SiO_2–OSO_3H nanoparticles: an efficient, versatile and new reagent for the one-pot synthesis of 2-amino-8-oxo-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile derivatives in water, a green protocol

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In a one-pot three-component reaction, an aromatic or aliphatic aldehyde, malononitrile and 5-hydroxy-2-hydroxymethyl-4H-pyran-4-one were condensed for the synthesis of 2-amino-8-oxo-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile derivatives in the presence of nano-silica sulfuric acid (SiO_2–OSO_3H nanoparticles) in improved yields. The catalyst is recoverable by simple filtration and can be used in the subsequent reactions.

Keywords: nano-silica sulfuric acid, solid acid, kojic acid, malononitrile, green chemistry, one-pot synthesis

Organic reactions in water without using hazardous organic solvents have attracted a great deal of interest in both academic and industrial research because, in addition to environmental concerns, there are beneficial effects of aqueous solvents on rate and selectivity of important organic transformations.[1–4]

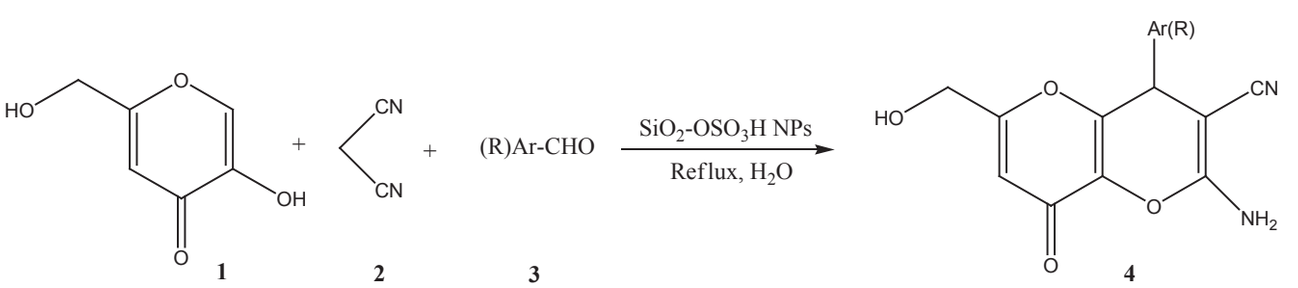
The pyran ring is an important class of structural motif of many numerous natural products, synthetic pharmaceuticals and molecular material which possess a high activity profile due to their wide range of biological activities such as anticancer,[5,6] anti-HIV,[7] antimicrobial,[8] anti-inflammatory[9] and calcium channel antagonist activity.[10] Therefore, considerable attention has been paid to develop efficient methods for the synthesis of pyrans or fused pyran derivatives.

Application of environmentally benign water and solid acid catalyst is a powerful green procedure. In this work, the application of a solid phase acidic green nano catalyst (SiO_2–OSO_3H nanoparticles) was investigated for the synthesis of 2-amino-8-oxo-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile derivatives by the reaction between aldehydes, malononitrile and 5-hydroxy-2-hydroxymethyl-4H-pyran-4-one under reflux in water.

Results and discussion

In continuation of our investigations of the application of solid acids in organic synthesis[11–15] we have investigated the synthesis of 2-amino-8-oxo-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile derivatives by the three-component condensation of 5-hydroxy-2-hydroxymethyl-4*H*-pyran-4-one (kojic acid) **1**, malononitrile **2** and an aliphatic or aromatic aldehyde **3** in the presence of 0.006 g nano-silica sulfuric acid as catalyst (Scheme 1).

