Candy and R. A. Jones, *J. Chem. Soc. (B)*, 1971, 1405.