Green Chemistry

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Proline confined FAU zeolite: heterogeneous hybrid catalyst for synthesis of spiroheterocycles via mannich type reaction

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Novel *L*-proline confined FAU zeolite catalyst system has been developed by confinement of *L*-proline in faujasite zeolite and their catalytic activity been tested in aqueous mediated synthesis of novel 1', 3'-di-(4-methylphenyl)-2', 3', 4', 6'-tetrahydro-1'*H*-spiro[indoline-3,5'-pyrimidin]-2-one (**4a**) and 1', 3'-di-(4-methylphenyl)-2',3',4',6'-tetrahydro-1'*H*-spiro[indene-2,5'-pyrimidin]-1(3*H*)-one (**4d**) first time via one pot three-component condensation of lactams/cyclic ketones, amines and aqueous formaldehyde . Recyclability of novel catalyst system was studied which resulted in no loss of catalytic activity upto five cycles.

Introduction

Organocatalysts, metal-free organic compounds of relatively low molecular weight and simple structure capable of promoting a reaction in a substoichiometric amount, has received paramount interest in last few years.[1] In particular the use of amino acid proline[2] can be regarded as the simplest 'enzyme 'and, successfully applied as a catalyst to many organic transformation.[3-6] The main advantages of this method are that the reaction can be performed in a stereoselective manner, under mild conditions and without the need of any metal. In addition, both enantiomers of proline are available. The classical Mannich reaction,[7] in which an aminomethyl group is introduced at the a-position to a carbonyl compound, is an important reaction in organic chemistry.[8] The products, so-called Mannich bases,[9] are 1,3-amino ketones, which are versatile intermediates in organic synthesis and have especially proven their value in the synthetic building blocks and precursors of pharmaceutically valuable alkaloids. The development of catalytic asymmetric Mannich-type reactions has received increased attention in recent years.[10]

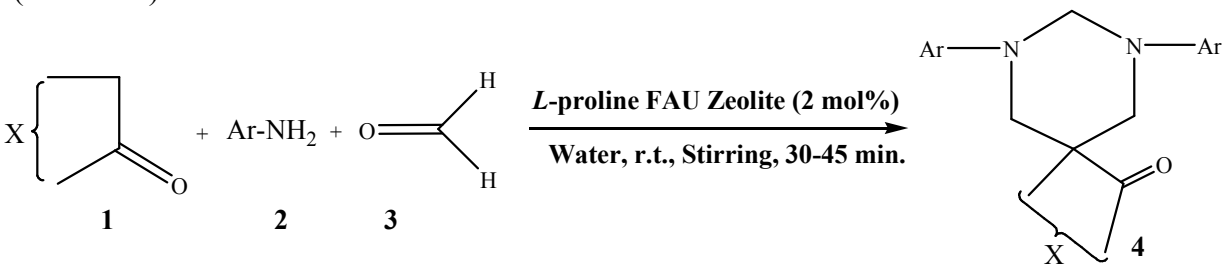
Direct catalytic Mannich-type reactions between ketones and imines are catalyzed by organometallic complexes[11] with high enantioselectivity. Moreover, organocatalytic direct asymmetric Mannich-type reactions have been developed which are catalyzed by Bronsted acids,[12] cinchona alkaloids,[13] proline derivatives[14,15] and linear amino acid derivatives. [16] In this context, one notable transformation is the proline-catalyzed, one-pot three-component Mannich reaction using ketones as nucleophiles reported by List and co-workers.[14a] Other important recent Mannich transformations, which were independently developed by Enders,[17] Westermann,[18] and Cordova,[19] for the synthesis of amino sugars and polyhydroxylated amino acids employ protected dihydroxyacetone derivatives, such as 2,2-dimethyl-1,3-dioxane-5-one, as donors. All these synthetic procedure serve several drawbacks like long reaction time and use of hazardous solvents and tedious workup. To the best of our knowledge, scanty reports are available for synthesis of spiro compounds via sequential introduction of two aminomethyl group on the same α-carbon of carbonyl moiety. Liang[20a] reported synthesis of spirohexahydropyrimidines via one-pot condensation of anilines, formaldehyde, and cyclohexanones, while Mukhopadhyay [20b] reported synthesis of hexahydropyrimidines and its spiro analogues via 1,3-dicarbonyl compounds in presence of Lewis acid in dichloromethane, but all these procedure do not come under greener approaches. In addition, when water was produced in the imine formation, most Lewis acids could not be used in such type of one-pot reactions.[20c] Therefore, there is a need to find the most suitable route like one-pot three-component in regard to green chemistry.

Research for efficient, convenient and recyclable catalytic system based on supported organocatalyst is still a major challenge. Search of green catalyst and our interest in synthesis of porous zeolite materials,[21] prompted us to explore new concept of immobilization in which organocatalyst such as proline is immobilized on a pure silica mesoporous materials so that the product purification can be facilitated and the catalyst can be recycled. One method to immobilize the catalyst is to covalently anchor the proline onto a solid carrier.

The main drawback of this approach is chemical bonding of proline to a solid surface that may limit the degrees of freedom of the substrate and even change the physicochemical properties of the proline.[22a] Hence the leaching of the organocatalyst was unavoidable under rigorous reaction conditions if the supported immobilized proline catalyst was prepared by physical adsorption sol gel technique or by having the proline as a thin layer on a support material. Therefore, a new concept of microporous confined proline catalyst systems has been adopted for greener catalytic process. Our interest in this area led us to explore confinement of organocatalyst such as proline in the channels of mesoporous and microporous materials such as zeolite, silica and Alumina. The key concept of designing and synthesizing such a catalyst system involves the physical confinement or encapsulation of organocatalyst through a traditional based hydrolysis of silicate to produce a solid matrix with desired pore sizes or cavities and channels. The proline acts as both catalyst and reaction media, and the solid matrix acts as the nanoscale reactor connected with inlets and outlets to contain mesoporous channels and to allow reactants and products to be transported in or out. The pore size of the Zeolite should be large enough to contain organocatalyst, while the channel size of the microporous materials should be small enough to prevent organocatalyst from leaching; however, the channel size must also be large enough for free transportation of reactant and product. Therefore, they are intrinsically different from previously reported supported or immobilized organocatalyst.[22b,c-23] FAU zeolite contains uniformed distribution of large mesopores in the range of 3-10 nm and high surface area served as a potentially new support for organocatalyst. Crystalline zeolite framework exhibited higher hydrothermal stability that makes them suitable for supporting materials compared to other mesoporous materials without crystalline framework.[24] Apart from this, water has aroused considerable attention in synthetic community and proved to be a promising solvent in organic synthesis due to its economic, environment friendly and polar nature.[25] In relation to this, significant efforts have been dedicated towards developing organic

reactions in water with many inherent advantages over reactions in conventional organic solvents.

