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Room-Temperature Synthesis of Pyrazoles, Diazepines, β-Enaminones, and β-Enamino Esters Using Silica-Supported Sulfuric Acid as a Reusable Catalyst Under Solvent-Free Conditions

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Abstract: Silica-supported sulfuric acid (H_2SO_4·SiO_2) has been utilized as a heterogeneous recyclable catalyst for a highly efficient regio- and chemoselective condensation of hydrazines/hydrazides, diamines, and primary amines with various β-dicarbonyl compounds at room temperature to afford pyrazoles, diazepines, and β-enaminones/β-enamino esters under solvent-free conditions within 5–15 min.

Keywords: Diazepines, β-enaminones/β-enamino esters, H_2SO_4·SiO_2, heterogeneous recyclable catalyst, pyrazoles, solvent-free conditions

INTRODUCTION

Pyrazoles and diazepines are valuable bio-active heterocycles, which are shown to possess important biological and pharmaceutical activities[1] such as antimicrobial, antiviral, antitumor, anti-inflammatory, antifungal, antidepressant, and anticonvulsant activities. Meanwhile, β-enaminones/β-enamino esters are useful synthones for the synthesis of various pharmaceuticals[2] and bioactive heterocycles.[3]

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Because of these prominent roles, the synthesis of these three kinds of compounds (pyrazoles, diazepines, and β-enaminones/β-enamino esters) has attracted considerable attention recently. By now, various synthetic approaches have been reported. For preparing pyrazoles, among the reported methods,[4] the most preferred are the reactions of 1,3-dicarbonyl compounds with hydrazines in the presence of acid, such as polystyrene-supported sulfonic acid (PSSA),[4a] sulfuric acid,[4b] and so on. In regard to synthesis of diazepines, several routes have been reported, such as microwave heating of diazepine-diones in boiling $POCl_3$,[5a] hydrogen transfer N-heterocyclization using catalyst $[Cp^*IrCl_2]_2/K_2CO_3$,[5b] condensation of 1,3-diketones with diamines using catalyst PSSA,[4a] and others.[5c–5e] Moreover, preparation of β-enaminones/β-enamino esters has been reported to proceed by condensation of β-dicarbonyl compounds with amines utilizing SiO_2/microwaves,[6a] montmorillonite K-10,[6b] $NaAuCl_4$,[6c] $Bi(TFA)_3$,[6d] $Zn(ClO_4)_2{\cdot}6H_2O$,[6e] $CeCl_3{\cdot}7H_2O$,[6f] $SiO_2/HClO_4$,[6g] and so on. However, most of the methods to prepare these three kinds of compounds suffer from certain drawbacks including long reaction times, unsatisfactory yields, higher temperatures, employment of organic solvents, and use of expensive nonreusable catalyst. Thus, there is still a need to develop greener and more efficient pathways for such synthesis.

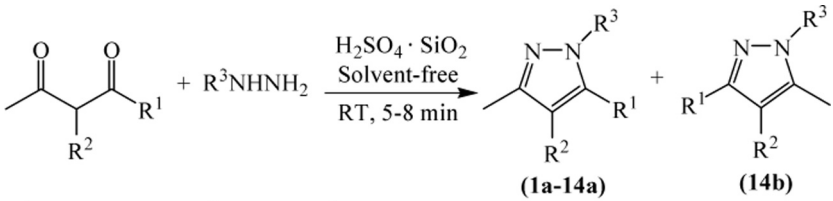
Recently, carrying out organic reactions under solvent-free conditions has become highly desirable.[7] Solventless organic reactions usually are rapid, are regio- or chemoselective, occur in high yields, and have environmental and economic advantages.[7a] These advantages become even more attractive if such reactions can be performed using reusable catalysts. Solid acid catalysts prepared by employing acid supported on oxides have been known and used for a long time; for instance, $H_2SO_4{\cdot}SiO_2$,[8] $HClO_4{\cdot}SiO_2$,[6g] and $NaHSO_4{\cdot}SiO_2$[9] have been reported to efficiently catalyze some reactions. As we know, $H_2SO_4{\cdot}SiO_2$ can easily be prepared from readily available silica gel and H_2SO_4, which is much cheaper and more stable than $HClO_4$, and $H_2SO_4{\cdot}SiO_2$ was also found to be a good protic acid source under milder and safer conditions than $HClO_4{\cdot}SiO_2$ in some reaction systems.[8] For these reasons, we studied synthesis of pyrazoles, diazepines, β-enaminones, and β-enamino esters by the solventless condensation of β-dicarbonyl compounds with hydrazines/hydrazides, diamines, and primary amines at room temperature using silica-supported sulfuric acid ($H_2SO_4{\cdot}SiO_2$) as a heterogeneous recyclable catalyst.

