Enamination of β-Dicarbonyl Compounds with Amines

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Enamination of a wide variety of primary amines was successfully described with excellent chemoselectivity in the presence of catalytic amounts of β-cyclodextrin in water under mild conditions. Aliphatic amines also reacted efficiently to produce the corresponding enaminones.

Keywords: Enaminones; β-Dicarbonyl compounds; β-Cyclodextrin; Water.

INTRODUCTION

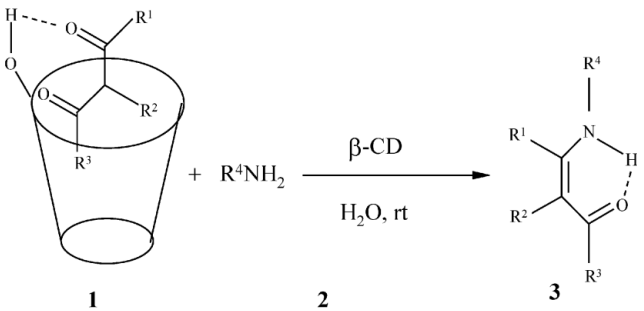
β-Enaminones are of pharmacological relevance[1] and represent useful synthetic building blocks for the synthesis of aminoacids,[2] peptides,[3] alkaloids[4] and heterocyclic compounds.[5] In spite of their importance in organic synthesis as intermediates and in pharmaceuticals, little attention has been paid to synthesis of these compounds. The traditional approach to the preparation of β-enaminones involves the direct condensation of β-dicarbonyl compounds with amines at reflux in an aromatic solvent with azeotropic removal of water.[6] Several catalysts like Al_2O_3,[7] clay K-10/US,[8] $NaAuClO_4$,[9] silica/MW[10] and $Bi(TFA)_3$/TBAB[11] have been reported to effect this synthesis. In addition, the reactions of β-dicarbonyl compounds with amines have been carried out in water[12] and solvent-free conditions.[13] However, some of these methods have limited synthetic scope due to the use of toxic solvents, long reaction times, unsatisfactory yields or low selectivity. Thus the development of a simple and high yielding method for the preparation of β-enaminones under mild conditions is desirable.

β-Cyclodextrins (β-CD) are important natural host compounds due to their encapsulating ability of drugs and bioactive substances.[14] In addition, they have lipophilic cavities, which bind substrates and catalyze chemical reactions selectively. In fact, a substrate hidden inside the β-CD cavity is less inclined to undergo transformation than a free one. It has been shown that in many β-CD catalysis examples,[15] formation of inclusion compounds may accelerate the unexpected reaction. They catalyze reactions by reversible formation of host-guest complexes by noncovalent bonding as seen in enzymes.[16] The size, shape and lipophilicity of the guest molecule have an affect on complexation. Rao and co-workers[17] reported that ring opening of epoxides and aziridines, conversion of oxiranes into thiiranes, allylation of aldehydes, synthesis of thiazoles, oxidation of THP ethers, and sulfides can be catalyzed by β-CD. Oxidation of alcohols with β-CD was also reported.[18]

RESULTS AND DISCUSSION

In this study, different types of primary amines were subjected to reaction with β-dicarbonyl compounds to prepare β-enaminones by β-CD in water (Scheme I).

Scheme I



1 **2** **3**

The results are summarized in Table 1. The reactions were completed at room temperature within 5-90 min. The products were obtained in excellent yields and chemo-selectivity to afford *Z*-β-enaminones, confirmed by ^{1}H NMR spectrum of the crude products (δ = 7.5-12.8 for NH).

