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SBA-15-Pr–SO_3H: An efficient, environment friendly and recyclable heterogeneous nanoreactor catalyst for the one-pot multicomponent synthesis of β-acetamido ketones

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Abstract. SBA-15-Pr–SO_3H catalyzes the multi-component condensation of aromatic aldehydes, ketones and acetonitrile in the presence of acetyl chloride at 80°C to afford β-acetamido ketones in excellent yields. The catalyst can be recovered and recycled for subsequent reactions without any appreciable loss of efficiency.

Keywords. Multicomponent reactions; β−acetamido ketones; nanoporous silica; nanoreactor

1. Introduction

The demand for structure diversification to synthesize compound libraries for screening in drug discovery is the driving force behind the development of new methodologies and structural motifs.

Multi-component reactions are a promising and vital field of chemistry because the synthesis of complex molecules can be accomplished in a very fast, efficient and time saving manner without the isolation of any intermediates and hence it has attracted organic chemists to develop new multi-component reactions[1] (figure 1).

β−Acetamido ketones are versatile intermediates in organic synthesis due to their polyfunctional nature and also their presence in a number of biologically or pharmacologically important compounds.[2,3] These compounds are also useful in the synthesis of other important organic molecules like 1,3-amino alcohols[4,5] units common in natural nucleoside peptide antibiotics, e.g., nikkomycines or neopolyoxins[6,7] (figure 2).

Owing to the versatile biological activity of β−acetamido ketones, development of an alternative synthetic methodology is of paramount importance. Earlier reports on the synthesis of β-acetamido ketones through multi-component reactions is mainly by using catalysts such as $CoCl_2$,[8a] $FeCl_3.6H_2O$,[8b] montmorillonite K10 clay,[9a] selectfluor,[9b] silica sulphuric acid,[10a] $CeCl_3.7H_2O$,[10b] various metal chlorides,[11a] TMSCl,[11b] Borax/$POCl_3$,[12a] solid acid Hβ-zeolite,[12b] and iodine.

However, in spite of their potential utility, some of these reported methods suffer from some drawbacks such as low yield, prolonged reaction time, use of hazardous and noxious reagents, use of excess amounts of reagents, and incompatibility of sensitive groups to the reaction conditions. In recent years, the development of more economical and environment-friendly conversion processes is gaining interest in the chemical community.

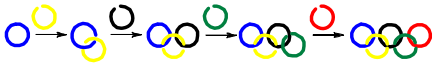
Mesoporous materials have attracted considerable attention since they possess potential applications as catalysts, catalysts supports, adsorbents as well as nanoreactors for making new materials.[13–18]

The SBA-15 is nanoporous silica with a hexagonal structure, large pore size, high surface area, high thermal stability and is also diffusion-free due to the thicker pore walls and larger pore size (figure 3). Integration of acidic functional groups (e.g., SO_3H) into SBA-15 has been explored to produce promising solid acids. Surface functionalization with sulfonic acid groups was carried out according to the known literature procedure[19] with modification in the oxidation step[20] (scheme 1). Typically, the acid content of SBA-15-Pr-SO_3H was measured by ion-exchange pH analysis. The acid amount of SBA-15-Pr-SO_3H was determined to be 1 mmolg^{-1}.

As a part of our continued activities in this area,[21] we have investigated a mild and suitable method for the preparation of β-acetamido ketones by multi-component reactions of an aromatic aldehyde, acetyl

*For correspondence

Stepwise reactions:



Multicomponent reactions:

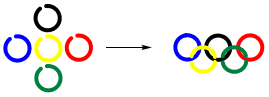


Figure 1. Stepwise reaction versus multi-component reaction.

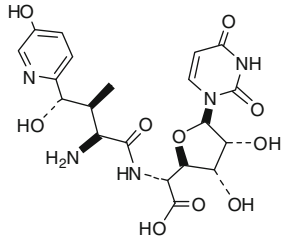
chloride, ketone and acetonitrile in the presence of sulfonic acid functionalized mesoporous SBA-15 as a heterogeneous recyclable nanoreactor catalyst (scheme 2).

2. Experimental

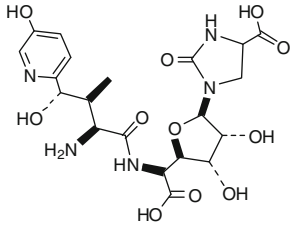
Products were known and characterized by comparison of their spectral data (NMR) and melting points with those reported in the literature. Monitoring of the reaction was accomplished by TLC on SIL G/UV 254 sheets. All yields refer to isolated products.

2.1 *General procedure for synthesis of β-acetamido ketones*

A mixture of aromatic aldehyde (1 mmol), acetophenone (1 mmol), acetyl chloride (2 mmol) and SBA-15-Pr–SO_3H (0.6 g, 0.6 mmol, –SO_3H groups) in acetonitrile (5 mL) was stirred at 80°C. After completion



Nikkomycine Z inhibits the formation of the fungal cell wall



Neopolyoxin B as chitin synthetase inhibitor

Figure 2. Structures of nikkomycine Z and neopolyoxin B as drug candidates.

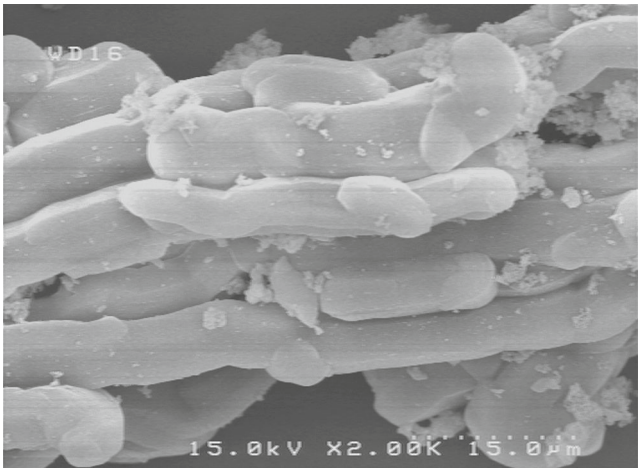


Figure 3. SEM images of SBA-15.

of the reaction as indicated by TLC, the reaction mixture was filtered, and the heterogeneous catalyst was separated. The organic portion was poured into cold water (10 mL). The solid was suction filtered, washed with cold water (20 mL × 2), filtered and recrystallized from ethyl acetate/*n*-hexane to afford pure *β*-acetamido ketone in good to excellent yields. The wet catalyst was recycled and no significant change in activity was observed after three cycles.

2.2 *Spectral data of some of the products*

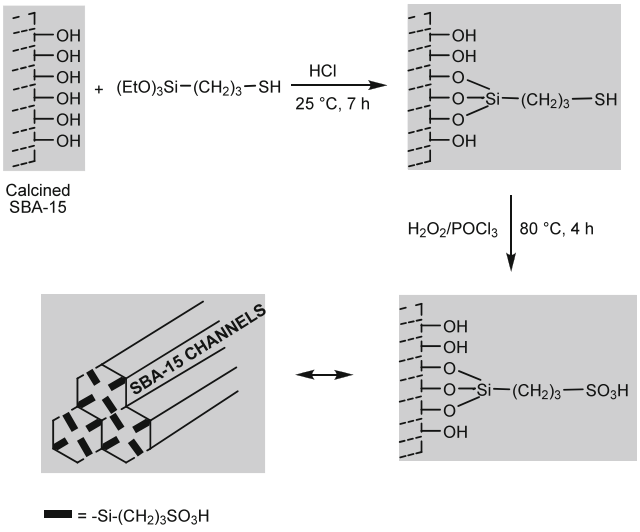
2.2a *N-(1-(4-Chlorophenyl)-3-oxo-3-phenylpropyl)-acetamide (**5g**)*: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.94 (s, 3H), 3.39 (dd, ^2J17.0 Hz and ^3J6.1 Hz, 1H), 3.65 (dd, ^2J17.0 Hz and ^3J5.7 Hz, 1H), 5.46 (m, 1H), 7.18–7.52 (m, 8H), 7.83–7.87 (m, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 22.9, 43.8, 49.0, 127.9, 128.1, 128.4, 128.5, 132.6, 133.3, 136.3, 140.3, 169.7, 197.4.

