Rate Measurements of Certain Vilsmeier–Haack Reactions. Part 2.[1] The Effect of *N*-Substituents in the Amide

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Rate measurements on the reaction between a series of amide–$POCl_3$ complexes (2a—h) and ethyl 2,4-dimethylpyrrole-3-carboxylate in 1,2-dichloroethane were used to study the effect of *N*-substituents in amides (1a—h) on the Vilsmeier–Haack reaction. The results obtained are generally consistent with the expected steric and *I* strain effects with the exception of the morpholide and the two *N*-substituted piperazides which showed unexpected reactivity; a reason for this exceptional reactivity is suggested. The morpholide is recommended for the benzoylation of pyrroles.

It is apparent from reviews [2] that the carboxamides favoured by the majority of workers using the Vilsmeier–Haack reaction [3] are *NN*-dimethylamides. Some workers,[4,5] however, used diethylamides, piperidides, or morpholides with the choice of reagent apparently being based on the availability of starting materials rather than any firm conviction that the reagent chosen was indeed the most appropriate. An investigation of the effect of the substituents borne by the nitrogen atom of the carboxamide was thus in order if our efforts [6] to develop the full potential of the reaction as a useful method for the aroylation of pyrroles were to be realized.

The rate of reaction was again taken as one of the criteria of the efficiency of a reagent combination. The methods used to examine each of a number of carboxamides were as set out in a previous paper.[1]

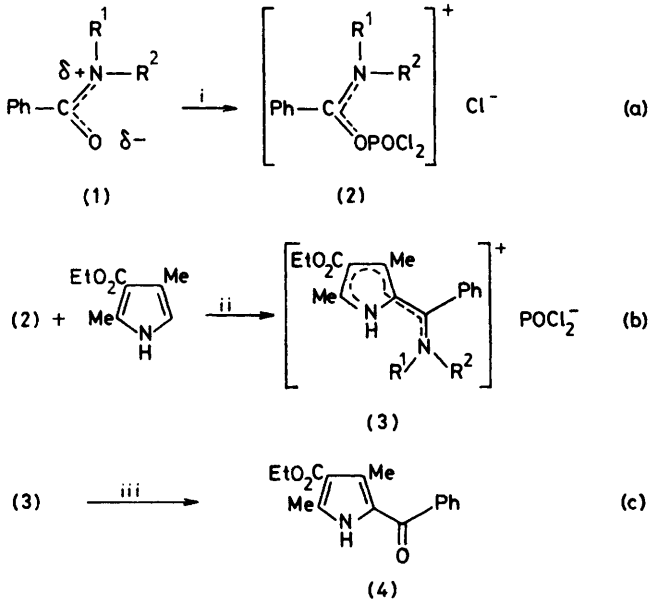
RESULTS AND DISCUSSION

The reaction and reagents studied are set out in the Scheme. Only *NN*-disubstituted carboxamides were examined as these, on treatment with $POCl_3$, do not suffer loss of a proton to form less reactive imidoyl derivatives.[7] In order to minimize steric effects the choice of carboxamides was further narrowed by exclusion of those with branched *N*-substituents.

As the nature of the substituents carried by the carboxamide nitrogen atom was expected to influence each step of the reaction shown in the Scheme, each of these steps was separately investigated.

Formation of the Amide–$POCl_3$ Complex (2) [*Scheme, Step* (*a*)].—The formation of the complexes of a number of *NN*-disubstituted benzamides (1a—h) with excess of $POCl_3$ at 35 °C was monitored by ^1H n.m.r. spectrometry [6] as pre-generation of the amide–$POCl_3$ complex is essential.[1,6] The approximate times for >98% complex formation are presented in the Experimental section.

Attempts to accelerate the reaction of the morpholide (1f) with $POCl_3$ (*ca.* 160 min at 35 °C for >99% completion) by warming the mixture led to incomplete reaction. After 24 min at 72 °C complex formation reached a maximum of 95% and exceeded 99% only when the mixture was cooled to 35 °C. The reversibility of the reaction was demonstrated by the observation that re-heating led to partial dissociation to the same concentration of complex and the result is consistent with the report [8] that the *NN*-dimethylformamide–$POCl_3$ complex product to reagent ratio is lowered by heating. Temperatures above 40 °C were not, therefore, used in subsequent reactions in the present series.



a; $R^1 = R^2 = Me$ e; $R^1R^2 = [CH_2]_5$
b; $R^1 = R^2 = Et$ f; $R^1R^2 = [CH_2]_2O[CH_2]_2$
c; $R^1R^2 = [CH_2]_3$ g; $R^1R^2 = [CH_2]_2NMe[CH_2]_2$
d; $R^1R^2 = [CH_2]_4$ h; $R^1R^2 = [CH_2]_2NCOPh[CH_2]_2$

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

The Vilsmeier–Haack Reaction [*Scheme, Step* (*b*)].—The reaction rates were determined by measuring spectrophotometrically the formation of the azafulvene (3). All the reactions were carried out at 35 °C in anhydrous 1,2-dichloroethane using solutions 0.2M with respect to both reagent and substrate. As before,[1] all reactions were allowed to proceed to at least 90% of completion and all showed excellent linearity of second-order plots based on measurement of their rates. In each case, the complete-

ness of the reaction was confirmed by hydrolysis of the azafulvene [Scheme, step (c)] and isolation of the ketone (4) so formed. The results are present in the Table.

