ADVANCES IN ORGANIC CHEMISTRY: Methods and Results
E. C. TAYLOR, *Editor*

Iminium Salts in Organic Chemistry
Part 2

Edited by

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Universität Marburg/Lahn, Germany

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Foreword

The exceptional role of the iminium grouping in many reactions that occur both in the laboratory and in nature has been recognized for a long time. Since then, however, organic chemistry has become such an extremely broad and diversified science that the enormous progress attained meanwhile in iminium chemistry, including new methods, reagents, ideas, new ways, and fields of application, may have escaped general attention. People engaged in this area have become aware that an urgent need exists for a book which not only gathers the vast amount of new material but reintegrates all of the recent achievements into a more general framework in terms of modern concepts of organic chemistry.

I strongly believe that the present work fulfills these requirements. Although I was engaged in the early discussions during the conception of this book, I am now very impressed at seeing the final result. Both the editors and the authors have succeeded in creating a book from which, I am sure, the chemical community will profit for a long time.

Z. ARNOLD

Prague, Czechoslovakia
February 1976

Series Editor's Note

Although most volumes in the *Advances in Organic Chemistry* series will continue to be multiauthored works presenting authoritative, critical, and timely discussions of new developments in synthetic and instrumental methodology, in line with the general objectives of the series as set forth in the Preface to previous volumes, the present volume, which will appear in two parts, marks a further expansion of the concept of *Advances*. The first departure from the normal format, as outlined above, will be found in Volume 7, which was a single-authored research monograph. The present volume is likewise devoted to a single topic, but is multiauthored and prepared under the general editorship of outside experts in the field. We hope that the rapidity of publication of the two types of research monographs in the *Advances* series will be attractive both to readers and to authors, and that the series as a whole will continue to present in a challenging, provocative, and stimulating manner new ideas, new techniques, and new methods that will become part of the classical repertoire of the practicing organic chemist.

EDWARD C. TAYLOR
Series Editor
Advances in Organic Chemistry

Preface

Research workers in nitrogen chemistry have felt the need for an adequate coverage of modern iminium salt chemistry. This book, we think, will satisfy this need.

Many discussions preceded the 1972 meeting in Marburg at which it was decided to "launch" this book. The project started with an encounter of H. G. Viehe with Z. Arnold in Prague, 1972, followed by others with L. Ghosez in Louvain, with H. Eilingsfeld, H. Pommer, and M. Pape in BASF-Ludwigshafen, with H. Bredereck in Stuttgart, with E. Kühle and E. Grigat in Bayer-Leverkusen, and with C. Jutz in Munich. We feel honored and thank the authors for their extensive work and for their trust and confidence. To Prof. E. C. Taylor, the series editor, we address our repeated thanks for his masterly streamlining of this book.

May all the work serve well now!

H. Böhme
H. G. Viehe

Marburg, Germany
Louvain-la-Neuve, Belgium
August 1976

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THE BACKGROUND OF CARBOXAMIDE SALT CHEMISTRY

By H. BREDERECK, *Institut für Organische Chemie Biochemie und Isotopenforschung der Universität, D-7-Stuttgart 80, Pfaffenwaldring 55, Germany*

As an introduction to the reviews by W. Kantlehner and G. Simchen on acid amide–acid halide and acid amide–dialkyl sulfate adducts and their subsequent reactions, we wish to describe briefly how we became involved in this research area. Such an historical review describing our initial experiments seems to be well justified, since this area has turned out to be a very rich and profitable one.

