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Simple and efficient synthesis of 3-aminopropenones and 3-aminopropenoates catalyzed by copper(II) nitrate trihydrate under solvent-free conditions

Geng-Chen Li

School of Material Science and Engineering, Shijiazhuang Railway Institute, Shijiazhuang, China

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Abstract A simple, efficient and environmentally begin method has been developed for the synthesis of 3-aminopropenones and 3-aminopropenoates through the reaction of 1,3-dicarbonyl compounds with amines in the presence of $Cu(NO_3)_2 \cdot 3H_2O$ under solvent-free conditions.

Keywords 3-Aminopropenones; 3-Aminopropenoates; 1,3-Dicarbonyl compounds; Amines; Copper(II) nitrate trihydrate.

Introduction

3-Aminopropenones and 3-aminopropenoates, also known as β-enaminones and β-enamino esters are versatile intermediates for the synthesis of various heterocycles [1], natural products [2], α- and β-amino acid compounds [3], alkaloids [4], and peptides [5]. Some synthetic approaches have been reported but the direct condensation of amines with 1,3-dicarbonyl compounds is one of most preferred synthesis approaches, which is usually catalyzed by protic acid [6], *Lewis* acid such as $Zn(ClO_4)_2 \cdot 6H_2O$ [7], $CeCl_3 \cdot 7H_2O$ [8], $NaAuCl_4$ [9], $Bi(OTf)_3$ [10], $InBr_3$ [11], $CoCl_2 \cdot 6H_2O$ [12], *CAN* [13], $Yb(OTf)_3$ [14], $SnCl_4 \cdot 5H_2O$ [15], $ZrCl_4$ [16], $ZrOCl_2 \cdot 8H_2O$ [17], $Zn(Ac)_2 \cdot 2H_2O$ [18], $Sc(OTf)_3$ [19], I_2 [20], and solid acids such as montmorillonite K10 [21], silica chloride [22], silica gel [23], natural clays [24], and sulfated zirconia [25]. Recently, $[EtNH_3]$-NO_3 [26] and $HClO_4 \cdot SiO_2$ [27] have also been used to promote this transformation. However, some of these methodologies have not been entirely satisfactory with disadvantage, such as low yields of products, longer reaction times, harsh reaction conditions, use of harmful organic solvents, and requirement of excess of catalysts and special apparatus. Hence, there is a need to develop an efficient, practically potential, and environmentally benign method for the synthesis of 3-aminopropenones and 3-aminopropenoates under mild and economically cheaper conditions.

Recently, copper salts have emerged as efficient *Lewis* acids in organic synthesis because these compounds are relatively non-toxic, easy to handle, of low cost, and good stability [28]. Among these, copper(II) nitrate has gained special attention because this compound not only is commercially available and inexpensive, but also of high stability. Copper(II) nitrate has been reported to be an efficient reagent for many important organic reactions, such as deprotection of 1,3-dithianes and 1,3-dithiolanes [29], chemoselective synthesis of 1,1-diacetates [30], aromatization of *Hantzsch* 1,4-dihydrpyridines [31], synthesis of bis(indolyl)methanes [32], *etc.* Inspired by reports of continuation of interest in catalytic applications of $Cu(NO_3)_2 \cdot 3H_2O$ for various organic transformations, we report herein a simple and convenient solvent-free method for the synthesis of 3-aminopro-

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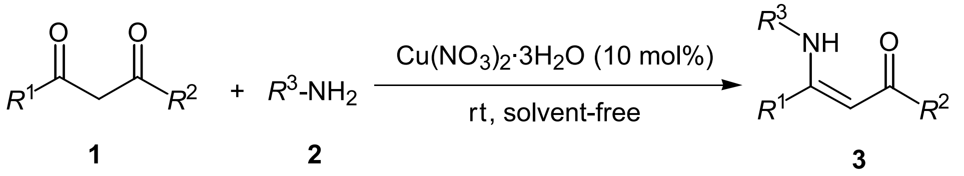
Correspondence: Geng-Chen Li, School of Material Science and Engineering, Shijiazhuang Railway Institute, Shijiazhuang 050043, China. E-mail: gengchenli@sina.com.cn



Scheme 1

penones and 3-aminopropenoates in the presence of a catalytic amount of $Cu(NO_3)_2 \cdot 3H_2O$ (Scheme 1).

Results and discussion

Initially, a model reaction of ethyl acetoacetate and aniline was performed under solvent-free conditions in the presence of a catalytic of $Cu(NO_3)_2 \cdot 3H_2O$ (10 mol%) at room temperature. To our delight, we observed the formation of ethyl 3-(phenylamino)but-2-enoate (**3i**) in 95% isolated yield after 50 min. In the absence of the catalyst, only 30% of the product was obtained even after 24 h stirring at room temperature. Increasing the amount of the catalyst did not show significant influence on the rate of the reaction as well as yield. Lower catalyst loading can be used with only a marginal drop in reaction rate. Various solvents such as *Et*OH, *Me*CN, CH_2Cl_2, *THF*, *DMF*, and *Et*O*Ac* were also screened for this reaction. However, the best results were observed under solvent-free conditions.

