SYNLETT Spotlight 55

Vilsmeier–Haack Reagent (Halomethyleneiminium Salt)

Compiled by Tasneem

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

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Introduction

The Vilsmeier–Haack reagent (halomethyleneiminium salt) formed from the interaction of dialkyl formamides such as DMF with POCl_3 has attracted the attention of synthetic organic chemists since its discovery in 1927.¹ It is one of the most commonly used reagents for the intro-

duction of an aldehydic (CHO) group into aromatic and heteroaromatic compounds.²

Some interesting cyclisation reactions have also been reported under Vilsmeier conditions.³ In addition, certain striking applications eg halogenation, alkylation (methylation) and haloalkylation have been recently reported.⁴

Abstract

(A) Rajanna et al reported that acetanilides, particularly deactivated acetanilides, undergo Vilsmeier–Haack cyclisation in micellar media to afford the corresponding 2-chloro-3-formyl quinoline derivatives in good yields. This procedure works efficiently in the presence of micelles i.e. CTAB (cetyltrimethylammonium bromide), SDS (sodium dodecylsulfate) and TX (Triton-X-100) under reflux conditions. Surprisingly, the reaction time was reduced up to 10-fold in the present method.⁵ Under ultrasonic irradiation, the reaction times were even more reduced with dramatic enhancement in the yield of reaction products.⁶

- (i) POCl_3 -DMF, CTAB, CH_3CN , reflux, 45–90 min.
- (ii) POCl_3 -DMF, SDS, CH_3CN , reflux, 45–90 min.
- (iii) POCl_3 -DMF, Triton-X-100, CH_3CN , reflux, 45–90 min.

(B) Alkyl diacylacetals are efficiently converted into 2,6-dichloro-3-formyl benzoates using the Vilsmeier–Haack reagent under microwave irradiation. The reaction time has been decreased from hours to seconds.⁷

(C) Cheng et al. reported the formation of unexpected products from the formylation of *N,N*-dimethylanilines with 2-formamidopyridine in POCl_3 under Vilsmeier–Haack reaction conditions. 2-Formamidopyridine in POCl_3 solution reacts with *N,N*-dimethylaniline to give tris(4-dimethylaminophenyl)methane in 80% yield, whereas with 4-*N,N*-dimethylaniline it gives 2-dimethylamino-5-phenyl(2-*N*-methylformamido-5X-Phenyl)(2-pyridylamino)methane.⁸

(D) 2-Chloro-3-pyridine carboxaldehydes were synthesised for the first time by Vilsmeier–Haack reaction of 4-aryl-3-buten-2-one oxime. The reaction proceeds via the formation of *N*-(2-arylethenyl) acetamides as intermediates.⁹

(E) Lellouche et al reported that the two electrophilic Vilsmeier–Haack complexes formed from POCl₃–DMF or (CF₃SO₂)₂O–DMF react with C₂-symmetrical dialkoxysilanes R¹O–Si(R²)₂–OR¹ affording the corresponding formates R¹CHO in low/medium to high yields depending on conditions and substrates.¹⁰

(F) POCl₃–DMF over silica gel has been used for the synthesis of β-chlorovinylaldehydes, 2-aryl-3-formylindoles, 2-chloro-3-formylquinolines and other aromatic aldehydes using solvent-free conditions and microwave irradiation. The Vilsmeier–Haack reaction was performed in 1.5–2.5 minutes under microwave irradiation in solvent-free conditions with good yields. Furthermore, the present method is rapid and efficient and avoids the use of the reagent as solvent and thus is environmentally friendly.¹¹

References

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