As part of our ongoing program to develop potential catalysts and suitable reaction conditions,[26] we developed FAU zeolite confined (*L*)-proline catalyzed efficient and environment friendly approach for the first synthesis of novel spiro[indoline-3,5'-pyrimidin]-2-one (**4a**) and spiro[indene-2,5'-pyrimidin]-1(3*H*)-one (**4d**) by reacting of lactams or cyclic ketones with amines and aqueous formaldehyde in aqueous medium at room temperature (Scheme 1).



X= Substituted Indole, 1-Indanone, 2-Indanone, Thiazolidinone

Ar= 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 4-BrC_6H_4, 3-ClC_6H_4, 3,4-di$CH_3C_6H_3$, 4-$(CH_3)_2CHC_6H_4$

13 examples

up to 94% isolated yield

Scheme 1 Preparation of spiro heterocycles through Mannich reaction

Results and discussion

L-proline confined zeolite catalyst were synthesized on the basis of the organic-additive-instant seed technology method.[21] A measure amount (10 mol %) of *L*-proline was added to an aluminosilicate gel containing 5.40 g of NaOH, 2.58 g of $NaAlO_2$, 3.57 g of SiO_2, and 50.0 g of H_2O. The gel was crystallized at 100 °C for 24 hrs. The resultant powder was separated from solution by centrifugation and then washed completely with deionized (DI) water to remove any physically absorbed species on the zeolite surface. The synthesized samples were dried at room temperature for further characterization and catalytic investigations. ICPMS analysis indicates that the concentration of proline incorporated in the zeolite is (0.80mmol/g, 8 mol %). To investigate confinement of *L*-proline on FAU zeolite, UV- Raman spectra of *L*-proline in solid

form and on Faujasite Y zeolite were obtained (Fig. 1). Band at 1380 cm-[1] corresponding to symmetric stretching vibration of the carboxylate group of free *L*-proline shifted to 1390cm-[1] after *L*-proline confined in zeolite. The Raman bands of *L*-proline became broad and some characteristic bands disappeared for the adsorbed *L*- proline. These changes indicate that *L*-proline strongly interacts with zeolite and that the carboxylate groups are involved in the interaction.[27] X-ray powder diffraction indicates that unmodified FAU zeolite and the *L*-proline confined FAU zeolite have the same structure (Fig. 2). In comparison with the unmodified FAU zeolite, *L*-proline confined FAU displays slightly higher 2θ values in all of its diffraction peaks. Both diffraction patterns match very well with that simulated for faujasite zeolites.[28] X-ray fluorescence analysis shows that the Si/Al ratio is 5.1 for FAU and 5.23 for confined zeolite, within the range of 5.1-5.2 for faujasite-Y zeolite. There is no evidence for any crystal phases attributable to *L*-proline compounds, indicating that *L*-proline confined zeolite is not highly crystalline.

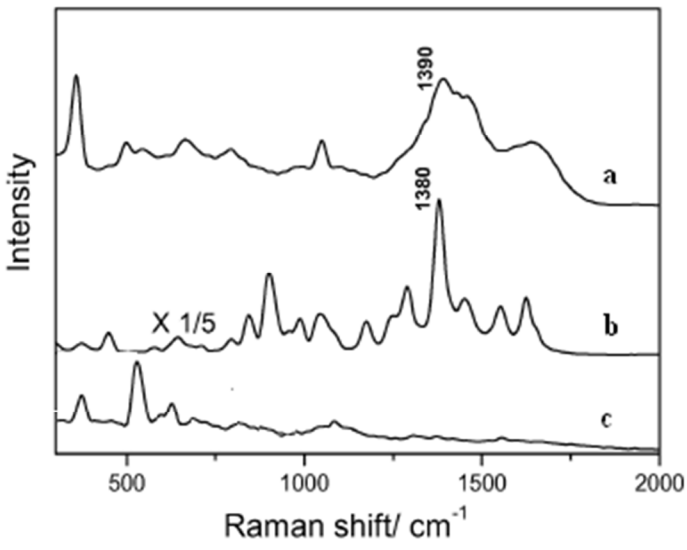


Fig. 1 UV-Raman Spectra of (a) *L*-proline confined in FAU zeolite catalyst system (b) *L*-proline, and (c) FAU zeolite

