HCIO₄–SiO₂ nanoparticles: an efficient and versatile catalyst for synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazoles

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The reaction between aromatic aldehydes, malononitrile and 3-methyl-1-phenyl-2-pyrazoline-5-one catalysed by silica supported perchloric acid nanoparticles ($HCIO_4$ -SiO_2 nanoparticles) in solvent H₂O under reflux provided a simple and efficient one-pot route for the synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazoles in excellent yields.

Keywords: $HClO_4$ -SiO₂ nanoparticles, 1,4-dihydropyrano[2,3-c]pyrazoles, 3-methyl-1-phenyl-2-pyrazoline-5-one, aromatic aldehydes, malononitrile

Green chemistry is the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances. 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 the rate and selectivity of important organic transformations.¹

There are a many procedures described to prepare 1,4-dihydropyrano[2,3-c]pyrazoles such as one-pot threecomponent condensations of malononitrile, aldehyde and 3-methyl-1-phenyl-2-pyrazolin-5-one using KF/Al₂O₂ in DMF at room temperature,² sulfamic acid in ethanol,³ CsF,⁴ solvent-free reaction conditions along with microwave irradiation technique using piperidine as the base have also been introduced for the synthesis of 1,4-dihydropyrano[2,3-c]pyrazoles.⁵ but most of them are toxic. The need to reduce the amount of toxic waste and by-products arising from chemical processes requires increasing emphasis on the use of less toxic and environmentally compatible materials in the design of new synthetic methods. One of the most promising approaches is using water as reaction media. Recently, much attention has focused on the use of water as green solvent in various organic transformations. Water is a desirable solvent for chemical reactions because it is safe, nontoxic, environmentally friendly, readily available, and cheap compared to organic solvents.5-8 Hence, we have developed an efficient procedure for the one-pot three-component synthesis of biologically active 1,4-dihydropyrano[2,3-c]pyrazoles in the presence of HClO₄-SiO₂ nanoparticles (HClO₄-SiO₂ NPs) as a solid phase acidic catalyst, and application of environmentally benign water and solid acid catalyst represents powerful green procedure.

Results and discussion

In continuation of our investigations of the application of solid acids in organic synthesis^{9–11} we investigated the synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazole derivatives by condensation

of 3-methyl-1-phenyl-2-pyrazoline-5-one 1, an aromatic aldehyde 2 and malononitrile 3 in the presence of 0.006 g $HClO_4$ -SiO, NPs catalyst in water (Scheme 1).

The stable catalyst is easily prepared¹¹ and used for preparation of 1,4-dihydropyrano[2,3-*c*]pyrazole derivatives. To optimise the reaction conditions, the reaction of benzaldehyde, malononitrile and 3-methyl-1-phenyl-2-pyrazoline-5-one was used as a model reaction. In order to establish the better catalytic activity of $HClO_4$ -SiO₂ NPs, we have compared the reaction using other catalysts at room temperature and for 20 min. The results are listed in Table 1. The results show that $HClO_4$ -SiO₂ NPs is a more efficient catalyst with respect to the reaction time and exhibits broad applicability giving products in similar or better yield (Table 1, entry 5).

In order to determine the optimum quantity of $HClO_4-SiO_2$ NPs, model reaction was carried out at reflux in water condition. $HClO_4-SiO_2$ NPs (0.006 g) gave an excellent yield in 20 min (Table 2, entry 2). We performed the effect of various solvents on the synthesis of **4a**. This reaction was carried out in various solvents such as water, ethanol, and CH_2Cl_2 . The best results in terms of yield and time obtained in water and the results are listed in Table 2 (Table 2).

It is also found that $HClO_4-SiO_2$ NPs can be effectively recovered from the reaction mixture during the work-up procedure. After completion of the reaction the mixture was filtered off to separate the catalyst and then dry the solid

Table 1 Evaluation of the activity of different catalysts and $\text{HCIO}_4-\text{SiO}_2$ NPs for the synthesis of 4a

| Entry | Catalyst | Time/min | Yield/% ^a |
|-------|---|----------|----------------------|
| 1 | - | 20 | 10 |
| 2 | KF/AI ₂ O ₃ | 20 | 40 |
| 3 | Sulfamic acid | 20 | 65 |
| 4 | CsF | 20 | 75 |
| 5 | HCIO ₄ -SiO ₂ NPs | 20 | 94 |

^alsolated yield.



