The Mechanism of the Vilsmeier–Haack Reaction. Part III.[1,2] Structural and Solvent Effects

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New kinetic data on the Vilsmeier–Haack reaction of heterocyclic compounds are reported which permit the conclusions that (i) the reaction is very selective, as shown by a ρ value of −7·3 for the formylation of thiophen derivatives in chloroform, (ii) the rate of substitution is only affected to a small extent by the polarity of the solvent, and (iii) the rate of substitution is highly dependent on the nature of amide. The reaction with *NN*-dimethylacetamide–carbonyl chloride complex proceeds *ca.* 5 × 10^3 times slower than the reaction with corresponding *NN*-dimethylformamide complex.

In previous papers [1,3] we have investigated the kinetic features of the Vilsmeier–Haack formylation of thiophen derivatives with dimethylformamide (DMF) and phosphoryl chloride or carbonyl chloride in 1,2-dichloroethane (DCE). The use of carbonyl chloride displayed great advantages over that of phosphoryl chloride. In the former case the electrophilic complex, which has an unequivocal structure, could be isolated as a crystalline salt and the reaction between this complex

[1] Part II, S. Alunni, P. Linda, G. Marino, S. Santini, and G. Savelli, *J.C.S. Perkin II*, 1972, 2070.

[2] This paper is considered as Part XVII of the series Electrophilic Substitutions in Five-membered Rings. Part XVI, S. Clementi, F. Fringuelli, P. Linda, G. Marino, G. Savelli, and A. Taticchi, *J.C.S. Perkin II*, 1973, 2097.

and the aromatic substrates exhibited very simple kinetics.

In continuation of our studies on the reaction between the $COCl_2$–amide complex and the heterocyclic compounds, we now report data on (*a*) the selectivity of the reaction, through the determination of the ρ constant for the formylation of thiophen derivatives in chloroform, (*b*) the influence of solvent on the reaction rate, and (*c*) the effect on the reactivity and the selectivity of the electrophilic reagent, due to the substitution of a methyl group for hydrogen in the amide.

RESULTS AND DISCUSSION

ρ *For the Formylation of Thiophen Derivatives.*—The rates of formylation of a number of thiophen derivatives with the carbonyl chloride–dimethylformamide complex have been determined in chloroform at 30°. The compounds examined include unsubstituted and 2-phenyl-, 2-methoxy-, 2-methyl-, 2-t-butyl-, 3-methyl-, 2-chloro-, and 2-bromo-thiophen. The first five compounds listed yielded a single substitution product, the 5-formyl isomer. The 3-methyl derivative gave a mixture of 86·5% 3- and 13·5% 4-methylthiophen-2-carbaldehyde. The reactions of the halogeno-derivatives were complicated by the occurrence of some side-reactions (halogen exchange and carbonyldehalogenation) and therefore the corresponding rate data could not be employed for the determination of the ρ constant.

The reactions were followed by titrating the acid present in the hydrolysed mixture using the procedure previously described.[1] The rate constants and the relative rates (referred to thiophen) are listed in Table 1.

TABLE 1

Rate data for the formylation of thiophen derivatives in chloroform

Substituent	$10^5 k_2$/l mol^{-1} s^{-1} [a]	k/k_H [b]
2-Methoxy	55,500	1·01 × 10^6
2-t-Butyl	21·8	398
2-Ethyl	11·9	217
2-Methyl	10·8	196
2-Phenyl	9·81	178
3-Methyl	2·83	7 [c]
Unsubstituted	0·11	1

