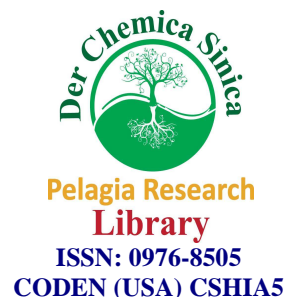




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Grinding induced solvent free, catalyst free synthesis of β -enaminones and β -enamino esters

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ABSTRACT

A simple, efficient, environmentally benign, catalyst free and solvent free protocol has been developed for the synthesis of β -enaminones and β -enamino esters by the reaction of amines with various 1, 3-dicarbonyl compounds under mild conditions. It constitutes a green approach which is a valuable addition to the existing methods for the synthesis of these compounds.

Keywords: Catalyst free, Solvent free, Grinding, β -enaminones and β -enamino Esters

INTRODUCTION

β -Enaminones and β -enamino esters are the valuable intermediates in synthetic organic chemistry and pharmaceutical chemistry; consequently have received attention of chemists. In fact these are utilized as synthons for the synthesis of various heterocyclic compounds. Literature survey reveals the availability of numerous catalysts and methods for the synthesis of these compounds. The most commonly exploited route for the synthesis of these compounds is the acid catalyzed reaction of amine with 1,3-dicarbonyl compound using various catalysts such as $P_2O_5 \cdot SiO_2$ [1], silica sulfuric acid [2], CAN [3], trichloroacetic acid [4], $NaHSiO_4/SiO_2$ [5], silica-supported $LiHSO_4$ [6], $[VO(acac)_2]$ [7], $Ga(OTf)_3$ [8], silica supported $Fe(HSO_4)_3$ [9] etc. However, many of the existing methods suffer from one or more major/minor drawbacks such as tedious work-up procedures, long reaction time, low yields, use of hazardous organic solvents or catalysts etc. Hence there is need to develop an environmentally benign approach for the synthesis of these compounds.

In recent years grinding induced solvent free and catalyst free organic synthesis has attracted the attention of chemists in order to follow the principles of green chemistry [10]. In the present work we wish to report grinding induced solvent free, catalyst free synthesis of β -enaminones and β -enamino esters by the reaction of amines with various 1,3-dicarbonyl compounds such as dimedone, acetyl acetone or ethyl acetoacetate under mild conditions (Scheme 1).

MATERIALS AND METHODS

All the chemicals were purchased from SD fine or Spectrochem chemical companies and were used without further purification. Progress of the reaction was monitored by Thin Layer Chromatography on silica gel precoated on

aluminium plates using 20 % ethyl acetate: n-hexane as the mobile phase. Melting points of the products were recorded in capillaries open at one end and were uncorrected. The compounds were confirmed by comparison of their physical constants with the literature values and spectral data.

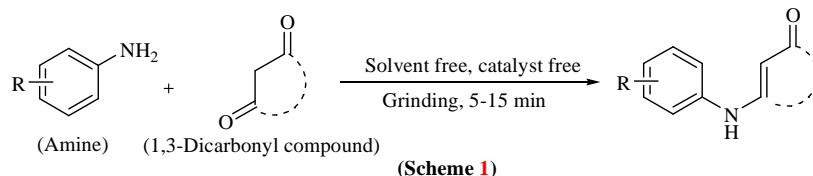


Table 1: Grinding induced solvent free, catalyst free synthesis of β -enaminones and β -enamino esters

Sr. No.	R	1,3-Dicarbonyl	Product	Time (min)	Yield (%) [@]	M. P. (°C) [Ref]
1	H			8	88	182-184 [2]
2	4-OCH ₃			5	92	191-193 [2]
3	C ₆ H ₅ CH ₂			7	85	125-127 [1]
4	4-Cl			10	87	190-192 [4]
5	4-Br			10	85	220-221 [2]
6	3-NO ₂			15	80	164-166 [4]
7	4-OCH ₃			10	90	68-70 [3]
8	4-CH ₃			12	86	65-66 [2]
9	4-OCH ₃			10	82	45-47 [2]
10	4-Br			15	85	52-54 [2]

[@] Yields were isolated after recrystallization from ethanol

General procedure for the synthesis of β -enaminones and β -enamino esters: In a typical procedure a mixture of aniline and 1, 3-dicarbonyl compound was ground in a mortar with the help of a pestle for appropriate time as specified in **Table 1**. The progress of reaction was monitored by TLC in ethyl acetate: n-hexane (20%). After

completion of the reaction as indicated by TLC; the reaction mass was collected and purified by recrystallization from ethanol.

