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$KAl(SO_4)_2.12H_2O$: an efficient heterogeneous alternative for one-pot synthesis of β-acetamido ketones

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Abstract: An efficient and improved procedure for the synthesis of β-acetamido ketones is developed by a solid acid catalyzed reaction. Enolizable ketones have been reacted in one-pot method with aromatic aldehydes, acetyl chloride and acetonitrile at room temperature with $KAl(SO_4)_2.12H_2O$ as a catalyst.

Keywords: $KAl(SO_4)_2.12H_2O$; MCRs; β-Acetamido ketones; One- pot Synthesis; Aldehydes.

Introduction

Multi-component reactions (MCRs) have proved to be remarkably successful in generating molecular complexity in a single synthetic operation. The search and discovery for new MCRs on one hand [1] and the full exploitation of already known multi-component reaction on the other hand, is therefore of considerable current interest. β-Acetamido ketones skeletons exist in a number of biologically or pharmacologically important compound [2,3]. α-Acetamido ketones in Dakin-West reaction [4] and β-acetamido ketones in Iqbal route based on condensation of an aromatic aldehyde, an enolizable ketone and acetonitrile in the presence of the acetyl chloride and a catalytic amount of an acid are obtained [5,6]. Many catalysts such as $CeCl_3.7H_2O$ [7], silica sulfuric acid [8], $H_6P_2W_{18}O_{62}$ [9], $K_5CoW_{12}O_{40}.3H_2O$ [10], ZnO [11], sulfated zirconia [12], $FeCl_3.6H_2O$ [13], some heteropoly acids [14,15], silica supported $H_3PW_{12}O_{40}$ [16], nano ZnO [17], sulfamic acid [18], $Sc(OTf)_3$ [19], $SnCl_2.2H_2O$ [20], $ZrOCl_2.8H_2O$ [21] and $SnCl_4.SiO_2$ [22] have been applied in this one-pot reaction.
$KAl(SO_4)_2.12H_2O$ (alum) with mild acidity involatility, and incorrositivity, is insoluble in common organic solvents and was used recently as an easily available acidic catalyst in different reactions.
$KAl(SO_4)_2.12H_2O$ (alum) as a solid acid catalyst has been used in some organic reaction, such as synthesis of some new oxindoles [23], Quinolines [24], some 4-substituted coumarins [25], 1,3,4-oxadiazoles [26], alkyl or aryl-14H-dibenzo [a,j] xanthenes [27], coumarins [28], trisubstituted imidazoles [29], 1,5-benzodiazepines [30] etc.
Based on our previous studies on the use of hetrogenous catalysts for carrying organic reactions [22,31], in the present research, we wish to describe a mild and efficient approach for the synthesis of β-acetamido ketones using a catalytic amount of $KAl(SO_4)_2.12H_2O$ as a solid acid catalyst.

Results and discussion

Initially, the reaction of benzaldehyde and acetophenone was examined in the presence of several catalysts and comparable with some other catalysts such as $ZrOCl_2.8H_2O$, $H_3[PW_{12}O_{40}]$, ZnO etc. (Table 1). According to the obtained data, the $KAl(SO_4)_2.12H_2O$ (12 mol%) in the presence of acetylchloride and acetonitrile was the best system for β-acetamido ketones formation (Table 1,entry 18). Therefore, various aromatic aldehydes and ketones were transformed into the corresponding β-acetamido ketones in the presence of $KAl(SO_4)_2.12H_2O$ (12 mol%) as a catalyst without the formation of any side products with improved yields (Table 2).

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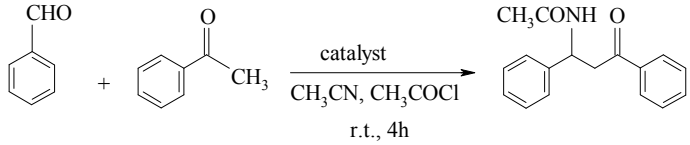
Table 1. Optimization of reaction condition for one-pot formation of β-acetamido ketone

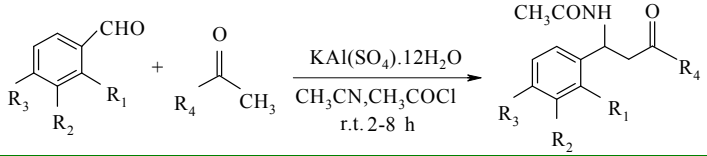


Entry	Catal. (mol%)	Ref.	Cond./Yield (%)[a]
1	$ZrOCl_2.8H_2O$ (20)	21	r.t. / 90[b]
2	Silica sufuric acid (78)	8	80°C / 91
3	$H_3[PW_{12}O_{40}]$	16	80°C / 65[b]
4	ZnO (50)	11	80°C /90
5	$FeCl_3.6H_2O$ (10)	13	r.t. / 88
6	$K_5CoW_{12}O_{40}.3H_2O$ (0.01)	10	r.t. / 86
7	$CeCl_3.7H_2O$ (10)	7	r.t. / 96
8	$Sc(OTf)_3$ (10)	19	r.t. / 82
9	$H_6P_2W_{18}O_{62}$ (0.14)	9	80°C /86
10	$AlCl_3$ (10)	-	r.t / 55
11	$ZnCl_2$ (10)	-	r.t. / 60
12	$ZrCl_4$(10)	-	r.t. / 62
13	$SnCl_4$ (10)	-	r.t. / 80
14	$BF_3{\cdot}Et_2O$ (10)	-	r.t. / 63
15	$SbCl_5$ (10)	-	r.t. / 78
16	$KAl(SO_4)_2.12H_2O$(2)	-	r.t. / 63
17	$KAl(SO_4)_2.12H_2O$(8)	-	r.t. / 89
18	$KAl(SO_4)_2.12H_2O$(12)	-	r.t. / 95
19	$KAl(SO_4)_2.12H_2O$(2nd run)	-	r.t. / 80
20	$KAl(SO_4)_2.12H_2O$(3rd run)	-	r.t. / 74

[a]Isolated yield
[b]Chromatographed yield

The reusability of $KAl(SO_4)_2.12H_2O$ catalyst was also examined. So that, after each run, the product filtered of, the solvent evaporated and the residue (catalyst) was washed with $CHCl_3$ and reused. Apparently, the treatment with $CHCl_3$ removed tars more efficiently from the catalyst surface (Table 1, entries 19, 20). This catalyst was reusable, although gradual decline of activity was observed. Consequently, acetylation of an aromatic hydroxyl group was observed while using 4-hydroxybenzaldehyde or vanillin and the corresponding β-acetamido ketones were isolated in an excellent yield. 4-dimethylaminobenzaldehyde, however, was inert to the present reaction conditions. The preparative efficacy of this one-pot synthesis was further checked by scaling-up (5 folds) of the reaction of 4-methyl benzaldehyde with 4-nitro acetophenone and other ingredients which proceeded with an 80% yield.

Table 2. One-pot condensation of aldehydes, ketones, acethyl chloride and acetonitrile to give the corresponding β-acetamido ketones catalyzed by $KAl(SO_4)_2,12H_2O$.[a]



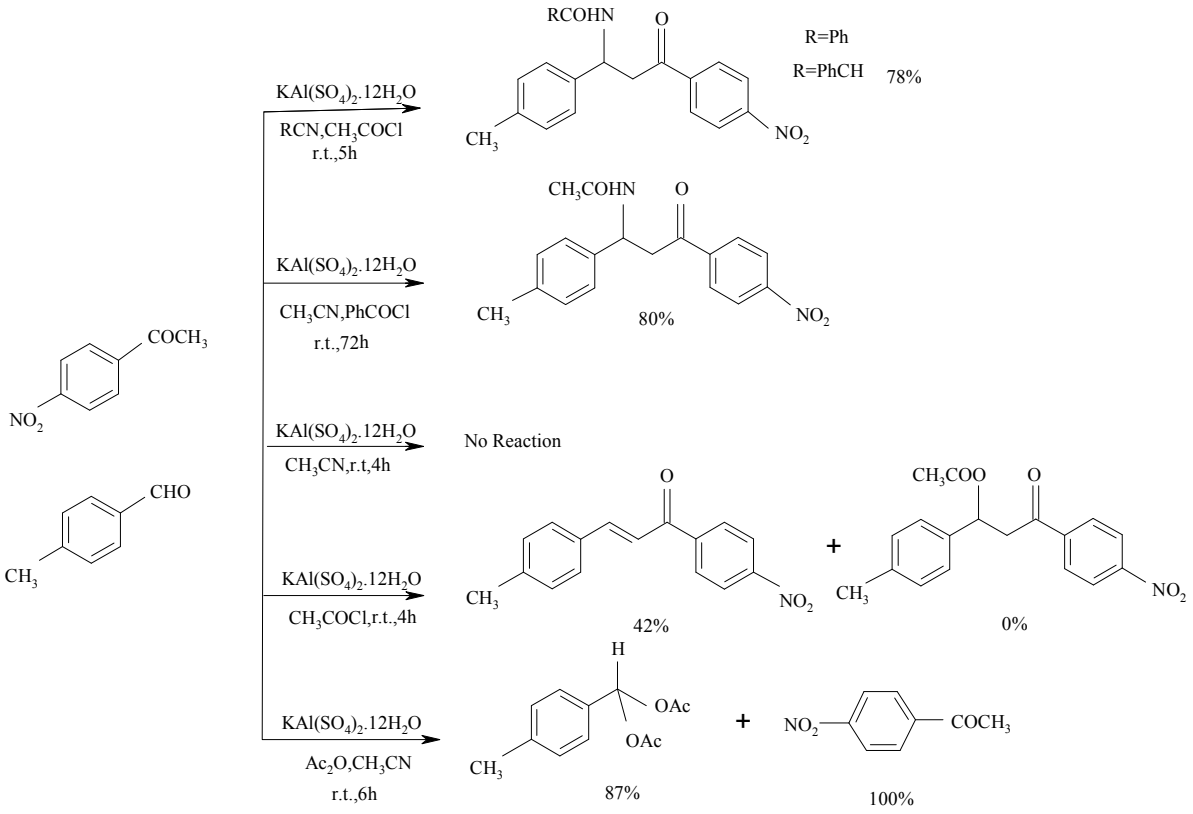
Entry	Product	Time (h)	Yield[b] (%)	Ref.	M.P(°C)
1	R_1,R_2,R_3=H, R_4=Ph	6	84	16	104-105
2	R_1,R_2,R_3=H, R_4=4-NO_2-C_6H_4	6	81	12	97-98
3	R_1=Cl, R_2,R_3=H, R_4=Ph	7	75	8	135-136
4	R_1=H, R_2=OCH_3, R_3=$OCOCH_3$, R_4= Ph	3	80	21	89-91

Table 2 continued

5	R_1,R_2 =H, R_3=CH_3, R_4=4-NO_2-C_6H_4	2. 5	74	15	84-85
6	R_2,R_3 =H, R_1=OCH_3, R_4=4-NO_2-C_6H_4	5	93	22	145-146
7	R_1,R_3 =H, R_2=NO_2, R_4=4-NO_2-C_6H_4	3	89	16	105-106
8	R_1,R_3=H, R_2=NO_2, R_4=4-Cl -C_6H_4	4	83	11	145-146
9	R_3,R_2 =H, R_1=Cl, R_4=3-OCH_3-C_6H_4	7	84	22	101-103
10	R_2, R_1 =H, R_3= Cl, R_4=Ph	3	81	13	149-148
11	R_2, R_3 =H, R_1= Cl, R_4=4-Cl -C_6H_4	2	93	22	168-169
12	R_1, R_2=H, R_3 =OCH_3, R_4=Ph	8	78	13	111-110

[a]Molar ratio of aldehyde(mmol):ketone(mmol):acetyl chloride(mL) :acetonitrile (mL): $KAl(SO_4)_2$,12H_2O (g)[mmol] equal to 1:1:0.3:1:0.05 [0.12]
[b]Isolated yield

Previously, four types of mechanisms for the Iqbal procedure β-acetamido ketone formation were proposed [8,10,13,17,19]. In our investigation, when the reaction was not subjected to acetonitrile, no β-acetoxy ketone [10,17,19], was formed and only crossed aldolcondensation reaction occurred. Meanwhile, in the preparation of β-acetamido ketones, no β-acetoxy ketones was obtained as a by-product, besides, a mixture of chalcone, acetyl chloride and acetonitrile in the presence of a catalyst failed to generate any β-acetamido ketones. In the absence of acetyl chloride or benzoyl chloride, the reaction failed to provide the desired product. The results obviously indicating that they play a necessary role in this reaction, although not involved in the final product. when benzyl cyanide or phenyl cyanide was used instead of acetonitrile, β-phenyl acetamido ketone or β-benzamido ketone were obtained, respectively. Note that neither a mixture of 4-methylbenzaldehyde, 4-nitroacetophenone, aceticanhydride and acetonitrile in the presence of $KAl(SO_4)_2.12H_2O$, nor a mixture of 4-methyl benzaldehyde acylal, 4-nitro acetophenone and $KAl(SO_4)_2.12H_2O$ in acetonitrile could produce any of the corresponding β-acetamido ketones(Scheme 1).



Scheme 1

Conclusion

A new catalytic activity of $KAl(SO_4)_2.12H_2O$ has been studied for the synthesis of β-acetamido ketones in excellent yields. $KAl(SO_4)_2.12H_2O$ is efficient, reusable and inexpensive catalyst with easy handling and usability. This catalyst is suitable for the large-scale operation with improved yield. The easy work-up procedure and simplicity of operation are some other advantages of this heterogeneous protocol.

Experimental

Aldehydes, ketones and other necessary chemical compounds were purchased from Fluka and Merck companies. The products were known and were characterized by IR and ^{1}H-NMR spectra and by comparing their physical properties with those reported in the literature. IR spectra were run on a Shimadzu IR-470 spectrometer. ^{1}H-NMR was obtained using a Bruker Avans 300 MHz spectrometer. Melting points were determined with a Barnstead Electrothermal Melting Point apparatus.

General procedure for one-pot synthesis of β-acetamido ketones

Enolizable ketone (1 mmol), aromatic aldehyde (1 mmol), acetyl chloride(0.3 mL), acetonitrile(1 mL) and $KAl(SO_4)_2.12H_2O$ (0.04 g, 0.12 mmol) were placed in a round bottom flask. The materials were mixed at ambient temperature. The progress of the reaction was followed by TLC (3:1:*n*-hexane:ethylacetate). After the completion of reaction, the mixture was poured into 30 mL ice water. The oily solid was isolated and washed with diethyl ether to remove any residual starting materials. The pure product was obtained from ethanol and water by crystallization or by the preparative thin layer chromatography (3:1:*n*hexane: ethylacetate).

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