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ANHYDROUS ZINC SULPHATE AS AN EFFICIENT AND ECO-FRIENDLY CATALYST FOR THE ONE-POT MULTICOMPONENT SYNTHESIS OF B-ACETAMIDO KETONES UNDER MILD AND HETEROGENEOUS CONDITIONS AND THEIR MICROBIAL STUDY

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Acetamido carbonyl compounds; aromatic aldehydes; enolizable ketones; zinc sulphate

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ABSTRACT

A variety of acetamido ketones and ketoesters are readily prepared in high yields under extremelymild conditions via a three component coupling of aromatic aldehydes, enolizable ketones or ketoesters andnitriles in the presence of 10 mol% of zinc sulphate and a stoichiometric amount of acetylchloride. A solution of 10 mol% of zinc sulphate in acetonitrile provides a convenient reaction medium to carry out a three component reaction under mild conditions with high yield. Synthesized compounds are studied for their microbial activity.

INTRODUCTION

Multi-component reactions (MCRs) have emerged as one of the most useful synthetic transformations in organic synthesis because of their wide applications in pharmaceutical chemistry for production of structural scaffolds and combinatorial libraries for drug discovery. They are preferred over other reactions as it provides useful products in a single step by the creation of several new bonds without isolation of any intermediate and thus reduces time and saves both energy and rawmaterials.1_-Acetamido carbonyl compounds are valuable intermediates for a large number of pharmaceutically 2 important compounds examples being for the preparation of 1,3-aminoalcohols 3,4,antibiotic nikkomycin or neopolyoximes.5,6 Therefore, the synthesis of acetamido carbonyl compounds continues to be a challenging endeavor. 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 parallelsynthesis.[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 orneopolyoxines.[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 coworkersin 1994 involves the one-pot condensation of a ketone, aldehyde and acetonitrile in thepresence of acetyl chloride.11Recently, other synthetic methods have been used for the formation of β-acetamido ketones through the multicomponent condensation of aryl aldehydes, enolizable ketones and acetylchloride in acetonitrile in the presence of Lewis or Bronsted acid catalysts such as sulfuric acid absorbed on silica gel,[12,13] Iodine,[14] montmorillonite K10 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 sulfatedzirconia.26In 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-acetamido ketones via four-component condensation reaction47 between aldehyde, enolizable ketone, acetyl chloride and acetonitrile in the presence of anhydrous ferrous sulphate catalyst (Scheme 1). Supported $Co(OAc)_2$26 and *p*-TSA. Although, a large number of methods are reported for this transformation, some of them lack the generality in producing beta amido ketone as they are

restricted to acetonitrile giving the corresponding beta acetamido ketones. Furthermore, many of these methods require either a long reaction time or harsh reaction conditions or the reaction has to be carried out under an inert atmosphere or the use of Expensive catalyst. Therefore, the development of simple, efficient and general methodology for this three-component reaction is still desirables a result, several strategies have been developed for the preparation of beta - acetamido ketones.

EXPERIMENTAL SECTION

Melting points were recorded on apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. H1 NMR spectra were recorded on Gemini-200 spectrometer in CDCl3 using TMS as internal standard.

***General Procedure**:*

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 zinc sulphate (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, zinc sulphate 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 ºC) / ethyl acetate (9/1). All the products were identified by comparison of their 1H NMR and IR data with those of authentic samples. The spectral data of representative β-acetamido ketones are given below

Table 1

Sr.no	Carbonyl compound	Aldehyde	Physical constant	Yield	Time
A	Acetophenone	Benzaldehyde	102	95	60 min
B	Acetophenone	P-methyl benzaldehyde	112	94	50 min
C	Acetophenone	P-methoxy benzaldehyde	112-114	86	55min
D	Acetophenone	3,4 di-methoxy benzaldehyde	118-120	76	60 min
E	Acetophenone	3,45 tri-methoxy benzaldehyde	170-172	67	65min
F	Acetophenone	P-chloro benzaldehyde	142-145	89	45 min
g	Acetophenone	P-bromo benzaldehyde	148-150	90	30 min

H	Acetophenone	O nitro benzaldehyde	185-190	94	30 min
I	Acetophenone	P-nitro benzaldehyde	148-152	93	30 min
J	Acetophenone	M -nitro benzaldehyde	137-140	85	30 min
K	Acetophenone	Cinnamaldehyde	119-120	87	30 min

Spectral analysis

1)β-Acetamido-β-(phenyl)propiophenone (Table 1,). IR (KBr) νmax/cm-1: 3286, 1693,

1650; 1H NMR (300 MHz; CDCl3; Me4Si) δH 2.04 (s, 3H, CH3), 3.45 (dd, J = 6.0 and 16.9 Hz,1H, CH2), 3.77 (dd, J = 5.2 and 16.9 Hz, 1H, CH2), 5.58 (m, 1 H, methyne H), 6.90 (br, d, J = 6.3Hz, 1H, NH), 7.24-7.60 (m, 8H, Ar-H), 7.91 (d, J =7.5 Hz, 2H, Ar-H).

2)β-Acetamido-β-(4-methylphenyl)propiophenone (Table 1,). IR (KBr) νmax/cm-1: 3290,

1675, 1645; 1H NMR (300 MHz; CDCl3; Me4Si) δH 2.17 (s, 3H, CH3), 2.23 (s, 3H, CH3), 3.55(dd, J= 6.2 and 16.7 Hz, 1H, CH2), 3.82 (dd, J=5.1 and 16.7 Hz, 1H, CH2), 5.56 (m, 1H, methyneH), 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).

