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Short Communication

$ZrCl_4$-Catalyzed Efficient Synthesis of Enaminones and Enamino Esters under Solvent-free Conditions

Jin Lin[1,*] and **Li-Feng Zhang**[2]

[1] The College of Chemistry & Material Science, Hebei Normal University, Shijiazhuang, China
[2] Hebei Chemical & Pharmaceutical Vocational Technology College, Shijiazhuang, China

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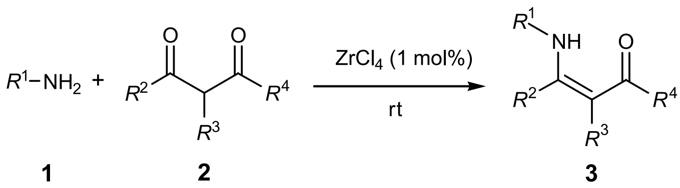
Summary. A facile synthesis of β-enaminones and enamino esters by condensation of β-dicarbonyl compounds with differently substituted amines in the presence of $ZrCl_4$ under solvent-free conditions is reported.

Keywords. β-Enaminones; β-Enamino esters; 1,3-Dicarbonyl compounds; Zirconium(IV) chloride; Solvent-free conditions.

Introduction

β-Enaminones and β-enamino esters have been extensively used as key intermediates in organic synthesis [1]. In particular, they have been employed as synthons of different important antibacterial [2], anticonvulsant, anti-inflammatory [3], and antitumour agents [4]. Due to their wide range application and importance, a simple and high yielding one-pot method for the synthesis of β-enaminones and β-enamino esters is highly desirable. The conventional approach for the preparation of β-enaminones and β-enamino esters is direct condensation of β-dicarbonyl compounds with amines under reflux in an aromatic solvent with azeotropic removal of water [5]. Various modified synthesis pathways have been reported, such as the addition of zinc ester enolates or amide enolates to nitriles [6], tosyl imines [7], or imidoyl halides [8], the addition of enamines to activated carboxylic acid derivatives [9], and the reaction of β-enamino esters with organolithium reagents [10]. Apart from these, several other improved methods for the enamination of 1,3-dicarbonyl compounds have been reported using catalyst systems, such as protic

* Corresponding author. E-mail: linjin64@126.com



Scheme 1

acid [11], *Lewis* acid [12], iodine [13], clays [14], silica gel [15], and sulfated zirconia [16], *etc*. More recently, [*Et*NH_3]NO_3 [17], $HClO_4 \cdot SiO_2$ [18] as well as silica chloride [19] have been used to effect this transformation. Although these methods improve reaction conditions and shorten reaction time, in many cases still drastic conditions are necessary for completion of the process, high temperatures and high catalyst loading are required, or non-readily available or very expensive reagents are used.

Organic reactions under solvent-free conditions are advantageous because of their enhanced selectivity and efficiency, ease of manipulation, and toxic or volatile solvents are avoided [20]. Inspired by reports of catalytic applications of zirconium tetrachloride for various organic transformations [21], we considered employing $ZrCl_4$ as a catalyst for the synthesis of β-enaminones and β-enamino esters under solvent-free conditions (Scheme 1).

Results and Discussion

An initial study was performed treating ethyl acetoacetate with aniline under solvent-free conditions in the presence of a catalytic amount of $ZrCl_4$ (5 mol%) at room temperature. To our delight, we observed the formation of ethyl 3-(phenylamino)but-2-enoate (**3p**). Complete conversion and 95% isolated yield were obtained after 30 minutes. Further studies established that 1 mol% of catalyst was also efficient in this reaction. Reactions in solvents such as *THF*, CH_2Cl_2, *DMF*, *Et*O*Ac* gave lower yields of the desired product after prolonged reaction time. So, we executed the reaction under solvent-free conditions.

To demonstrate the generality of this method, we next investigated the scope of this reaction under optimized conditions and the results are summarized in Table 1. Thus, a variety of amines including primary, benzylic, and aromatic amines were condensed with various β-dicarbonyl compounds to produce a range of β-enaminones and β-enamino esters. This reaction is very clean and free from side reactions. Unlike reported methods, the present protocol does not require high temperature. In general, for primary and benzylic amines the condensation reactions usually afforded the corresponding β-enaminones and β-enamino esters in over 90% yields in short time. However, anilines with an electron-withdrawing group (**1g** and **1s**) afforded low yields of the products. It should be pointed out that in the reaction of 1-benzoylacetone with amines the regioselective amination of the aliphatic carbonyl group (**2h** and **2i**) was observed. When 1,3-diaminopropane was used as an amine, two equivalents of methyl acetoacetate were required to give the product with two enamino ester groups (**3k**). Moreover, the optically active amine was converted into the corresponding β-ketoester (**3n**) without any racemization or inversion. From linear β-diketones and β-ketoesters we always obtained the corre-

Table 1. $ZrCl_4$-catalyzed synthesis of β-enaminones and β-enamino esters

Entry	R^1	R^2	R^3	R^4	Time/min	Yield/%[a]
a	*Me*	H	*Me*	$CH_3(CH_2)_3$	18	93
b	*Me*	H	*Me*	*Ph*CH_2	15	94
c	*Me*	H	*Me*	*Ph*	12	96
d	*Me*	H	*Me*	4-*Me*-C_6H_4	10	95
e	*Me*	H	*Me*	4-O*Me*-C_6H_4	12	93
f	*Me*	H	*Me*	4-O*Et*-C_6H_4	12	92
g	*Me*	H	*Me*	4-Cl-C_6H_4	240	81
h	*Me*	H	*Ph*	*Ph*	60	85
I	*Me*	H	*Ph*	3-*Me*-C_6H_4	50	81
j	*Me*	H	O*Et*	$CH_3(CH_2)_3$	12	94
k	*Me*	H	O*Me*	$H_2NCH_2CH_2CH_2$	15	95[b]
l	*Me*	H	O*Et*	C_3H_5	10	94
m	*Me*	H	O*Me*	*Ph*CH_2	10	94
n	*Me*	H	O*Et*	(*R*)-*Ph*$CH(CH_3)$	12	93
o	*Me*	H	O*Me*	*Ph*	45	95
p	*Me*	H	O*Et*	*Ph*	40	95
q	*Me*	H	O*Me*	4-O*Me*-C_6H_4	40	92
r	*Me*	H	O*Et*	4-O*Me*-C_6H_4	40	91
s	*Me*	H	O*Et*	4-Br-C_6H_4	180	85
t	*Me*	$(CH_2)_2O$		*Ph*CH_2	25	95
u	*Me*	$(CH_2)_2O$		*Ph*	30	95
v	*Me*	$(CH_2)_2O$		4-*Me*-C_6H_4	30	92
w	*Me*	$(CH_2)_2O$		2-*Me*-C_6H_4	40	92
x	$(CH_2)_3$		O*Et*	*Ph*	90	92
y	$(CH_2)_3$		O*Et*	4-O*Me*-C_6H_4	80	93

[a] Isolated yield; [b] 2 equiv of β-dicarbonyl compounds (with respect to propane-1,3-diamine) were used

sponding β-enaminones and β-enamino esters having a (*Z*)-configuration of the carbon-carbon double bond due to the formation of intramolecular hydrogen bonding, as evidenced by ^{1}H NMR analysis following the procedure reported by *Das et al.* [18].

In conclusion, we demonstrated that $ZrCl_4$ is a remarkably efficient catalyst for the synthesis of β-enaminones and β-enamino esters from β-dicarbonyl compounds and amines. The present method is associated with several advantages such as mild conditions, short reaction times, excellent yields of products, simple workup procedure, and low cost of catalyst. The use of solvent-free reaction conditions employed in the present protocol makes it environmentally friendly and suitable for large scale synthesis.

Experimental

Melting points were recorded on a X-4 apparatus. IR spectra were recorded on a Perkin Elmer 781 spectrophotometer. ^{1}H NMR spectra were recorded with a Bruker spectrometer at 300 MHz using *TMS* as internal standard. Elemental analyses were performed on an elementar vario EL analyser. Their results agreed favourably with the calculated values.

