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Alumina Supported Synthesis of Some α,β– Unsaturated Heterocyclic Acids

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Abstract

Solid supported synthesis of some novel 3- (5'- substituted-2-furyl/thienyl) propen -2- oic acids has been carried out from malonic acid and 5- substituted furan/thiophene-2-carboxaldehydes under microwave irradiations in solvent free condition. The reaction completed in one step via condensation affording 88-96% of yield within 4-6 minutes. The reactions are accompanied with easy work-up, limited use of organic solvents and the use of inexpensive and hazard- free chemicals.

Keywords: *Solid support, microwave irradiations, condensation, decarboxylation, one pot synthesis, heterocyclic acids.*

Introduction

Heterocyclic compounds cover a wider range of chemotherapeuties[1-3]. Among them, α, β-unsaturated acids have drawn the interest in diverse area of medicinal and biochemistry[4,5]. These are essential units of variety of substances of natural origin like fruits, foods, pheromones,insecticides, pesticides, etc.[6-8] Introduction of heterocyclic moieties into the α, β- unsaturated acids has become an essence of synthetic chemistry for their medical, biochemical and industrial applications.[9,10] Thus, These acids are to be synthesized by efficient and novel methods. The classical method of limited scope is Perkin reaction[11] which is not explored further as it does not seem to be applicable in large molecular diversity. One of the straightforward approaches to these unsaturated acids is Doebner modifications of Knoevenagel reaction[12] which employs aromatic aldehyds, malonic acid and pyridine. This route is fairly large in scope with few exceptions like use of strong organic bases, acids and carcinogenic solvents which are harmful to environment as well[13]. So, several other alternative procedures have been developed using graphite[14], piperidine acetate[15] etc. But most of these processes are hazardous, expensive and very slow with poor yield, which lays the foundation of the development of new efficient synthetic routes.

There are several methods for the synthesis of organic compounds of versatile use, e.g., Biginelli reaction[16], Pechmann's reaction[17] to synthesize quinolines, isoquinolines, quinolinic acids, quinazolinones, oxadiazoles, benzodiazepine, etc. by using alums[18] as catalyst which is a cheap and household material. This ongoing interest in alum catalyst has got recent application in Doebner reaction[19,20] for the synthesis of several homocyclic[21] and heterocyclic[22,23] unsaturated acids or acrylic acids. These recent trends in organic synthesis prompted the author to synthesize novel heterocyclic α, β-unsaturated acids under the solid support of alumina by adopting microwave irradiations in solvent free-condition. A series of 3-(5'- substituted-2'- furyl/thienyl) propen-2-oic acids have been synthesized from molenic acid and furan-2-carboxaldehyde/thiophene-2- carboxaldehyde under solid supported microwave irradiations.

Nowadays, the development of one-pot method has become popular in synthetic organic chemistry. This method requires shorter reaction time and easy work-up with better yield.[24] one-pot method involves

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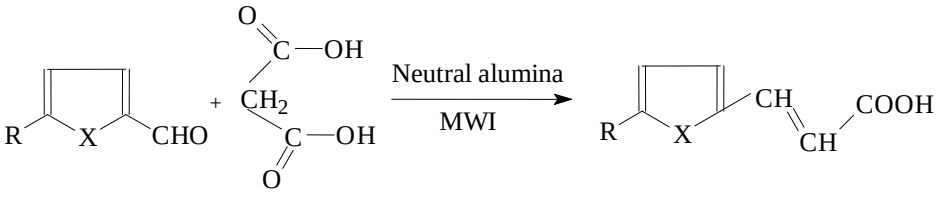
the condensation of reactants in one step to produce the target molecules. On the top of this, synthesis in aqueous media has gained popularity as it is an eco-friendly and economic method which avoids the use of hazardous solvents, acids and bases in the synthetic steps.[25] Aqueous reactions accompanied with microwave irradiations add in green aspects in organic synthesis. Microwave assisted organic synthesis proceeds with facile reactions to provide high yield with less reaction time and avoids the use of excess solvent, and harmful acid and bases that are generally used in the catalysis of the reactions.[26] Reactions can be carried out at ambient pressure in open vessels under solid supports even by using domestic microwave ovens.[27] Different varieties of alumina can be used as solid acids, bases and neutral supports to catalyze the reactions, which reduce the amount of toxic wastes and by- products arising from chemical processes.[28]

Experimental Methods

The reactions were carried out in Kenstar Microwave oven model no. OM9925E at the frequency 2450 MHz and 800W. IR spectra were recorded on Nicolet 5PC FT-IR spectrometer in KBr pellets and the frequency (ν) was measured in cm^{-1}. ^1H NMR spectra were recorded on Brucker DRX-300 FT-NMR spectrometer using tetramethyl silane (TMS) as internal reference at 300 MHz in deuterated chloroform ($CDCl_3$) and chemical shifts (δ) were measured in ppm. Elemental analysis was performed by means of Heraeus CHN-Rapid Analyzer and temperature was measured on Az Mini-Gun Non-contact IR thermometer model no 8868. Melting points were determined on Thomas Hoover melting point apparatus and are uncorrected. The purity of compounds was checked on silica gel G plates using iodine vapour as visualizing agent. All the chemicals were purchased from SD Fine Chemicals Co. Ltd.



