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Solvent-Free Biginelli Reactions Catalyzed by Hierarchical Zeolite Utilizing Ball Mill Technique: Green Sustainable Process

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Abstract

A sustainable green one pot procedure for the synthesis of dihydropyrimidinones (DHPMs) derivatives by a three-component reaction of *β*-ketoester derivatives, aldehyde and urea or thiourea over the alkali-treated H-ZSM-5 zeolite under ball-milling has been developed. The product was isolated by simple washing of the crude reaction residue with ethyl acetate followed by evaporation of solvent. The hierachical zeolite catalyst (MFI27_6) showed high yield (86–96%) of dihydropyrimidinones (DHPMs), in very short time (10-30 min). The catalyst is recycled for subsequent reactions in four runs without appreciable loss of activity and high yields of products provide efficient protocol for Biginelli reactions.

Keywords: Hierarchical; MFI27; Biginelli; dihydropyrimidinones; Ball mill

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Introduction

Primary measures in sustainable chemistry must remain the domain of chemists who continue to improve synthetic processes by avoiding wastes or pollution and who try to save resources, energy and labor while synthesizing common and better products. Various approaches exist that improve the sustainability of known processes. some of them including (i) non-classical energizing by ultrasound, microwave or mechanochemical process, (ii) catalysis instead of stoichiometric processes, (iii) solvent-free reactions (iv) solid-phase syntheses, All of these tools may be helpful in various instances; however, the necessary workup procedures will detract from their sustainability because liquid state reactions are rarely quantitative.

Moreover, catalysis has been, and will remain, one of the most important research subjects, because this is the only rational means of producing useful compounds in an economical, energy–saving and environmentally benign way, in addition to, catalysis is one of the most important principles of green chemistry. Ideally, we should aim at synthesizing target compounds with a 100% yield, 100% selectivity and avoid the production of wastes. This process must be economical, safe, resource-efficient, energy-efficient and environmentally benign. In this regard, the atom economy [1] and the E-factor [2] should be taken into account.

On the other hand, multicomponent are key source of molecular diversity which makes them powerful tool in modern drug discovery processes. Furthermore, the one-pot character furnishes fewer by-products in comparison to classical stepwise synthetic route with lower cost, time and energy. Among the multicomponent reactions, Biginelli reaction is one of the most studied reactions since the product of this reaction is dihydropyrimidinones (DHPMs) which are vital medicinal synthones that display a wide range of biological activities such as antibacterial, anti-inflammatory, antiviral, anti-tumour [3-5]. A large number of dihydropyrimidinones derivatives

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are pharmacologically important as antagonists, antihypertensive agents, significant calcium channel blockers, and neuropeptide antagonists [6-11]. The efforts on structural modification of DHPMs **1** led to the discovery of pharmacologically active compounds as represented in DHPMs scaffold (Figure 1).

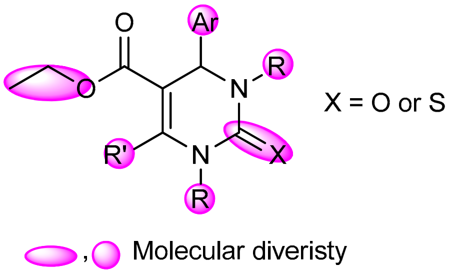
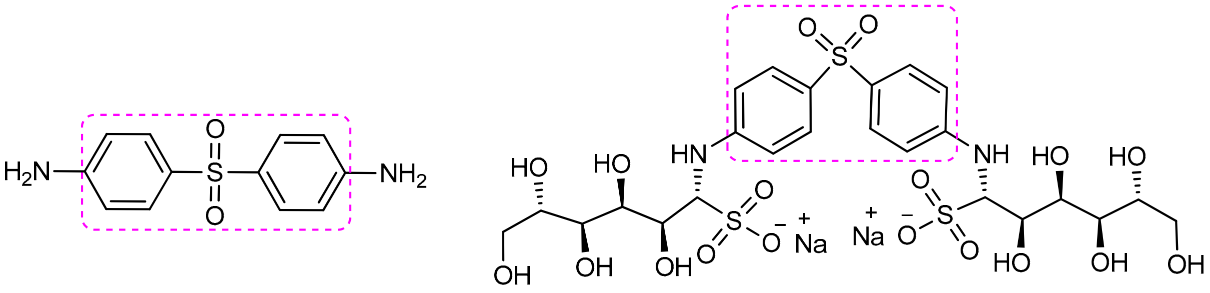


Fig.1: The design of bioactive DHPMs scaffold has many variables parts.

Furthermore, the diaryl sulfone function was found as potent antimicrobial agent [12]. Some well-known medicines are available in the market, for example Dapsone [13] and Promine [14]; as shown in Figure. 2. Noticeably, the combination of a diaryl sulfone ring system with various types of heterocyclic analogues has shown significant biological activities [15-19]. Therefore, the insertion of diaryl sulfone moiety to the DHPMs could provide novel derivatives of expected biological and pharmacological activities.



Dapsone ***Promin***

Fig. 2: Examples of drugs molecules containing the diaryl sulfone moiety

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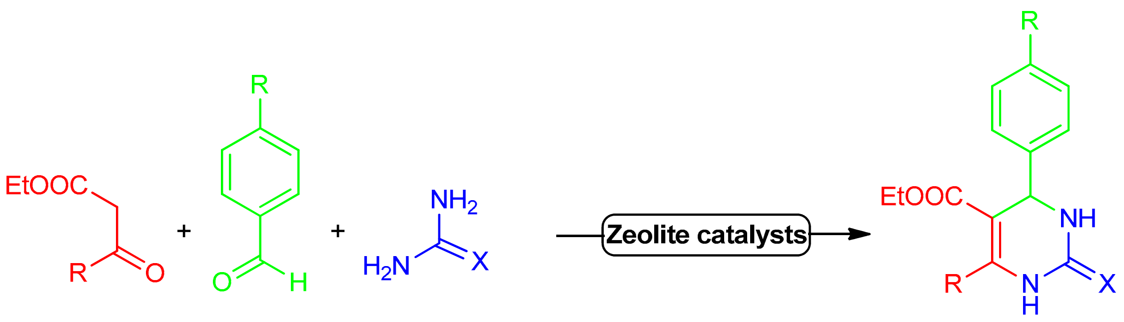
The commonly used homogeneous catalysts for Biginelli reaction, such as $BF_3 \cdot Et_2O$, $InCl_3$, $LaCl_3$, $Sr(NO_3)_2$, and ceric ammonium nitrate suffer from several disadvantages, including difficulty in separation, recovery, disposal of used catalyst, corrosion and high toxicity [20-24]. The utilization of solid heteropolyacids (HPAs) as alternate heterogamous catalysts for conventionally used reagents, such as HF, H_2SO_4 is well known for many years [25]. Heteropolyacids are also used as an acid catalyst for this transformation [26]. However, the difficulties with polyoxometalates are their recovery and reuse in presence of water and organic solvents [27,28]. To overwhelm this shortcoming, heterogenization of these polyoxometalates into various host supports like silica [29] and activated carbon [30] has already been reported. Nevertheless, these supported catalysts tend to have restricted POM loading, show some leaching and susceptible for agglomeration [31]. On the other hand, KSF montmorillonite [32] and zeolite [33] in refluxing toluene have been used for Biginelli cyclocondensation to give dihydropyrimidinones. A moderate yield using environmentally unfavorable solvent in long reaction time was attained. M. Tajbakhsh et al. [34] used natural zeolite Heulandite possessed good dihydropyrimidinones derivatives yield (75%) in 4-5 h at 100ºC. Table 1 summarizes the utilization of zeolites as catalyst for Biginelli reaction in the last two decades.