Scheme 1 The condensation of aromatic aldehydes, malononitrile and 3–methyl-1-phenyl-2-pyrazoline-5-one using HClO₄–SiO₂ NPs as a catalyst.

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Table 2 Optimisation amount of HCIO₄–SiO₂ NPs for the synthesis of 4a^a

| Entry | Catalyst (amount) | Cond./Sol. | Time/min | Yield/% ^b |
|-------|--|---------------------------------------|----------|----------------------|
| 1 | $HCIO_4 - SiO_2$ NPs (0.004 g) | 100 °C/H ₂ 0 | 20 | 85 |
| 2 | $HCIO_4 - SiO_2 NPs$ (0.006 g) | 100 °C/H,0 | 20 | 94 |
| 3 | $HCIO_4 - SiO_2 NPs (0.008 g)$ | 100 °C/H ₂ 0 | 20 | 95 |
| 4 | $HCIO_4 - SiO_2 NPs (0.006 g)$ | 80 °C/EtOH | 20 | 87 |
| 5 | $HCIO_4 - SiO_2 NPs (0.006 g)$ | 40 °C/CH ₂ Cl ₂ | 20 | 83 |
| 6 | HClO ₄ -SiO ₂ NPs (0.006 g), 2 nd run | 100 °C/H ₂ 0 | 20 | 88 |
| 7 | $HCIO_4$ -SiO ₂ NPs (0.006 g), 3 rd run | 100 °C/H ₂ 0 | 20 | 85 |

^aReaction condition: 5 mL of solvent under reflux, 1 mmol of benzaldehyde, 1 mmol of 3-methyl-1-phenyl-2-pyrazoline-5-one, and 1 mmol of malononitrile.

^blsolated yields.

residue. When the model reaction was carried out by the recovered $HClO_4$ -SiO₂ NPs for two cycles, the corresponding 1,4-dihydropyrano[2,3-*c*]pyrazole was obtained in good yield.

To study the scope of the reaction, a series of aromatic aldehydes, malononitrile and 3-methyl-1-phenyl-2-pyrazoline-5-one catalysed by $HClO_4$ -SiO₂ NPs were examined. The results are shown in Table 3. In all cases, aromatic aldehyde substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and gave products in excellent yields.

The compounds **4a–g** were characterised by their ¹H NMR and IR spectroscopy and elemental analyses.^{5,12}

In summary, HClO_4 -SiO₂ NPs has been prepared as a new catalyst and it has advantages in the preparation of 1,4-dihydropyrano[2,3-c]pyrazole such as shorter reaction times, simple work-up, and affords excellent yield. The solid phase acidic catalyst was re-usable several times without appreciable loss of activity. The present method does not involve any hazardous organic solvent. Therefore, this procedure could 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. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ¹H NMR spectra were recorded on Bruker DRX-500 Avance spectrometer for solutions in d₆-DMSO using TMS as an internal standard. The chemicals for this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification. HClO₄–SiO₂ NPs was prepared as previously described in the literature.¹¹

The reagent was prepared by a combination of 70% aqueous $HCIO_4$ (1.8 g, 12.5 mmol) and 23.7 g of nano silicagel in 70 mL diethyl ether were stirred for 3 h at room temperature. The mixture was concentrated and the residue dried under vacuum at 100 °C for 72 h to afford $HCIO_4$ –SiO₂ NPs (0.5 mmol g⁻¹) as a free flowing power. The dimensions of nanoparticles were observed with SEM (Fig. 1). The sizes of particles are between 20 and 30 nm.

Preparation of compounds **4a**–**g**; general procedure

A mixture of 3-methyl-1-phenyl-2-pyrazoline-5-one (1 mmol), aromatic aldehyde (1 mmol), malononitrile (1 mmol), $HCIO_4-SiO_2$ NPs (0.006 g) and H_2O (5 mL) was placed in a round-bottom flask. The materials were mixed and refluxed in water for the 20 min. After completion of the reaction, the solvent was evaporated and then, dichloromethane was added to the mixture and filtered to remove the catalyst. By evaporation of the solvent, the crude product was re-crystallised from hot ethanol to obtain the pure compound.



Fig. 1 The SEM images of $HCIO_4$ -SiO₂ NPs.

