$NaHSO_4•H_2O$ as an efficient and eco-friendly catalyst for the one-pot multicomponent synthesis of β-acetamido ketones under mild and heterogeneous conditions

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Abstract
A new, one-pot, four-component condensation of benzaldehyde derivatives, acetophenone derivatives, acetyl chloride and acetonitrile in the presence of sodium hydrogen sulfate as catalyst is described for the synthesis of β-acetamido ketones.

Keywords: β-Acetamido ketones, multicomponent reactions, acetyl chloride, $NaHSO_4·H_2O$

Introduction

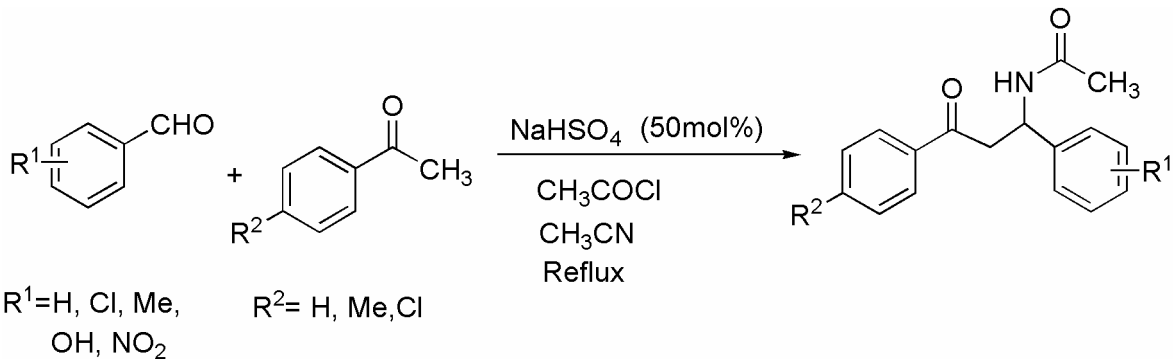
Multicomponent reactions (MCRs) play a key role in organic chemistry due to the fact that highly complex structures can be formed in a simple one-pot process.[1] MCRs contribute to the requirements of an environmentally friendly process by reducing the number of synthetic steps, energy consumption and waste production. Researchers have transformed this powerful technology into one of the most efficient and economic tools for combinatorial and parallel synthesis.[2,3] Due to their inherent simple experimental procedures and their one-pot character, they are perfectly studied for automated synthesis. Thus, MCRs have attracted considerable interest owing to their exceptional synthetic efficiency.[4]

Acetamido- or amino- ketone derivatives are important for their biological and pharmaceutical properties,[5,6] and in the preparation of antibiotic drugs such as nikkomycine or neopolyoxines.[7,8] The best known route for the synthesis of this class of compounds is the Dakin–West reaction,[9] the condensation of an α-amino acid with acetic anhydride in the presence of a base provides the α-acetamido ketones via an azalactone intermediate.[10] The simple and direct method for the synthesis of β-acetamido ketones reported by Iqbal and co-workers in 1994 involves the one-pot condensation of a ketone, aldehyde and acetonitrile in the presence of acetyl chloride.[11]

Recently, other synthetic methods have been used for the formation of β-acetamido ketones through the multicomponent condensation of aryl aldehydes, enolizable ketones and acetyl chloride in acetonitrile in the presence of Lewis or Brønsted acid catalysts such as sulfuric acid absorbed on silica gel,[12,13] Iodine,[14] montmorillonite K_{10} clay,[15] $CoCl_2$,[11,16] BiOCl,[17] $ZrOCl_2.8H_2O$,[18] $CeCl_3.7H_2O$,[19] $Sc(OTf)_3$,[20] heteropoly acid,[21-24] Nafion-H,[25] and sulfated zirconia.[26]

In recent years, sodium hydrogen sulfate has gained much interest in the synthesis of octahydroxanthenes,[27] protection and deprotection,[28-36] nitration,[37,38] nitrosation,[39] oxidation,[40-42] synthesis of halide derivatives,[43, 44] coupling of indoles [45] and synthesis of quinazolinones.[46]

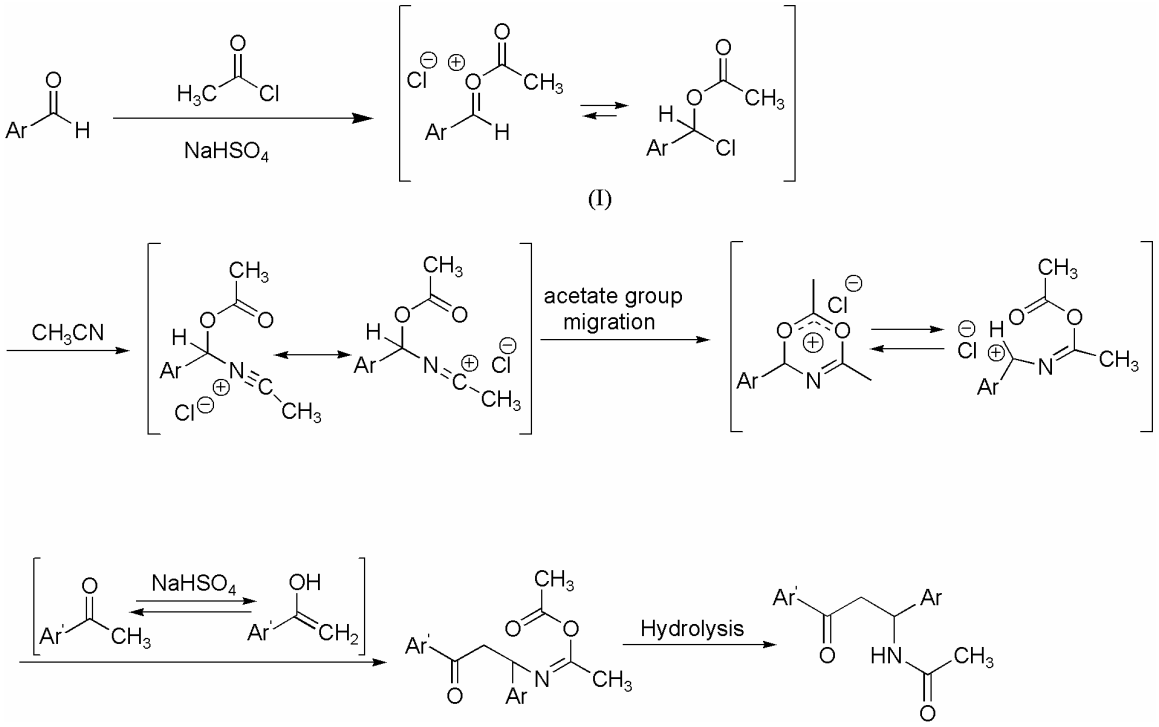
Herein, we describe a new, simple, mild and effective procedure for the one-pot synthesis of β-acetamido ketones via four-component condensation reaction[47] between aldehydes, enolizable ketones, acetyl chloride and acetonitrile in the presence of sodium hydrogen sulfate as catalyst (Scheme 1). The MCRs for the preparation of β-acetamido ketones were carried out under reflux at 85 °C.



Scheme 1

Results and Discusion

Thus, we prepared a series of β-acetamido ketones under the optimized reaction conditions: aldehyde (4 mmol), ketone (4 mmol), acetyl chloride (2 mL) and acetonitrile (6 mL) in the presence of sodium hydrogen sulfate (50 mol%) (Table 1). As shown in the Table 1, aromatic aldehydes or acetophenones with both electron-withdrawing and donating substituents produced β-acetamido ketones without the formation of any side products, in high to excellent yields at reflux (Table 1, entries 1-11). It is interesting to mention that the OH group in the product was obtained as acylated group (Table 1, entry 11). Although it is not clear how sodium hydrogen sulfate acts as a catalyst for the reaction, on the basis of previously reported mechanism,[12,13] it is suggested that the aldehyde is first acylated (in the presence of enol form of acetophenone derivative) to an intermediate (**I**) which then reacts with the acetonitrile to produce the desired β-acetamido ketone.



Scheme 2

Table 1. Preparation of β-acetamido ketones from aldehydes and enolizable ketones in the presence of acetyl chloride and acetonitrile catalysed using sodium hydrogen sulfate under reflux at 85 °C

Entry	Aldehyde	Ketone	Time (h)	Yield (%)[a]	(m.p. ºC) Found	Reported [Ref][b]
1	C_6H_5CHO	$C_6H_5COCH_3$	2.5	83	103-105	102-104[25]
2	4-$CH_3C_6H_5CHO$	$C_6H_5COCH_3$	3	82	112-114	112 [18]
3	3-$NO_2C_6H_5CHO$	$C_6H_5COCH_3$	4.5	77	130-132	110-112[22]
4	4-$NO_2C_6H_5CHO$	$C_6H_5COCH_3$	5	75	147-149	148-149[15]
5	4-ClC_6H_5CHO	$C_6H_5COCH_3$	4.5	81	147-149	147-148[25]
6	C_6H_5CHO	4-$ClC_6H_5COCH_3$	3	78	112-114	115-117[25]
7	4-ClC_6H_5CHO	4-$ClC_6H_5COCH_3$	3	80	142-144	141-143[12]
8	4-$NO_2C_6H_5CHO$	4-$ClC_6H_5COCH_3$	4.5	70	126-128	123-125[25]
9	C_6H_5CHO	4-$CH_3C_6H_5COCH_3$	3	86	120-122	119-121[25]
10	4-$NO_2C_6H_5CHO$	4-$CH_3C_6H_5COCH_3$	5	72	67-70	liquid [13]
11	3-OHC_6H_5CHO	$C_6H_5COCH_3$	3.5	87	115-117	114-115[18]

[a]Yields refer to the pure isolated products. [b]Refer to the references of known products in the literature.

In summary, we have demonstrated sodium hydrogen sulfate as a cheap, commercially available, reusable and non-corrosive catalyst for the synthesis of β-acetamido ketones in

excellent yields under mild reaction conditions. The simple experimental procedure combined with the easy work-up and excellent yields of products are salient features of the presented method.

Experimental Section

General Procedeures. Melting points recorded on an open capillary and IR spectra were measured on a Shimadzu IR-*470* spectrophotometer. The ^{1}H NMR spectra were recorded on a Bruker-*300* MHz instrument using tetramethylsilane (TMS) as an internal standard. All of the products are known and were characterized by their spectral and physical data.

General experimental procedure for the one-pot preparation of β-acetamido ketones
A solution of aryl aldehyde (4 mmol), aryl ketone (4 mmol), acetyl chloride (2 mL), acetonitrile (6 mL) and sodium hydrogen sulfate (2 mmol, 50 mol%) was heated at 85°C under reflux conditions. The progress of the reaction was followed by TLC. After completion of the reaction, sodium hydrogen sulfate was isolated and could be reused (after the evaporation of water and solvent). Then the mixture was cooled and poured into 100 mL of ice-water. The solid residue was separated and dissolved in dichloromethane. The organic phase was absorbed on silica gel and purified by column chromatography petroleum ether (60-80 °C) / ethyl acetate (9/1). All the products were identified by comparison of their ^{1}H NMR and IR data with those of authentic samples. The spectral data of representative β-acetamido ketones are given below.
β-Acetamido-β-(phenyl)propiophenone (Table 1, entry 1). IR (KBr) ν_{max}/cm^{-1}: 3286, 1693, 1650; ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ_H 2.04 (s, 3H, CH_3), 3.45 (dd, J = 6.0 and 16.9 Hz, 1H, CH_2), 3.77 (dd, J = 5.2 and 16.9 Hz, 1H, CH_2), 5.58 (m, 1 H, methyne H), 6.90 (br, d, J = 6.3 Hz, 1H, NH), 7.24-7.60 (m, 8H, Ar-H), 7.91 (d, J =7.5 Hz, 2H, Ar-H).
β-Acetamido-β-(4-methylphenyl)propiophenone (Table 1, entry 2). IR (KBr) ν_{max}/cm^{-1}: 3290, 1675, 1645; ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ_H 2.17 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 3.55 (dd, J= 6.2 and 16.7 Hz, 1H, CH_2), 3.82 (dd, J=5.1 and 16.7 Hz, 1H, CH_2), 5.56 (m, 1H, methyne H), 7.05 (d, J=7.7 Hz, 2H, Ar-H), 7.28-7.58 (m, 5H, Ar-H), 7.88 (d, J=7.6 Hz, 2H, Ar-H), 8.70(br, d, J = 7.5 Hz, 1H, NH).
β-Acetamido-β-(3-nitrophenyl)propiophenone (Table 1, entry 3). IR (KBr) ν_{max}/cm^{-1}: 3291, 1689, 1653; ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ_H 2.11 (s, 3 H, CH_3), 3.54 (dd, J= 5.5 and 17.6 Hz, 1 H, CH_2), 3.83 (dd, J=5.0 and 17.5 Hz, 1 H, CH_2), 5.68 (m, 1H, methyne H), 7.18 (d, J=7.8 Hz, 1H, NH), 7.45-7.53 (m, 3H, Ar-H), 7.61 (t, J=7.5 Hz, 1H, Ar-H), 7.74 (d, J=7.7 Hz, 1H, Ar-H), 7.91(d, J =8.2 Hz, 2H, Ar-H), 8.10(d, J =8.2 Hz, 1H, Ar-H), 8.24(s, 1H, Ar-H).
β-Acetamido-β-(4-nitrophenyl)propiophenone (Table 1, entry 4). IR (KBr) ν_{max}/cm^{-1}: 3291, 1689, 1653; ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ_H 2.01 (s, 3 H, CH_3), 3.38 (dd, J= 5.6 and 17.4 Hz, 1 H, CH_2), 3.85 (dd, J=7.1 and 17.4 Hz, 1 H, CH_2), 5.60 (m, 1H, methyne H), 7.19-7.54(m, 7H, Ar-H) 7.87 (d, J =7.7 Hz, 2H, Ar-H), 9.18 (br, 1H, NH).

β-Acetamido-β-(4-chlorophenyl)propiophenone (Table 1, entry 5). IR (KBr) ν_{max}/cm^{-1}: 3291, 1689, 1652; ^1H NMR (300 MHz; $CDCl_3$; Me_4Si) δ_H 2.14 (s, 3 H, CH_3), 3.49 (dd, J = 7.1 and 13.9 Hz, 1 H, CH_2), 3.82 (dd, J=7.1 and 14.5 Hz, 1 H, CH_2), 5.56 (m, 1H, methyne H), 7.25-7.58 (m, 7H, Ar-H), 7.83(br, 1H, NH), 7.91 (d, J =7.3 Hz, 2 H, Ar-H).

β-Acetamido-β-(phenyl)-4-chloropropiophenone (Table 1, entry 6). IR (KBr) ν_{max}/cm^{-1}: 3480, 1690, 1653; ^1H NMR (300 MHz; $CDCl_3$; Me_4Si) δ_H 2.09 (s, 3H, CH_3), 3.48 (dd, J = 6.2 and 17.4 Hz, 1 H, CH_2), 3.80 (dd, J=5.8 and 17.4 Hz, 1 H, CH_2), 5.56 (m, 1H, methyne H), 7.16-7.40 (m, 7H, Ar-H), 7.82(d, J =8.6 Hz, 2H, Ar-H), 8.32 (br, d, J =7.5 Hz, 1H, NH).

β-Acetamido-β-(4-chlorophenyl)-4-chloropropiophenone (Table 1, entry 7). IR (KBr) ν_{max}/cm^{-1}: 3266, 1673, 1638; ^1H NMR (300 MHz; $CDCl_3$; Me_4Si) δ_H 2.19 (s, 3 H, CH_3), 3.50 (dd, J= 7.3 and 10.9 Hz, 1 H, CH_2), 3.81 (dd, J= 7.3 and 10.9 Hz, 1 H, CH_2), 5.56 (m, 1H, methyne H), 7.21 (br, 1 H, NH), 7.28-7.47 (m, 6H, Ar-H), 7.85 (d, J= 8.2, 2H, Ar-H).

