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A Facile Multicomponent Synthesis of Ethyl-1,2,3,4-tetrahydro-6-methyl-2-oxo pyrimidine-5 carboxylate and Its Derivatives

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ABSTRACT

Multicomponent one pot synthesis of dihydropyrimidinone with different aldehydes reacts with ethyl acetoacetate, urea in presence of zirconium chloride on refluxing with ethanol. This multicomponent synthesis is novel in the sense that it preserves the simplicity, time consuming and improves the yields.

Keywords: Ethylacetoacetate, Urea, Zirconium chloride, Dihydropyrimidinone

INTRODUCTION

Multicomponent component reactions constitute an especially attractive, rapid conversion to large libraries of organic compounds with high yield and diverse substitution patterns. Multicomponent is a one-pot reactions, it is easier to carry out than multi step synthesis. In this view considering an important development in the drug discovery with rapid identification, optimization of biologically and pharmacologically important compounds. This multicomponent reaction is used for time consuming with high yield production process for new compound synthesis. With a small set of starting materials, very large libraries can be buildup within a short time, which can then be used for research on medicinal substances with good yield. The development of new and synthetically valuable multicomponent reactions remains a challenge for both academic and industrial researchers. Reactant can be converted into desired product is called as 'ideal synthesis'.

A few steps as possible with good yield and by using environmentally compatible reagents. In multistep syntheses, if the number of steps increased with decrease the yield of final product. Number of steps in multistep reaction increase with increase time for production of compound. Strecker [1], first modern contribution to the development of multicomponent chemistry was made. Further in 1882, progress of multicomponent reaction work by Hantzsch [2]. He synthesized substituted dihydropyridines from ammonia, aldehydes and two equivalents of β-ketoesters. Radziszewski [3] reported the multicomponent synthesis of imidazole by the reaction with diketone, formaldehyde, methylamine and ammonia. Hantzsch [4] synthesis of pyrroles by reacting primary amines, β-ketonesters and α-halogenated β-ketoesters. In 1883, the Biginelli reaction [5] represents multicomponent synthesis of substituted dihydropyrimidines by acid-catalyzed cyclocondensation of β-ketoesters with aromatic aldehydes and urea.

The first important application of multicomponent reaction in natural product synthesis was done by Robinson [6] in 1917 on synthesis of alkaloid tropinone from succinic dialdehyde with methylamine and dimethyl-3-oxopentanedioate. Passerini [7] discovered in 1921, the first MCR involving isocyanide. Bucherer and Bergs [8,9], described a four-component (multicomponent) reaction for the synthesis of hydantoins. One-pot reaction of hydrogen cyanide, aldehyde, ammonia and Carbon dioxide afforded hydantoins, which can be easily transformed into α-amino acids by hydrolysis. Gewald [10] studied on the synthesis of polysubstituted thiophenes. Four-component reaction of the isocyanides introduced by Ugi et al. [11], referred to as the Ugi reaction. The U-4CRs are one pot reactions of amines, carbonyl compounds, acids, and isocyanides. A mixture of a secondary amine, cyclic keto compound, hydrazoic acid and isocyanide on refluxing together undergoes U-4CR to form substituted tetrazole [12]. Asinger and Offermanns [13] reported the synthesis of thiazolines from α-halogenated carbonyl compounds and sodium hydrogen sulfide *in situ* thiols reacted with carbonyl compounds and ammonia.

U-4C Reaction of a mixture of isocyanide, an amine, an oxo compound and CO_2 under pressure leads to the formation of α-aminoamide [14]. A-4CR and U-4CR are proved to be shortest known synthesis of penicillin derivative. A-4CR (Asinger-4 component reaction) of a mixture of NaSH, the α-bromoaldehyde, the aldehyde and ammonia leads to the formation of thiazolidine. This thiazolidine undergoes U-4CR reaction with β-amino acid, oxo compound and an isocyanide to yield penicillin derivative containing β-lactam ring [15]. According to Nuclear Magnetic Resonance (NMR) studies, the product has the same relative configuration as natural penicillin Grieco et al. [16], reported the three component synthesis of piperidine by the reaction of benzaldehyde, aniline, cyclopenta-1,3-diene in the presence of Trifluoroacetic Acid (TFA) and methyl cyanide.

The concepts of unions of two or more multiple component reactions have been recently reported. Such combinations of Multi-component Reactions (MCRs) are possible if the starting materials are well-chosen. The reactions resulting from the union concept offer a greater structural variety than the simple MCRs. A remarkable "seven compound reaction" is, for example, the transformation of the α-bromoaldehyde with NaSH, another oxo compound and ammonia in an A-4CR reaction to form the thiazoline which undergoes a U-4CR reaction with the isocyanide in methanol and under CO_2, affording the thiazolidine [17].

