

SYNLETT Spotlight 272

Alkyl Orthoformate: A Versatile Reagent in Organic Synthesis

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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

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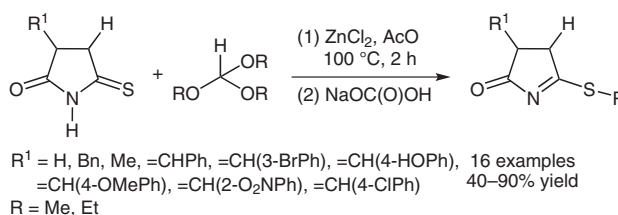
Introduction

Alkyl orthoformates are important intermediates for organic synthesis, widely used in medicines, pesticides and flavors. Alkyl orthoformates, in general, are transparent liquids that decompose in water and are soluble in methanol and chloroform. Alkyl orthoformates in acid media generate alkoxonium, which is a powerful electrophilic agent used as one carbon building block, and two alcohol

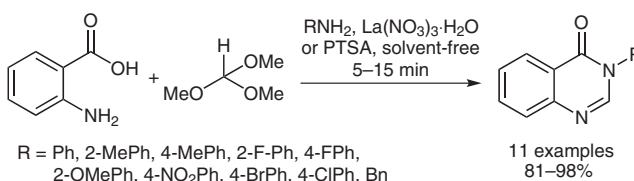
molecules, which constitutes an important protecting groups. Alkyl orthoformates have also been reported as highly selective O, S and C-alkylating agents due to their ability to furnish methyl groups by releasing methyl formate, which is a good leaving group. Thus, alkyl orthoformates are versatile chemical reagents, used to supply nucleophilic oxygen and electrophilic carbon atoms. Recent applications of alkyl orthoformates are shown below.

Abstracts

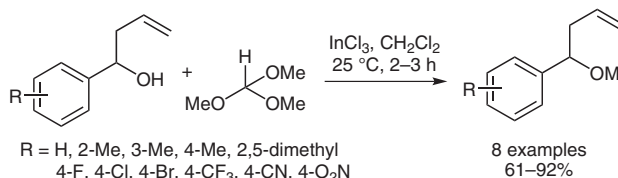
(A) Thiohydantoin and their derivatives represent an important class of biologically active molecules with many medicinal and agrochemical applications. Thiohydantoin underwent a one-pot chemoselective S-alkylation and acetylation by alkyl orthoformate in the presence of ZnCl_2 and acetic anhydride. The reaction furnished the desired S-alkylated products in moderate to good yields.¹



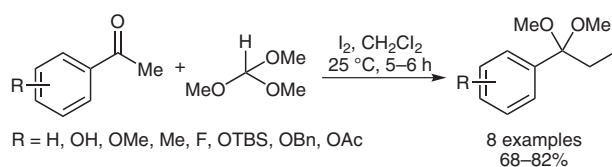
(B) Trimethyl orthoformates have been used extensively in heterocyclic synthesis. 4(3*H*)-Quinazolinones were chosen over other heterocycles because of their numerous biological properties. 4(3*H*)-Quinazolinones were obtained in good yields from the reaction of trimethyl orthoformate and 2-aminobenzoic acid in Lewis or Brønsted acid.^{2–4}



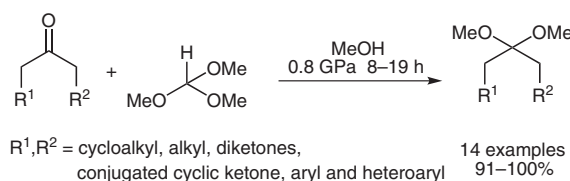
(C) Recently, Beifuss et al. developed a new synthesis for homoallyl ethers by the reaction of trimethyl orthoformate with 1-arylbut-3-en-1-ols with a Lewis acid.⁵ The homoallyl ethers were isolated in moderate to good yields.