We had developed, some years ago, new syntheses of imidazoles and oxazoles through an extensive research program (1). Among other features of this program, it was found that α-haloketones reacted with formamide to give either imidazoles or oxazoles, depending on the reaction conditions. In order to obtain more detailed information about the control of halogens in these reactions, we treated numerous halogen compounds with formamide at 150°C (Table I). The alkyl halides yielded either formylamino compounds (*N*-substituted formamides) (**1a**) or formates (**1b**). Formation of a relatively stable

$$\mathrm{R{-}Hal + 2HCONH_2 \xrightarrow{a} RNHCHO + CO + NH_4Hal}$$

(1a)

$$\mathrm{R{-}Hal + 2HCOHN_2 \xrightarrow{b} ROCHO + HCN + NH_4Hal}$$

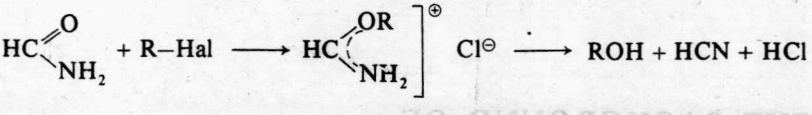
(1b)

TABLE I

Reactions of Formamide with Halogen Compounds

Halide	Products
Octyl bromide	Octyl formate
Benzyl chloride, benzyl bromide, benzyl iodide	Benzyl formate + *N*-benzylformamide
Benzhydryl chloride	*N*-Benzhydrylformamide
Trityl chloride	*N*-(Triphenylmethyl)formamide

Translated from German by Dr. W.-J. Richter, MPI für Kohleforschung, D 4330 Mühlheim.

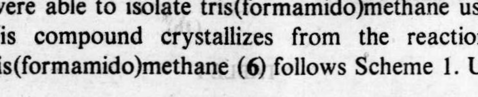


(2)

carbonium ion from the alkyl halide is essential to the formation of a formylamine (path *a*). Formates are formed from intermediate imino esters (path *b*), very likely by dissociation of the alkyl halide; the imino ester (**2**) decomposes to ROH and HCN at the high reaction temperatures used during the reactions. Formates then form by formylation of the hydroxy compound with formamide/HCl:

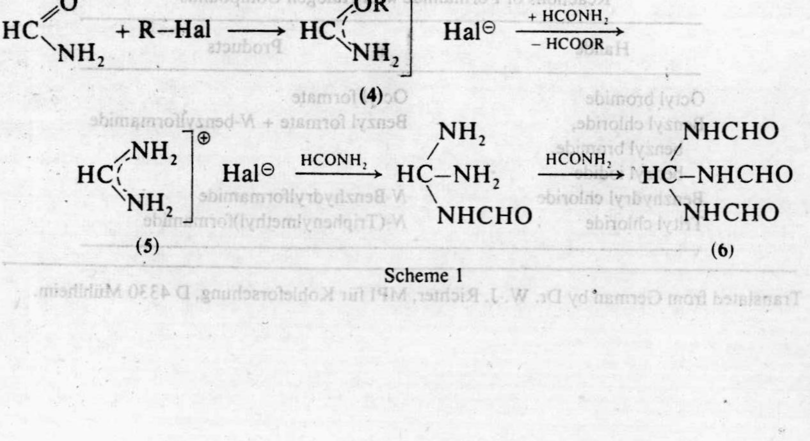
$$ROH + HCONH_2 + HCl \longrightarrow ROCHO + NH_4Cl$$

At the beginning of this research program, we restricted ourselves to an experimental test of this proposed mechanism for the formation of formates. We failed to trap the formimino ester, our proposed intermediate, by quenching the reaction, but we did succeed in isolating the thioformimino ester hydrohalides (**3**) from alkyl halides and thioformamide. Although formamides require a reaction temperature of about 150°C, thioformamides reacted satisfactorily at about 60°C. At 150°C thioformimino ester hydrohalides undergo decomposition to give mercapto compounds and HCN.



(3)

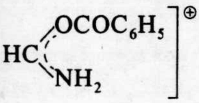
Obviously the next step was to attempt the synthesis of formimino esters from formamides and alkyl halides at temperatures lower than 150°C. For the first time, we were able to isolate tris(formamido)methane using an excess of formamide; this compound crystallizes from the reaction mixture. The formation of tris(formamido)methane (**6**) follows Scheme 1. Using only 1 or 2



Scheme 1

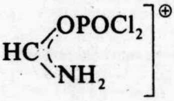
moles of formamide, one obtains formimino ester (**4**) and formamidine salts (**5**) as well as tris(formamido)methane. According to the above scheme, formimino esters as well as formamidine salts are converted to tris(formamido)methane (**6**) by an excess of formamide.