2.2b *N-(1-(2-Chlorophenyl)-3-oxo-3-phenylpropyl)-acetamide (**5h**)*: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.10 (s, 3H), 3.52 (dd, ^2J 16.7 Hz and ^3J 5 Hz, 1H), 3.82 (dd, ^2J 16.7 Hz and ^3J 5.8 Hz, 1H), 5.89 (m, 1H), 7.13–7.62(m, 9H), 7.96 (d, J7.4Hz, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 23.3, 41.4, 48.1, 127.0, 128.1, 128.4, 128.7, 129.9, 132.5, 133.6, 136.4, 138.1, 198.8.

2.2c *N-(3-(4-Chlorophenyl)-1-(4-chlorophenyl)-3-oxopropyl)acetamide (**5i**)*: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.01 (s, 3H), 3.36 (dd, ^2J17.0 Hz and ^3J6.1 Hz, 1H), 3.7 (dd, ^2J17.0 Hz and ^3J5.0 Hz, 1H), 5.50



Scheme 1. Schematic representation for the preparation of SBA-15-Pr–SO_3H as a nanoreactor catalyst.

(m, 1H), 6.69 (d, *J* 7.9 Hz, 1H), 7.41(d, *J*8.6 Hz, 4H), 7.83 (d, *J*8.6 Hz, 4H).

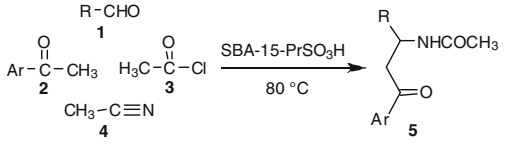
^{13}C NMR ($CDCl_3$, 50 MHz): δ 23.4, 43.0, 49.3, 127.9, 128.8, 129.1, 129.5, 133.3, 134.7, 139.3, 140.2, 169.6, 197.0.

2.2d *N-(1-(3-Nitrophenyl)-3-oxo-3-phenylpropyl)-acetamide (**5j**)*: ^{1}H NMR ($CDCl_3$, 200 MHz): δ1.98 (s, 3H), 3.42 (dd, ^2J17.6 Hz and ^3J5.2 Hz, 2H), 3.71 (dd, ^2J17.6 Hz and ^3J8.5 Hz, 2H), 5.54–563(m, 1H), 6.99–8.14 (m, 10H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 23.0, 42.4, 48.7, 120.9, 122.0, 128.0, 128.4, 129.1, 132.6, 133.5, 135.8, 143.1, 148.0, 169.4, 197.5.

2.2e *N-(1-(4-Chlorophenyl)-3-(4-nitrophenyl)-3-oxopropyl)acetamide (**5k**)*: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.70 (s, 3H), 3.40 (dd, ^2J17.0 Hz and ^3J6.0 Hz, 1H), 3.54 (dd, ^2J 17.0 Hz and ^3J 4.5Hz, 1H), 5.43 (m, 1H), 6.51 (s, 1H), 7.21(s, 4H), 8.00 (d, *J*8.5 Hz, 2H), 8.22 (d, *J*8.5 Hz, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ22.9, 43.5, 49.0, 123.6, 127.6, 128.5, 128.8, 133.1, 138.5, 140.3, 150.1, 169.3, 196.1.



Scheme 2. Synthesis of β-acetamido carbonyl compounds.

