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Copper(II) tetrafluoroborate 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 10 mol% of copper(II) tetrafluoroborate and a stoichiometric amount of acetyl chloride. A solution of 10 mol% of $Cu(BF_4)_2$ in acetonitrile provides a convenient reaction medium to carry out a three component reaction under mild conditions

Keywords: β-Acetamido carbonyl compounds; aromatic aldehydes; enolizable ketones; copper(II) tetrafluoroborate.

1. 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],

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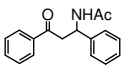
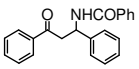
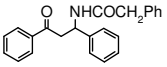
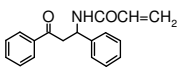
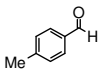
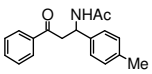
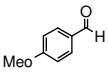
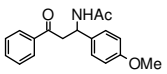
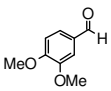
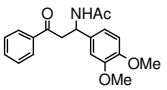
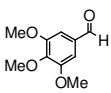
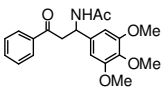
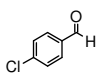
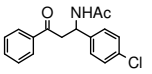
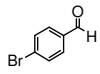
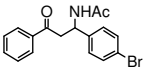
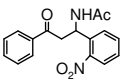
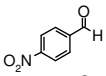
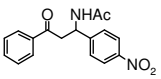
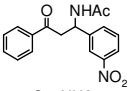
heteropoly acid [16], $Sc(OTf)_3$ [17], $FeCl_3$ [18], ZnO [19], $H_6P_2W_{18}O_{62}$ [20], Amberlyst-15 [21], $H_3PW_{12}O_{40}$ [22], Silica/Sulfuric acid [23], $CeCl_3.7H_2O$ [24], $SiCl_4$-$ZnCl_2$ [25], Polyaniline supported $Co(OAc)_2$ [26] and *p*-TSA [27]. Although, a large number of methods 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. Therefore, the development of simple, efficient and general methodology for this three-component reaction is still desirable.

Table 1. $Cu(BF_4)_2{\cdot}nH_2O$-Catalyzed three-component reaction for the preparation of β- acetamido ketones

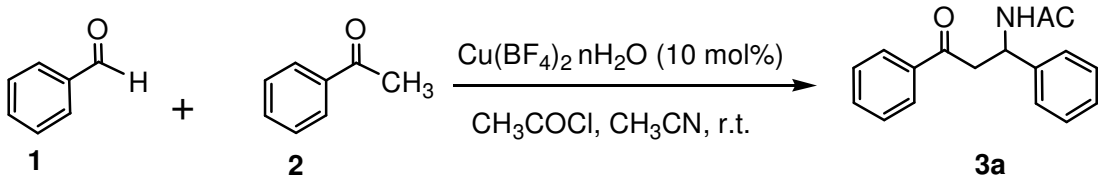
Entry	Carbonyl Compounds	Aldehydes	β-Acetamido Ketones (**3**)[a]	Time (h)	m.p.(°C)	ref.	Yield (%)[b]
a				3.5	102-104	18	95
b				3.0	153-155	18	80[c]
c				3.0	151-153	-	72[c]
d				4.0	90-92	-	70[c]
e				4.5	112	15	92
f				4.5	112-114	18	92
g				5.0	118-120	18	95
h				6.0	170-172	18	92
i				5.0	146-148	18	95
j				5.0	148-150	18	95
k				6.0	186-188	18	90
l				5.0	148-150	18	95
m				6.0	139-140	18	90
n				5.0	120-121	18	90
o				3.5	101-103	-	68
p				2.5	105-107	-	75

[a]All products were characterized by ^1H NMR, IR and mass spectrometry
[b]Yield refers to pure products after purification
[c] PhCN,$PhCH_2CN$, CH_2=CH-CN was used instead of CH_3CN

2. Results and Discussion

Recently, the use of $Cu(BF_4)_2{\cdot}nH_2O$ has received a considerable importance in organic synthesis. It is a blue crystalline solid and stable under normal conditions and is readily soluble in water and sparingly soluble in alcohols. It has emerged as one of the most useful catalysts in various transformations such as acylation reactions, *gem*-diacetate formation and thia-Michael reaction.[28,29] It has been found to be superior to other Lewis acids such as triflates, halides and perchlorates.

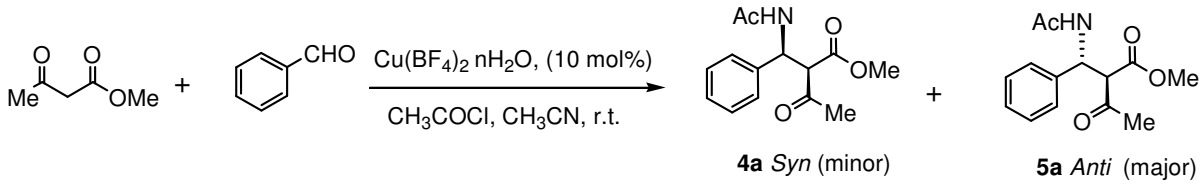
In this article, we wish to report a mild, convenient and efficient protocol for the synthesis of β-acetamido ketones using $Cu(BF_4)_2{\cdot}nH_2O$ as a novel catalyst. In preliminary study, benzaldehyde (**1**) was treated with acetophenone (**2**) in the presence of acetyl chloride in acetonitrile. The reaction went to completion in 3.5 h at room temperature in the presence of 10 mol% $Cu(BF_4)_2{\cdot}nH_2O$ and the product, β-acetamido-β-(phenyl)propiophenone **3a** was obtained in 95% yield (Scheme 1).



Scheme 1. Preparation of β-acetamido ketones

Similarly, various aromatic aldehydes having electron donating as well as electron withdrawing substituents participated in this reaction (entries **e**-**m**, Table 1). Acid sensitive, cinnamaldehyde was also so effective for this conversion (entry **n**, Table 1). Like acetophenone, 2-acetylthiophene and 2-acetylnaphthalene also reacted effectively under these conditions (entries **o** and **p**, Table 1). The reaction proceeded even with other nitriles such as benzonitrile, acrylonitrile and benzyl cyanide (entries **b, c** and **d,** Table 1). The scope of this methodology is illustrated in Table 1.

These results provided incentive for further study of reactions with other carbonyl compounds including β-ketoesters and 1,3-diketones. Interestingly, methyl acetoacetate reacted effectively with benzaldehyde in the presence of acetyl chloride in acetonitrile to furnish the corresponding β-acetamido esters in good yields and with moderate diastereoselectivity (Table 2). However, the products were obtained as a mixture of *syn* and *anti* isomers favoring *anti*-isomer (entries **a-e,** Table 2, Scheme 2).

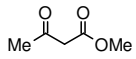
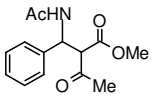
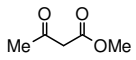
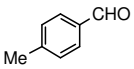
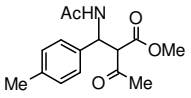
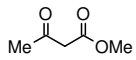
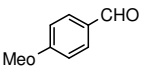
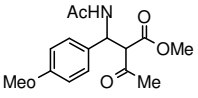
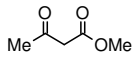
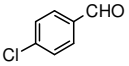
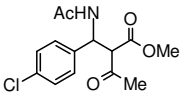
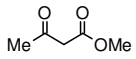
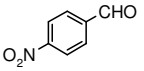
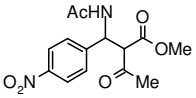
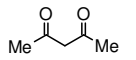
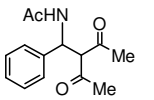
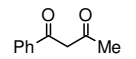
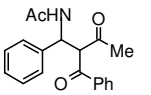
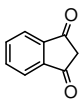
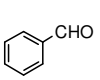
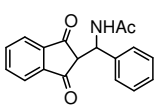


Scheme 2. Preparation of β-acetamido ketoesters

Similarly, 1,3-diketones such as acetyl acetone, benzoyl acetone and 1,3-indanone participated well in this reaction (entries **f**, **g** and **h**, Table 2). In all the cases, the reactions proceeded rapidly at room temperature with high efficiency. The products were characterized by ^1H, ^{13}C NMR,

IR and mass spectrometry and also by comparison with authentic samples.[9-20] Unlike reported methods, the present protocol does not require harsh conditions to produce β-acetamido ketones. This method not only offers substantial improvements in reaction rates and yields but also avoids the use of hazardous acids and harsh reaction conditions. The effects of various copper(II) salts such as $Cu(OAc)_2$, $CuCl_2$, and $Cu(acac)_2$, were examined for this reaction. Of these catalysts, $Cu(BF_4)_2.nH_2O$ was found to be the most effective in terms of conversion and the results are presented in Table 3. It is a simple and convenient approach to produce a wide range of β-amido ketones and esters in excellent yields in short reaction times in a single-step.

Table 2. $Cu(BF_4)_2{\cdot}nH_2O$-Catalyzed three-component reaction for the preparation of β-acetamido ketoesters

Entry	1,3-Dicarbonyl compounds	Aldehydes	β-Acetamido Ketones & esters (**4**/**5**)	Time (h)	m.p.(°C)	ref.	Yield (%)[b]	*syn:anti*[c]
a				5.0	130-132	11	75	25:75
b				5.0	138-140	11	80	10:90
c				5.0	142-144	11	80	20:80
d				6.0	131-133	11	75	–
e				6.0	149-151	11	72	–
f				3.0	126-128	-	85	–
g				4.0	133-135	-	75	–
h				5.0	110-112	-	70	–

[a]All products were characterized by ^{1}H NMR, IR and mass spectrometry.
[b]Yield refers to pure products after chromatography
[c]The *syn:anti* ratio was determined from ^{1}H NMR spectrum.

3. Conclusion

In conclusion, $Cu(BF_4)_2 nH_2O$ has demonstrated to be a mild and efficient catalyst for the three-component coupling of aldehydes, enolizable ketones or β-ketoesters and nitriles to produce β-amido ketones and ketoesters. The yields are generally high to quantitative, though moderate selectivity. This method is useful especially to the preparation of β-amido ketones from benzonitrile, benzyl cyanide and acrylonitrile under extremely mild conditions.

Table 3. Effects of various copper(II) catalysts in the preparation of **3a**

S.No	Catalyst (10mol %)	Temp (°C)	Time (h)	Yield (%)[a]
1	$CuCl_2$	RT	30	79
2	CuO	RT	20	40
3	$Cu(OTf)_2$	RT	30	64
4	$Cu(OAc)_2$	RT	15	60
5	$Cu(acac)_2$	RT	10	65
6	$Cu(BF_4)_2$	RT	3.5	95

[a] Isolated yields after coloumn Chromatography

4. Experimental section

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. H^1 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 spectrometer operating at 70 eV.

4.1 *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 copper(II) tetrafluoroborate hydrate 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%).

***N*-1-(3-oxo-1,3-diphenylpropyl)-2-phenylacetamide (3c, Table 1).** Yield: 72%; Solid, M.p. 93-94 °C; IR (KBr): υ 3432, 2945, 1775, 1705, 1486, 1374, 1282, 1183, 1034, 714 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.80-7.84 (m, 2H), 7.13-7.51 (m, 13H), 5.43 (m, 1H), 3.37 (dd, *J* = 5.2, 16.9 Hz, 1H), 3.25 (dd, *J* = 6.0, 16.9 Hz, 1H), 3.53 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 43.5, 45.0, 53.0, 126.2, 126.6, 126.9,127.3, 127.5, 128.6, 129.7, 130.0 132.6, 136.2, 142.2, 170.6, 197.4. ESI-MS: *m/z*(%): 344 (M+1)

***N*-1-(3-oxo-1,3-diphenylpropyl)acrylamide ((3d, Table 1).** Yield: 70%; Solid, M.p. 88-89 °C; IR (KBr): υ 3428, 2958, 1815, 1765, 1492, 1364, 1291, 1180, 1054, 714 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.91-7.95 (m, 2H), 7.19-7.55 (m, 8H), 6.52-6.55 (m, 1H), 5.85-6.02 (m, 2H), 5.55 (m, 1H), 3.72 (dd, *J* = 4.9, 17.5 Hz, 1H), 3.45 (dd, *J* = 5.6 , 17.5 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): 43.3,