Table 1: Utilization of zeolites as catalyst for Biginelli reaction in last two decades

General Biginelli Reaction:



Entry	**Type of zeolite used**	**Method**	**Time**	**Yield**	**Ref.**	**Temp.**
1	Commercial HZSM-5	Reflux in toluene	24h	21%	[33][a]	100 **ºC**
2	Commercial HY	Reflux in toluene	24h	80%	[33][a]	100 **ºC**
3	MCM-41	Reflux in toluene	24h	38%	[33][a]	100 **ºC**
4	Natural zeolite Heulandite	Reflux in acetic acid	5h	75%	[34][a]	100 **ºC**
5	Metal/Y zeolite	Reflux in ethanol	12h	20-38%[b]	[39][a]	70 **ºC**

[a] The results obtained for the-the reaction of ethyl acetoacetate , benzaldehyde, and urea

b Depending on the type of metal used

However, the drawback of the published work using zeolite catalysts for the Biginelli reaction is the long time working up under hazards conditions procedures and the moderate product yield (Table 1). It was reported that, the desilication and subsequent dealumination of HZSM5 shorten the diffusion path length and enhance the transport rate of all aromatic molecules [35-37], leading to enhanced activity and selectivity compared to the parent material [37,38].

Regarding the efficient green methods applied to distribute energy for chemical processes, it was found that ball milling technique compared to other methods leaving their marks on the road to sustainable synthesis (e.g. microwave, ultrasound, ionic liquids), chemistry in ball mills is rather underrepresented in the knowledge of organic chemists. Especially, in the last ten years the interest in this technique raised continuously, culminating in several high-quality synthetic procedures covering the whole range of organic synthesis [40, 41]. More recently a solvent free ball milling Biginelli reaction utilizing subcomponent synthesis was reported [42]. The main drawback of this reported method is the two step synthesis procedures, a tedious working up, purification of the products required column chromatography and high cost of the self-catalyst's precursor.

In the present work, the strategy to synthesize hierarchical ZSM-5 by post treatments of commercial H-ZSM-5 to improve its catalytic performance towards Biginelli reaction and introduce novel DHPMs derivatives contains diarylsulfone moiety under solvent free condition utilizing ball mill technique in one pot fashion. The catalyst is easily recoverable and reused up to four times without significant loss of its activity. Hence, short reaction time, facile recovery and recycling of the catalyst and solvent free condition makes our process more advantageous to that of the other processes.

2. Results and Discussions

2.1. Powder x-ray diffraction (PXRD)

X-ray diffraction of as-received ZSM-5 and alkali-treated zeolite samples are presented in Fig. 3. All the diffraction patterns are assigned to MFI structure, where the diffraction patterns at around 23°, 23.07° and 23.25°, respectively were detected. The MFI did not change in intensity and the lattice parameters were the same for all the investigated samples. However, MFI27_6 showed slightly lowering in peak intensities and little line broadening than the other treated zeolites. This slight change in diffraction patterns after alkali-treatment for long time probably because smaller crystalline domains and pore widening are formed upon silicon extraction [43].

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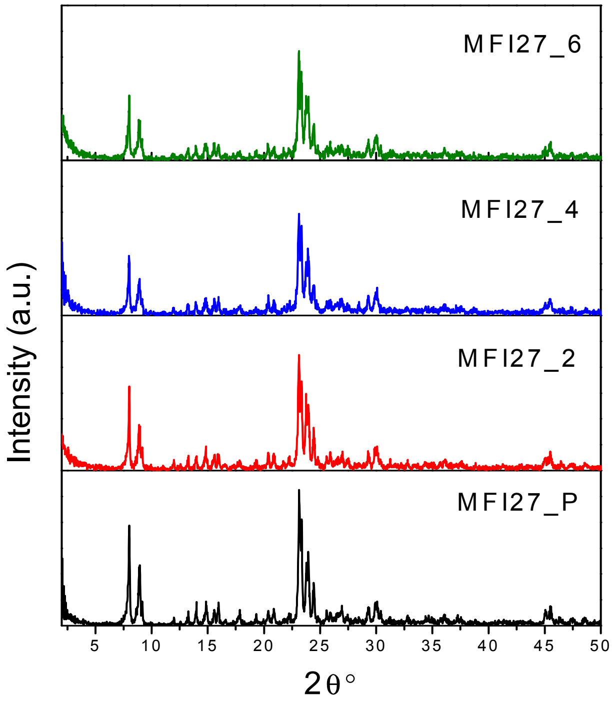

Fig. 3: XRD patterns for as-received and alkali-treated ZSM-5 catalysts.

2.2. N_2 physisorption

The alkali-treatment of ZSM-5 as received usually leads to selective extraction of Si [43]. Table 2 shows the Si/Al ratio calculated for MFI samples decreases upon increasing the time of alkali-treatment while no significant structural changes takes place as shown from X-ray diffraction patterns. A pronounced difference in the textural properties between as-received MFI27_P and alkali-treated samples was recorded by N_2-adsorption measurements. Fig.4 shows the N_2 adsorption/desorption isotherms on as-received MFI27_P and other treated zeolite samples. MFI27_P shows a type I, while the alkali-treated samples show a combined type I and IV isotherm. The horizontal shape of hysteresis loop in isotherms of alkali-treated samples indicates inkbottle-type mesopores [44].

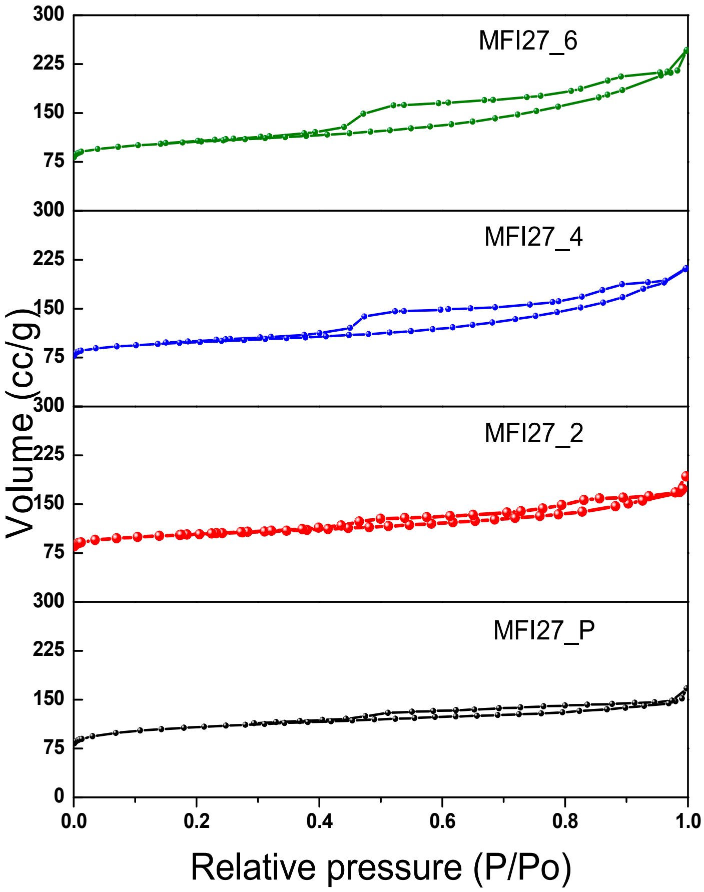

Fig. 4: N_2 adsorption/desorption isotherms of as-received ZSM-5 and alkali-treated zeolite samples

Fig. 5 illustrates the pore size distributions using NLDFT method for the adsorption branch of isotherms. There is right shift in the pore size towards mesoporous range with the extended period of alkali-treatment, the diameter of the mesopores slightly increased and a sharp distribution around 7 nm was observed after 6 hours of alkali-treatment (MFI27_6).

Table 2 shows the BET surface area (S_{BET}), micropore surface area (S_{micro}), mesopore surface area (S_{meso}), total pore volume (V_{total}) micropore volume (V_{micro}), and mesopore volume (V_{meso}) of all the investigated samples. The values of V_{micro} and S_{micro} were decreased from their original

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values, while those of V_{meso} and S_{meso} increased by alkali-treatment for MFI27_P sample. The increase in the pore volume with diameters of approximately 4–7 nm for the desilicated samples confirmed the generation of mesopores by desilication. Deposition of the dissolved amorphous SiO_2 overlayer decreased the micropore volume and BET-surface area due to blocking of some pores [45,46]. The hierarchy factor (HF) increases after the alkali treatment of the parent sample which indicates that the external surface area enhanced with a significant reduction in the micropore volume. However all alkali treated samples (MFI27_2, MFI27_4 and MFI27_6) have approximately the same HF.

