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Synthesis 3 and 4-Dihydropyrimidinone and Thiones using Multi-Walled Carboxylated Carbon Nanotube Catalysts

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Abstract

In the present study, the synthesis of 3 and 4-dihydropyrimidinone and thiones was investigated by Biginelli reaction in the presence of carbon dioxide nanoparticles (MWCNT COOH) as a catalyst. The use of carbon nanotubes has many advantages, including ease of product separation, catalyst recovery capability, and environmental compatibility compared to liquid acidic catalysts. These catalysts are insoluble in most organic solvents and cause little corrosion. In addition, the catalyst is recovered without any reduction in its activity. Therefore, these catalysts can be used as a substitute for catalysts such as sulfuric acid. To investigate the effect of the catalyst on the organic reaction mentioned and to find the optimal conditions, first the synthesis of a derivative is selected as the reaction model and the effect of different reaction conditions such as the amount of catalyst, solvent type and temperature on it is examined. Other derivatives were then prepared under optimal conditions. In most cases, high product efficiency was achieved in a relatively short period of time. Comparing the conditions and results of the reactions performed in this study with other methods reported in the articles shows that the catalyst studied in this study was able to make the conditions of the reaction discussed in terms of time and efficiency, simple separation of products possible.

Keywords: 3 and 4-dihydro pyrimidine and thiones, carbon dioxide multi-walled carbon nanotubes, Biginelli reaction, heterogeneous catalyst, solvent-free reaction

Introduction

It is always desirable for chemists to design reactions in which several reactions can be performed in one step, and very close to the economic goals of this science. Multi-particle reactions are convergence reactions in which three or more components react simultaneously so that all the atoms that initiate the reaction can be seen in the product. The main factor of the multi-component reaction is to guide the reaction to produce the desired product so that the least by-products are created. Biginelli reaction is an example of a multi-particle reaction [1].

For the first time in the late nineteenth century (1891), the 4.3-dihydropyrimidinone compounds, abbreviated DHPMS, by Italian chemist, Pietro Biginelli was synthesized as a one-step, three-part reaction, using a simultaneous reaction of an aromatic aldehyde, urea, and ethyl acetate in the presence of hydrochloric acid as a catalyst, ethanol solvent, and reflux temperature [2].

In recent years, the use of the Bijanelli reaction to synthesize DHPMS compounds has attracted much attention because it provides an easy and efficient process. DHPMS has important biological activities including calcium channel blocker, antihypertensive, antibiotic and anti-cancer. The use of catalysts such as silica, alumina, resin, magnetic nanoparticles, and organic metal frames has been reported.

Using HNMR1 and CNMR13 spectroscopy and intermediate trapping methods, Kope was able to suggest a mechanism. The intermediate is then attacked by the anabolic form of ethyl acetate. In fact, this three-part compression reaction can be thought of as a process between carbonic compounds containing acidic C-H, aldehydes, and urea-like structures[3,4].

Using $HNMR^{1}$ and $CNMR^{13}$ spectroscopy and intermediate trapping methods, Kappe was able to suggest a mechanism. The intermediate is then attacked by the enolizedform of ethyl acetate. In fact, this three-part compression reaction can be thought of as a process between carbonic compounds containing acidic C-H, aldehydes, and urea-like structures. Finally, the closed loop is obtained after removing the DHPM water molecule[5].(Figure 1).

