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Supported *L*-pyrrolidine-2-carboxylic acid-4-hydrogen sulphate on silica gel as an economical and efficient catalyst for the one-pot preparation of β-acetamido ketones *via* a four-component condensation reaction

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Abstract. An efficient, one-pot, four-component condensation of aldehydes, acetophenone (or propiophenone), acetyl chloride and acetonitrile in the presence of catalytic amounts of *L*-pyrrolidine-2-carboxylic acid-4-hydrogen sulphate (supported on silica gel), a green and non-toxic catalyst, is described for the preparation of β-acetamido ketones in good to excellent yields.

Keywords. β-Acetamido ketones; *L*-pyrrolidine-2-carboxylic acid-4-hydrogen sulphate; one-pot; four-component; catalyst.

1. Introduction

During the last few years, multi-component reactions (MCRs) have proved to be remarkably successful in generating molecular complexity in a single synthetic operation.[1] These processes consist of two or more synthetic steps, which are performed without isolation of any intermediate thus reducing time and saving both energy and raw materials. MCRs are powerful tools in the modern drug discovery process and allow fast, automated and high throughput generation of organic compounds.[2] Furthermore, a field of increasing interest is the synthesis of useful synthetic building blocks *via* MCR chemistry. For this reason, the discovery of novel MCRs is of interest.[3–5]

β-Acetamido ketones are versatile intermediates in that their skeletons exist in a number of biologically or pharmacologically important compounds.[6] The best known route for the synthesis of these compounds is the Dakin–West reaction,[7] which involves the condensation of an amino acid with acetic anhydride in the presence of a base *via* an intermediate azalactone to give the acetamido ketones.[8] Bhatia *et al*.[9] proposed another procedure for the formation of these compounds through the condensation of an aryl aldehyde, acetophenone, and acetyl chloride in acetonitrile in the presence of $CoCl_2$ or montmorillonite K-10 clay.[10] Other catalysts such as heteropolyacids,[11] $HClO_4$-SiO_2,[12] $CeCl_3$,[13] ZnO,[14] cyanuric chloride,[15] Amberlyst-15,[16] and $POCl_3$/borax,[17] have also been used. Although these methods are valuable, most of them employ expensive catalysts, long reaction times or harsh reaction conditions.

2. Experimental

Chemicals were purchased from Fluka, Merck and Aldrich chemical companies. The known products were characterized by comparison of their spectral (^{1}H NMR, and ^{13}CNMR) and physical data with those of authentic samples. Unknown compounds were identified by their ^{1}H and ^{13}CNMR spectra and elemental analysis.

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

Supported *L*-pyrrolidine-2-carboxylic acid-4-hydrogen sulphate on silica gel (0.274 g) was added to the mixture of aryl aldehyde (1 mmol), aryl ketone (1 mmol), acetyl chloride (0.3 mL) and acetonitrile (reagent as well as solvent) (3 mL). The reaction mixture was heated under reflux conditions and stirred for appropriate time (reaction progress was monitored by TLC). After completion of the reaction, the reaction mixture was filtered off and the solvent (acetonitrile) was evaporated. For further purification and separation of diastereomers, the crude product was dissolved in dichloromethane and purified by P-TLC (*n*-hexane/acetone, 8/2).

*For correspondence

2.2 *Representative NMR Data*

2.2a *N-(1-(naphthalen-2-yl)-3-oxo-3-phenylpropyl) acetamide*: Mp: 114–117°C; ^{1}H NMR (400 MHZ, $CDCl_3$): δ = 7.93 (d, 2H, J = 7.2 HZ), 7.8 (t, 4H, J = 8 HZ), 7.58 (t, 1H, J = 6.8 HZ), 7.47 (t, 6H, J = 6.8 HZ), 6.81 (d, 1H, J = 7.6 HZ), 5.76–5.74 (m, 1H), 3.87 (dd, 1H, J = 12, 4.8 HZ), 3.56 (dd, 1H, J = 10.8, 6 HZ), 2.08 (s, 3H) ppm.

2.2b *N-(1-(4-bromophenyl)-2-methyl-3-oxo-3-phenyl-propyl)acetamide (anti-isomer)*: Mp: 156–159°C; ^{1}H NMR (400 MHZ, $CDCl_3$): δ = 7.79 (d, J = 7.6 HZ, 2H), 7.59–7.55 (m, 2H), 7.45–7.41 (m, 2H), 7.36 (d, J = 8.4 HZ, 2H), 7.15 (d, J = 8.4 HZ, 2H), 5.35–5.33 (m, 1H), 4.09–4.05 (m, 1H), 2.12 (s, 3H), 1. 37 (d, J = 7.2 HZ, 3H) ppm; ^{13}C NMR (100 MHZ, $CDCl_3$): δ = 204.9, 170.1, 140.2, 136.1, 133.8, 131.6, 128.8, 128.2, 128.1, 121.1, 55.2, 44.2, 23.4, 16.8 ppm.

Anal. Calcd for $C_{18}H_{18}BrNO_2$: C, 60.01; H, 5.04; N, 3.82. Found: C, 60.68; H, 4.86; N, 3.89.

2.2c *N-(1-(4-bromophenyl)-2-methyl-3-oxo-3-phenyl-propyl)acetamide (syn-isomer)*: Mp: 146–147°C; ^{1}H NMR (400 MHZ, $CDCl_3$): δ = 7.9–7.88 (m, 2H), 7.59–7.22 (m, 7H), 6.57 (m, 1H), 5.46–5.44 (m, 1H), 4.08–4.04 (m, 1H), 1.99 (s, 3H), 1.25 (d, J = 7.2 HZ, 3H) ppm; ^{13}C NMR (100 MHZ, $CDCl_3$): δ = 201.7, 169.7, 139.6, 136.1, 133.5, 131.7, 128.9, 128.8, 128.18, 121.4, 54.5, 45.2, 23.3, 13.8 ppm.

Anal. Calcd for $C_{18}H_{18}BrNO_2$: C, 60.01; H, 5.04; N, 3.82. Found: C, 63.05; H, 5.39; N, 4.04.

2.2d *N-(2-methyl-1-(3-nitrophenyl)-3-oxo-3-phenyl-propyl)acetamide (anti-isomer)*: Mp: 142–146°C; ^{1}H NMR (400 MHZ, $CDCl_3$): δ = 8.03–8.22 (m, 2H), 7.81–7.29 (m, 8H), 5.50 (m, 1H), 4.16 (m, 1H), 2.16–2.1 (s, 3H), 1.46–1.30 (m, 3H) ppm; ^{13}C NMR (100 MHZ, $CDCl_3$): δ = 204.2, 170.4, 148.3, 143.4, 135.8, 134, 132.8, 129.5, 128.9, 128.2, 128.2, 122.3, 121.4, 55.2, 44.3, 23.3, 16.8 ppm.

Anal. Calcd for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 65.81; H, 5.51; N, 7.79.

2.2e *N-(2-methyl-1-(3-nitrophenyl)-3-oxo-3-phenyl-propyl)acetamide (syn-isomer)*: Mp: 128–133°C; ^{1}H NMR (400 MHZ, $CDCl_3$): δ = 8.25 (s, 1H), 8.1 (d, J = 6.8 HZ, 1H), 7.9 (d, J = 7.6 HZ, 2H), 7.74 (d, J = 7.6 HZ, 1H), 7.6–7.57 (m, 2H), 7.49–7.43 (m, 3H), 6.69 (m, 1H), 5.54 (t, J = 7.6 HZ, 1H), 4.16–4.09 (m, 1H), 2.05 (s, 3H), 1.29 (d, J = 6.8 HZ, 3H) ppm; ^{13}C NMR (100 MHZ, $CDCl_3$): δ = 201.4, 170.1, 148.3, 143, 135.4, 134.2, 133.69, 129.5, 129, 128.2, 128.2, 122.5, 122.7, 54.6, 45.2, 23.2, 14.1 ppm.

Anal. Calcd for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 65.49; H, 5.84; N, 8.30.

2.2f *N-(-2-methyl-1-(naphthalen-2-yl)-3-oxo-3-phenyl-propyl)acetamide (anti-isomer)*: Mp: 177–179°C; ^{1}H NMR (400 MHZ, CDCl3): δ = 7.8–7.68 (m, 7H), 7.53–7.36 (m, 6H), 5.58 (dd, J = 8.8, 4 HZ, 1H), 4.26–4.23 (m, 1H), 2.17 (s, 3H), 1.47 (d, J = 7.2 HZ, 3H) ppm; ^{13}C NMR (100 MHZ, CDCl3): δ = 205.2, 170.1, 138.5, 136.3, 133.6, 133.2, 132.6, 128.7, 128.4, 128.21, 128, 127.5, 126.1, 125.8, 125.2, 124.6, 55.9, 44.4, 29.7, 23.5, 16.9 ppm.

Anal. Calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 77.82; H, 6.34; N, 4.15.

2.2g *N-(-2-methyl-1-(naphthalen-2-yl)-3-oxo-3-phenyl-propyl)acetamide (syn-isomer)*: Mp: 196–198°C; ^{1}H NMR (400 MHZ, $CDCl_3$): δ = 7.95 (d, J = 4 HZ, 2H), 7.8–7.77 (m, 4H), 7.58–7.45 (m, 6H), 6.31 (m, 1H), 5.69 (t, J = 7.6 HZ, 1H), 4.24–4.19 (m, 1H), 2.02 (s, 3H), 1.28 (d, J = 6.8 HZ, 3H) ppm; ^{13}C NMR (100 MHZ, $CDCl^3$): δ = 201.9, 169.7, 137.8, 136.3, 133.3, 133.2, 132.3, 128.8, 128.5, 128.2, 127.9, 127.6, 126.3, 126, 125.8, 125, 54.9, 45.6, 23.3, 13.6 ppm.

Anal. Calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 78.42; H, 6.88; N, 3.96.

2.2h *N-(-1-(4-fluorophenyl)-2-methyl-3-oxo-3-phenyl-propyl)acetamide (anti-isomer)*: Mp: 128–132°C; ^{1}H NMR (400 MHZ, $CDCl_3$): δ = 7.78 (d, J = 7.2 HZ, 2H), 7.59–7.53 (m, 2H), 7.42 (t, J = 8 HZ, 2H), 7.29–7.22 (m, 2H) 6.92 (t, J = 8.8 HZ, 2H), 5.36 (dd, J = 4, 8.8 HZ, 1H), 4.11–4.07 (m, 1H), 2.1 (s, 3H), 1.38 (d, J = 7.2 HZ, 3H) ppm; ^{13}C NMR (100 MHZ, $CDCl_3$): δ = 205, 170, 163, 160.6, 136.9, 136.9, 136.3, 133.7, 128.8, 128.2, 128, 128, 115.4, 115.2, 55.2, 44.5, 23.4, 16.7 ppm.

Anal. Calcd for $C_{18}H_{18}FNO_2$: C, 72.22; H, 6.06; N, 4.68. Found: C, 71.42; H, 6.20; N, 4.55.

2.2i *N-(-1-(4-fluorophenyl)-2-methyl-3-oxo-3-phenyl-propyl)acetamide (syn-isomer)*: Mp: 107–111°C; ^{1}H NMR (400 MHZ, $CDCl_3$): δ = 7.91 (d, J = 7.2 HZ, 2H), 7.59 (t, J = 7.6 HZ, 1H), 7.48 (t, J = 8 HZ, 2H), 7.33–7.29 (m, 2H), 6.99 (t, J = 8.8 HZ, 2H), 6.07–6.05 (m, J = 7.6 HZ, 1H), 5.44 (t, J = 7.6 HZ, 1H), 4.09–4.02 (m, 1H), 2.01 (s, 3H), 1.24 (d, J = 7.2 HZ, 3H) ppm; ^{13}C NMR (100 MHZ, $CDCl_3$): δ = 201.8,169.6, 163.2, 160.8, 136.2, 136.2, 133.42, 128.9, 128.7, 128.6, 111.6, 115.4, 54.5, 45.4, 29.7, 23.4,13.7 ppm.

Anal. Calcd for $C_{18}H_{18}FNO_2$: C, 72.22; H, 6.06; N, 4.68. Found: C, 70.75; H, 6.11; N, 4.65.

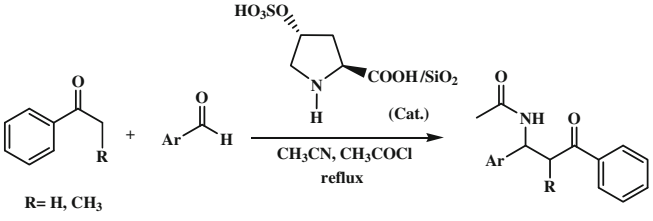
3. Results and discussion

In order to improve above mentioned drawbacks, we decide to introduce a new, simple, mild and effective procedure for the one-pot synthesis of β-acetamido ketones *via* four-component condensation reaction between aldehydes, enolizable ketones, acetyl chloride and acetonitrile in the presence of supported *L*-pyrrolidine-2-carboxylic acid-4-hydrogen sulphate on silica gel (which has been prepared according to our previously reported procedure)[18] as catalyst under reflux conditions (scheme 1).

In this study, we wish to report a convenient and efficient procedure for synthesis of β-acetamido ketones using *L*-pyrrolidine-2-carboxylic acid-4-hydrogen sulphate (supported on silica gel) as catalyst.

Initially, in order to find appropriate amount of catalyst, *p*-chlorobenzaldehyde (1 mmol), acetophenone (1 mmol), acetyl chloride (0.3 mL) and acetonitrile (3 mL) was subjected to condensation under reflux conditions in the presence of different amounts of supported *L*-pyrrolidine-2-carboxylic acid-4-hydrogen sulphate on silica gel (scheme 2 and table 1).

Also, the results of the preparation of 3-(acetoxyamino)-3-(4-chlorophenyl)-1-phenylpropan-1-one as a function of the amounts of catalyst is shown in figure 1. By optimizing the reaction conditions, it was found that 65 mol% of *L*-pyrrolidine-2-carboxylic acid-4-hydrogen sulphate (supported on silica gel) was enough for completion of the reaction.



Scheme 1. Synthesis of *β*-acetamido ketones.

Table 1. Preparation of 3-(acetoxyamino)-3-(4-chlorophenyl)-1-phenylpropan-1-one from *p*-chlorobenzaldehyde and acetophenone in the presence of acetyl chloride and acetonitrile catalysed by *L*-pyrrolidine-2-carboxylic acid-4-hydrogen sulphate (supported on silica gel) under reflux conditions.

Entry	Catalyst (mol %)	Time (h)	Yield(%)[a]
1	0	4	0
2	10	4	16
3	20	4	33
4	30	4	40
5	40	4	55
6	50	4	69
7	65	4	90

[a]Isolated yield

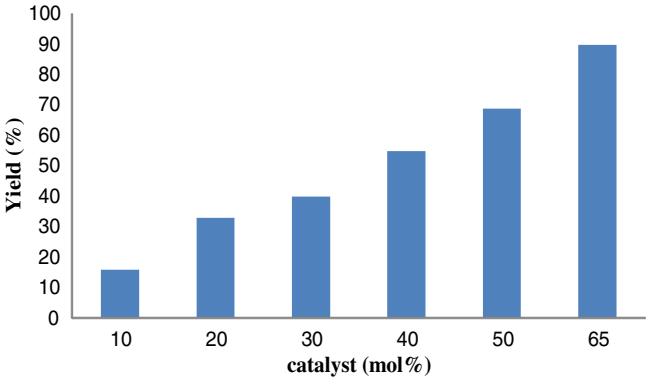
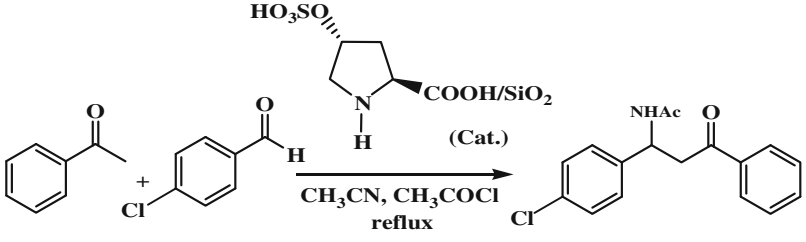


Figure 1. Preparation of 3-(acetoxyamino)-3-(4-chlorophenyl)-1-phenylpropan-1-one as a function of the catalyst amount.

With the optimal reaction conditions in hand, we have explored the generality of this catalyst-mediated β-acetamido ketone synthesis with various aldehydes and enolizable ketones. The results are summarized in table 2.

Results from the reactions of aryl aldehydes, aryl ketones and acetyl chloride in presence of optimized catalyst in acetonitrile under reflux conditions are shown in table 2. The electronic features and position of the substituent on the aromatic ring of aldehyde had no significant effect on the outcome of reaction. Also, both



Scheme 2. Effect of catalyst on the outcome of the reaction.

Table 2. Preparation of β-acetamido ketones from aldehydes and enolizable ketones in the presence of acetyl chloride and acetonitrile catalysed by *L*-pyrrolidine-2-carboxylic acid-4-hydrogen sulphate (supported on silica gel) under reflux conditions.

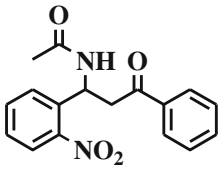
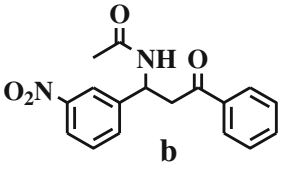
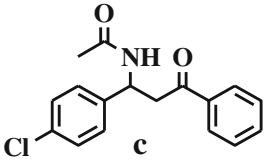
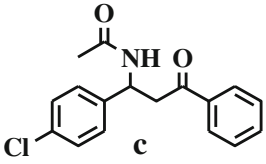
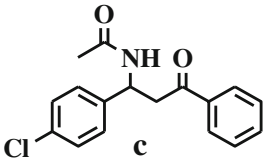
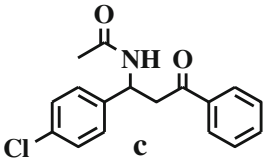
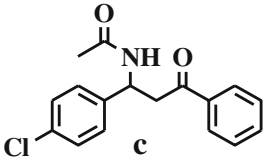
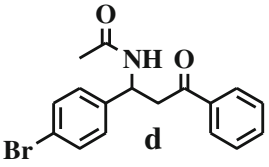
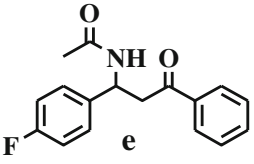
Entry	Product	Time (h)	Yield (%)[a]	syn/anti (%)
1	 **a**	4	90	–
2	 **b**	4	78	–
3	 **c**	4	90	–
4	 **c**	24	0[b]	–
5	 **c**	6	0[c]	–
6	 **c**	6	0[d]	–
7	 **c**	6	26[e]	–
8	 **d**	4	71	–
9	 **e**	4	65	–

Table 2. (Continued).

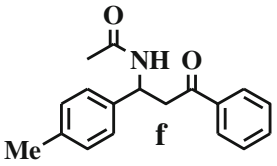
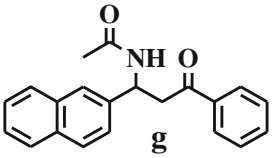
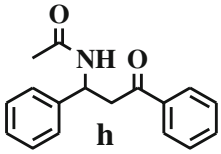
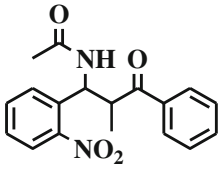
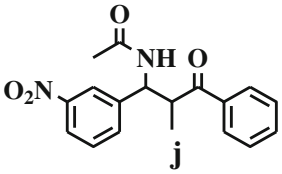
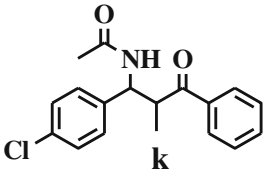
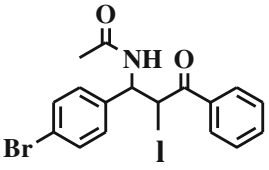
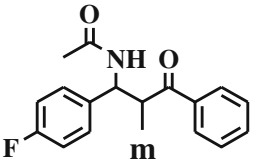
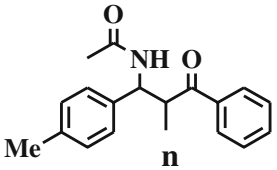
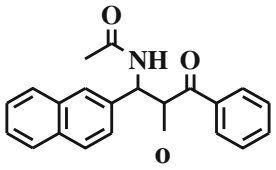
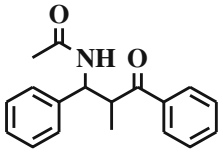
Entry	Product	Time (h)	Yield (%)[a]	syn/anti (%)
10	 **f**	4	61	–
11	 **g**	4	55	–
12	 **h**	4	70	–
13	 **i**	4	80	52:48
14	 **j**	4	68	47:53
15	 **k**	4	75	44:56
16	 **l**	4	98	42:58
17	 **m**	4	80	42:58
18	 **n**	4	68	55:45

Table 2. (Continued).

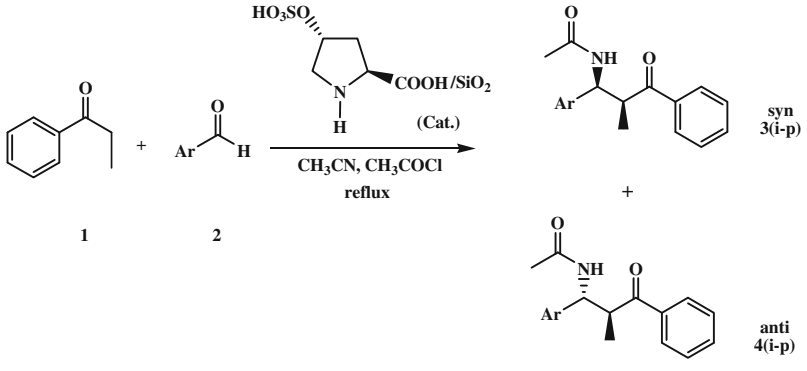
Entry	Product	Time (h)	Yield (%)[a]	syn/anti (%)
19	 o	4	67	50:50
20	 p	4	98	34:66

[a]Isolated yield.
[b]In the absence of catalyst.
[c]In the presence of SiO_2.
[d]In the presence of 4-hydroxy-*L*-proline.
[e]In the presence of catalyst without SiO_2.

