

**SILICA AMMONIUM ACETATE(SiO₂-NH₄OAc)
CATALYZED FACIAL SYNTHESIS OF
DIHYDROPYRAZOLO[4',3':5,6]PYRANO[2,3-
d]PYRIMIDINE-5,7-DIONES**

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Abstract: Silica ammonium acetate (SiO₂-NH₄OAc) was applied as an inexpensive, practical and heterogeneous catalyst for the preparation of new and known dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine-5,7-diones *via* one-pot four-component reaction of hydrazine hydrate, ethyl acetoacetate aldehydes and barbituric acid/ dimethyl barbituric acid under solvent-free conditions. Silica supported ammonium acetate (SiO₂-NH₄OAc) was prepared according to easy procedure under ambient condition. After completion of the reaction, the catalyst was separated by filtration and reused. So, recycling system, simple work-up, using non-toxic materials, excellent yields and short reaction times makes our research green and convenient for preparation of these classes of organic compounds.

Keywords: barbituric acid; solvent-free; heterogeneous catalyst; green chemistry

Introduction

Although the first multi-component reactions(MCRs),¹⁻³ was reported more than one century ago, only some of MCRs have been known

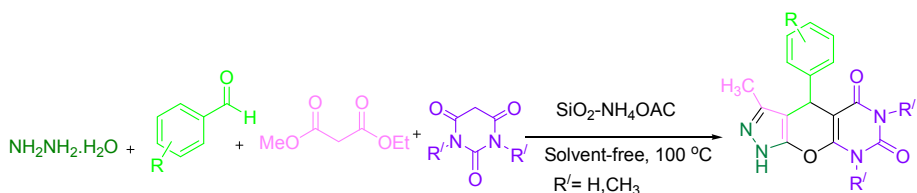
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to be green synthetic methodologies for the preparation of heterocycles compounds.⁴ However, not all multi-component reactions are actually green if one or more of the twelve green chemistry principles⁵ are violated, such as utilization of non-recoverable catalysts, poisonous solvents, pollutants chemical reagents etc.

Some many MCRs have been reported for the synthetic of heterocyclic compounds such as pyranopyrazoles and pyranopyrimidines,⁶⁻⁸ because of these classes of heterocyclic compounds can act as antidepressant⁹ antileishmanial,¹⁰ hypoglycemic¹¹ anticancer¹² and antibronchitic¹³ agents.

Silica supported ammonium acetate ($\text{SiO}_2\text{-NH}_4\text{OAC}$) as heterogeneous, recyclable and easy handling solid base catalyst, was prepared by simple mixing of silica and ammonium acetate at room temperature¹⁴ and used for synthesis of 4H-pyran¹⁴ and Knoevenagel condensation.¹⁵

In continuation of our developments of efficient methods for synthesis of multi-component reaction using heterogeneous and recyclable catalysts,¹⁶⁻¹⁸ herein, we report a convenient and green method for preparation of dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine-5,7-diones *via* four-component reaction of hydrazine hydrate, ethyl acetoacetate, aromatic aldehydes and barbituric acid/ dimethylbarbituric acid under thermal and solvent-free conditions in presence of $\text{SiO}_2\text{-NH}_4\text{OAC}$ as a catalyst (Scheme 1).



Scheme 1. Preparation of dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine-5,7-diones.

Results and Discussion

First, we studied the reaction of hydrazine hydrate (1 mmol) and ethyl acetoacetate (1 mmol), barbituric acid (1 mmol), benzaldehyde (1 mmol) as a model reaction under solvent-free conditions in different temperatures and variety of amount of SiO₂-NH₄OAC to choose the optimum conditions which is described in Table 1. As shown from Table 1, the optimum condition was obtained at 100 °C and 0.09 g of the catalyst.

Table 1. Optimization of the reaction conditions for the synthesis of dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine-5,7-diones under thermal and solvent-free conditions.

Entry	Catalyst(g)	T(°C)	Time(min)	Yield (%)
1	0.08	90	7	88
2	0.08	100	6	89
3	0.08	110	5	91
4	0.09	100	5	93
5	0.10	100	4	92
6	0.15	100	4	93

Reaction of hydrazine hydrate (1 mmol) and ethyl acetoacetate (1 mmol), barbituric acid (1 mmol), 4-chlorobenzaldehyde (1 mmol) as a model reaction

In order to generalize the optimum conditions, different derivatives of substituted dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine-5,7-diones were prepared under solvent-free condition at 100 °C (Table 2). Aromatic aldehydes carrying both electron-donating and electron-withdrawing groups were used and desired products were obtained in high yields and short reaction times (Table 2, Entry 1 -20).

