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# Highly efficient, mild and chemo- and stereoselective synthesis of enaminones and enamino esters using silica supported perchloric acid under solvent-free conditions☆

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**Abstract**

Silica supported perchloric acid ($HClO_4{\cdot}SiO_2$) has been utilized as a heterogeneous recyclable catalyst for a highly efficient and chemo- and stereoselective conversion of β-dicarbonyl compounds by treatment with amines at room temperature into β-enaminones and β-enamino esters under solvent-free conditions.


*Keywords:* β-Dicarbonyl compound; β-Enaminone; β-Enamino ester; $HClO_4{\cdot}SiO_2$; Recyclable heterogeneous catalyst; Solvent-free conditions

## 1. Introduction

β-Enaminones and β-enamino esters are useful synthones for the synthesis of various pharmaceuticals [1] and bioactive heterocycles [2]. They have been utilized for the preparation of different important antibacterial [3a,b], anticonvulsant [3b], anti-inflamatory [3b] and antitumour agents [3b,c]. They are the intermediates for the synthesis of several aminoacids [4a–c], aminols [4b], peptides [4d] and alkaloids [4e,f]. Classically, β-enaminones are prepared by direct condensation of β-dicarbonyl compounds with amines under reflux in an aromatic solvent with azeotropic removal of water [5]. Several other improved methods for the preparation of β-enaminones and β-enamino esters have been reported to utilize $Al_2O_3$ [6a], $SiO_2$/microwaves [6b], montmorillonite K-10 [6c], $NaAuClO_4$ [6d], $Bi(TFA)_3$ [6e], $Zn(ClO_4)_2{\cdot}6H_2O$ [6f], $CeCl_3{\cdot}7H_2O$ [6g], etc. However, most of the methods suffer from certain drawbacks including long reaction times, unsatisfactory yields, low selectivity, lack of general applicability, higher temperatures, applications of non-available and costly reagents, uses of hazardous solvents and tedious experimental procedures. Thus, there is still a need to develop a suitable method for the synthesis of enaminones and enamino esters conveniently.

In continuation of our work [7] on the synthetic applications of heterogeneous catalysts we have recently observed that silica-supported perchloric acid ($HClO_4{\cdot}SiO_2$) is a highly efficient catalyst for the preparation of β-enaminones and β-enamino esters from β-dicarbonyl compounds by treatment with amines (Scheme 1).

The generality of the method has been shown by the preparation of a series of β-enaminones and β-enamino esters using various β-dicarbonyls and amines (Table 1). The conversion proceeded at room temperature and under solvent-free conditions. The reaction took place within only a few minutes to afford the product in excellent yields. As for an example, acetylacetone reacted with aniline in the presence of $HClO_4{\cdot}SiO_2$ to form the corresponding β-enaminone (entry 3a) in 14 min (yield 98%) while in the presence of $Bi(TFA)_3$ [6e], $Zn(ClO_4)_2{\cdot}6H_2O/MgSO_4$ [6f] and $CeCl_3{\cdot}7H_2O$ [6g] the reaction was reported to undergo in 1 h (yield 64%), 4 h (yield 95%) and 35 min (yield 76%), respectively. The β-dicarbonyl

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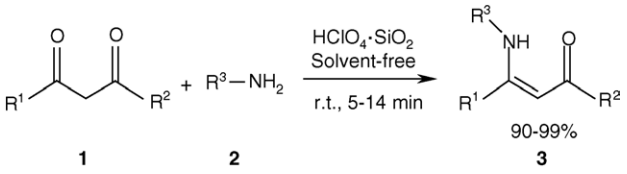



Scheme 1.

compounds included here both β-diketones (linear and cyclic) and β-ketoesters. They reacted equally with aromatic as well as aliphatic amines. Both activated and weakly activated amines afforded β-enaminones and β-enamino esters in high yields. For instance, aniline reacted with ethylacetoacetate (entry 3p) to form the product in 95% yield but earlier some methods reported only moderate yields [6e]. However, aniline with a strong electron-withdrawing group afforded low yield of the products. As for an example, 4-nitroaniline reacted with ethylacetoacetate in the presence of $HClO_4{\cdot}SiO_2$ to form the corresponding β-enamino esters in an yield of only 31%. Previously, the similar reaction carried out using $Bi(TFA)_3$ yielded no any product [6e]. When 1,2-diaminoethane was used as an amine two equivalents of β-dicarbonyl compounds were required to form the products with two enamino groups (entries 3h and 3y).

The method was found to be highly chemoselective. Amine attack only at the ketone carbonyl for both diketones and β-ketoesters. The (*Z*)-selectivity in the products derived from acyclic diketones and β-ketoesters was secured by intramolecular hydrogen bonding. In the $^1$H NMR spectra the proton of the –NH– group appeared in the region of $\delta$ 8.5–12.5. However, the β-enaminones derived from cyclic diketone, 5,5′-dimethyl-1,3-cyclohexadione, displayed the $^1$H NMR spectra having the signals for the non-hydrogen bonded proton of the –NH– group in the region of $\delta$ 4.5–6.5 and thus indicating the (*E*)-configuration. The X-ray crystallographic analyses [8] of these molecules also supported this stereostructure. The X-ray structure of one representative β-enaminone (**3i**) derived from aniline and 5,5′-dimethyl-1,3-cyclohexadione is shown in Fig. 1.

The catalyst, $HClO_4{\cdot}SiO_2$ works under solvent-free heterogeneous conditions. It can easily be prepared [9] from readily available $HClO_4$ and silica gel. It can conveniently be handled and removed from the reaction mixture. Thus the process is environmentally benign. The catalyst was recovered, activated and reused for three consecutive times with only slight variation in the yields of the products.

In conclusion, we have developed a novel and highly efficient method for the synthesis of β-enaminones and β-enamino esters by treatment of β-dicarbonyl compounds with amines in the presence of $HClO_4{\cdot}SiO_2$ as a heterogeneous catalyst. The solvent-free conditions, mildness of the conversion, simple experimental procedure, clear reaction profiles, high yields and chemo- and stereoselectivities, short reaction times and reusability of the catalyst are the noteworthy advantages of the protocol. We feel the procedure can be utilized for large-scale eco-friendly preparation of β-enaminones and β-enamino esters.

## 2. Experimental

### 2.1. General procedure

To a mixture of a dicarbonyl compound (1 mmol) and an amine (1.2 mmol) $HClO_4{\cdot}SiO_2$ (50 mg) was added. The mixture was stirred at room temperature. The reaction was monitored by TLC. After completion of the reaction mixture was diluted with EtOAc (5 ml) and filtered. The catalyst was recovered from the residue. The filtrate was concentrated and the gummy mass was subjected to column chromatography over silica gel using hexane–EtOAc (4:1) as eluent to obtain pure β-enaminone.

When ethanediamine (1.2 mmol) was used as an amine a dicarbonyl compound (2 mmol) was required and with *iso*-propylamine (2.5 mmol) a dicarbonyl compound (1 mmol) while with *iso*-butylamine (2.5 mmol) 5,5′-dimethyl-1,3-cyclohexadione (1 mmol) were reacted.

The spectral (IR, $^1$H NMR and MS) and analytical data of some representative compounds are given below.

