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Silica immobilized nickel complex: An efficient and reusable catalyst for microwave-assisted one-pot synthesis of dihydropyrimidinones

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ABSTRACT

Dihydropyrimidinones (DHPM's) have been prepared by one-pot condensation of aldehydes, urea and 1,3-dicarbonyl compounds in presence of covalently anchored nickel complex on silica as catalyst in microwave under solvent-free conditions. The prepared catalyst was characterized by elemental analysis, BET surface area, atomic absorption spectroscopy (AAS), FT-IR spectroscopy and ^{13}C CPMAS spectral studies. This method in comparison to previously reported methods offers high yields, eliminates the use of organic solvents, reduces reaction time from several hours to few minutes and also the catalyst can be reused without appreciable loss in catalytic activity.

The catalysts which make the organic reactions environmentally benign and economically feasible are extremely demanded by chemical industries [1,2]. Homogeneous catalysis is gaining considerable interest due to their high activity and selectivity at milder reaction conditions for a wide variety of reactions. However, their practical applications have been limited due to difficulties in achieving industrially viable catalyst-product separation [3]. Heterogenization of homogeneous catalysts is one of the means to integrate the advantages of both homogeneous and heterogeneous catalysis into one chemical process which would lead to clean chemical synthesis from both environmental and commercial point of view. The massive increase in the use and the broad range of applications for polymeric supports in chemistry illustrate the immense significance of the techniques to the chemists. In this present work, silica gel is chosen as solid support for immobilization of catalysts due to their tunable pore sizes and surface areas, high thermal and mechanical stability, and the ease with which the surfaces can be functionalized [2,4–9]. In the present work, we have designed and synthesized sustainable silica immobilized nickel complex and investigated its catalytic activity for synthesis of dihydropyrimidinones (DHPM's).

The production of DHPM's via well established Biginelli reaction certainly ranks as one of the most recognized and often used multicomponent reactions (MCR) for the generation of novel pyrimidine scaffolds that possess wide range of biological activities, pharmaceutical and therapeutic properties [10–12]. The standard procedure for the Biginelli condensation involves one-pot condensation of β-ketoester with an aryl aldehyde and urea (or thiourea) in ethanol using a strong acidic catalyst i.e. HCl. The major drawback of this procedure includes long reaction times, reflux temperatures, lower yields of the desired product particularly in case of substituted aldehydes and loss of sensitive functional groups during the reaction. This has led to the development of a number of improved protocols, many of them involving Lewis acids [13–17] including metal triflates [18,19]; silica-sulfuric acid [20], ion exchange resin [21], $KAl(SO_4)_2.12H_2O$ supported on silica gel [22], alumina supported MoO_3 [23], poly(4-vinylpyridine-*co*-divinylbenzene)–Cu(II) complex [24], l-proline [25] and microwave-assisted reactions [26,27].

Synthesis of silica immobilized nickel complex is illustrated in Scheme 1. Activated silica gel was first reacted with 3-aminopropyltriethoxysilane to obtain aminopropyl silica gel [28]. 2-acetylpyridine was then directly anchored to functionalized silica through its ketone functionality followed by metallation with nickel chloride [29]. The efficacy of heterogenized catalyst was investigated for Biginelli reaction in microwave under solvent-free conditions which is an efficient and environmental friendly procedure for the synthesis of 3,4-dihydropyrimidinones [30].

The structure of catalyst was characterized by surface area analysis (BET), atomic absorption spectroscopy (AAS), elemental analysis, FTIR and ^{13}C CPMAS spectral studies.

Incorporation of organic groups onto the surface of silica gel blocks the access of nitrogen gas molecules and results in progressive decrease in their surface area in the sequential order of silica gel (SG) > aminopropyl silica gel ($SG-NH_2$) > ligand immobilized silica ($SG-NH_2$-AcPy) (Table 1).

