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A simple and efficient one-pot multicomponent synthesis of β-acetamido carbonyl compounds with $Zn(HSO_4)_2$ and $Co(HSO_4)_2$ as catalysts

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$Zn(HSO_4)_2$ and $Co(HSO_4)_2$ has been used as efficient catalysts for the preparation of β-acetamido carbonyl compounds by Dakin-West reaction.

Key Words: Darking-West reaction, metal catalysis, acatamido carbonyl compounds.

Introduction

Metal hydrogen sulfates have been used as an efficient reagent in organic chemistry. A broad range of reactions including deprotection, oxidation, C-C, C-N, and C-O bond formation and cleavage took place in the presence of these reagents under mild and heterogeneous conditions. In addition, stability, cheapness, ability to produce highly efficient products in a short time, and, in many cases, reusability is among other important advantages of these reagents.[1−5]

$\beta-$acetamido ketones are useful intermediate in different organic synthesis due to their polyfunctional nature and presence in several bioactive compounds.[6−7] Conventionally, this class of compounds is prepared by Dakin-West reaction.[8] Recently, other synthetic methods have been used for synthesis of β-acetamido ketones through the multicomponent reaction of aldehyde, enolizable ketone, acetyl chloride, and acetonitrile in the presence of $CoCl_2$,[9] $Cu(OTf)_2/Sc(OTf)_3$,[10] silica sulfuric acid,[11] BiOCl,[12] $FeCl_3$,[13] $ZrOCl_2\cdot 8H_2O$,[14] $CeCl_3\cdot$

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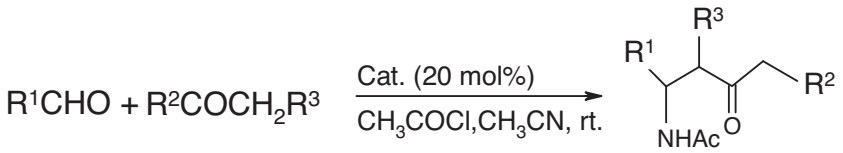
$7H_2O$,[15] $K_5CoW_{12}O_{40}\cdot 3H_2O$,[16] Amberlyst-15,[17] Nafion-H,[18] Montmorillonite K-10 clay,[19] Heteropolyacid,[20–22], PCl_3,[23] ZnO,[24] I_2,[25] and $La(OTf)_3$[26] as catalysts.

In continuation of our work[27–31] on the development of useful synthetic methodologies, here in we report a mild, simple, and effective method for the preparation of β-acetamido carbonyl compounds using $Zn(HSO_4)_2$ and $Co(HSO_4)_2$ as readily available, cheap and, non-toxic catalysts (Scheme 1).



Scheme 1

Experimental

A mixture of aromatic aldehyde (1 mmol), acetophenone or β-keto ester (1 mmol), acetyl chloride (0.3 mL) and $Zn(HSO_4)_2$ or $Co(HSO_4)_2$ (20 mol%) in acetonitrile (3 mL) was stirred at room temperature. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into 50 mL of ice water. The solid product was filtered, washed with ice water, and recrystallized from ethyl acetate/n-hexane to give the pure product. All products were characterized by comparing their physical constant and spectral data with the values of authentic samples.[11–20]

Results and discussion

A series of β-acetamido carbonyl compounds were prepared from various aldehyde and enolizable keton and keto esters. At first, a mixture of benzaldehyde, acetophenone, acetyl chloride, and acetonitrile was stirred under various reaction conditions (Table 1). In the absence of the catalyst, β-acetamido ketone was obtained in 25% yield after 20 h as the product. The best conditions to prepare the β-acetamido ketones were achieved when 20 mol% of $Zn(HSO_4)_2$ and $Co(HSO_4)_2$ were used, and any excess of the catalysts did not lead to an increase in the conversion and yield.

Table 1. Optimization of the $Zn(HSO_4)_2$ and $Co(HSO_4)_2$ catalyzed multi-component reaction.

