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The Role of HCl in Carrying out Biginelli Reaction for the Synthesis of 3,4-Dihydropyrimidine-2-(1-(H)ones Derivatives

Yasin Mohamed Shams[1]*, Maryam HosseinN[2], Majid al-Samrai[3]

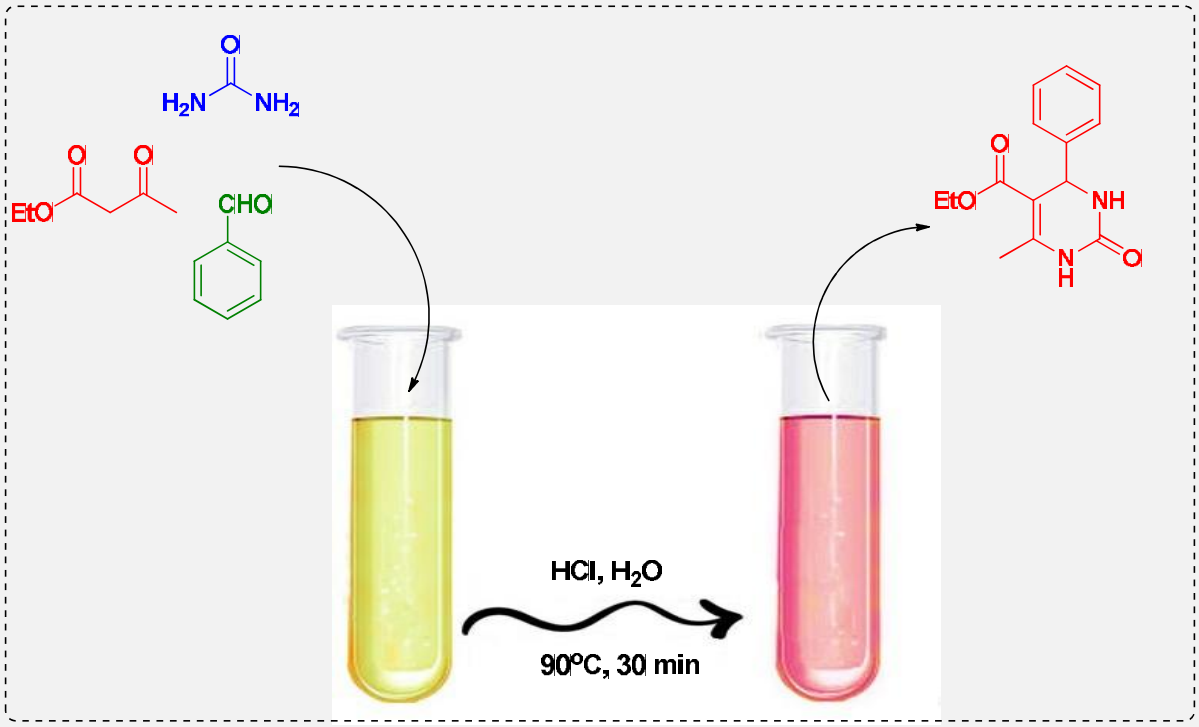
[1] Institute of Chemical Nanotechnology and Material Science, Baghdad, Iraq.

[2]Department of Analytical chemistry, Baghdad, Iraq.

[3]Department of Chemistry, Faculty of Sciences. Diwaniyeh, Iraq.

Mail corresponding-author: ymshams1985@gmail.com

ABSTRACT: The chemicals 3,4-Dihydropyrimidine-2-(1-(H)ones have biological and therapeutic uses. This study reports on the synthesis of these chemicals' derivatives using the Biginelli reaction method using HCl as an eco-friendly acid. Derivatives of 3,4-Dihydropyrimidine-2-(1-(H)ones substituted in positions 2, 4, 5, and 6 were produced from the condensation of ethyl acetoacetate with urea and aromatic aldehydes in the presence of HCl at a temperature of 90 °C in water solvent. Using data from spectroscopy, the structure of the chemicals synthesized has been verified. This process has several advantages, including a high yield, quick reaction times, a single container, no requirement for a solvent, no intermediate separation, and environmental compatibility of the catalyst.



KEYWORDS: 3,4-Dihydropyrimidine-2-(1-(H)one, Biginelli, Ethyl Acetoacetate, Urea.