Table 3Reaction between an aromatic aldehyde, malononitrile and 3-methyl-1-phenyl-2-pyrazoline-5-one using $HCIO_4$ -SiO_ NPs (0.006 g) in H_2O at reflux.

| Entry | Ar | Product | Time/min | Yield/% | M.p./°C | |
|-------|---|---------|----------|---------|---------|-----------------|
| | | | | | Found | Reported [Ref.] |
| 1 | C_6H_5 | 4a | 20 | 94 | 171–172 | 170–171 [5] |
| 2 | 4-MeC ₆ H ₄ | 4b | 20 | 86 | 177–179 | 177–178 [12] |
| 3 | 4-CIC ₆ H ₄ | 4c | 20 | 91 | 176–177 | 175–176 [5] |
| 4 | 4-MeOC ₆ H ₄ | 4d | 20 | 93 | 173–176 | 171–172 [5] |
| 5 | 4-NO ₂ C ₆ H ₄ | 4e | 20 | 87 | 196–198 | 195–196 [5] |
| 6 | 4-OHC ₆ H ₄ | 4f | 20 | 85 | 213-215 | 210–212 [12] |
| 7 | 3-NO ₂ C ₆ H ₄ | 4g | 20 | 91 | 191–193 | 190–191 [5] |

^aPure isolated product.

4a: ¹H NMR (DMSO-d₆, 500 MHz) $\delta_{\rm H}$ (ppm): 1.90 (s, 3H, CH₃), 4.66 (s, 1H,), 4.71 (s, 2H, NH₂), 7.13–7.30 (m, 10H, Ph); IR (KBr) ($v_{\rm max}$, cm⁻¹): 3468, 3315, 2184, 1660.

4b: ¹H NMR (DMSO-d₆, 500 MHz) $\delta_{\rm H}$ (ppm): 1.75 (s, 3H, CH₃), 2.32 (s, 3H, CH₃), 4.60 (s, 1H), 6.90 (s, 2H, NH₂), 7.03–7.84 (m, 9 H, Ph); IR (KBr) ($\nu_{\rm max}$, cm⁻¹): 3419, 3310, 2165, 1652.

4c: ¹H MMR (DMSO-d₆, 500 MHz) $\delta_{\rm H}$ (ppm): 1.81 (s, 3H, CH₃), 4.78 (s, 1H), 6.30 (s, 2H, NH₂), 7.31–7.80 (m, 9 H, Ph); IR (KBr) ($\nu_{\rm max}$, cm⁻¹): 3473, 3329, 2201, 1659.

4d: ¹H NMR (DMSO-d₆, 500 MHz) $\delta_{\rm H}$ (ppm): 1.71 (s, 3H, CH₃), 3.76 (s, 3H, CH₃), 4.83 (s, 1H), 6.94 (s, 2H, NH₂), 6.87–7.59 (m, 9 H, Ph); IR (KBr) ($\nu_{\rm max}$, cm⁻¹): 3392, 3325, 2190, 1660.

4e: ¹H NMR (DMSO-d₆, 500 MHz) $\delta_{\rm H}$ (ppm): 1.81 (s, 3H, CH₃), 4.92 (s, 1H), 6.95 (s, 2H, NH₂), 7.30–8.26 (m, 9 H, Ph); IR (KBr) ($\nu_{\rm max}$, cm⁻¹): 3432, 3345, 2197, 1666.

4f: ¹H NMR (DMSO-d₆, 500 MHz) $\delta_{\rm H}$ (ppm): 1.78 (s, 3H, CH₃), 4.51 (s, 1H), 6.73–7.80 (m, 9 H, Ph), 7.14 (s, 3H, OH, NH₂); IR (KBr) ($v_{\rm max}$, cm⁻¹): 3414, 3323, 2172, 1653.

4g: ¹H NMR (DMSO-d₆, 500 MHz) $\delta_{\rm H}$ (ppm): 1.92 (s, 3H, CH₃), 4.77 (s, 1H), 4.95 (s, 2H, NH₂), 8.10–8.98 (m, 9 H, Ph); IR (KBr) ($v_{\rm max}$, cm⁻¹): 3456, 3324, 2196, 1660.

Received 4 January 2015; accepted 23 January 2015 Paper 1503119 doi: 10.3184/174751915X14229010768505 Published online: 13 February 2015

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