

# Vilsmeier–Haack–Arnold Formylations of Aliphatic Substrates with *N*-Chloromethylene-*N,N*-dimethylammonium Salts

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Received June 1st, 1999, respectively July 16th, 1999

*Dedicated to Professor Siegfried Dähne on the Occasion of his 70th Birthday*

**Keywords:** Aldehydes, Reagents, Synthetic methods, Formylation reactions, Vilsmeier–Haack–Arnold Formylations

**Abstract.** The classical electrophilic substitution of activated aromatics with the Vilsmeier–Haack reagent *N*-chloromethylen-*N,N*-dimethylammonium chloride (Schemes 1 and 2) has been more recently extended to a great variety of aliphatic substrates, mainly due to the work of Arnold. In this review, a collection of representative examples for these henceforth called Vilsmeier–Haack–Arnold (VHA) formylation reaction of aliphatics is given: the reaction of polymethine cyanines, merocyanines, and other vinylogous iminium salts with the VHA reagent gives, after hydrolysis of the primary substitution products, trialdehydes such as triformylmethane (Scheme 3); VHA reaction with ene-diamines and diene-diamines yields *N,N*-dialkylaminomalonaldehydes and tetraal-

dehydes such as 1,1,2,2-tetraformylethane, respectively (Schemes 4 and 5); aldehyde acetals, enol ethers, and carboxylic acids deliver with VHA reagents 2-substituted malonaldehydes (Scheme 6), and  $\alpha$ -amino acids give derivatives of the unstable aminomalonaldehyde (Scheme 7); alkenes and polyenes react with VHA reagents to give  $\alpha,\beta$ -unsaturated or higher vinylogous aldehydes (Schemes 8 and 9), and alkenes with donor substituents yield alkylidene-malonaldehydes (Scheme 10); enolizable methyl and methylene ketones produce with VHA reagents 3-chlorovinylaldehydes (Scheme 11). Eventually, the VHA reagent can be used for the intermediate preparation of nucleophilic amino-chlorocarbenes (Scheme 12).

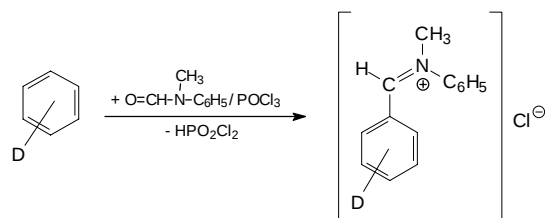
In 1927, Anton Vilsmeier, a young thirty-three years old German chemist at the University of Erlangen [1], published with his coworker Albrecht Haack [2] a rather short paper [3], dealing with the formylation of aromatics, activated by electron-donating substituents, with phosphorus oxytrichloride ( $\text{POCl}_3$ ) and *N*-methylformanilide (MFA) to give, after hydrolysis of the primary electrophilic substitution product, the corresponding aromatic aldehydes according to Scheme 1.

A first, singular example of such a formylation reaction was already found by Dimroth and Zoeppritz in 1902 [4]. However, Vilsmeier and Haack discovered the general applicability of this formylation reaction to a variety of activated

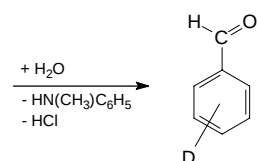
aromatic and heteroaromatic substrates [3]. The mechanistic classification of the Vilsmeier–Haack (VH) formylation reaction into the group of common electrophilic substitution reactions was later on proposed by Wizinger [5]. Nowadays, the VH formylation reaction of activated benzenoid and non-benzenoid aromatics as well as heteroaromatics belongs to the canon of classical name reactions, which can be found in all modern text-books of organic chemistry and has to be learned by students of chemistry [6].

However, what is surprisingly less well known and what has not yet found its way into modern text-books, is the extension of the VH reaction from aromatics and heteroaromatics to a great variety of aliphatic compounds such as polymethines, alkenes and cycloalkenes, enol ethers, ketones, amides, carboxylic acids, etc. This extension has been mainly done by Zdeněk Arnold, a Czech chemist from Prague [7], with a large series of altogether forty papers published 1958–1978 and entitled “Synthetic Reactions of Dimethylformamide” [8]. Particularly this important work, together with the following work of many other chemists [6], as for example the introduction of vinylogous VH reagents by Jutz [6j, 9], has made the VH reaction to a valuable C–C bond forming reaction with a tremendous synthetic potential, which justifies its renaming as to Vilsmeier–Haack–Arnold (VHA) formylation, or, more general, acylation reaction [6j].