Introduction

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Six-membered heterocycles are classified as electron-deficient ring π in Albert's classification [1]. Additional nitrogen atoms or electronegative groups substituting in the ring are the main causes of increased π electron deficit [2]. Additionally, these circumstances weaken the game, making the aromatic nucleophilic substitution reaction easier and the aromatic electrophilic substitution reaction harder [3]. For instance, 2-aminopyrimidine is created when the chlorine atom in 2-chloropyrimidine is substituted. In comparison to pyridine, pyrimidine has less access to the lone pair of electrons, or playing power [4]. Nitrogen is more harder to oxidize and alkylate than pyridine. Pyrimidine protonation has a pKa value of 1.23 as opposed to 5.3 for pyridine. Due to further deactivation by the second nitrogen, protonation and other increases in electron affinity only happen at one nitrogen [5].

The nitrogens in positions 1 and 3 of the three diazines, which are six-membered heterocycles with two nitrogen atoms in the ring, are found in pyrimidine [6]. Pinner began the basic investigations of pyrimidines in 1884 when he reacted amidines with ethyl acetate to create pyrimidine derivatives. The term "pyrimidine" was initially proposed by Pinner in 1885 [7]. In 1900, Gabriel and Kalman synthesized pyrimidine for the first time by reducing barbituric acid to 2-, 4-, and 6-trichloropyrimidine in hot water, followed by a zinc reduction [8]. Three major categories encompass the majority of pyrimidine core synthesis techniques. The majority of typical pyrimidine synthesis processes entail the condensation of a species possessing an N-C-N structure with a three-carbon unit [9]. This process can be used with a wide range of compounds, making it highly adaptable. A β-dialdehyde, β-ketoaldehyde, β-ketoester, malonic ester, β-ketonitrile, or other compounds containing these functional groups could be examples of the three-carbon unit. The nitrogenous unit may be thiourea, amide, urea or guanidine [10].

In multicomponent reactions (MCRs), three or more reactants are combined in a single vessel to create a final product that possesses characteristics from each reactant component [11]. For more than a century, chemists have been fascinated by MCRs because they are flexible instruments for creating heterocycles [12]. The terms "cascade," "domino," and "one-pot" are also frequently used to describe MCRs. Strecker made the first contribution to the field of multicomponent chemistry in 1850 [13]. Numerous MCRs, such as the Hantzsch reaction, Passerini reaction, Ugi reaction, etc., have been described since then [14]. Following a year from Hantzsch's discovery of dihydropyridine (DHP), Pietro Biginelli reported in 1893 that 3,4-dihydropyrimidin-2(1H)-ones (DHPMs) could be synthesized in one pot using an acid catalyst and three readily available starting materials: benzaldehyde, ethyl acetoacetate, and (thio)urea in protic solvents (cf. DHPMs) [15]. Despite receiving little attention until the early 1980s, this MCR protocol's popularity grew from there [16]. The Biginelli reaction has been the focus of numerous book chapters and reviews as it is now recognized as a significant reaction in heterocyclic synthesis [17]. The fundamental cause of the increased interest in this reaction is the pharmacological and therapeutic qualities of Biginelli products, including DHPMs [18]. The Biginelli reaction involves the multicomponent chemical reaction of urea, an aryl aldehyde, and ethyl acetoacetate to produce 3,4-Dihydropyrimidine-2-(1-(H)one. Pietro Biginelli, an Italian chemist, made this reaction's discovery in 1891 [19]. Biginelli conducted this reaction in an acidic atmosphere with ethanol under reflux circumstances. Dihydropyrimidinones, the reaction's byproduct, are frequently utilized as calcium blockers and hypertension medications in the pharmaceutical sector [20]. This response It had a low yield at initially, but because of its many uses, scientists were motivated to find

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better ways to synthesise it by utilizing different solvents and new catalysts, as well as creating a variety of derivatives [21].

the most recent instance being The synthesis of nanomaterials with complex structures has advanced, and these materials are employed as catalysts in multicomponent processes. A appropriate procedure for the synthesis of 3,4-Dihydropyrimidine-2-(1-(H)one was suggested in this study. HCl acid was used to carry out the reaction of 3,4-Dihydropyrimidine-2-(1-(H)ones, which was cost-effective, eco-friendly, and highly efficient.

Results and Discussion

Due to the wide-ranging applications of 3,4-Dihydropyrimidine-2-(1-(H)ones compounds in medicine and biology, it appears important to develop new synthetic techniques and produce novel derivatives of these compounds. One of the most popular techniques for creating 3,4-Dihydropyrimidine-2-(1-(H)ones is Biginelli's reaction, which has been carried out using a variety of catalysts.In this study, high yield 3,4-Dihydropyrimidine-2-(1-(H)one derivatives were produced in a water solvent at 90°C with urea and β-ketoester substituted at position 4 of aromatic aldehydes in the presence of acid.

