

Cyanuric Chloride Catalysed Rapid Conversion of β -Ketoesters into β -Enaminoesters under Mild and Solvent-Free Conditions

V.T. Kamble*, N.S. Joshi and S.T. Atkore

Organic Chemistry Research Laboratory, School of Chemical Sciences, Swami Ramanand Teerth Marathwada University, Nanded-431606, Maharashtra, India

(Received 27 July 2009, Accepted 29 October 2009)

Cyanuric chloride is shown to be an extremely efficient catalyst for the synthesis of β -enaminoesters from β -ketoesters under solvent-free conditions by grinding in a mortar with pestle at 25 °C. A short reaction time, an inexpensive and easily available catalyst, mild reaction conditions and excellent yields of the products are attractive features of this methodology.

Keywords: Amines, β -Enaminoesters, β -Ketoesters, Cyanuric chloride

INTRODUCTION

β -Enamino acid derivatives, particularly β -enaminoesters are important and versatile building blocks in organic synthesis [1] for example in the synthesis of biologically active compounds such as β -amino acids [2a], γ -aminols (3-hydroxy amines) [2b], alkaloids [3], peptides [4] and heterocycles [5]. In particular, cyclic β -enamino esters have been used for the synthesis of many natural products such as pyrrolizidines, indolizidines, quinolizidines and other alkaloids [1c-d].

Various methods have been reported for the preparation of β -enaminoesters, including addition of an ester or amide enolate to a nitrile [6], tosyl imines [7] and imidoyl halides [8] and via addition of enamines [9], or ketimines [10] to activated carboxylic acid derivatives. These compounds can also be successfully obtained by direct condensation of β -ketoesters with amines [11]. However, long reaction times, low chemical yields, drastic reaction conditions and a lack of general applicability are the limitations associated with most

of the reported methods. Recently $Zr(ClO_4)_2 \cdot 6H_2O$ has been reported to convert β -ketoesters into β -enaminoesters within 3-30 h. However, this methodology required $MgSO_4$ (30 mol%) as an additive to obtain the best results [12]. Consequently, there is a scope for the development of general, mild and efficient methodology for the synthesis of β -enaminoesters.

Organic chemists continue to explore novel synthetic methods involving new reagents and catalysts to carry chemical transformations. One of these novel synthetic methods is to carry out reactions on the surface of solids or solid supported reagents. Organic reactions were found to occur efficiently and selectively in solid state [13]. Since solid surfaces have properties different than that of the solution or gas phase, totally new chemistry may occur. Even in the absence of new chemistry, a surface reaction may be more desirable than a solution counterpart, because the reaction is more convenient to run, or a high yield of product is attained. Solid state synthetic organic chemistry has some advantages such as (i) easy isolation of products (ii) high yields of products and suppression of by-product formation (iii) improved selectivity of catalyst. For these reasons, solid state synthetic organic chemistry is a rapidly growing field of study.

*Corresponding author. E-mail: vtgd@rediffmail.com

EXPERIMENTAL

The ^1H NMR spectra were recorded in CDCl_3 at 300 MHz using TMS as internal standard. IR spectra were recorded using KBr pellets for solids and neat for liquid samples. Column chromatography was performed using silica gel (100-200 Mesh). Chemical shifts are given in ppm with respect to internal TMS and J values are quoted in Hz.

General Procedure

The amine (1.5 mmol), β -ketoester (1 mmol) and a cyanuric chloride (2 mol%) were ground together in a mortar with a pestle for the specified time. After completion of the reaction (TLC), water was added and the product was extracted with diethyl ether. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel 100-120 mesh, petroleum ether:ethyl acetate = 9:1).

Spectroscopic Data of Compounds

3a. IR: $\nu = 1115, 1370, 1609, 1654, 3320 \text{ cm}^{-1}$; ^1H NMR: $\delta = 1.21$ (d, $J = 6.5$ Hz, 6H), 1.24 (t, $J = 7.0$ Hz, 3H), 1.94 (s, 3H), 3.6 (m, 1H), 4.08 (q, $J = 7.0$ Hz, 2H), 4.39 (s, 1H), 8.49 (br, s, 1H); Mass: m/z : 171 (M^+).