Subsequently we reacted the now readily accessible tris(formamido)methane in numerous ways. Since the intermediate formation of formimino esters is essentially an *O*-alkylation, we expected that formation of tris(formamido)methane from formamide and alkylating agents would be a general reaction. Thus we obtained this compound not only from alkyl halides but also in a very smooth reaction from dialkyl sulfates (dimethyl, diethyl, and diisopropyl sulfate) and from alkyl sulfonates (benzene- and *p*-toluenesulfonic acid esters). Triethyloxonium tetrafluoroborate may also be used as a strong alkylating agent; in this case, the reaction proceeds at room temperature. In addition to alkylating agents, acylating agents (acid chlorides) also yield tris(formamido)methane. We employed the following acid chlorides: acetyl chloride, benzoyl chloride, ethyl chloroformate, phosphorus oxychloride, phosphorus trichloride, and sulfuryl chloride. In all these cases, the reaction proceeds via compounds analogous to formimino esters. We isolated such compounds as the hygroscopic crystalline product **7**, using formamide and benzoyl chloride, and the formamide–phosphorus oxychloride adduct **8** analogously. The structures of these compounds were determined by IR analysis of the DMF–phosphorus oxychloride adduct **9**, which was isolated crystalline. This adduct (the same one on which the Vilsmeier–Haack–Arnold aldehyde synthesis is based) was used for many subsequent reactions.



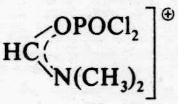
$\left[\mathrm{HC}\begin{array}{l}\diagup \mathrm{OCOC_6H_5} \\ \diagdown \mathrm{NH_2}\end{array}\right]^{\oplus} \mathrm{Cl}^{\ominus}$

(7)



$\left[\mathrm{HC}\begin{array}{l}\diagup \mathrm{OPOCl_2} \\ \diagdown \mathrm{NH_2}\end{array}\right]^{\oplus} \mathrm{Cl}^{\ominus}$

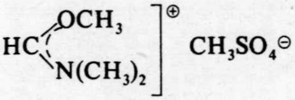
(8)



$\left[\mathrm{HC}\begin{array}{l}\diagup \mathrm{OPOCl_2} \\ \diagdown \mathrm{N(CH_3)_2}\end{array}\right]^{\oplus} \mathrm{Cl}^{\ominus}$

(9)

In the course of the formation of tris(formamido)methane, the formamide-alkylating agent (the formimino ester salt) appeared to be the key intermediate. Consequently, we became interested in the behaviour of *N*-alkylated formamides in the presence of alkylating agents, especially dialkyl sulfates. Despite some initial negative results, we were subsequently able to isolate the *N*,*N*-dimethylformiminomethylester salt (**10**) from dimethylformamide and dimethyl sulfate.



$\left[\mathrm{HC}\begin{array}{l}\diagup \mathrm{OCH_3} \\ \diagdown \mathrm{N(CH_3)_2}\end{array}\right]^{\oplus} \mathrm{CH_3SO_4}^{\ominus}$

(10)

This marked the beginning of what has turned out to be an extensive research program on the synthesis and properties of acid amide–dialkyl sulfate and acid amide–acid chloride adducts, which are the subjects of the chapters by W. Kantlehner and G. Simchen.

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ADDUCTS FROM ACID AMIDES AND ACYLATION REAGENTS (VILSMEIER–HAACK ADDUCTS)

By W. KANTLEHNER, *D-7080-AALEN-Dewangen, Laachweg 14, Germany*

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Translated from German by Dr. W.-J. Richter, MPI für Kohleforschung, D 4330 Mühlheim.

