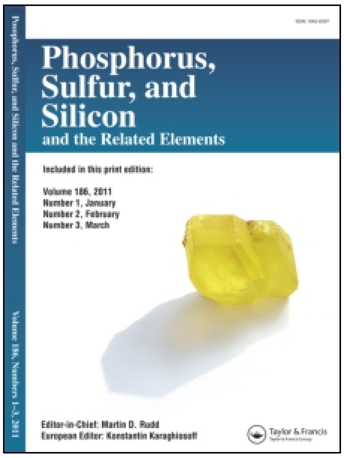

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Tebby, John C. and Willetts, Stuart E.(1987) 'Structure and Reactivity of the Vilsmeier Formylating Reagent', Phosphorus, Sulfur, and Silicon and the Related Elements, 30: 1, 293 — 295

To link to this Article: DOI: 10.1080/03086648708080579

URL: http://dx.doi.org/10.1080/03086648708080579

Phosphorus and Sulfur, 1987, Vol. 30, pp. 293–296
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STRUCTURE AND REACTIVITY OF THE VILSMEIER FORMYLATING REAGENT

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Abstract Phosphoryl chloride and dimethylformamide react to give a Vilsmeier reagent which is an equilibrium mixture of two iminium salts, the more reactive being the beta-phosphoryliminium chloride (1) rather than the beta-chloroiminium phosphate (2) as previously suggested.

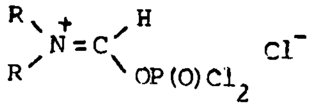
INTRODUCTION

The Vilsmeier-Hack reaction provides a very convenient method for the formylation of alkenes, enolisable ketones, activated arenes and many heterocycles. Nevertheless the structure of the formylating reagent and the factors governing reactivity have not been fully established. Due to the poor understanding of the reaction mechanism the Vilsmeier reaction often requires considerable effort to optimise the yields of formylated product.

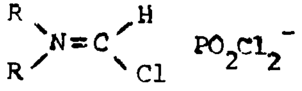
RESULTS AND DISCUSSION

A wide range of acyclic formamides have been prepared. Reaction with phosphoryl chloride converted them to their corresponding Vilsmeier reagent. The structure of these reagents and their reactivities with a standard substrate, thiophene, has been studied with the aid of ^{1}H and ^{31}P NMR spectroscopy. The reagent derived from morpholine was the most reactive. Replacement of phosphoryl chloride by other acid chlorides led to reduced reactivities.

The electronic properties of the beta-substituents of the two iminium salts (1) and (2) were estimated by



(1)



(2)

the application of the Nelson and Taft equations which relate Hammett substituent constants (divided into their inductive and resonance contributions) and the C-3 and C-4 NMR chemical shifts of the corresponding phenyl derivatives. The ^{13}C NMR data (see Table) showed that when bonded to sp^2 aryl carbon the dichlorophosphate group has Hammett substituent constant $\sigma = 0.73$ which indicates electron-accepting properties approaching that of the nitro group $\sigma = 0.82$. On the other hand the chloro group, $\sigma = 0.37$, in this situation has considerably weaker electron accepting properties.

Table of Hammett Substituent Constants

Compound	σ_I	σ_R^o	σ_{total}
PhCl	0.59	-0.22	0.37
$PhOPOCl_2$	0.99	-0.26	0.73

The ^{31}P NMR spectra of the reagents provided evidence for the existence of an equilibrium mixture of iminium salts. The more reactive reagents gave signals at lowest field indicating a higher proportion of the beta-phosphoryliminium chloride (1) (cf PhOPOCl$_2$ with δ_P= 1.5 ppm) whereas the less reactive reagents gave signals at higher field (cf PO$_2$Cl$_2^-$ with δ_P= -11 ppm)

The addition of Lewis acids increased the yield of formylated product. This is in accordance with complexation of the halide anion with the Lewis acid producing a further shift in the equilibrium towards the beta-phosphoryliminium salt (1).

The combined evidence points to the existence of an equilibrium mixture of two iminium salts (1) and (2). The former being more electrophilic and thus more reactive towards electron-rich substrates. This is supported by the lower reactivity of the Vilsmeier reagent derived from phosgene which can only give a beta-chloroiminium salt. Calculations of pK$_a$ values and comparison of bond strengths for model compounds also support these conclusions.

The NMR studies during the course of formylation of thiophene showed that the iminium salts are not thermally stable. Raising the temperature of the reaction increases the rate of formylation,as expected,but at about 100° the rate of decomposition of the reagent becomes appreciable and needs to be taken into consideration when optimising the reaction conditions. The improved formylating power of the reagent derived from morpholine is due to its increased thermal stability as well as the increased proportion of the more reactive iminium salt. A change in electrophilic properties with change in formamide structure may also be a factor.