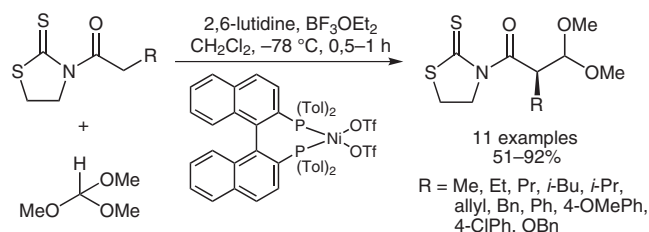
(D) Recently, Yadav et al. prepared α -iodo dimethyl acetal using molecular iodine and trimethyl orthoformate in good yields.⁶ The advantage of this reaction is that the protocol tolerated common protecting groups such as *tert*-butyldimethylsilyl, benzyl and acetate.



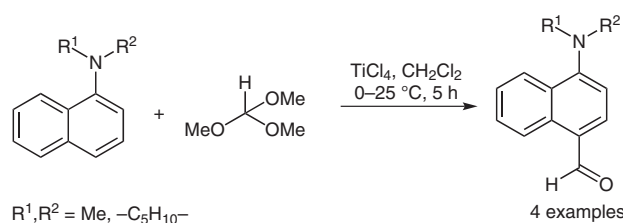
(E) The reaction of aldehydes and ketones with trimethyl orthoformate is one route to obtain the protection of the carbonyl group. The water scavenger property of trimethyl orthoformate is explored in a high-pressure-promoted uncatalyzed acetalization of ketones. The acyclic and cyclic acetals were obtained in excellent yields.⁷



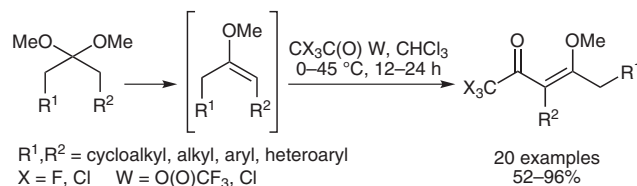
(F) Evans and Thonsom developed a nickel(II) (*S*)-Tol-BINAP catalyzed trimethyl orthoformate alkylation of *N*-acylthiazolidinethiones.⁸ This study demonstrates an effective method for introducing acetal functionality with high enantioselectivity. The *N*-acylthiazolidinethione moiety formed is cleaved to alcohol, ester or Weinreb amide, and the acetal can serve as an effective functional handle for numerous transformations.



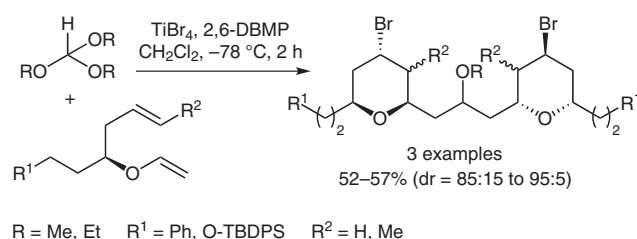
(G) Periasamy et al. reported the use of trimethyl orthoformate in formylation reactions of aromatic amines.⁹ The reaction was performed using TiCl_4 at room temperature to give the formyl derivatives in good yields. Since these formyl derivatives are readily accessed using the $\text{TiCl}_4/(\text{MeO})_3\text{CH}$ reagent system, this procedure has considerable synthetic potential.



(H) One important application of trimethyl orthoformate is in acylation reactions in which the acetal generated vinyl ethers in situ. This one-pot procedure furnished 4-alkoxy-1,1,1-trihalo-3-alken-2-ones, an important building block in heterocyclic synthesis.¹⁰⁻¹²



(I) The Mukaiyama aldol–Prins reaction is an alternative tandem process in which an oxocarbenium generated from the Mukaiyama aldol addition undergoes an intramolecular Prins reaction to produce tetrahydropyrans. A modified Mukaiyama aldol–Prins reaction involved cyclization of vinyl ethers with alkyl orthoformates using a Lewis acid. Overall, six new stereocenters were generated in this single reaction.¹³



References

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