

## Rate Measurements of Certain Vilsmeier–Haack Reactions. Part 4.<sup>1</sup> The Reactivities of Various Arenecarboxamide–Phosphoryl Chloride Complexes

Julian White

Department of Chemistry, University of South Africa, Pretoria, South Africa

Measurement of the rates of the Vilsmeier–Haack reaction of several amide– $\text{POCl}_3$  complexes (2) on ethyl 2,4-dimethylpyrrole-3-carboxylate (3) in 1,2-dichloroethane was used to observe the effect of changing the aryl group of the amide (1). The results for the 4- and 3-substituted benzamides are in accord with the Hammett relationship when  $\sigma^+$  constants are employed. The reaction constant,  $\rho$ , was found to remain essentially the same on using *N*-benzoylmorpholines instead of *NN*-dimethylbenzamides (1.09 and 1.08, respectively). The presence of excess of  $\text{POCl}_3$  increased the reaction rate of methoxy- and nitro-benzamide complexes and to a lesser extent those of furan-2- and thiophene-2- but not pyrrole-2-carboxamides; an explanation is offered for this unexpected reactivity.

In the course of exploring the preparative scope of Vilsmeier–Haack benzoylation a number of 2-(3- or 4-substituted benzoyl)pyrroles were prepared. As expected the reactions of the respective Vilsmeier–Haack reagents with pyrrolic substrates were faster when electron-withdrawing groups were attached to the phenyl nucleus. It was decided, therefore, to examine these substituent effects quantitatively to establish whether the Hammett equation was applicable to the Vilsmeier–Haack reaction.

Although such an examination could have been carried out by means of the so-called competitive procedure,<sup>2</sup> the limited applicability of this technique to other aspects of the present study<sup>3</sup> indicated the desirability of using kinetic methods throughout. Accordingly rate measurements were made using a variety of 4- and 3-substituted *NN*-dimethylbenzamides and *N*-(4-substituted benzoyl)morpholines to prepare the Vilsmeier–Haack reagents required. Several heteroaromatic carboxamides were also employed in order to compare the reactivities of the respective ring systems.

The substrate used was ethyl 2,4-dimethylpyrrole-3-carboxylate (3) employed under experimental conditions set out in previous papers.<sup>3</sup>

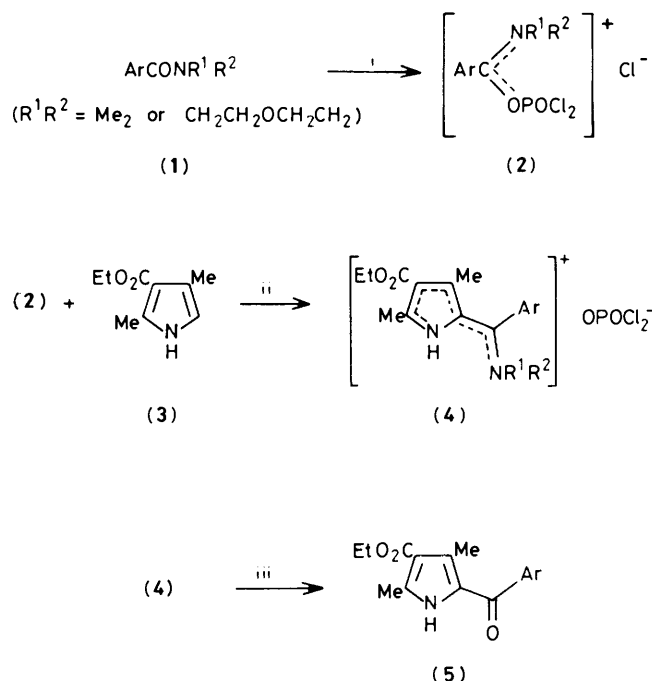
### Results and Discussion

The reaction studied is set out in the Scheme and the results of the rate measurements appear in the Table. All the reaction mixtures were worked up with the resulting ketones being isolated as products of good quality in yields of 80–96%.

