Performing Biginelli Reaction using Catalytic System of Melamine Sulfonic Acid and ZnO Nanotube

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Abstract: In the current investigation, the catalytic effect of ZnO nanotube in presence of solid melamine sulfonic acid in Biginelli compression reaction is studied. Melamine sulfonic acid, as the solid acid resulted from the reaction between chlorine sulfonic acid and melamine synthesis in presence of ZnO nanotubes, was used as catalyst of Biginelli compression reaction. The compression reaction between ethyl acetoacetate, urea, and different aromatic aldehydes in this catalytic system was studied without solvent and at the temperature of 110° C. the results of reactions' progress with TLC shows successful compression reaction. Consequently, urea was changed to thiourea and the experiment was repeated. In all cases, products were separated with favorable efficiency and in proper time.

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1-Introduction

1-1-Reactions in Absence of Solvent

Performing reactions when there is no solvent has several advantages.Tanka and Toda (2000) presented pollution reduction, cost reduction, and simplicity in process, which are of great importance in the industry.

In recent years, researchers have tried to find environmental friendly reactions, due to increment of concerns about environmental and economic issues. Toda (1987) invented a method, known as rubbing method, in which solid materials are grinded by a mortar to generate products. This method is able to form products with high efficiency and perform without solvent, which helps to achieve green chemistry objectives.

1-2-Multicomponent Reactions

Multicomponent reactions are a set of equilibrium reactions, which end in an irreversible stage. They have been developed as an interesting synthesis method for simple production and quick approach to a wide range of organic compositions. Multicomponent reactions are single capacity reactions, which take place easier than multistage reactions.

Based on their mechanism, multicomponent reactions are divided into three categories:

Multicomponent reactions, first group: In these kinds of reactions, ingredients, intermediate products and final products are in equilibrium. In these reactions, final products are a mixture of intermediate products and ingredients. Stearic reaction is an example of this group.

Multicomponent reactions, second group: These equations consist of a chain of reversible reactions that end with a stage of irreversible reactions, which helps in progress of reactions. Often, this final stage consists of a pyrogenic reaction, such as becoming aromatic and closing the loop. The Biginelli Reaction is included in this category.

Multicomponent reactions, third group: These reactions, which are common in cells that produce biochemistry materials consist of chains of irreversible reactions. However, the number of these reactions is very small in chemistry.

Many known reactions have acids as their catalysts. One popular acid is sulfuric acid, which is corrosive, and working with it has some risks. To overcome these shortcomings, it is preferred not to use it or utilize a substitute material.

Many solid acids are used as catalysts, including Melamine Sulfonic Acid, Silica Sulfuric Acid, Aluminum Hydrogen Sulfate on a Silica gel base, Heteropoly Acids, and Cellulose Sulfonic Acid etc.

1-3-Zinc Oxide Nanotubes

Zinc oxide is an n-type semi-conductive compound with large energy gap (3.37 eV). This property makes it suitable for application in electronics, photo electronics, and sensors. In recent years, great advances have taken place in ZnO nanostructures, such as Nanowire (Elias et al., 2008), Nano rod (Biswas et al., 2008) and Nano sheet (Qi et al., 2008).

Since introduction of carbon nanotubes by Lijima (1991), many investigations have been conducted in this field. Many nanotubes have been produced by different methods; ZnO nanotubes can be mentioned in this regard. Oxide nanotubes have drawn attention in efficient performance of sensors, photo voltage cells, and hydrogen utensils, due to their high permeability and large area. Different methods, such as solution-thermal synthesis (Kar and Santra, 2008), chemical vapor precipitation (CVD) (Yuan et al., 2007), hydrothermal synthesis (Chunlei et al., 2007), and cell-gel (Xiaohong, 2006) can be employed to produce zinc oxide nanotubes. This oxide has different structures, including nanowires, tower-like structures, Nano rods, Nano belts, Nano heckles, and Nano loops. For example, Nanowires can be produced using chemical vapor precipitation, in which the vapor is exposed to a catalyst like Au particles.