The spectral data of the representative compounds is mentioned below:

5,5-Dimethyl-3-(phenylamino)cyclohex-2-enone (Table 1, entry 1): $^1\text{H NMR}$ (CDCl_3) δ ppm 1.07 (s, 6H, CH_3), 2.18 (s, 2H, CH_2), 2.30 (s, 2H, CH_2), 5.54 (s, 1H, CH), 7.18 (s, 1H, NH), 7.25-7.35 (m, 5H, ArH); IR (KBr): cm^{-1} 3232, 3061, 2960, 1598, 1569, 1523, 1492, 1445, 1370, 1149, 1125.

(Z)-Ethyl 3-(4-bromophenylamino)but-2-enoate (Table 1, entry 10): $^1\text{H NMR}$ (CDCl_3) δ ppm 1.27 (t, $J = 7.00$ Hz, 3H), 1.95 (s, 3H), 4.18 (q, $J = 7.2$ Hz, 2H), 4.70 (s, 1H), 6.93 (d, $J = 8.2$ Hz, 2H), 7.40 (d, $J = 8.2$ Hz, 2H), 10.35 (br s, 1H, NH) IR (KBr) cm^{-1} 3271, 2973, 1648, 1608, 1580, 1478, 1381, 1258, 1165, 1059, 852, 786, 545 cm^{-1} .

RESULTS AND DISCUSSION

To make the reaction catalyst free; initially we tried the reaction of aniline with dimedone using polar solvents such as methanol, ethanol, 2-propanol, acetonitrile etc. under catalyst free conditions at room temperature. However these reactions required longer time and in several cases no product formation was observed. Then we switched over to the reaction using solvent under grinding induced conditions. Acetonitrile under grinding induced conditions was found to be better rather than the use of other polar solvents but the reaction was not complete even after grinding the reactants for more than 30 minutes.

However when the reaction was carried out by grinding the equimolar mixture of aniline and dimedone under catalyst free conditions; the reaction was completed within 8 minutes. We extended this grinding induced solvent free and catalyst free protocol to various amines and 1, 3-dicarbonyl compounds such as acetyl acetone and ethyl acetoacetate. Electron donating amines were found to react rapidly as compared to amines possessing electron withdrawing groups. Among the 1, 3-dicarbonyl compounds; dimedone was more reactive affording the corresponding products in better yields than ethyl acetoacetate and acetyl acetone.

After completion of the reaction; a yellow syrupy liquid was observed which on solidification at room temperature afforded solid product. The product thus formed was clean on TLC. It was further purified by recrystallization from ethanol.

Table 2 shows comparative study of the present method for the synthesis of β -enaminones and β -enamino esters with some of the literature methods for the synthesis of these compounds.

Table 2: Comparative study of present protocol with some literature methods for the synthesis of β -enaminones and β -enamino esters

Entry	Conditions	Time	Yield (%)	[Reference]
1	SSA, 80 °C, Solvent free	3-35 min	82-96	[2]
2	CAN (1 mol%), r.t., Catalyst free	10-360 min	80-96	[3]
3	$\text{LiHSO}_4/\text{SiO}_2$ (20 mol%), 80 °C, Solvent-free	3-40 min	84-95	[6]
4	$\text{VO}(\text{acac})_2$ (10 mol %) r.t., Solvent-free	10-90 min	76-93	[7]
5	$\text{Ga}(\text{OTf})_3$ (5 mol%), 30 °C, Solvent free	30-50 min	65-95	[8]
6	Solvent free, Catalyst free, Grinding	5-15 min	80-92	Present work

CONCLUSION

In summary; the present method involves catalyst free and solvent free synthesis of β -enaminones and β -enamino esters using grinding technique; making it a green and environmentally benign approach for the synthesis of these compounds.

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