FT-IR spectroscopy

Figure 1 shows the FT-IR measurement of ethoxycarbonyl-6-methyl-4-(pheny)-3,4-dihydropyrimidine-2-(1-(H)one. In the IR spectrum of this compound, the absorption peak of NH groups at 3240 cm^{-1} and 3125 cm^{-1} and the absorption peak of C=O groups at 1720 cm^{-1} corresponding to the ketone group and at 1645 cm^{-1} corresponding to the carbamide group are observed.

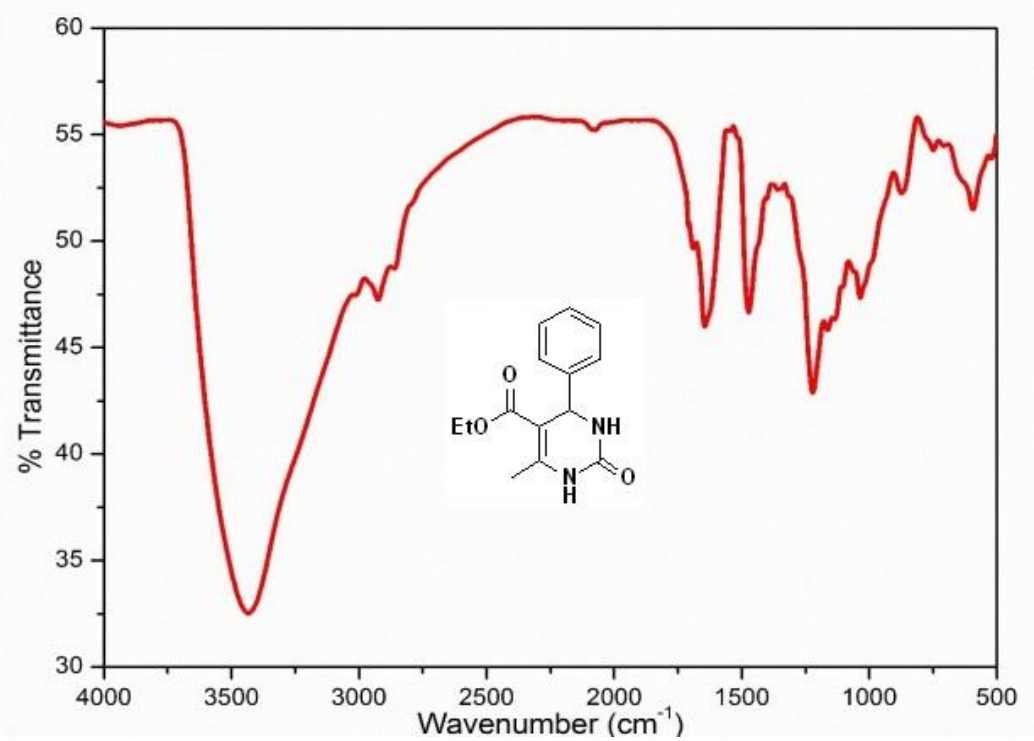

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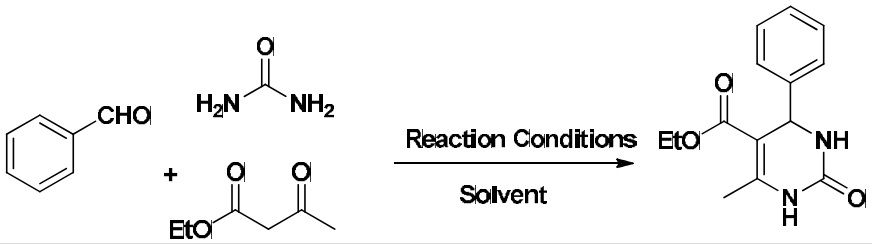
Figure 1. FT-IR spectroscopy of ethoxycarbonyl-6-methyl-4-(pheny)-3,4-dihydropyrimidine-2-(1-(H)one.

To optimize the reaction conditions, the reaction of benzaldehyde, urea and ethyl acetoacetate was used as the base reaction. In this reaction, the effect of solvents, temperature and acid amounts on the reaction yield was investigated. The results of the reactions are shown in Table (1). According to the obtained results, the maximum yield of the reaction is related to the use of 20 mol% HCl in water solvent at a temperature of 90 °C and for 30 minutes Table1, entry 8. According to the table, the use of larger amounts of acid has reduced the yield of the reaction, which is due to the increase in the volume of the liquid, which causes the closing of the reaction mixture to take place later. The reaction did not take place without the presence of acid. This reaction was carried out in different solvents, and the results showed that the yield of products is higher in polar solvents. These optimal conditions were used for the synthesis of 3,4-dihydropyrimidine-2-(1-(H)one derivatives substituted in position 4.

