

Application of Vilsmeier-Haack Reagent in the Synthesis of Heterocyclic Compounds

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Abstract

The present article is a review highlighting the utility of Vilsmeier-Haack reagent in the synthesis of heterocyclic compounds. The synthesis of heterocyclic compounds are achieved by reactivity of Vilsmeier Haack reagent towards activated methyl and methylene moiety of the substrate leading to its cyclization or the sequential transformation involving the use of nitrogen and oxygen of substrate as nucleophile under vilsmeier condition.

Keywords:

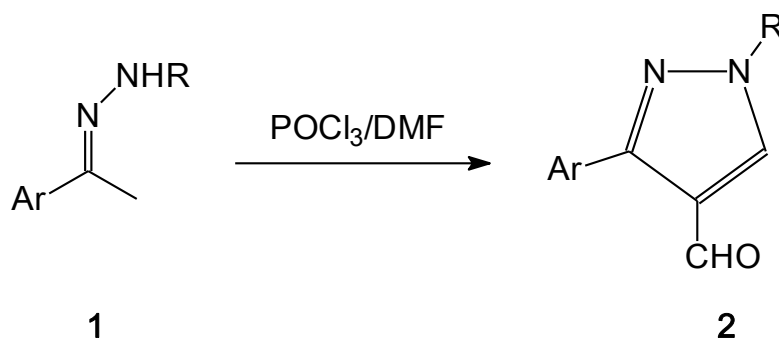
Vilsmeier-Haack Reagent, formyl pyrazole, quinolines, chromones.

Heterocycles belong to one of the most important and widely studied branch of organic chemistry. They have attracted interest of chemists, biologists and pharmaceutical chemists due to their significant biological and therapeutic activities. Furthermore most of the natural products are also associated with heterocyclic system. All the alkaloids are

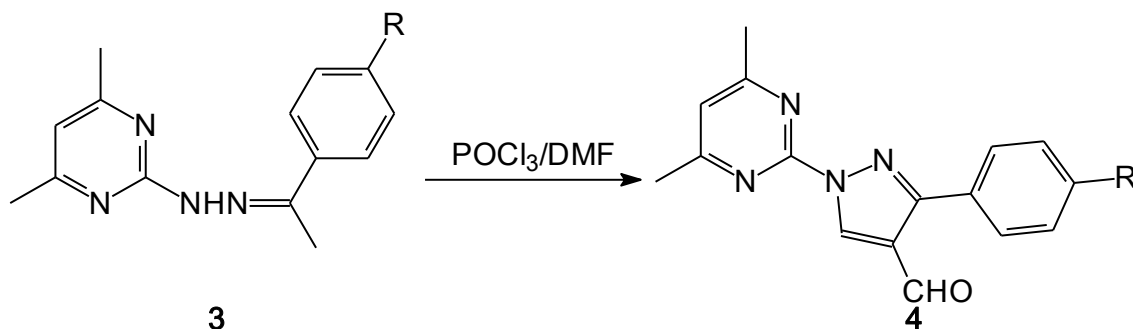
derived from heterocyclic compounds. Moreover, heterocycles are also present in fossil fuels. Continuous research work in the area of heterocyclic chemistry has led to the discovery of various medicinally important compounds.

The Vilsmeier Haack reagent has attracted the attention of synthetic organic chemists since its discovery. Besides a very useful formylating agent,¹⁻⁴ the reagents have been used for the synthesis of various heterocyclic compounds.⁵⁻¹⁴ The synthesis of heterocyclic compounds are achieved either by cyclization of open chain substrates by using POCl₃/DMF or the sequential transformation of substrate heterocyclic compounds using POCl₃/DMF to obtain heterocyclic compounds