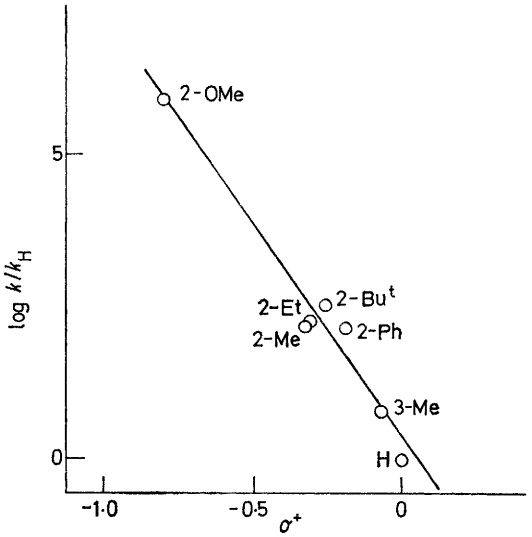
[a] At 30°. [b] Relative rates of substitution at the 5-position. The values are corrected for the statistical factor. [c] Calculated from overall rate and isomeric distribution.

Following a procedure already used by us [4-6] and other authors [7,8] in similar studies, the σ_p^+ and σ_m^+ constants (derived for benzenes) were used for the determination of the ρ constant (−7·3) for the reaction of the thiophen ring (Figure) (correlation coefficient $r = 0{\cdot}982$).

Comparison with other reactions shows that formylation by dimethylformamide and phosgene is almost as selective as chlorination by molecular chlorine [6] (ρ −8·7) and hydrogen exchange [7a] (ρ −7·2) and definitely more selective than tin tetrachloride catalysed acetylation (ρ −5·7).

Solvent Effects.—A study on the effect of solvent on the rate of substitution has been carried out for the formylation of furan and 2-methylfuran.

The range of solvents suitable for a kinetic study is limited by many factors. Solvents of very low polarity such as benzene or hexane cannot be used because of the very low solubility of the DMF–$COCl_2$ complex in these solvents. Protic solvents, such as water, alcohols, and carboxylic acids cannot be used since they induce



Plot of log k/k_H against σ^+ constants for the formylation of substituted thiophens by DMF–$COCl_2$ in chloroform at 30°

hydrolytic decomposition of the complex. Dimethylformamide cannot be used since the kinetics are complicated by a reaction between the electrophilic complex and dimethylformamide itself.[9] The solvents examined in this study were chloroform (ε 4·7), 1,2-dichloroethane (ε 10·35), and acetonitrile (ε 38·8). In all these solvents the reactions follow pure second-order kinetics, first order in substrate and first order in complex. The rate constants are reported in Table 2.

TABLE 2

Solvent effects on formylation rates

	$10^5 k_2$/l mol^{-1} s^{-1} at 20°		
Substrate	Chloroform	1,2-Dichloroethane	Acetonitrile
Furan	6·99	12·5	3·94
2-Methylfuran	2820	4270	964

Polar solvents should stabilize the electrophilic cation (in which the positive charge is more localized) more than the intermediate and consequently slow down the

[3] P. Linda, G. Marino, and S. Santini, *Tetrahedron Letters*, 1970, 4223.
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[5] S. Clementi and G. Marino, *J.C.S. Perkin II*, 1972, 71.
[6] G. Marino, *Adv. Heterocyclic Chem.*, 1971, **13**, 298.
[7] (*a*) A. R. Butler and C. Eaborn, *J. Chem. Soc.* (*B*), 1968, 370; (*b*) A. R. Butler and J. B. Hendry, *ibid.*, 1970, 848.
[8] D. S. Noyce and G. V. Kaiser, *J. Org. Chem.*, 1969, **34**, 1008.
[9] G. J. Martin, S. Poignant, M. L. Filleux, and M. T. Quemeneur, *Tetrahedron Letters*, 1970, 5061.

reaction rate; this would explain the smaller rate of substitution observed in the most polar solvent, acetonitrile.

However, the rate observed in chloroform is smaller than that in the more polar 1,2-dichloroethane: it is possible that specific hydrogen bond interactions are responsible for this inversion. Anyhow, solvent effects are, on the whole, small.

Amide Structure Effect.—It is well known that the use of dimethylacetamide (DMA) in place of dimethylformamide leads to acetyl derivatives. However, no quantitative comparison between the rates of these two reactions (acetylation and formylation) has been reported so far.