Chemical analysis of $SG-NH_2$ (Anal. Found: C: 4.22%, N: 1.11%, H: 1.37%) corresponds to 0.79 $mmolg^{-1}$ of aminopropyl group based

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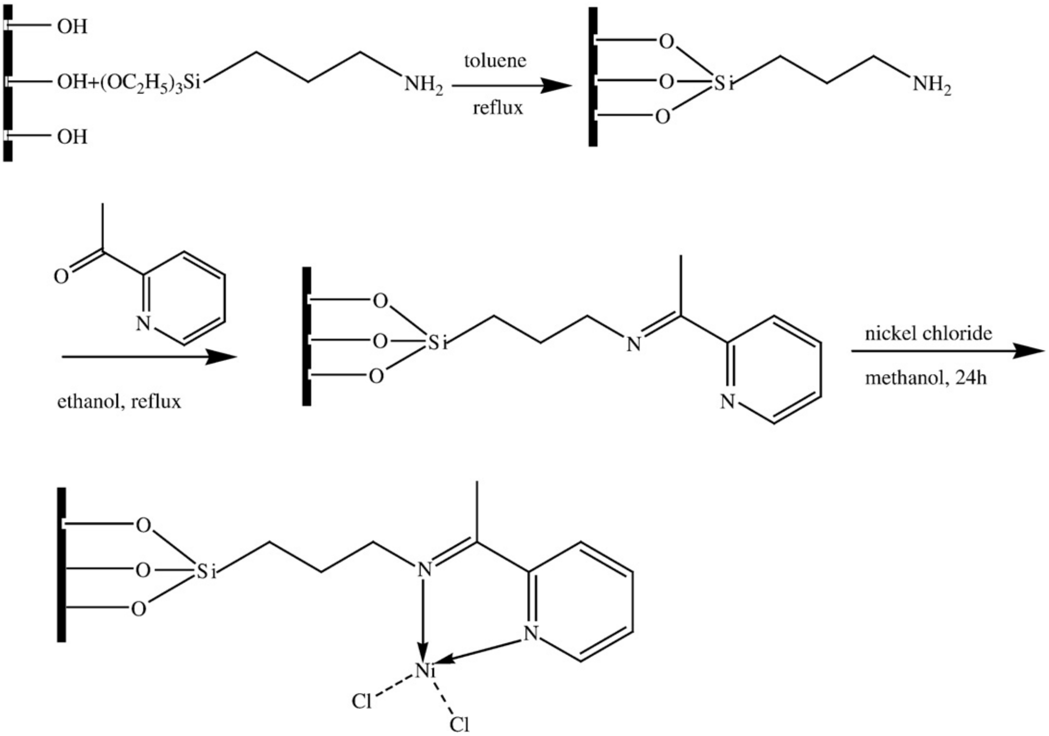

Scheme 1. Synthesis of covalently anchored nickel complex onto functionalized silica.

on the nitrogen percentage; whereas for the catalyst (Anal Found: C: 9.36%, N: 1.96%, H: 1.86%), the loading of organic moiety onto the silica gel is only 0.42 mmolg^{-1}. The metal loading in catalyst was determined by atomic absorption spectrometer (AAS) and found to be 0.40 mmol g^{-1} of nickel.

FT-IR spectrum of silica gel displays characteristic bands at 3467, 1083 and 967 cm^{-1} which corresponds to the OH-stretching, asymmetric and symmetric stretching of siloxane group and bending vibrations of silanol groups (Si–OH) respectively (Fig. 1a). The significant feature observed for the aminopropyl silica gel is characterized by the appearance of peaks at 2924 and 2851 cm^{-1} assigned to $-CH_2$ stretch of the propyl group (Fig. 1b). No significant changes in peaks are observed for silica gel or modified silica which is an indication that its framework remained unchanged. The spectrum of the immobilized ligand shows a strong band at 1647 cm^{-1} due to C=N stretching vibration (Fig. 1c). This confirms that 2-acetylpyridine functionalized group is chemically bonded to the surface of functionalized silica. On complexation of nickel with the ligand, prominent C=N stretching frequency shifted to lower wave number, indicating strong metal–ligand interaction [31].