I. Acid Amide–Phosphorus Oxychloride Adducts

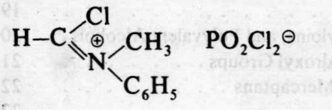
A. STRUCTURE OF ACID AMIDE–PHOSPHORUS OXYCHLORIDE ADDUCTS

1. Dimethylformamide–Phosphorus Oxychloride Adduct

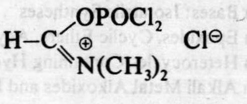
From the studies by Dimroth and Zoeppritz (1) and Vilsmeier and Haack (2, 3), it has long been known that aromatic and heteroaromatic compounds are formylated when treated with *N,N*-disubstituted formamides and $POCl_3$ (Vilsmeier–Haack reaction). Reviews have been published in various languages (4–10), but only rather recently has the nature of the formylating agents been studied.

Vilsmeier and Haack (2) did synthesize the *N*-methylformanilide–phosphorus oxychloride adduct in a pure state. Later H. Bredereck et al. (11) successfully obtained the *N,N*-dimethylformamide–phosphorus oxychloride adduct in a crystalline form; it was characterized by elementary analysis. Thus the suggestion of several authors (2, 12–15) was experimentally verified, namely, formation of the acid amide–phosphorus oxychloride adduct in a 1:1 molar ratio.

Lorenz and Winzinger (16) postulated that the *N*-methylformanilide–$POCl_3$ adduct was a chloromethyleneiminium dichlorophosphate (**1**), whereas Smith (13), Silverstein et al. (14), and Jutz (15) proposed a dichlorophosphato-iminium chloride structure (**2**) for the DMF/$POCl_3$ adduct.



(1)



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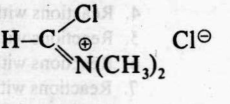
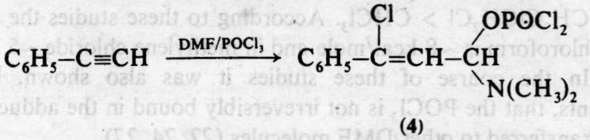


(3)

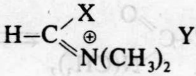
To establish the true structure the IR spectrum of the DMF/$POCl_3$ adduct was studied (11). The experiments apparently indicated that the phosphorus of the $POCl_3$ is bound to the amide oxygen, thus indicating structure **2** for the amide–$POCl_3$ adducts. Bosshard and Zollinger (17) reached the same conclusion by comparing the formylating activity of chloromethyleniminium chlorides like **3** with that of the amide–$POCl_3$ adducts. Both formylating agents should display roughly the same reactivity toward activated aromatic aromatic compounds provided that the gegenion does not influence the reactivity. Actually the DMF–$POCl_3$ adduct was found to be much more reactive. These qualitative results were confirmed by kinetic measurements of the formylation of thiophene derivatives (18, 19). The difference in reactivity between **3** and DMF–$POCl_3$ may be attributed to the different solubilities of the iminium salts or to different degrees of dissociation of the ion pairs; thus these observations are not unequivocal proof for either structure **1** or **2**. Additionally it was shown that the reaction of the DMF–$POCl_3$ adduct and aluminum chloride yields a salt-like compound, whose IR spectrum displays a band attributable to the C–O–P valence vibration; the same band is observed in the IR spectrum of the DMF–$POCl_3$ adduct (17). Ziegenbein and Francke (20) proposed the same structure **2** for the DMF–$POCl_3$ adduct. They were also able to isolate the primary addition product (**4**) from phenylacetylene and the DMF–$POCl_3$ adduct, and elucidated its structure. The nature of the reaction product (**4**) permitted a conclusion as to the nature of the formylating agent and the assignment of structure **2** to it, as already proposed by Bredereck (11).



$$C_6H_5{-}C{\equiv}CH \xrightarrow{DMF/POCl_3} C_6H_5{-}\overset{Cl}{\overset{|}{C}}{=}CH{-}CH\begin{matrix}OPOCl_2\\ N(CH_3)_2\end{matrix}$$

(**4**)