1-4-Biological and Pharmaceutical Effects of Dihydropyrimidones (DHPMs)

In the past decade, a wide range of biological properties, including anti-bacterial, anti-fungal, anti-virus, anti-inflammatory, and anti-oxidant effects for dihydropyrimidone derivatives have been reported and studied. It has been pointed out that some derivatives of dihydropyrimidone act as edible anti-blood pressure and anti-stress drugs (Kolosov et al., 2009).

2-Experimental Studies

All used materials in laboratory are products of Merck, ALDRICH, and FLUKA companies. Employed solvents have been drought, using common methods. Silica gel has been drought under microwaves with output power of 1000 W for duration of four minutes. Products are known compounds and are validated by comparison of their physical and spectral properties with references. Progress and required time for reactions have been defined using thin film chromatography. In order to identify and detect products, TLC-Cards Silicagel-G/uv 254nm, St-Jean Baptiste Ave (4000-400 cm-1), Bomem 450, and SEM (LEO 1455 VP model) have been employed.

2-1 Zinc Oxide Nano tube Production

In this study, moist chemical method has been employed to produce ZnO nanotubes, which is the most popular method in nanomaterial forming, due to simplicity in procedure and low cost of ingredients. In addition, controlling is easy in this method due to low temperature (70° C) and environmental atmospheric pressure.

To produce ZnO nanotubes, Zinc Nitrate Salt, Polyethylene Glycol with molecular weight of 2000, and Ammonia solution (1M) are used. In the first stage, zinc nitrate and Polyethylene Glycol were solved in 250 mL of deionized water. Then the ammonia solution was added until the pH of solution reached 11. In the second stage, the solution was stirred in 70 °C for duration of 24 hours. ZnO nanotubes that are white sediments were filtered and washed four times with ethanol and deionized water, and then were drought in oven (60 °C) for duration of 12 hours. Figure 1-3 illustrates the general method of ZnO nanotubes.

2-2 Melamine Sulfonic Acid Production

Melamine Sulfonic Acid catalyst is produced from the reaction of melamine and Chlorine Sulfonic Acid. To this end, 7 grams of melamine is added to a vacuum flask. Then 25 mL of dry Chloroform is added to Melamine and a magnet is placed in the flask. 15 mL of Chlorine Sulfonic acid is poured in a separating hopper and 15 mL of dry chloroform solvent is added to it.

Chloroform is drought by addition of calcium chloride, which should be rested to dehydrate. The flask is heated and stirred with magnet, a cap containing a hole is placed on top it, and the materials in separating hopper are added to gradually. The whole system is connected to vacuum pump or the flask containing soda for neutralizing HCL. In this stage, separating hopper is opened to start the reaction. Released gas vapors are observable on the flask wall, which indicates progress of the reaction. When the separating hopper was emptied, we stir the solution for duration of 30 minutes. As a result, a brown colored solid is obtained, which is Melamine Sulfonic Acid and should remain in the oven at 45-50 °C for 12 hours. Afterward, we cover it with foil to protect it from moisture and light.

2-3 Specification of Acid Capacity of Obtained Acid

To define acidity of solid acid, 0.2 gram of the acid was mixed with 0.1 molar soda, in presence of phenolphthalein and in marine environment. Results showed that to reach 34 mL of soda should be employed, and for each gram of solid acid, the volume of consumed soda is 170 mL. Since the volume of acid is equal to volume of soda, the acid capacity of resulting compound is 17 mL of H^+ for each gram of solid acid.

2-4 General Method of performing Biginelli reaction between different aldehydes, Ethyl Acetoacetate, and Urea; in Presence of Catalytic System of Melamine Sulfonic Acid/ZnO Nanotube

In a large tube, 1 mmol Aromatic Aldehyde, 1 mmol Ethyl Acetoacetate, 3 mmol Urea, 0.05 gram ZnO Nanotube, and 0.2 gram Melamine Sulfonic Acid were mixed using a glass mixer. Then the mixture was placed in an oil bath at 110 °C for about 30-45 minutes. After formation of sediments, the mixture's temperature was allowed to reach ambient temperature and the mixture was washed with cold distilled water. After being drought, it was crystalized in hot Ethanol. Therefore, dihydropyrimidone with efficiency of about 30-65% was resulted.