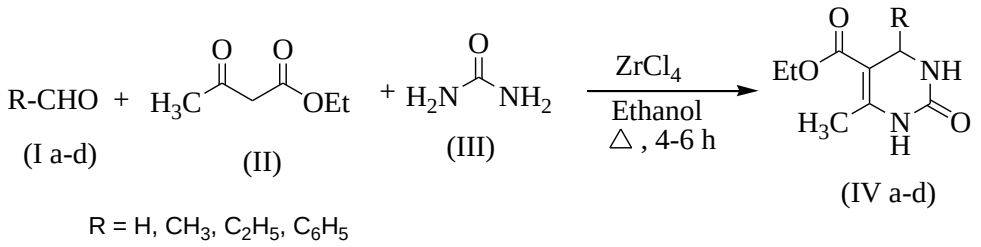
EXPERIMENTAL SECTION

Melting points were determined in open capillary tube with anhydrous substance and were uncorrected. Infra-Red (IR) spectra of the newly synthesized compound were recorded with potassium bromide pellets technique, ^{1}H-NMR spectra were recorded with the help of Avance 300 MHz Spectrometer in Dimethyl sulfoxide (DMSO) using Tetramethylsilane (TMS) as internal standard. Mass spectra of the compound were recorded on a FT VG-7070H. Mass Spectrometer using EI technique at 70 eV is used. All the reactions of the newly synthesized were monitored by Thin Layer Chromatography (TLC).

MATERIAL AND METHODS

Multicomponent synthesis of ethyl-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate and its derivatives (IVa-d)

The multicomponent reaction of aldehydes (I a-d) with ethylacetoacetate (II) and urea (III) in presence of 10 mol% zirconium chloride on refluxing with ethanol to give the ethyl-1,2,3,4-tetrahydro-6-methyl-oxopyrimidine-5-carboxylate and its derivatives (IVa-d). This multicomponent synthesis is novel in the sense that it preserves the simplicity, time consuming and improves the yields (Scheme 1).



Scheme 1: Multicomponent synthesis

Multicomponent synthesis of ethyl-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate (IV-a)

The reaction of formaldehyde (I-a) with ethylacetoacetate (II) and urea (III) in the presence of 10 mol % zirconium chloride on refluxing with ethanol to give the ethyl-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate and its derivatives (IVa).

Multicomponent synthesis of ethyl-1,2,3,4-tetrahydro-4,6-dimethyl-2-oxopyrimidine-5-carboxylate (IV-b)

The reaction of acetaldehyde (I-b) with ethylacetoacetate (II) and urea (III) in the presence of 10 mol % zirconium chloride on refluxing with ethanol to give the ethyl-1,2,3,4-tetrahydro-4,6-dimethyl-2-oxopyrimidine-5-carboxylate and its derivatives (IVb).

Multicomponent synthesis of ethyl-4-ethyl-1,2,3,4-tetrahydro-4,6-dimethyl-2-oxo pyrimidine-5-carboxylate (IV-c)

The reaction of propionaldehyde (I-c) with ethylacetoacetate (II) and urea (III) in the presence of 10 mol % zirconium chloride on refluxing with ethanol to give the ethyl-4-ethyl-1,2,3,4-tetrahydro-4,6-dimethyl-2-oxopyrimidine-5-carboxylate and its derivatives (IVc).

Multicomponent synthesis of ethyl-1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenyl pyrimidine-5-carboxylate (IV-d)

The reaction of benzaldehyde (I-d) with ethylacetoacetate (II) and urea (III) in the presence of 10 mol % zirconium chloride on refluxing with ethanol to give the ethyl-1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenyl pyrimidine-5-carboxylate and its derivatives (IV-d).

RESULTS AND DISCUSSION

Multicomponent reactions is very important for time consuming and high yielding one pot reaction, especially attractive recent synthetic strategy used for large number of organic compounds synthesized very easily with diverse substitution pattern. In this research, we report the multicomponent synthesis of novel fused heterocyclic compound, ethyl-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate and its derivatives.

CONCLUSION

A facile multicomponent one pot synthesis has been developed for the synthesis of title compounds using readily available starting materials. Ethyl-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate and its derivatives exhibits a diverse range of biological activities such as calcium channel blockers, anticarcinogenic, anti-inflammatory activity etc.

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