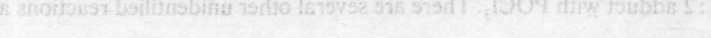
Arnold and Holy (21) studied extensively halomethyleniminium salts and the DMF–$POCl_3$ adduct by IR measurements. They pointed out that the IR bands at 1040 and 1160 cm^{-1}—attributed to the P–O–C vibrations by Bredereck et al. (11) and by Bosshard and Zollinger (17)—also appear in the spectra of the iminium salts **5–8**, and result from the C=N vibrations of the iminium structure $-C{=}N^{\oplus}(CH_3)_2$.



$$H{-}C\begin{matrix}X\\ \overset{\oplus}{=}N(CH_3)_2\end{matrix}\quad Y^{\ominus}$$

(**5**) X = Y = Cl
(**6**) X = Y = Br
(**7**) X = Y = I
(**8**) X = Cl, Y = $SbCl_6$

Arnold and Holy (21) further demonstrated that both chloride and dichlorophosphate anions exist in the DMF–$POCl_3$ adduct. These results are interpreted most satisfactorily by assuming an equilibrium of forms **2** and **9**. Such an equilibrium had been suspected by Bosshard and Zollingen (17), and the NMR studies by Martin et al. (22–24) do not rule out such an equilibrium. However, in solution the equilibrium is almost completely on the side of the *N,N*-dimethylchloromethyleniminium dichlorophosphate (**9**), as the ^{31}P NMR spectrum shows (24). No conclusions can be made about the equilibrium in the solid state, since solvation effects are lacking here. The ^1H NMR spectrum of the DMF–$POCl_3$ adduct in chloroform shows signals at $\tau_{HC} = -0.17$ and



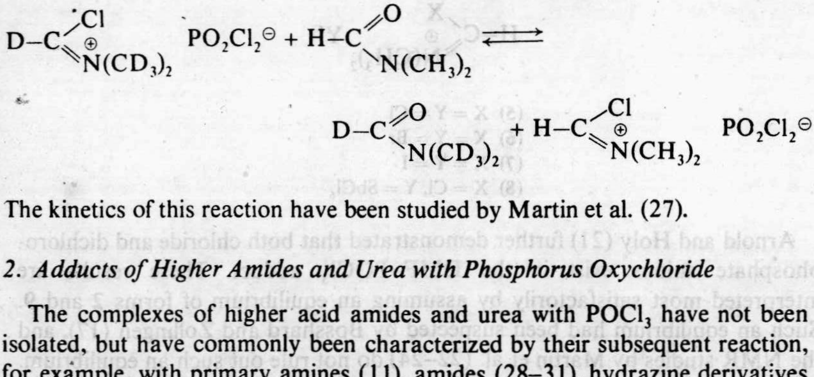
$$H{-}C\begin{matrix}OPOCl_2\\ \overset{\oplus}{=}N(CH_3)_2\end{matrix}\quad Cl^{\ominus} \rightleftharpoons H{-}C\begin{matrix}Cl\\ \overset{\oplus}{=}N(CH_3)_2\end{matrix}\quad PO_2Cl_2^{\ominus}$$

(**2**) (**9**)

$\tau_{N^{\oplus}(CH_3)_2} = 6.07$ at room temperature (23); contrarily, Smith (25) reports a τ value of 0.25 for the formyl hydrogen. More recently several authors have attributed solely the chloromethyleniminium structure **9** to the DMF–$POCl_3$ adduct, based on spectroscopic results (23) and on studies of vinylogous amides (26).

Martin et al. (22, 24) were the first to report kinetic studies on the DMF–$POCl_3$ adduct formation. The reaction is first order with respect to DMF and $POCl_3$. The reaction velocity is solvent dependent and decreases in the order $CH_2Cl_2 > CH_2ClCH_2Cl > CHCl_3$. According to these studies the activation energy in chloroform is ~8 kcal/mole and in methylene chloride ~5 kcal/mole (22, 24). In the course of these studies it was also shown, by NMR measurements, that the $POCl_3$ is not irreversibly bound in the adduct, but can be further transferred to other DMF molecules (22, 24, 27).