50.1, 124.6, 125.3, 126.2, 126.9, 127.5, 27.9, 129.7, 132.0, 133.4, 142.9, 162.9, 198.3. ESI-MS: *m/z*(%): 280 (M+1)

***N*-1-[3-(2-napthyl)-3-oxo-1-phenylpropyl]acetamide(3o, Table 1).** Yield: 68%; Solid, M.p.121-122 ^{o}C; IR (KBr): υ 3422, 2975, 1793, 1664, 1392, 1271, 1175, 1054, 714 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.75-7.92 (m, 5H), 7.21-7.32 (m, 4H), 7.08-7.12 (m, 3H), 5.45 (m, 1H), 3.22 (dd, *J* = 5.2, 16.9 Hz, 1H), 2.97 (dd, *J* = 6.0, 16.9 Hz, 1H), 2.03 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.0, 43.5, 51.7, 123.6, 125.5, 127.4, 127.8, 127.9, 128.2, 128.3, 128.8, 130.5, 132.6, 134.4, 136.2, 143.7, 168.2, 198.5. ESI-MS: *m/z*(%): 318 (M+1)

***N*-1-[2-oxo-1-phenyl-2-(2-thienyl)ethyl]acetamide (3p, Table 1).** Yield:75%; Solid, M.p.101-103 ^{o}C; IR (KBr): υ 3280, 3072, 1680, 1641, 1283, 1088, 812, 690 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.66-7.68 (m, 1H), 7.59-7.61 (m, 1H), 7.15-7.28 (m, 5H), 7.06-7.09 (m, 1H), 5.48 (m, 1H), 3.57 (dd, *J* = 5.5, 17.4 Hz, 1H), 3.31 (dd, *J* = 6.0, 17.4 Hz, 1H), 2.01 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.5, 43.3, 50.0, 126.6, 127.5, 127.9,128.2, 128.5 128.8, 133.6, 141.6, 169.6, 199.3. ESI-MS: *m/z*(%): 260 (M+1)

***N*-1-(2-Methyl-3-oxo-1-phenylpropyl)acetamide (4f, Table 2).** Yield: 85%; Solid, m.p. 127-128 ^{o}C. IR (KBr): υ 3292, 3034, 2924, 1757, 1718, 1647, 1530, 736 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.14-7.34 (m, 5H), 5.32 (d, *J* = 5.9Hz, 1H), 4.33 (d, *J* = 5.9 Hz, 1H), 2.17 (s, 3H), 1.84 (s, 6H). EI-MS: *m/z*(%): 247 (M^+,10), 224 (30), 176 (80), 118 (70) 91(32).

***N*-1-(2-benzoyl-3-0xo-1-phenylbutyl)acetamide (4g, Table 2).** Yield: 75%; Solid, m.p. 121-122 ^{o}C. IR (KBr): υ 3334, 3024, 2950, 1785, 1710, 1655, 1532, 715 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.31-7.52 (m, 7H), 7.12-7.20 (m, 3H), 5.63 (m, 1H), 4.86 (d, *J* = 6.5 Hz, 1H), 2.05 (s, 3H), 1.92 (s, 3H). EI-MS: *m/z*(%): 309 (M^+,24), 282 (26), 163 (70), 109 (50).

***N*-1-[(1,3-dioxo-2,3–dihydro-1*H*-2-indenyl)(phenyl)methyl]acetamide (4h, Table 2).** Yield: 70%; Solid, M.p.115-116 ^{o}C; IR (KBr): υ 3422, 2982, 1793, 1664, , 1271, 1185, 1082, 715 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.08-8.11 (m, 2H), 7.70-7.95 (m, 3H), 7.43-7.55 (m, 3H), 7.04-7.07 (m, 1H), 5.92 (m, 1H), 5,52 (m, 1H), 2.16 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.4, 50.8, 55.9, 121.6, 126.5, 128.3, 128.8 132.1, 140.5, 142.6, 165.3, 199.7. EI-MS: *m/z*(%): 293 (M^+,16), 254 (32), 163 (70), 112 (50).

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