Signals at 9.3, 22.3 and 42.9 ppm observed in the ^{13}C CPMAS NMR spectrum of SG-NH$_2$ due to –Si–CH$_2$–, –CH$_2$– and –N–CH$_2$– groups, respectively authenticate the synthesis of aminopropyl silica (Fig. 2a). In the spectrum of ligand grafted silica gel (SG-NH$_2$-AcPy), nine well-formed peaks were observed (Fig. 2b). These peaks are numbered sequentially in Fig. 2c. First three peaks are attributed to the precursor carbon atoms numbered 1, 2 and 3 as indicated in Fig. 2c. On complexation, the –N–CH$_2$– peak shifts to 57.9 ppm, whereas the peak at 42.8 ppm refers to the uncomplexed –N–CH$_2$– group. The aromatic carbon atoms at meta position to nitrogen were assigned to that numbered 5 at 121.8 ppm whereas the one at para position was assigned 6th peak at 134.7 ppm. The aromatic carbons bonded to nitrogen were numbered 7 and 8 with the peaks at 147.0 and 157.1 ppm respectively. The Schiff base condensation was also confirmed by the presence of C=N peak (assigned number 9) at 165.4 ppm. The peak with asterisk sign (*) in Fig. 2c has been merged into the aminopropyl peaks.

Table 1
Physico-chemical parameters of silica gel, aminopropyl silica gel and catalyst.

Material	Elemental analysis (wt.%)			BET surface area (m^2/g)
	%C	%N	%H	
SG	–	–	–	235.67
SG-NH$_2$	4.22	1.11	1.37	151.91
SG-NH$_2$-AcPy	9.36	1.97	1.86	141.93

Catalytic activity

The model reaction of benzaldehyde (15 mmol), ethyl acetoacetate (15 mmol) and urea (20 mmol) was studied under microwave radiation and solvent-free conditions using different types of catalysts (Table 2). The reaction did not proceed in the absence of catalyst or only silica as the catalyst. When nickel chloride or silica immobilized catalyst was used, high yield of the product was obtained. Lack of recyclability of homogenously catalyzed nickel chloride as catalyst limits its application for further use. We further examined the effect of microwave power and irradiation time on Biginelli reaction. 100 W power was optimized for carrying out the reaction. Increasing the power did not show a significant yield enhancement. We next dealt with the issue of reaction time and temperature. After a few optimization cycles, we found that 80 °C proved to be efficient reaction temperature. Higher temperatures would lead to decreased yields because of the formation of undesired by-products; lower reaction temperatures on the other hand required longer reaction times for complete conversion. For the model system, the total irradiation time of 5 min at 80 °C in presence of silica immobilized nickel catalyst resulted in 96% isolated yield of pure product. Based on the optimization results, variety of aldehydes with ethyl acetoacetate and urea were run and variety of substituted DHPM's was obtained (Table 3). Both electron-withdrawing and electrondonating substituents on the aldehyde aryl ring produced the desired products in high yields (90%-quantitative). Thiourea also gave similar results for the generation of S-analogues of dihydropyrimidinones. As evident from Table 4, our catalyst showed good results in terms of reaction conditions compared to those reported in literature so far.