Table 2. Synthesis of substituted dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine-5,7-diones under solvent-free conditions in presence of SiO₂-NH₄OAc as a catalyst at 100 °C

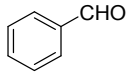
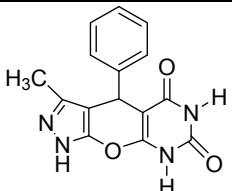
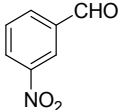
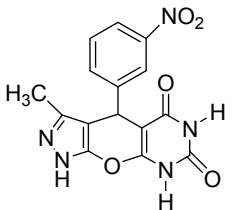
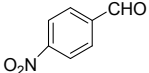
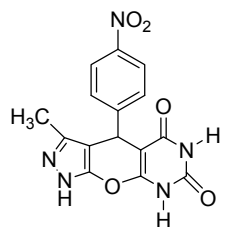
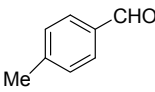
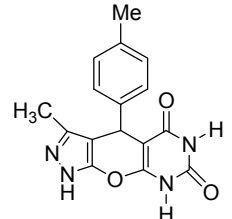
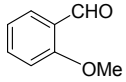
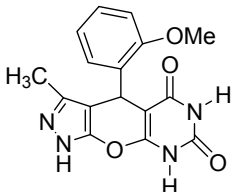
Entry	Substrate	Product	Time (min)	Yield ^a Yield ^b (%)	M.p °C [find] ^c M.p[literature]
1			5	95 95 ²⁰	210 218-219 ²⁰
2			6	93 92 ¹⁹	259 267 ¹⁹
3			5	96 92 ²⁰	221 233-234 ²⁰
4			6	94 90 ²⁰	198 200-201 ²⁰
5			6	92 84 ¹⁹	227 232 ¹⁹

Table 2 Continued

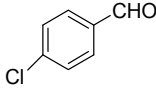
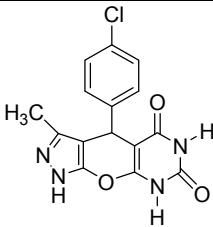
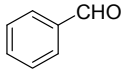
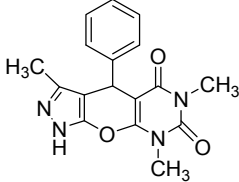
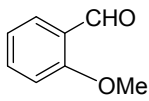
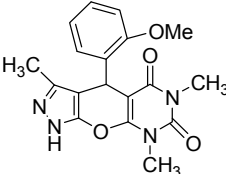
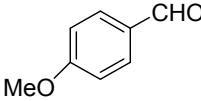
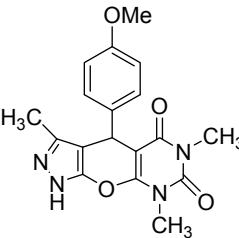
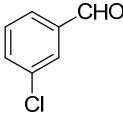
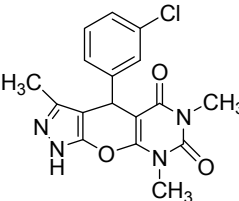
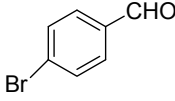
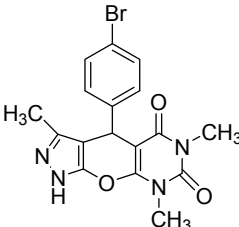
6			5	93 92 ²⁰	220-221 222-223 ²⁰
7			5	94 93 ²¹	196-198 199-201 ²¹
8			4	93 90 ²¹	184-186 185-189 ²¹
9			4	94	186-188 ^d
10			3	95 92 ²¹	154-156 151-155 ²¹
11			3	96	195-198 ^d