Effect of *N*-substituents on the rate of formation of azafulvene (3)

Amide–$POCl_3$ complex [a]	10^3k/l mol^{-1} s^{-1} [b]	$t_{0.5}$/ min [b]	Relative reactivity	Yield (%) [c]
(2a)	5.72	14.6	1.00	99 (91)
(2b)	0.81	103	0.14	95 (86)
(2c)	7.1 [d]	11.7 [d]		(10) [e]
(2d)	2.09	39.8	0.37	93 (80)
(2e)	2.64	31.6	0.46	97 (85)
(2f)	45.0	1.85	7.9	>99 (92)
(2g)	104	0.80	18	96 (87)
(2h) [f]	44.4	1.88	7.8	94 (87)

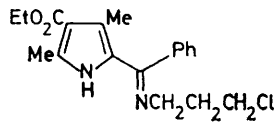
[a] Fully preformed at 35 °C using 2.16 mol. equiv. $POCl_3$. [b] For the formation of (3) at 35 °C in 0.2M solution in 1,2-dichloroethane, precision 1 in 200. [c] Yield of (4) determined by u.v. assay (isolation, first crop only) and corrected for sample withdrawal. [d] Relates to the simultaneous formation of a spurious product by decomposition of (3). [e] Isolated by column chromatography. [f] A much larger excess of $POCl_3$ (8 ml per 10 mmol of amide) was necessary to ensure complete complex formation at both sites and prevent crystallization of the complex.

As expected on steric grounds, the diethylamide complex (2b) reacted much less readily than the dimethylamide complex (2a) or the cyclic amide complexes. Moreover, the difference in the reactivities of the pyrrolidide (2d) and piperidide (2e) complexes was substantially in accord with predictions based on the concept that diminished sp^2 character of the nitrogen atom would be favoured to a greater extent in the six- than in the five-membered ring.[9]

The azetidide complex (2c) reacted with the pyrrolic substrate rather faster than either the pyrrolidide or piperidide complexes which is, of course, consistent with predictions based on the principle of *I* strain. From a preparative point of view it is unfortunate, therefore, that the azafulvene underwent subsequent reaction to form another product. This was evident from a shift in the absorption maximum from 352 to 348 nm during the reaction and the abnormally high molar absorptivity (*ca.* 36 000 *versus* 16 000—18 000 in the other cases) of the unwanted product. Hydrolysis in the usual way afforded only *ca.* 10% yield of the ketone together with 87% of a pale yellow oil whose spectral properties were consistent with those of the imine (5). This unwanted product underwent slow and incomplete acid-mediated hydrolysis to yield the desired ketone but survived basic hydrolysis under even quite harsh conditions using hot 10% sodium hydroxide solution.

Clearly then, the small quantity of ketone isolated after work-up of the original reaction mixture came from residual azafulvene present in that mixture. This too is consistent with the inference that opening of the azetidine ring, ultimately to form protonated (5), occurred after azafulvene formation. It is likely that cleavage resulted from nucleophilic attack by chloride ion on a carbon atom adjacent to the protonated azetidine nitrogen atom. Such protonation is in accord with the hypothesis that the lone pair on the azetidine nitrogen atom in the azafulvene is not involved in delocalization to any marked extent.

The morpholide complex (2f), which was originally expected to be only slightly more reactive than the piperidide complex (2e), proved to be much more so than even the dimethylamide complex (2a). It was felt that the observed eight-fold increase in rate could not reasonably be ascribed wholly to the inductive effect of the



(5)

rather remote oxygen atom and an alternative explanation was sought.

Our hypothesis that co-ordination by $POCl_3$ occurred at both oxygen atoms of *N*-benzoylmorpholine, thereby giving rise to a lower electron density on the amide nitrogen atom, was tested by examining the piperazide complexes (2g and h) in which co-ordination by $POCl_3$ of the second nitrogen atom is quite feasible. It was found that they too exhibited enhanced reactivity.

Complex (2h) formed from *NN'*-dibenzoylpiperazine and two molar equivalents of $POCl_3$ reacted with the substrate at almost the same rate as the morpholide complex (2f). Only one of the activated amide groups took part in the reaction as shown by the isolation of *N*-benzoylpiperazine on hydrolysis of the azafulvene (3h). Since complex (2h) is larger than the morpholide complex (2f) it may reasonably be inferred that the co-ordination of the second carboxamide group gives rise to somewhat more efficient activation of the complex (2h) than is evident in the morpholide case. The activating effect was even more marked in the case of the *N*-methylpiperazide complex (2g) and it is conceivable that the tertiary amino-group became covalently linked to phosphorus by displacement of a chloride ion. Protonation of the methylamino-group by hydrogen chloride generated in the course of azafulvene formation would, it may be argued, give rise to a similar effect. This possibility may be discounted inasmuch as the hydrogen chloride concentration increases with time. If the proton acid were indeed involved a steady increase in rate would be observed. No such effect was evident here or in the morpholide case as all reactions exhibited normal second-order kinetics up to at least 90% of completion.

