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Research Article

SODIUM SULPHATE AS MILD AND VERSATILE CATALYST FOR THE RAPID SYNTHESIS OF β-ACETAMIDO KETONES AND KETOESTERS VIA A THREE COMPONENT REACTION

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ABSTRACT

A variety of β-acetamido ketones and ketoesters are readily prepared in high yields under extremely mild conditions via a three component coupling of aromatic aldehydes, enolizable ketones or β-ketoesters and nitriles in the presence of Sodium Sulphate and a stoichiometric amount of acetyl chloride. A solution of 10 mol% of Sodium Sulphate in acetonitrile provides a convenient reaction medium to carry out a three component reaction under mild conditions

Keywords: β-Acetamido Carbonyl Compounds, Aromatic Aldehyde, Enolizable Ketones, Sodium Sulphate, Heteropoly Acid.

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 raw materials[1]. β-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 β-acetamido carbonyl compounds continues to be a challenging endeavor.

As a result, several strategies have been developed for the preparation of β-acetamido ketones and the best known method for the synthesis of these compounds is the Dakin-West reaction[7,8]. The direct method for the preparation of β-acetamido ketones involves the coupling of aryl aldehyde, enolizable ketone and acetonitrile in the presence of acetyl chloride and Lewis acids such as $CoCl_2$[9-11], Montmorillonite K-10 clay[12], SiO_2/H_2SO_4[13], $BiCl_3$ generated from BiOCl[14], $ZrOCl_2.8H_2O$[15,16], $Sc(OTf)_3$[17], $FeCl_3$[18], ZnO[19], H6P2W18O6220, Amberlyst-15[21], H3PW12O40[22], Silica/ Sulfuric acid[23], CeCl3.7H2O24, SiCl4-ZnCl2[25], Polyaniline supported Co(OAc)2[26] and p-TSA[27]. Although large number of methods are reported for this transformation, some of them lack the generality in producing β-amido ketones as they are restricted to acetonitrile giving the corresponding β-acetamido ketones. 9-16 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[28,29]. Therefore, the development of simple, efficient and general methodology for this three-component reaction is still desirable.

MATERIALS AND METHODS

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. ^1H NMR spectra were recorded on Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finning MAT 1020 spectrophotometer operating at 70 eV.

General Procedure:

A mixture of the acetophenone (1.0 mmol), benzaldehyde (1.0 mmol) and acetyl chloride (1.0 mmol) in acetonitrile (2 mL) was stirred in the presence of sodium sulphate at room temperature for the specified time (see Table 1 and 2). After completion of the reaction as indicated by TLC, the reaction mixture was extracted with ethyl acetate (15 mL). Evaporation of the solvent followed by purification on silica gel (10 g, Merck, 100-200 mesh, ethyl acetate-hexane (3:1), afforded pure β-acetamido derivative 3a (254.5 mg, 95%).

RESULTS AND DISCUSSION

Table 1: Physicochemical Data

Sl.No	Carbonyl compound	Aldehyde	Physical constant	Yield	Time
a	Acetophenone	Benzaldehyde	102	95	70 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	70 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

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

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

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).

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 anhydrous sodium sulphate (Table 1). As shown in the Table 1, aromatic aldehydes or acetophenones with both electron-withdrawing and donating substituents producedβ-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 anhydrous sodium 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 acetophenonederivative) 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.

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