Table 1. Optimization parameters for 3,4-dihydropyrimidine-2-(1-(H)one derivatives [a]



Entry	Acid (mol%)	Temperature (°C)	Solvent	Time (min)	Yield (%) [a]
1	--	90	H_2O	60	No
2	5	90	H_2O	30	32
3	10	90	H_2O	30	57
4	15	90	H_2O	30	76
5	20	rt	H_2O	30	69
6	20	50	H_2O	30	70
7	20	80	H_2O	30	82
8	**20**	**90**	**H_2O**	**30**	**98**
9	20	100	DMF	30	39
10	20	110	PEG	30	89
11	20	90	EtOH	30	73
12	20	90	CCl_4	30	41
13	20	90	THF	30	58
14	20	90	Hexane	30	35

[a] Isolated yields

The reaction of benzaldehyde and its derivatives with urea and ethyl acetoacetate in water solvent, 20 mol% acid and 90 °C temperature, 3,4-dihydropyrimidine-2-(1-(H)ones substituted in position 4 were synthesized with high yield. The results in Table (2) is shown. The reaction was performed with different electron-donating and electron-withdrawing substituents. The results of the table indicate that a higher efficiency has been obtained for electron-donating substituents.

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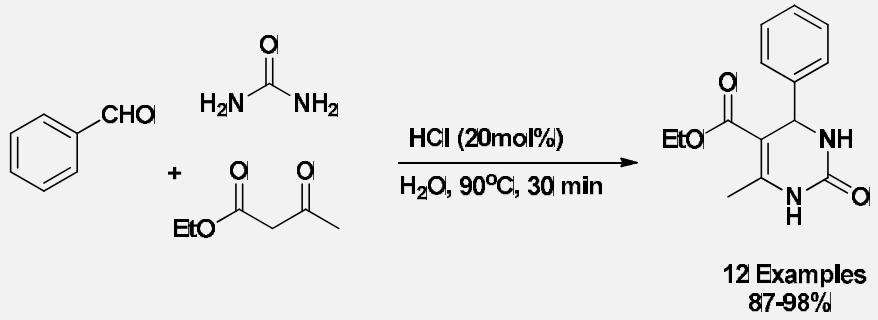
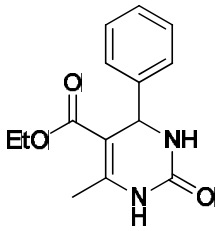
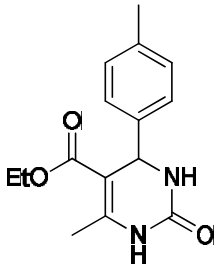
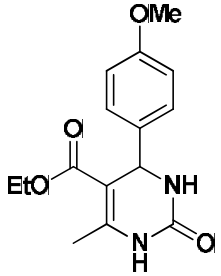
Table 2. Reaction of derivatives for 3,4-dihydropyrimidine-2-(1-(H)one

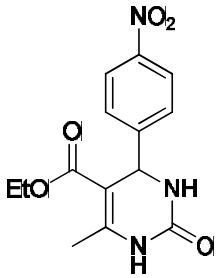



3a (98%)

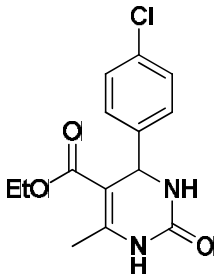

3b (94%)



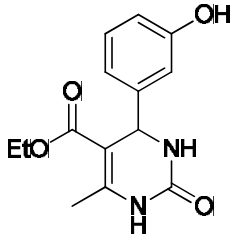
3c (95%)



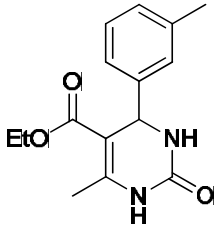
3d (95%)

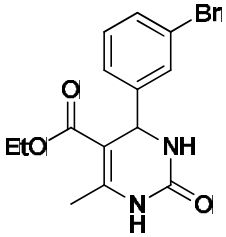


3e (93%)

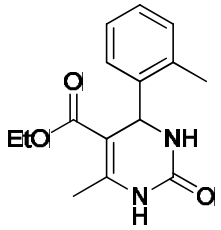


3f (89%)


3g (90%)



3h (91%)


3i (88%)

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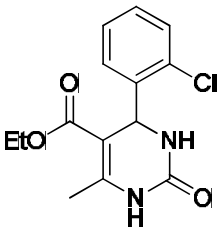
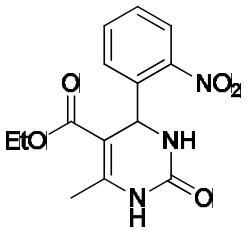


3j (89%)