3. Results and Discussion

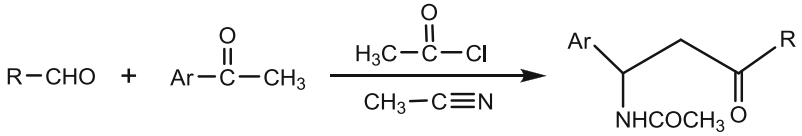
In order to carry out such a multi-component reaction in a more efficient way, some experimentation varying the molar ratio of the reactants, reaction temperature, reaction time and possible solvents were conducted. The optimized condition utiliziing a 1:1:2 ratio of aldehyde, ketone and acetyl chloride in a one-pot reaction employing refluxing acetonitrile (reagent as well as solvent), 0.6 equivalent of propylsulfonic acid functionalized mesoporous silica (SBA-15-Pr–SO_3H) with respect to the aldehyde suffices for complete conversion of the starting materials.

The reaction remains incomplete if lower amounts of catalyst are used. The effect of temperature was studied by carrying out the model reaction in the presence of SBA-15-Pr–SO_3H (0.6 g, 0.6 mmol, –SO_3H groups) in acetonitrile at different temperatures (room temperature, 60 and 80°C). It was observed that the time reaction was decreased and the yield was increased as the reaction temperature was raised. From these results, 80°C is selected as the best temperature for all subsequent studies. It is noteworthy that, increasing the amount of SBA-15-Pr–SO_3H and time did not increase the yield of product in the model reaction.

The used catalyst could be washed with dichloromethane and subjected to a second run of the reaction process with benzaldehyde and acetophenone. The results of the first experiment and subsequent experiments were almost consistent in yields (93, 94 and 91% after three runs). Thus, the catalyst can be recycled several times with negligible loss of catalytic activity and there is no need for regeneration of the catalyst.

To show the generality of this method, a wide range of aldehydes and acetophenones were subjected to optimized reaction conditions and the results are summarized in table 1. It is evident from table 1 that this method is effective for the preparation of β-acetamido ketones from both aldehydes as well as acetophenone derivatives. Aromatic aldehydes or acetophenones with activating and deactivating groups underwent smooth transformation to the corresponding β-acetamido ketones, without the formation of any side products, in high to excellent yields and reasonable reaction times, emphasizing the generality of our methodology. The results also showed that the reaction times for the substrates containing electron withdrawing groups are slightly longer. Several functionalities such as bromo, chloro, hydroxyl, methoxy and nitro were compatible with this procedure. The experiment for this reaction is remarkably simple and requires no inert atmosphere. Anyway, this protocol has its

Table 1. One-pot condensation of aryl aldehydes, ketones, acetyl chloride and acetonitrile to give the corresponding β-acetamido ketones catalyzed by SBA-15-Pr-SO_3H.