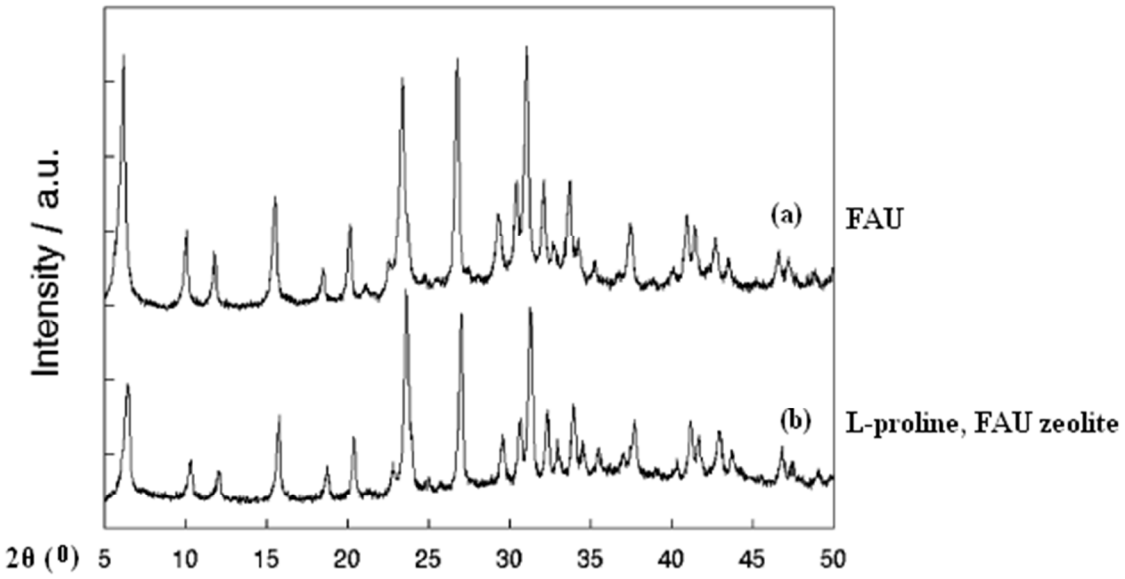
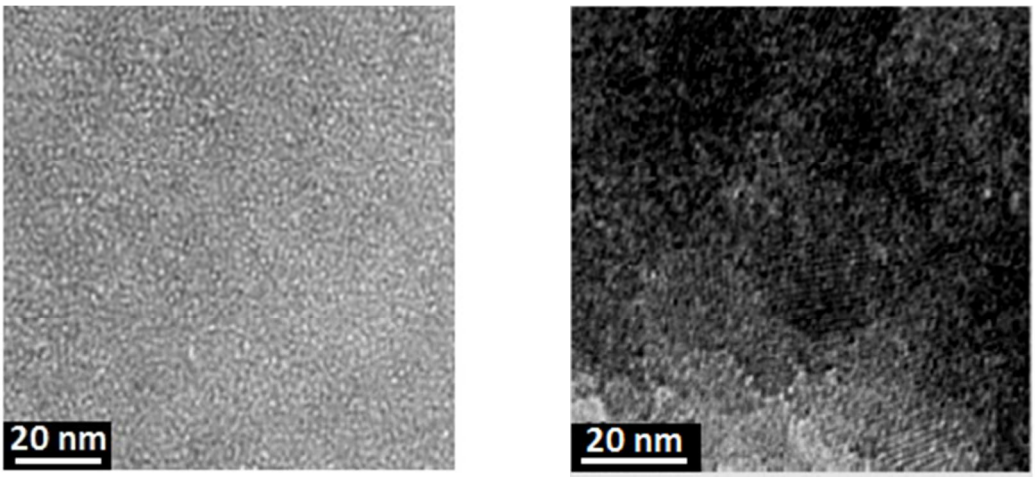


Fig. 2 XRD pattern of (a) FAU zeolite, and (b) *L*-proline confined FAU zeolite

The morphology and particle sizes of *L*-proline in FAU zeolite were characterized using high-resolution TEM, as shown in Figure 3. The additional homogeneously distributed dark spots in *L*-proline-FAU sample (Fig. 3b) not seen in pure FAU zeolite (Fig. 3a). Figure 3 clearly indicates that these dark spots are very uniform, in the size range 1.3 $\pm$ 0.2 nm. This is the same size as the supercages in FAU zeolite. The *L*-proline is likely incorporated into the supercages of FAU zeolite during the hydrothermal crystallization process, and the growth of *L*-proline is constrained by the rigid zeolitic framework. Furthermore, due to the structure of FAU zeolite, with larger supercages tetrahedrally connected by smaller 12-membered rings, once incorporated, the *L*-proline is physically confined in the supercages and cannot diffuse out through the relatively narrow channels. This physical occlusion, supported by the catalytic results (vide infra), is of significance in the prevention of leaching of the active sites, a common problem for supported transition-metal catalysts.[29]

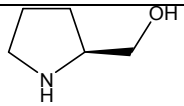
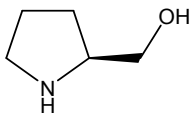
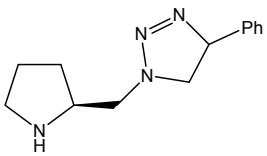


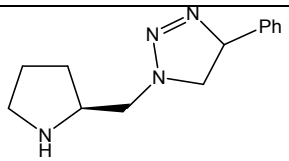
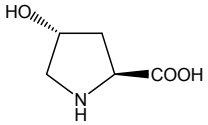
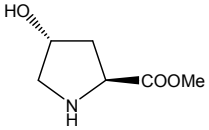
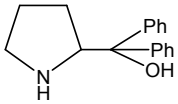
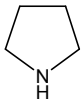
(a) (b)

Fig. 3 High resolution TEM image of (a) FAU zeolite, and (b) *L*-proline confined FAU zeolite

Encouraged by the recent focus on the green chemical theme of eliminating the use of solvents and importance of aqueous mediated reactions, we began our investigations by treating various cyclic ketone/ lactams **1**, amines **2** and formaldehyde **3** in the presence *L*-proline confined FAU zeolite in water at room temperature (Scheme 1). Here we have chosen Mannich type one pot three component reaction of Indole **1a**, 4-methylaniline **2a**, formaldehyde **3** as a simple model substrate. Different solvents such as methanol, NMP, dimethyl formamide (DMF), dimethyl sulphoxide (DMSO), methyl cyanide (CH_3CN), tetrahydrofuran (THF) and water were explored in presence of different catalyst system. The results are summarized in Table 1.

Table1 Catalyst and Solvent screen for Mannich type reaction[a] of **1a**, **2a** and **3** at room temperature

Entry	Catalyst	Solvent	Yield[b](%)	Time (min.)
1.		Water	45	280
2.		MeOH	32	300
3.		Water	48	180

4.		DMSO	30	340
5.		Water	42	210
6.		Water	38	180
7.		Water	30	180
8.		Water	22	240
9.	(*L*)-Proline	Water	80	180
10.	(*L*) -Proline	DMSO	22	300
11.	(*L*) -Proline	MeOH	20	330
12.	(*L*) -Proline	CH_3CN	89	300
13.	(*L*) -Proline	THF	40	360
14.	FAU zeolite	Water	65	300
15.	FAU zeolite	DMSO	42	480
16	FAU zeolite	MeOH	38	400
17.	FAU zeolite	CH_3CN	33	360
18.	*L*-proline/FAU zeolite	Water	94	30
19.	*L*-proline/FAU zeolite	DMSO	42	120
20.	*L*-proline/FAU zeolite	MeOH	28	140
21.	*L*-proline/FAU zeolite	CH_3CN	32	140
22.	*L*-proline/FAU zeolite	THF	18	180
23.	Neat	-	Traces of product	480

[a] Experimental conditions: a mixture of Indole (1 mmol, 1 equiv), 4-methylaniline (2 mmol, 2 equiv), formaldehyde (4 mmol, 4 equiv, 36% aqueous solution), and *L*-proine/FAU zeolite (2gm, 2 mol %) in 10 mL of water was stirred at room temperature for appropriate time. The crude product obtained after aqueous workup. [b] Isolated yields.