3b. IR: $\nu = 1249, 1577, 1606, 3312 \text{ cm}^{-1}$; ^1H NMR: $\delta = 1.18$ (t, $J = 6.9$ Hz, 3H), 1.27 (m, 10H), 1.35 (m, 1H), 1.95 (s, 3H), 4.02 (q, $J = 6.9$ Hz, 2H), 4.91 (s, 1H), 11.0 (br, s, 1H); Mass: m/z : 211 (M^+).

3c. IR: $\nu = 1492, 1599, 1655, 2926, 3264 \text{ cm}^{-1}$; ^1H NMR: $\delta = 1.26$ (t, $J = 7.1$ Hz, 3H), 1.96 (s, 3H), 3.70 (q, $J = 7.1$ Hz, 2H), 4.67 (s, 1H), 6.85-7.21 (m, 5H), 10.33 (br, s, 1H); Mass: m/z : 205 (M^+).

3d. IR: $\nu = 1150, 1720, 3300 \text{ cm}^{-1}$; ^1H NMR: $\delta = 1.28$ (t, $J = 7.2$ Hz, 3H), 2.00 (s, 3H), 3.94 (q, $J = 7.2$ Hz, 2H), 4.41 (d, $J = 6.6$ Hz, 2H), 5.14 (s, 1H), 7.30-7.42 (m, 5H), 11.63 (t, $J = 6.6$ Hz, 1H); Mass: m/z : 219 (M^+).

3e. IR: $\nu = 1135, 1320, 1480, 1580, 1615, 2950, 3210 \text{ cm}^{-1}$; ^1H NMR: $\delta = 1.25$ (t, $J = 7.2$ Hz, 3H), 1.91 (s, 3H), 2.36 (s, 3H), 4.08 (q, $J = 7.2$ Hz, 2H), 4.50 (s, 1H), 7.20 (d, $J = 7.0$ Hz, 2H), 7.25 (d, $J = 7.0$ Hz, 2H), 8.95 (br, s, 1H); Mass: m/z : 219 (M^+).

3f. IR: $\nu = 1105, 1321, 1470, 1585, 1605, 3045 \text{ cm}^{-1}$; ^1H NMR: $\delta = 1.24$ (t, $J = 6.9$ Hz, 3H), 1.90 (s, 3H), 3.75 (s,

3H), 4.06 (q, $J = 6.9$ Hz, 2H), 4.49 (s, 1H), 7.10 (d, $J = 7.1$ Hz, 2H), 7.35 (d, $J = 7.0$ Hz, 2H), 9.10 (br, s, 1H); Mass: m/z : 235 (M^+).

3g. IR: $\nu = 1110, 1325, 1575, 1607, 3020 \text{ cm}^{-1}$; ^1H NMR: $\delta = 1.22$ (t, $J = 7.0$ Hz, 3H), 1.89 (s, 3H), 4.10 (q, $J = 7.0$ Hz, 2H), 4.51 (s, 1H), 7.21 (d, $J = 7.2$ Hz, 2H), 7.25 (d, $J = 7.0$ Hz, 2H), 9.10 (br, s, 1H); Mass: m/z : 239 (M^+).

3h. IR: $\nu = 1125, 1330, 1570, 1625, 3010 \text{ cm}^{-1}$; ^1H NMR: $\delta = 1.25$ (t, $J = 7.0$ Hz, 3H), 1.92 (s, 3H), 4.12 (q, $J = 7.0$ Hz, 2H), 4.55 (s, 1H), 7.21-7.55 (m, 4H), 9.15 (br, s, 1H); Mass: m/z : 239 (M^+).