*General Procedure for the Synthesis of β-Enaminones and β-Enamino Esters **3***

$ZrCl_4$ (23 mg, 0.1 mmol) was added to a mixture of β-dicarbonyl compound (10 mmol) and amine (10 mmol). The mixture was stirred magnetically under solvent-free conditions at room temperature. After completion of the reaction (monitored by TLC), 20 cm^3 ethyl acetate were added to the reaction mixture and the organic phase was washed with 2×10 cm^3 brine. The combined organic layer was dried ($MgSO_4$) and concentrated under vacuum to obtain a product in almost pure form. Further purification was carried out by column chromatography over silica gel using ethyl acetate:*n*-hexane (2:8) as the eluent.

Ethyl 3-(cyclopropylamino)but-2-enoate (**3l**, $C_9H_{15}NO_2$)

Yellowish oil; IR (neat): $\bar{\nu}$ = 3292, 2981, 1688, 1655, 1610, 1492, 1440, 1340, 1268, 1161, 1027, 903 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.56–0.63 (m, 2H), 0.72–0.80 (m, 2H), 1.24 (t, *J* = 7.2 Hz, 3H), 2.06 (s, 3H), 2.53–2.62 (m, 1H), 4.08 (q, *J* = 7.2 Hz, 2H), 4.49 (s, 1H), 8.55 (br s, 1H, NH) ppm.

Ethyl (R)-3-(1-phenylethylamino)but-2-enoate (**3n**, $C_{14}H_{19}NO_2$)

Colorless liquid; $[\alpha]_D^{20}$: −630 $cm^2 g^{-1}$ (*c* = 1.02, *Et*OH); IR (neat): $\bar{\nu}$ = 3279, 2979, 1650, 1610, 1494, 1445, 1385, 1265, 1054, 844, 785 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.30 (t, *J* = 7.2 Hz, 3H), 1.54 (d, *J* = 6.9 Hz, 3H), 1.79 (s, 3H), 4.15 (q, *J* = 7.2 Hz, 2H), 4.89 (s, 1H), 4.66 (m, 1H), 7.23–7.38 (m, 5H), 9.02 (br s, 1H, NH) ppm.

Ethyl 3-(4-methoxyphenylamino)but-2-enoate (**3r**, $C_{13}H_{17}NO_3$)

Pale yellow solid, mp 44.5–45.5°C; IR (KBr): $\bar{\nu}$ = 3265, 2950, 2836, 1655, 1614, 1514, 1246, 1161, 1035, 977, 786 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.27 (t, *J* = 7.2 Hz, 3H), 1.87 (s, 3H), 3.79 (s, 3H), 4.15 (q, *J* = 7.2 Hz, 2H), 4.64 (s, 1H), 6.85 (d, *J* = 8.1 Hz, 2H), 7.02 (d, *J* = 8.1 Hz, 2H), 10.18 (br s, 1H, NH) ppm.

Ethyl 3-(4-bromophenylamino)but-2-enoate (**3s**, $C_{12}H_{14}BrNO_2$)

Pale yellow solid, mp 52.5–53°C; IR (KBr): $\bar{\nu}$ = 3275, 2979, 1650, 1611, 1581, 1480, 1385, 1261, 1064, 853, 789 cm^{-1}; ^1HNMR ($CDCl_3$): δ = 1.29 (t, *J* = 7.2 Hz, 3H), 1.99 (s, 3H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.72 (s, 1H), 6.95 (d, *J* = 8.1 Hz, 2H), 7.43 (d, *J* = 8.1 Hz, 2H), 10.35 (br s, 1H, NH) ppm.

3-(1-(3-Toluidino)ethylidene)dihydrofuran-2(3H)-one (**3w**, $C_{13}H_{15}NO_2$)

Pale yellow solid, mp 121–122°C; IR (KBr): $\bar{\nu}$ = 3465, 2978, 1632, 1514, 1460, 1359, 1283, 1124, 1022, 954, 760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.02 (s, 3H), 2.33 (s, 3H), 2.80 (t, *J* = 7.2 Hz, 2H), 4.32 (t, *J* = 7.2 Hz, 2H), 6.85–6.88 (m, 2H), 6.96 (d, *J* = 7.2 Hz, 1H), 7.20 (t, *J* = 7.2 Hz, 1H), 9.95 (br s, 1H, NH) ppm.

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