Compound **3a**: (Viscous); IR (Neat) ($cm^{-1}$) 3209, 2924, 1597, 1570, 1278, 752; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 12.48 (brs, 1H), 7.39–7.18 (m, 2H), 7.20–7.02 (m, 3H), 5.14 (s, 1H), 2.08 (s, 3H), 2.0 (s, 3H); EIMS (*m*/*z*) 175 ($M^{\bullet+}$); Anal. Calcd

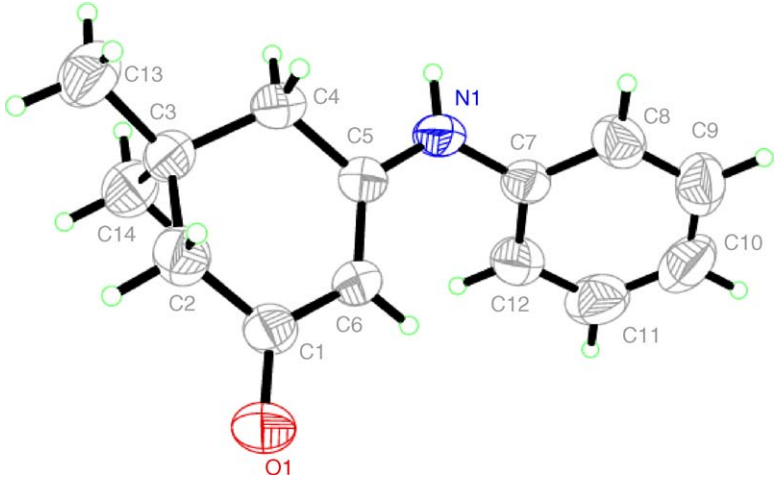



Fig. 1. X-ray structure of β-enaminone (**3i**).

Table 1
Synthesis of β-enaminones and β-enamino esters using $HClO_4{\cdot}SiO_2$ under solvent-free conditions[a]

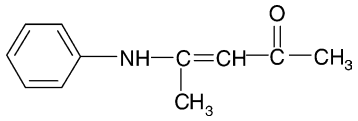
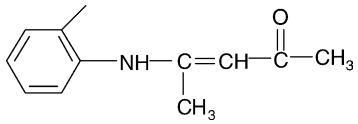
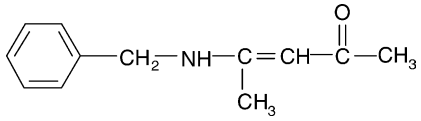
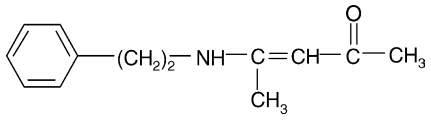
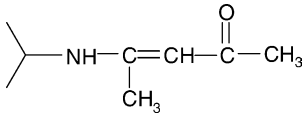
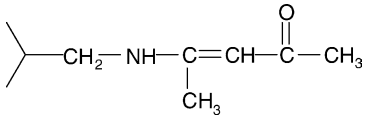
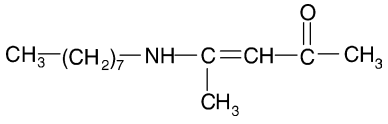
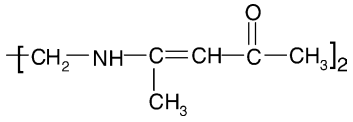
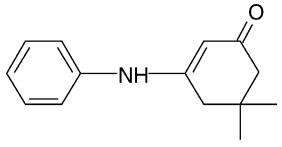
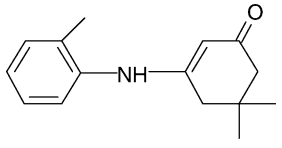
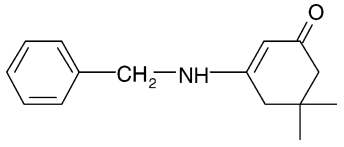
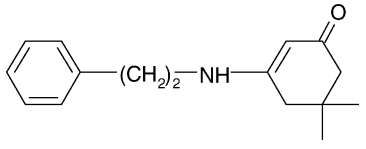
| Entry | $R^1$ | $R^2$ | $R^3$ | Time (min) | Product | Isolated yield (%) |
|---|---|---|---|---|---|---|
| a | Me | Me | Ph | 14 |  | 98 |
| b | Me | Me | *o*-Me-Ph | 14 |  | 90 |
| c | Me | Me | Ph-$CH_2$ | 12 |  | 93 |
| d | Me | Me | Ph-$(CH_2)_2$ | 10 |  | 97 |
| e | Me | Me | $(CH_3)_2CH$ | 10 |  | 99 |
| f | Me | Me | $(CH_3)_2CH$-$CH_2$ | 10 |  | 97 |
| g | Me | Me | $CH_3$-$(CH_2)_7$ | 10 |  | 98 |
| h | Me | Me | $H_2N$-$(CH_2)_2$ | 12 |  | 95 |
| i | $CH_2$-$C(CH_3)_2$-$CH_2$ | | Ph | 10 |  | 92 |
| j | $CH_2$-$C(CH_3)_2$-$CH_2$ | | *o*-Me-Ph | 10 |  | 91 |
| k | $CH_2$-$C(CH_3)_2$-$CH_2$ | | Ph-$CH_2$ | 10 |  | 96 |
| l | $CH_2$-$C(CH_3)_2$-$CH_2$ | | Ph-$(CH_2)_2$ | 8 |  | 98 |