The aim of this short report is to collect some representative examples of the VHA formylation reaction of



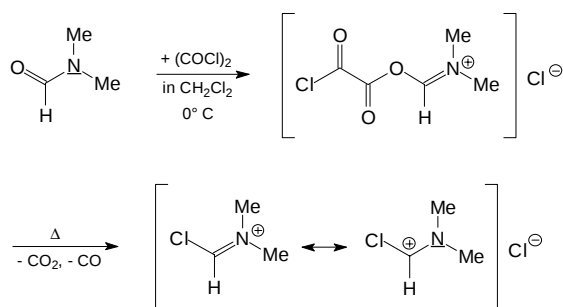
D = ring-activating electron-donor substituent



**Scheme 1** Vilsmeier–Haack formylation of activated aromatic compounds

non-aromatic, aliphatic substrates in order to demonstrate their usefulness in modern synthetic organic chemistry. An excellent comprehensive compilation of all kinds of syntheses using VHA reagents has been recently given by Marson and Giles [10].

VHA reagents are halomethyleneiminium salts [6i] such as for example *N*-chloromethylene-*N,N*-dimethylammonium chloride,  $[\text{Cl}-\text{CH}=\text{NMe}_2]^+\text{Cl}^-$ , usually prepared from an *N,N*-disubstituted formamide (typically DMF or MFA) and an acid chloride [e.g.  $\text{POCl}_3$ ,  $\text{PCl}_5$ ,  $(\text{POCl}_2)_2\text{O}$ ,  $\text{COCl}_2$ ,  $(\text{COCl})_2$ ,  $\text{SOCl}_2$ ] in chloroalkane solvents (e.g.  $\text{CH}_2\text{Cl}_2$ ,  $\text{CHCl}_3$ ,  $\text{ClCH}_2\text{CH}_2\text{Cl}$ ) at general working temperatures of 70–80 °C. A typical clean and convenient VHA-reagent forming reaction is the reaction between DMF and oxalyl chloride (a liquid of b.p. 63–64 °C) in chloroform according to Scheme 2 [11]. The reaction proceeds through an ionic adduct which then loses  $\text{CO}_2$  and CO to yield the desired iminium chloride.

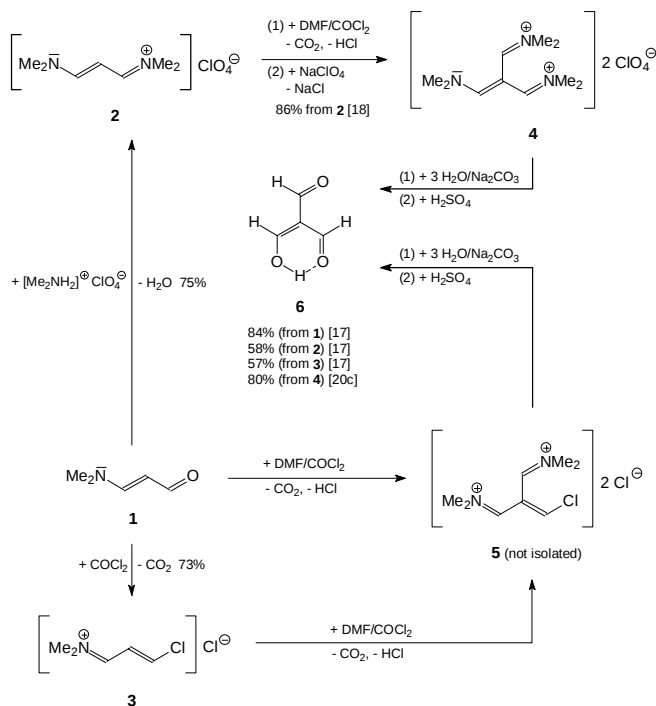


**Scheme 2** Preparation of *N*-chloromethylene-*N,N*-dimethylammonium chloride [11]

The use of a similar reagent, i.e. *N*-dichloromethylene-*N,N*-dimethylammonium chloride,  $[\text{Cl}_2\text{C}=\text{NMe}_2]^+\text{Cl}^-$ , also known as Viehe's salt, has been recently reviewed in this journal [12].