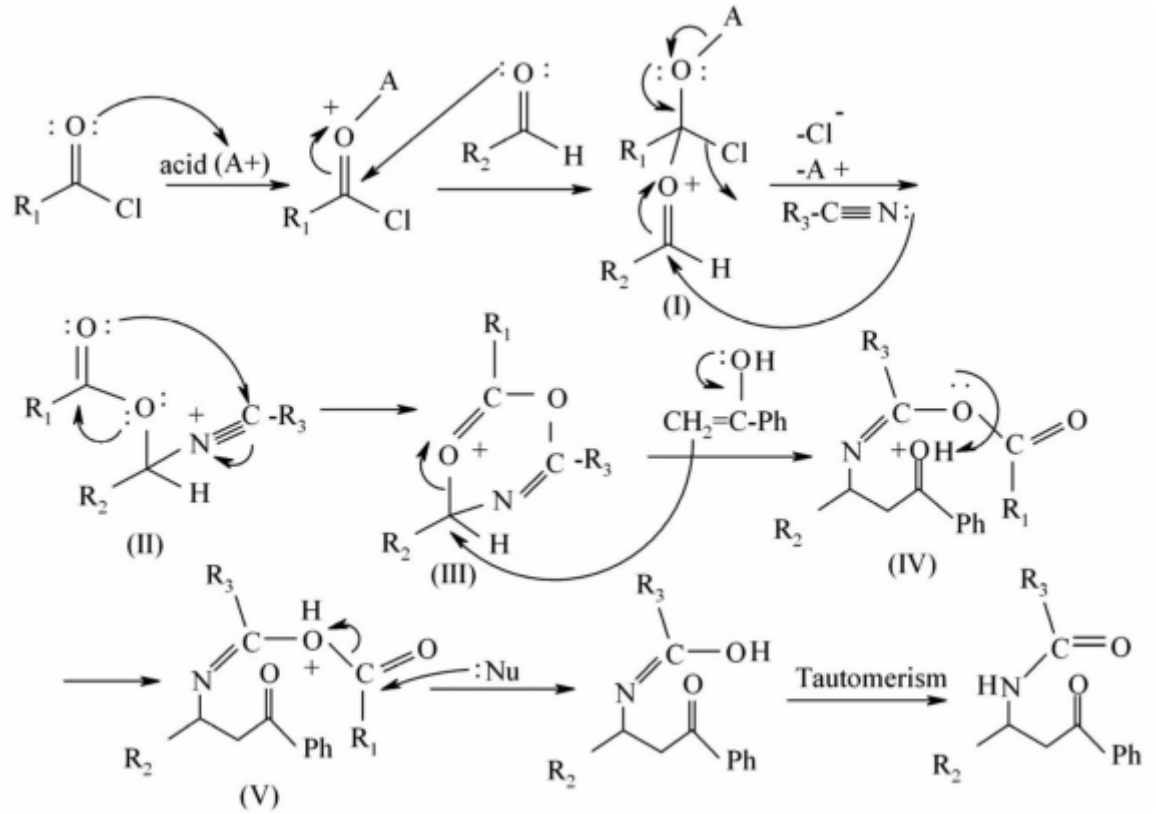
3)β-Acetamido-β-(3-nitrophenyl)propiophenone (Table 1,). IR (KBr) νmax/cm-1: 3291,

1689, 1653; 1H NMR (300 MHz; CDCl3; Me4Si) δH 2.11 (s, 3 H, CH3), 3.54 (dd, J= 5.5 and 17.6Hz, 1 H, CH2), 3.83 (dd, J=5.0 and 17.5 Hz, 1 H, CH2), 5.68 (m, 1H, methyne H), 7.18 (d, J=7.8Hz, 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, ArH), 8.24(s, 1H, Ar-H).

4)β-Acetamido-β-(4-nitrophenyl)propiophenone (Table 1,). IR (KBr) νmax/cm-1: 3291,

1689, 1653; 1H NMR (300 MHz; CDCl3; Me4Si) δH 2.01 (s, 3 H, CH3), 3.38 (dd, J= 5.6 and 17.4Hz, 1 H, CH2), 3.85 (dd, J=7.1 and 17.4 Hz, 1 H, CH2), 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).

Mechanism of reaction



CONCLUSION

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 zinc sulphate (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. It is interesting to mention that the OH group in the product was obtained as acylated group. Although it is not clear how ferrous sulphate 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 ketones 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. Compound show good antifungal and antibacterial activity listed in table 2 and 3.

Table 2 -Antibacterial activity of some β-acetamido ketones

Bacterial	Benzaldehyde	3-nitrobenzaldehyde	Ciprofloxacin,	Cloxacillin
G (+)	In mm	In mm	In mm	In mm
1.*Staphylococcus epidermidis*	5	6	10	10
2.*Staphylococcus aureus*	6	5	8	11
3. *Bacillus paludi*	7	7	11	11
4. *Bacillus subtilis*	8	8	10	11
G (-)				
1. *Escherichia coli*	6	8	7.5	5.5
2. *Pseudomonus aeruginosa*	7	8	6	5.5
3. *Shigella flaxinely*	8	9	5.5	8
4. *Enterobacter aergenes*	7	10	6	7

Table-3 Table-1 Antifungal activity of β-acetamido ketones

Fungus	Benzaldehyde	3-nitrobenzaldehyde	Penicil	Tetrax
1. *Candida albicans*	10	11	15	14
2. *Aspergillus fumigates*	09	12	11	4
3. *Aspergillus niger*	12	10	09	5

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