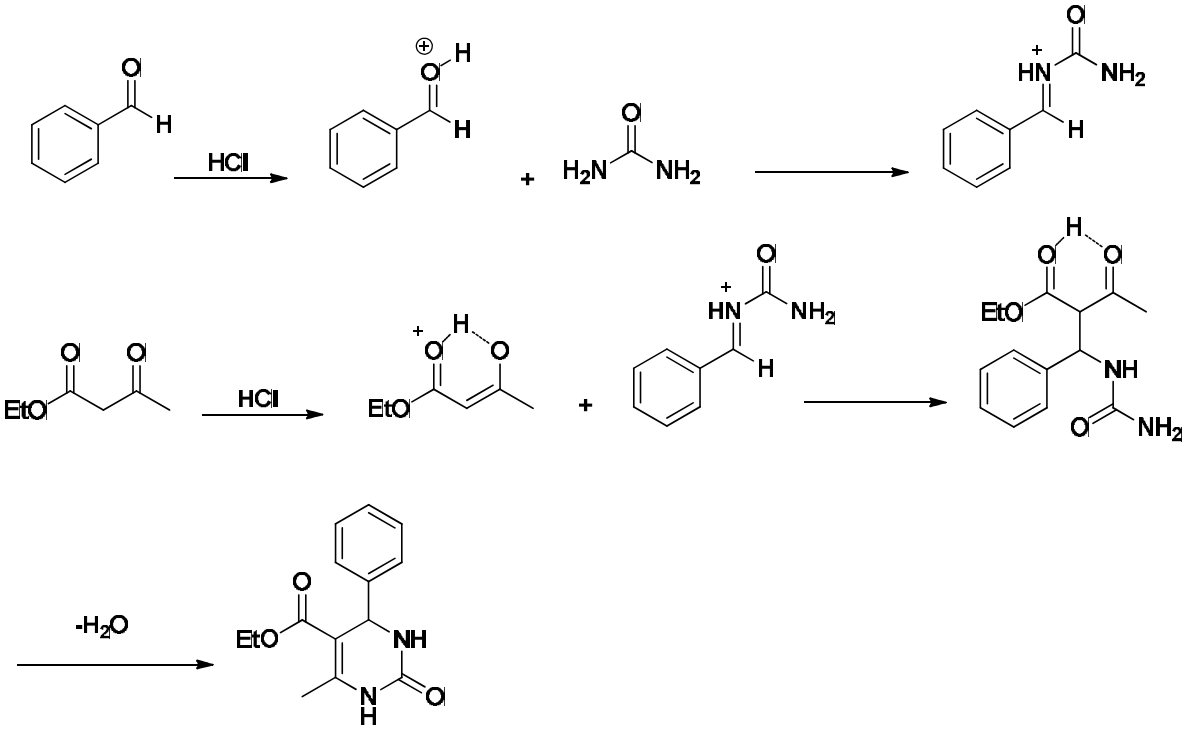
3k (87%)

[a] Isolated yields

The mechanism of this reaction is shown in scheme 1. Based on that, the proposed mechanism for this reaction includes two steps, in each of which HCl plays a key role as an activator.

A) Formation of -N-acyl iminium (Rate determining step)

B) Increasing nucleophilicity, cyclization and water removal



Scheme 1. The proposed mechanism for the synthesis of 3,4-dihydropyrimidine-2-(1-(H)one.

■ Conclusion

In this research process, derivatives of 3,4-dihydropyrimidine-2-(1-(H)ones were synthesized from the reaction of benzaldehyde with urea and a β-dicarbonyl compound. The following are the features of this method:

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1- The one-pot nature of the main reaction; There is no need to separate the intermediates and the reaction in the next steps when the yield of the reaction becomes less.

2- performing the reaction in green solvent; Organic solvents are toxic and polluting the environment.

3- No harmful acid catalysts were used in this reaction.

4- Using an acid that is easily separated from the reaction medium, soluble in water, non-toxic and environmentally friendly.

5- High reaction efficiency

6- Short reaction time

■ Experimental

High purity chemicals were purchased from Fluka and Merck. The melting points in the capillary tube were determined using the Electrothermal 9100 device. FTIR spectrum was recorded by VERTEX 70 device (Bruker). 1H and 13C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at frequencies of 300.13 and 75.46 MHz and on a BRUKER DRX-400 AVANCE spectrometer at frequencies of 400.22 and 100.63 MHz, respectively. Determination of purity Products and reaction monitoring were performed by TLC on polygram silica gel SILG/UV 254 plates.