It can be seen from the Table 1 that the reaction performed in presence of novel catalyst system yielded product in very shorter reaction time at room temperature. To find out the

efficiency of novel catalyst system, we tried out the reaction in presence of blank FAU zeolite (entry 14-17, table 1) in different solvents and obtained very low yield of titled compounds with increasing reaction time. Apart from this, same reaction was also tried out in neat condition in absence of any catalyst and solvent (entry 23, table 1) resulting traces of product. Thus, It can be concluded that the aqueous mediated *L*-proline FAU zeolite catalyst system is best reaction medium in which resulted product was obtained in higher yield with shorter reaction time (Table 1).

To search of better reaction parameters, we adjusted the ratio of the reactants, and the processes are shown in Table 2. The reaction proceeded in water in presence of *L*-proline FAU zeolite as catalyst. The amount of arylamines and formaldehyde was up to 2:4 (entry 7). Further increase in the amounts of amines and formaldehyde resulted in a slight decrease in yield (entries 8 to 13).

Table 2 Effect of molar quantity of arylamine and formaldehyde on product yield

Entry	Indole (**1a**) (mmol)	4-methylaniline (**2a**) (mmol)	Formaldehyde (**3**) (mmol)	Yield[a] (%)
1.	1	1	1	30
2.	1	1	1.5	35
3.	1	2	2	40
4.	1	2	2.5	42
5.	1	2	3	48
6.	1	2	3.5	65
7.	1	2	4	94
8.	1	3	3	50
9.	1	3	4	58
10.	1	3	4.5	62

11.	1	3	5	80
12.	1	3	5.5	75
13.	1	3	6	68

[a]Isolated yields

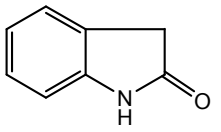
As can be seen from Table 1 and 2, the best result can be obtained by using 2:4 molar quantities of arylamines and formaldehyde in presence of *L*-proline FAU zeolite catalyst system and water as solvent (Table 1, entry 14; Table 2, entry 7).

After optimization of the conditions, to delineate this approach, particularly in regard to library construction, and in order to check the general applicability of the reaction for the synthesis of novel spiro heterocycles derivatives, we extended the reaction of aqueous formaldehyde with electron donating and electron withdrawing groups containing aryl amines and various lactams/cyclic ketones (Table 3). Aryl amines with electron-withdrawing groups behave low actively in the reaction, and only medium yields were obtained (entries 8, 12, and 13).

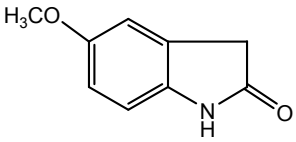
Table 3 Synthesis of spiro heterocycles via one pot reaction of ketone, amine and formaldehyde

Entry	Ketone moiety (X)	Amine	Product	Time (min.)	Yield[a] (%)	M.P. (^{o}C)
1.	1a	2a	4a	30	94	198-200
2.	1b	2a	4b	20	90	250-252
3.	1c	2b	4c	35	88	176-178
4.	1d	2a	4d	30	87	210-212
5.	1d	2b	4e	40	90	228-230
6.	1e	2a	4f	35	93	285-287

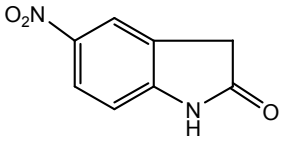
7.	1f	2a	4g	45	90	184-186
8.	1a	2c	4h	45	65	172-174
9.	1a	2f	4i	35	80	190-192
10.	1a	2g	4j	30	88	183-185
11.	1d	2e	4k	40	78	205-207
12.	1d	2d	4l	35	68	218-220
13.	1d	2c	4m	40	70	246-248



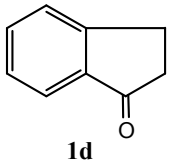
1a



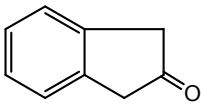
1b



1c



1d



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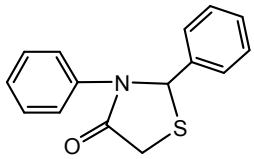
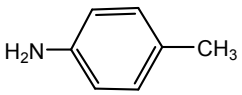
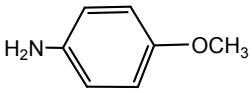


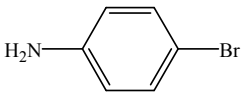
1f



2a



2b



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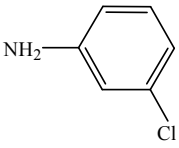

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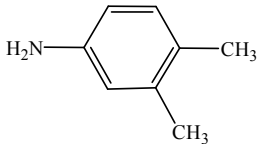
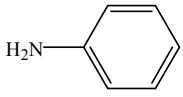
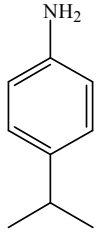


