



# STUDY OF VILSMEIER-HAACK REAGENT

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**Introduction:** The Vilsmeier-Haack reagent has attracted the attention of synthetic organic chemists since its discovery in 1927. The application of Vilsmeier-Haack reagent for formylation of a variety of both aromatic and heteroaromatic substrates is well documented. Beside this, the reagent has also been extensively used for effecting various chemical transformations from other class of compounds. Many of these reactions have led to a novel and convenient routes for the synthesis of various heterocyclic compounds. In addition, certain striking applications e.g. halogenation, alkylation and haloalkylation have also been recently appeared. A number of reviews dealing with specific aspects of Vilsmeier-Haack reaction have appeared. The reaction between phosphorylchloride and *N*-methylacetanilide led Vilsmeier and Haack to develop the versatile reagent. The reagent obtained from *N*-methylformanilide and phosphorylchloride, represented as salt, reacts with *N,N*-dimethylaniline to give 4-*N,N*-dimethylaminobenzaldehyde. Other *N,N*-dialkylaniline derivatives are also successfully used as substrates to prepare aromatic aldehyde derivatives. The gradual development of the reagent for synthesizing heterocyclic compounds is accompanied by the interest in the nature of reagent.



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## Synthesis of Heterocyclic Compounds

Synthesis of heterocyclic compounds are achieved either by cyclization of open chain substrates by using POCl<sub>3</sub>/DMF or the sequential transformations of substrate heterocyclic compounds using POCl<sub>3</sub>/DMF to obtain new heterocyclic derivatives. Here, we are representing synthesis of some five membered heterocyclic compounds using Vilsmeier-Haack reagent.

### A. Five membered ring heterocycles

- (i) Furans
- (ii) Pyrroles and related compounds



- (iii) Oxazoles and Oxazolines
- (iv) Imidazoles
- (v) Pyrazoles

## A: Five membered ring heterocycles

### (i) Furans

Treatment of  $\gamma$ -dicarbonyl compound with  $\text{POCl}_3/\text{DMF}$  gives furan-3-carboxaldehyde. Thus, reaction of hexan-2,5-dione (**1**) with  $\text{POCl}_3/\text{DMF}$  provides the corresponding furancarboxaldehyde, i.e. 2,5-dimethyl-3-furancarboxaldehyde (**2**) in 60% yield (**Scheme 1.1**).



**Scheme 1.1**

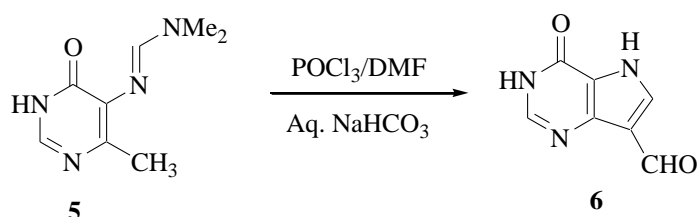
### (ii) Pyrroles and related compounds

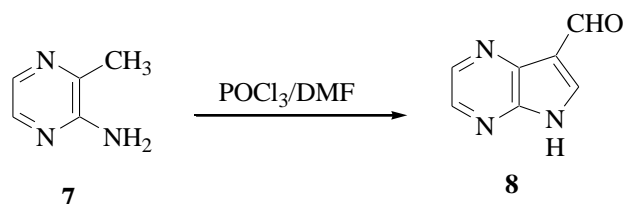
Cyclization of *N*-acetylamino acid with  $\text{POCl}_3/\text{DMF}$  is known to furnish substituted pyrrole derivatives. *N*-Acetylglycine (**3**) on treatment with  $\text{POCl}_3/\text{DMF}$  at a temperature of 90 °C leads to the formation of diformylated product, namely, 2,4-dichloro-3,5-diformylpyrrole (**4**) in 82% yield (**Scheme 1.2**).



**Scheme 1.2**

Vilsmeier-Haack reaction of pyrimidinyl methyl group in compound **5** provides the synthesis of pyrrolopyrimidine carboxaldehyde **6** (**Scheme 1.3**). Similarly, reaction of 2-amino-3-methylpyrazine (**7**) with  $\text{POCl}_3/\text{DMF}$  gives pyrrolopyrazine carboxaldehyde **8** in 56 % yield (**Scheme 1.4**).

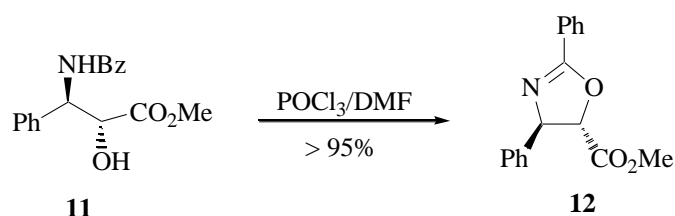



**Scheme 1.3**

**Scheme 1.4**
**(iii) Oxazoles and Oxazolines**

An unprecedented attack of the azide functionality by iminium species generated *in situ* under Vilsmeier-Haack conditions, provides a novel route for the construction of nitrogen heterocycles. e.g.; 2-Azidoacetophenones **9** on reaction with  $\text{POCl}_3/\text{DMF}$  under reflux conditions gives 5-aryl-4-oxazolecarboxaldehydes (**10**) (**Scheme 1.5**).

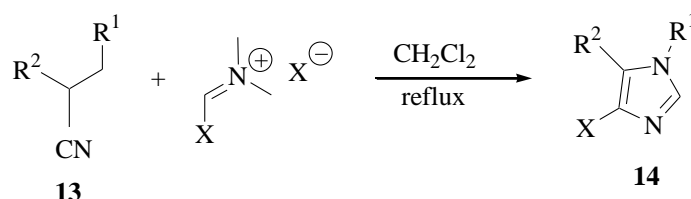

**Scheme 1.5**

One pot synthesis of oxazole-4-carboxaldehydes (**10**) from 2-bromoacetophenones by dehalogenation-Vilsmeier cyclization sequence provides better yield. Vilsmeier reagent very efficiently converts the anti-amido alcohol **11** to the oxazoline derivatives **12** with inversion of configuration in nearly quantitative yield (**Scheme 1.6**). The use of  $\text{SOCl}_2$  in place of  $\text{POCl}_3$  gives 70% yield.


**Scheme 1.6**
**(iv) Imidazoles**



Pawar *et al* have reported the synthesis of pharmaceutically important 1,5-disubstituted-4-haloimidazoles **14** by reaction of  $\alpha$ -aminonitriles **13** with Vilsmeier reagent (Scheme 1.7).



**Scheme 1.7**

### (v) Pyrazoles

Synthesis of 3-aryl-1-(4,6-dimethyl-2-pyrimidinyl)-4-formylpyrazoles **16** has been reported by the reaction of 4,6-dimethylpyrimidinyl hydrazones **15** of various acetophenones with  $\text{POCl}_3/\text{DMF}$  (Scheme 1.8).



R = H, Cl,  $\text{NO}_2$ , F, OH, Me

**Scheme 1.8**

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