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단 신

촉매로서의 VCl_3를 사용한 β-아세트아마이도 카르보닐 화합물의 간단하고 효율적인 One-Pot 합성

V. Siddaiah*, G. L. V. Damu, D. Sudhakar, C. Venkata Rao, and V. Christopher
Department of Organic Chemistry & FDW, Andhra University, Visakhapatnam-530 003, India
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VCl_3 Catalyzed, A Simple and Efficient One-Pot, Multi-Component Synthesis of β-Acetamido Carbonyl Compounds

V. Siddaiah*, G. L. V. Damu, D. Sudhakar, C. Venkata Rao, and V. Christopher
Department of Organic Chemistry & FDW, Andhra University, Visakhapatnam-530 003, India
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주제어: 방향족 알데히드, 에놀형성 케톤, 염화에세틸, 바나듐클로라이드(III), β-아세트아마이도 카르보닐 화합물

Keywords: Aromatic Aldehydes, Enolizable Ketones, Acetylchloride, Vanadium(III) Chloride, β-Acetamido Carbonyl Compounds

INTRODUCTION

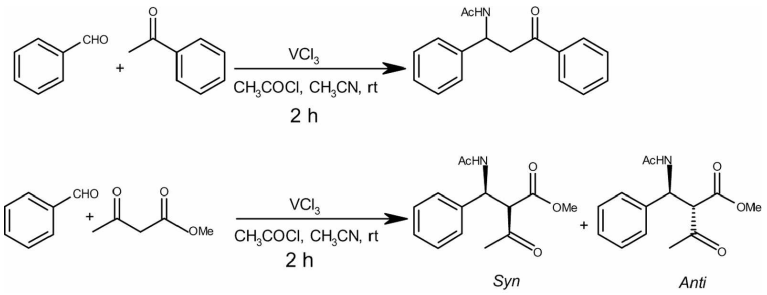
Multi-component reactions (MCRs) are one of the most important protocals in organic synthesis and medicinal chemistry.[1] β-Acetamido carbonyl compounds are useful building blocks for a number of biologically and pharmaceutically valuable compounds.[2] These are precursors of 1,3-amino alcohols[3] present antibiotic nikkomycins or neopolyoximes.[4] Generally these compounds were synthesized through Dakin West reaction.[5] β-Acetamido ketones have also been synthesized using Zn(II), Bi(II), Sn(II), Sc(III) triflates,[6] $CoCl_2$,[7] montmorillonite k-10 clay,[8] H_2SO_4/SiO_2,[9] BiOCl,[10] or heteropoly acid[11] as a catalyst. Although these methods are valuable, they suffer from disadvantages such as high temperature, long reaction times, low yields and tedious workup.

In continuation of our work[12] on the development of useful synthetic methodologies we have investigated a simple and efficient method using a readily available, cheap and non-toxic reagent.

VCl_3 is a relatively cheap and non-toxic reagent. It is able to activate carbonyl functionalities for nucleophilic attack and has been used as a Lewis acid for several transformations.[13] Herein, we report a simple and efficient protocol for the synthesis of β-acetamido ketones or esters by multi-component reactions of an aromatic aldehydes, acetonitrile, an enolizable ketones or β-ketoesters and acetylchloride in the presence of 10 mol% of vanadium (III) chloride (*Scheme* 1).

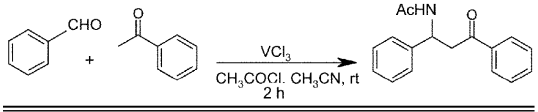
RESULTS AND DISCUSSION

To establish the optimal conditions we have carried out the reaction with *p*-methoxybenzaldehyde (1 mmol), acetophenone (1 mmol), acetyl chloride (2 mmol) and acetonitrile (5 mL) under various conditions (*Table* 1). In the absence of catalyst the yield of the product β-acetamido ketone was 5% only after 24 h. When we used 5 mol% of catalyst the yield of the product was found to increase to 75% within 10 h. Further it was observed that when



Scheme 1.

Table 1. Optimization of the VCl_3 catalyzed multi-component reaction.



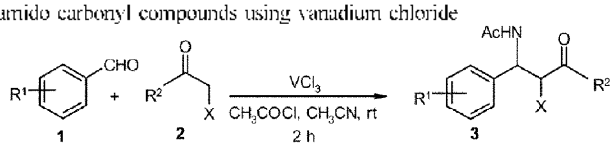
Entry	Catalyst VCl_3(mol%)	Time (h)	Yield[a] (%)
1	0	24	5
2	5	10	75
3	10	2	96

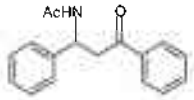
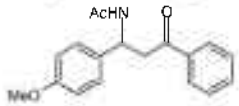
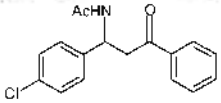
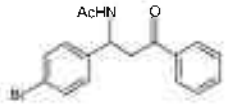
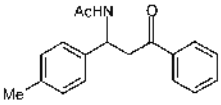
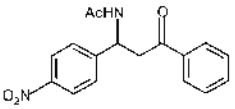
[a]Crude yields.

the catalyst concentration was increased to 10 mol% the product yield increased to 96% within 2 h.

After optimization various aromatic aldehydes or acetophenones having electron withdrowing as well as electron donating substituents were used for the reaction (*Table* 2). The conversion was completed within 2 h at room temperature and the products were obtained in excellent yields. 1, 3-diketones formed the corresponding β-acetamido ketoesters in good yields with high diastereoselectivities. In

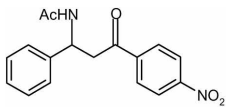
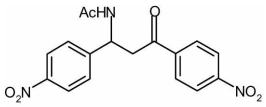
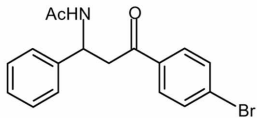
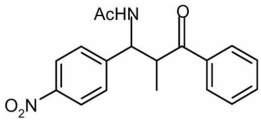
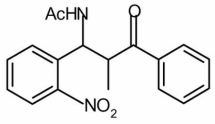
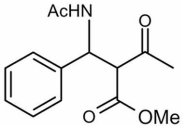
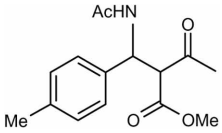
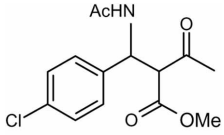
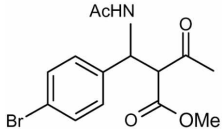
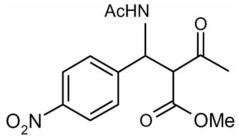
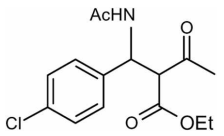
Table 2. Synthesis of β-acetamido carbonyl compounds using vanadium chloride



Entry	R^1	X	R^2	Product (3)	Isolated yield (%)	Syn-anti[a]
1	H	H	Ph		96	-
2	4-MeO	H	Ph		96	-
3	4-Cl	H	Ph		94	-
4	4-Br	H	Ph		90	-
5	4-Me	H	Ph		95	-
6	4-NO_2	H	Ph		90	-

[a]Ratio of the *syn* and *anti* isomers (by ^{1}H NMR)

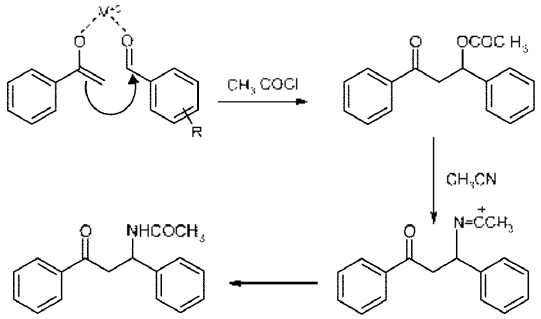
Table 2. (Continued) Synthesis of β-acetamido carbonyl compounds using vanadium chloride

Entry	R^1	X	R^2	Product (**3**)	Isolated yield (%)	Syn-anti[a]
7	H	H	4-$NO_2C_6H_4$		79	-
8	4-NO_2	H	4-$NO_2C_6H_4$		85	-
9	H	H	4-BrC_6H_4		87	
10	4-NO_2	Me	C_6H_5		82	25:75
11	2-NO_2	Me	C_6H_5		80	30:70
12	H	COOMe	Me		80	25:75
13	4-Me	COOMe	Me		84	25:75
14	4-Cl	COOMe	Me		82	25:75
15	4-Br	COOMe	Me		84	30:70
16	4-NO_2	COOMe	Me		81	35:65
17	4-Cl	COOEt	Me		86	30:70

[a]Ratio of the *syn* and *anti* isomers (by ^{1}H NMR)

Table 3. Comparison of the results for the preparation of β-acetamido ketone (entry **1**, *Table* 2) using multi-component reactions with other catalysts

Catalyst	mol%	Reaction time	Reaction temperature (°C)	Yields (%)
Montmorillonite K-10	80	7 h	70	80
SiO_2/H_2SO_4	78	65 m	80	91
$Sc(OTf)_3$	10	30 h	Rt	82
$CoCl_2$	20	5 h	Rt	90
BiOCl	20	7 h	Rt	92
VCl_3	10	2 h	Rt	96



Scheme 2. A plausible mechanism for the VCl_3 catalyzed multi-component reaction for the presentation of β-acetamido carbonyl compounds.

case of ketoesters both syn and anti products were formed (confirmed by ^{1}H-NMR). In most of the cases anti isomer was the major product. All the products were identified by comparison of analytical data (IR, NMR and MS) of those reported for authentic samples.