General Procedure for 3,4-dihydropyrimidine-2-(1-(H)one derivatives

Pour aromatic aldehyde (0.15 mmol), ethyl acetoacetate (0.2 mmol), urea (0.12 g), H_2O (5 cc), HCl (20 mol%) into the flask, then add the above ingredients. It was placed at 90 ^{o}C and checked by TLC every 5 minutes. After the completion of the reaction was confirmed by TLC, the sediments in the dry oven were then washed again with cold methanol solvent for further purification and dried at 60 ^{O}C.

Supplementary Information

(R)-(-)-Ethyl 6-methyl-4-(4-nitrophenyl)-2-oxo-3,4-dihydropyrimidine-5-carboxylate (3d): yellow solid (129 mg, 9% yield); mp 207–209 °C . 1H NMR (200 MHz, DMSO-d6): δ = 9.27 (s, 1H), 8.16 (d, J = 8.6 Hz, 2H), 7.80 (s, 1H),7.43 (d, J = 8.6 Hz, 2H), 5.20 (s, 1H), 3.94 (q, J = 7.0 Hz, 2H), 2.18 (s, 3H), 1.02 (t, J = 7.0 Hz, 3H); 13C NMR (50 MHz, DMSO-d6): δ = 165.6, 152.6, 152.4, 150.1, 147.3, 128.2, 124.4, 98.8, 60.1, 54.3, 18.4, 14.6.

(R)-(-)-Ethyl 6-methyl-4-(2-tolyl)-2-oxo-3,4-dihydropyrimidine-5-carboxylate (3i): pale yellow solid (141 mg, 88% yield); mp 195–197 °C. 1H NMR (200 MHz, DMSO-d6): δ = 10.12 (s, 1H), 9.41 (s, 1H), 7.05–7.02 (m, 4H), 5.35 (d, J = 3.9 Hz, 1H), 3.85 (q, J = 7.0 Hz, 2H), 2.35 (s, 3H), 2.24 (s, 3H), 0.98 (t, J = 7.0 Hz, 3H); 13C NMR (50 MHz, DMSO-d6): δ = 174.0, 165.7, 145.4, 142.8, 135.6, 130.7, 128.2, 127.7, 127.2, 101.6, 60.1, 51.3, 19.2, 17.1, 14.4.

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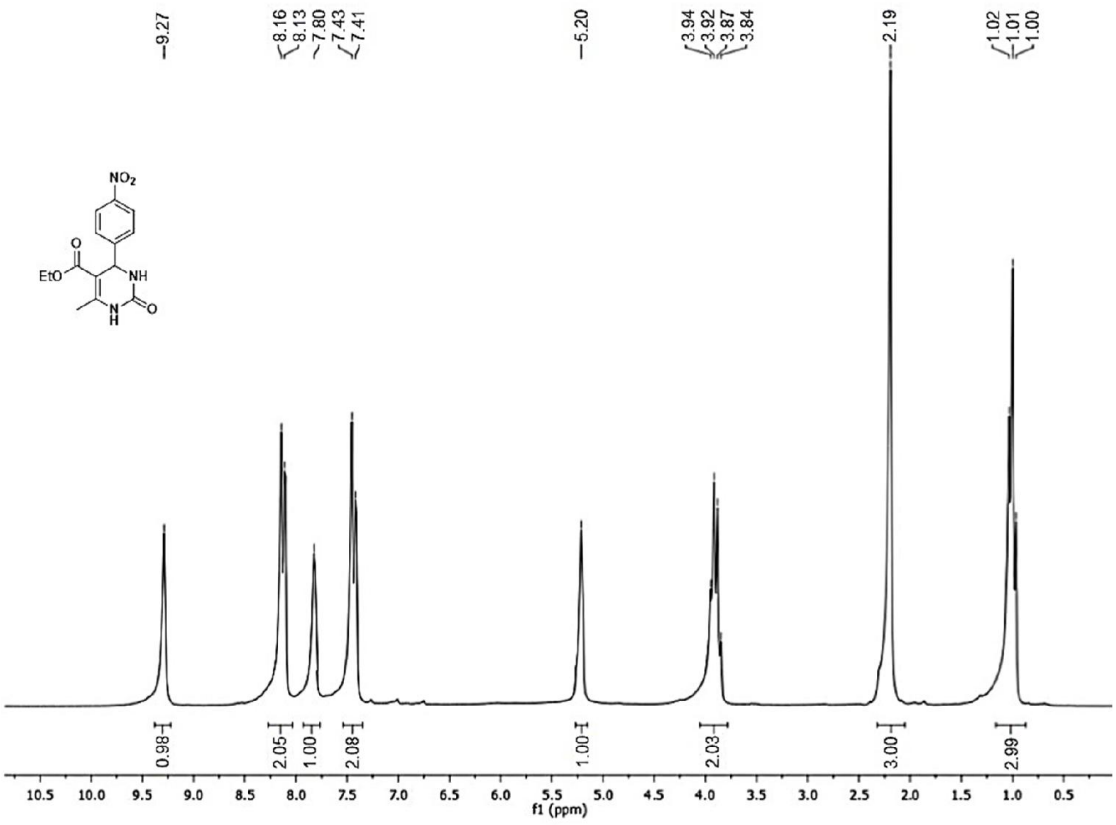