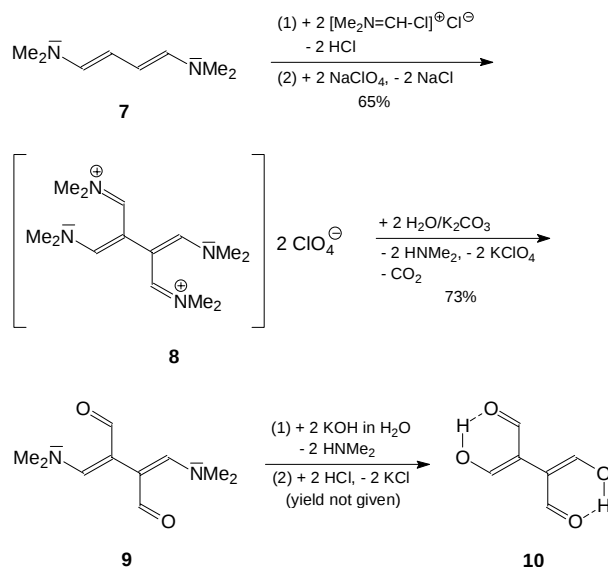
According to the Triad Theory of Dähne, there are three main groups of conjugated organic compounds, characterized by their ideal  $\pi$ -electronic states: the aromatic, the polyenic, and the polymethinic state [13]. Polymethines, most of them known as vinylogous amidinium salts („vinamidinium salts“ [14]), share with aromatic compounds the strong  $\pi$ -electron delocalization and consequently their suitability for electrophilic substitutions such as nitration and bromination [15]. Therefore, the VHA formylation of polymethines seems to be a logical extension of the VH formylation of aromatic compounds.

Electrophilic substitution of the trimethinium salt **2** with  $\text{DMF}/\text{COCl}_2$  yields indeed the methinylogous [16] guanidinium salt **4**, which can be isolated or directly hydrolyzed to give triformylmethane **6**, the simplest trialdehyde, as stable crystalline compound (Scheme 3)



**Scheme 3** Synthesis of triformylmethane **6** [17]

[17, 18]. VHA formylation of the corresponding merocyanine **1** or the vinylogous VHA reagent **3** yields also, via **5**, the trisaldehyde **6** [17]. The molecular fine structure of **4** and **6** is that of a propeller-like, Y-conjugated dication with  $\text{C}_3$  symmetry [19], and that of an enolized, intramolecularly H-bonded formylmalonaldehyde [16a], respectively. The synthesis of triformylmethane and its precursor **4** by means of VHA formylations has been later improved by using as starting material 3-diethylaminoacrolein [16a], bromoacetic acid [20, 21],



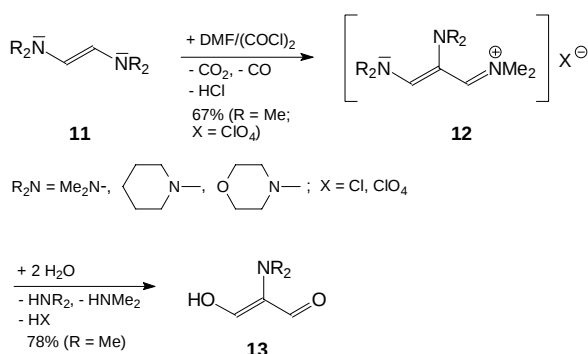
**Scheme 4** Synthesis of 1,1,2,2-tetraformylethane **10** [26]

malonic acid [22], and phosphonoacetic acid [23] instead of **1–3**. All these VHA reactions pass through trimethinium intermediates. The trialdehyde **6** and its precursor **4** are valuable intermediates for three-fold condensation reactions to yield for example [6]helicenes [22], trinuclear [2,2,2]heptamethinedium cyanine dyes [16, 24], and various interesting heterocyclic compounds [21, 25].