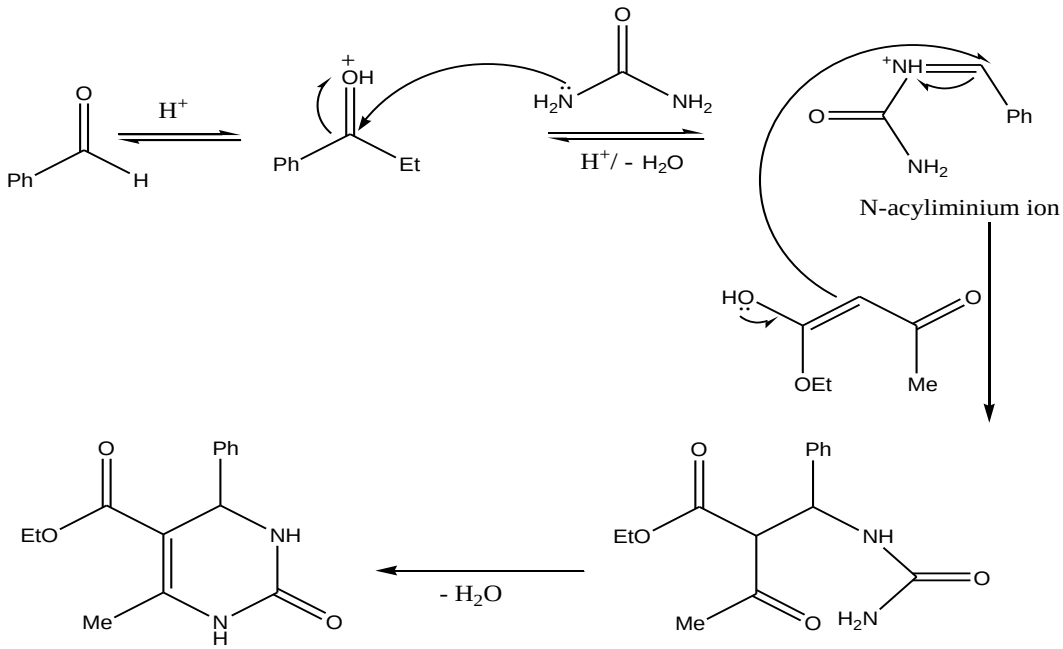


Figure 1: Suggested mechanism of Biginelli reaction

Biginelli reaction is usually better with aromatic aldehydes. They can have reductions in ortho, metaphara, or electron donor or electron donor positions. However, in most cases, the efficiency of the reaction for aromatic aldehydes with lethal electrons is higher in meta or para situations, and the spatial congestion factor slightly reduces the operating efficiency of orthotic situations[1].

but with the development of this reaction, other compounds such as benzyl acetate esters, acetoacetamide , and β-di ketones were also used.

Urea molecules have been used in most of the reactions, but more or less articles have been reported on urea-like structures. Thiourea and its derivatives are also as effective as urea in the Biginelli reaction, albeit with slightly longer reaction times. Below are some urea and thiourea-like compounds that have been used to perform this reaction (Figure 2)[1].

It is also possible to perform a biginelli reaction in heterocyclic aldehydes such as furan, thiophene and pyridine. In some cases, bis-aldehydes have also been used in these reactions[6].

However, the classic carbonyl compound has an acidic C-H that was originally chosen for the Biginelli reaction. Alkyl was a steostat

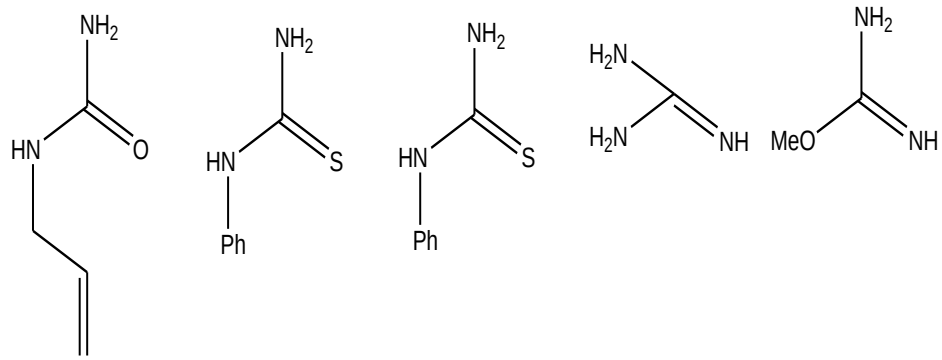
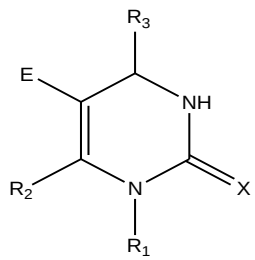


Figure 2: Urea and thiourea compounds used in Biginelli reaction

Examining the more than 650 DHPM compounds that have been synthesized and published since the Biginelli reaction until 2001, the general structure of these compounds can be considered as follows:

DHPM derivatives



R_1: H,alkyl
R_2: H,alkyl,aryl
R_3:H,alkyl,(het)aryl,carbohydrate
E:ester,acyl,amide,nitro,nitrile,phosphono

X:O,S,NR

Figure 3: Combination of synthesized DHPM with Biginelli reaction

Today, there is a great variety of conditions for performing this compression reaction. For the concentration of ethyl acetate with benzoic acid and urea, more than one hundred different laboratory conditions have been reported.