In a more recent kinetic study of the adduct formation of DMF and $POCl_3$ in 1,2-dichloroethane, Alumi et al. (18) determined the activation energy to be 15.8 kcal/mole and the activation entropy to be −20.7 kcal/mole. Their values differ from those reported by Martin (22) by nearly 100%. Fritz and Oehl (26) demonstrated halide–oxygen exchange between DMF and the DMF–$POCl_3$ adduct:



$$D{-}C(Cl){=}N^{\oplus}(CD_3)_2\ PO_2Cl_2^{\ominus} + H{-}C({=}O)N(CH_3)_2 \rightleftharpoons D{-}C({=}O)N(CD_3)_2 + H{-}C(Cl){=}N^{\oplus}(CH_3)_2\ PO_2Cl_2^{\ominus}$$

The kinetics of this reaction have been studied by Martin et al. (27).

2. *Adducts of Higher Amides and Urea with Phosphorus Oxychloride*

The complexes of higher acid amides and urea with $POCl_3$ have not been isolated, but have commonly been characterized by their subsequent reaction, for example, with primary amines (11), amides (28–31), hydrazine derivatives (11), or activated aromatic compounds (15, 17) (see also the chapter on "Amidinium Salts" in this volume). Thus it was shown that aliphatic and aromatic monocarboxylic acid dialkylamides do form adducts with $POCl_3$ (11).

With dicarboxylic acid bis(dialkylamides) the type of adduct formed depends on the distance between the two carboxamide functions in the molecule (29). Complex formation does not occur with oxalic acid bis(dimethylamide), but malonic acid bis(dimethylamide) does form a 1 : 1 adduct with $POCl_3$ (29). Succinic acid bis(dimethylamide) gives, in low yield a 1 : 2 adduct with $POCl_3$. There are several other unidentified reactions as well.

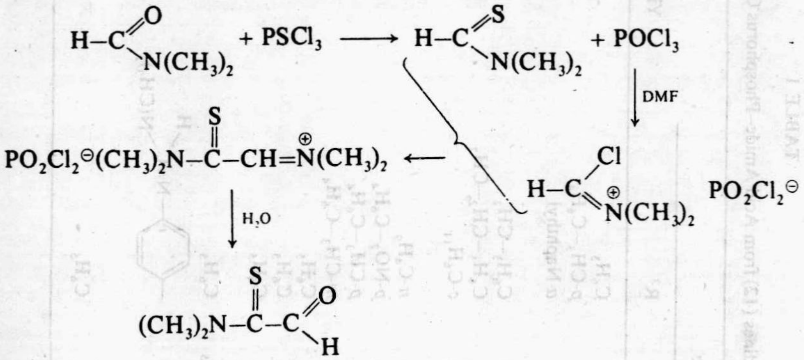
On the other hand, adipic acid bis(dimethylamide) and terephthalic acid bis(dimethylamide) form 1:2 adducts without remarkable side reactions. Five-, six-, and seven-membered lactams as well as their *N*-alkylated and arylated derivatives (*α*-pyrrolidones, *α*-piperidones, *ε*-caprolactams, and 1-methylquinolone) are capable of adduct formation with $POCl_3$ (29).

Bis adduct formation with $POCl_3$ was demonstrated for 2,5-diketopiperazine and sarcosine anhydride by subsequent reactions (29).

3. Thioamide–Phosphorus Oxychloride and Amide–Phosphorus Sulfochloride Adducts

N,N-Dimethylthioformamide also forms an adduct with $POCl_3$, which can be used for formylating heterocycles, and is said to be more reactive than the DMF–$POCl_3$ adduct (32).

DMF undergoes self-condensation in the presence of phosphorus sulfochloride; the following mechanism has been proposed for this reaction (33):



B. REACTIONS OF ACID AMIDE–PHOSPHORUS OXYCHLORIDE ADDUCTS

1. Reactions with Amines

Bureš and Kundera (34) and Davis and Yelland (35) were the first to report experiments investigating the formylation of primary amines with amides and $POCl_3$. Davis and Yelland succeeded in transforming *n*-butylamine into *N,N'*-di-*n*-butylformamidine—isolated as the picrate—with the aid of *N*-*n*-butylformamide–$POCl_3$ complex: