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Short Communication

A new silica based substituted piperidine derivative catalyzed expeditious room temperature synthesis of homo and hetero bis-Knoevenagel condensation products

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ABSTRACT

A new silica based piperidine derivative has been designed, synthesized and characterized by solid state carbon 13 CP MAS NMR, BET surface area analysis, IR, TGA studies, elemental analysis and pH experiment. This has been efficiently utilized as a recyclable catalyst for both homo and hetero bis-Knoevenagel condensation products in aqueous-ethanol. This is the first report of the synthesis of hetero bis-Knoevenagel condensation products by our designed catalyst.

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1. Introduction

The increasing demands of environmental legislation promote the chemical industries to minimize waste production in chemical manufacture [1]. The use of heterogeneous catalyst, in particular organosilane [2] having a covalently anchored organic spacer to create organic–inorganic hybrid catalysts, have greatly developed in different areas of organic synthesis due to their environmental compatibility combined with good yield and selectivities. In fact, the last decade has witnessed a growing interest in the building up of organic–inorganic hybrid catalysts using several types of supports and immobilization strategies [3–8]. Our present work is directed to immobilize 1-(2-chloroethyl)piperidine onto the silica support and to apply it towards the synthesis of homo and hetero-bis-Knoevenagel condensation products. Interestingly, 1-(2-chloroethyl)piperidine chemistry may provide straightforward possibilities for catalyst design, together with a simple immobilization procedure compared to other less-functionalized organocatalysts.

In our present study, we report the formation of hetero-Knoevenagel-dicondensation as well as homo-dicondensation products. This is the first report of the synthesis of hetero-Knoevenagel-dicondensation products. Here lies the novel application of our catalyst towards such synthesis. In addition, the synthesis of homo-bis-Knoevenagel condensation products is very rare. It is mainly for this reason that we took up the idea of synthesizing bis-homo and the challenge of preparing hetero-Knoevenagel-dicondensation products. The non-formation of bis-hetero product with most of the earlier reported catalysts is due to the enhanced reactivity of active methylene compounds towards the benzene-dicarboxaldehydes. The same active methylene compound attacks at both aldehyde functionalities simultaneously thereby resulting in the formation of homo-dicondensation products. Our strategy was to decrease the reactivity of active methylene compounds, so that, after addition of one of the active methylene compounds, the mono-Knoevenagel-condensation intermediate could be isolated. Then, adding the other active methylene compound, it would be possible to prepare hetero-dicondensation product. The subsequent discussion describes the unique property of our catalyst over previously reported basic catalysts in isolating the mono-Knoevenagel-condensation intermediate.

2. Results and discussion

Scheme 1: On the basis of the high advantages of heterogeneous solid catalysts, we designed the synthesis of the following new silica based basic catalyst containing substituted piperidine as basic unit (Scheme 1).

2.1. Characterization of the catalyst

The catalyst (4) was characterized by solid state carbon 13 CP MAS NMR (Fig. 1), BET analysis (Fig. 2), TGA studies, IR, elemental analysis and pH experiment. The normal solution phase ^{13}C NMR spectra of 3-(mercaptopropyl)-trimethoxysilane (1) showed peaks at δ 50.3 (–OMe), 27.3 (b,c) and 8.03 (a), and that of 1-(2-chloroethyl) piperidine (3) showed peaks at δ 57.7 (d), 53.5 (f), 36.4 (e), 22.4 (g),

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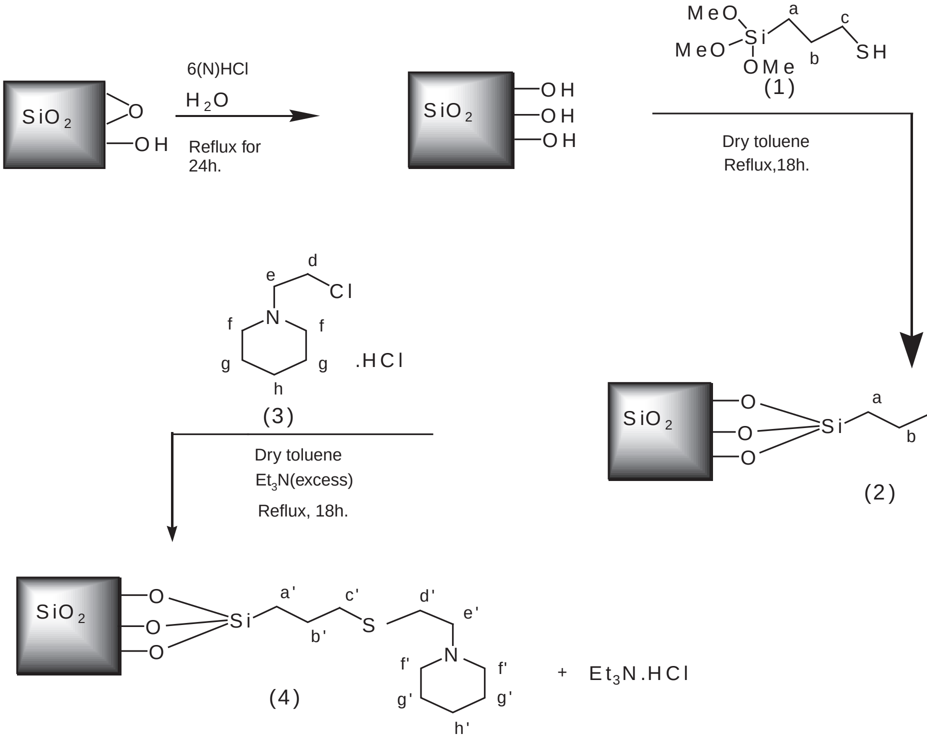


Scheme 1. Preparation of silica based substituted piperidine catalyst (4).

21.5 (h). However, in the product (Fig. 1) obtained by the reaction of 3-(mercaptopropyl)-trimethoxysilane (1) and 1-(2-chloroethyl) piperidine (2), the peak at δ 57.7 (d) vanished and appeared at 24.0 along with (b, c, g, h) since bond formation has taken place through carbon (d) and atom S and the peak at 36.4 for (e) showed slight deviation and appeared at 34.4. The other peaks appeared more or less in same position. When the solid state silica based substituted piperidine catalyst (4) is prepared the peak at δ 50.3 for –OMe vanished due to substitution of –OMe by the silanol group. In the catalyst the remaining peaks for carbons showed very slight deviations and appeared at δ 53.7 for (f′), 34.6 for (e′), a very broad peak at 23.5 (b′, c′, d′, g′, h′), and at 11.8 for (a′). This confirms the structure of the prepared silica based substituted piperidine catalyst.

In addition to structural confirmation, quantitative determination of covalently anchored substituted piperidine group onto the surface of catalyst (4) was performed by elemental analysis and ion-exchange pH analysis and TGA. The elemental analysis of mercaptopropyl silica [9–15] (2) showed the carbon and sulfur content to be 2.49% and 2.15% respectively [16]. From this 0.67 mmol/g loading of the mercaptopropyl group on the silica surface is obtained. In the silica based substituted piperidine catalyst (4) the carbon, sulfur and nitrogen content was found to be 7.71%, 2.05% and 0.90% respectively which corresponds to a loading of 0.64 mmol/g. Therefore 95.55% conversion of the mercapto group to the S-substituted piperidine unit is achieved. To check the basic property of the prepared catalyst (4), the nitrogen atom of piperidine unit in the catalyst (4) was protonated with diluted HCl (details in the

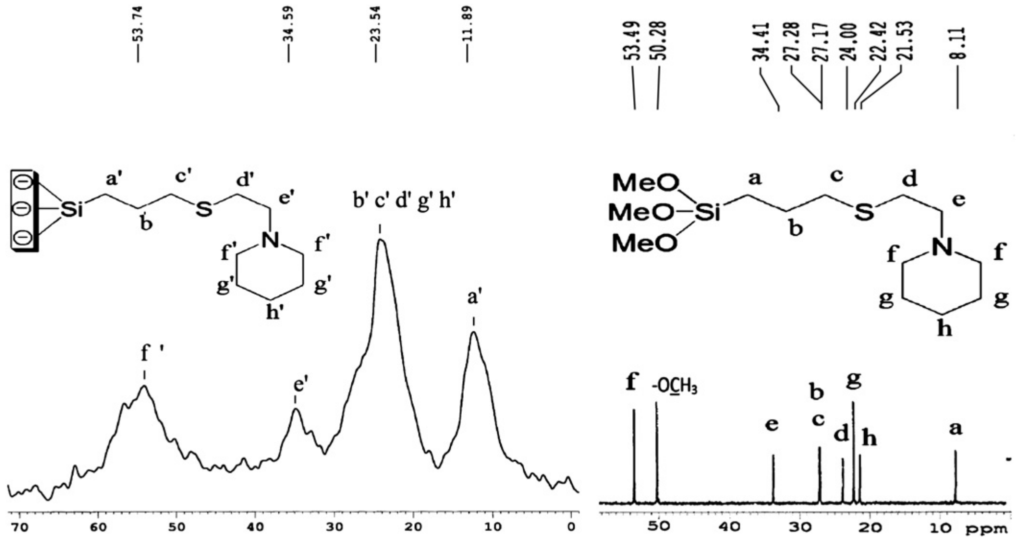


Fig. 1. Comparison solid state carbon-13 CP MAS NMR spectrum of the prepared catalyst (4) with the homogeneous analog of the grafted unit of catalyst (4).

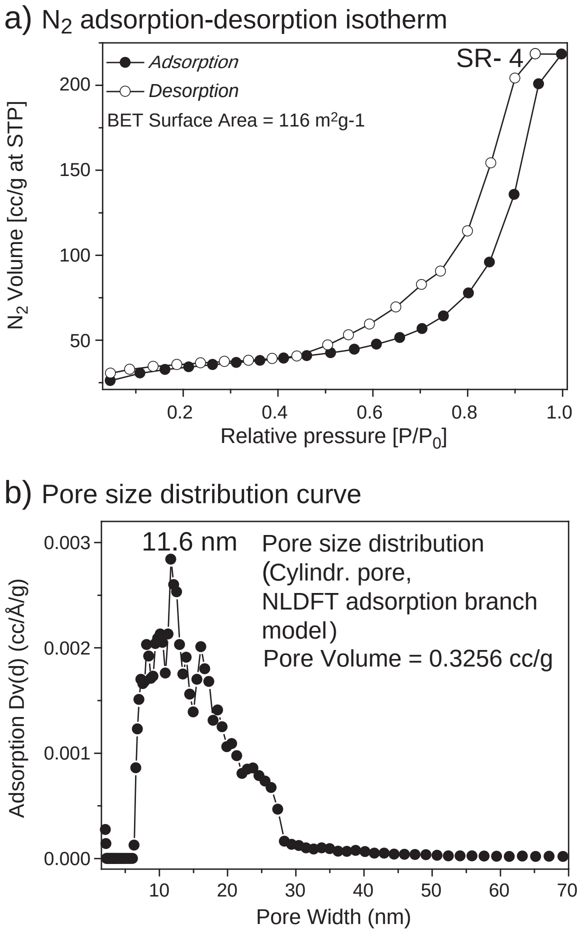


Fig. 2. a) N_2 adsorption–desorption isotherm, and b) Pore size distribution curve of silica based substituted piperidine (4).

supplementary material) and when 1 g of the protonated species was placed in 100 ml saturated NaCl solution, the pH of the resultant solution dropped to 3.50 since ion exchange occurred between sodium ions and protons. From this ion-exchange pH analysis the same catalyst loading was obtained as that from elemental analysis. These results are in good agreement with the result obtained from thermogravimetric analysis from which 95.57% conversion of the mercapto group to the S-substituted piperidine unit and a loading of catalyst of 0.67 mmol/g is obtained.

Physical characterization of silica surface was done by (i) specific surface area ($m^2\ g^{-1}$), (ii) specific pore volume; distribution of pore size or pore area and (iii) particle size measurement. The Brunnauer–Emmett–Teller surface area was obtained using N_2 adsorption–desorption isotherm (Fig. 2) and found out to be 116 m^2/g. Pore size and pore volume is calculated to be 11.6 nm and 0.3256 cm^3/g.

Scheme 2: As a part of our research program concerning the Knoevenagel condensation [17] we report here, a very simple and efficient method in which a variety of active methylene compounds were allowed to react either with benzene-1, 4-dicarboxaldehyde or with benzene-1, 3-dicarboxaldehyde in 2:1 mole ratio (active methylene compounds:dialdehyde) and 5 mg of silica based substituted piperidine catalyst in aqueous-ethanol at room temperature with stirring (Scheme 2).

It was exciting to observe that, except a few cases, all the reactions occurred rapidly and were completed in few minutes giving excellent yield of bis-Knoevenagel products. In most of the cases the products precipitated out from the medium once their formation started.

2.2. Role of catalyst

2.2.1. Our strategy

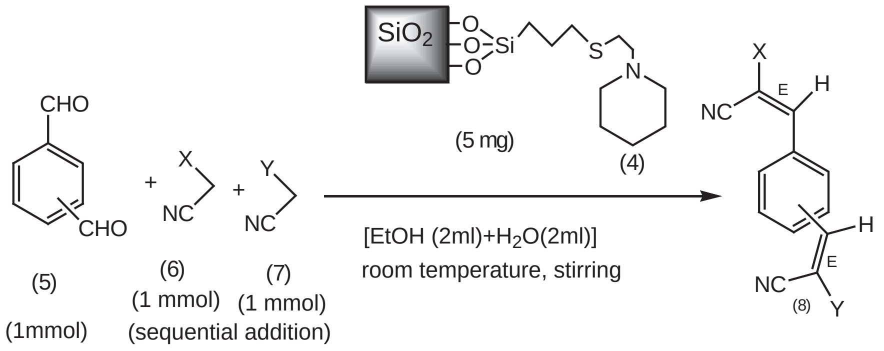
Initially we thought that, by control addition of one of the active methylene compounds, it is possible to obtain the intermediate in which one of the aldehyde functionality is free. The electrophilicity of one free aldehyde group in the mono-Knoevenagel condensation product would be much less than the di-aldehyde because of the net extensive conjugation with the olefinic bond formed on one side. So in presence of limited amount of one active methylene compound, it is possible to prepare the mono Knoevenagel condensation intermediate where, one aldehyde group remains free. Then, on adding the other active methylene compound and keeping it for some time, it would be possible to get the bis-hetero-dicondensation products.

2.2.2. Reason of failure with previously reported catalysts

Homogeneous bases are soluble in aqueous ethanol and behaved as comparatively stronger bases and thus the active methylene compounds attacked at both aldehyde functionalities and mono Knoevenagel condensation intermediate cannot be isolated. Therefore, the reaction failed with NaOH, NaOAc in presence of AcOH, piperidine, ethylpiperidine, triethylamine, 1-(2-chloroethylpiperidine) etc.

2.2.3. Unique property of our catalyst over the previously reported catalysts

Our catalyst is of moderate basicity, since it is a heterogeneous catalyst in aqueous-ethanolic medium. This is the greatest advantage of our catalyst (4) and without this catalyst we were unable to synthesize the hetero-dicondensation product. Initially it generates the carbanion donor from the active methylene compounds by abstracting one proton from it. The carbanion thus generated coordinate with sulfur atom of the heterogeneous catalyst (4) or



Scheme 2. Synthesis of bis-homo and hetero-Knoevenagel condensation products [except for Table 1, entries 10, 11 where, either (6) or (7) is rhodanine] (for various X and Y, refer to Table 1).

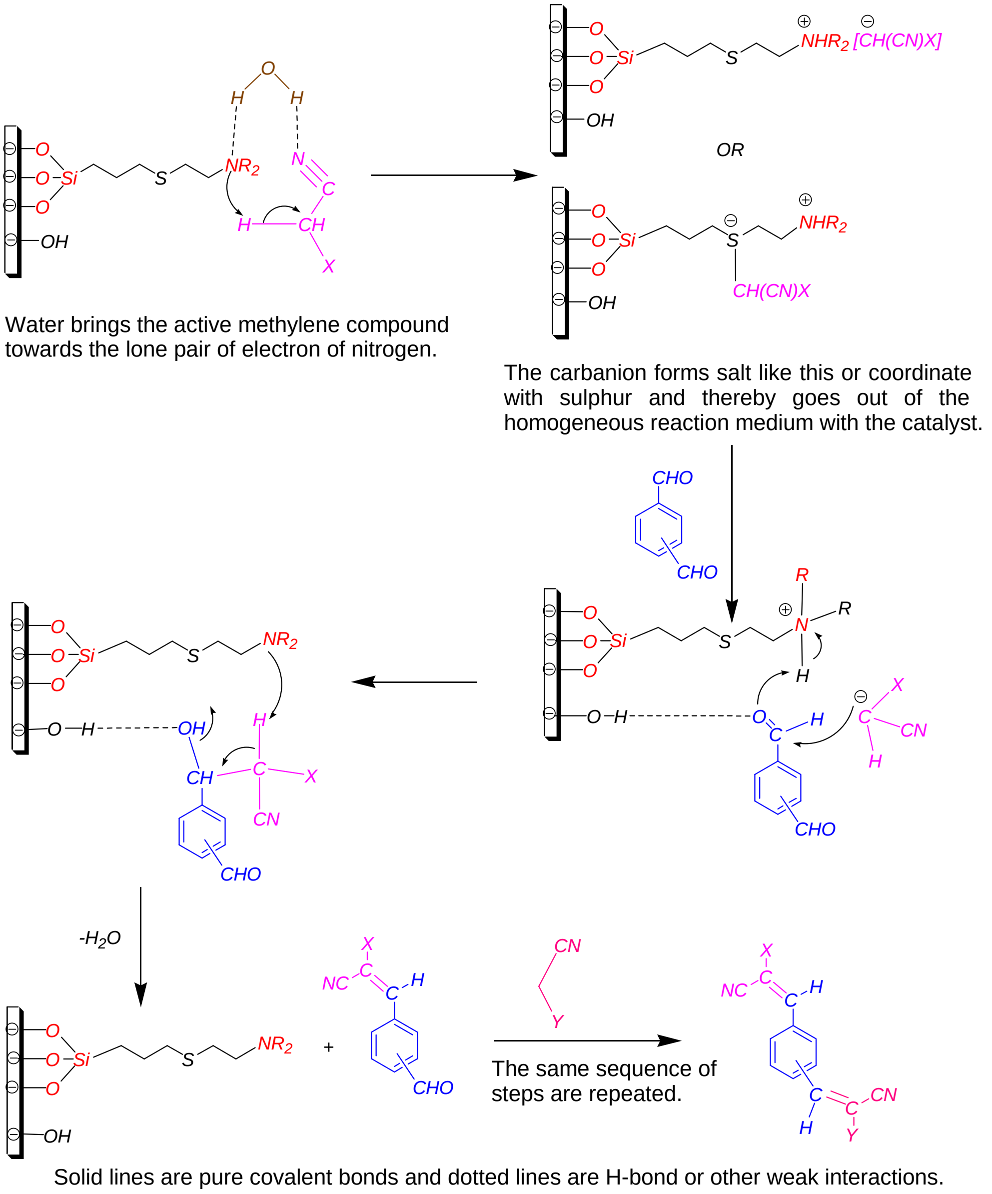
forms salt like $[-R_2NH]^+[CH(CN)_2]^-$ with the protonated nitrogen of the catalyst (4) and thereby goes out of the homogeneous reaction medium (Fig. 3). Therefore, the concentration of carbanion cannot increase largely in the homogeneous reaction medium and this renders the isolation of mono-Knoevenagel-condensation intermediate possible.

Again, the contribution from the inorganic porous structure of silica to the formation of the mono-Knoevenagel condensation intermediate is also justified. Knoevenagel condensation involves aldehydes and products both having relatively large dimensions and solid catalysts having small pores would impose a shape selective limitation to the adsorption and desorption of the bulky molecules, [18] which then makes the reaction slower. Due to the slow reaction rate the active methylene compounds do not attack at both aldehyde functionalities and mono-Knoevenagel condensation intermediate can be isolated. The intermediate of rhodanine (Table 1, entry 10) with benzene-1,4-dicarboxaldehyde has been isolated and characterized.

The model reaction was also carried out separately in the presence of silica or MPS (2). No product was observed with silica as catalyst. For the other case, the final product was obtained in very low yields. The desired product was obtained in excellent yield and at room temperature only with catalyst (4). So, this proves that, a combined effect of silica and the side chain is essential for the catalytic activity. To study the performance of other catalysts the reaction of benzene-1,4-dicarboxaldehyde with cyanoacetamide and ethylcyanoacetate was taken as model reaction and the results are summarized in Table 2.

2.2.4. Mechanism

Here, the surface basic sites of the catalyst produce carbanion from active methylene compounds which attack on the aldehyde and form condensation product by simple neucleophillic substitution reaction [19]. However some notable features involving heterogeneous catalyst and the choice of solvent must be addressed. Here, the active methylene compounds and aldehydes remain in the homogeneous reaction medium in aqueous-ethanol. Since, catalyst is heterogeneous, it remains out of the homogeneous reaction medium. Here, water brings the active methylene compounds to the lone pair of electrons of piperidine nitrogen of the catalyst through hydrogen-bonding (Fig. 3) and thereby favoring the ionization into carbanion donor [20,21]. The carbonyl oxygen coordinates with the silanol [21]



Water brings the active methylene compound towards the lone pair of electron of nitrogen.

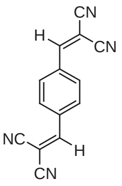
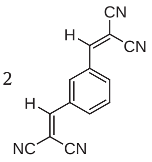
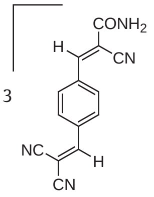
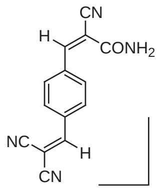
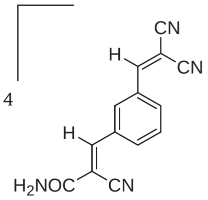
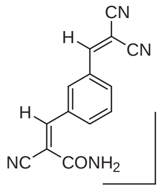
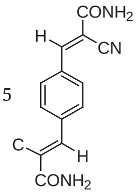
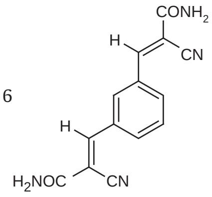
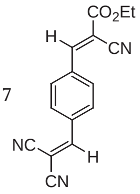
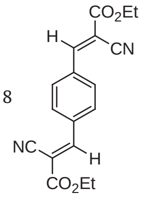
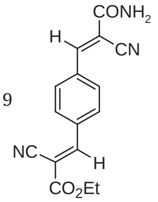
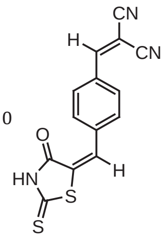
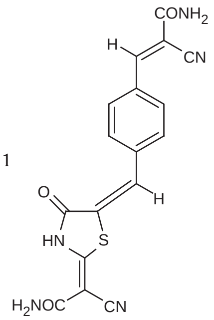
The carbanion forms salt like this or coordinate with sulphur and thereby goes out of the homogeneous reaction medium with the catalyst.

The same sequence of steps are repeated.

Solid lines are pure covalent bonds and dotted lines are H-bond or other weak interactions.

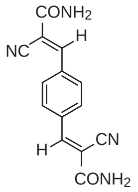
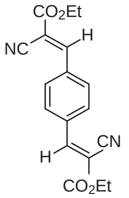
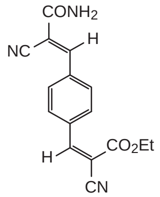
Fig. 3. Mechanism showing the role of catalyst in the bis homo and hetero Knoevenagel dicondensation product formation.

Table 1
Synthesis of homo and hetero-bis-Knoevenagel condensation products with solid silica based substituted piperidine derivative catalyst (4).

Entry products	Diastereo selectivity	Time (min)	Yields (%) isolated	References
1 	–	12	97	[22]
2 	–	13	97	[25]
3 	E[a] (52.7%)	15	94	–
	Z[a] (47.3%)			
4 	E[a] (56.5%)	15	93	–
	Z[a] (43.5%)			
5 	E[a]	30	95	[23]
6 	E[a]	30	94	–
7 	E[a]	30	90	–
8 	E[a] (92%)	35	85	[24]
9 	E[a]	50	92	–
10 	E[a]	25	94	–
11 	E[a]	40	85	–

[a] The E/Z ratio was obtained by ^{1}H NMR integration of the crude reaction products.

Table 2
Study of performance of different catalysts towards hetero-dicondensation product formation.[a]

Entry	Catalysts	Time (min.)	Product yields[b] (%)		
			 Entry 5	 Entry 8	 Entry 9
1	NaOH (1 eqv.)	25	41	42	0
2	NaOAc (1 eqv)	30	38	37	0
3	Piperidine (0.2 eqv)	35	47	48	0
4	Ethylpiperidine (0.2 eqv)	35	36	12	34
5	Et_3N (0.2 eqv)	36	34	13	33
6	1-(2-chloroethyl)-piperidine (0.2 eqv)	40	20	22	40
7	Silica (5 mg)	2 h	0	0	0
8	MPS (5 mg)	60	25	22	17
9	[c]Silica based substituted catalyst (4) (5 mg)	50	0	0	92

[a] Reaction condition: Benzene-1,4-dicarboxaldehydes (1 mmol), cyanoacetamide (1 mmol), ethylcyanoacetate (1 mmol), different catalysts, aqueous ethanol [(2 + 2) ml], room temperature, stirring.

[b] Isolated yield.

[c] The TON for silica based substituted piperidine catalyst (4) (Table 2, entry 9) is 287.5 and TOF is 345/h.

group on silica surface increasing the electrophilicity of the carbonyl carbon and thereby making it possible to carry out the reaction at room temperature.

2.2.5. Study on optimization of catalyst loading and choice of solvent

To study the effect of catalyst loading on Knoevenagel condensation the reaction of benzene-1, 4-dicarboxaldehyde with malononitrile was chosen as model reaction. The results show clearly that silica based substituted piperidine (4) is an effective catalyst for this transformation and 5 mg of the catalyst was the optimum usage under this condition and the yields did not increase largely with higher amount of catalyst. It should be noted that, the yield was best with EtOH-water [(2 + 2) ml]. The yield decreased substantially when the reaction was conducted in the presence of other solvents, such as CH_2Cl_2, ACN, and THF etc. (Table 3).

2.2.6. Recycling experiment

The possibility of recycling the catalyst was examined using the reaction of benzene-1, 4-dicarboxaldehyde with cyanoacetamide under optimized conditions. The recycled catalyst could be used at least eight times without any further treatment. However yield decreased to 84% in 8th run in comparison with 94% in first run and also the reaction time is extended (Table 4). This is probably due to loss of some amount of catalyst in the time of filtration.

This is the first report of the synthesis of the bis-hetero-Knoevenagel product. Both homo and hetero-bis-Knoevenagel products could be prepared in excellent yields and thus the protocol is a very general one.

In this context, we would like to mention that due to amorphous nature of all the products, it was not possible to do X-ray crystal structure analysis of any of them.

The NMR spectra of some selected compounds are given in the Supplementary material.

3. Conclusion

In conclusion, we have shown that our designed and synthesized silica based substituted piperidine (4) prepared from commercially available and cheap starting materials, catalyzed very efficiently the formation of both the bis-homo and hetero-Knoevenagel condensation products at room temperature. The catalyst shows high thermal stability and was recovered and reused without any noticeable loss of activity. Mild reaction condition, simplicity of procedure, general applicability, high yields makes this method practical for multistep synthesis.

Table 3
Optimization of the amount of silica based substituted piperidine catalyst (4) under various solvents for the synthesis of 2-cyano-3-[4-(2,2-dicyano-vinyl)-phenyl]-acrylonitrile (Table 1, entry 1).[a]

Entry	Amount of catalyst (mg)	Solvent (ml)	Time (min)	Yields[b] (%)	TON	TOF/h
1	0	[H_20 (2) + EtOH (2)]	10	0	–	–
2	01	[H_20 (2) + EtOH (2)]	10	23	71.88	431.25
3	02	[H_20 (2) + EtOH (2)]	10	44	137.50	825.00
4	03	[H_20 (2) + EtOH (2)]	10	66	206.25	1237.5
5	04	[H_20 (2) + EtOH (2)]	10	80	250.00	1500.00
6	05	[H_20 (2) + EtOH (2)]	10	92	287.50	1725.00
7	08	[H_20 (2) + EtOH (2)]	10	92	287.50	1725.00
8	10	[H_20 (2) + EtOH (2)]	10	92	287.50	1725.00
9	20	[H_20 (2) + EtOH (2)]	10	91	284.34	1706.25
10	05	CH_2Cl_2 (5)	10	43	134.34	806.25
11	05	THF (5)	10	50	156.25	937.50
12	05	ACN (5)	10	50	156.25	937.50
13	05	EtOH (5)	10	64	200.00	1200.00

[a] Reaction conditions: Benzene-1,4-dicarboxaldehyde (1 mmol), malononitrile (2 mmol), room temperature, different solvents, stirring.

[b] Isolated yield.

Table 4
Recycling of silica based substituted piperidine catalyst (4) for Knoevenagel condensation reaction of benzene-1,4-dicarboxaldehyde with cyanoacetamide.[a]

Cycles[b]	Time (min)	Yield[c] (%)
1	30	95
2	30	91
3	33	91
4	35	89
5	35	89
6	38	88
7	39	85
8	43	84

[a] Reaction condition: Benzene-1,4-dicarboxaldehydes (1 mmol), cyanoacetamide (2 mmol), catalyst (4) (5 mg), aqueous ethanol [(2 + 2) ml], room temperature, stirring.

[b] Reaction was carried with recovered catalyst.

[c] Isolated yield.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.catcom.2011.05.033.

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