2e



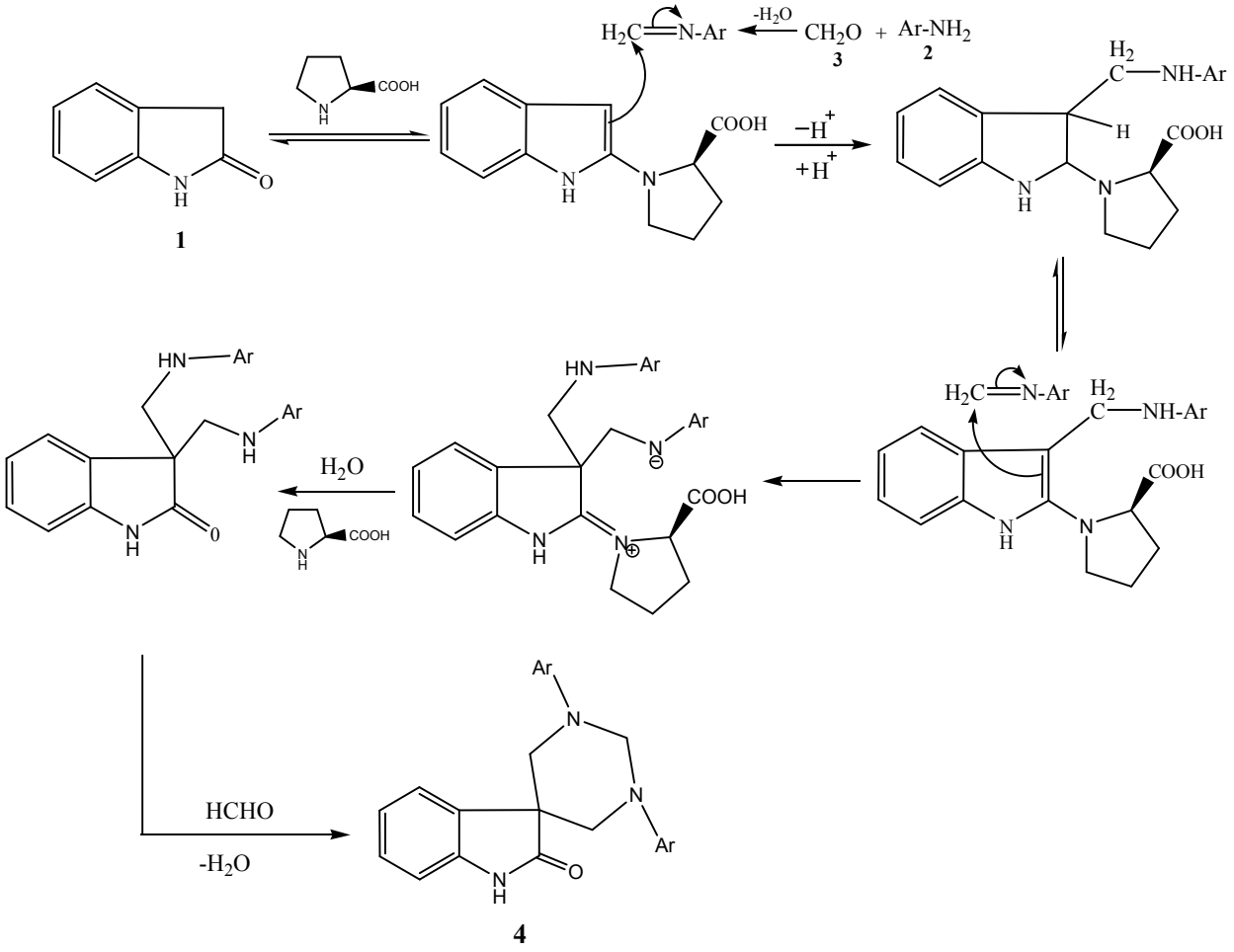
2f



2g

[a] Isolated yield of purified compounds that exhibited physical and spectral properties in accordance with the assigned structure.

A plausible mechanism for the reaction, proposed in Scheme 2. The ketone undergoes twice α-aminomethylation reactions in succession on the same α-carbon of carbonyl-catalyzed by proline. The condensation of the resulting substituted propane- 1,3-diamine with formaldehyde furnishes the desired novel spiro[indoline-3,5'-pyrimidin]-2-one and spiro[indene-2,5'-pyrimidin]-1(3*H*)-one. This is first example in which indol-2-one act for enamine-catalysis without use of H-bond donor catalyst.



Scheme 2 Plausible mechanism for the Mannich type one pot three component reaction

To the best of our knowledge, this new procedure provides the first example of an efficient and ecofriendly approach for exclusive synthesis of novel spiro [indoline-3,5'-pyrimidin]-2-one (**4a-c**) and spiro[indene-2,5'-pyrimidin]-1(3*H*)-one (**4d-f**) derivatives with higher yield in shorter reaction times . The structures of all the products **4** were established by IR, ^{1}H NMR, ^{13}C NMR and HRMS spectroscopy.

From economic point of view, the stability and sustained activity of the catalyst are of great importance. Thus the recovery and reusability of catalyst was investigated in one pot reaction of Indole-2-one, 4-methyl aniline and aqueous formaldehyde in the presence of *L*-

proline FAU zeolite and result was summarized in Table 4. Result shows that no loss of catalyst activity was found even after five cyclic times in *L*-proline FAU catalyst system (Table 4) (Fig. 4). For recycling study of the catalyst, after each cycle catalyst was washed with water and drayed at 300°C.

Table 4 Comparative Catalyst recycling study using *L*-proline FAU zeolite catalyst system (Entry 1, Table 3)

Cycle	Product	
	Yield[a] (%)	Time (min.)
Fresh	94	30
1st recycle	94	30
2nd recycle	94	31
3rd recycle	93	30
4th recycle	93	31
5th recycle	93	30

[a] Isolated yields

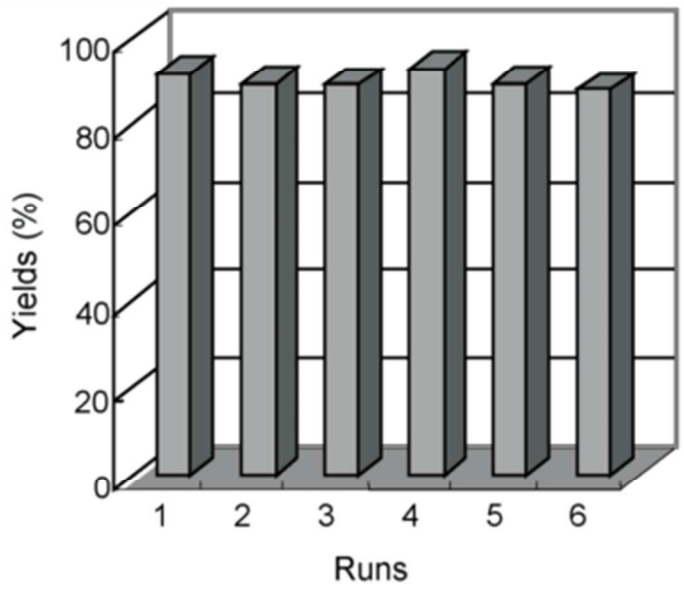


Figure 4 *L*-proline FAU zeolite catalyst recycling study

Experimental Section

IR spectra (KBr) were recorded on a Shimadzu FT IR-8400S spectrophotometer and ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-300, at 300.15 and 200 MHz, respectively, using $CDCl_3$ as solvent. High-resolution mass spectra (HRMS) were obtained on a Finnigan MAT 8200 system using sector double focus and an electron-impact source with an ionizing voltage of 70 eV. DIPMS (direct insertion probe mass spectrum) values are reported in m/z.

General procedure for Synthesis of 1', 3'-di-(4-methylphenyl)-2', 3', 4', 6'-tetrahydro-1'H-spiro[indoline-3,5'-pyrimidin]-2-one (4a):

A mixture of Indole (1 mmol), 4-methylaniline (2 mmol), formaldehyde (4 mmol, 36% aqueous solution), and a catalytic amount of *L*-proline FAU zeolite (2mg, 2 mol%) in 10 ml of water was stirred at room temperature for appropriate time mentioned in Table-3. After the completion of reaction (TLC analysis), reaction mixture was allowed to cool to room temperature. In next step, reaction mixture was filtered and washed with water and CPME (cyclopentyl methyl ether). The organic phase was separated and dried over anhydrous Na_2SO_4 afforded pure crystalline product (**4**) with no need of further purification. In the recycling experiment, catalyst was washed thoroughly with water, dried under vacuum and reused without any pretreatment.

Compounds **4b-g** were similarly prepared by the above method and confirmed by spectroscopic methods.

1', 3'-di-(4-methylphenyl)-2', 3', 4', 6'-tetrahydro-1'H-spiro[indoline-3,5'-pyrimidin]-2-one (4a): R_f= 0.61 (ethyl acetate/hexane=1:4);^{1}H NMR (300 MHz,$CDCl_3$):δ= 9.02 (s, 1H, NH), 7.99-6.58 (m, 12 H, Ar-H), 4.75 (d, J = 11.4 Hz, 1H), 4.09 (d, J=11.4 Hz, 1H), 3.53 (d, J =12.6 Hz, 2H), 3.27 (d, J =12.6 Hz, 2H), 2.12 ppm (s, 6H, CH_3). ^{13}C NMR (200 MHz, $CDCl_3$): δ

=171.6 (C=O), 141.8 (C-N), 134.2, 130.4, 128.4, 124.8, 120.8, 119.7, 116.2, 114.5, 71.5 (CH_2), 65.4(CH_2), 60.9 (CH_2), 50.9 (C), 22.7 ppm (CH_3). IR (KBr): 3130, 2970, 1640, 1550, 1420, 1210 cm^{-1}. Mass: m/z 383 [M^+]. Analysis: Found (calcd) for $C_{25}H_{25}N_3O$: C, 78.40 (78.30); H, 6.48 (6.57); N, 10.89 (10.96).

1',3'-di-(4-methylphenyl)-5-methoxy-2', 3', 4', 6'-tetrahydro-1'H-spiro[indoline-3,5'-pyrimidin]-2-one (4b): R_f= 0.66 (ethyl acetate/hexane=1:4).^{1}H NMR (300 MHz,$CDCl_3$):δ= 9.20 (s, 1H, NH), 7.79-6.43 (m, 11H, Ar-H), 4.78 (d, J = 11.4 Hz, 1H), 4.08 (d, J=11.4 Hz, 1H), 3.70 (s, 3H, OCH_3), 3.51 (d, J =12.6 Hz, 2H), 3.38 (d, J =12.6 Hz, 2H), 2.27 ppm (s, 6H, CH_3). ^{13}C NMR (200 MHz, $CDCl_3$): δ =175.8 (C=O), 160.3, 145.7 (C-N), 130.4, 127.9, 125.1, 123.4, 120.4, 118.4, 114.3, 112.8, 69.4 (CH_2), 64.1 (CH_2), 59.8 (CH_2), 56.03 (OCH_3), 52.7 (C), 20.5 ppm (CH_3). IR (KBr): 3170, 2928, 1650, 1540, 1452, 1234, 1150, 811 cm^{-1}. Mass: m/z 413 [M^+]. Analysis: Found (calcd) for $C_{26}H_{27}N_3O_2$: C, 75.45 (75.52); H, 6.64 (6.58); N, 10.22 (10.16).

1', 3'-di-(4-methoxylphenyl)- 5-nitro-2', 3', 4', 6'-tetrahydro-1'H-spiro[indoline-3,5'-pyrimidin]-2-one (4c): R_f= 0.75 (ethyl acetate/hexane=1:4).^{1}H NMR (300 MHz,$CDCl_3$):δ= 9.38 (s, 1H, NH), 8.09-7.12 (m, 11H, Ar-H), 4.89 (d, J = 11.4 Hz, 1H), 4.15 (d, J=11.4 Hz, 1H), 3.76 (s, 6H, OCH_3), 3.49 (d, J =12.6 Hz, 2H), 3.35 ppm (d, J =12.6 Hz, 2H). ^{13}C NMR (200 MHz, $CDCl_3$): δ =177.8 (C=O), 161.8, 147.2 (C-N), 142.3, 135.7, 132.3, 128.1, 126.9, 124.2, 122.8, 120.3, 118.7, 70.2 (CH_2), 67.3(CH_2), 61.9 (CH_2), 56.38 (OCH_3), 51.7 ppm (C). IR (KBr): 3150, 2943, 1660, 1510, 1430, 1220, 1140 cm^{-1}. Mass: m/z 460 [M^+]. Analysis: Found (calcd) for $C_{25}H_{24}N_4O_5$: C, 65.15 (65.21); H, 5.33 (5.25); N, 12.08 (12.17).

1',3'-di-(4-methylphenyl)-2',3',4',6'-tetrahydro-1'H-spiro[indene-2,5'-pyrimidin]-1(3H)-one (4d): R_f= 0.68 (ethyl acetate/hexane=1:4).^{1}H NMR (300 MHz,$CDCl_3$):δ= 7.88-6.63 (m, 12H, Ar-H), 4.83 (d, J = 11.4 Hz, 1H), 4.20 (d, J=11.4 Hz, 1H), 3.60 (d, J =12.6 Hz, 2H), 3.30 (d, J

=12.6 Hz, 2H), 2.72 (s, 2H, CH_2), 2.16 ppm (s, 6H, CH_3). ^{13}C NMR (200 MHz, $CDCl_3$): δ = 174.2 (C=O), 142.0 (C-N), 135.8, 132.1, 128.2, 124.9, 121.3, 119.7, 115.8, 113.7, 70.9 (CH_2), 65.9 (CH_2), 61.5 (CH_2), 52.8 (C), 31.7 (CH_2), 20.9 ppm (CH_3). IR (KBr): 2965, 1650, 1560, 1410, 1230 cm^{-1}. Mass: m/z 382 [M^+]. Analysis: Found (calcd) for $C_{26}H_{26}N_2O$: C, 81.72 (81.64); H, 6.77 (6.85); N, 7.41 (7.32).