The study was initiated by using benzaldehyde, malononitrile and kojic acid as model substrates for the preparation of **4a**. There was no reaction without nano-silica sulfuric acid in H_2O under reflux (Table 1, entry 1). The transformation of benzaldehyde with malononitrile and kojic acid proceeded smoothly with nano-silica sulfuric acid (0.006 g) in H_2O (5 mL), and at the end of the reaction (about 15 min later), the product was collected by filtration and recrystallised from ethanol, affording the nicely crystalline **4a** in good yield (95%, Table 1, entry 2). Different solvents and catalysts were screened in the model reaction, and the results are collected in Table 1. In the presence of pyridine, Na_2CO_3, $ZrCl_4$, $SnCl_2.2H_2O$, $SbCl_3$ and $ZnCl_2$ in H_2O, the reactions became sluggish (Table 1, entries 3–8). Different solvents, for example, CH_2Cl_2, EtOH, CH_3CN and DMF were tested in the presence of nano-silica sulfuric acid as the catalyst, but unfortunately they resulted in low yields or no reaction (Table 1, entries 9–13). Decreasing the catalyst loading from 0.006 to 0.002 g, lowered the yield of the reaction significantly (Table 1, entries 14 and 15). The yields of **4a** were not further improved using increased amount of the catalyst (Table 1, entry 16). Thus, it is clear from the experiments that the best conditions for **4a** could be entry 2, employing nano-silica sulfuric acid (0.006 g) as the solid acid and H_2O as the solvent under reflux. An interesting feature of this method is that the reagent can be regenerated at the end of the reaction and can be used several times without losing its activity. To recover the catalyst, after completion of the reaction, the mixture was filtered and recrystallised from hot ethanol, the catalyst was separated and washed with ethanol and then dried. This process was repeated for two cycles and the yield of product **4a** did not change significantly (Table 1, entries 17 and 18).



Scheme 1 Synthesis of 2-amino-8-oxo-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile derivatives by condensation of an aldehyde, kojic acid and malononitrile using SiO_2–OSO_3H nanoparticles as catalyst.

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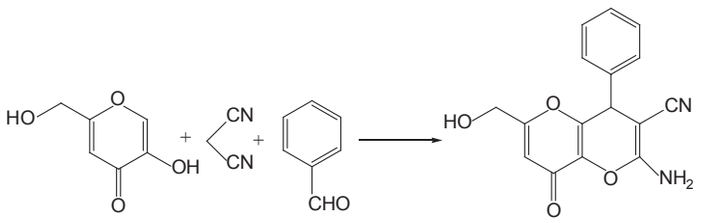
Table 1 Optimisation of the reaction conditions for synthesis of **4a**[a]



Entry	Catalyst/g	Solvent	Time/h	Yield/%[b]
1	Nano-silica sulfuric acid (0)	H_2O	24	0
2	Nano-silica sulfuric acid (0.006)	H_2O	0.25	95
3	Pyridine (0.006)	H_2O	0.25	Trace
4	Na_2CO_3 (0.006)	H_2O	0.25	18
5	$ZrCl_4$ (0.006)	H_2O	0.25	27
6	$SnCl_2.2H_2O$ (0.006)	H_2O	0.25	Trace
7	$SbCl_3$ (0.006)	H_2O	0.25	15
8	$ZnCl_2$ (0.006)	H_2O	0.25	Trace
9	Nano-silica sulfuric acid (0.006)	CH_2Cl_2	0.5	Trace
10	Nano-silica sulfuric acid (0.006)	EtOH	0.5	35
11	Nano-silica sulfuric acid (0.006)	CH_3CN	0.5	Trace
12	Nano-silica sulfuric acid (0.006)	DMF	0.5	46
13	Nano-silica sulfuric acid (0.006)	n-Hexane	0.5	0
14	Nano-silica sulfuric acid (0.002)	H_2O	0.25	79
15	Nano-silica sulfuric acid (0.004)	H_2O	0.25	82
16	Nano-silica sulfuric acid (0.008)	H_2O	0.25	96
17	Nano-silica sulfuric acid (0.006) 2nd run	H_2O	0.25	93
18	Nano-silica sulfuric acid (0.006) 3rd run	H_2O	0.25	89

[a]Reaction condition: 5 mL of solvent under reflux, 1 mmol of benzaldehyde, 1 mmol of kojic acid, and 1 mmol of malononitrile.
[b]Isolated yields.