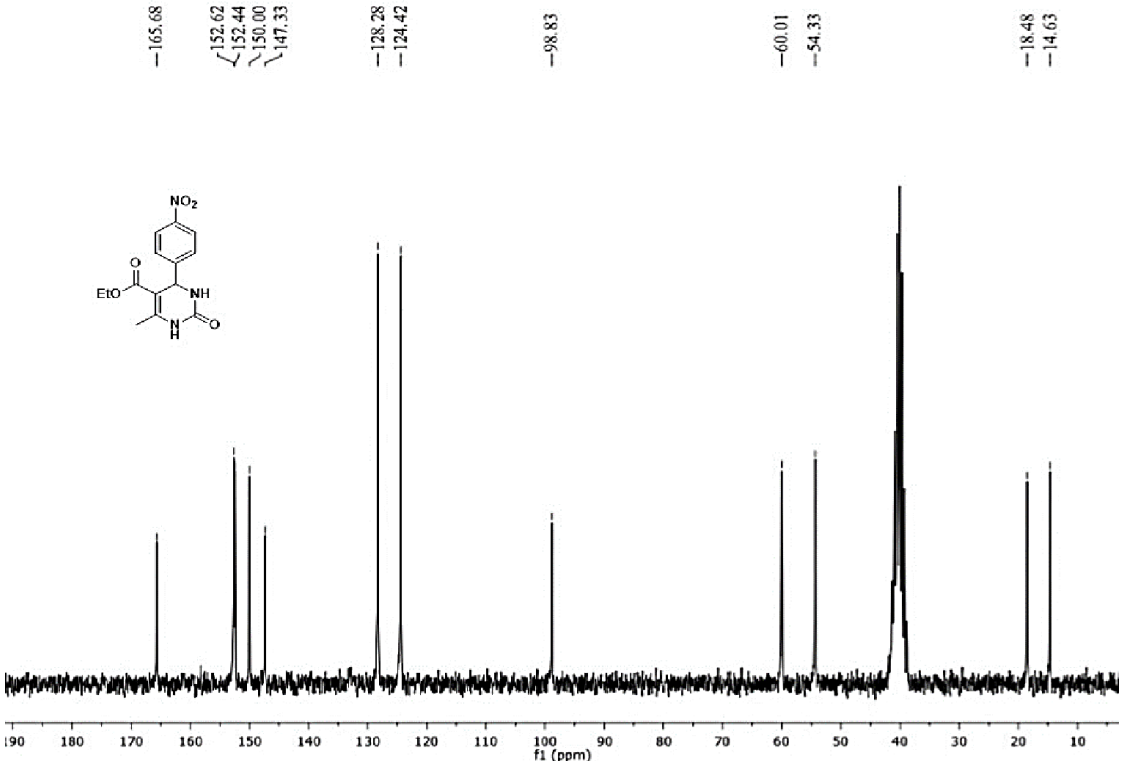

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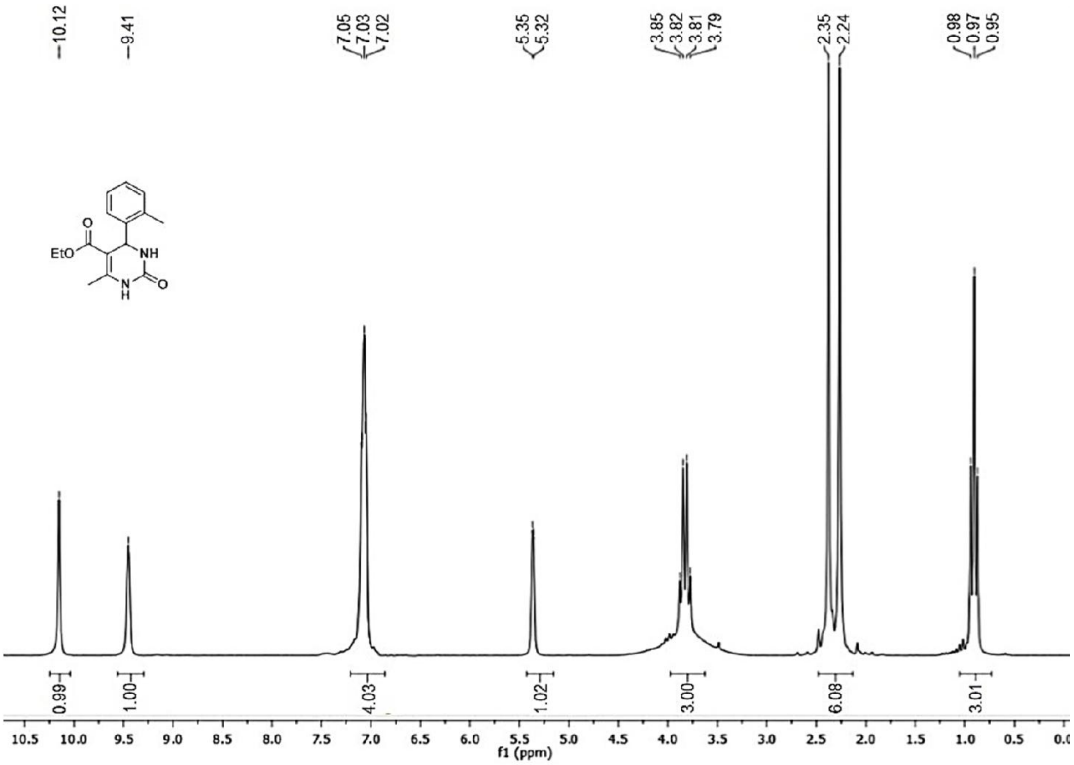