Preparation of $H_2SO_4{\cdot}SiO_2$: To a slurry of silica gel (10 g, 200–400 mesh) in dry diethyl ether (50 mL) was added commercially available concd. H_2SO_4 (3 mL) with shaking for 5 min. The solvent was evaporated under reduced pressure resulting in free-flowing $H_2SO_4{\cdot}SiO_2$, which was then dried at 110 °C for 3 h.

RESULTS AND DISCUSSION

Initially, condensation of hydrazines/hydrazides (1.1 mmol) and 1,3-dicarbonyl compounds (1 mmol) with $H_2SO_4{\cdot}SiO_2$ (20 mg) under solvent-free conditions was examined. Hydrazines/hydrazides reacted efficiently with various β-diketones to afford the desired pyrazoles in good to excellent yields (Table 1). All of the reactions between hydrazines/hydrazides and symmetrical β-diketones gave single components **1a–10a** (entries 1–10 in Table 1). When an unsymmetrical β-diketone, 1-phenylbutane-1,3-dione, was employed to react with $PhNHNH_2$, two regioisomers, **14a** and **14b**, were obtained in the ratio of 19:1 (entry 14 in Table 1). Moreover, the β-ketoesters can also be used as a substitute

Table 1. Room temperature solventless synthesis of pyrazoles using $H_2SO_4{\cdot}SiO_2$[a]



R^1 = Me, Ph, OEt; R^2= H, Me; R^3= Ph, 4-MePh, 4-ClPh, H, CH_3CO

Entry	R^1	R^2	R^3	Time (min)	Yield (%)[b]
1	Me	H	Ph	6	93
2	Me	Me	Ph	7	85
3	Me	H	4-MePh	5	95
4	Me	Me	4-MePh	5	90
5	Me	H	4-ClPh	7	89
6	Me	Me	4-ClPh	8	85
7	Me	H	H	5	96
8	Me	Me	H	5	93
9	Me	H	CH_3CO	6	92
10	Me	Me	CH_3CO	7	89
11	OEt	H	Ph	8	87[c]
12	OEt	H	4-MePh	8	90[c]
13	OEt	H	4-ClPh	8	82[c]
14	Ph	H	Ph	8	94

[a]Reactions performed with 1.0 mmol of β-dicarbonyl compound, 1.1 mmol of hydrazine/hydrazide, and 20 mg of $H_2SO_4{\cdot}SiO_2$ mixed for 5–8 min under solvent-free condition, at room temperature.

[b]Isolated yields after column chromatography.

[c]Yields of reactions performed in 50°C.

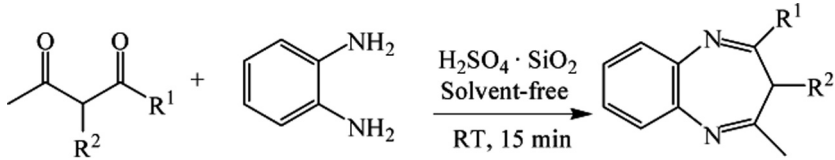
for diketones in this synthesis (entries 11–13 in Table 1). In such case, only single components were afforded, in low yields at room temperature and in high yields at 50 °C.