After optimising the reaction conditions, a series of aromatic aldehydes were employed under similar circumstances to evaluate the substrate scope of this reaction. The results are summarised in Table 2. In all cases, aromatic aldehydes substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and gave products in excellent yields. As a result, aldehydes with electron-withdrawing groups reacted rapidly, while electron-donating groups decreased the reactivity, requiring longer reaction times. Having these data in hand, we have decided to apply this method for heterocyclic benzaldehydes. Furfural, thiophene-2-carbaldehyde and pyridine-4-carboxaldehyde reacted with malononitrile and kojic acid under optimum reaction conditions, and gave products **4i**–**k** in somewhat lower yields than those with aromatic aldehydes (Table 2, entries 9–11). To our surprise, aliphatic aldehydes did react

Table 2 Synthesis of 2-amino-8-oxo-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile derivatives[a]

Entry	Ar (R)	Product	Time/min	Yield/%[b]	M.p./°C	
					Found	Rep.[16]
1	C_6H_5	**4a**	15	95	220–221	220–222
2	2,4-$Cl_2C_6H_3$	**4b**	20	90	239–241	240–242
3	2-ClC_6H_4	**4c**	16	88	211–213	210–213
4	2-FC_6H_4	**4d**	10	96	206–208	207–208
5	4-FC_6H_4	**4e**	25	95	248–249	248–250
6	3-BrC_6H_4	**4f**	20	94	243–245	242–244
7	3-$CH_3C_6H_4$	**4g**	33	86	220–222	219–221
8	3,5-$(CH_3O)C_6H_3$	**4h**	30	84	271–273	271–273
9	2-Furyl	**4i**	20	88	223–225	223–225
10	2-Thienyl	**4j**	25	87	236–237	235–237
11	4-Pyridyl	**4k**	25	91	234–236	233–235
12	3-$O_2NC_6H_4$	**4l**	15	96	258–260	–
13	2-HO-3-$CH_3OC_6H_3$	**4m**	20	92	248–250	–
14	4-Cl-3-$O_2NC_6H_3$	**4n**	12	98	245–247	–
15	4-NCC_6H_4	**4o**	15	94	239–241	–
16	n-Butyl	**4p**	20	91	184–186	–

[a]Reaction condition: 1 mmol of aldehyde, 1 mmol of kojic acid, 1 mmol of malononitrile, 5 mL of water under reflux condition.
[b]Isolated yields.

with malononitrile and kojic acid as well as aromatic aldehydes. Butyraldehyde reacted with malononitrile and kojic acid under optimum reaction conditions with good yield (Table 2, entry 16).The compounds **4a**–**k** were characterised by their ^{1}H NMR and IR spectroscopy and elemental analyses. Spectral data were compared with the literature data.[16] Compounds **4l**–**p** were new and their structures were deduced by elemental and spectral analysis. The IR spectrum of compound **4n** shows two sharp bands at region 3395 and 3373 cm^{-1} one broad band at region 3245 cm^{-1}. These bands are due to the NH_2 and OH groups, respectively. The predominant absorbance peak at 2235 cm^{-1} was due to the nitrile group. The ^{1}H NMR spectrum of compound **4n** exhibited a proton of methine at 5.08 ppm and the NH_2 protons are observed at 7.41 ppm, and the OH proton is observed as a triplet signal at 5.70 ppm which disappears after addition of some D_2O to the DMSO solution of **4n**. The diastereotopic hydrogens of the methylene group on the hydroxymethyl substituent shows two doublets for each of the hydrogens between 4.12 and 4.23 ppm. Such signals are often complex because of small differences in the chemical shift, overlap and an additional strong coupling between the geminal hydrogens. Aromatic protons are observed between 7.69 and 8.10 ppm. The ^{13}C NMR spectrum of compound **4n** showed 16 signals in agreement with the proposed structure. The mass spectrum of compound **4n** showed the molecular ion peak at 375.

In conclusion, an efficient, environmentally benign, atom economical, and simple methodology for the preparation of 2-amino-8-oxo-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile derivatives in a three-component reaction in water has been reported. Prominent among the advantages of this method are operational simplicity, mild reaction conditions, higher yields, and environmental friendliness. Meanwhile, solid phase acidic catalyst could be reused a number of times without appreciable loss of activity. The present method does not involve any hazardous organic solvent. Therefore, this procedure can be classified as green chemistry.

Experimental

Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Costech ECS 4010 CHNS-O analyser of the analytical laboratory of the Science and Research Unit of the Islamic Azad University. Mass spectra were recorded on a Finnigan-Mat 8430 mass spectrometer operating at an ionisation potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-400 Avance spectrometer at solution in DMSO using TMS as internal standard. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

The stable silicagel nanoparticles was prepared[17] and used for the preparation of the catalyst (nano-silica sulfuric acid).

Synthesis of nano-silica sulfuric acid

The reagent was prepared by combination of chlorosulfonic acid (23.3 g) drop by drop over 10 min *via* a syringe to nano-silica gel powder (60 g) in a 100 mL flask at 0 °C. The reaction mixture was then stirred and then after 30 min, the white powder was centrifuged and separated. The dimensions of nanoparticles were observed with SEM. The size of particles is between 28 and 32 nm.

Synthesis of compounds **3a**–**p***; general procedure*

A mixture of aromatic aldehyde (1 mmol), malononitrile (1 mmol), kojic acid (1 mmol) nano-silica sulfuric acid as catalyst (0.006 g) and H_2O (5 mL) was placed in a round-bottomed flask. The materials were stirred magnetically and refluxed for the appropriate time as mentioned in Table 2. After completion of the reaction, by evaporation of the solvent, the crude product was recrystallised from hot ethanol to obtain the pure compound.

2-Amino-6-hydroxymethyl-4-(3-nitrophenyl)-8-oxo-4,8-dihydropyrano[3,2-b]pyran-3-carbonitrile (**4l**): Reddish-brown solid, m.p. 258–260 °C; IR (ν_{max}, cm^{-1}): 3384 and 3375 (NH_2), 3315 (OH), 2245 (CN), 1675 (C=O), 1530 and 1345 (NO_2); ^{1}H NMR (400 MHz, DMSO-d6): δ 4.14 (dd, 1H, *J* = 16.4, *J* = 6.0 Hz, aliphatic), 4.18 (dd, 1H, *J* = 16.4, *J* = 6.0 Hz, aliphatic), 5.12 (s, 1H, methine), 5.65 (t, 1H, *J* = 6.0 Hz, OH), 6.32 (s, 1H, =CH), 7.37 (s, 2H, NH_2), 7.71 (d, 1H, *J* = 8 Hz, aromatic), 7.80 (d, 1H, *J* = 6.4 Hz, aromatic), 8.16–8.20 (m, 2H, aromatic) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.1, 59.5, 111.9, 114.7, 114.8, 119.1, 122.9, 123.5, 131.1, 135.1, 143.3, 148.2, 148.5, 159.9, 168.7, 170.0 ppm; MS (*m/z*, %): 341 (M^+, 5). Anal. calcd for $C_{16}H_{11}N_3O_6$: C, 56.30; H, 3.25; N, 12.31; found: C, 56.29; H, 3.28; N, 12.23%.

2-Amino-4-(2-hydroxy-3-methoxyphenyl)-6-hydroxymethyl-8-oxo-4,8-dihydropyrano[3,2-b]pyran-3-carbonitrile (**4m**): Cream solid, m.p. 248–251 °C; IR (ν_{max}, cm^{-1}): 3375 and 3345 (NH_2, OH), 2190 (CN), 1660 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.80 (s, 3H, OCH_3), 4.10–4.19 (m, 2H, CH_2), 5.15 (s,1H, methine), 5.58 (t, 1H, *J* = 6.0 Hz, OH), 6.25 (s, 1H, =CH), 6.97–7.05 (m, 3H, aromatic), 7.09 (s, 2H, NH_2), 9.23 (s, 1H, OH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.2, 55.3, 59.1, 105.8, 111.3, 114.3, 119.1, 123.7, 132.4, 136.4, 136.9, 143.3, 148.7, 159.3, 160.7, 168.3, 169.5 ppm; MS (*m/z*, %): 342 (M^+, 8). Anal. calcd for $C_{17}H_{14}N_2O_6$: C, 59.65; H, 4.12; N, 8.18; found: C, 59.58; H, 4.10; N, 8.16%.

2-Amino-4-(4-chloro-3-nitrophenyl)-6-hydroxymethyl-8-oxo-4,8-dihydropyrano[3,2-b]pyran-3-carbonitrile (**4n**): Bright cream solid, m.p. 228–234 °C; IR (ν_{max}, cm^{-1}): 3395 and 3373 (NH_2), 3245 (OH), 2235 (CN), 1677 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.15 (dd, 1H, *J* = 16, *J* = 6.0 Hz, aliphatic), 4.20 (dd, 1H, *J* = 16, *J* = 6.0 Hz, aliphatic), 5.08 (s,1H, methine), 5.70 (t, 1H, *J* = 6.4 Hz, OH), 6.34 (s, 1H, =CH), 7.41 (s, 2H, NH_2), 7.70 (dd, 1H, *J* = 8.4, *J* = 2.0 Hz, aromatic), 7.81 (d, 1H, *J* = 8.4 Hz, aromatic), 8.10 (d, 1H, *J* = 2 Hz, aromatic) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 54.3, 59.0, 111.4, 118.9, 124.3, 124.9, 132.1, 133.3, 136.9, 141.6, 147.1, 147.8, 159.3, 159.3, 168.2, 169.5 ppm; MS (*m/z*, %): 375 (M^+, 7). Anal. calcd for $C_{16}H_{10}ClN_3O_6$: C, 51.14; H, 2.68; N, 11.18; found: C, 51.12; H, 2.65; N, 11.10%.

2-Amino-4-(4-cyanophenyl)-6-hydroxymethyl-8-oxo-4,8-dihydropyrano[3,2-b]pyran-3-carbonitrile (**4o**): Cream solid, m.p. 239–242 °C; IR (ν_{max}, cm^{-1}): 3340 and 3315 (NH_2), 3215 (OH), 2190 (CN), 2185 (CN), 1662 (C=O); ^{1}H NMR (400 MHz, DMSO-d6): δ 4.13 (dd, 1H, *J* = 15.9 Hz, *J* = 6.0 Hz, aliphatic), 4.21 (dd, 1H, *J* = 15.9 Hz, *J* = 6.0 Hz, aliphatic), 4.99 (s,1H, methine), 5.69 (t, 1H, *J* = 6.0 Hz, OH), 6.34 (s, 1H, =CH), 7.36 (s, 2H, NH_2), 7.53 (d, 2H, *J* = 8.3 Hz, aromatic), 7.87 (d, 2H, *J* = 8.3 Hz, aromatic) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 54.6, 58.9, 110.7, 111.4, 115.3, 117.9, 118.5, 128.9, 130.6, 132.9, 133.1, 136.6, 146.0, 147.7, 159.6, 168.2, 169.4 ppm; MS (*m/z*, %): 321 (M^+, 10). Anal. calcd for $C_{17}H_{11}N_3O_4$: C, 63.55; H, 3.45; N, 13.07; found: C, 63.47; H, 3.40; N, 13.05%.