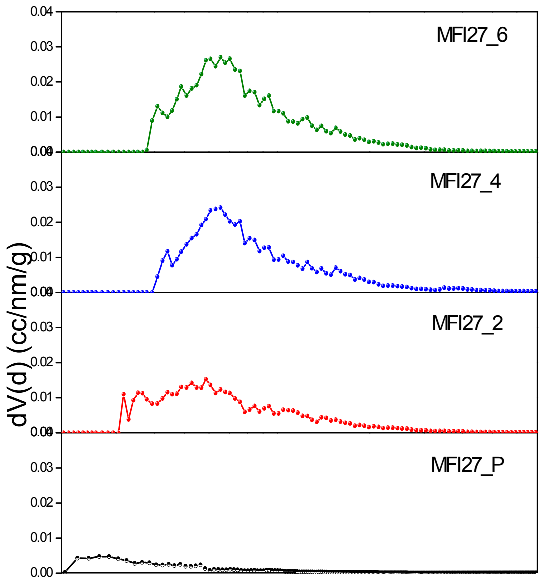

Fig. 5: Pore size distribution of as-received ZSM-5 and alkali-treated zeolite samples

Table 2: Si/Al ratio, physicochemical properties of the parent and post modified zeolites

Samples	**Si/Al**	**S_{BET}^{a} (m^2/g)**	**S_{micro} (m^2/g)**	**S_{meso} (m^2/g)**	**V_{Total}^{b} (cm^3/g)**	**V_{micro}^{c} (cm^3/g)**	**V_{meso}^{d} (cm^3/g)**	**Hierarchy factor ^{e} (-)**

MFI27_P	13	399	360	39	0.25	0.16	0.09	0.063
MFI27_ 2	10.9	356	268	88	0.29	0.12	0.17	0.102
MFI27_ 4	9.8	334	196	138	0.32	0.08	0.24	0.103
MFI27_ 6	8.6	363	200	163	0.38	0.08	0.30	0.095

[a] BET surface area
[b] Total pore volume at $P/P_o = 0.997$
[c] Micropore volume from t-plot
[d] $V_{meso} = V_{Total} - V_{micro}$
[e] Hierarchy factor = $(V_{micro} / V_{total}) \times (S_{meso} / S_{BET})$

2.3. Evaluation of the acid sites

In order to evaluate the acidity of alkali-treated ZSM-5 zeolite compared with the as-received one, the acidic properties of H-form zeolites were investigated. Almost no change in acidity was observed after treatment. Fig. 6 shows the NH_3-TPD profile for all the investigated samples, the peak intensities slightly decreased with prolonged alkali-treatment, and the peaks became broadened. As a result, the amounts of acid sites calculated from the desorption at the higher temperature, were 0.822 mmol g^{-1} zeolite for as-received ZSM-5, 0.667, 0.732, and 0.559 mmol g^{-1} for MFI27_2, MFI27_4, MFI27_6, respectively. Typical results of FTIR spectra for pyridine adsorption are illustrated in Fig. 7. The band at 1520 cm^{-1} assigned to Brønsted acid sites did not change, while the relative intensity of band due to Lewis acid sites at 1460 cm^{-1} slightly increased by alkali-treatment. Similar results were reported by M. Ogura et al. [35], where little dealumination of the zeolite sample occurred due to alkali-treatment.

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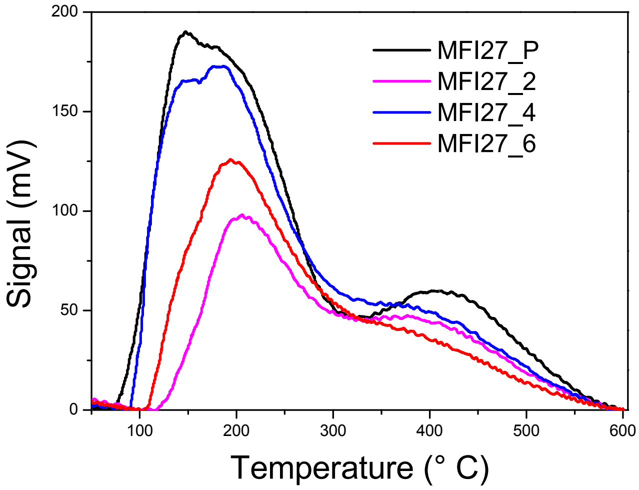


Fig. 6. NH_3-TPD profile of as-received ZSM-5 and alkali-treated zeolite samples

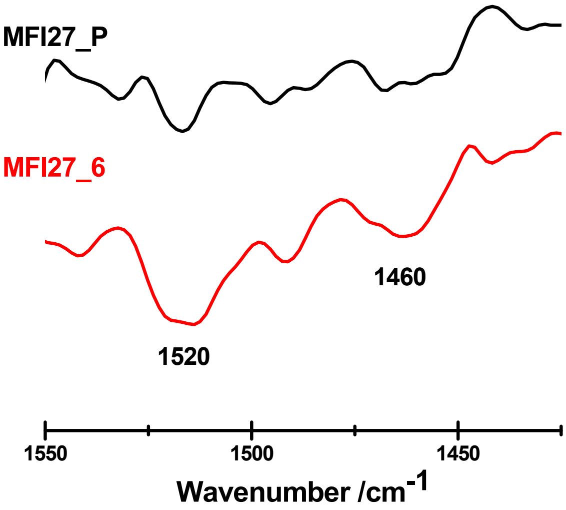
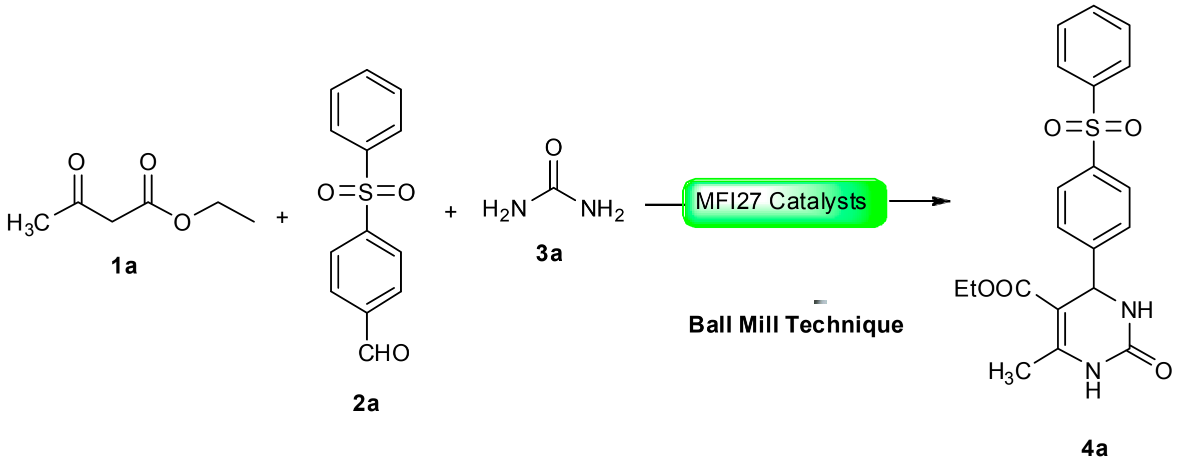


Fig. 7. FTIR spectra of as-received MFI27_P and MFI27_6 zeolite samples

2.4. Evaluation of the catalytic activity of the catalysts in the DHPM synthesis

The catalytic activity of the prepared zeolite catalysts were evaluated in the synthesis of DHPMs through the Biginelli reaction, where multicomponent reaction between ethyl acetoacetate **1a**, benzaldehyde derivative **2a**, and urea **3a** (Scheme 1) was chosen. A ball-mill, solvent free technique, was applied and optimization of the reaction conditions for this particular reaction was studied. The results obtained from the catalytic test reaction are cited in Table 3. It is found that MFI27_6 catalyst showed highest product % yield (91%) in shortest time (20 min) utilizing 0.25 g of catalyst and 30 Hz ball-mill frequency. To optimize the effect of catalyst's weight, different amounts of MFI_6 catalyst was used under the same reaction conditions, where 0.35 g of catalyst afforded products in excellent yields 96 % in 10 min. Moving forward to the investigation of the effect of frequency of ball mill on this catalytic system, three reactions were performed with 15Hz, 25Hz and 30 Hz of the best catalyst loading (entries 5,6,7).