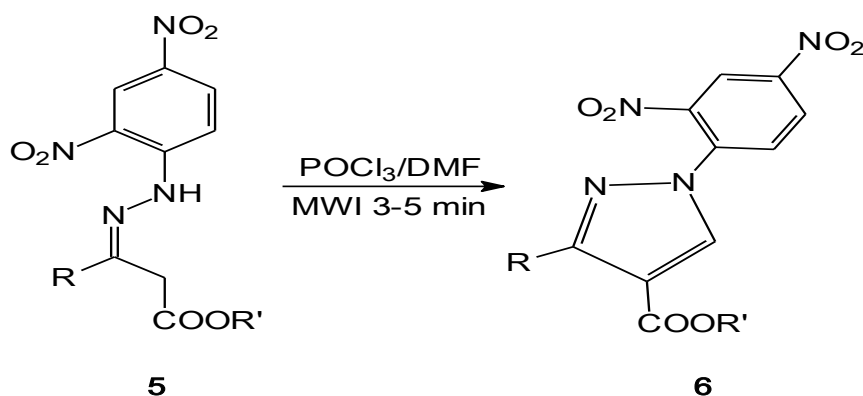
Vilsmeier Haack reaction has been used extensively for the carbon-carbon bond formation and is a very useful method for the formylation of active methylene. As in case of acetophenone hydrazones **1** double formylation followed by cyclization has been reported to yield 4-formyl pyrazoles **2**.¹⁵



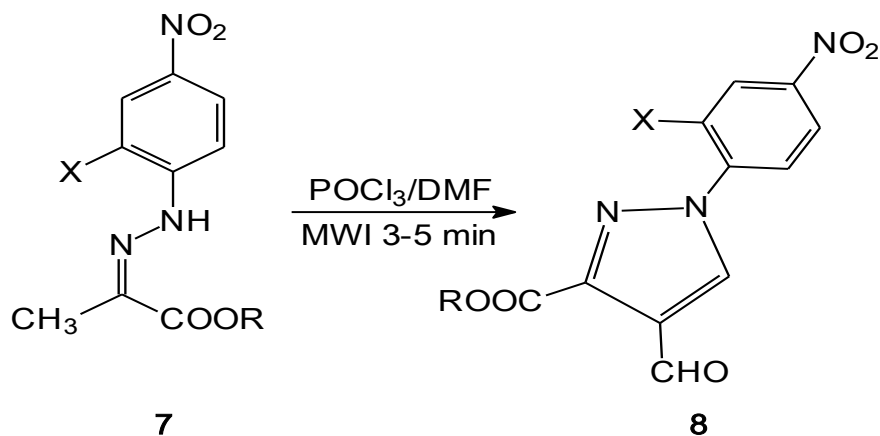
Synthesis of 3-aryl-1-(4,6-dimethyl-2-pyrimidinyl)-4-formylpyrazoles (**4**) has been reported by reaction of 4,6-dimethylpyrimidinyl hydrazones of various acetophenones **3** with POCl_3/DMF ¹⁶



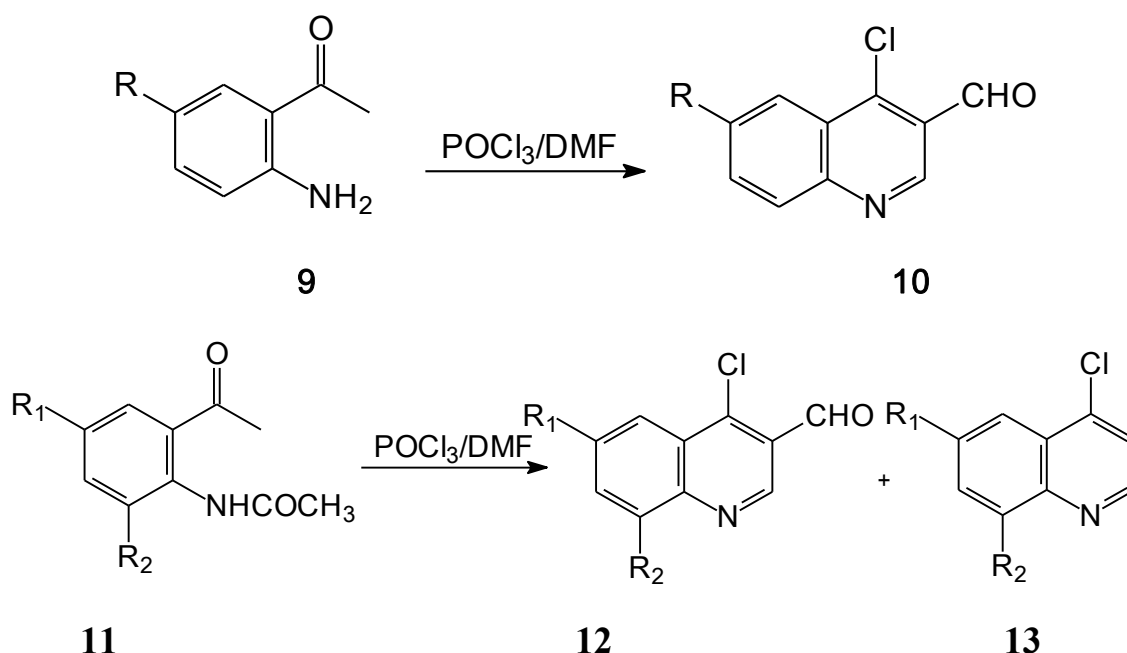
Hydrazones of β -keto esters **5** upon treatment with three equivalents of Vilsmeier reagent gives 1(*H*)-pyrazole-4-carboxylate **6**.^{17,18}