Table 1 (*Continued*)

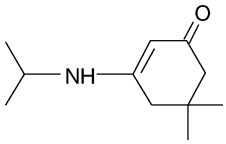
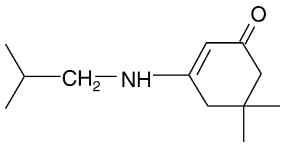
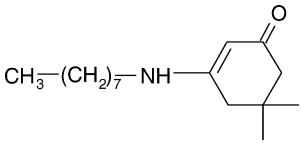
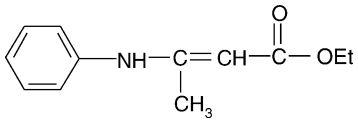
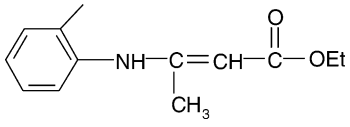
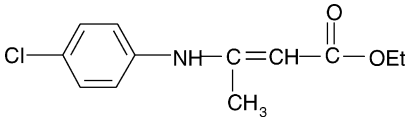
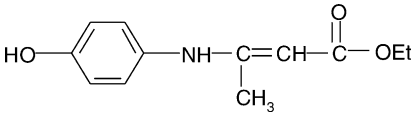
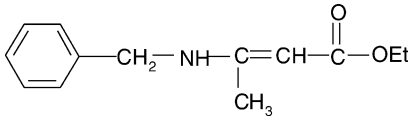
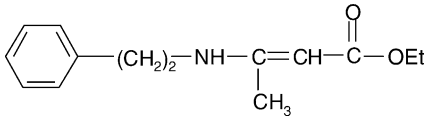
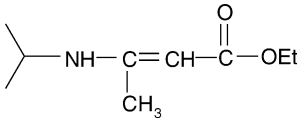
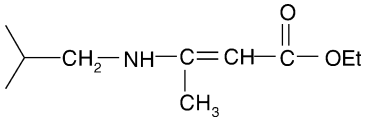
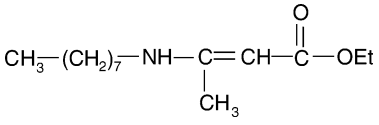
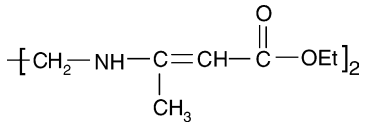
| Entry | $R^1$ | $R^2$ | $R^3$ | Time (min) | Product | Isolated yield (%) |
|---|---|---|---|---|---|---|
| m | $CH_2$-$C(CH_3)_2$-$CH_2$ | | $(CH_3)_2CH$ | 6 |  | 99 |
| n | $CH_2$-$C(CH_3)_2$-$CH_2$ | | $(CH_3)_2CH$-$CH_2$ | 6 |  | 99 |
| o | $CH_2$-$C(CH_3)_2$-$CH_2$ | | $CH_3$-$(CH_2)_7$ | 7 |  | 97 |
| p | Me | OEt | Ph | 8 |  | 95 |
| q | Me | OEt | *o*-Me-Ph | 10 |  | 93 |
| | Me | OEt | *p*-Cl-Ph | 10 |  | 94 |
| s | Me | OEt | *p*-OH-Ph | 12 |  | 92 |
| t | Me | OEt | Ph-$CH_2$ | 5 |  | 98 |
| u | Me | OEt | Ph-$(CH_2)_2$ | 5 |  | 98 |
| v | Me | OEt | $(CH_3)_2CH$ | 5 |  | 99 |
| w | Me | OEt | $(CH_3)_2CH$-$CH_2$ | 5 |  | 99 |
| x | Me | OEt | $CH_3$-$(CH_2)_7$ | 5 |  | 98 |