2-Methylfuran and 2-methoxythiophen proved to be substrates of suitable reactivity for such a comparative study. Accordingly the rate constants for the acetylation of these two compounds by the DMA–$COCl_2$ complex have been determined at 20° in 1,2-dichloroethane and compared with the rate constants obtained using DMF under the same experimental conditions (Table 3). The data of Table 3 show a dramatic rate

TABLE 3

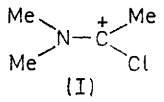
Effects of amide structure

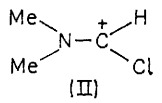
	k_2/l mol^{-1} s^{-1} at 20° in DCE		
Substrate	DMF–$COCl_2$	DMA–$COCl_2$	k_{DMF}/k_{DMA}
2-Methoxythiophen	0·2	$4{\cdot}10 \times 10^{-5}$	$4{\cdot}9 \times 10^{3}$
2-Methylfuran	$4{\cdot}27 \times 10^{-2}$	$1{\cdot}15 \times 10^{-5}$	$3{\cdot}7 \times 10^{3}$

decrease (*ca.* 4—5 $\times$ 10^3 fold) in passing from formylation to acetylation of a given substrate.

With regard to the sensitivity to substituent effects of these reactions, we have obtained data which permit a comparison of the effects of a 2-methyl group on the reactivity of position 5 in the pyrrole nucleus. Owing to the very high reactivity of pyrrole derivatives in formylation, we were unable to use the direct kinetic method; accordingly we determined the relative rates by a competitive procedure, which had been used successfully in previous studies.[10] The relative rates of 2-methylpyrrole with respect to pyrrole were 12·0 and 53·2 for formylation and acetylation, respectively (the values are not corrected for the statistical factor).

The lower reactivity and the higher selectivity of acetylation relative to formylation should be the result of a greater stability of cation (I), compared with (II), due to the electron-donating effects of the methyl group bonded to the positively charged carbon. Also steric effects, due to the larger size of the methyl group,


(I)


(II)

operate in the same direction and can contribute to the observed difference in reactivity between the two reagents.

EXPERIMENTAL

Materials.—All the substrates and some products were available from previous studies. 5-Chloro-,[11] 5-bromo-,[12] 5-ethyl-,[11] 5-t-butyl-,[13] 5-phenyl-,[14] and 5-methoxy-thiophen-2-carbaldehyde,[15] 5-methylfuran-2-carbaldehyde,[16] 5-methylpyrrole-2-carbaldehyde,[17] and 2-methoxy-5-acetylthiophen [18] were prepared according to the literature. 1,2-Dichloroethane, chloroform, dimethylformamide, dimethylacetamide, and acetonitrile were purified by standard procedures. Commercial carbonyl chloride (20% solution in toluene) was used without further purification.

Product Analysis.—All the substrates examined, except 2-chloro- and 2-bromo-thiophen, gave, under kinetic conditions, the expected aldehydes or ketones in very high yield, as checked by g.l.c. analysis of the products. Both 2-chloro- and 2-bromo-thiophen gave comparable amounts of 5-chlorothiophen-2-carbaldehyde and thiophen-2-carbaldehyde as main products.

Kinetics.—The preparation of the DMF–$COCl_2$ complex and the kinetic method were described previously.[1] An identical procedure was applied to the dimethylacetamide–carbonyl chloride complex.

Competitive Experiments.—Stock solutions of 2-methylpyrrole, pyrrole, and the appropriate amide–carbonyl complex in 1,2-dichloroethane (molar ratio 1 : 5 : 0·1) were left at 20° for 1 h and then poured into a 10% aqueous NaOH solution. The mixture was extracted with chloroform, the organic layer was washed twice with water, dried (Na_2SO_4), and finally distilled off. The residue was analysed by g.l.c. on a C. Erba fractometer model GI, equipped with a flame ionization detector, using a 2 m $\times$ 2 mm column packed with Carbowax 20M 10% and operated at 150°.

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