Probably, the reaction proceeds through the activa-

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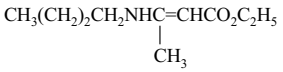
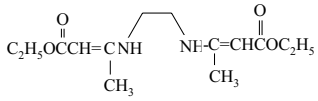
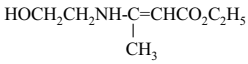
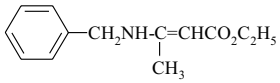
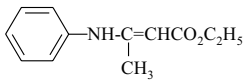
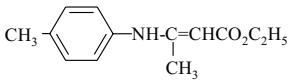
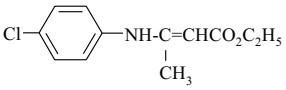
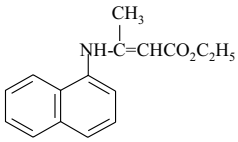
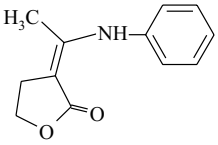
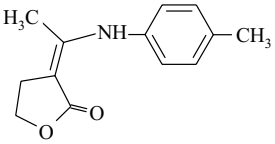
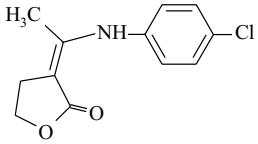
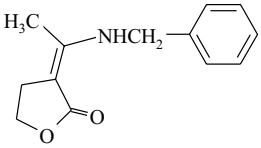
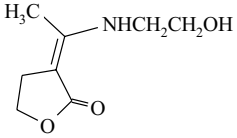
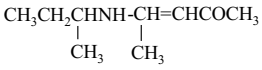
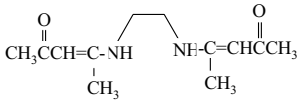
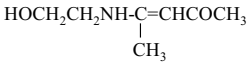
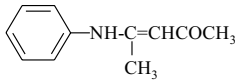
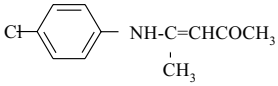
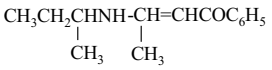
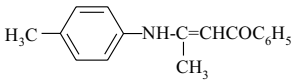
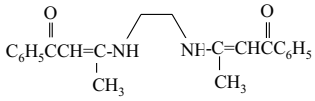
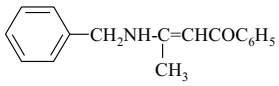
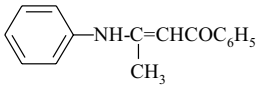
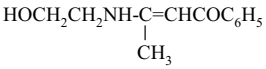
Table 1. Enamination reaction catalyzed with β-CD in water at room temperature

Entry	R^1	R^2	R^3	R^4	Time (min)	Yield (%)	Product
1[19]	CH_3	H	OC_2H_5	$CH_3(CH_2)_2CH_2$	5	99	
2[12]	CH_3	H	OC_2H_5	$H_2NCH_2CH_2$	5	99	
3[12]	CH_3	H	OC_2H_5	$HOCH_2CH_2$	5	95	
4[12]	CH_3	H	OC_2H_5	$C_6H_5CH_2$	8	97	
5[20]	CH_3	H	OC_2H_5	C_6H_5	10	85	
6[19]	CH_3	H	OC_2H_5	4-$CH_3C_6H_4$	13	90	
7[21]	CH_3	H	OC_2H_5	4-ClC_6H_4	20	70	
8[22]	CH_3	H	OC_2H_5	α-naphthyl	15	80	
9[19]	CH_3	CH_2CH_2R	O	C_6H_5	90	90	
10[13]	CH_3	CH_2CH_2R	O	4-$CH_3C_6H_4$	60	96	
11[23]	CH_3	CH_2CH_2R	O	4-ClC_6H_4	20	95	
12[13]	CH_3	CH_2CH_2R	O	$C_6H_5CH_2$	90	96	
13[23]	CH_3	CH_2CH_2R	O	$HOCH_2CH_2$	80	95	
14[19]	CH_3	H	CH_3	$CH_3CH_2CHCH_2$	40	91	

15[12]	CH_3	H	CH_3	$H_2NCH_2CH_2$	30	90	
16[12]	CH_3	H	CH_3	$HOCH_2CH_2$	30	90	
17[20]	CH_3	H	CH_3	C_6H_5	20	80	
18	CH_3	H	CH_3	4-ClC_6H_4	20	78	
19[12]	CH_3	H	Ph	$CH_3CH_2CHCH_2$	35	90	
20[23]	CH_3	H	Ph	4-$CH_3C_6H_4$	35	92	
21[23]	CH_3	H	Ph	$H_2NCH_2CH_2$	30	92	
22[24]	CH_3	H	Ph	$C_6H_5CH_2$	15	82	
23[19]	CH_3	H	Ph	C_6H_5	20	75	
24[12]	CH_3	H	Ph	$HOCH_2CH_2$	30	88	

[a] All products were identified by comparison of their physical or spectral data with those reported in the literature.
[b] Isolated yields.

tion of the carbonyl group of the acetyl part by complexation with β-CD followed by nucleophilic addition of amines to the carbonyl group and subsequently the enaminone formation.

