SYNLETT Spotlight 362

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

Aqueous Formaldehyde

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Introduction

Between the different sources of formaldehyde as a C_1 synthon in organic synthesis, the use of a commercial aqueous solution is the most convenient. It avoids the tedious and harmful procedures to generate the formaldehyde monomer from formaldehyde oligomers such as paraformaldehyde and trioxane. Besides being an inexpensive and commercially available reagent, aqueous formaldehyde is a good electrophile and has been used in various organic transformations, such as N-methylation

and α -methylation of carbonyl compounds, aminomethylation, hydroxymethylation, Prins reaction and Wittig-type methylenation. A recently published Spotlight on formaldehyde¹ has mentioned only one case of use of the aqueous solution, the synthesis of propargylamines.² In this review a more complete extension of the use of aqueous formaldehyde is presented. The usual process for producing formaldehyde is by oxidative dehydrogenation of methanol using iron metal or its mixtures with molybdenum.³

Abstracts

(A) Aminomethylation of Organic Halides:

Estevam et al. developed a one-pot, three-component reaction of secondary amines, aqueous formaldehyde and organic halides promoted by zinc in aqueous medium to obtain tertiary amines. The Mannich reaction Barbier-type alkylation and allylation of iminium ions generated in situ is conducted in the presence of copper(I) iodide in high yield.⁴

(B) Reductive Methylation of Amines:

Selective mono- or dimethylation of primary amines and amino acids with aqueous formaldehyde is promoted by non-activated zinc in aqueous medium. Secondary amines are also easily methylated by this methodology. The method is based on the reduction of iminium ions and high to quantitative yields are obtained under mild conditions.⁵

(C) Asymmetric Hydroxymethylation:

Ishikawa et al. reported the hydroxymethylation of silylenol ethers with aqueous formaldehyde to obtain α -hydroxymethylated ketones with high enantioselectivity using a novel chiral scandium complex. The α -hydroxymethylation was conducted in H_2O -DME (1:9) and the products were obtained in moderate to excellent yields.⁶

(D) α -Hydroxymethylation of Cycloalkanones:

Mase et al. recently reported the synthesis of the (*S*)- α -hydroxymethylcycloalkanones using aqueous formaldehyde in the presence of L-threonine. These compounds, obtained in moderate to good yields, are important intermediates in the synthesis of chiral lactones.⁷

(E) Synthesis of 1,3-Dioxanes:

The class of 1,3-dioxane compounds has received much attention because of their useful pharmacological properties. Direct use of aqueous formaldehyde in the Prins cyclization is highly desirable from the viewpoint of both economy and safety. 1,3-Dioxane derivatives were prepared from styrenes in moderate to high yields using trifluoromethanesulfonic acid as catalyst.⁸

(F) Synthesis of Diarylmethanes:

Hua et al. demonstrated that ReCl(CO)₅ catalyzes the condensation of aromatic compounds with aqueous formaldehyde to afford diarylmethane derivatives. This dehydration-type reaction was conducted in solvent-free conditions to give products in good yields.⁹

(G) α -Methylenation of Aldehydes:

Erkkila et al. described a rapid and convenient method for the methylenation of aldehydes to 2-substituted acroleins using aqueous formaldehyde and pyridine/propanoic acid as catalyst. In this Mannich-type reaction the products were obtained in good to excellent yields.¹⁰

(H) Aza-Diels–Alder Reaction:

Córdova and co-workers reported a one-pot three-component direct catalytic enantioselective aza-Diels–Alder reaction. (*S*)-Proline catalyzed the reaction between α,β -unsaturated cyclic ketones, aqueous formaldehyde, and aryl amines. Azabicyclic ketones were prepared in moderate to high yield and very good enantioselectivity.¹¹

References

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