2-5 General Method of Biginelli compression reaction between aldehyde, Ethyl Acetoacetate, and Thiourea; in Presence of Catalytic System of Melamine Sulfonic Acid/ZnO Nanotube

In a large tube, 1 mmol Aromatic Aldehyde, 1 mmol Ethyl Acetoacetate, 3 mmol Thiourea, 0.05 gram ZnO Nanotube, and 0.2 gram Melamine Sulfonic Acid were mixed using a glass mixer. Then the mixture was placed in an oil bath at 110 °C for about 30-45 minutes. After formation of sediments, the mixture's temperature was allowed to reach ambient temperature, and was then washed with cold distilled water. After being drought, it was crystalized in hot Ethanol. Therefore, dihydropyrimidone with efficiency of about 30-45% was resulted.

3. Results and Discussion

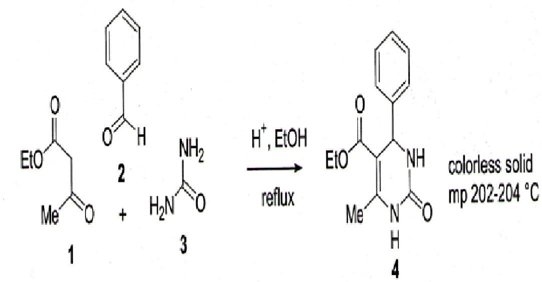
Considering the great importance of dihydropyrimidones and their application in pharmaceutical industries, and increasing attention of organic chemists toward this reaction, several trends have been put forward to optimize this reaction by employing different catalysts. In most of these methods, the catalyst is expensive or its production is difficult. In some cases, prolix reaction and high temperature is reported. Hence, developing cheap catalysts, simple and

effective synthesis methods, which lead to products with high efficiency and mild conditions, are important.
Furthermore, due to the importance of reducing environmental pollution and preventing the formation of subsidiary products in chemical reactions, it is important to develop environmental friendly synthesis methods. In most chemical reactions, the solvent plays an important role and is used in large amounts. Most organic solvents are environmentally harmful; thus, their use should be minimized or eliminated. However, in industry, solvents are often recycled; however, recycling

efficiency is low and causes environmental pollution (Toda 1995). Therefore, to solve this issue, solvents like water (Li and Chan; 1997) or super critical gas fluids, such as carbon dioxide, are used .
It goes without saying that the best solution is to do reactions without solvents, which is cost-effective as well as being environmental friendly. Besides, organic reactions are performed with higher efficiency and more selectivity without solvents (Clark 1994). All the mentioned approaches are known as green chemistry. One of its main principles is to maximize usage of ingredients by adding them according to their stoichiometric value and to employ appropriate catalyst, which is separable after reaction and can be used several times (Tire 1995).
In this regard, to achieve less reaction time and high efficiency in formation of derivatives of dihydropyrimidones, solid melamine sulfonic acid and ZnO nanotube are used as catalysts without solvent. These catalysts are cheap, available, and separable.
In recent decades, multicomponent and single capacity reactions have drawn researchers' attention. The obvious advantages of these reactions compared to existing classic systems can be summarized as follows:

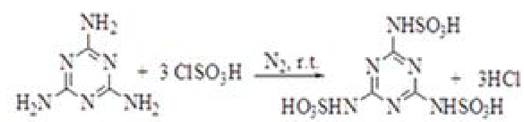
1) Reduction of reaction stages;
2) Obtaining products with higher purity in less time, and
3) Using an appropriate solvent system in all stages of reactions.

Perhaps the most popular multicomponent reaction is Biginelli compression reaction, which was introduced about 120 years ago by Professor Biginelli. This reaction is a compression reaction among Aldehyde, Ethyl Acetoacetate, and Urea (reaction 1).