Another remarkable aliphatic aldehyde is 1,1,2,2-tetraformylethane **10**, which has been obtained by two-fold VHA formylation of 1,4-bis(dimethylamino)buta-1,3-diene **7** via the bis(trimethinium) salt **8** and the partial-hydrolysis intermediate **9** (Scheme 4) [26]

Astonishingly, oxidation of **10** to the corresponding cross-conjugated tetraformylethene has not been reported up to now. The latter tetraaldehyde should have chemical properties similar to that of the  $\pi$ -acceptor and dienophile tetracyanoethene.

VHA formylation of the lower-vinyllogous ene-diamine **11** leads via the trimethinium intermediate **12** to 2-(dialkylamino)malonaldehydes **13** (Scheme 5) [27, 28].

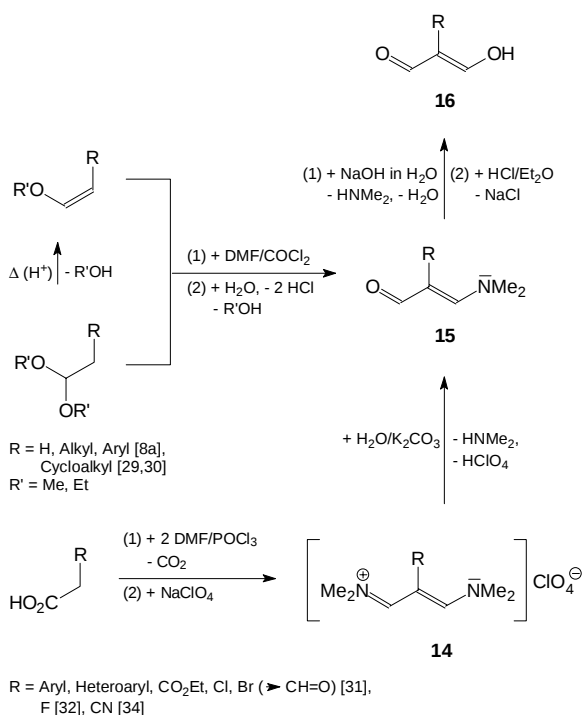


**Scheme 5** Synthesis of *N,N*-dialkylaminomalonaldehydes **13**

Numerous other 2-substituted malonaldehydes and its precursors have been obtained by VHA formylations of appropriate educts, via the corresponding trimethinium intermediates and their hydrolysis.

In the first paper of the series “Synthetic Reactions with DMF” [8a], Arnold and Šorm describe 1958 the formylation of aldehyde acetals and the corresponding enol ethers, which leads to 2-alkyl(aryl)-substituted 3-(dimethylamino)acroleins **15** and malonaldehydes **16**, depending on the conditions for work-up (Scheme 6). This was the first general synthesis for 2-substituted malonaldehydes, which has been extended later on to cycloalkyl- [29] as well as 1- and 2-adamantylmalonaldehydes [30].

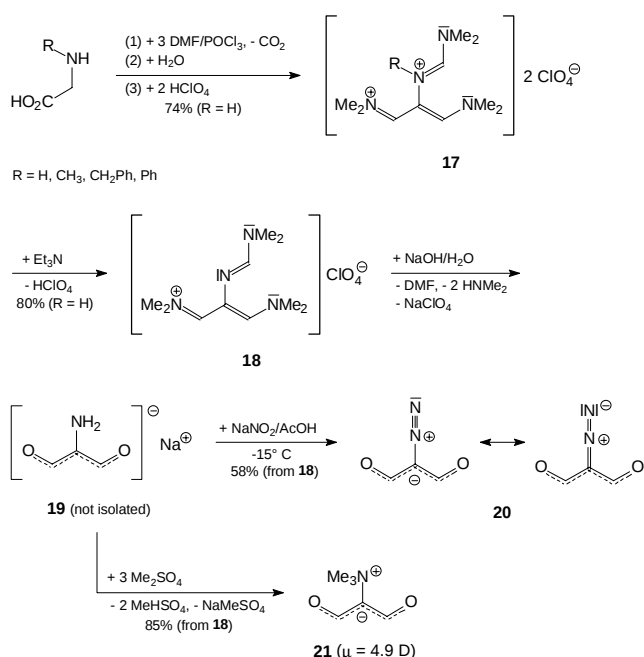
The synthesis of 2-substituted malonaldehydes can be simplified by using carboxylic acids R–CH<sub>2</sub>–CO<sub>2</sub>H (with R = aryl, heteroaryl, CO<sub>2</sub>Et, Cl, etc.) as educts in the VHA formylation reaction, which then proceeds via the 3-(dimethylamino)acrolein **15** to the desired dialde-