It was found that the process leading ultimately to 4-methoxybenzoylation occurred at a markedly lower rate than that of 4-toluoylation. It was clear, therefore, that a Hammett correlation using  $\sigma$  values could not possibly be linear since, according to these values, a methyl group is more electron-releasing than a methoxy-group.<sup>4</sup> This conclusion is consistent with the mechanistic features of the present reaction.<sup>5,6</sup>

Substitution of the half-reaction times obtained by using the Vilsmeier–Haack reagents derived from the *NN*-dimethylbenzamides shown in the Table in the Hammett equation (1) resulted in values which, when plotted against the appropriate  $\sigma^+$ -constants,<sup>7</sup> gave a smooth curve passing through the origin. However, similar treatment of the data in respect of the substituted *N*-benzoylmorpholines gave a plot of excellent linearity. These observations are illustrated in Figures 1 and 2 (solid lines).

$$\log_{10}(t_{0.5}^0/t_{0.5}) = \rho\sigma^+ \quad (1)$$



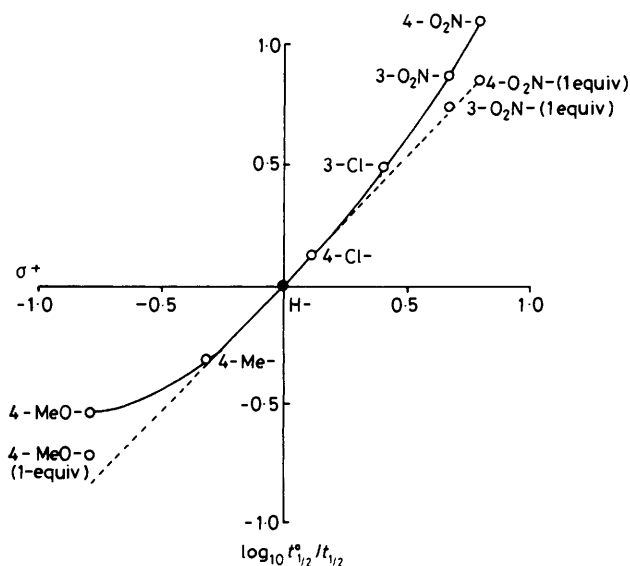
Scheme. Reagents: i,  $\text{POCl}_3$ ; ii,  $-\text{HCl}$ ; iii, aqueous  $\text{Na}_2\text{CO}_3$

Since it was unlikely that the Vilsmeier–Haack reaction would conform to the Hammett relationship in one case but not the other, a closer examination of the situation represented by Figure 1 was made. This showed that, if the points for the methoxy- and nitro-substituent were ignored, a reasonably straight line could be obtained. The nature of the deviation of the aberrant points indicated that, in each case, the reaction had occurred at an unexpectedly high rate. This suggested that a superactivation factor was operative in the case of Vilsmeier–Haack reagents in which methoxy- and nitro-, but not methyl- or chloro-groups, were present. It seemed very likely, therefore, that this was due to a measure of co-ordination between the excess of phosphoryl chloride used to generate the complexes and the methoxy- or nitro-group present in the benzamide. Such co-ordination could well be expected to reduce the contribution of the methoxy oxygen lone pairs to the deactivation of the Vilsmeier–Haack reagent on the one hand and to increase the electron-withdrawing, and thus activating, effect of the nitro-group on the other.

Table.

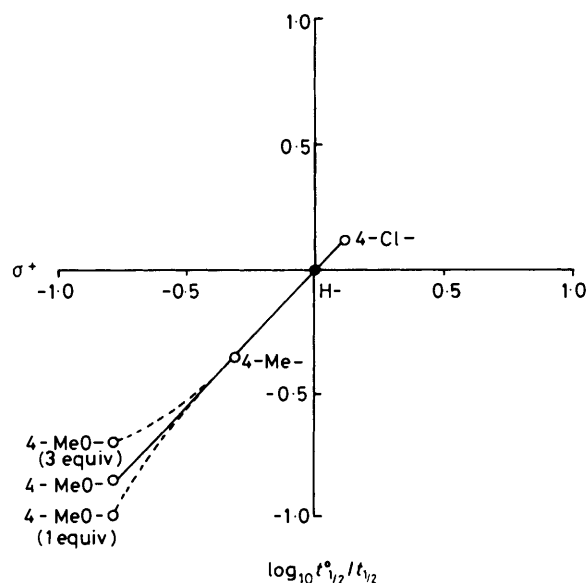
(3)	(1) ArCOA-POCl <sub>3</sub> (2) aq Na <sub>2</sub> CO <sub>3</sub>	Mol. equiv. POCl <sub>3</sub>	<i>t</i> <sub>0.5</sub> /min <sup>a</sup>	10 <sup>3</sup> <i>k</i> /l mol <sup>-1</sup> s <sup>-1</sup> <sup>a</sup>	% Yield <sup>b</sup>
[Ar]	[A]				
4-Methoxyphenyl	Dimethylamide	2.16	50.5	1.65	84 (96)
4-Methoxyphenyl	Dimethylamide	1.08	76.3	1.09	86 (96)
4-Methoxyphenyl	Morpholide	3.24	6.55	12.7	90 (96)
4-Methoxyphenyl	Morpholide	2.16	13.2	6.31	90 (96)
4-Methoxyphenyl	Morpholide	1.08	18.2	4.58	89 (94)
4-Tolyl	Dimethylamide	2.16	29.9	2.79	82 (90)
4-Tolyl	Morpholide	2.16	4.22	19.7	85 (92)
Phenyl	Dimethylamide	2.16	14.6	5.71	91 (99)
Phenyl	Dimethylamide	1.08	14.8	5.63	92 (99)
Phenyl	Morpholide	2.16	1.85	45.0	92 (99)
4-Chlorophenyl	Dimethylamide	2.16	11.0	7.58	90 (93)
4-Chlorophenyl	Morpholide	2.16	1.41	59.1	87 (95)
3-Chlorophenyl	Dimethylamide	2.16	4.71	17.7	88 (94)
4-Nitrophenyl	Dimethylamide	2.16	1.16	71.8	96 <sup>c</sup>
4-Nitrophenyl	Dimethylamide	1.08	2.04	40.8	94 <sup>c</sup>
4-Nitrophenyl	Morpholide	2.16	— <sup>d</sup>		
3-Nitrophenyl	Dimethylamide	2.16	1.95	42.7	87 (90)
3-Nitrophenyl	Dimethylamide	1.08	2.63	31.7	90 (94)
2-Pyrrolyl	Dimethylamide	2.16	648	0.129	86 <sup>c</sup>
2-Pyrrolyl	Dimethylamide	1.08	641	0.130	82 <sup>c</sup>
2-Furyl	Dimethylamide	2.16	1.08	77.2	80 (87)
2-Furyl	Dimethylamide	1.08	1.23	67.8	81 (87)
2-Thienyl	Dimethylamide	2.16	1.66	50.2	86 (88)
2-Thienyl	Dimethylamide	1.08	1.83	45.6	87 (90)

<sup>a</sup> For the formation of azafulvene (4) at 35 °C in 0.2M solution in 1,2-dichloroethane, precision 1 in 100. <sup>b</sup> First crop only, the second figure is by u.v. assay, corrected for sample withdrawal. <sup>c</sup> The product crystallized out before the u.v. assay could be performed. <sup>d</sup> *N*-4-Nitrobenzoylmorpholine did not react completely with POCl<sub>3</sub> at 35 °C.



**Figure 1.** Hammett relationship for azafulvene formation from *NN*-dimethylbenzamides-POCl<sub>3</sub>-(3) (2 mol. equiv. of POCl<sub>3</sub> used unless otherwise indicated)

The objection that this effect was apparently inoperative when morpholides rather than dimethylamides were used was easily countered. Previous investigation<sup>3b</sup> had shown that a very strong likelihood existed that *N*-benzoylmorpholine, on treatment with a two-fold molar excess of phosphoryl chloride, underwent the usual reaction at the carbonyl oxygen atom and also co-ordination by a second molecule of phosphoryl chloride at the morpholine oxygen atom. This being so the addition of



**Figure 2.** Hammett relationship for azafulvene formation from *N*-benzoylmorpholines-POCl<sub>3</sub>-(3) (2 mol. equiv. of POCl<sub>3</sub> used unless otherwise indicated)

2.16 mol. equiv. of the acid chloride to the amide (rather than 2.00 because of the greater precision associated with measuring the latter quantity by volume of phosphoryl chloride), involved an excess of 0.16 rather than 1.16 mol. equiv. in the present case. Only a rather small quantity of phosphoryl chloride could thus have been available for co-ordination at any other point.

These hypotheses were put to the test by repeating certain of the rate measurements using different quantities of phosphoryl

chloride for complex generation. Reduction of the quantity of phosphoryl chloride used to prepare the *NN*-dimethylbenzamide complexes to a little over one mol. equiv. had virtually no effect in the unsubstituted case but led to a marked reduction in rate in the case of the 4-methoxy- and 4- and 3-nitro-*NN*-dimethylbenzamide. Substitution of the redetermined half-reaction times in the Hammett equation gave values which, when plotted against  $\sigma^+$ , gave a straight line as shown in Figure 1 (interrupted line). Slight deviation on the part of the methoxy compound was still evident but did not appear to invalidate the superactivation hypothesis.

As a further test the rates of reaction using the Vilsmeier-Haack reagent generated by treatment of *N*-(4-methoxybenzoyl)morpholine with phosphoryl chloride in the molar ratios of 3.24:1 and 1.08:1 were measured. Experimental support for the postulated co-ordination of the methoxy oxygen atom was provided by the observed increase in rate with the larger quantity of acid chloride. Moreover, the earlier hypothesis involving superactivation of morpholide complexes by co-ordination with the morpholine oxygen atom was further supported by the decrease in rate when only sufficient phosphoryl chloride was present to form the usual complex. The deviations from linearity so caused are shown by the interrupted lines in Figure 2.

The slopes of the straight lines shown in Figures 1 and 2 were found to be remarkably similar with the  $\rho$  values obtained therefrom being 1.08 and 1.09 for the dimethylamides and morpholides, respectively. This indicated that the mechanism of the Vilsmeier-Haack reaction was unchanged on replacement of the dimethylamino-group by the morpholino-group and it is not unreasonable to assume that this would hold for other amino-groups as well.

The positive  $\rho$  value obtained is, of course, consistent with a situation where the reaction site tends to become less positive in the transition state and provides further support for the assumption that attachment of the nucleophilic pyrrole to the carbonyl carbon atom of the activated amide is the rate-determining step in the reaction. Further speculation as to the processes leading to the formation of the transition state will here be avoided inasmuch as the possibility of multi-step processes involving equilibrium reactions cannot be discounted. Moreover, while it is commonly accepted that '... small values suggest that little charge is developed in the transition state',<sup>8</sup> the validity of assigning diagnostic significance to  $\rho$ -values in assessing the extent of charge development in the transition state of a kinetic process is not beyond doubt.<sup>9</sup>

This superactivation process is also operative albeit to a much smaller extent when *NN*-dimethylfuran-2-carboxamide and *NN*-dimethylthiophene-2-carboxamide, but not *NN*-dimethylpyrrole-2-carboxamide, are employed to generate Vilsmeier-

Haack reagents. Those derived from the first two carboxamides are both highly reactive and very much more so than that derived from the pyrrolic amide.

Superactivation resulting from co-ordination of the heteroatom with excess of phosphoryl chloride is more likely in the case of furan- and thiophene-carboxamides than in the pyrrole. In the oxygen- or sulphur-bearing heteroaromatic compounds co-ordination of the heteroatom *via* one of the two lone pairs would give rise to superactivation without necessarily impairing the aromaticity of the system. However, in the pyrrole case, involvement of the nitrogen lone pair in such co-ordination could occur only at the expense of the aromatic  $\pi$ -electron system. Co-ordination would thus be unfavourable and superactivation, if operative at all, would be greatly reduced.

### Experimental

Amide-phosphoryl chloride complexes were pre-formed at 35 °C using 2.16 mol. equiv. of phosphoryl chloride except where otherwise specified. Rate measurements [taken at 35 °C in 0.2M solution in 1,2-dichloroethane using equimolecular quantities of complex (2) and substrate (3)], half-reaction time and rate constant determination, azafulvene hydrolysis, and yield determination were carried out as previously described.<sup>3</sup>

### Acknowledgements

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