2-Amino-6-hydroxymethyl-8-oxo-4-propyl-4,8-dihydropyrano[3,2-b]pyran-3-carbonitrile (**4p**): Bright cream solid, m.p. 184–188 °C; IR (ν_{max}, cm^{-1}): 3335 and 3315 (NH_2, OH), 2955 (C–H, aliphatic), 2195 (CN), 1640 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.94 (t, 3H, *J* = 7.6 Hz, CH_3), 1.35–1.48 (m, 2H, CH_2), 1.63–1.81 (m, 2H, CH_2), 3.71 (t, 1H, *J* = 4.4 Hz, OH), 4.34–4.39 (dd, 2H, *J* = 12, *J* = 6 Hz, CH_2), 5.83 (t, 1H, *J* = 6 Hz, methine), 6.4 (s,1H, =CH), 7.1 (s, 2H, NH_2) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.81, 17.58, 35.46, 53.30, 59.17, 111.30, 119.54, 136.99, 139.21, 150.26, 156.48, 160.09, 167.99 ppm; MS (*m/z*, %): 262 (M^+, 4). Anal. calcd for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.38; N, 10.68; found: C, 59.50; H, 5.34; N, 10.59%.

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References

1 C-J. Li, *Chem. Rev.,* 2008, **105**, 3095.
2 S. Kobayashi and K. Manabe, *Acc. Chem. Res*., 2002, **35**, 209.
3 U.M. Lindstrom, *Chem. Rev.,* 2002, **102**, 2751.
4 A. Solhy, A. Elmakssoudi, R. Tahir, M. Karkouri, M. Larzek, M. Bousmina and M. Zahouily, *Green Chem.,* 2010, **12**, 2261.
5 D.R. da Rocha, A.C.G. de Souza, J.A.L.C. Resende, W.C. Santos, E.A. dos Santos, C. Pessoa, M.O. de Moraes, L.V. Costa-Lotufo, R.C. Montenegro and V.F. Ferreira, *Org. Biomol. Chem.,* 2011, **9**, 4315.
6 Y. Dong, Q. Shi, K. Nakagawa-Goto, P.-C. Wu, S.L. Morris-Natschke, A. Brossi, K.F. Bastow, J.-Y. Lang, M.-C. Hung and K.-H. Lee, *Org. Biomol. Chem.,* 2010, **18**, 803.
7 M.Z. He, N. Yang, C.L. Sun, X.J. Yao and M. Yang, *Med. Chem. Res.,* 2010, **20**, 200.
8 H. Hussain, S. Aziz, B. Schulz and K. Krohn, *Nat. Prod. Commun.,* 2011, **6**, 841.
9 S.M. Wang, G.W.A. Milne, X.J. Yan, I.J. Posey, M.C. Nicklaus, L. Graham and W.G. Rice, *J. Med. Chem.,* 1996, **39**, 2047.
10 A. Shahrisa, M. Zirak, A.R. Mehdipour and R. Miri, *Chem. Heterocycl. Compd,* 2011, **46**, 1354.
11 B. Sadeghi, B.B.F. Mirjalili, S. Bidaki and M. Ghasemkhani, *J. Iran. Chem. Soc.,* 2011, **8**, 648.
12 B. Sadeghi, A. Hassanabadi and M. Kamali, *J. Chem. Res*., 2012, **36**, 9.
13 B. Sadeghi, S. Zavar and A. Hassanabadi, *J. Chem. Res*., 2012, **36**, 343.
14 B. Sadeghi, A. Namakkoubi and A. Hassanabadi, *J. Chem. Res*., 2013, **37**, 11.
15 B. Sadeghi, *J. Chem. Res*., 2013, **37**, 171.
16 S.H. Banitaba, J. Safari and S.D. Khalili, *Ultrason. Sonochem*., 2013, **20**, 401.
17 K. Lee, A.N. Sathyagal and A.V. McCormick, *Colloids Surfaces A*, 1998, **144**, 115.