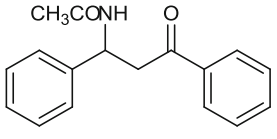
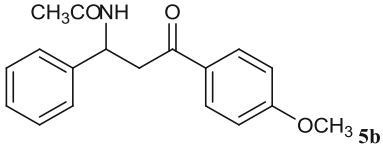
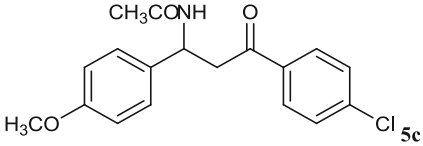
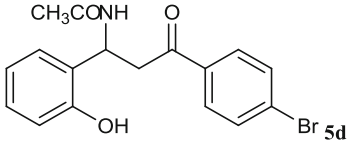
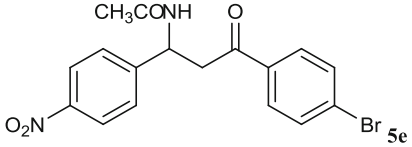
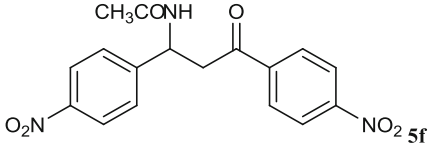
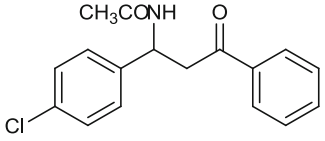
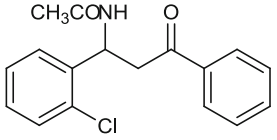
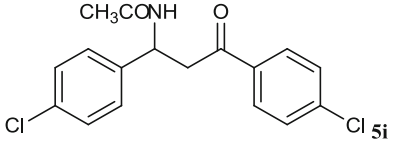
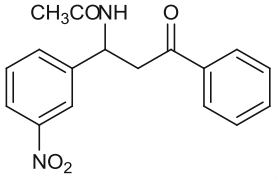
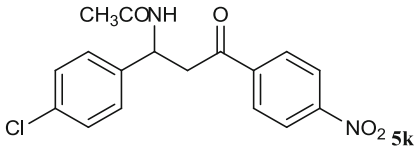
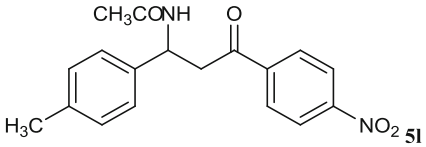
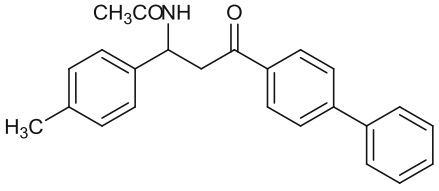
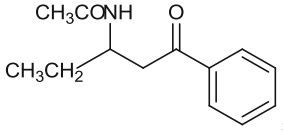
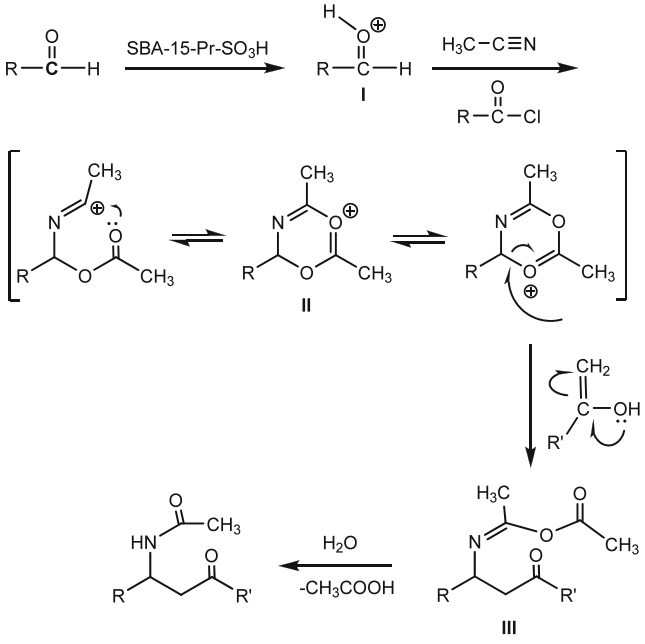
Entry	Ar	R	Product	Yield %b/t(min)	M.p. (°C)[Ref]
1	C_6H_5	C_6H_5	 **5a**	93 (60)	99–102 (102–104)[22]
2	C_6H_5	4-$CH_3OC_6H_4$	 **5b**	75 (45–50)	128–129 (130)[23]
3	4-$CH_3OC_6H_4$	4-ClC_6H_4	 **5c**	80 (50–60)	17–119 (120)[24]
4	2-HOC_6H_4	4-BrC_6H_4	 **5d**	85 (60)	127 (126–128)[25a]
5	4-$NO_2C_6H_4$	4-BrC_6H_4	 **5e**	90 (75)	181 (182–183)[25b]
6	4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	 **5f**	83 (130)	176 (176–179)[25c]
7	4-ClC_6H_4	C_6H_5	 **5g**	94 (50)	146–148 (146–148)[10]
8	2-ClC_6H_4	C_6H_5	 **5h**	95 (85)	147–149 (149–151)[26]
9	4-ClC_6H_4	4-ClC_6H_4	 **5i**	94 (70)	141–143 (141–143)[10]
10	3-$NO_2C_6H_4$	C_6H_5	 **5j**	90 (85)	113 (114–116)[25b]