Scheme 1

The best frequency for this reaction protocol proved to be 30Hz (entry 5), in which the desired product was isolated in 96% yield.

The isolated product **4a** gave satisfactory elemental analysis and the obtained spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR, MS) was consistent with their assigned structure. The IR spectrum of the product showed the presence of NH absorption band at 3218 cm^{-1}and two carbonyl absorption bands at 1735, 1680 cm^{-1} and two characteristic symmetrical and asymmetrical absorption band of sulfone group at 1310 and 1145cm^{-1}. The mass spectra of the isolated product

4a, showed a peak corresponding to the molecular ion at m/z 400. Its ^{1}H NMR spectrum revealed a singlet signal at δ a triplet signal at δ 1.16 (CH_3 ester, J = 6.8 Hz), 2.35 (CH_3), a quartet signal at δ 4.07 (CH_2 ester, J = 6.8 Hz), a doublet signal at δ 5.41 (CH-4) and two D_2O exchangeable signals at δ 5.53, 7.56 due to two NH protons, respectively, in addition to aromatic protons as a multiplet at δ 6.90-7.33.

Table 3: optimization the reaction conditions for the Biginelli reaction

Entry	Catalyst	Catalyst wt. (g)	Time (min)	Yield (%)	Ball-mill Frequency (Hz)
1	MFI27_P	0.25	60	21	30
2	MFI27_2	0.25	40	83	30
3	MFI27_4	0.25	35	86	30
4	MFI27_6	0.25	20	91	30
5	MFI27_6	0.35	10	96	30
6	MFI27_6	0.35	10	90	25
7	MFI27_6	0.35	10	81	15

The scope and generality of this protocol was tested by various derivatives of reactants **1a-c**, **2a,b** and **3a,b** using MFI27_6 catalyst as shown in the Scheme 2. The reaction conditions were optimized, where 0.35 g catalyst and 30 Hz Ball-mill frequencies were applied and the corresponding DHPM products were obtained in excellent yields (86–96%, Table 4).

The reusability of the MFI27_6 catalyst was checked for several reaction cycles under the optimized reaction conditions, the catalyst removed after the completion of the reaction by filtration, washed with ethyl acetate and dried under vacuum. The recovered catalyst was reused for five times using the same reaction conditions. Fig. 8 shows that the regenerated catalyst performs the reactions efficiently under the same reaction conditions even after being used till five times. The slight decay observed in the catalytic activity of the MFI27_6 catalyst on the

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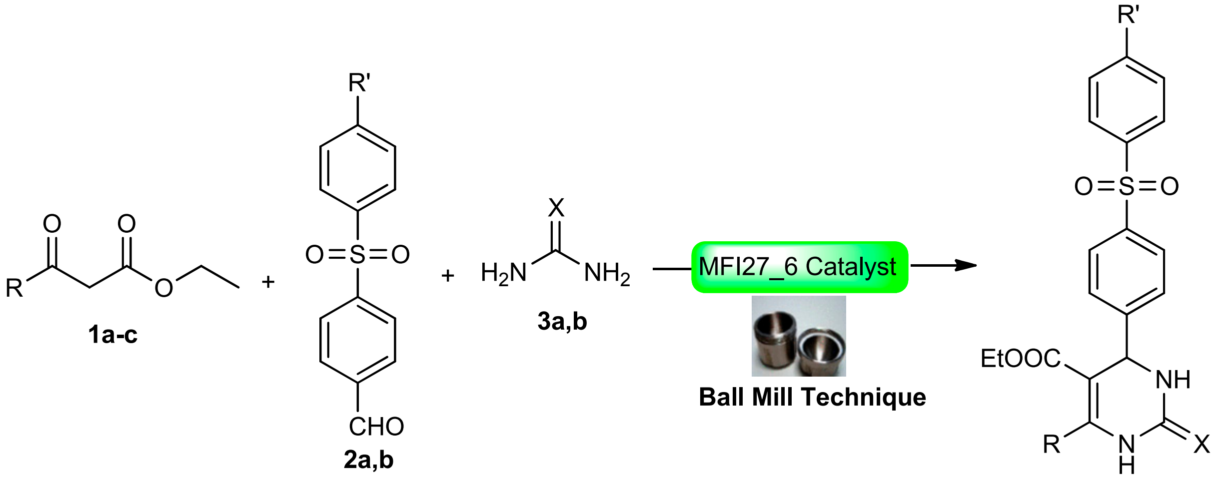
fourth and fifth time could be attributed to the weight loss of the catalyst during the working up in each time [47,48]. These results are indicating the robust nature of the MFI27_6 catalyst for Biginelli reaction.



1-4	R	R'	X
a	CH_3	H	O
b	CH_3	H	S
c	CH_3	CH_3	O
d	CH_3	CH_3	S
e	CF_3	H	O
f	CF_3	H	S
g	CF_3	CH_3	O
h	CF_3	CH_3	S
i	Ph	H	O
j	Ph	H	S
k	Ph	CH_3	O
l	Ph	CH_3	S

Scheme 2

The structure of DHPM derivatives **4a–l** was assigned and found in line with of their elemental analyses and spectral data (*cf.* experimental part), notably, the ^{19}FNMR spectrum of compounds **4e-h** is the key analysis for fluorine containing compounds. Taking compound **4e** as an example, only the signals of trifluoromethyl group were observed in the ^{19}F NMR spectra at δ -61.66 ppm (*cf.* experimental part).

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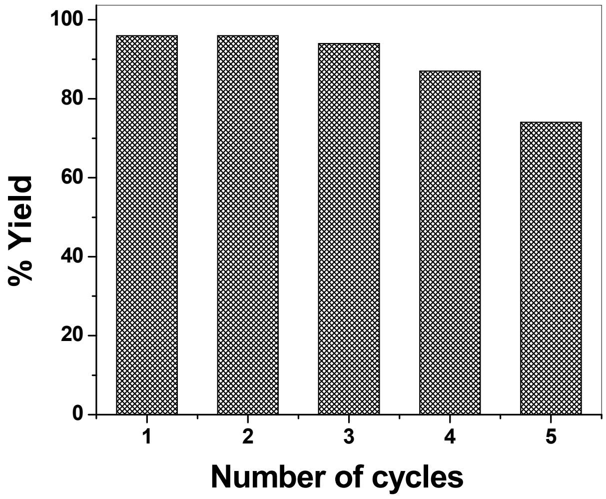

Fig. 8. Re-usability of MFI27_6 catalyst

The mechanism of the Biginelli reaction is still a controversial subject; however, it is already known that the reaction that leads to the formation of the DHPMs product can occur through three different pathways in which the process starts by the formation of three possible intermediates: Knoevenagel, iminium, or enamine [49]. To gain insight into the reaction mechanism in the presence of the MFI27_6 catalyst, a time-dependent ^{1}H NMR mechanistic studies have been done in order to investigate whether the reaction proceeds through which intermediate. The progress of the reaction of ethyl acetoacetate **(1)** with aldehyde **2** and urea **(3a)** was monitored by ^{1}H NMR at regular time intervals of 2 min. The ^{1}H NMR was recorded (Fig. 9), and a new signal at 8.62 ppm which is corresponding to the =CH- grew simultaneously with a decrease in the intensity of the aldehyde proton signal at 9.98 ppm. Both signals disappeared after 6 min. Time-dependent ^{1}H NMR studies suggest that the reaction occurs *via* the Knovenagel intermediate (Scheme 3).