Table 2 Continued

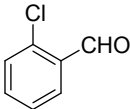
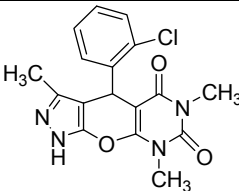
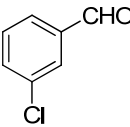
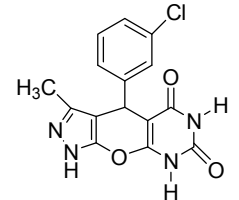
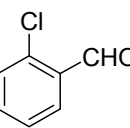
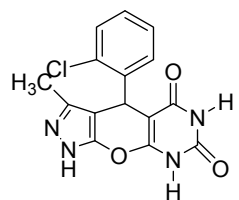
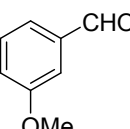
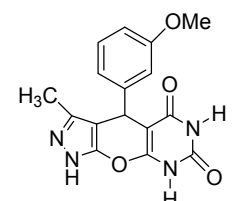
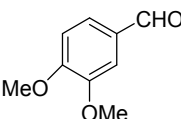
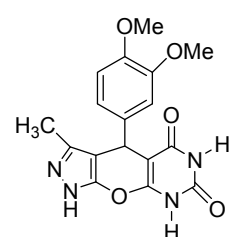
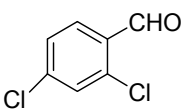
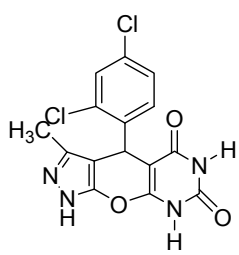
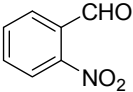
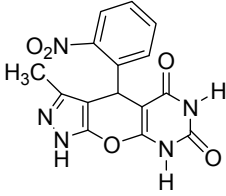
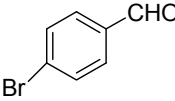
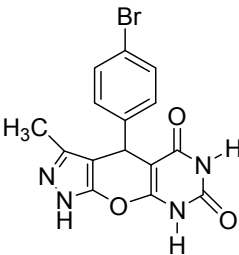
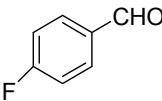
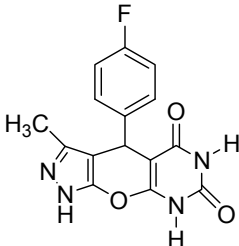
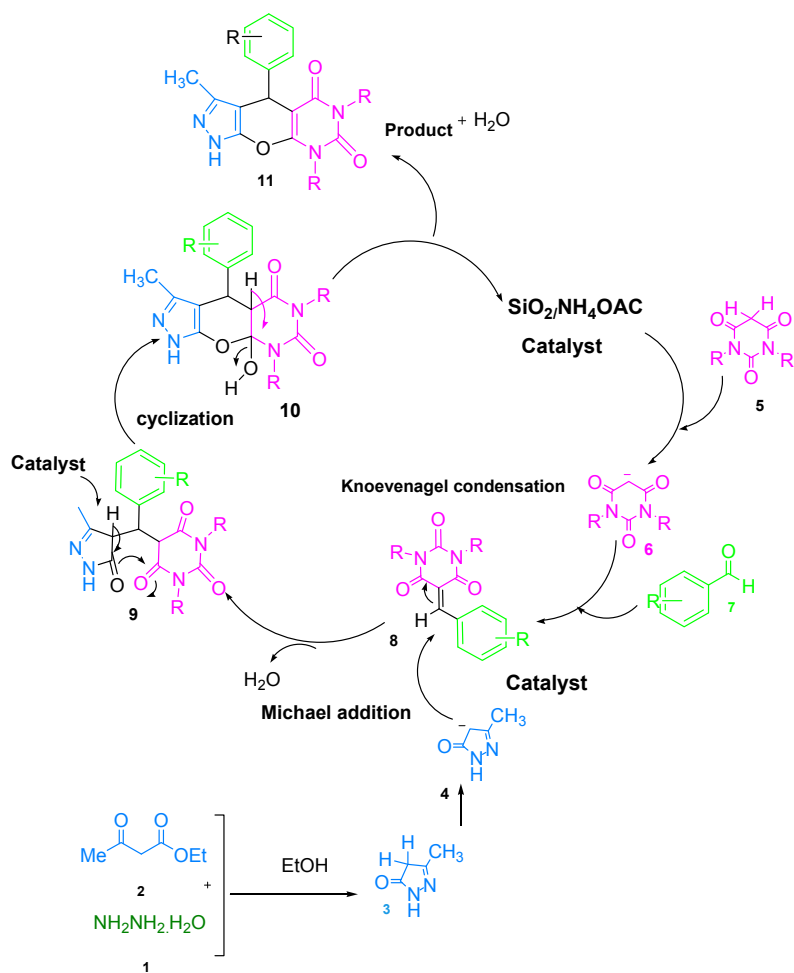
12			3	96 95 ²¹	154-157 151-155 ²¹
13			6	89 90 ²⁰	247-248 246-247 ²⁰
14			6	88 89 ²⁰	222-224 223-225 ²⁰
15			6	90 89 ²⁰	223-224 221-222 ²⁰
16			6	87 89 ²⁰	273-275 275-276 ²⁰
17			6	91 90 ²⁰	231-232 233-234 ²⁰

Table 2 Continued

18			6	87 90 ²⁰	210-211 208-209 ²⁰
19			5	93 91 ²⁰	208-210 211-212 ²⁰
20			6	87 94 ²⁰	234-237 237-238 ²⁰

^a isolated yield in this work. ^b yield was reported in literature. ^c The structure of known products was confirmed by comparison of their physical properties with those of known samples in the literature. ^{19,20,21} ^d New compound.

The plausible mechanism which is reported in literature ²⁰ for preparation of dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine-5,7-diones has been shown in Scheme 3. First, the reaction between hydrazine hydrate (1) and ethylacetoacetate (2) produced pyrazolone (3). Subsequently; Knoevenagel condensation between (6) and (7) gave compound (8). Michael addition of (4) with (8) followed by cyclization obtained an intermediate (10) which has a driving force to lose a molecule of H₂O, which in later step produced the final product (11).



Scheme 2. The plausible mechanism for preparation of dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine-5,7-diones.

For investigation of reusability of the catalysts, we studied the reaction of hydrazine hydrate, ethyl acetoacetate, dimethylbarbituric acid, 2-methoxybenzaldehyde and SiO₂-NH₄OAC (0.09 g) at 100°C under solvent-free conditions as a model. After completion of reactions, the catalyst was separated by simple filtration and washed with ethanol and

dried in the oven at 65 °C. The recovered catalyst was reused for at least four runs without any loss of its activities (Figure. 1).

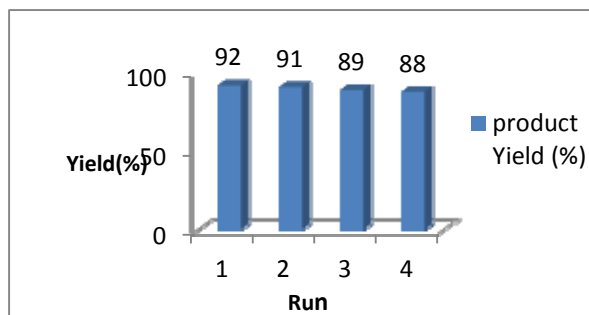


Figure 1. Reusability of the SiO₂-NH₄OAC.

To show the advantages of our method, we compared the results of SiO₂-NH₄OAC with the other reported catalysts in literatures¹⁹⁻²³ for preparation of dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine-5,7-diones by four-component reaction (Table 3).

Table 3. Comparison results of SiO₂-NH₄OAC for the preparation of dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine-5,7-diones as a catalyst with the other reported catalyst.

Entry	Catalyst	Conditions	Time	Yield(%) ^a
1	SiO ₂ -NH ₄ OAC (this work)	Solvent-free, 100 °C	6 min	92
2	Meglumine ²⁰	H ₂ O, r.t	25 min	89
3	[BNPs-Caff]HSO ₄ ²²	H ₂ O, 50 °C	50 min	85
	OMWCNTs ²³	H ₂ O, reflux	45 min	90
5	DABCO ¹⁹	H ₂ O, reflux	45 min	84
6	Cu ²⁺ @MSNs-(CO ₂) ₂ ²⁴	H ₂ O, r.t	80 min	89

^aIsolated Yields ^b The reaction of hydrazine hydrate, ethyl acetoacetate, barbituric acid, 2-methoxybenzaldehyde

According to Table 3, $\text{SiO}_2\text{-NH}_4\text{OAC}$ can act as more effective catalyst with respect to yields and reaction times for the synthesis of dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine-5,7-dione derivatives. Also, other methods have many disadvantages such as expensive procedure for preparation of the catalyst, long reaction times and non-recoverability of catalyst.

Experimental

Materials and Measurements: All reagents were purchased from Merck or Aldrich and used without further purification. All yields refer to isolated products after purification. Nuclear magnetic resonance (NMR) spectra were recorded using a Bruker Advance DPX 300 MHz instrument. The spectra were measured in $\text{DMSO-}d_6$ relative to tetramethylsilane. Infrared (IR) spectra were recorded using a JASCO FT-IR 460 Plus spectrophotometer. Melting points were determined in open capillaries using a BUCHI 510 melting point apparatus. Thin layer chromatography (TLC) was performed on silica-gel Poly Gram SIL G/UV 254 plates.