As a model reaction, the present method for the preparation of β-acetamido-β-(phenyl)-propiophenone (entry **1**, *Table* 2) showed an excellent efficiency compared to some recently reported procedures (*Table* 3). Moreover, in the absence of catalyst the reaction proceeds with only little amounts even after 24 h. But the products were obtained in excellent yields within 2 h when the vanadium (III) chloride was used as a catalyst. So we believe that the vanadium chloride activates the aldehyde group for nucleophillic attack and facilitate enolization (*Scheme* 2).

CONCLUSIONS

We have developed an efficient and simple method for the preparation β-acetamido ketones or esters with 10 mol% of VCl_3. The major advantages of this method include short reaction times, mild reaction conditions, and easy work up procedure.

EXPERIMENTAL

Melting points of the compounds were recorded on an electro-thermal apparatus and were uncorrected. Elemental analysis was carried out on CHNS OEA 1108 elemental enalyzer. ^{1}H NMR spectra were recorded on BRUKER AMX-200 spectrometer operating AT 200 MHz. LC-MS spectra were recorded on a AGILENT-1100 periods LC/MSD (VL). Starting materials and solvents were purchased from Merck or Aldrich.

General procedure for the synthesis of β-acetamido ketones or esters: A mixture of aromatic aldehyde (1 mmol), acetophenone or β-ketoester (1 mmol), acetyl chloride (2 mmol) and 10 mol% of VCl_3 in acetonitrle (5 ml) was stirred at room temperature. After completion of the reaction as indicated by TLC, the reaction mixture was extracted with dichloromethane. The combined organic layer was concentrated under vacuum and the product was purified by silica gel column chromatography eluted by an ethyl acetate and hexane (1:1) mixture to afford pure β-acetamido ketone or an ester in good yield.

The spectral and analytical data of some representative β-acetamido carbonyl compounds are given below.

β-Acetamido-β-(4-methoxyphenyl)propiophenone (entry 2, *Table* 2): mp: 115-117 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.92 (s, 3H), 3.20 (dd, J = 7.2, 10.0 Hz, 1H), 3.63 (dd, J = 7.2, 10.0 Hz, 1H), 3.65 (s, 3H), 5.42 (m, 1H), 6.82 (d, J = 8.0 Hz, 2H),

7.25 (d, J = 8.0 Hz, 2H), 7.49 (s, 1H), 7.52 (m, 5H); FABMS: *m/z* 270 $[M+H]^-$; Anal. Calcd. For $C_{17}H_{19}NO_2$: C, 75.80; H, 7.06; N, 5.20. Found: C, 75.76; H, 7.10; N, 4.92.

β-Acetamido-β-(4-nitrophenyl)propiophenone (entry 6, *Table* 2): mp: 148-130 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.02 (s, 3H), 3.46 (dd, J = 12.0, 3.0 Hz, 1H), 3.79 (dd, J = 12.0, 2.0 Hz, 1H), 5.60 (m,1H), 6.98 (d, J = 6.0 Hz, 1H), 7.60-7.42 (m, 5H), 7.86 (d, J = 8.0 Hz, 2H), 8.15 (d, J = 8.0 Hz, 2H); FABMS: *m/z* 313 $[M+H]^+$; Anal. Calcd. For $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.13; N, 8.97. Found: C, 65.41; H, 5.22; N, 8.92.

β-Acetamido-β-(phenyl)-4-bromopropiophenone (entry 9, *Table* 2): mp: 97-99 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.16 (s, 3H), 3.41 (dd, J = 8.20, 10.05 Hz, 1H), 3.85 (dd, J = 8.2, 10.0 Hz, 1H), 5.40 (s, 1H), 6.81 (d, J = 6.2 Hz, 1H), 7.40-7.11 (m, 5H), 7.59 (d, J = 8.2 Hz, 2H), 7.81 (d, J = 8.2 Hz, 2H); FABMS: *m/z* 346, 348 $[M+H]^-$; Anal. Calcd. For $C_{17}H_{16}NO_2Br$: C, 58.95; H, 4.62; N, 4.05. Found: C, 58.90; H, 4.65; N, 4.09.

Methyl-2-acetyl-3-acetamido-3-(p-methyl)propionate (entry 13, *Table* 2) (anti): mp: 112-114 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.05 (s, 3H), 2.18 (s, 3H), 2.32 (s, 3H), 3.70 (s, 3H), 4.06 (d, J = 5.90 Hz, 1H), 5.72 (m, 1H), 6.90 (d, J = 9.3 Hz, 1H), 7.21-7.05 (m, 4H); FABMS: *m/z* 278 $[M+H]^-$; Anal. Calcd. For $C_{15}H_{19}NO_4$: C, 64.98; H, 6.86; N, 5.05. Found: C, 64.91; H, 6.90; N, 5.12.

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