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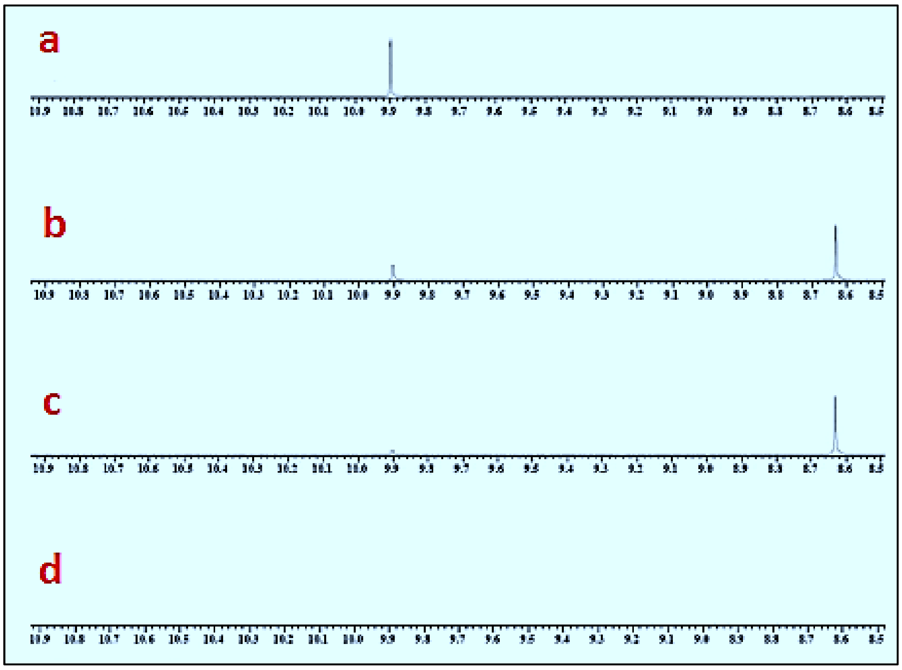

Fig. 9. Time-dependent ^{1}H NMR spectra for Biginelli reaction, Formation of 4a. Each spectrum was recorded atregular time intervals: (a) 0 min., (b) 2 min. (c) 4 min. (d) 6 min.

Therefore, we performed an experiment under optimal reaction conditions without urea to get the Knoevenagel product (used as authentic sample for intermediate comparing TLC), then the reaction was carried under optimal condition, in which the composition of the reaction medium was monitored by thin layer chromatography (TLC) at regular time intervals (3 min.). A Knoevenagel adduct as well as a new product spots were detected by TLC. As the reaction proceeded, the intermediate spot (Knoevenagel adduct) decreased quickly till vanishes whereas the new product spot increased. This finding supports that the reaction evaluated under optimal reaction conditions occurs via Knoevenagel intermediate **c** (through carbenium ion intermediate **b**) Scheme 3.

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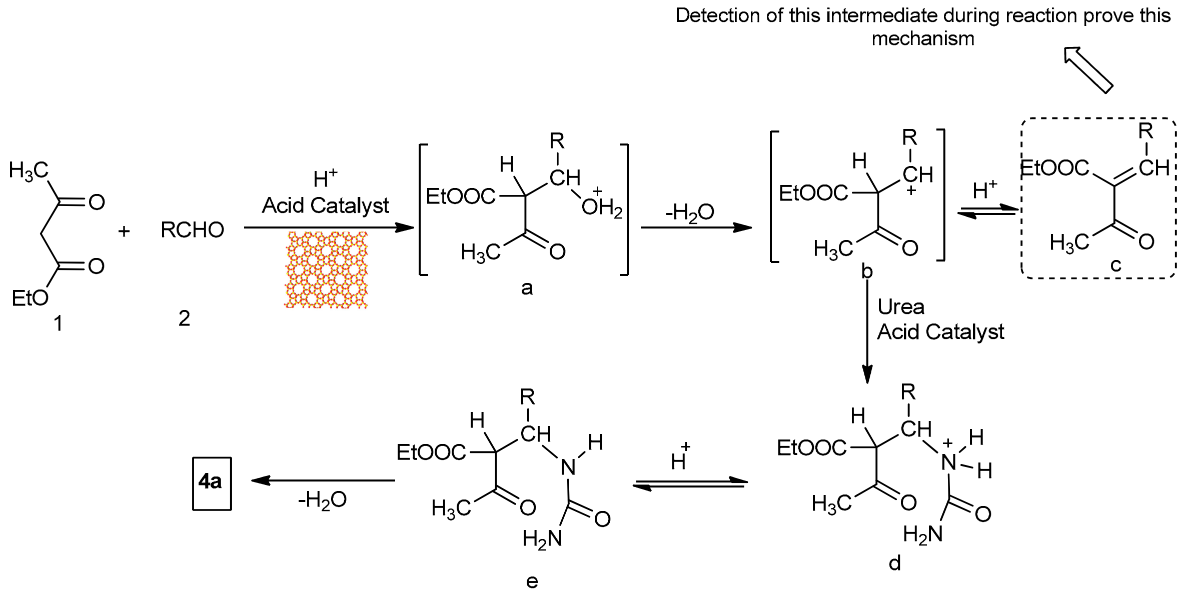

Scheme 3

Table 4: Synthesis of DHPM derivatives using MFI127_6 catalyst under solvent free conditions.

Compound	Time (min.)	Yield%	Compound	Time (min.)	Yield%
4a	10	96	**4g**	30	86
4b	10	96	**4h**	30	89
4c	20	89	**4i**	20	90
4d	20	90	**4j**	20	92
4e	30	88	**4k**	30	86
4f	30	91	**4l**	30	88

The superior catalytic activity and high yield of the desired products in very short reaction time was a result of different parameters: i) the physicochemical properties of the catalyst i.e. porous and acidic nature ii) the mechano-chemical effect caused by ball mill technique during the reaction process. Alkali-treatment is another way of modifying zeolite, where the results of chemical analyses and crystallography clearly show that the alkali-treatment led to extraction of a siliceous species from the framework of ZSM-5. It is shown from surface area measurements that the increase in the time of alkali treatment resulted in a pronounced increase in the mesopore volume/ surface area and hierarchically of the alkali treated MFI27_6 catalyst. Mesopores are then formed with no collapse in crystal structure of the as-received ZSM-5, resulting in the enlargement of external surface area of the zeolite. The porous nature of alkali treated catalyst enables the reaction to occur easily, although the bulky groups in the reagents, due to the induced shape selectivity of the zeolite as a result of its pore widening. Therefore, we can conclude that alkali-treatment increases mesopores and the external surface of zeolite, increases the number of adsorption sites located near the pore mouth on the external surface of zeolite, and as a result, promotes the diffusion of reactant through mesoporous zeolite. Noteworthy, the high yield and very short reaction time not only due to the used solid acid catalyst but also, the ball mill technique mentioned here for chemical transformations, the term mechanochemistry coined. According to IUPAC a mechano-chemical reaction is defined as ‘‘a chemical reaction that is induced by the direct absorption of mechanical energy’’ [50]. However, mechanochemistry is more than the reactive treatment of substances. It was known that, the mechanical activation of solids leads to an increase of external surface area, surface energy and number of defects. The increased surface energy can result in a mechano-chemical activation if alterations in structure, chemical composition or chemical reactivity occurred throughout milling. [51].

3. Conclusions

Alkali treated ZSM-5 zeolite in NaOH solution at different time interval was characterized. The catalytic activity of the as-received and alkali treated catalysts was investigated towards Biginelli reaction. A siliceous species was selectively dissolved from relatively weaker parts of the framework of zeolite, resulting in creation of mesoporous hierarchical structure with better

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crystallinity of the remaining zeolite on alkali-treated zeolite. The acidity was slightly changed, with pronounced increase in the number of adsorption sites. The superior catalytic activity and high yield of the desired products in very short reaction time was mainly due to the adsorptive-diffusive property of ZSM-5 is improved by alkali-treatment and mechanochemical effect introduced by ball mill technique.

