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

Formaldehyde
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Introduction

Formaldehyde is one of the most used one-carbon synthons in organic chemistry. It is widely applied in industrial and laboratorial processes, namely in the synthesis of polyoxymethylene plastics or in the preparation of important synthetic intermediates and bioactive compounds in pharmacological research. Formaldehyde, both in mono and polymeric form (called paraformaldehyde) is a versatile building block being used in a large variety of chemical reactions at different conditions. Formaldehyde exhibits most of the chemical properties of other aldehydes, and thus, it is a good electrophile both in electrophilic addition and electrophilic aromatic substitution or condensation reactions. Over the past five years, formaldehyde was used in Mannich-type and Kabachnik–Fields multicomponent condensations for the preparation of aminomethyl derivatives with potential biological application. Also, it is suitable to undergo Wittig or Horner–Wadsworth–Emmons olefinations, Pictet–Spengler reaction in aqueous media, Diels–Alder cycloadditions, and microwave-assisted solvent-free reactions.

Preparation

Formaldehyde is industrially prepared by the catalytic vapor-phase oxidation of methanol using either silver metal or iron and molybdenum mixtures as catalysts, to yield a colorless gas. It is also commercially available as its polymeric form paraformaldehyde or in aqueous or organic stock solutions. Paraformaldehyde forms slowly in aqueous formaldehyde solutions as a white precipitate.

Abstracts

(A) Mannich-Type Synthesis of Propargylamines:
Bieber and da Silva reported a mild, easy, and efficient synthesis of propargylamines by copper(I) iodide catalyzed Mannich reaction of terminal alkynes with aqueous formaldehyde and secondary amines. The aminomethylation was conducted in DMSO and high to quantitative yields were obtained.

(B) Synthesis of Mannich Bases Related to Gramine:
Indoles have potent biological activity and are one of the most important subjects in heterocyclic chemical research. The preparation of several gramines by Mannich reaction of paraformaldehyde, a secondary amine and indole/N-methylindole was reported by Dai et al. Using zinc(II) chloride as mediator, the indoles were obtained in 58–98% yields.

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(C) Piperazines by Ugi Four-Component Condensation:
Giovenzana et al. described the preparation of diamines by modified Ugi four-component reaction of several isocyanides, paraformaldehyde, carboxylic acids, and diamines. The method was particularly useful in the preparation of piperazines in methanolic solution, and good to quantitative yields were achieved. In addition, the authors extended the applicability of the Ugi multicomponent reaction in synthetic and medicinal chemistry research.5

(D) Solvent-Free, Microwave-Assisted Synthesis of Phosphono- and Phosphinoxidomethylated N-Heterocycles:
Keglevich and co-workers prepared N-phosphono and N-phosphino derivatives from the condensation of paraformaldehyde, N-heterocycles, and diethylphosphite or diphenylphosphine. The reactions were conducted in environmentally friendly manner under solvent-free, microwave-assisted conditions, representing a green alternative to traditional techniques. A variety of N-phospho derivatives was swiftly synthesized in high yields (70–92%) with excellent purity levels.6

(E) Diastereoselective Synthesis of Pyrrolidines by Horner–Wadsworth–Emmons Olefination:
In the reported synthesis, oxoalkanones undergo reaction with hexyl- or benzylamines to yield phosphorylpyrrolidinones. The Horner–Wadsworth–Emmons olefination of these intermediates with paraformaldehyde yields 60–95% of pyrrolidinones with excellent diastereoselectivity.7

(F) Synthesis of 1,3-Dioxanes via Prins Reaction:
1,3-Dioxanes are important compounds in drug discovery, displaying potent biological activity. Recently, Yadav et al. reported a new eco-friendly method for the preparation of 1,3-dioxane derivatives using molecular iodine as catalyst. The Prins reaction of a variety of alkyl- or aryl-substituted alkenes with paraformaldehyde afforded a library of these compounds in excellent yields.8

(G) Glycosyls via Diels–Alder Reaction:
Vankar and co-worker described the synthesis of C-glycosyl aminoacids via Diels–Alder reaction of methyl nitroacetate and formaldehyde, generating in situ α-nitro methyl acrylate, with glacial dienes. Single-pot reduction and acetylation of the resulting cycloadducts afforded the glycosyls in good yields with considerable stereoselectivity (85:15). This class of compounds is target of extensive research in drug discovery due to its biological properties.9

References