Entry	Catalyst mol%	$Zn(HSO_4)_2$	$Co(HSO_4)_2$
		Time (min)/Yield (%)	Time (min)/Yield (%)
1	0	20(h)/25	20(h)/25
2	5	150/40	100/60
3	10	100/50	80/70
4	15	60/75	70/85
5	20	30/90	55/92

Under optimal conditions, a wide variety of aromatic aldehydes and acetophenones, containing both electron withdrawing and donating substituents, were treated and the corresponding β-acetamido ketones (Table

Table 2. $Zn(HSO_4)_2$ and $Co(HSO_4)_2$ catalyzed multi-component reaction for the preparation of β-acetamido ketones and keto esters.

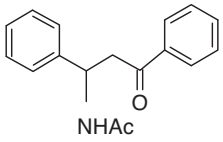
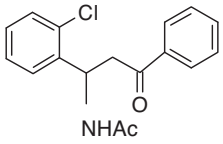
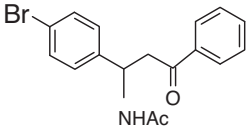
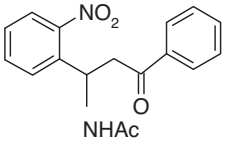
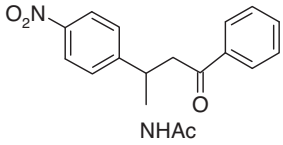
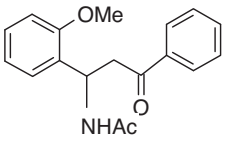
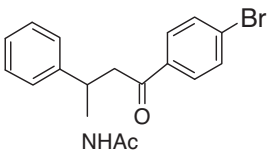
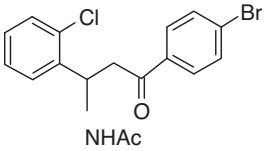
Entry	R^1	R^2	R^3	Product[a]	Time (min)/Yield(%)	
					$Zn(HSO_4)_2$	$Co(HSO_4)_2$
1	C_6H_5	C_6H_5	H		30/87	55/92 6(h)/20[b]
2	2-ClC_6H_4	C_6H_5	H		30/95	45/90
3	4-BrC_6H_4	C_6H_5	H		30/90	40/90 7(h)/22[b]
4	2-NO_2 C_6H_4	C_6H_5	H		60/87	60/85
5	4-$NO_2C_6H_4$	C_6H_5	H		55/90	65/89 10(h)/25[b]
6	2-$CH_3OC_6H_4$	C_6H_5	H		35/95	45/91
7	C_6H_5	4-BrC_6H_4	H		25/90	45/91
8	2-ClC_6H_4	4-BrC_6H_4	H		25/95	40/90

Table 2. Contunied.

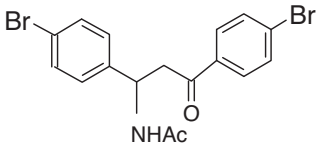
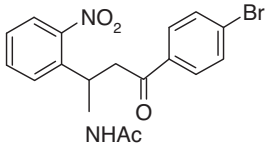
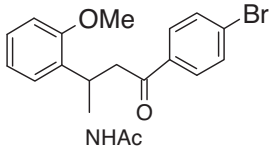
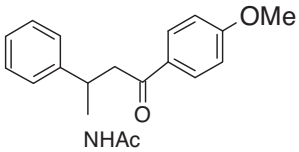
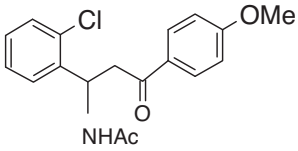
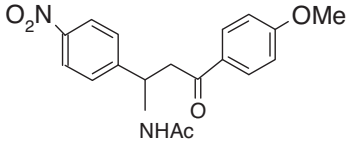
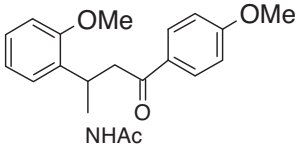
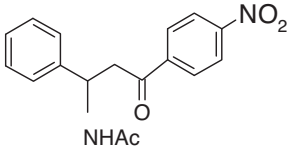
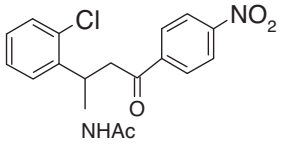
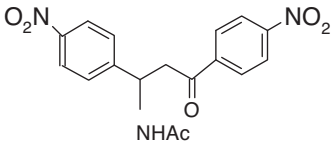
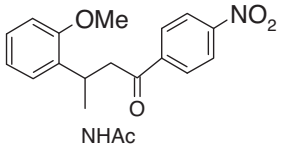
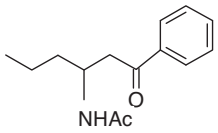
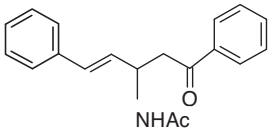
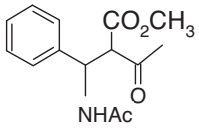
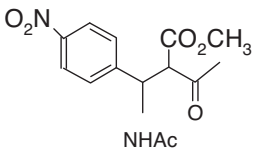
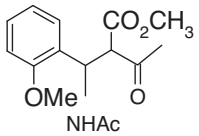
Entry	R^1	R^2	R^3	Product[a]	Time (min)/Yield(%)	
					$Zn(HSO_4)_2$	$Co(HSO_4)_2$
9	$4\text{-}BrC_6H_4$	$4\text{-}BrC_6H_4$	H		30/97	40/92
10	$2\text{-}NO_2C_6H_4$	$4\text{-}BrC_6H_4$	H		45/90	60/82
11	$2\text{-}CH_3OC_6H_4$	$4\text{-}BrC_6H_4$	H		35/90	50/90
12	C_6H_5	$4\text{-}CH_3OC_6H_4$	H		30/88	45/90
13	$2\text{-}ClC_6H_4$	$4\text{-}CH_3OC_6H_4$	H		30/90	60/89
14	$4\text{-}NO_2C_6H_4$	$4\text{-}CH_3OC_6H_4$	H		50/85	60/90
15	$2\text{-}CH_3OC_6H_4$	$4\text{-}CH_3OC_6H_4$	H		30/90	65/90
16	C_6H_5	$4\text{-}NO_2C_6H_4$	H		30/90	55/85

Table 2. Contunied.

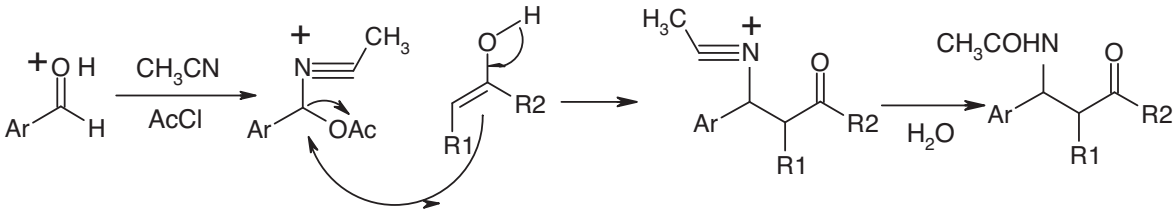
Entry	R^1	R^2	R^3	Product[a]	Time (min)/Yield(%)	
					$Zn(HSO_4)_2$	$Co(HSO_4)_2$
17	2-Cl C_6H_4	4-$NO_2C_6H_4$	H		30/92	60/82
18	4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	H		45/85	70/80
19	2-$CH_3OC_6H_4$	4-$NO_2C_6H_4$	H		25/90	65/87
20	C_3H_7	C_6H_5	H		120/20	240/25
21	C_8H_7	C_6H_5	H		25/80	120/80
22	C_6H_5	CH_3	CH_3O_2C		30/70 23:77[c]	120/79 30:70[c]
23	4-$NO_2C_6H_4$	CH_3	CH_3O_2C		40/80 30:70[c]	180/70 35:65[c]
24	2-$CH_3OC_6H_4$	CH_3	CH_3O_2C		35/90 30:70[c]	80/75 32:68[c]

[a] All the products were fully characterized by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy and their data were compared with authentic data (ref. 11-20).

[b] The reaction was carried out in the presence of acetic anhydride.

[c] Ratio of syn and anti isomers (by ^{1}H NMR).

2) were obtained in good to excellent yields. All the products were fully characterized by spectroscopic methods and compared with the authentic spectra. α,β-unsaturatedaldehydes, such as cinnamaldehyde, also reacts under the same experimental conditions and provide the desired product (Table 2, entry 21). The minimum yield and longer time was obtained with aliphatic aldehyde (Table 2, entry 20). β-Dicarbonyl compounds, such as methyl acetoacetate, was also applied in the reaction to afford the corresponding β-acetamido keto esters in good yields and diastereoselectivities (Table 2, entries 22-24). We also examine the efficiency of acetic anhydride instead of acetyl chloride in the presence of $Co(HSO_4)_2$ as a catalyst, and the reaction proceeded in long reaction time and low yield (Table 2, entries 1, 3, 5). Next, using benzylcyanid in place of acetonitrile, a variety of aldehydes were transformed to their corresponding β-acetamido ketones in 20%-35% yield after 6-8 h. The probable mechanism for this reaction was shown in Scheme 2.



Scheme 2

Conclusion

In conclusion, we have demonstrated a mild and simple method for the preparation of β-acetamido ketones and esters using $Zn(HSO_4)_2$ and $Co(HSO_4)_2$ as catalysts. The major advantages of this protocol are short reaction times, mild reaction conditions, easy work-up procedure, and ready availability of the catalysts.

The spectral data of some of the representative β-acetamido ketones and β-acetamido esters:

β-Acetamido-β-(phenyl)propiophenone (Table 2, entry 1), mp: 104-106 °C, ^{1}H NMR (300 MHz, $CDCl_3$), δ: 2.03 (s, 3H), 3.46 (dd, J = 6.0 and 16.8 Hz, 1H), 3.75 (dd, J = 5.2 and 16.8 Hz, 1H), 5.54-5.61 (m, 1H), 6.94 (d, J = 6.3 Hz, 1H), 7.23-7.37 (m, 5H), 7.44 (t, J = 8 Hz, 2H), 7.55 (t, J =7.6 Hz, 1H), 7.91 (d, J = 7.5 Hz, 2H); ^{13}C NMR (75MHz, $CDCl_3$), δ: 23.34, 43.19, 49.98, 126.51, 127.48, 128.13, 128.7, 133.56, 136.56, 140.87, 169.72, 198.52; IR (KBr, cm^{-1}): 3272, 3093, 1690, 1643, 1557, 1451, 1347, 1295, 993, 754.

β-Acetamido-β-(2-chlorophenyl)propiophenone (Table 2, entry 2), mp: 155-157 °C, ^{1}H NMR (300 MHz, $CDCl_3$), δ: 2.04 (s, 3H), 3.46 (dd, J = 5.5 and 16.8 Hz, 1H), 3.76 (dd, J = 5.9 and 16.8 Hz, 1H), 5.80-5.87 (m, 1H), 7.22 (m, 5H), 7.50 (m, 3H), 7.90 (d, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), IR (KBr, cm^{-1}) 3290, 3079, 1692, 1653, 1547, 1441, 1356, 1296, 1229, 996, 749, 691, 620.

β-Acetamido-β-(2-nitrophenyl)propiophenone (Table 2, entry 4), mp: 148-150 °C, ^{1}H NMR (300 MHz, $CDCl_3$), δ: 2.08 (s, 3H), 3.50 (dd, J = 5.5 and 17.6 Hz, 1H), 3.80 (dd, J = 5.1 and 17.6 Hz, 1H), 5.63-5.69 (m, 1H), 7.11 (d, J = 7.9 Hz, 1H), 7.44-7.63 (m, 5H), 7.89 (d, J = 8.5 Hz, 2H), 8.16 (d, J = 8.8 Hz, 2H); IR (KBr, cm?[1]) 3304, 3066, 1699, 1653, 1600, 1527, 1349, 1296, 1230, 992, 751, 695.

β-Acetamido-β-(4-bromophenyl)-4-bromopropiophenone (Table 2, entry 9), mp: 142-145 °C,

^{1}H NMR (300 MHz, $CDCl_3$), δ: 2.03 (s, 3H), 3.35 (dd, J = 6.0 and 17.1 Hz, 1H), 3.71 (dd, J = 4.3 and 17.1 Hz , 1H), 5.47-5.53 (m, 1H), 6.80 (d, J = 7.8 Hz, 1H), 7.21 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.5 Hz, 2H), 7.76 (d, J = 8.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ: 23.32, 42.89, 49.39, 121.47, 128.29, 129.06, 129.60, 131.80, 132.12, 135.07, 139.73, 169.78, 197.23; IR (KBr, cm^{-1}) 3269, 3061, 1684, 1638, 1586, 1541, 1300, 1073, 995, 826.