In a preparative context it is clear that the use of *NN'*-dibenzoylpiperazide complex (2h) offers no advantage over the use of the morpholide complex (2f) and, indeed, requires unnecessary consumption of carboxylic acid, $POCl_3$, and base. Nor is the *N*-benzoyl-*N'*-methylpiperazide complex (2g) much more attractive, despite its high reactivity, because of the expense and the greater difficulty involved in isolating and purifying a liquid amide. It is clear from the foregoing discussion that in the present case the greater reactivity of the

morpholide complex (2f) renders it markedly superior to the others examined. It should be borne in mind, however, that morpholide complex formation may be incomplete when the morpholide carries groups which are electron withdrawing in the presence of $POCl_3$.[6] In such cases the use of the corresponding dimethylamide complex is indicated.

Hydrolysis of the Azafulvene (3) [*Scheme, Step* (*c*)].—The facility with which the hydrolysis of a wide variety of azafulvenes occurred suggested that the nature of the *N*-substituents was of little practical significance. Accordingly, this step was not further examined.

EXPERIMENTAL

The preparation and purification of reagents were carried out as previously described.[6,10] Amide–$POCl_3$ complex formation at 35 °C using 2.16 mol. equiv. of $POCl_3$ was monitored [6] by observing the disappearance of the ^1H n.m.r. signals due to the aromatic protons of the amides and their replacement by signals at *ca.* 0.3 p.p.m. downfield. Approximate times required for >98% complex formation were: (1a) 5 min; (1b) 65 min; (1c) 300 min; (1d) 45 min; (1e) 30 min; (1f) 160 min; (1g) 200 min. In the case of (1h) the complex crystallized from solution even in the presence of an eight-fold excess of $POCl_3$.

Rate measurements, half-reaction time and rate constant determinations, azafulvene hydrolysis, and yield determinations were carried out as previously described.[1,6]

Reaction of the N-*Benzoylazetidine*–$POCl_3$ *Complex* (2c).—*N*-Benzoylazetidine (0.805 g, 5 mmol) was dissolved in $POCl_3$ (1.00 ml, 10.8 mmol) and the solution allowed to stand for 5 h at 35 °C. A solution of ethyl 2,4-dimethylpyrrole-3-carboxylate (0.835 g, 5 mmol) in dry 1,2-dichloroethane (25 ml) was added and the progress of the reaction at 35 °C monitored by absorbance measurements at 352—348 nm. After 18 h the mixture was treated with hot aqueous sodium carbonate solution and the product, a yellow oil, isolated from the organic phase. Purification by chromatography on alumina (activity II—III; 1,2-dichloroethane used for elution) gave two components. The more polar component was ethyl 5-benzoyl-2,4-dimethylpyrrole-3-carboxylate (4) (0.136 g, 10%), m.p. 109—110 °C (lit.,[4] 109—110.5 °C). The less polar component, a pale yellow oil (1.51 g, 87%) gave the following data which are consistent with the structure of α-(4-*ethoxycarbonyl*-3,5-*dimethylpyrrol*-2-*yl*)*benzylidene*-3-*chloropropylamine* (5), $\lambda_{max.}$ ($ClCH_2CH_2Cl$) 297 nm (ε 17 000) shifted to 348 nm (ε 35 000) on addition of CF_3CO_2H; $\nu_{max.}$ (neat) 3 370 (NH) and 1 600 cm^{-1} (C=N); *m/e* 346 (M^+; $C_{19}H_{23}ClN_2O_2$ requires *M* 346); δ (60 MHz; $CDCl_3$) 8.52br (1 H, s, NH), 7.32 (5 H, m, Ph), 4.25 (2 H, q, *J* 7 Hz, CH_2CH_3), 3.45 (4 H, overlapping ts, $NCH_2CH_2CH_2Cl$), 2.53 (3 H, s, CH_3), 2.12 (2 H, m, $CH_2CH_2CH_2$), 1.63 (3 H, s, CH_3), and 1.29 (3 H, t, *J* 7 Hz, CH_2CH_3).

Hydrolysis of Imine (5).—(a) The imine (0.100 g) in 1,2-dichloroethane (10 ml) and aqueous sodium hydroxide solution (10%; 10 ml) were heated under reflux with vigorous stirring for 90 min. The u.v. spectrum showed no ketone to be present and the starting material to be unchanged.

(b) The above mixture was cooled and cautiously treated with concentrated hydrochloric acid (6 ml). Heating under reflux for 90 min gave a mixture of unchanged imine (0.036 g) and ethyl 5-benzoyl-2,4-dimethylpyrrole-3-carboxylate (4) (0.044 g, 49%).

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