1',3'-di-(4-methoxylphenyl)-2',3',4',6'-tetrahydro-1'H-spiro[indene-2,5'-pyrimidin]-1(3H)-one (4e) : R_f= 0.77 (ethyl acetate/hexane=1:4).^1H NMR (300 MHz,$CDCl_3$):δ= 8.02-6.91 (m, 12H, Ar-H), 4.92 (d, J = 11.4 Hz, 1H), 4.25 (d, J=11.4 Hz, 1H), 3.68 (d, J =12.6 Hz, 2H), 3.55 (s, 6H, OCH_3), 3.28 (d, J =12.6 Hz, 2H), 2.59 ppm (s, 2H, CH_2).^{13}C NMR (200 MHz, $CDCl_3$): δ = 171.9 (C=O), 165.2, 145.7 (C-N), 138.9, 135.1, 131.7, 127.5, 123.6, 120.8, 117.2, 113.7, 71.3 (CH_2), 68.5 (CH_2), 64.2 (CH_2), 58.9 (OCH_3), 55.6 (C), 32.9 ppm (CH_2). IR (KBr): 2965, 1650, 1560, 1410, 1230 cm^{-1}. Mass: m/z 414 [M^+]. Analysis: Found (calcd) for $C_{26}H_{26}N_2O_3$: C, 75.42 (75.34); H, 6.39 (6.32); N, 6.83 (6.76).

1',3'-di-(4-methylphenyl)-2',3',4',6'-tetrahydro-1'H-spiro[indene-1,5'-pyrimidin]-2(3H)-one (4f) : R_f= 0.70 (ethyl acetate/hexane=1:4).^1H NMR (300 MHz,$CDCl_3$):δ= 7.95-6.79 (m, 12H, Ar-H), 4.80 (d, J = 11.4 Hz, 1H), 4.17 (d, J=11.4 Hz, 1H), 3.76 (d, J =12.6 Hz, 2H), 3.42 (d, J =12.6 Hz, 2H), 3.29 (s, 2H, CH_2), 2.28 ppm (s, 6H, CH_3). ^{13}C NMR (200 MHz, $CDCl_3$): δ = 176.4 (C=O), 143.9 (C-N), 134.7, 130.4, 127.3, 124.7, 121.9, 119.8, 116.5, 114.3, 69.2 (CH_2), 67.9(CH_2), 60.5 (CH_2), 54.3 (C), 44.8 (CH_2), 22.8 ppm (CH_3). IR (KBr): 2965, 1640, 1540, 1390, 1210 cm^{-1}. Mass: m/z 382 [M^+]. Analysis: Found (calcd) for $C_{26}H_{26}N_2O$: C, 81.57 (81.64); H, 6.93 (6.85); N, 7.25 (7.32).

2,3-diphenyl-7,9-di-(4-methylphenyl)-1-thia-3,7,9-triaza-spiro[4,5]decan-4-one(4g): R_f = 0.75 (ethyl acetate/hexane=1:4).^1H NMR (300 MHz,$CDCl_3$):δ= 8.12-6.35 (m, 18H, Ar-H), 5.85

(s, 1H, CH), 5.23 (d, J = 11.4 Hz, 1H), 4.56 (d, J=11.4 Hz, 1H), 4.12 (d, J =12.6 Hz, 2H), 3.89 (d, J =12.6 Hz, 2H), 2.38 ppm (s, 6H, CH_3). ^{13}C NMR (200 MHz, $CDCl_3$): δ = 178.7 (C=O), 150.2 (C-N), 141.3, 137.8, 134.2, 130.7, 127.5, 123.7, 119.5, 113.8, 80.5 (CH_2), 72.7 (CH_2), 60.8 (CH), 54.9 (C), 51.8 (CH_2), 21.4 ppm (CH_3). IR (KBr): 2965, 1680, 1510, 1360, 1220 cm^{-1}. Mass: m/z 505 [M^+]. Analysis: Found (calcd) for $C_{32}H_{31}N_3OS$: C, 76.12 (76.01); H, 6.09 (6.18); N, 8.42 (8.31).

1', 3'-di-(4-bromophenyl)-2', 3', 4', 6'-tetrahydro-1'H-spiro[indoline-3,5'-pyrimidin]-2-one (4h): R_f= 0.74 (ethyl acetate/hexane=1:4);^1H NMR (300 MHz,$CDCl_3$):δ= 8.95 (s, 1H, NH), 7.84-6.72 (m, 12 H, Ar-H), 4.68 (d, J = 11.4 Hz, 1H), 4.12 (d, J=11.4 Hz, 1H), 3.58 (d, J =12.6 Hz, 2H), 3.23 (d, J =12.6 Hz, 2H). ^{13}C NMR (200 MHz, $CDCl_3$): δ =172.8 (C=O), 139.5 (C-N), 133.5, 131.3, 127.3, 123.5, 121.2, 118.9, 115.9, 113.8, 111.6, 72.9 (CH_2), 69.3 (CH_2), 61.8 (CH_2), 51.4 ppm (C). IR (KBr): 3120, 2960, 1635, 1510, 1430, 1180, 710 cm^{-1}. Mass: m/z 515 [M+2], 513[M^+]. Analysis: Found (calcd) for $C_{23}H_{19}Br_2N_3O$: C, 53.72 (53.83); H, 3.75 (3.73); N, 8.15 (8.19).

1', 3'-di-phenyl-2', 3', 4', 6'-tetrahydro-1'H-spiro[indoline-3,5'-pyrimidin]-2-one (4i): R_f= 0.70 (ethyl acetate/hexane=1:4);^1H NMR (300 MHz,$CDCl_3$):δ= 9.12 (s, 1H, NH), 7.95-6.54 (m, 14 H, Ar-H), 4.79 (d, J = 11.4 Hz, 1H), 4.17 (d, J=11.4 Hz, 1H), 3.65 (d, J =12.6 Hz, 2H), 3.31 (d, J =12.6 Hz, 2H). ^{13}C NMR (200 MHz, $CDCl_3$): δ =174.3 (C=O), 141.5 (C-N), 136.3, 133.3, 129.5, 125.9, 123.8, 120.7, 119.8, 116.2, 114.8, 68.3 (CH_2), 66.7 (CH_2), 61.3 (CH_2), 52.8 ppm (C). IR (KBr): 3150, 2950, 1640, 1530, 1450, 1190. Mass: m/z 355 [M^+]. Analysis: Found (calcd) for $C_{23}H_{21}N_3O$: C, 77.90 (77.72); H, 5.90 (5.96); N, 11.88 (11.82).