**Scheme 6** Synthesis of 2-substituted malonaldehydes

hydes **16** (Scheme 6) [31]. In case of bromoacetic acid as educt, the 2-bromotrimethinium salt **14** reacts further with a third mole of VHA reagent, to give the methinylogous guanidinium salt **4** (Scheme 3), the precursor of triformylmethane **6** [20, 21]. VHA formylation of fluoroacetic acid sodium salt in the presence of triethylamine gave the 2-fluorotrimethinium salt **14** (R = F), which could be hydrolyzed to fluoromalonaldehyde **16** (R = F) [32], an important starting material for the preparation of various fluoro-substituted carbo- and heterocycles [33]. VHA formylation of cyanoacetic acid gives 2-cyano-3-(dimethylamino)acrolein **15** (R = CN) [34], the precursor of the otherwise difficult obtainable cyanomalonaldehyde. Even acetonitrile can be formylated with DMF/POCl<sub>3</sub> to give **15** (R = CN) [34]. The chemistry of halomalonaldehydes has been reviewed [35].

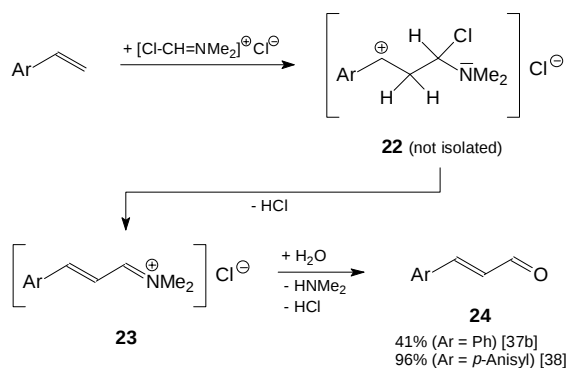
Even  $\alpha$ -amino acids undergo VHA formylations to yield various kinds of valuable, otherwise not accessible aminomalonaldehyde derivatives, according to Scheme 7 [36]. The primary formylation intermediates **17** and **18** (for R = H) [36a] can be hydrolyzed to give, in case of **18**, *in situ* the aminomalonaldehyde sodium salt **19** [36b]. Diazotization of **19** leads to diazomalonaldehyde **20**, a pale-yellow explosive liquid [36b], whereas alkylation with dimethyl sulfate yields the zwitterionic trimethylammonio-diformylmethid **21**, a stable colourless crystalline compound with high dipole moment [36d]. By alkylation of **19** with different haloalkanes various other trisalkylammonio-diformylmethids can be



**Scheme 7** Synthesis of aminomalonaldehyde derivatives from  $\alpha$ -amino acids

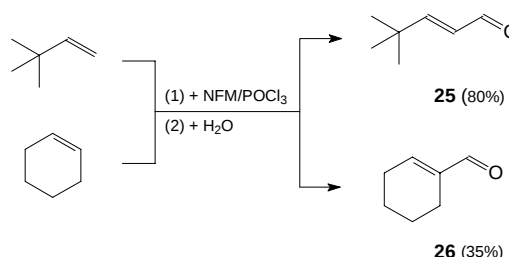
prepared [36c, 36e], the molecular fine structure of which has been carefully studied [36f].