Although ethanol was a common solvent for the Bijaneli reaction, various protic and aprotic solvents have been used in recent years. Among the aprotic solvents used are Tetrahydrofuran, dioxane or acetonitrile. On the other hand, acetic acid, water and ionic liquids have also acted as solvents [1]. Even this reaction has taken place in solvent-free conditions[5].

The Biginelli reaction is highly dependent on the amount and type of acid used in the process. In the past, bronsted acids such as hydrochloric or sulfuric acid were commonly used to catalyze this reaction, but today the use of Lewis acids has expanded and become more widely used, some of which are listed below[7]:

$LaCl_3$, $FeCl_3$, $NiCl_2$, $Yb(OTf)_3$ $La(OTf)_3$, $InCl_3$, $InBr_3$, I_2 , VCl_3 , $LiClO_4$, $Mn(OAC)_3$
$ZrCl_4$, $Zn(OTf)_2$, L - proline , $TiCl_4$, TMSCl , heteropoly zcids ,
amberlyst , zeolite , acidic clay.

To perform this reaction, the use of substances such as sulfuric acid embedded on silica[8], iodine-embedded iodine[9] and various nanoparticles such as iron-silica nanoparticles [1] have also been reported as heterogeneous catalysts.

Usually, the rate at which a biginelli reaction occurs at room temperature is very slow and slow[10] Therefore, the need to provide activation energy required for process progress is obvious. For this purpose, in addition to the conventional method of thermal heating reaction (reflux conditions), the use of other methods such as microwave radiation, ultrasonic radiation, infrared radiation and photochemical methods have also been used[11]. The effort to produce new space products have been reported.

Major problems such as high reaction temperature, long reaction time, strong catalyst acidity, catalyst stoichiometry values, high price, and low availability have led to extensive research to find an alternative catalyst in the synthesis of pyrimidones.

Advances in nanoscience and nanotechnology have been made with the discovery of a variety of carbon nanostructures over the past thirty years. Carbon is the sixth element in the periodic table elements, due to its unique chemical properties, thermal stability, as well as superior mechanical performance for a wide range of applications. The well-known carbon allotropic diamond was first observed by Kroto et al. The discovery of fullerenes in 1985 marks the beginning of the period of artificial carbon allotropes and to the sight of carbon nanotubes (CNTs) in 1991 and graphene in 2004 - important milestones in the evolution of carbon allotropes. The properties of carbon nanostructures

are ideal for use in catalytic applications. The use of this catalyst has many advantages such as high acidity, thermal and chemical stability, ease of recovery and environmental compatibility. In the present study, the application of acid carbon nanotube catalyst in the preparation of various derivatives of dihydropyrimidinone and thiones has been investigated[12].

Experimental section

Materials

Carboxyl-walled multi-walled carbon nanotubes

Purchased carbon nanotubes have characteristics including the average distance between the layers is 0.34 nm, the specific surface area is in the range of 50-350 square meters per gram and the purity percentage is 98%.

Organic compounds for Biginelli reaction

Chemicals and solvents used from the German company Merck. The progress of the reactions was controlled by thin layer (TLC) chromatography with n-hexane-ethyl acetate solvent. Infrared spectra with the Tensor 27 spectrophotometer are recorded by the KBr waveform in cm-1 and the magnetic resonance spectra of the HNMR1 and CNMR13 cores by the 400 broker in solvent methyl sulfoxide and duct chloroform.

Laboratory methods

General method of preparation of derivatives 3, 4- Dihydropyrmidinone and thion with acid nanocarbon catalyst catalyst