1', 3'-di-(4-isopropylphenyl)-2', 3', 4', 6'-tetrahydro-1'H-spiro[indoline-3,5'-pyrimidin]-2-one (4j): R_f= 0.64 (ethyl acetate/hexane=1:4);^1H NMR (300 MHz,$CDCl_3$):δ= 9.05 (s, 1H, NH),

8.02-6.74 (m, 12 H, Ar-H), 4.68 (d, J = 11.4 Hz, 1H), 4.22 (d, J=11.4 Hz, 1H), 3.59 (d, J =12.6 Hz, 2H), 3.23 (d, J =12.6 Hz, 2H), 3.01 (m, 2H), 1.32-1.18 (m, 12H). ^{13}C NMR (200 MHz, $CDCl_3$): δ =173.5 (C=O), 143.3 (C-N), 139.6, 135.8, 131.6, 128.2, 124.9, 121.8, 118.5, 116.9, 113.5, 65.9 (CH_2), 62.3 (CH_2), 58.4 (CH_2), 55.4 (C), 32.3 (CH), 21.9 (CH_3). IR (KBr): 3165, 2930, 1620, 1510, 1445, 1205. Mass: m/z 439 [M^+]. Analysis: Found (calcd) for $C_{29}H_{33}N_3O$: C, 79.15 (79.23); H, 7.62 (7.57); N, 9.51 (9.56).

1',3'-di-(3,4-dimethylphenyl)-2',3',4',6'-tetrahydro-1'H-spiro[indene-2,5'-pyrimidin]-1(3H)-one (4k): R_f= 0.69 (ethyl acetate/hexane=1:4).^{1}H NMR (300 MHz,$CDCl_3$):δ= 7.72-6.34 (m, 10H, Ar-H), 4.85 (d, J = 11.4 Hz, 1H), 4.12 (d, J=11.4 Hz, 1H), 3.65 (d, J =12.6 Hz, 2H), 3.35 (d, J =12.6 Hz, 2H), 2.83 (s, 2H, CH_2), 2.16 (s, 6H, CH_3), 2.08 ppm (s, 6H, CH_3). ^{13}C NMR (200 MHz, $CDCl_3$): δ = 178.3 (C=O), 144.1 (C-N), 140.2, 131.8, 129.3, 125.7, 120.8, 118.6, 114.3, 112.5, 72.9 (CH_2), 69.1 (CH_2), 63.8 (CH_2), 53.9 (C), 30.4 (CH_2), 21.9 (CH_3), 18.2 ppm (CH_3). IR (KBr): 2980, 1635, 1550, 1390, 1210 cm^{-1}. Mass: m/z 410 [M^+]. Analysis: Found (calcd) for $C_{28}H_{30}N_2O$: C, 81.80 (81.91); H, 7.42 (7.37); N, 6.77 (6.82).

1',3'-di-(3-chlorophenyl)-2',3',4',6'-tetrahydro-1'H-spiro[indene-2,5'-pyrimidin]-1(3H)-one (4l): R_f= 0.75 (ethyl acetate/hexane=1:4).^{1}H NMR (300 MHz,$CDCl_3$):δ= 7.95-6.43 (m, 12H, Ar-H), 4.72 (d, J = 11.4 Hz, 1H), 4.21 (d, J=11.4 Hz, 1H), 3.71 (d, J =12.6 Hz, 2H), 3.53 (d, J =12.6 Hz, 2H), 2.77 ppm (s, 2H, CH_2). ^{13}C NMR (200 MHz, $CDCl_3$): δ = 175.2 (C=O), 147.3 (C-N), 141.8, 135.3, 132.8, 128.5, 122.7, 120.1, 117.3, 113.4, 73.9 (CH_2), 68.7 (CH_2), 62.4 (CH_2), 55.9 (C), 28.7 ppm (CH_2). IR (KBr): 2990, 1645, 1530, 1360, 1190, 740 cm^{-1}. Mass: m/z 424 [M+2], 422 [M^+]. Analysis: Found (calcd) for $C_{24}H_{20}Cl_2N_2O$: C, 67.97 (68.09); H, 4.72 (4.76); N, 6.67 (6.62).

1',3'-di-(4-bromophenyl)-2',3',4',6'-tetrahydro-1'H-spiro[indene-2,5'-pyrimidin]-1(3H)-one (4m) R_f= 0.78 (ethyl acetate/hexane=1:4).^{1}H NMR (300 MHz,$CDCl_3$):δ= 7.85-6.42 (m, 12H, Ar-H), 4.63 (d, J = 11.4 Hz, 1H), 4.19 (d, J=11.4 Hz, 1H), 3.74 (d, J =12.6 Hz, 2H), 3.45 (d, J =12.6 Hz, 2H), 2.88 ppm (s, 2H, CH_2). ^{13}C NMR (200 MHz, $CDCl_3$): δ = 172.2 (C=O), 142.4 (C-N), 139.7, 135.8, 131.5, 127.6, 121.9, 116.4, 113.8, 110.4, 70.4 (CH_2), 67.3 (CH_2), 62.5 (CH_2), 49.7 (C), 28.4 ppm (CH_2). IR (KBr): 3010, 1640, 1530, 1370, 1190, 715 cm^{-1}. Mass: m/z 512 [M+2], 510 [M$^+$]. Analysis: Found (calcd) for $C_{24}H_{20}Br_2N_2O$: C, 56.18 (56.27); H, 3.88 (3.94); N, 5.52 (5.47).

Conclusion

In conclusion, we have succeeded in developing novel green catalyst system and tested their catalytic activity for the Mannich type reaction in aqueous medium , and generate the first report on the synthesis of a series of novel spiro[indoline-3,5'-pyrimidin]-2-one and spiro[indene-2,5'-pyrimidin]-1(3*H*)-one derivatives. In this novel one-pot three-component reaction, six molecules of reactants are involved and six new covalent bonds are generated which make the reaction highly atom economic. Functionalisation at the α-position of the carbonyl/ lactam occurs twice which makes this reaction significant and increases the interest for further modification to molecular diversity.

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