Next, reactions of diamines with β-dicarbonyl compounds were investigated (Table 2). 1,2-Diaminobenzene reacted efficiently with pentane-2,4-diketone and 3-methylpentane-2,4-diketone to yield diazepines in a single step (entries 1 and 2 in Table 2). The reaction proceeded at room temperature, delivering excellent yields. The reaction of 1,2-diaminobenzene with β-ketoesters, however, failed to give the desired products (entries 3 and 4 in Table 2).

Finally, this protocol was also extended to the synthesis of various β-enaminones and β-enamino esters by the condensation of primary amines with various β-diketones and β-ketoesters at room temperature under solvent-free conditions, and the results are summarized in Table 3. All of the reactions between primary amines and symmetrical β-diketones and β-ketoesters gave single components in good to high yields (entries 1–13 in Table 3). In the case of the reaction of unsymmetrical diketone 1-phenylbutane-1,3-dione with $PhNH_2$, two regioisomers (**14a** and **14b**) were obtained in the ratio of 27:1 (entry 14 in Table 3).

The method was found to be highly chemo- and regioselective. Groups $-NH_2$ in RNH_2 and $RNHNH_2$ attack only at the ketone carbonyl for β-ketoesters (entries 11–13 in Table 1, entries 12 and 13 in Table 3) and in priority at the certain ketone carbonyl connecting with a relatively

Table 2. Room-temperature solventless synthesis of diazepines using $H_2SO_4{\cdot}SiO_2$[a]



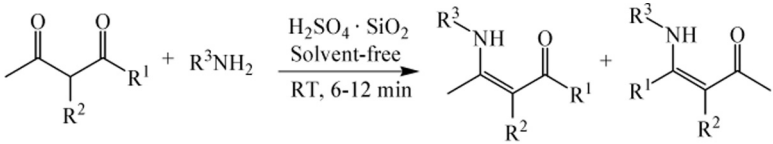
R^1 = Me, OMe, OEt; R^2= H, Me

Entry	R^1	R^2	Yield (%)[b]
1	Me	H	93
2	Me	Me	90
3	OMe	H	NR
4	OEt	H	NR

[a]Reactions performed with 1.0 mmol of *β*-dicarbonyl compound, 1.1 mmol of diamine, and 20 mg of $H_2SO_4{\cdot}SiO_2$ mixed for 15 min under solvent-free conditions at room temperature.

[b]Isolated yields after column chromatography.

Table 3. Room-temperature solventless synthesis of β-enaminone/β-enamino ester using $H_2SO_4{\cdot}SiO_2$[a]



R^1 = Me, Ph, OEt; R^2= H, Me; R^3= 4-OMePh, 4-MePh, Ph, 4-ClPh, 2-MePh, Benzyl, alkyl

Entry	R^1	R^2	R^3	Time (min)	Yield (%)[b]
1	Me	H	4-OMePh	6	97
2	Me	Me	4-OMePh	6	94
3	Me	H	4-MePh	6	95
4	Me	Me	4-MePh	6	90
5	Me	H	Ph	7	94
6	Me	Me	Ph	8	88
7	Me	H	4-ClPh	9	87
8	Me	Me	4-ClPh	9	82
9	Me	H	2-MePh	8	90
10	Me	H	Benzyl	6	94
11[c]	Me	H	$NH_2CH_2CH_2$	6	95
12	OEt	H	4-OMePh	10	95
13	OEt	H	Benzyl	12	95
14	Ph	H	Ph	10	91

[a]Reactions performed with 1.0 mmol of β-dicarbonyl compound, 1.1 mmol of primary amines, and 20 mg of $H_2SO_4{\cdot}SiO_2$ mixed for 6–12 min under solvent-free conditions at room temperature.

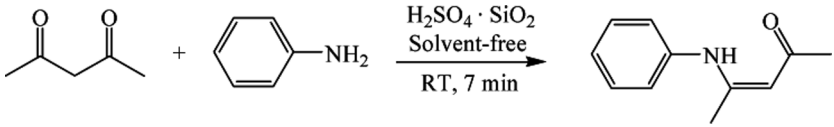
[b]Isolated yields after column chromatography.

[c]Reactions performed with 2.0 mmol of β-dicarbonyl compound, 1.1 mmol of primary amines, and 20 mg of $H_2SO_4{\cdot}SiO_2$ mixed for 6–12 min under solvent-free conditions at room temperature.

weaker electron-donating group when using unsymmetrical diketone (entry 14 in Table 1, entry 14 in Table 3). Moreover, the (*Z*)-selectivity in the products β-enaminones/β-enamino esters (entries 1–14 in Table 3) derived from β-dicarbonyl compounds with primary amines was secured by intramolecular hydrogen bonding. In the ^1H NMR spectra the proton of the –NH– group appeared in the region of δ 8.5–13.5.

The possibility of recycling the catalyst was examined. For this reason, the reaction of pentane-2,4-diketone and aniline at room temperature in the presence of $H_2SO_4{\cdot}SiO_2$ was studied (Table 4). After

Table 4. Recycle experiment of $H_2SO_4{\cdot}SiO_2$[a]



Run	Yield (%)[b]
1	94
2	95
3	94
4	92
5	94
6	94

[a]Reactions performed with 1.0 mmol of pentane-2,4-diketone, 1.1 mmol of aniline, and 20 mg of $H_2SO_4{\cdot}SiO_2$ mixed for 7 min under solvent-free condition at room temperature.

[b]Isolated yields after column chromatography.

completion of the reaction, the catalyst was recovered by simple filtration and reused in subsequent reactions with consistent activity.

CONCLUSION

In conclusion, we have developed a green and efficient approach for room-temperature solventless synthesis of pyrazoles, diazepines, β-enaminones, and β-enamino esters by condensation of hydrazines/hydrazides, diamines, and primary amines with various β-dicarbonyl compounds in the presence of $H_2SO_4{\cdot}SiO_2$ as a heterogeneous catalyst, which may provide a useful route for drug discovery. The solvent-free conditions, simple experimental procedure, mildness of the conversion, clear reaction profiles, high yields and chemo- and regioselectivities, short reaction times, and low cost, stability, and reusability of the catalyst are the noteworthy advantages of the protocol.

EXPERIMENTAL

General Considerations

Silica-supported sulfuric acid was prepared by a reported method.[8] All the reagents were obtained from commercial sources. ^{1}H NMR spectra were recorded on a Bruker Avance DMX 500-MHz spectrometer in $CDCl_3$

solution. Low-resolution MS analyses were measured on a Bruke Esquire 3000 spectrometer using the ESI (electrospray ionization) technique.

General Procedure for the Synthesis of Pyrazoles, Diazepines, and β-Enaminones/β-Enamino Esters

To a mixture of a dicarbonyl compound (1 mmol) and a hydrazine/hydrazide (a diamine, a primary amine) (1.2 mmol), $H_2SO_4{\cdot}SiO_2$ (20 mg) was added. The mixture was stirred for 5–8 min (15 min, 6–12 min) at room temperature. After completion of the reaction, the reaction mixture was diluted with ethyl acetate (2 ml) and filtered. The catalyst was recovered from the residue. The filtrate was concentrated. The residue, on purification by column chromatography (silica gel, petroleum ether-ethyl acetate) afforded pure pyrazole (diazepine, β-enaminone/β-enamino ester).

Condensation of β-enamino esters (1 mmol) with hydrazine (1.2 mmol) was conducted at both room temperature and 50 °C.

When ethanediamine (1.2 mmol) was used as an amine, a dicarbonyl compound (2 mmol) was required.