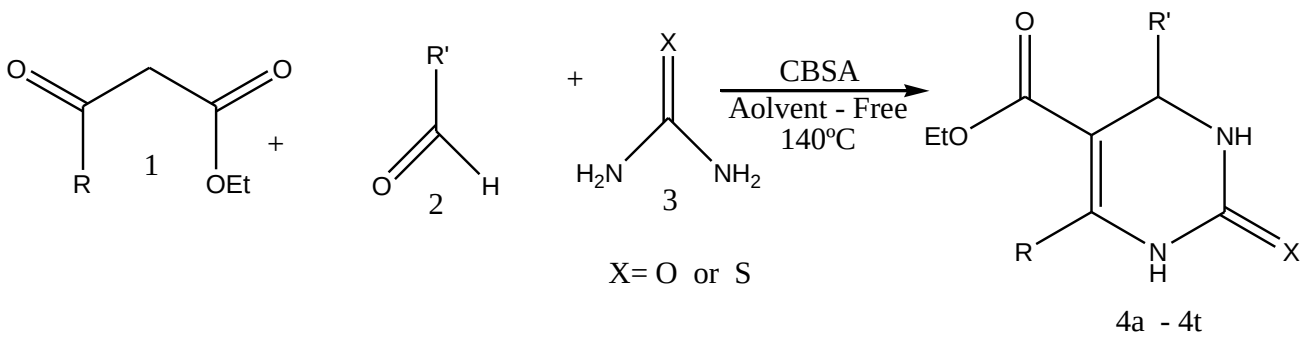


Figure 4: General outline of the reaction of synthesis of 3 and 4-dihydropyrimidinone and thion

To prepare a mixture of different aldehydes (4 mmol), β-cathoster (4 mmol), urea or thiodere (5 mmol) and MWCNT COOH catalyst (0.1 g) taking into account the overall reaction, at the right time in the oil bath were stirred at 140 C. Progression and completion of the reaction were controlled with TLC (n-hexane: ethyl acetate). After the reaction was complete, the reaction mixture was cooled to room temperature and the resulting precipitate was crystallized again after smoothing with ethanol. All compounds are known. The melting points as well as the spectral information of the products are completely consistent with the data reported in the scientific sources. The results are reported in Table 2. The catalyst was also recycled.

Results and Discussion

Nanocatalyst MWCNT COOH characteristic

Based on the results of FT-IR analysis, the presence of C-H, C-O and O-H functional groups on the surface of carbon nanotubes has been confirmed

Determining the optimal conditions for the synthesis of derivatives 3, 4- Dihydro pyrimidine and thiones

Initially, several reactions were designed and performed under different conditions to obtain optimal conditions, the results of which are summarized in Table 1. The use of different solvents, different values of the catalyst, as well as changing the temperature conditions of the reaction are among the parameters examined to obtain the optimal conditions. All results in Table 1 are the result of the reaction of 4-chloro benzaldehyde, ethyl acetate and urea in the presence of an acid carbon nanotube catalyst.

Table 1: Results from optimization of synthesis reaction conditions 3, 4-dihydro pyromidinone and thiones *

Entry	Solvent	Catalyst(g)	Time(min)	Condition	Yeild(%)
1	Solvent free	-	180	140˚C	-
2	Solvent free	0.05	15	90˚C	92
3	Solvent free	0.08	15	90˚C	85
4	Solvent free	0.10	15	90˚C	72
5	Solvent free	0.15	15	90˚C	70
6	Solvent free	0.20	25	90˚C	63
7	Solvent free	0.05	15	25˚C	none
8	Solvent free	0.05	15	60˚C	63
9	Solvent free	0.05	15	80˚C	63
10	Solvent free	0.05	15	90˚C	92
11	Solvent free	0.05	25	90˚C	92
12	Ethanol	0.05	180	Reflux	38
13	Acetonitrile	0.05	240	Reflux	25
14	Chloroform	0.05	300	Reflux	15
15	Tetrahydrofuran	0.05	360	Reflux	10

* The results of Table 1 are the result of the reaction of ethyl acetate (4 mmol), 4-chloro benzaldehyde (4 mmol) and urea (5 mmol) in the presence of different amounts of acid carbon nanotube catalyst under the specified temperature and time conditions against each row.

The results of Table 1 show that the best conditions for this reaction include 120 C, no solvent, and the use of 0.05 g of acidic carbon nanotube catalyst (Row 2). Since increasing the temperature increases the effective collisions between the reaction molecules and the catalyst, as can be seen, with increasing temperature, the reaction rate increases and the temperature of 120 C is the optimum temperature. (Rows 7-10) The results show that the product cannot be produced without a catalyst (row 1), so the presence of a catalyst is essential for the reaction. 0.5 g of catalyst is sufficient to achieve the desired results and increasing the catalyst plays a deterrent role in product efficiency (rows 3-6). Among the various solvents that were tested, the highest yield was ethanol and the lowest yield was Tetrahydrofuran (Rows 12-15).

Unresolved reactions without solvent are more efficient and selective than soluble phase reactions. Avoiding organic solvents during synthetic reactions leads to an effective economic

method and is less polluting, increased safety, and the operation of purification is dramatically simplified and excess or unreacted material is removed with simple filler. And reaction time is reduced. The increase in reaction time and temperature to 140 C (rows 10 and 11) has little effect on the reaction results.

