SYNLETT
Spotlight 293Methyl Acetoacetate: A Useful
Reagent in Multicomponent
Reactions

Tasneem Parvin

Tasneem Parvin was born in Cooch Behar, West Bengal, India, in 1983. After obtaining her B.Sc. degree in 2004 from North Bengal University, she joined the Indian Institute of Technology Guwahati and obtained her M.Sc. degree in chemistry in 2006. Subsequently, she started her doctoral work in the same institute under the supervision of Prof. Khan. Her current research interest includes multicomponent reactions, development of new synthetic methodologies using both homogeneous and heterogeneous catalysts, and synthesis of bioactive natural products.

Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati-781 039, India
E-mail: t.parvin@iitg.ernet.in

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

Introduction

Methyl acetoacetate is considered as a model β -keto ester, and widely used in various multicomponent reactions for the creation of diverse molecular scaffolds. The dawn of methyl acetoacetate as an important multicomponent substrate began in 1982 by the discovery of Hantzsch's dihydropyridine synthesis.¹ The reagent exhibits interesting

reactivity pattern in multicomponent reactions depending on the reaction conditions, type of reactions, and involved catalysts. The highly synthetic potential of this easily accessible reagent has found numerous applications, especially in the synthesis of complex heterocyclic structures.² An overview of the different reactivity of this versatile substrate in multicomponent reaction is presented below.

Abstracts

(A) *Synthesis of 1,5-Benzodiazepines*: Fujioka et al. developed a one-pot, three-component reaction of aromatic aldehydes, 1,2-phenylenediamine, and methyl acetoacetate in the presence of a catalytic acid producing 1,5-benzodiazepines.³ This reaction involves the γ -selective C–C bond formation of methyl acetoacetate.

(B) *Synthesis of Piperidines*: Recently Khan et al. reported a convenient method for the preparation of highly functionalized piperidines from the combination of aromatic aldehydes, amines, and methyl acetoacetate in the presence of a catalytic amount of bromodimethylsulfonium bromide (BDMS).⁴ Replacing methylacetoacetate by diethyl malonate in the presence of the same catalyst yields the Mannich-type products.⁵

(C) *Synthesis of Substituted Pyrazoles*: Substituted pyrazoles have received much attention because of their useful pharmacological properties. Quian et al. reported a convenient synthesis of substituted pyrazoles via a three-component condensation of phenylhydrazine, aldehydes, and methyl acetoacetate using [Yb(PFO)₃] as catalyst.⁶

(D) *Synthesis of Polyhydroquinolines*: Kumar and co-workers synthesized polyhydroquinolines using a four-component coupling reaction of cyclic 1,3-diketone, aldehydes, methyl acetoacetate, and ammonium acetate in aqueous micelles catalyzed by PTSA.⁷ These derivatives possess a variety of biological activities such as vasodilator, bronchodilator, antitumor, hepatoprotective, and geroprotective activity.

(E) *Multicomponent One-Step Fusion of Biopertinent Pyrimidine Heterocycles*: Biginelli's dihydropyrimidone (DHPM) synthesis has recently attracted a great deal of attention since DHPM is an important heterocyclic motif with a wide spectra of biological activities. Recently, Kwak and co-workers developed an efficient, simple, and high-yielding protocol for the synthesis of DHPMs and DHPM thiones involving a three-component, one-pot assembly of aldehydes, methyl acetoacetate, and urea/thiourea using readily available tetrachlorosilane as a catalyst.⁸

(F) *One-Pot Synthesis of Tetrahydropyridines*: The multicomponent condensation of methyl acetoacetate, acrolein and (S)-2-phenylglycinol was found to provide a one-pot access to chiral 6-carbonyl-3-phenyl-2,3,8,8a-tetrahydro-7H-[1,3]oxazolo[3,2-a]pyridines⁹ which are proved to be useful intermediates for the preparation of various natural products such as matrine, cytosine, and tashiromine.

(G) *Synthesis of 4-Aryl-2-cyanoimino-3,4-dihydro-1H-pyrimidines*: Recently, Hulme et al. explored the construction of 4-aryl-2-cyanoimino-3,4-dihydro-1H-pyrimidine (aryl-CIDHPM) compounds containing the N-cyanoguanidiny moiety.¹⁰ Methyl acetoacetate has played a vital role in this reaction. The authors have explored the multicomponent reaction of arene or hetero arene carb-aldehyde, methyl acetoacetate, and cyanamide under acidic conditions for the preparation of these compounds.

(H) *Synthesis of β-acetamido carbonyl compounds*: Khan et al. reported a new methodology for the one-pot synthesis of β-acetamido carbonyl compounds using aldehydes, methyl acetoacetate, acetonitrile/benzonitrile, and acetyl chloride in presence of a Lewis acid catalyst.^{11,12} These compounds are valuable building blocks for the preparation of 1,3-amino alcohols or β-amino acids, as well as for the synthesis of various bioactive molecules.

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