Selected Data

5-Ethoxy-3-methyl-1-phenyl-1*H*-pyrazole (Table 1, Entry 12)

^{1}H NMR ($CDCl_3$): d 1.42–1.45 (t, $J = 7.0$ Hz, 3H, CH_3), 2.28 (s, 3H, CH_3), 4.11–4.16 (q, $J = 7.1$ Hz, 2H, CH_2), 5.48 (s, 1H, CH), 7.21–7.72 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): d 14.77, 14.86, 68.01, 86.49, 121.97, 125.94, 128.96, 139.03, 148.94, 155.07. MS (ESI) m/z 203 ($[M + H]^+$).

3-Methyl-1,5-diphenyl-1*H*-pyrazole (Table 1, Entry 14a)

^{1}H NMR ($CDCl_3$): d 2.39 (s, 3H, CH_3), 6.55 (s, 1H, CH), 7.32–7.91 (m, 10H, Ph). ^{13}C NMR ($CDCl_3$): d 13.76, 107.97, 125.41, 127.40, 128.34, 128.63, 128.87, 129.09, 130.89, 140.27, 143.37, 149.70. MS (ESI) m/z 235 ($[M + H]^+$).

5-Methyl-1,3-diphenyl-1*H*-pyrazole (Table 1, Entry 14b)

^{1}H NMR ($CDCl_3$): d 2.40 (s, 3H, CH_3), 6.33 (s, 1H, CH), 7.22–7.32 (m, 10H, Ph). ^{13}C NMR ($CDCl_3$): d 12.75, 104.57, 125.16, 125.90, 127.79, 127.94, 128.75, 129.27, 133.52, 140.10, 140.36, 151.67. MS (ESI) m/z 235 ($[M + H]^+$).

(1Z,4Z)-2,4-Dimethyl-3*H*-benzo[*b*][1,4]diazepine (Table 2, Entry 1)

^{1}H NMR ($CDCl_3$): d 2.34 (s, 6H, CH_3), 2.81 (s, 2H, CH_2), 7.20–7.22 (m, 2H, Ph), 7.35–7.38 (m, 2H, Ph). ^{13}C NMR ($CDCl_3$): d 27.87, 43.38, 125.09, 127.68, 140.43, 157.99. MS (ESI) m/z 173 ($[M+H]^+$).

(Z)-Ethyl-3-(benzylamino)but-2-enoate (Table 3, Entry 13)

^{1}H NMR ($CDCl_3$): d 1.25–1.28 (t, $J=7.0$ Hz, 3H, CH_3), 1.92 (s, 3H, CH_3), 4.09–4.13 (q, $J=7.1$ Hz, 2H, CH_2), 4.43–4.44 (d, $J=6.4$ Hz, 2H, CH_2), 4.55 (s, 1H, CH), 7.26–7.36 (m, 5H, Ph), 8.96 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): d 14.83, 19.54, 47.00, 58.57, 83.45, 126.92, 127.54, 128.98, 138.98, 161.97, 170.79. MS (ESI) m/z 220 ($[M+H]^+$).

(Z)-1-Phenyl-3-(phenylamino)but-2-en-1-one (Table 3, Entry 14a)

^{1}H NMR ($CDCl_3$): d 2.16 (s, 3H, CH_3), 5.92 (s, 1H, CH), 7.19–7.95 (m, 10H, Ph), 13.13 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): d 20.66, 94.48, 124.98, 125.99, 127.28, 128.50, 129.38, 131.12, 138.85, 140.23, 162.44, 188.88. MS (ESI) m/z 238 ($[M+H]^+$).

(*Z*)-4-Phenyl-4-(phenylamino)but-3-en-2-one (Table 3, Entry 14b)

^{1}H NMR ($CDCl_3$): d 2.24 (s, 3H, CH_3), 5.44 (s, 1H, CH), 6.77–7.35 (m, 10H, Ph), 9.71 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): d 29.62, 100.33, 122.98, 123.79, 127.64, 128.20, 128.59, 129.18, 135.40, 139.60, 159.50, 197.36. MS (ESI) m/z 238 ($[M+H]^+$).

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