Then, taking into account the optimal conditions obtained from the above experiments, using different aldehyde derivatives, the desired reaction was performed to obtain different 3 and 4-dihydro-pyrimidine derivatives and thiones. The results are summarized in Table 2.

Table 2: Results for synthesis 3, 4- Dihydropyrmidinone and thiones using optimal conditions

Entry	R	R'	X	Time(min)	Yeild(%)	Product	Melting point(˚C) Reported Observed
1	Me	3-BrC_6H_4	O	15	85	4a	195-197 195-196[13]
2	Me	2-ClC_6H_4	O	15	86	4b	220-22 222-224[14]
3	Me	4-ClC_6H_4	O	15	92	4c	215-21 212-214[14]
4	Me	3-OHC_6H_4	O	15	85	4d	168-170 163-165[14]
5	Me	4-OHC_6H_4	O	15	88	4f	236-23 230-232[14]
6	Me	4-$MeOC_6H_4$	O	10	85	4g	203-205 198-200[15]
7	Me	4-MeC_6H_4	O	10	89	4h	210-212 216-218[13]
8	Me	3-$NO_2C_6H_4$	O	15	85	4i	223-225 232-234[13]
9	Me	4-$NO_2C_6H_4$	O	15	85	4j	208-210 206-208[15]
10	Me	4-ClC_6H_4	S	5	88	4k	192-193 192-194[14]
11	Me	4-OHC_6H_4	S	5	86	4l	200-202 193-194[15]
12	Ph	Ph	O	15	85	4m	152-154 152-155[16]
13	Ph	Ph	S	15	85	4n	185-187 183-185[17]
14	Ph	4-$MeOC_6H_4$	S	15	85	4o	150-152 151-152[17]

3-3 Comparison of the results of synthesis of synthesis derivatives 3, 4-dihydro pyrimidine and thiones in the presence of acid carbon nanotube catalyst with other catalysts

Examination of the various methods used in the preparation of dihydropyridimine ions derivatives shows that the use of carbon-based acid catalysts has many advantages over other methods (Table 3). The reaction is performed in a shorter time and with higher efficiency.

Table 3: Comparison of the results of synthesis of dihydropyridimine derivatives and thiols in the presence of acidic carbon nanotubes with other catalysts.

Entry	Catalyst(g)	Solvent	Temperature(˚C)	Time(h)	Yield (%)	Reference
1	HEU type zeolite	AcOH	100	4-12	44-87	[18]
2	$InBr_3$	EtOH	reflux	7-36	68-98	[14]
3	CuI	CH_3CN	reflux	0.75-2	70-87	[19]
4	[bmim][$FeCl_4$]	-	90	2-3	68-92	[13]
5	SCM	-	140	0.25-0.5	80-92	[5]
6	MWCNT COOH	-	90	0.05-0.15	85-92	Current work

A closer look at the published articles shows that this catalytic method has many advantages over other methods (Table 3). Organic and hazardous solvents have not been used for reactions.

Check the catalyst recovery capability

The catalyst used in the model reaction was recovered after the reaction was completed and reused. The reaction efficiency did not change significantly after 5 consecutive uses of the catalyst and the catalytic activity was maintained. The catalyst recovery diagram (Figure 4) is shown below.

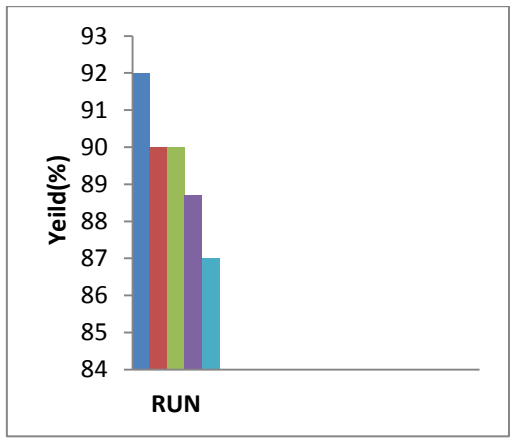


Figure 5: SCNT catalyst recovery diagram considering the 4c response

Suggested mechanism for synthesis of synthesis derivatives 3, 4- Dihydro pyrimidine and thiones in the presence of acid carbon nanotube catalyst

The reaction is done in a single step and its proposed mechanism is as follows:

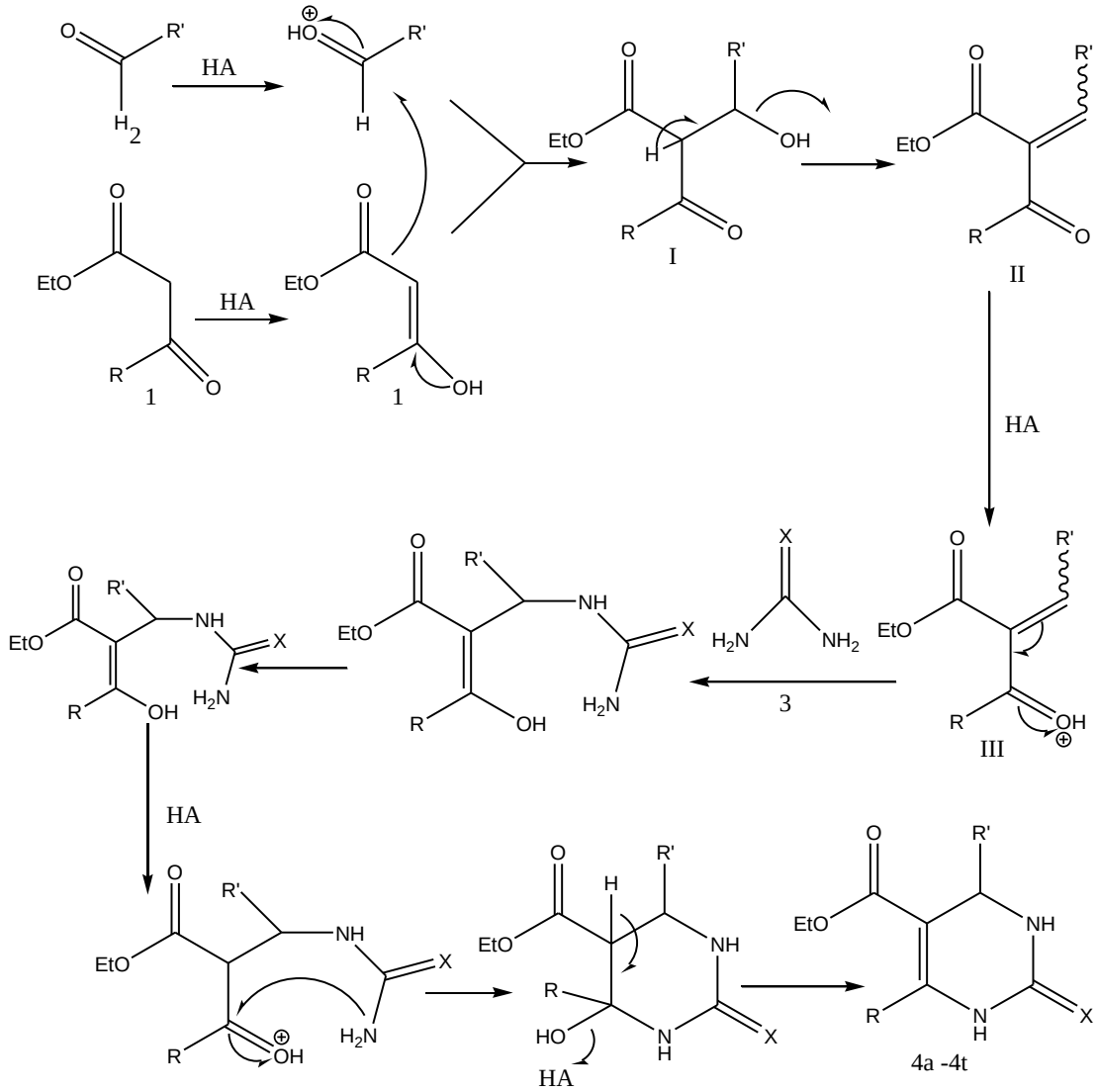


Figure 6: Mechanism for the production of derivatives 3, 4-dihydropyrimidine and thiones in the presence of SCNT catalyst

As seen in Schematic 4, in the first stage, the reaction is carried out in the presence of acid catalyst of vessel and Nagel density and the intermediate (I) is formed, then the elimination of hydrogen olefin (II) is obtained. An increase in urea or thiourea nucleophilia (3) to carbon β combines with the α-β compound of unsaturated proteon carbonyl (III), and finally the intra-molecular rounding forms the final products (4a-4t).