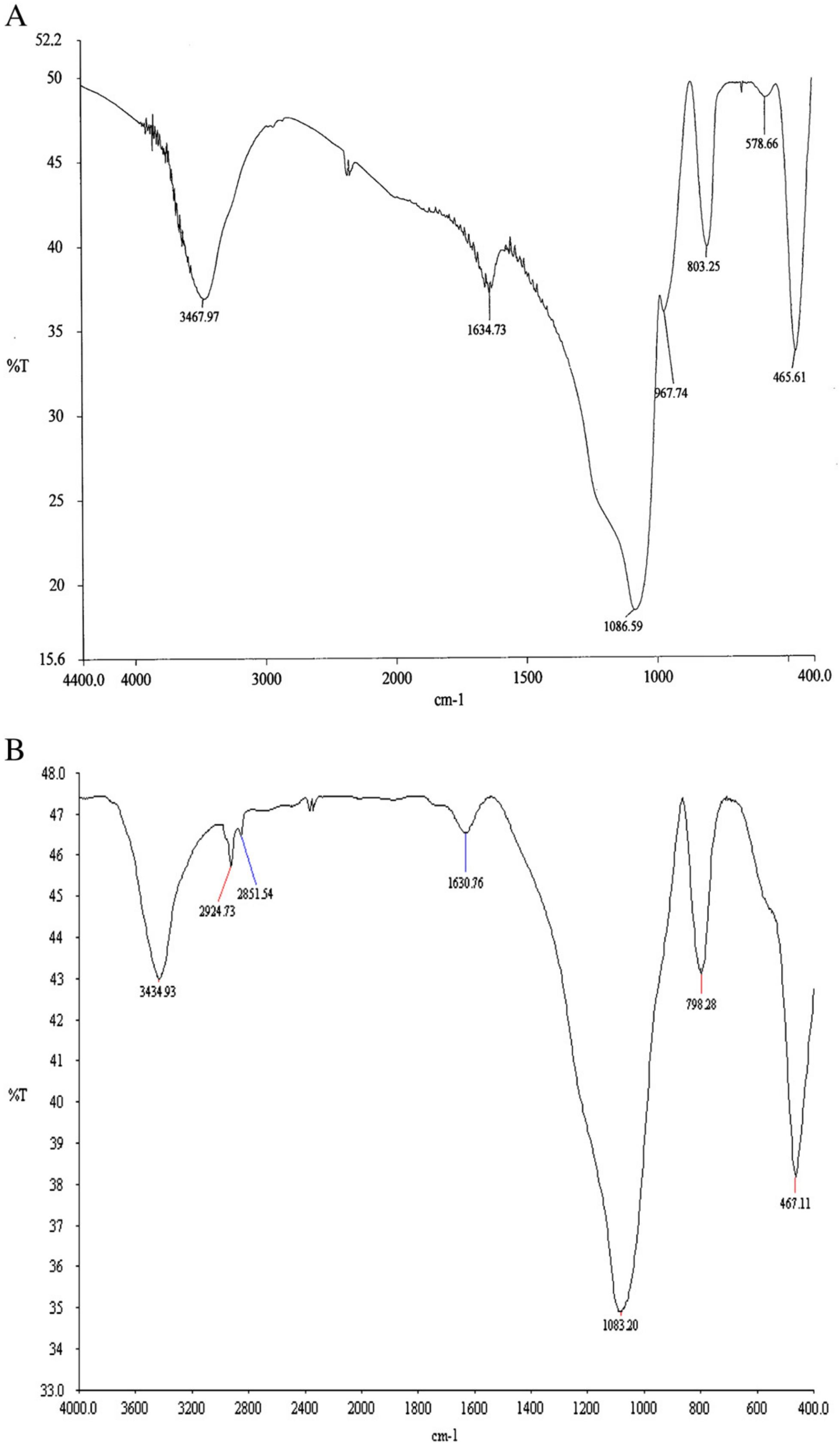

Fig. 1. FTIR spectra of a) silica gel (SG) b) aminopropyl silica gel (SG-NH_2) c) ligand grafted silica gel (SG-NH_2-AcPy).

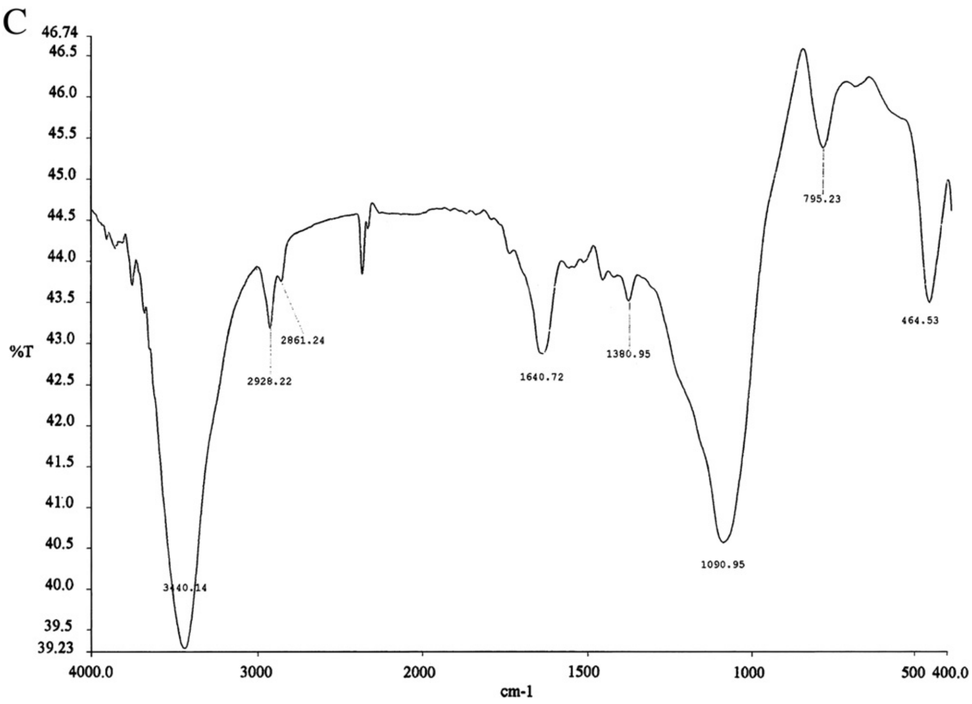

Fig. 1 (*continued*)

Recyclability of the catalyst is another important parameter while using heterogeneous catalyst from an industrial point of view. The silica immobilized nickel catalyst was recovered from reaction media by simple filtration after dilution of with ethyl acetate. The recovered catalyst was dried in vacuum oven at 100 °C and was reused for further catalytic cycles. The results showed that catalyst can be effectively used for five consecutive cycles without much appreciable loss in its catalytic activity (shown in Fig. 3). The filtrate (after removal of catalyst) was tested for the presence of nickel after each catalytic cycle by AAS. Negligible leaching was observed which indicates the true heterogeneous nature of the catalyst.

In conclusion, we have developed a greener method for the synthesis of DHPM's using silica immobilized nickel catalyst in microwave. Reduced reaction times, high yields of products, absence of solvent and recyclability of catalyst make our catalyst a valuable system addition to previously reported methods. This green methodology should be amenable to construct new substituted DHPM scaffolds with potential biological applications.

Acknowledgement

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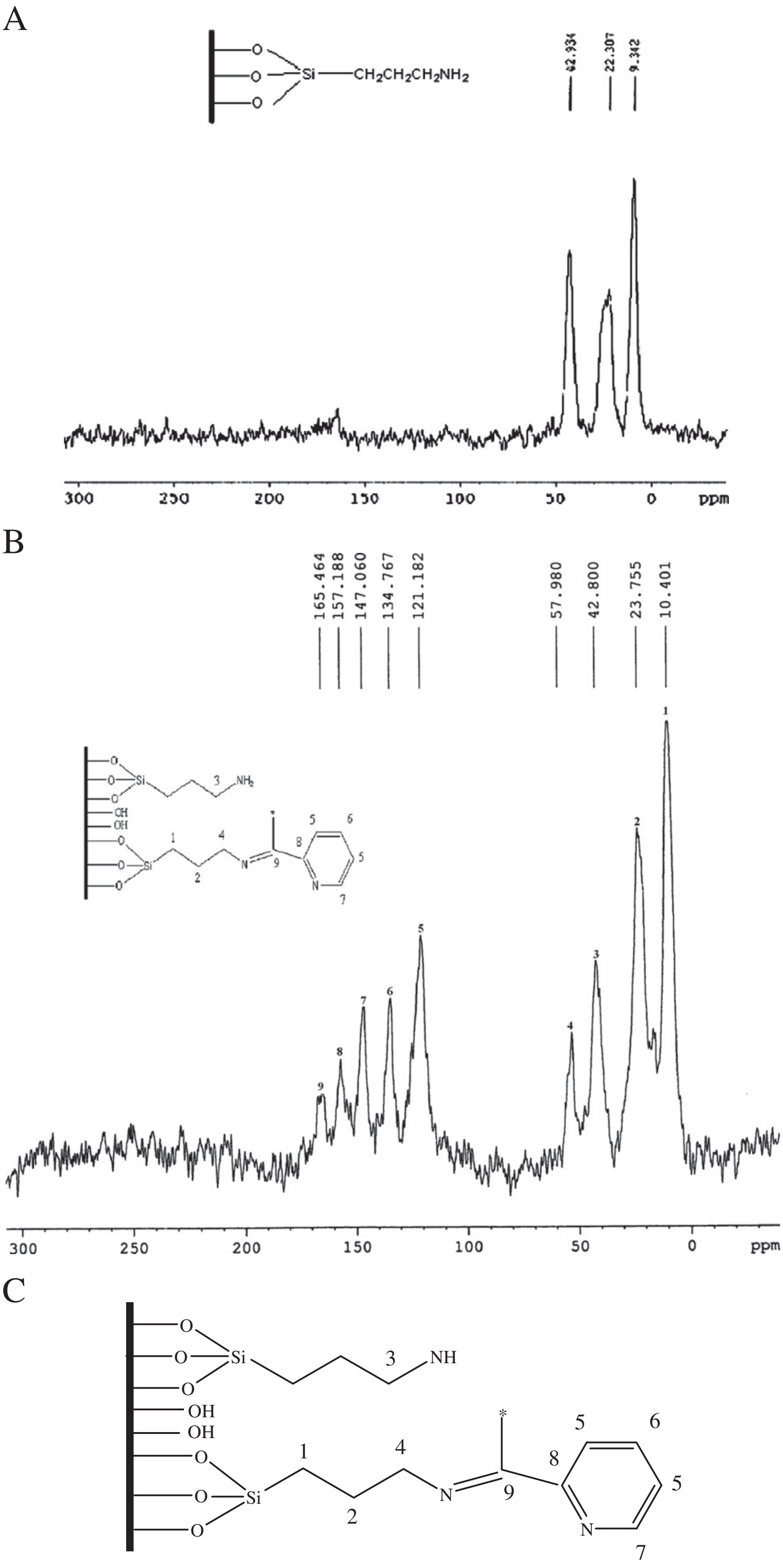

Fig. 2. a) ^{13}C CP MAS NMR spectrum of aminopropyl silica gel (SG-NH_2). b) ^{13}C CP MAS NMR spectrum of ligand grafted silica gel (SG-NH_2-AcPy). c) Labelling of carbon atoms in SG-NH_2-AcPy in order of the peaks obtained in the spectrum of panel b.

Table 2
Screening of catalysts on the model reaction[a].

Entry	Catalyst	Amount	Yield[b] (%)
1.	No catalyst	–	Nil
2.	Silica gel	0.5 g	Nil
3.	$NiCl_2.6H_2O$	10 mol%	98
4.	$SG\text{-}NH_2\text{-}AcPy\text{-}Ni$	5 mol%	96

[a] Reaction conditions: benzaldehyde (15 mmol), urea (20 mmol) and ethyl acetoacetate (15 mmol), catalyst under microwave radiation (100 W) for 5 min.
[b] Isolated yields.

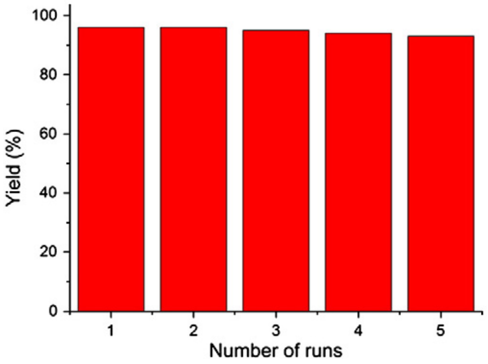

Fig. 3. Recyclability of catalyst for the synthesis of dihydropyrimidinones.