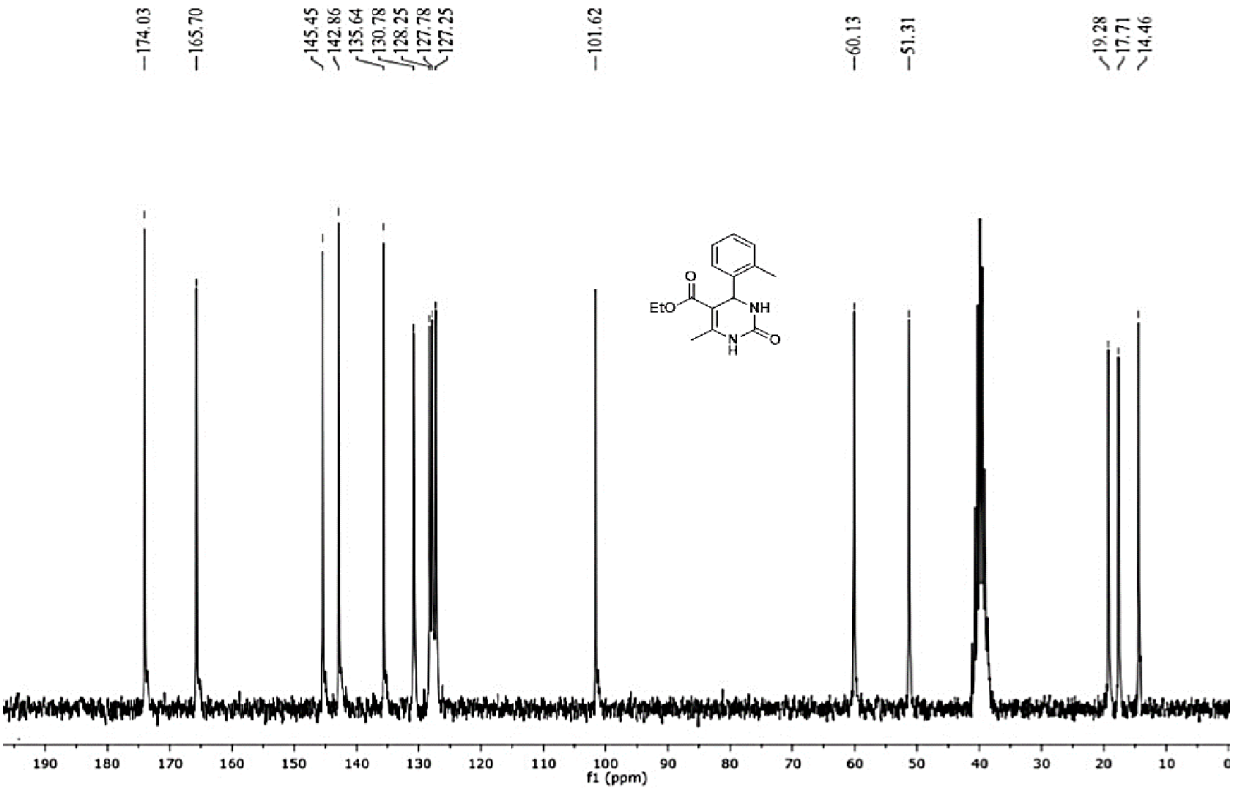

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