3i. IR: $\nu = 1120, 1350, 1595, 1609, 2995 \text{ cm}^{-1}$; ^1H NMR: $\delta = 1.25$ (t, $J = 7.1$ Hz, 3H), 1.90 (s, 3H), 4.50 (s, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 7.22 (d, $J = 7.1$ Hz, 2H), 7.24 (d, $J = 7.0$ Hz, 2H), 8.75 (br, s, 1H); Mass: m/z : 250 (M^+).

3j. IR: $\nu = 1150, 1745, 3315, \text{ cm}^{-1}$; ^1H NMR: 1.25 (t, $J = 7.1$ Hz, 3H), 2.52 (m, 4H), 3.15 (t, $J = 7.3$ Hz, 2H), 4.01 (q, $J = 6.6$ Hz, 2H), 6.90-7.15 (m, 5H), 11.05 (br, s, 1H); Mass: m/z : 231 (M^+).

3k. IR: $\nu = 1115, 1645, 3295 \text{ cm}^{-1}$; ^1H NMR: 1.98 (t, $J = 7.0$ Hz, 3H), 4.03 (q, 2H), 4.50 (s, 1H), 6.90-7.65 (m, 10H), 11.02 (br, s, 1H); Mass: m/z : 255 (M^+).

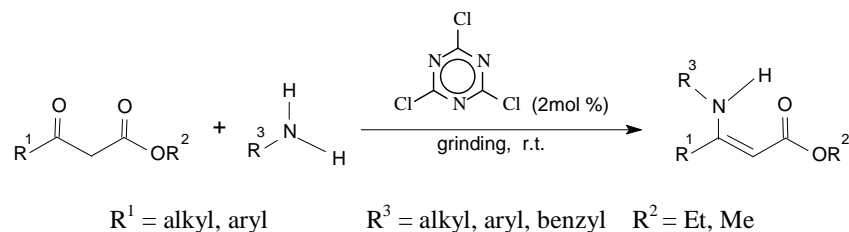
3l. IR: $\nu = 1152, 1740, 3310, \text{ cm}^{-1}$; ^1H NMR: 0.94 (t, $J = 7.2$ Hz, 3H), 1.28 (t, $J = 7.1$ Hz, 3H), 1.30 (m, 2H), 1.52 (m, 2H), 1.82 (m, 2H), 2.50 (m, 4H), 3.20 (t, $J = 7.3$ Hz, 2H), 3.94 (q, $J = 6.6$ Hz, 2H), 11.24 (br, s, 1H); Mass: m/z (%) = 211 (M^+).

RESULTS AND DISCUSSION

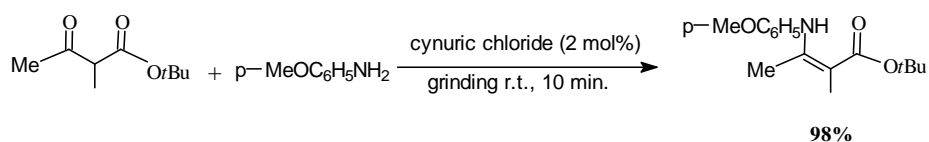
Over the last few years, there has been a considerable growth in interest in the use of cyanuric chloride or its derivatives in organic synthesis [14]. In this communication, we wish to report cyanuric chloride as a highly efficient catalyst for the synthesis of β -enaminoesters under solvent-free and mild conditions (Scheme 1).

Initially, a systematic study was carried out for the evaluation of cyanuric chloride as a promoter for the reaction of aniline and ethylacetoacetate under various conditions (Table 1). Reaction between ethyl acetoacetate and aniline, in the absence of a catalyst produced only a trace amount of product after 20 h (entry 1) and inferior results were obtained in the presence of solvents (Table 1, entries 2-5). Next we

Cyanuric Chloride Catalysed Rapid Conversion of β -Ketoesters



Scheme 1



Scheme 2

Table 1. Reaction between Aniline and Ethyl Acetoacetates under Various Conditions