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[29] Aminopropyl silica (5 g) was added to absolute ethanol (100 ml) followed by addition of 2-acetylpyridine (0.302 g, 2.5 mmol) and the reaction mixture was stirred at 60 °C for 24 h to obtain corresponding ligand grafted silica gel ($SG\text{-}NH_2\text{-}AcPy$). The catalyst was prepared by stirring mixture of appropriate ligand grafted silica (4 g) and nickel chloride (0.2 mmol) in methanol (100 ml) at room temperature for 24 h. The solid was filtered, washed with methanol and dried in vacuum at 120 °C for 4 h to obtain silica supported nickel catalyst ($SG\text{-}NH_2\text{-}AcPy\text{-}Ni$) was filtered and washed with ethanol and dried under vacuum at 120 °C for 4 h.
[30] General experimental procedure: A mixture of aldehyde (15 mmol), urea (20 mmol), ethyl acetoacetate (15 mmol), and catalyst (5 mol%) was placed in a microwave vessel and irradiated in the microwave reactor (100 W) at 80 C for 5 minutes. After the completion of reaction, the mixture was diluted with ethyl acetate and the catalyst was removed by filtration. The mixture was concentrated and the crude product was kept into crushed ice. The solid was then filtered and washed with cold water and recrystallized from ethanol to afford pure product.
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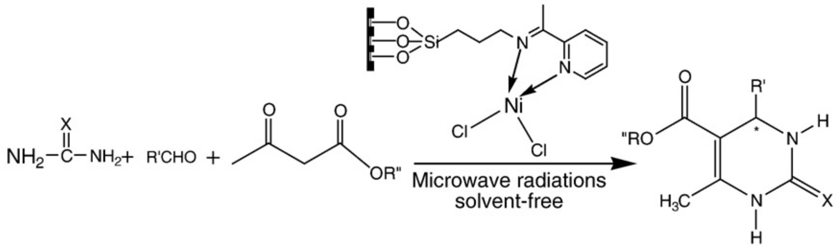
Table 3
One-pot synthesis of 3,4-dihydropyrimidinone catalyzed by covalently anchored nickel catalyst under microwave radiation.[a]



Entry	Product	R′	R″	X	Yield[b] (%)	Observed Mp (°C)	Reported Mp (°C)
1[c].	4a	C_6H_5	C_2H_5	O	96,96,95,94,93	201–203	200–202 [25]
2.	4b	$4\text{-}(CH_3)\text{-}C_6H_4$	C_2H_5	O	95	212–214	213–216 [20]
3.	4c	$4\text{-}(CH_3O)\text{-}C_6H_4$	C_2H_5	O	94	202–204	202–204 [25]
4.	4 d	$4\text{-}(Cl)\text{-}C_6H_4$	C_2H_5	O	94	208–210	211–213 [26]
5[d].	4e	$4\text{-}(NO_2)\text{-}C_6H_4$	C_2H_5	O	93	207–209	207–209 [25]
6.	4f	$4\text{-}(OH)\text{-}C_6H_4$	C_2H_5	O	93	231–233	230–232 [25]
7.	4 g	$4\text{-}(Br)\text{-}C_6H_4$	C_2H_5	O	94	213–215	215 [28]
8[d].	4 h	$3\text{-}(NO_2)\text{-}C_6H_4$	C_2H_5	O	92	228–230	229–230 [27]
9.	4i	C_6H_5	CH_3	O	96	208–210	208–211 [28]
10[d].	4j	$C_6H_5CH{=}CH$	C_2H_5	O	80	228–230	225–227 [25]
11.	4 k	C_6H_5	C_2H_5	S	96	207–209	208–210 [25]
12.	4 l	$4\text{-}Br\text{-}C_6H_4$	C_2H_5	S	95	216–218	–
13.	4 m.	$4\text{-}Cl\text{-}C_6H_4$	CH_3	S	93	180–183	184–185 [26]

[a] Reaction conditions: aldehyde (15 mmol), urea (20 mmol) and 1,3-dicarbonyl compound (15 mmol), catalyst (5 mol%) under microwave radiation (100 W) for 5 min.
[b] Isolated yields. All the products obtained were fully characterized by spectroscopic methods such as IR, ^1H NMR and also comprised the reference compounds.
[c] Recycling experiments.
[d] 10 min.

Table 4
Comparison of catalytic activity of nickel supported catalyst with other catalysts reported in literature for synthesis of 3,4 DHPM's.

Catalyst	Conditions	Time (h)	Yield (%)	Reference
Silica/sulphuric acid	Ethanol/reflux	6.0 h	91	[20]
$InCl_3$	THF/reflux/under N_2/100 °C	7.0 h	95	[15]
$KAl(SO_4)_2.12H_2O$ supported on silica gel	Solvent free/80 °C	4 h	92	[22]
Silica supported tungstophosphoric acid	Acetonitrile/80 °C	1.0 h	95	[24]
Our catalyst	Solvent free/microwave	5 min	98	[Present work]