Table 1 (*Continued*)

| Entry | $R^1$ | $R^2$ | $R^3$ | Time (min) | Product | Isolated yield (%) |
|---|---|---|---|---|---|---|
| y | Me | OEt | $H_2N$-$(CH_2)_2$ | 6 |  | 96 |

[a] The structures of the products were determined from their spectroscopic ($^1$H NMR and MS) data.

for $C_{11}H_{13}NO$: C, 75.4; H, 7.4; N, 8.0. Found: C, 75.7; H, 7.1; N, 7.4.

Compound **3e**: (Viscous); IR (Neat) ($cm^{-1}$) 3390, 2925, 1633, 1597, 1236, 871; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 10.80 (brs, 1H), 4.87 (s, 1H), 3.72 (m, 1H), 1.96 (s, 3H), 1.94 (s, 3H), 1.26 (d, $J$ = 7.0 Hz, 6H); EIMS ($m/z$) 141 ($M^{\bullet+}$); Anal. Calcd for $C_8H_{15}NO$: C, 68.0; H, 10.6; N, 9.9. Found: C, 68.3; H, 10.9; N, 10.2.

Compound **3h**: (Colorless crystals); mp 112–114 °C; IR (Neat) ($cm^{-1}$) 3105, 2948, 1684, 1608, 1086, 738; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 10.94 (brs, 2H), 4.98 (s, 2H), 3.46–3.41 (m, 4H), 2.0 (s, 6H), 1.94 (s, 6H); EIMS ($m/z$) 224 ($M^{\bullet+}$); Anal. Calcd for $C_{12}H_{20}N_2O_2$: C, 64.3; H, 8.9; N, 12.5. Found: C, 63.9; H, 8.3; N, 12.9.

Compound **3j**: (Brown color crystals); mp 108–110 °C; IR (Neat) ($cm^{-1}$); 3208, 2960, 1576, 1521, 1038, 726; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 7.22–7.04 (m, 4H), 6.68 (brs, 1H), 4.96 (s, 1H), 2.33 (s, 2H), 2.18 (s, 3H), 2.22 (s, 2H), 1.08 (s, 6H); EIMS ($m/z$) 229 ($M^{\bullet+}$); Anal. Calcd for $C_{15}H_{19}NO$: C, 78.6; H, 8.3; N, 6.1. Found: C, 78.0; H, 8.7; N, 6.3.

Compound **3k**: (Pale yellow color crystals); mp 185–187 °C; IR (Neat) ($cm^{-1}$); 3227, 3032, 1684, 1540, 1151, 731; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 7.60–7.42 (m, 5H), 5.48 (brs, 1H), 5.22 (s, 1H), 4.42 (d, $J$ = 7.0 Hz, 2H), 2.43 (s, 2H), 2.24 (s, 2H), 1.16 (s, 6H); EIMS ($m/z$) 229 ($M^{\bullet+}$); Anal. Calcd for $C_{15}H_{19}NO$: C, 78.6; H, 8.3; N, 6.1. Found: C, 78.9; H, 8.1; N, 6.8.