Although it was reported that the synthesis of β-enaminones is limited to soluble amines in water, we achieved that in the presence of β-CD; water insoluble amines were also converted efficiently to the corresponding enaminones in high yields. However, anilines with strong electron withdrawing groups such as 4-nitroaniline did not give any product under the present reaction conditions. Aliphatic amines also reacted efficiently to produce the corresponding enaminones. This method was successfully applied to linear (Table 1, entries 1-8), and cyclic β-ketoesters (Table 1, entries 9-13), and β-diketones (Table 1, entries 14-24). The use of β-CD showed rate enhancements, high yields and short reaction times. It was found that when one or two equivalents of β-dicarbonyl compound reacted with one equivalent of ethylene diamine, the diamination product was produced as a sole product and no monoamination product was observed (Scheme II).

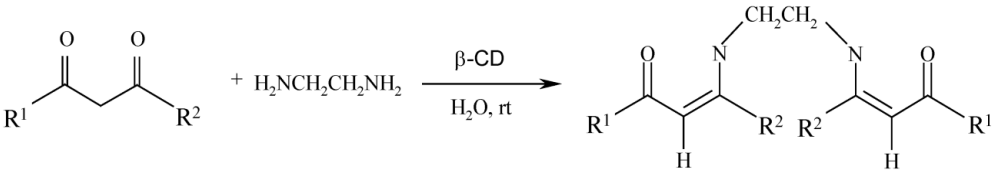
However, the reaction of one equivalent of β-dicarbonyl compound with one equivalent of ethylene diamine was not complete.

In conclusion, β-CD is a highly efficient catalyst for enamination of β-dicarbonyl compounds. Short reaction times, mild reaction conditions, high chemo-selectivity and high yield products are noteworthy advantages of this procedure. Water insoluble amines were also converted efficiently to the corresponding enaminones in high yields. Moreover, stability and non-toxicity of the catalyst are the other merits of this method.

EXPERIMENTAL SECTION

Products are known compounds and were character-

Scheme II



$R^1 = CH_3$, Ph, C_2H_5; $R^2 = CH_3$

ized by comparison of their spectral data (^{1}H NMR, IR) or melting points with those reported in the literature. Monitoring of the reactions was accomplished by TLC on precoated silica gel 60 F_{254} sheets. All yields refer to isolated products.

General experimental procedure for synthesis of enaminones

In a 25 mL round bottomed flask β-cyclodextrin (0.5 mmol, 568 mg) in water (4 mL) was prepared. The mixture was stirred at 50 °C for 10 min. Then β-dicarbonyl compound (1 mmol) and primary amine (1 mmol) were added to the solution. The mixture was stirred at room temperature for an appropriate time as indicated in Table 1. The progress of the reaction was monitored with TLC. On completion of the reaction, water was added and the product was extracted with dichloromethane (3 × 10 mL). The organic layer was dried and the solvent was evaporated. The resulting crude material was purified on a silica gel plate with n-heptane/ethyl acetate: 4/1 to afford the pure β-enaminones in 70-99% yields.

Spectroscopic data for entries **7** and **18**. **Entry 7**: Liquid, ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.30 (t, J = 7.4 Hz, 3H), 2.05 (s, 3H), 4.12 (q, J = 7.4 Hz, 2H), 4.75 (s, 1H), 7.08 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 10.38 (br, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 14.9, 20.8, 60.4, 88.5, 118.2, 119.4, 127.5, 133.2, 139.1, 158.8. IR (KBr) ν: 3350, 2985, 1620, 1490, 1425, 1260, 1155, 820 cm^{-1}. MS: *m/z* = 239 [M+], 167, 149, 111, 88, 71, 57, 45. Anal. Calcd for $C_{12}H_{14}NO_2Cl$: C, 60.24; H, 5.90; N, 5.85. Found: C, 60.50; H, 5.93; N, 5.71. **Entry 18**: Mp 59-60 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.97 (s, 3H), 2.17 (s, 3H), 5.2 (s, 1H), 7.12 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 8.3 Hz, 2H), 12.3 (br, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 20.6, 29.8, 98.8, 118.7, 126.5, 132.7, 139.2, 160.2, 197.9. IR (KBr) ν: 3382, 2980, 1606, 1462, 1264, 1180, 807 cm^{-1}. MS: *m/z* = 209 [M$^+$], 194, 152, 127, 111, 65, 43. Anal. Calcd for $C_{11}H_{12}NOCl$: C, 63.15; H, 5.30; N, 6.69. Found: C, 63.37; H, 5.39; N, 6.51.

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