To explore the generality and scope of this method, a wide variety of amines including primary, benzylic, and aromatic amines were reacted with various 1,3-dicarbonyl compounds and the results are summarized in Table 1. In general, primary and benzylic amines reacted with a broad range of structurally diverse 1,3-dicarbonyl compounds to afford the cor-

Table 1 Synthesis of 3-aminopropenones and 3-aminopropenoates catalyzed by $Cu(NO_3)_2 \cdot 3H_2O$

Entry	R^1	R^2	R^3	Time/min	Yield[a]/%	Ref.
a	*Me*	O*Et*	$CH_3(CH_2)_3$	15	92	[25]
b	*Me*	O*Bn*	$CH_3(CH_2)_3$	18	90	[34]
c	*Me*	O*Me*	$CH_2{=}CHCH_2$	15	95	[12]
d	*Me*	O*Me*	C_6H_{11}	15	93	[14b]
e	*Me*	O*Me*	*Ph*CH_2	12	93	[25]
f	*Me*	O*Bn*	*Ph*CH_2	18	90	[34]
g	*Me*	O*Me*	*Ph*CH_2CH_2	15	92	[11]
h	*Me*	O*Me*	(*R*)–*Ph*CH(*Me*)	15	95	[12]
i	*Me*	O*Et*	*Ph*	50	95	[19]
j	*Me*	O*Bn*	*Ph*	60	90	[34]
k	*Me*	O*Et*	4-*Me*–C_6H_4	40	94	[12]
l	*Me*	O*Me*	2-*Me*–C_6H_4	90	91	[12]
m	*Me*	O*Me*	2,6-Et_2–C_6H_3	360	75	[11]
n	*Me*	O*Et*	4-O*Me*–C_6H_4	40	95	[25]
o	*Me*	O*Et*	4-Cl–C_6H_4	480	80	[12]
p	*Me*	*Me*	$CH_3(CH_2)_3$	20	92	[12]
q	*Me*	*Me*	$H_2NCH_2CH_2CH_2$	15	95[b]	[11]
r	*Me*	*Me*	$CH_2{=}CHCH_2$	15	96	[15]
s	*Me*	*Me*	*Ph*	10	92	[15]
t	*Me*	*Me*	4-*Me*–C_6H_4	10	95	[25]
u	*Me*	*Me*	2-*Me*–C_6H_4	15	90	[25]
v	*Me*	*Me*	4-O*Me*–C_6H_4	10	91	[15]
w	*Me*	*Me*	2-O*Et*–C_6H_4	45	90	[11]
x	*Me*	*Me*	4-Cl–C_6H_4	300	80	[25]
y	*Me*	*Ph*	*Ph*	50	85	[15]
z	*Me*	*Ph*	2-O*Et*–C_6H_4	80	80	[25]

[a] Yield refer to pure, isolated products; [b] Propane-1,3-diamine:methyl acetoacetate molar ratio = 1:2

responding β-enaminones or β-enamino esters in high yields in short time. We have also observed delicate electron effects for aromatic amine. Aniline with electron-rich groups (Table 1, entries **2k**, **2n**, **2t**, and **2v**) reacted rapidly, while substitution ivolving electron-withdrawing groups (Table 1, entries **2o** and **2x**) on the benzene ring decreased the reactivity requiring longer reaction times. It was also found that the substituted groups (**2l**, **2m**, **2w**, and **2z**) on the ortho position in the anilines influenced the reaction rates. Moreover, the optically active (*R*)-(+)-α-methyl benzyl amine (**2h**) was converted into the corresponding 3-aminopropenoates without any racemization or inversion confirmed by measuring its optical rotation. When 1,3-diaminopropane (**2q**) was used as an amine, two equivalents of acetylacetone were used and the product was formed with two enaminone groups. It should be pointed out that 1,3-diketones with two different substituents, such as 1-benzoylacetone, reacted with amines in a regioselective amination of the aliphatic carbonyl group (**2y** and **2z**).

The products with (*Z*)-configuration were favored over the (*E*)-isomers. It is postulated that the formation of intramolecular hydrogen bonding could be responsible for the observed shift towards the (*Z*)-isomer [33].

In conclusion, $Cu(NO_3)_2 \cdot 3H_2O$ was found to be an efficient catalyst in the reaction of 1,3-dicarbonylic compounds and amines to afford 3-aminopropenones and 3-aminopropenoates. The main advantages of this method are mild, clean, and solvent-free reaction conditions, good to excellent yields, short reaction times, and an environmentally begin reagent.

Experimental

Melting points were measured on X-4 apparatus. IR spectra were obtained on a Perkin Elmer 793 instrument. ^{1}H NMR spectra were recorded as $CDCl_3$ solutions on a Bruker spectrometer at 300 MHz using *TMS* as internal standard. Elemental analyses were performed on a PE 2400 CHNS/O Analyzer and their results agreed favourably with the calculated values.

*General procedure for the synthesis of 3-aminopropenones and 3-aminopropenoates (**3**)*

To the mixture of 10 mmol 1,3-dicarbonylic compound and 10 mmol amine, 1 mmol $Cu(NO_3)_2 \cdot 3H_2O$ was added and stirred vigorously at room temperature until the disappearance of the starting amine. When the reaction was complete, 20 cm^3 of ethyl acetate was added and washed with brine (2×10 cm^3). The combined organic layer was dried ($MgSO_4$) and concentrated under vacuum. The residue was subjected to column chromatography over alumina using ethyl acetate (10%) in *n*-hexane to obtain the pure product. All compounds prepared proved to be identical with those already reported (Table 1) with respect to their spectroscopic properties.

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