Compound **3n**: (Yellow color crystals); mp 113–115 °C; IR (Neat) ($cm^{-1}$): 3031, 2954, 1684, 1558, 1153, 812; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 5.12 (s, 1H), 4.60 (brs, 1H), 2.82 (t, $J$ = 7.0 Hz, 2H), 2.34 (s, 2H), 2.28 (s, 2H), 1.79 (m, 1H), 1.14 (s, 6H), 0.88 (d, $J$ = 7.0 Hz, 6H); EIMS ($m/z$) 195 ($M^{\bullet+}$); Anal. Calcd for $C_{12}H_{21}NO$: C, 73.8; H, 10.7; N, 7.2. Found: C, 74.2; H, 10.6; N, 6.9.

Compound **3t**: (Viscous); IR (Neat) ($cm^{-1}$): 3289, 2925, 1651,1605, 1231, 1026; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 8.92 (brs, 1H), 7.35–7.27 (2H, m), 7.25–7.18 (m, 3H), 4.49 (s, 1H), 4.41 (d, $J$ = 7.0 Hz, 2H), 4.07 (q, $J$ = 7.0 Hz, 2H), 1.88 (s, 3H), 1.24 (t, $J$ = 7.0 Hz, 3H); EIMS ($m/z$) 219 ($M^{\bullet+}$); Anal. Calcd for $C_{13}H_{17}NO_2$: C, 69.4; H, 7.7; N, 6.4. Found: C, 69.3; H, 7.9; N, 6.8.

Compound **3v**: (Viscous); IR (Neat) ($cm^{-1}$): 3363, 2972, 1652, 1606, 1268, 771; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 8.50 (brs, 1H), 4.31 (s, 1H), 4.02 (q, $J$ = 7.0 Hz, 2H), 3.66 (m, 1H), 1.92 (s, 3H), 1.25 (t, $J$ = 7.0 Hz, 3H), 1.22 (d, $J$ = 7.0 Hz, 6H); EIMS ($m/z$) 171 ($M^{\bullet+}$); Anal. Calcd for $C_9H_{17}NO_2$: C, 63.1; H, 9.9; N, 8.2. Found: C, 63.6; H, 9.3; N, 7.7.

Crystal data of compound **3i**: X-ray data were collected on Bruker Smart Apex CCD diffractometer with graphite monochromated Mo Kα radiation ($\lambda$ = 0.71073 Å). The structure was solved by direct methods using SHELXS97 (SHELDRICK, 1997) and refinement was carried out by full-matrix least-squares technique using SHELXL97 (SHELDRICK, 1997). Anisotropic thermal parameters were included for all non-hydrogen atoms. All hydrogen atoms were geometrically fixed and were allowed to ride on the parent atoms. $C_{14}H_{17}NO$, M = 215.29, Pale yellow, crystal of size 0.30 mm × 0.18 mm × 0.11 mm, Unit cell dimension $a$ = 10.2805(6) Å, $b$ = 13.0301(8) Å, $c$ = 9.4757(6) Å and $\beta$ = 105.502(1)°, $V$ = 1223.15(13) Å$^3$, crystal system: monoclinic, space group: $P2_1/c$, $Z$ = 4, $D_c$ = 1.169 Mg m$^{-3}$, $\mu$ (Mo Kα) = 0.073 mm$^{-1}$, $F(0\,0\,0)$ = 464, measured reflections = 13820, unique reflections = 2902, $R1$ = 0.0445 for 2408 $I > 2\sigma(I)$ and 0.0523 for 2902 reflections, $wR2$ = 0.1212 for 2408 $I > 2\sigma(I)$ and 0.1280 for 2902 reflections, GOOF = 1.056.

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