Entry	Solvent	Catalyst (mol%)	Time min/[h]	Yield (%)
1	neat	–	[20]	15
2	CH ₂ Cl ₂	2.0	45	65
3	THF	2.0	60	70
4	CH ₃ CN	2.0	45	60
5	CHCl ₃	2.0	45	65
6	neat	0.5	[1]	50
7	neat	1.0	[1]	65
8	neat	1.5	[1]	85
9	neat	2	10	98
10	neat	2.5	10	98
11	neat	3.5	10	98

optimized the quantity of cyanuric chloride at room temperature under solvent-free conditions for this reaction (Table 1, entries 6-11) and it was observed that with just 2 mol% of cyanuric chloride, the reaction was complete in 10 min and an almost quantitative yield of the corresponding β -enaminoester (98%) was obtained (entry 9). It is important to note that when the amount of cyanuric chloride was increased,

there was no improvement in the yield or decrease in reaction time (entries 10-11). With less than 2 mol% of cyanuric chloride, the reaction was incomplete and resulted in a low yield of the product (50-85%) even after grinding the reaction mixture for 1 h.

The results presented in Table 2 showed that the methodology is successful for primary, benzylic and aromatic amines. β -Ketoesters such as methyl and ethyl acetoacetates were efficiently transformed into the corresponding β -enaminoesters. Excellent yields and short reaction times are noteworthy advantages of the present method over the reported ones. More important is the requirement only 2 mol% of cyanuric chloride for all the examples selected for the present study. It was reported [12] that this reaction suffers from steric hindrance in the case of β -ketoesters carrying a substituent different from hydrogen in the α -position, or with a bulky amine, therefore requiring long reaction times and drastic reaction conditions.

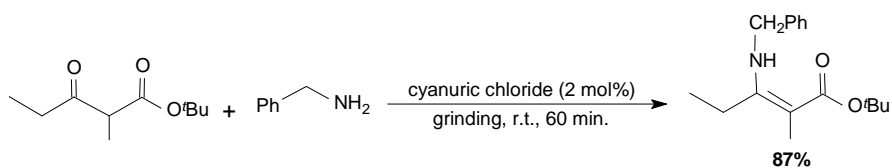
However the present methodology (Scheme 2 and Scheme 3) was found much superior in terms of reaction times compared to the reported method [12] (48 h and 26 h). High yields of products were obtained even in the case of cyclic and aromatic β -ketoesters (Table 2, entries, j, k and l). We also assessed our methodology with a β -diketone (Scheme 4).

The condensation of pentane-2,4-dione with aniline proceeded smoothly in an almost quantitative yield in 10 min

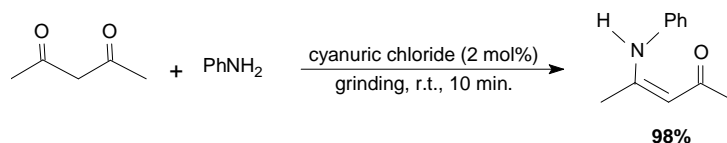
Table 2. Cyanuric Chloride Catalyzed Synthesis of β -Enaminoesters from β -Ketoesters and Amines

Entry	Amine	β -Ketoester R=Me/Et	Product	Time (min)	Yield ^{a,b} (%)
a				10	98
				10	97
b				10	98
				10	97
c				10	98
				10	98
d				15	96
				15	97
e				45	91
				50	94
f				60	90
				60	91
g				30	90
				30	91
h				40	89
				35	88
i				45	80
				50	81
j				10	90
k				10	96
l				10	98

^aYields of pure isolated products. ^bProducts were characterized by IR, ¹H NMR and Mass spectroscopy.

*Scheme 3*

Cyanuric Chloride Catalysed Rapid Conversion of β -Ketoesters



Scheme 4

whereas the reported method [12] took a longer reaction time (4 h) for the same conversion.

In conclusion we have developed a novel, mild and highly efficient protocol for the synthesis of β -enaminoesters under solvent-free conditions. The use of an inexpensive and easily available catalyst, experimental simplicity, a simple work-up procedure, and rapid reaction are the important attractive features of this method.

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