The VHA formylation reactions mentioned before start with or pass through polymethinium salts as educts and intermediates, respectively. In addition to polymethines, activated alkenes and polyenes also undergo VHA formylation reactions [5, 6g, 6j, 6n, 6o], usually giving  $\alpha,\beta$ -unsaturated aldehydes, as shown in Scheme 8 for the VHA formylation of styrenes. Addition of the VHA reagent leads first to a resonance-stabilized benzylic carbenium ion **22**, which loses in a fast reaction HCl to give **23**, which on hydrolysis gives cinnamaldehydes **24** in satisfactory yields [37]. Likewise, 5-aryl-penta-2,4-dien-1-als can be prepared from vinylogous 1-aryl-buta-1,3-dienes [38] or its precursor alcohols [39].



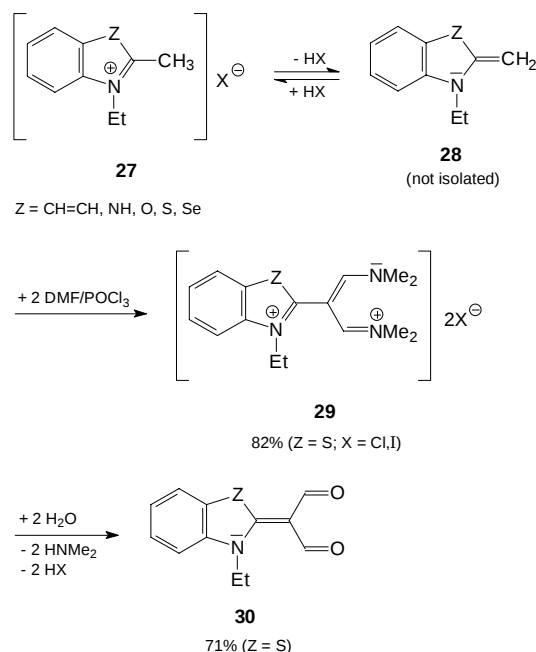
**Scheme 8** Synthesis of cinnamaldehydes from styrenes [37–39]

By using *N*-formylmorpholine (NFM)/ $\text{POCl}_3$  as VHA reagent, even simple unactivated alkenes such as *t*-butyl-ethene and cyclohexene can be monoformylated to give the corresponding  $\alpha,\beta$ -unsaturated aldehydes **25** and **26** (Scheme 9) [40]. Careful reaction of some of these polyenealdehydes with VHA reagents leads to vinylogous VHA reagents, e.g.  $[\text{Me}_2\text{N}=\text{CH}-(\text{CH}=\text{CH})_n-\text{Cl}]^+\text{X}^-$ , which on reaction with dimethylamine and  $\text{NaClO}_4$  give simple polymethinium salts such as  $[\text{Me}_2\text{N}=\text{CH}-(\text{CH}=\text{CH})_n-\text{NMe}_2]^+\text{ClO}_4^-$  with  $n = 2-5$  [41]. Addition of VHA reagents to alkynes such as 1-methoxy-but-1-en-3-yne leads to 3-halogeno-substituted pentamethinium salts [42].



**Scheme 9** Synthesis of aliphatic and cycloaliphatic  $\alpha,\beta$ -unsaturated aldehydes [40]

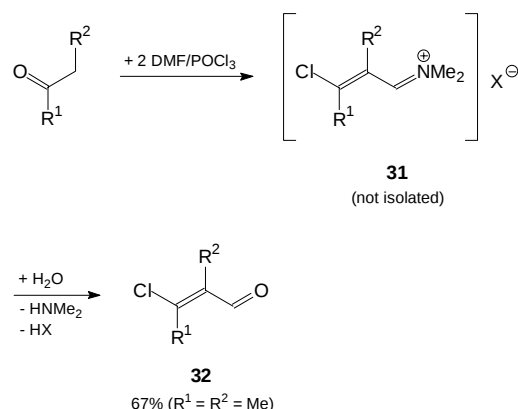
Alkenes activated by electron-donor substituents such as the enamines **28**, which are in solution in equilibrium with the corresponding quaternary imonium salts **27**, are twofold formylated by VHA reagents, to give the trimethinium salts **29**, which can be hydrolyzed to the alkylidenmalonaldehydes **30** (Scheme 10) [5b, 43].