4. Experimental

4.1. Materials

Commercial ZSM-5 zeolites (ALSI PENTA, SM27, Si/Al = 13) with a nominal SiO_2/Al_2O_3 of 27 was used as a parent zeolite. It was calcined at 550 °C for 5 hours under the flow of synthetic air to get proton form and labelled as MFI27.

4-(phenylsulfonyl)benzaldehyde [52] and 4-tosylbenzaldehyde [53] were prepared according to literature procedures.

4.2 Alkali-treatment of ZSM-5

Typically 50 ml of 0.2 M NaOH solution was used to treat 1.5 g of zeolite powder under stirring condition. The treatment was carried out at 80°C for 2, 4, 6 hours and labelled as MFI27_2, MFI27_4, MFI27_6 respectively. After the treatment, the sample was quenched in an ice bath, filtered thoroughly washed with distilled water and subsequently dried at 100°C overnight. To convert the alkali treated sample into H-form, 1 g of alkali treated zeolite powder was ion-exchanged three times with 1mol L^{-1} NH_4NO_3 under stirring condition for 8 hours at 25°C. The pH of the solution was adjusted at 7 with NH_4NO_3. The ion exchanged powder was filtered, washed and dried at 100°C overnight. Subsequently the post modified sample was calcined at 550°C for 5 hours under the flow of synthetic air. The post treatment modified commercial zeolites by alkali treatment are labelled as MFI27_2, MFI27_4 and MFI27_6.

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4.3 Characterization techniques

XRD diffraction patterns were obtained from X'pert Pro diffractometer from Phillips Analytical. CuKα radiation ($\lambda = 1.54056$ Å) was used. The samples were measured in sample holders with a smaller exposure area. Diffraction patterns of the calcined samples were measured by using the following program: 2Θ angle from 2 to 50° with a step of 0.02° and increasing duration of 5 s per step. Concentrations of Si and Al were determined by means of inductively coupled plasma-optical emission spectrometry (ICP-OES Plasma 400, Perkin Elmer, USA). N_2 physisorption measurements were performed using Quadrasorb^{TM} SI instrument (Quantachrome, USA) at a temperature of −196°C. The samples were outgassed by heating at 250 °C under high vacuum and kept at these conditions for 12 h prior to the adsorption/desorption measurements. Specific surface areas were calculated according to the Brunauer, Emmet and Teller (BET) equation from the adsorption isotherm. The pore-size distribution of zeolite samples was calculated from adsorption branch using the NLDFT method. Ammonia temperature programmed desorption (NH_3-TPD) of as-received and alkali-treated zeolites was measured using TPDRO 1100 Thermo-electron corporation. The sample was placed between the layers of quartz wool in a glass tube and then pre-treated in the helium flow at 550°C for 30 min. with a ramp of 10°C/min. The saturation of zeolite sample with gaseous ammonia was carried out at 120°C for 30 minutes. Finally the ammonia was removed in the helium flow at 600°C for 60 min. with a ramp of 10 °C/min. The gas coming out of glass tube was analysed by a thermal conductivity detector (TCD). DRIFT spectra were collected at room temperature using Perkin-Elmer Spectrum 100 FTIR spectrometer. The samples were subjected to a pyridine adsorption and the analysis was carried out over a catalyst disk which was treated at 100ºC under vacuum for 5 h. Later, the

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sample was treated with pyridine vapor and finally heated at 100ºC under vacuum for 30 min prior to each measurement.

4.4. Characterizations of the reaction products

All melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. The infrared spectra were recorded for the compounds in Perkin Elmer SP 100 infrared spectrophotometer. The ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a Bruker WM 400 MHz spectrometer, respectively using TMS (0.00 ppm). The signal of the deuterated solvents was used as internal standard. Chemical shifts (δ) are given in ppm relative to the signal for TMS as a standard, and coupling constant in Hz. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 eV. Elemental analyses (C, H, N and S) were carried out at the Microanalytical Center of Cairo University, Giza, Egypt, the results were found to be in good agreement (±0.3%) with the calculated values. Ball milling experiment were carried out using RETSCH™ ball mill (cryo mill model without cryogenic grinding) utilizing 25 ml stainless steel gar and two 12mm stainless steel balls

4.5. Typical procedure for the catalytic test reaction

MFI27 catalysts (0.35 g), were added to *β*-ketoester derivatives **1a-c** [(**1a:** 0.65g, **1b**: 0.92g, **1c:** 0.96g) (5 mmol)], benzadehyde derivatives **2a,b** [(**2a:** 1.23g, **2b:** 1.3g)(5 mmol)] and urea derivatives **3a,b[**(**3a**: 0.36g, **3b:**0.46g) (6 mmol)**]** in a mortar, the mixture was ground with a pestle at room temperature then placed in the 25 mL stainless steel jar equipped with two stainless steel balls (15mm in diameter). The jar was closed and milling was conducted at the frequency given in Table 3. After 3 min, the progress of the reaction was checked by thin layer chromatography (TLC). If necessary, the milling cycle was repeated until the reaction was complete. The product was isolated by simple washing of the crude reaction residue with hot ethyl acetate and sonicated for 5 min. to desorb all adsorbed product on the surface of catalyst then remove the catalyst by filtration. The reaction product was separated as a solid after evaporation of ethyl acetate under reduced pressure to give pure compounds **(4a–l)** in excellent yield.

The catalyst used was redeemed by washing with hot ethyl acetate. Compound **4a** was obtained in the presence of various catalysts (such as MF127_P, MF127_2, MF127_4 and MF127_6) using ball mill technique. It was found that all catalysts used exhibited catalytic activity but MF127_6 was the most effective of all the catalysts tested to promote the reaction with high yield in short time (Table 2).

Physical and spectral data of the title compounds 4a-l are listed below:

Ethyl 6-methyl-2-oxo-4-(4-(phenylsulfonyl)phenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4a)

mp 271-273 °C; IR (KBr) ν/cm^{-1}: 3218 (NH), 1735, 1680 (CO), 1310, 1145 (SO_2); ^{1}H NMR (DMSO-*d*$_6$) : δ 1.16 (t, *J* = 6.8 Hz, 3H, CH_3 ester), 2.36 (s, 3H, CH_3), 4.08 (q, *J* = 6.8 Hz, 2H, CH_2 ester), 5.41 (s, 1H, CH-pyrimidine), 5.53 (s, 1H, NH, D_2O exchangeable), 6.73-7.32 (m, 7H, ArH), 7.57 (s, 1H, NH, D_2O exchangeable), 7.89-7.96 (m, 2H, ArH); ^{13}C-NMR (DMSO-*d*$_6$): δ 19.29 (CH_3 ester), 22.99 (CH_3), 59.19 (C-4), 64.40 (CH_2 ester), 104.48 (C-5), 128.17 (Cph), 128.25(Cph), 131.47 (Cph), 132.47 (Cph), 133.60 (Cph), 141.91 (Cph), 147.58 (Cph), 150.09 (C-6), 153.57 (Cph), 157.37 (C-2), 170.55 (CO ester); MS: 400 (M^+); Anal. calcd. for $C_{20}H_{20}N_2O_5S$ (%): C 59.99, H 5.03, N 7.00, S 8.01 Found: C 60.21, H 4.99, N 6.89, S 7.94.

Ethyl 6-methyl-4-(4-(phenylsulfonyl)phenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4b)

mp 259-261 °C; IR (KBr) ν/cm^{-1}: 3211 (NH), 1729, 1684 (CO), 1306, 1145 (SO_2); ^{1}H NMR (DMSO-*d*$_6$) : δ 1.17 (t, *J* = 7.2 Hz, 3H, CH_3 ester), 2.37 (s, 3H, CH_3), 4.11 (q, *J* = 7.2 Hz, 2H, CH_2 ester), 5.41 (s, 1H, CH-pyrimidine), 6.95 (s, 1H, NH, D_2O exchangeable), 7.28-7.36 (m, 7H, ArH), 7.48 (s, 1H, NH, D_2O exchangeable), 7.77-7.86 (m, 2H, ArH); ^{13}C-NMR (DMSO-*d*$_6$): δ 13.98 (CH_3 ester), 17.13 (CH_3), 53.99 (C-4), 59.56 (CH_2 ester), 100.66 (C-5), 126.35 (Cph),127.66 (Cph), 128.11 (Cph), 128.54 (Cph), 128.86 (Cph), 143.45 (Cph), 145.01(Cph), 151.81 (C-6), 165.09 (Cph), 174.17 (CO ester), 183.79 (C-2); MS: 416 (M^+); Anal. calcd. for $C_{20}H_{20}N_2O_4S_2$ (%): C 57.67, H 4.84, N 6.73, S 15.40 Found: C 57.92, H 4.79, N 6.61, S 15.32.