General procedure for the preparation of Silica supported ammonium acetate ($\text{SiO}_2\text{-NH}_4\text{OAC}$): Silica (1 g) was ground with ammonium acetate (0.5 g) in a pestle and mortar at room temperature. Then the white powder was stored in desiccators to obtain $\text{SiO}_2\text{-NH}_4\text{OAC}$.¹⁴

General procedure for the preparation of dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine-5,7-diones: hydrazine hydrate (1 mmol) and ethyl acetoacetate (1 mmol) were mixed at 100 °C until a white solid was formed (10 min). Then barbituric acid/dimethylbarbituric acid (1 mmol), aromatic aldehyde (1 mmol) and $\text{SiO}_2\text{-NH}_4\text{OAC}$ (0.09 g) was added to this solid state mixture at 100 °C. The

completion of reaction is monitored on TLC. After completion of reaction, the mixture was cooled to room temperature, then the solid residue was dissolved in hot ethanol and catalyst filtered. The filtrate solution was concentrated and the solid product was recrystallized in EtOH to give pure products.

The structure of all known products was confirmed by comparison of their physical properties with those of known samples in the literature.^{19,20} Also, the spectral data of them (Table 2 Entry 7, 14), are according to the literature.^{19,20}

Selected spectra:

3-methyl-4-(2-chlorophenyl)-1,4-dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine-5,7(6H,8H)-dione (Table 2 Entry 14): white powder; IR (KBr)cm⁻¹: 3021(b), 1719, 1605, 1469, 1493, 1468, 1400, 1365, 1297,807,779,539.¹H NMR (300MHz, DMSO-*d*₆) δ (ppm) 2.2 (s, 3H), 5.1(s, 1H), 7.02-7.60 (m, 4H), 10.2(s, 2H), 12.0 (s, 1H, br) ¹³C NMR (75 MHz, DMSO-*d*₆) δ (ppm): 10.1, 20.7, 31.5, 54.5, 90.2,105.2, 126.2, 127.5, 129.4, 130.4, 132.5, 139.6, 151.6, 159.2, 162.9

3,6,8-trimethyl-4-phenyl-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine-5,7(1H,4H)-dione (Table 2 Entry 7): white powder; IR (KBr): 3059, 2949, 1683, 1573, 1493, 1468, 1447, 1346, 823,735,510 cm⁻¹; ¹H NMR (300 MHz, DMSO-*d*₆) δ (ppm): 2.24 (s, 3H), 3.11(s, 6H), 5.5 (s, 1H), 7.02-7.20 (m, 5H), 12.0 (s, 1H, br). ¹³C NMR (75 MHz, DMSO-*d*₆) δ (ppm): 9.9, 17.2, 27.7, 27.7, 31.9, 56.8, 91.0, 105.0, 125.2, 126.6, 127.8, 143.5, 142.5, 151.6, 163.5.

3,6,8-trimethyl-4-(4-bromophenyl)-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine-5,7(1H,4H)-dione (Table 2 Entry 11): IR (KBr): white powder; 3100, 2960, 2915, 1686, 1615, 1577, 1488, 1235, 1090,1048, 864, 796 cm⁻¹; ¹H NMR

(300MHz, DMSO- d_6) δ (ppm): 2.21 (s, 3H), 2.23(s, 3H), 3.11(s, 6H), 5.51 (s, 1H), 6.90 (d, 2H, $J = 9$ Hz), 6.98 (d, 2H, $J = 6$ Hz), 12.0 (s, 1H, br). ^{13}C NMR (75 MHz, DMSO- d_6) δ (ppm): 9.9, 19.9, 20.47, 27.7, 27.7, 31.5, 51.0, 91.2, 106.1, 126.5, 128.4, 134.0, 139.3, 143.5, 151.6, 158.9.

3,6,8-trimethyl-4-(4-methoxyphenyl)-6,8-

dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine-5,7(1H,4H)-5,

7(1H,4H)-dione (Table 2 Entry 9): white powder IR (KBr): 3122.2, 2961.9, 1688, 1615, 1567, 1470,1387, 1280,1387, 1048, 962, 765 cm^{-1} ; ^1H NMR (300MHz, DMSO- d_6) δ (ppm): 2.25 (s, 3H), 3.11(s, 6H), 5.53 (s, 1H), 7.03 (d, 2H, $J = 9$ Hz), 7.23(d, $J = 9\text{Hz}$, 2H), 12.0 (s, 1H, br). ^{13}C NMR (75MHz, DMSO- d_6) δ (ppm): 9.9, 16.9, 27.7, 27.7, 31.6, 52.9, 94.6, 108.3, 127.7, 128.5, 129.9,143.1, 141.8, 151.6, 162.7

Conclusions

The present protocol is an efficient synthetic route to achieve various substituted dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine-5,7-dione derivatives using silica ammonium acetate ($\text{SiO}_2\text{-NH}_4\text{OAC}$) as an inexpensive, convenient and recoverable catalyst. Moreover, this method has some many advantages such as short reaction times, recycling system, simple work-up, non-toxic materials, excellent yields, and solvent-free conditions.

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