Reaction 1

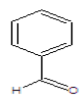
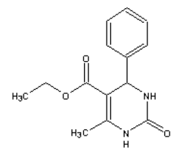
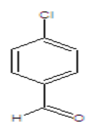
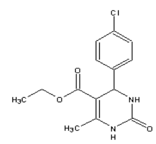
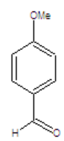
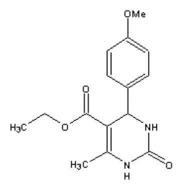
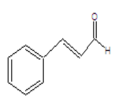
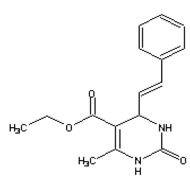
Products of this reaction become different with variation in aldehyde structure and present pharmaceutical properties; dihydropyrimidones are important in pharmaceutical industries.
In this work, capability of nanotubes in setting an appropriate environment for reactions was considered. In this regard, ZnO nanotube and nitrate zinc were selected. $6H_2O$ with Ammonia solution in presence of Ethylene Glycol stabilizer was produced using the method described in section 2-2. Consequently, Melamine Sulfonic Acid was resulted from the reaction of Melamine Chlorine Sulfonic Acid in the absence of solvent (reaction 2).



Reaction 2

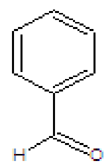
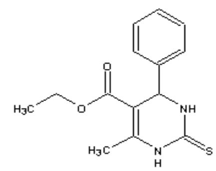
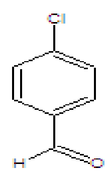
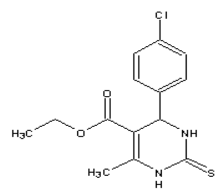
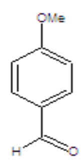
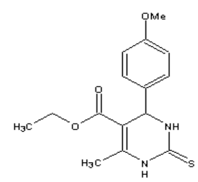
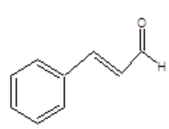
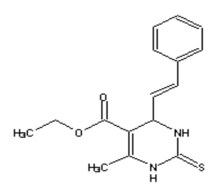
The subsidiary product of this reaction is HCl gas that can exit the container of reaction. To form a powder of Melamine Sulfonic Acid and usage of microcell environment in nanotubes, Melamine Sulfonic Acid and ZnO nanotubes were mixed in mass ratio of 4:1. This catalytic system was employed in Biginelli compression reaction. At first, Benzaldehyde, as the simplest aromatic aldehyde, was selected and mixed with ethyl acetoacetate and urea in molar ratio of 1:1:3; in presence of 0.25 gram of Melamine Sulfonic Acid mixture and ZnO nanotube as the catalytic system were added. Then the reaction was performed at temperature of 105-110 °C. After 45 minutes, sediments formed in the container, showing completion of the reaction. Results are depicted in Table (1).
Obtained products were crystalized in hot Ethanol after being washed with distilled water and the pure product was separated with efficiency of 65%. The IR spectrum of product has two groups of Carbonyl as well as NH elements. In addition to IR spectrometry, which confirms the structure of the product, the melting point of the product was specified and as a physical parameter of material, approves the structure of compound (melting point: 183° C).

Table 1- Compression of aldehyde, ethyl acetoacetate, and urea; in presence of melamine sulfonic acid/ ZnO nanotube without solvent

	Initial aldehyde	Product	Time (minute)	Efficiency (%)
1			30	65
2			45	46
3			45	31
4			45	35

To vary the products, we used Thiourea instead of Urea, and the reaction was repeated under similar conditions. The results are depicted in Table (2).

Table 2- Compression of aldehyde, ethyl acetoacetate, and thiourea; in presence of melamine sulfonic acid/ ZnO nanotube without solvent

	Initial aldehyde	Product	Time (minute)	Efficiency (%)
5			30	42
6			45	40
7			45	30
8			45	30

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