β-Acetamido-β-(4-nitrophenyl)-4-chloropropiophenone (Table 1, entry 8). IR (KBr) ν_{max}/cm^{-1}: 3346, 1693, 1690; ^1H NMR (300 MHz; $CDCl_3$; Me_4Si) δ_H 2.09 (s, 3 H, CH_3), 3.48 (dd, J= 5.6 and 17.6 Hz, 1 H, CH_2), 3.81 (dd, J = 4.9 and 17.6 Hz, 1 H, CH_2), 5.66 (m, 1H, methyne H), 6.94 (br, d, J=7.6 Hz, 1 H, NH), 7.45 (d, J =8.6 Hz, 2H, Ar-H), 7.52 (d, J =8.7 Hz, 2H, Ar-H), 7.85 (d, J =8.6 Hz, 2H, Ar-H), 8.18 (d, J =8.7 Hz, 2H, Ar-H).

β-Acetamido-β-(phenyl)-4-methylpropiophenone (Table 1, entry 9). IR (KBr) ν_{max}/cm^{-1}: 3276, 1684, 1651; ^1H NMR (300 MHz; $CDCl_3$; Me_4Si) δ_H 2.13 (s, 3 H, CH_3), 2.30 (s, 3 H, CH_3), 3.52 (dd, J= 6.1 and 16.3 Hz, 1 H, CH_2), 3.79 (dd, J=5.5 and 17.3 Hz, 1 H, CH_2), 5.56(m, 1H, methyne H), 7.12-7.27 (m, 5H, Ar-H), 7.40 (d, J =7.2 Hz, 2H, Ar-H), 7.78 (d, J =7.7 Hz, 2H, Ar-H), 8.65 (br, d, J =7.1 Hz, 1H, NH).

β-Acetamido-β-(4-nitrophenyl)-4-methylpropiophenone (Table 1, entry 10). IR (KBr) ν_{max}/cm^{-1}: 3346, 1663, 1609; ^1H NMR (300 MHz; $CDCl_3$; Me_4Si) δ_H 2.10 (s, 3 H, CH_3), 2.41 (s, 3 H, CH_3), 3.48 (dd, J= 5.4 and 16.8 Hz, 1 H, CH_2), 3.80 (dd, J= 4.9 and 17.7 Hz, 1 H, CH_2), 5.65 (m, 1H, methyne H), 7.26(m,3 H, NH, Ar-H), 7.53(d, J =8.7 Hz, 2H, Ar-H), 7.79(d, J =8.2 Hz, 2H, Ar-H), 8.15(d, J =8.7 Hz, 2H, Ar-H).

β-Acetamido-β-(3-Acetoxy-phenyl)-propiophenone (Table 1, entry 11). IR (KBr) ν_{max}/cm^{-1}: 3280, 1767, 1685, 1655, 1610; ^1H NMR (300 MHz; $CDCl_3$; Me_4Si) δ_H 2.05 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 3.47 (dd, J = 5.8 and 17.0 Hz, 1H, CH_2), 3.79 (dd, J = 5.7 and 17.1 Hz, 1H, CH_2), 5.60 (m, 1 H, methyne H), 6.80 (br, d, J = 8.5 Hz, 1H, NH), 6.99 (dd, J = 2.2 and 7.8 Hz, 1H, Ar-H), 7.10 (t, J = 2.1 Hz, 1H, Ar-H), 7.19 (d, J = 8.0 Hz, 1H, Ar-H), 7.32(t, J = 7.8 Hz, 1H, Ar-H), 7.46-7.48(m, 2H, Ar-H), 7.56-7.60(m, H, Ar-H), 7.90 (d, J = 7.6 Hz, 2H, Ar-H).

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