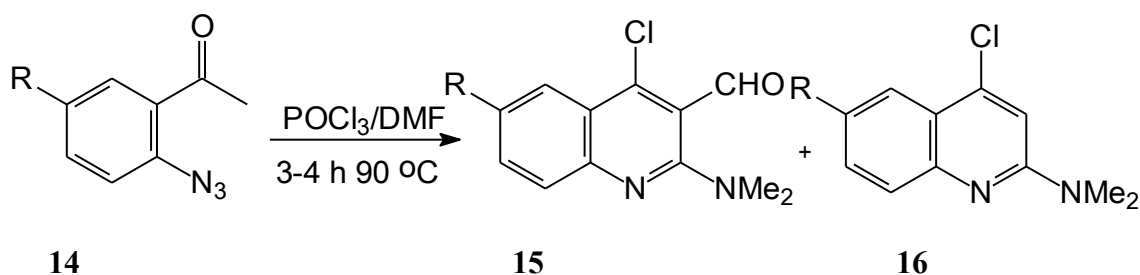
Synthesis of 2,4-dinitrophenyl-4-formyl-1(*H*)-pyrazole-3-carboxylate (**8**) has been achieved from hydrazones of α -keto esters **7** upon treatment with Vilsmeier reagent.¹⁹



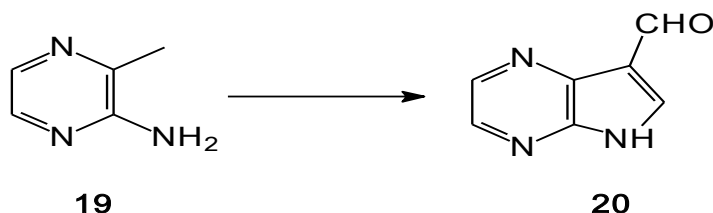
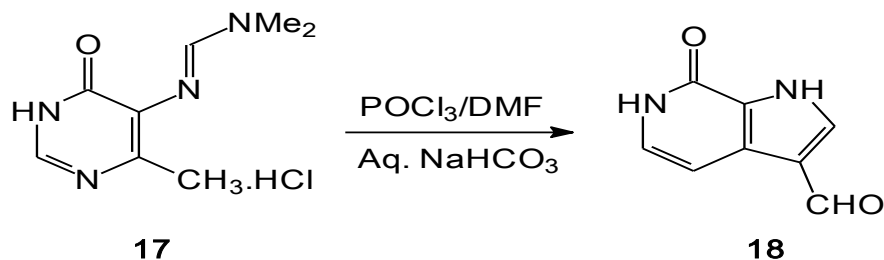
Vilsmeier cyclization of various substituted *o*-aminoacetophenones have also been reported. 1-(2-aminophenyl)ethanone **9** on treatment with Vilsmeier reagent at 90 °C for 3-6 hours yield 4-Chloro-3-quinolinecarboxaldehyde **10** whereas substituted *N*-[2-(1-oxoethyl)phenyl]acetamides **11** afford both 4-Chloro-3-quinolinecarboxaldehyde **12** and 4-chloroquinoline **13**.^{20,21}