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Ethyl 6-methyl-2-oxo-4-(4-tosylphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4c)

mp 290-292 °C; IR (KBr) ν/cm^{-1}: 3221 (NH), 1723, 1687 (CO), 1310, 1149 (SO_2); ^{1}H NMR (DMSO-*d$_6$*) : δ 1.14 (t, *J* = 6.8 Hz, 3H, CH_3 ester), 2.37 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 4.17 (q, *J* = 6.8 Hz, 2H, CH_2 ester), 5.34 (s, 1H, CH-pyrimidine), 6.49 (s, 1H, NH, D_2O exchangeable), 7.07-7.79 (m, 8H, ArH), 7.59 (s, 1H, NH, D_2O exchangeable), ^{13}C-NMR (DMSO-*d$_6$*): δ 13.62 (CH_3 ester), 17.06 (CH_3), 20.68 (CH_3-tosyl), 53.85 (C-4), 60.12 (CH_2 ester), 103.41 (C-5), 127.31 (Cph), 127.56 (Cph), 128.47 (Cph), 131.56 (Cph), 139.52 (Cph), 140.81 (Cph), 141.06 (Cph), 145.83 (C-6), 150.69 (Cph), 160.15 (C-2), 174.00 (CO ester); MS: 414 (M^+); Anal. calcd. for $C_{21}H_{22}N_2O_5S$ (%): C 60.85, H 5.35, N 6.76, S 7.74 Found: C 61.07, H 5.31, N 6.66, S 7.66.

Ethyl 6-methyl-2-thioxo-4-(4-tosylphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4d)

mp 282-284 °C; IR (KBr) ν/cm^{-1}: 3204 (NH), 1731, 1685 (CO), 1314, 1145 (SO_2); ^{1}H NMR (DMSO-*d$_6$*) : δ 1.09 (t, *J* = 6.8 Hz, 3H, CH_3 ester), 2.33 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 4.23 (q, *J* = 6.8 Hz, 2H, CH_2 ester), 5.36 (s, 1H, CH-pyrimidine), 6.58 (s, 1H, NH, D_2O exchangeable), 7.09-7.74 (m, 8H, ArH), 7.61 (s, 1H, NH, D_2O exchangeable); ^{13}C-NMR (DMSO-*d$_6$*): δ 13.82 (CH_3 ester), 17.54 (CH_3), 19.98 (CH_3-tosyl), 55.05 (C-4), 59.72 (CH_2 ester), 101.47 (C-5), 126.74 (Cph), 127.92 (Cph), 128.02 (Cph), 130.93 (Cph), 139.86 (Cph), 141.85 (Cph), 142.03 (Cph), 147.56 (C-6), 158.41 (Cph), 166.53 (CO ester), 178.10 (C-2); MS: 430 (M^+); Anal. calcd. for $C_{21}H_{22}N_2O_4S_2$ (%): C 58.58, H 5.15, N 6.51, S 14.90 Found: C 58.82, H 5.09, N 6.40, S 14.83.

Ethyl 2-oxo-4-(4-(phenylsulfonyl)phenyl)-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4e)

mp 218-220 °C; IR (KBr) ν/cm^{-1}: 3216 (NH), 1723, 1688 (CO), 1310, 1142 (SO_2); ^{1}H NMR ($CDCl_3$) : δ 1.16 (t, *J* = 6.8 Hz, 3H, CH_3 ester), 4.07 (q, *J* = 6.8 Hz, 2H, CH_2 ester), 5.39 (s, 1H, CH-pyrimidine), 6.29 (s, 1H, NH, D_2O exchangeable), 6.99-7.29 (m, 4H, ArH), 7.99-8.06 (m, 5H, ArH), 8.69 (s, 1H, NH, D_2O exchangeable); ^{13}C-NMR ($CDCl_3$): δ 14.16 (CH_3 ester), 54.92 (C-4), 60.11 (CH_2 ester), 101.22 (C-5), 121.88 (CF_3), 128.26 (Cph), 128.34 (Cph), 128.71 (Cph), 128.80 (Cph), 133.70 (Cph), 139.64 (Cph), 139.67 (C-6), 146.49 (Cph), 153.74 (Cph), 163.52 (C-2), 165.55 (CO ester); ^{19}F NMR ($CDCl_3$): δ -61.66; MS: 454 (M^+); Anal. calcd. for $C_{20}H_{17}F_3N_2O_5S$ (%): C 52.86, H 3.77, N 6.16, S 7.06 Found: C 53.12, H 3.69, N 6.05, S 6.99.

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Ethyl 4-(4-(phenylsulfonyl)phenyl)-2-thioxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4f)

mp 199-201 °C; IR (KBr) ν/cm^{-1}: 3227 (NH), 1731, 1686 (CO), 1310, 1145 (SO_2); ^{1}H NMR ($CDCl_3$) : δ 1.11 (t, *J* = 7.2 Hz, 3H, CH_3 ester), 4.19 (q, *J* = 7.2 Hz, 2H, CH_2 ester), 5.75 (s, 1H, CH-pyrimidine), 6.33 (s, 1H, NH, D_2O exchangeable), 7.06-7.34 (m, 4H, ArH), 8.01-8.15 (m, 5H, ArH), 8.21 (s, 1H, NH, D_2O exchangeable); ^{13}C-NMR ($CDCl_3$): δ 14.02 (CH_3 ester), 55.45 (C-4), 60.89 (CH_2 ester), 103.00 (C-5), 121.56 (CF_3), 128.10 (Cph), 128.27 (Cph), 128.84 (Cph), 128.96 (Cph), 132.15 (Cph), 139.52 (Cph), 140.01 (Cph), 147.98 (Cph), 153.12 (C-6), 162.23 (CO ester), 174.19 (C-2); ^{19}F NMR ($CDCl_3$): δ -61.52; MS: 470 (M^+); Anal. calcd. for $C_{20}H_{17}F_3N_2O_4S_2$ (%): C 51.06, H 3.64, N 5.95, S 13.63 Found: C 51.30, H 3.59, N 5.87, S 13.52.

Ethyl 2-oxo-4-(4-tosylphenyl)-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4g)

mp 219-221 °C; IR (KBr) ν/cm^{-1}: 3222 (NH), 1729, 1681 (CO), 1312, 1145 (SO_2); ^{1}H NMR ($CDCl_3$) : δ 1.12 (t, *J* = 6.8 Hz, 3H, CH_3 ester), 2.46 (s, 3H, CH_3), 4.17 (q, *J* = 6.8 Hz, 2H, CH_2 ester), 5.21 (s, 1H, CH-pyrimidine), 6.40 (s, 1H, NH, D_2O exchangeable), 6.94-7.21 (m, 4H, ArH), 7.79-7.95 (m, 4H, ArH), 8.24 (s, 1H, NH, D_2O exchangeable); ^{13}C-NMR ($CDCl_3$): δ 14.23 (CH_3 ester), 19.35 (CH_3 tosyl), 54.16 (C-4), 60.61 (CH_2 ester), 102.00 (C-5), 121.19 (CF_3), 127.96 (Cph), 128.21 (Cph), 128.36 (Cph), 129.47 (Cph), 133.98 (Cph), 139.59 (Cph), 140.62 (C-6), 147.08 (Cph), 151.05 (Cph), 157.96 (C-2), 167.35 (C-ester); ^{19}F NMR ($CDCl_3$): δ -61.54; MS: 468 (M^+); Anal. calcd. for $C_{21}H_{19}F_3N_2O_5S$ (%): C 53.84, H 4.09, N 5.98, S 6.84 Found: C 54.06, H 4.04, N 5.88, S 6.77.