**Scheme 10** Synthesis of substituted alkylidenmalonaldehydes [43]

Likewise, 4-methylene-4*H*-pyranes formed from 4-methylpyrylium salts, are twofold formylated to yield the corresponding 4*H*-pyranylidenmalonaldehydes [44]. These dialdehydes belong to a new class of cross-conjugated methylenmalonaldehydes, the chemistry of which, studied more recently (see for example [45]), has been reviewed already [46].

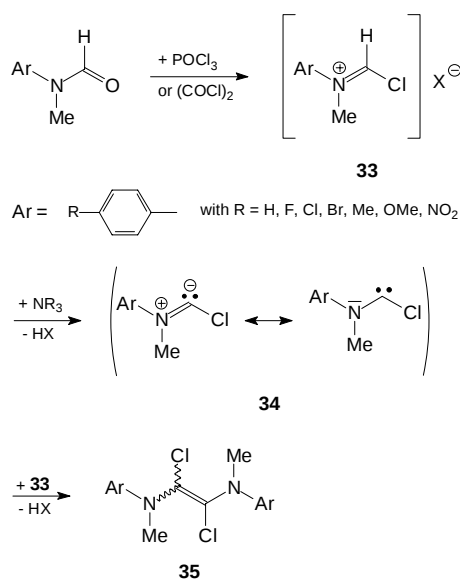
Enolizable acyclic, cyclic, heterocyclic, and benzo-fused methyl and methylene ketones react with VHA reagents *via* the intermediate imonium salts **31** to compounds **32** containing the 3-chlorovinylaldehyde moiety (Scheme 11) [47, 48]. These 3-chloroacrolein derivatives have proved to be useful intermediates in organic syntheses: the chlorine atom can be easily replaced by nucleophiles, and the aldehyde group can be transformed by means of condensation reactions, often followed by base-catalyzed cyclizations to form a wide variety of heterocycles such as thiophenes, isoxazoles, pyrimidines, and pyrazoles. Using this Vilsmeier methodology, more than fifty different ring systems have been synthesized [6l, 6n, 10]. The chemistry of 3-chlorovinylaldehydes has been extensively reviewed [6j, 6l, 6m, 10, 49].



**Scheme 11** Synthesis of 3-chlorovinylaldehydes [47]

The recent interesting discovery that VHA reagents can be readily deprotonated to give amino-chlorocarbenes as transient intermediates opens up new possibilities in the field of VHA chemistry (Scheme 12) [50, 51]. VHA reagents **33**, generated from *N*-methylformanilides (MFA) by the action of oxalyl chloride in THF solution, react with *N*-ethyl-diisopropylamine to give 1,2-diamino-1,2-dichloroethanes **35** [50]. The same reaction takes place when MFA's in  $\text{POCl}_3$  solution are treated with tertiary amines [51]. However, in the latter case, a mixture of products consisting of dimers **35**, trimers, isatins, and tetramers results [51].

This reaction is best explained by deprotonation of the VHA reagent **33** to give an amino-chlorocarbene **34**, which then reacts with **33** to yield the dimer **35**. In



**Scheme 12** Nucleophilic carbenes from VHA reagents [50, 51]

that way, the electrophilic VHA reagent is converted into a nucleophilic carbene, *i.e.* into an ‘umpoled’ VHA reagent [50, 51].

The few examples of VHA formylation reactions selected in this short overview demonstrate impressively the synthetic potential of this now 72-years old reaction; a comprehensive survey of syntheses with VHA reagents can be found in a recent monograph [10].

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- [2] Dr. phil. Albrecht Haack (Südende bei Berlin 06. 12. 1898 – Munich 22.09.1976) Study of natural sciences and chemistry 1919–24 in Erlangen; Diploma examination in Erlangen 1924; Ph. D. Thesis in Erlangen 1926 (with Prof. O. Fischer and Dr. A. Vilsmeier). From 1928 – 41 “Betriebschemiker” at the “Milchzentrale” in Karlsruhe/Baden. 1941 – 45 War service; afterwards work unrelated to his vocation as chemist (*e.g.* tax offices in Erlangen and Nuremberg); 1963 Retirement. – I thank Dr. D. Haack, Erlangen, for providing me with the biographical data of his father.
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