Spectrums

Ethyl-4-(3-bromophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate(4a): ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.10 (t, 3H,J=7.0Hz, CH_3), 2.25 (s, 3H, CH_3), 3.95-4.05 (m, 2H ,

CH_2), 5.14 (d, 1H,J=3.2Hz, CH), 7.23(d, 1H,J= 7.7Hz, arom-H), 7.45 (dt, 1H, J=7.9,0.9Hz,arom-H), 7.77 (s, 1H, NH), 9.25 (s, 1H, NH);

IR (KBr disc): υ 3238(NH), 3114(NH), 1706(C=O), 1654(C=O) cm^{-1}.

Ethyl-4-(2-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate(4b): ^1H NMR (500 MHz, DMSO-d_6): δ 1.05 (t, 3H, CH_3), 2.29 (s, 3H, CH_3), 3.09-3.91 (m, 2H , CH_2), 5.62 (d, 1H, CH), 7.24-7.32(m, 2H, arom-H), 7.40 (dt, 1H,arom-H), 7.67 (s, 1H, NH), 9.24 (s, 1H, NH);

IR (KBr disc): υ 3236(NH), 3113(NH), 1703(C=O), 1650(C=O) cm^{-1}.

Ethyl-4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate(4c): ^1H NMR (500 MHz, DMSO-d_6): δ 1.09 (t, 3H,J=7.1Hz, CH_3), 2.25 (s, 3H, CH_3), 3.95-4.05 (m, 2H , CH_2), 5.15 (d, 1H,J=3.2Hz, CH), 7.25(d, 2H,J= 7.7Hz, arom-H), 7.39 (d, 2H, J=7.7Hz,arom-H), 7.75 (s, 1H, NH), 9.22 (s, 1H, NH);

IR (KBr disc): υ 3233(NH), 3114(NH), 1703(C=O), 1650(C=O) cm^{-1}

Ethyl-4-(4-fluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate(4d): IR (KBr disc): υ 3351(NH), 3243(NH), 1725(C=O), 1677(C=O) cm-1.

Ethyl-4-(3-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4e): 1H NMR (500 MHz, DMSO-d6): δ 1.02 (t, 3H, CH3), 2.25 (s, 3H, CH3), 4.0 (q, 2H , CH2), 5.15 (d, 1H, CH), 6.7(d, 1H, arom-H), 7.5 (d, 2H, arom-H), 7.6 (s, 1H, NH), 9.3 (s, 1H, OH);

IR (KBr disc): υ 3330(NH), 3104(NH), 1708(C=O), 1631(C=O) cm-1.

Ethyl-4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate(4f): 1H NMR (500 MHz, DMSO-d6): δ 1.10 (t, 3H,J=7.1Hz, CH3), 2.27 (s, 3H, CH3), 3.72 (s, 3H , CH3O), 3.99 (q, 2H,J=7.1Hz , CH2), 5.25(d, 1H , J=2.4Hz.CH), 6.20 (s, 1H, NH), 6.75 (d, 2HJ=8.7Hz ,arom-H), J.

IR (KBr disc): υ 3247(NH), 3118 (NH), 1703(C=O), 1649(C=O) cm-1.

Ethyl-4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate(4g): IR (KBr disc): υ 3244(NH), 3117(NH), 1706(C=O), 1650(C=O) cm-1.

Ethyl-4-(4-methylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate(4h): 1H NMR (500 MHz, DMSO-d6): δ 1.10 (t, 3H,J=7.1Hz, CH3), 2.29 (s, 3H, CH3), 3.95-4.05 (m, 2H , CH2), 5.17 (s, 1H,CH), 7.22(d, 1H,J= 8.3Hz, arom-H), 7.42(d, 2H, J=8.3,arom-H), 9.65 (s.br., 1H, NH), 10.36 (s.br., 1H, NH);

IR (KBr disc): υ 3238(NH), 3175(NH), 1673(C=O) cm-1.

Conclusion

In the present study, a new method for the synthesis of 3 and 4-dihydropyrimidinone and thiones using an acid carbon nanotube catalyst has been proposed. The catalyst used is safe for the environment due to its lack of corrosion, safety, low amount of waste and separability. The advantages of this method are environmental compatibility, easy separation, preparation of purer products, and reduction of by-products and high speed of reaction.

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