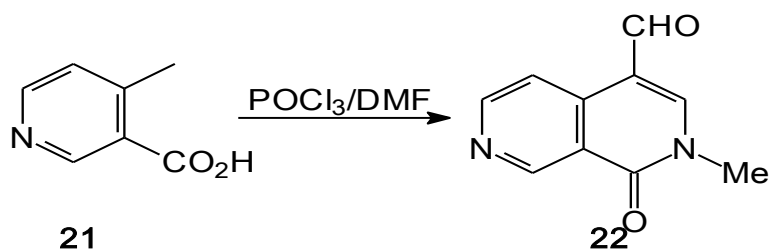
1-(2-azidophenyl)ethanone on treatment with Vilsmeier reagent yields 4-chloro-2-dimethylamine-3-quinoline carboxaldehyde and 4-chloro-2-dimethylaminoquinoline. Thus, Vilsmeier Haack reaction of *o*-azidoacetophenone **14** at 90 °C for 3-4 hours affords 4-chloro-2-dimethylamino-3-quinoline carboxaldehyde (**15**) in 35% yield along with 4-chloro-2-dimethylaminoquinoline (**16**) in 55% yield.^{22,23}



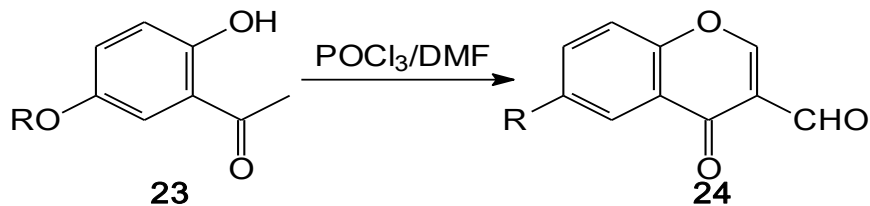
Vilsmeier-Haack reaction of pyrimidinyl methyl group in compound **17** provides the synthesis of pyrrolopyrimidine carboxaldehyde **18**.²⁴ Similarly reaction of 2-amino-3-methylpyrazine (**19**) with POCl_3/DMF gives pyrrolopyrazine carboxaldehyde (**20**) in 56% yield.²⁵



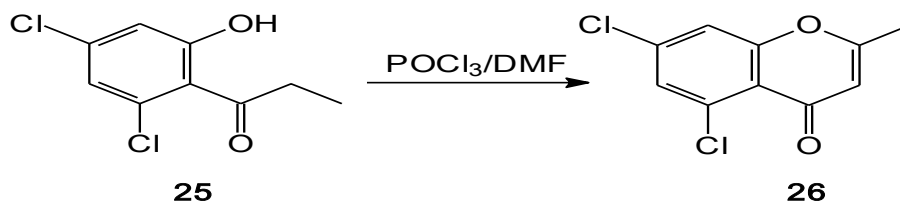
Carboxy group attached to the aromatic ring as in compound **21**, in an adjacent position to active site or group on cyclization with POCl_3/DMF provides a 2-pyridine moiety **22**.²⁶



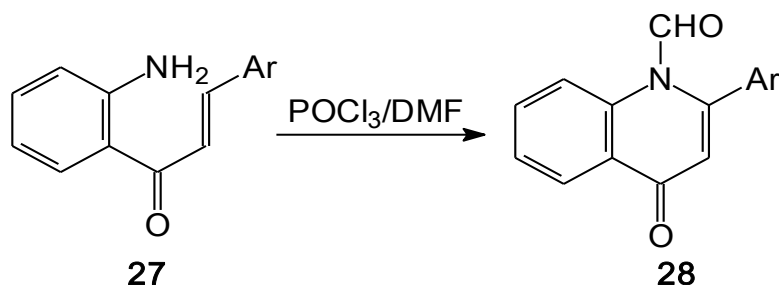
In case of *o*-hydroxyacetophenones **23** double formylation followed by cyclization has been reported to yield 3-formyl chromones **24**.²⁷



3-Methylchromones **26** can also be obtained from propiophenone **25** by treating with POCl_3/DMF .²⁸



2'-Aminochalcones **27** under Vilsmeier condition undergo *N*-formylation followed by ring closure to give 2-aryl-4-chloro-*N*-formyl-1,2-dihydroquinolines (**28**).²⁹



Conclusion: The search for new, efficient synthetic routes with high degree of selectivity to various heterocycles, remains the focus of intense exploration. The main objectives for evolving new synthetic strategies are i) to synthesize new heterocyclic systems with specified structural variations as demanded for medicinal purposes ii) to simplify the existing multistep syntheses.

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