Table 1. (Continued)

11	4-ClC_6H_4	4-$NO_2C_6H_4$	 **5k**	85 (110)	118–120 (116–118)[26]
12	4-$CH_3C_6H_4$	4-$NO_2C_6H_4$	 **5l**	70 (60)	87–90 (83–85)[9]
13	4-$CH_3C_6H_4$	4-Ph C_6H_4	 **5m**	90 (100)	137 (138–140)[27]
14	CH_3CH_2	C_6H_5	 **5n**	30 (60)	97 (98–100)[25]

[a] All products were characterised by comparison of their spectral and physical data with those of the authentic samples.
[b] Yields refer to pure isolated products.



Scheme 3. A plausible mechanism for the preparation of β-acetamido carbonyl compounds.

Table 2. Comparison of some of the results obtained with some of those reported in the literature.

Entry	Substrate	Conditions [Ref.]	Yield %/(Time)
1	**5a**	this work	93 (1 h)
		ZnO/80°C[28]	90 (6 h)
		silica sulfuric acid/80°C[10]	91 (65 min)
		$H_7SiW_9V_3O_{40}$/80°C[29]	70 (4 h)
		$HClO_4$-SiO_2/80°C[30]	89 (2.5 h)
2	**5e**	this work	94 (50 min)
		ZnO/80 °C[28]	93 (5.5 h)
		silica sulfuric acid/80°C[10]	89 (70 min)
		$H_7SiW_9V_3O_{40}$/80°C[29]	76 (3 h)
		$HClO_4$-SiO_2/80°C[30]	94 (2.5 h)
3	**5h**	this work	90 (85 min)
		ZnO/80°C[28]	88 (5.5 h)
		silica sulfuric acid/80°C[10]	82 (110 min)
		$H_7SiW_9V_3O_{40}$/80°C[29]	88 (5 h)
		$HClO_4$-SiO_2/80°C[30]	82 (3 h)

limitations, for example, it produces low yields for aliphatic aldehydes (table 1, entry 15).

The suggested mechanism for this reaction is presented in scheme 3. It is suggested that the first protonation of the aldehyde produces intermediate **I** which then reacts with acetonitrile to produce intermediate **II**. Next, the enol form of acetophenone derivative attacks **II** to give **III**. Hydrolysis of **III** with elimination of acetate gave the desired β-acetamido ketone.

A comparison of the efficiency of this method to previously selected methods is gathered in table 2. As can be seen, the present protocol is indeed superior to several other protocols.

4. Conclusion

We have described an efficient method for the one-pot synthesis of β-acetamido ketones using an environment friendly, heterogeneous nanoreactor catalyst. Simplicity, excellent yield of products, reusability of the catalyst, and clean reaction conditions are established. This methodology also overcomes the formation of unwanted by-product. Thus, we believe that the present methodology opens up new possibilities for medicinal chemistry and material sciences, and can prove to be an important addition to the existing methodologies. Further investigations into the scope and synthetic applications of this nanoreactor catalyst are currently under investigation in our laboratory.

Supplementary Information

Complete experimental procedures and relevant spectra (^{1}H NMR and ^{13}C NMR spectra) for some compounds (figure S1–S8) are given in Supplementary Information, which is available free of charge in www.ias.ac.in/chemsci.

Acknowledgments

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