Ethyl 2-thioxo-4-(4-tosylphenyl)-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4h)

mp 211-213 °C; IR (KBr) ν/cm^{-1}: 3221 (NH), 1734, 1685 (CO), 1312, 1145 (SO_2); ^{1}H NMR ($CDCl_3$) : 1.16 (t, *J* = 6.8 Hz, 3H, CH_3 ester), 2.39 (s, 3H, CH_3), 4.24 (q, *J* = 6.8 Hz, 2H, CH_2 ester), 5.29 (s, 1H, CH-pyrimidine), 6.51 (s, 1H, NH, D_2O exchangeable), 6.98-7.24 (m, 4H, ArH), 7.91-8.11 (m, 4H, ArH), 8.19 (s, 1H, NH, D_2O exchangeable); ^{13}C-NMR ($CDCl_3$): δ 14.39 (CH_3 ester), 19.98 (CH_3 tosyl), 54.65 (C-4), 61.86 (CH_2 ester), 102.84 (C-5), 123.16 (CF_3), 128.02 (Cph), 128.16 (Cph), 128.29 (Cph), 128.97 (Cph), 137.16 (Cph), 139.54 (Cph), 140.96

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(Cph), 146.01 (Cph), 152.89 (C-6), 168.09 (CO ester), 176.00 (C-2); ^{19}F NMR ($CDCl_3$): δ -61.57; MS: 484 (M^+); Anal. calcd. for $C_{21}H_{19}F_3N_2O_4S_2$ (%): C 52.06, H 3.95, N 5.78, S 13.24 Found: C 52.27, H 3.92, N 5.68, S 13.16.

Ethyl 2-oxo-6-phenyl-4-(4-(phenylsulfonyl)phenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4i)

mp 219-222 °C; IR (KBr) ν/cm^{-1}: 3228 (NH), 1725, 1689 (CO), 1310, 1148 (SO_2); ^{1}H NMR ($CDCl_3$) : δ 1.19 (t, *J* = 7.2 Hz, 3H, CH_3 ester), 4.17 (q, *J* = 7.2 Hz, 2H, CH_2 ester), 5.32 (s, 1H, CH-pyrimidine), 6.02 (s, 1H, NH, D_2O exchangeable), 6.99-7.47 (m, 9H, ArH), 7.84-8.03 (m, 5H, ArH), 8.41 (s, 1H, NH, D_2O exchangeable); ^{13}C-NMR ($CDCl_3$): δ 14.35 (CH_3 ester), 54.02 (C-4), 60.47 (CH_2 ester), 101.89 (C-5), 126.12 (Cph), 126.85 (Cph), 127.56 (Cph), 128.03 (Cph), 128.30 (Cph), 128.69 (Cph), 129.41 (Cph), 131.45 (Cph), 134.51 (Cph), 139.60 (Cph), 141.55 (C-6), 141.95 (Cph), 147.58 (Cph), 150.12 (C-2), 167.32 (CO ester); MS: 462(M^+); Anal. calcd. for $C_{25}H_{22}N_2O_5S$ (%): C 64.92, H 4.79, N 6.06, S 6.93 Found: C 65.18, H 4.73, N 5.94, S 6.85.

Ethyl 6-phenyl-4-(4-(phenylsulfonyl)phenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4j)

mp 178-180 °C; IR (KBr) ν/cm^{-1}: 3219 (NH), 1725, 1682 (CO), 1315, 1149 (SO_2); ^{1}H NMR ($CDCl_3$) : δ 1.15 (t, *J* = 7.2 Hz, 3H, CH_3 ester), 4.11 (q, *J* = 7.2 Hz, 2H, CH_2 ester), 5.09 (s, 1H, CH-pyrimidine), 6.92 (s, 1H, NH, D_2O exchangeable), 7.05 -7.46 (m, 9H, ArH), 7.89-8.08 (m, 5H, ArH), 9.78 (s, 1H, NH, D_2O exchangeable); ^{13}C-NMR ($CDCl_3$): δ 14.74 (CH_3 ester), 56.21 (C-4), 61.52 (CH_2 ester), 101.45 (C-5), 126.36 (Cph), 126.74 (Cph), 126.98 (Cph), 127.45 (Cph), 127.89 (Cph), 128.56 (Cph), 128.94 (Cph), 130.09 (Cph), 133.54 (Cph), 139.60 (Cph), 140.78 (Cph), 141.65 (Cph), 150.02 (C-6), 166.25 (CO ester), 177.00 (C-2); MS: 478(M^+); Anal. calcd. for $C_{25}H_{22}N_2O_4S_2$ (%): C 62.74, H 4.63, N 5.85, S 13.40 Found: C 62.98, H 4.59, N 5.74, S 13.31.

Ethyl 2-oxo-6-phenyl-4-(4-tosylphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4k)

mp 262-264 °C; IR (KBr) ν/cm^{-1}: 3218 (NH), 1735, 1681 (CO), 1310, 1143 (SO_2); ^{1}H NMR (DMSO-d_6) : δ 1.17 (t, *J* = 6.8 Hz, 3H, CH_3 ester), 2.39 (s, 3H, CH_3), 4.11 (q, *J* = 6.8 Hz, 2H, CH_2 ester), 5.28 (s, 1H, CH-pyrimidine), 6.14 (s, 1H, NH, D_2O exchangeable), 6.92 -7.33 (m, 9H, ArH), 7.69-7.92 (m, 4H, ArH), 8.26 (s, 1H, NH, D_2O exchangeable); ^{13}C-NMR (DMSO-d_6):

δ 14.22 (CH_3 ester), 20.16 (CH_3 tosyl), 53.51 (C-4), 61.45 (CH_2 ester), 103.45 (C-5), 126.69 (Cph), 126.85 (Cph), 127.89 (Cph), 128.56 (Cph), 128.69 (Cph), 128.88 (Cph), 129.96 (Cph), 131.48 (Cph), 135.78 (Cph), 139.02 (Cph), 142.45 (C-6), 142.99 (Cph), 148.25 (Cph), 156.10 (C-2), 168.13 (CO ester); MS: 476 (M^+); Anal. calcd. for $C_{26}H_{24}N_2O_5S$ (%): C 65.53, H 5.08, N 5.88, S 6.73 Found: C 65.75, H 5.06, N 5.75, S 6.66.

Ethyl 6-phenyl-2-thioxo-4-(4-tosylphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4l)

mp 236-238 °C; IR (KBr) ν/cm^{-1}: 3217 (NH), 1735, 1685 (CO), 1312, 1145 (SO_2); ^{1}H NMR (DMSO-d_6) : δ 1.15 (t, *J* = 6.8 Hz, 3H, CH_3 ester), 2.41 (s, 3H, CH_3), 4.22 (q, *J* = 6.8 Hz, 2H, CH_2 ester), 6.01 (s, 1H, CH-pyrimidine), 6.93 (s, 1H, NH, D_2O exchangeable), 7.21 -7.42 (m, 9H, ArH), 7.83-8.06 (m, 4H, ArH), 8.34 (s, 1H, NH, D_2O exchangeable); ^{13}C-NMR (DMSO-d_6): δ 14.45 (CH_3 ester), 20.39 (CH_3 tosyl), 55.91 (C-4), 60.11 (CH_2 ester), 102.59 (C-5), 126.96 (Cph), 127.52 (Cph), 127.95 (Cph), 128.27 (Cph), 128.79 (Cph), 128.93 (Cph), 130.02 (Cph), 136.00 (Cph), 138.11 (Cph), 139.85 (Cph), 140.02 (Cph), 148.24 (Cph), 157.15 (C-6), 169.19 (CO ester), 175.03 (C-2); MS: 492 (M^+); Anal. calcd. For $C_{26}H_{24}N_2O_4S_2$ (%): C 63.39, H 4.91, N 5.69, S 13.02 Found: C 63.62, H 4.88, N 5.59, S 12.93.

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