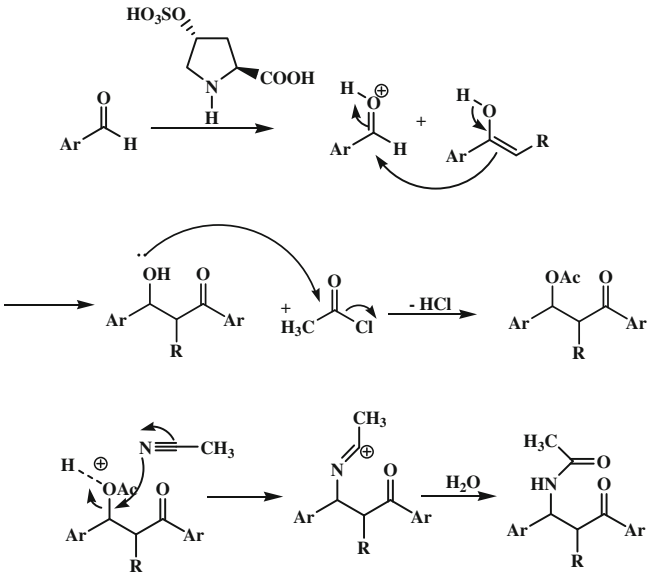
aromatic aldehydes and ketones bearing either electron-donating or electron-withdrawing groups afforded the β-acetamido ketones without the formation of any side products, in good to excellent yields.

Given the successful delineating of described procedure, we were encouraged to consider the stereochemistry of obtained product with propiophenone. As shown in table 2, reaction of this ketone with different aldehydes catalysed by *L*-pyrrolidine-2-carboxylic acid-4-hydrogen sulphate (supported on silica gel), the reaction yielded a mixture of the anti- and syn-isomers (scheme 3). The catalyst that was used in this project was increased amount of syn-isomer compared with the previously reported studies.[9,19,20] Also, we were able to separate the two diastereomers from each other by P-TLC and measure the proportion of each isomer (entries 13–20, table 2), (the ratio of syn/anti diastereomers was determined by ^{1}H NMR spectroscopy of the crude product). The results show that the amount of syn-isomer is nearly close to the anti-isomer. Also, in table 2 entries 13 and 18, showed that the syn-diastereomer is slightly larger than anti-diastereomer. However, in the previous reports, the products were obtained as a mixture of syn and anti isomers favouring anti-isomer or rarely syn-isomer.

In order to investigate the role of catalyst for preparation of β-acetamido ketones, one of the reactions was designed in the absence of supported *L*-pyrrolidine-2-carboxylic acid-4-hydrogen sulphate on silica gel; in the presence of *L*-pyrrolidine-2-carboxylic acid-4-hydrogen sulphate without silica gel, SiO_2 and 4-hydroxy-L-proline were designed. Surprisingly, we have observed no product in the absence of catalyst or in the presence of silica gel or 4-hydroxy-L-proline. Also,



Scheme 3. Diasteroselectivity on the synthesis of β-acetamido ketones.



Scheme 4. Mechanism of β-acetamido ketone synthesis.

the yield of reaction in the presence of *L*-pyrrolidine-2-carboxylic acid-4-hydrogen sulphate without silica gel was 26% (table 2, entries 4–7).

Suggested mechanism for this transformation has been outlined in scheme 4, based on previously reported studies.[21–23]

4. Conclusion

In conclusion, we have reported an efficient, inexpensive and straightforward procedure for one-pot synthesis of β-acetamido ketones using supported *L*-pyrrolidine-2-carboxylic acid-4-hydrogen sulphate on silica gel as catalyst. The important features provided by this procedure are the use of effective, non-toxic and cost-effective catalyst and increasing the amount of syn-isomer.

Supplementary information

The supplementary information for compounds g, i, j, o and m can be seen in the website (www.ias.ac.in/chemsci).

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