β-Acetamido-β-(2-metoxyphenyl)-4-bromopropiophenone (Table 2, entry 11), mp: 161-162.5 °C, ^{1}H NMR (300 MHz, $CDCl_3$), δ: 2.02 (s, 3H), 3.43 (dd, J = 6.7 and 15.72 Hz, 1H), 3.55 (dd, J = 6.0 and 15.9 Hz, 1H), 3.89 (s, 3H), 5.71 (m, 1H), 6.86-6.94 (m, 5H), 7.59 (d, J = 8.5 Hz, 2H), 7.77 (d, J = 8.5 Hz, 2H); IR (KBr, cm^{-1}) 3312, 3074, 1694, 1648, 1543, 1301, 1242, 1197, 1100, 811, 758, 516.

β-Acetamido-β-(phenyl)-4-nitropropiophenone (Table 2, entry 16), mp: 101-103 °C, ^{1}H NMR (300 MHz, $CDCl_3$), δ: 2.06 (s, 3H), 3.49 (dd, J = 6.5 and 16.7 Hz, 1H), 3.86 (dd, J = 5.1 and 16.8 Hz, 1H), 3.54 (m, 1H), 6.66 (s, 1H), 7.27-7.35 (m. 5H), 8.07 (d, J = 8.7 Hz, 2H), 8.29 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75MHz, $CDCl_3$), δ: 23.28, 44.07, 50.35, 123.94, 126.60, 128.01, 128.95, 129.22, 140.04, 140.87, 169.92, 196.74; IR (KBr, cm^{-1}) 3297, 3079, 1698, 1640, 1518, 1345, 1203, 996, 850, 749.

β-Acetamido-β-(2-chlorophenyl)-4-nitropropiophenone (Table 2, entry 17), mp: 192-195 °C, ^{1}H NMR (300 MHz, $CDCl_3$), δ: 2.13 (s, 3H), 3.53 (dd, J = 4.8 and 16.7 Hz, 1H), 3.85 (dd, J = 4.0 and 17.53 Hz, 1H), 5.85 (s, 1H), 6.79 (s, 1H), 7.19-7.46 (m, 4H), 8.08 (d, J = 8.5 Hz, 2H), 8.30 (d, J = 8.35 Hz, 2H); IR (KBr, cm?^{1}) 3295, 3077, 1699, 1654, 1525, 1345, 1245, 997, 849, 753.

β-Acetamido-β-(4-nitrophenyl)-4-nitropropiophenone (Table 2, entry 18), mp: 176-179 °C, ^{1}H NMR (300 MHz, $CDCl_3$), δ: 2.09 (s,3H), 3.58 (dd, J = 5.8 and 17.8 Hz, 1H), 3.90 (dd, J = 4.9 and 17.8 Hz, 1H), 5.65-5.71 (m, 1H), 6.74 (d, J = 7. 7 Hz, 1H), 7.54 (d, J = 8.6 Hz, 2H), 8.09 (d, J = 8. 8 Hz, 2H), 8.20 (d, J = 8.7 Hz, 2H), 8.32 (d, J = 8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$)δ 23.39, 43.36, 46.15, 124.0, 124.09, 127.52, 129.18, 140.33, 147.28, 147.77, 150.73, 169.83, 196.34; IR (KBr, cm^{-1}) 3277, 3078, 1699, 1660, 1527, 1408, 1348, 1235, 1196, 1109, 997, 851, 751.

Methyl 2-acetyl-3-acetamido-3-phenyl propionate (Table 2, entry 22), mp: 142-144 °C, ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.99 (s, 3H), 2.16 (s, 3H), 3.69 (s, 3H), 4.1 (d, J = 5.7 Hz, 1H), 5.77 (dd, J = 5.8 and 8.8 Hz, 1H), 7.03 (d, J = 8.3 Hz, 1H), 7.26-7.32 (m, 5H); IR (KBr, cm^{-1}) 3331, 3059, 2956, 1753, 1720, 1649, 1533, 1436, 1371, 1268, 1035, 712.

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