(**1a-h**) (**2**) (**3a-h**)

		X/R
a / b	O / S	H / H
c / d	O / S	CH_3 / CH_3
e / f	O / S	Cl / Cl
g / h	O / S	NO_2 / NO_2

Scheme 1

General procedure for the synthesis of 3-(5'- substituted-2'-furyl/thienyl) Propen-2-oic Acids, 3a-h Conventional Method

An equimolar amount (0.01 mole) of malonic acid and 5- substituted-furan/thiophene-2-carboxaldehyde was mixed and dissolved in 25 ml of ethanol in a round bottomed flask. The reactions mixture was then refluxed for 6-8 hours for the completion of reactions. The progress of the reaction was monitored by thin Layer Chromatography (TLC) using silic gel G plates. After completion of the reaction as monitored by TLC, Crude product was cooled, washed with water and filtered out to get solid product, which was then recrystallized from ethanol to obtain 75-82% of yield.

Microwave Method

A mixture of malonic acid and 5- substituted- furan/thiophene-2- carboxaldehyde in the amount of 0.01 mole each was mixed with 10 gram of neutral alumina in an Erlenmeyer flask thoroughly for 5 minutes. The reactants were adsorbed on alumina properly. The reaction mixture was then irradiated under microwave for 4-6 minutes. The progress of the reaction was monitored by TLC at an interval of 30 seconds. After the completion of reaction, the crude product was eluted with ethanol (4×15ml). Then the solvent was recovered by distillation under reduced pressure to obtain the products (3a-h) in solid state. The product was then recrystallised from ethanol to afford 88-96% of yield.

Table 1: *Reaction time and yield of heterocyclic acids, 3a-h*

Comp.no.	Value of X/R	Conventional Method	Microwave method	M.P (^oC)
		Time (hrs)/yield(%)	Time (mins)/yield(%)	
3a	O/H	8.0/75	6.0/88	140
3b	S/H	7.8/76	5.8/89	144
3c	O/CH_3	7.7/76	5.5/90	158
3d	S/CH_3	7.5/77	5.3/91	165
3e	O/Cl	7.2/78	5.0/90	180
3f	S/Cl	7.0/79	4.5/92	176
3g	O/NO_2	6.5/80	4.2/94	198
3h	S/NO_2	6.0/82	4.0/96	185

Results and Discussion

Malonic acid and 5-substituted furan/thiophene-2-carboxaldehyde undergo condensation reaction via dehydration and decarboxylation processes to give α, β- unsaturated heterocylic propenoic acids. The reactions were carried out by conventional heating and microwave irradiation methods. Conventional heating methods took 6-8 hours for the completion of reactions with comparatively low yield of 75-82%. Whereas, microwave irradiation reactions took 4-6 minutes for completion of reactions to afford 88-96% of the products (Table 1). Microwave reactions seem much beneficial in terms of reaction time, yield, usage of solvents, etc. These reactions consume limited amount of organic solvent under the solid support of alumina in eco-friendly aspects, where the solvents and the solid supports can be re-used.

The condensation leading to the formation of 3-(5'- substituted-2'- furyl/thienyl) propen-2- oic acids (3a-h), completes in one step with the evolution of carbondioxide and water molecules under the catalysis of neutral alumina. Formation of heterocyclic α, β- unsaturated acids was confirmed by different analytical and characterization data. All the compounds gave satisfactory elemental analysis within the variation of ± 0.5%. The IR and ^1H NMR data have revealed the condensation reactions. Appearance of IR band at 1640 cm^{-1} indicates the C=C linkage in alkyl system in conjugation with aromatic ring. The C–H stretching in vinyl system has appeared at 3010 cm^{-1} is the compounds synthesized.

Similarly, appearance of IR bands at 1710 cm^{-1} and a broad band at 3225 cm^{-1} have indicated the C=O and O–H linkage in carboxylic acid group present in the α, β-unsaturated heterocyclic acids. In ^1H NMR analysis, the extra-ring vinylic protons experience much deshielding due to aromatic ring on one hand and carboxylic acid group on the other hand. The vinylic proton directly linked to aromatic ring gave the duplet signal at 6.5 ppm whereas, the next proton which is linked with carbonyl carbon has shown signal at 7.4 ppm due to greater extent of deshielding effect. Further, the O–H hydrogen has shown

it's presence by giving the signal at 11.1 ppm in the synthesized compounds 3a-h. All the aromatic and aliphatic protons have shown their usual ^{1}H NMR signals.

Conclusion

Solid supported synthesis of α, β- unsaturated heterocyclic acids 3a-h from malonic acid and 5-substituted - furan/thiophene- 2- carboxaldehyde completed in one step. Aqueous work -up in conventional method and solvent- free reaction condition in microwave irradiation method has made the synthesis eco-friendly. Microwave reaction method has been proved beneficial in terms of reaction time, yield, purity, work-up and use of inexpensive chemicals. Microwave reactions have adopted neutral alumina as solid support and ethanol as solvent, both of which are non-hazardous chemicals. These reactions completed within 4-6 minutes affording 88-96% yield. On the other hand, conventional reactions took 6-8 hours with 75-82% of yield.

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