

Silica in Water: A Potentially Valuable Reaction Medium for the Synthesis of Pyrano[2,3-*c*]pyrazoles

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In the last decade, multicomponent reactions have been much utilized for the synthesis of diverse highly functionalized molecules¹ *via* the formation of carbon-carbon and carbon-heteroatom bonds in one pot; as an outcome, they have appeared as a significant tool in organic synthesis.² These reactions are straightforward one step transformations involving a pair of reactions in which the product of the first is a substrate for the second. This technique becomes even more attractive and efficient if it works under greener reaction conditions.

Green chemistry has created its own position in organic chemistry, since it has been demonstrated that how fundamental scientific methodologies can protect human health and the environment in an economically beneficial manner.³ Therefore, there has been great quest towards the development of greener chemical processes. A part of this quest involves the search of surrogates for the traditionally employed homogenous catalysts.

In this regard, many efforts have been made to prepare heterogeneous catalysts for the use in organic reactions.⁴ Although these catalysts have some advantages in terms of improved product yield and shortened reaction time, their high cost and need of organic solvents still offer challenge to researchers for the exploitation of catalytic activity of readily available heterogeneous materials that are compatible in aqueous media. But while tackling this problem, there is need to understand that a suitable heterogeneous system must not only minimize the production of waste, but should also exhibit activities and selectivities comparable or superior to existing homogeneous routes.

Silica gel is one of the best inorganic heterogeneous materials that can be used for this purpose. There are many advantages to use this support, *viz.* its surface being both thermally and chemically stable during the reaction process, and it is also an abundant and inexpensive material. The structure of silica presents a rigid continuous network of spherical colloidal particles and the bulk structure can be described as a random packing of SiO₄ tetrahedrons.⁵ The presence of silanol groups on silica surface manifests the Brønsted acid behavior.⁵⁻⁷ This fact could be attributed to the presence of water molecules in silica which converts in the form of silicic acid, a so called Brønsted acid.⁸ (weakly acidic in nature with pH 5.5-7.5).⁹

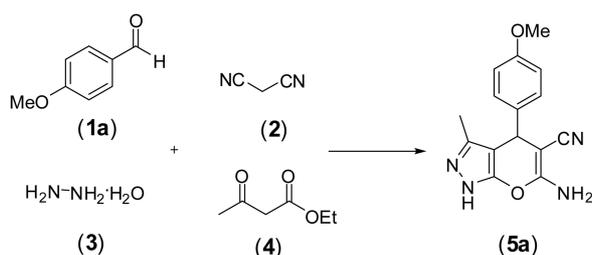
Recently, it has been investigated that silica-water reaction medium keeps an ability of catalyzing various organic transformations.¹⁰ This promising method built-up by the combination of silica with a very unique solvent, *i.e.* water¹¹ is based on the adsorptive nature of silica gel.^{10a} This potential of silica-water system becomes more authentic if it could be applicable for the construction of biodynamic heterocycles.

Pyrano[2,3-*c*]pyrazoles constitute one of the privileged heterocyclic scaffolds known to exhibit important biological activities such as analgesic,¹² antitumor, anticancer,¹³ anti-inflammatory¹⁴ and also serve as potential inhibitors of human Chk1 kinase.¹⁵ Furthermore, heterocyclic compounds bearing 4*H*-pyran units have played increasing roles in synthetic strategies to promising compounds in the field of medicinal chemistry.¹⁶ Junek and co-worker¹⁷ first established the synthesis of pyrano[2,3-*c*]pyrazole derivatives from 3-methyl-1-phenylpyrazolin-5-one and tetracyanoethylene in presence of triethylamine. Later on, a number of synthetic approaches have also been made for the synthesis of 6-amino-4-aryl-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazoles employing triethylamine, piperazine¹⁸ and piperidine¹⁹ as prominent catalysts. Recently, some methods involving the use of cupreine,²⁰ per-6-amino- β -cyclodextrin,²¹ glycine,²² γ -alumina,^{23a} L-proline,^{23b} nanosized magnesium oxide,²⁴ and Mg/Al hydrotalcite²⁵ are developed. But, in all these articles there is no report for the reaction on large scale. Furthermore, almost all the methods lack reusability of catalyst with an exception,^{21,25} and majority of the protocols works only at higher temperature.

Therefore, drive continues towards improved methods for the preparation of pyrano[2,3-*c*]pyrazoles in terms of mild reaction conditions, cleaner reaction medium, easily available and reusable catalytic system, simple isolation of the product and scalable approach. In consideration of this need and in connection with our general interest to exploit greener synthetic strategies²⁶ for bioactive heterocycles, herein, we wish to describe results that successfully led to the development of a novel and simple method for the synthesis of pyrano[2,3-*c*]pyrazoles in silica-water system.

Results and Discussion

As shown in Scheme 1, our investigation was initiated



Scheme 1. Model reaction.

with the optimization of four component reaction between 4-methoxy benzaldehyde **1a**, malononitrile **2**, hydrazine hydrate **3** and ethyl acetoacetate **4**.

Before proceeding towards the actual experimental part, a thorough analysis of the mechanistic path leading to the formation of the desired pyrano[2,3-*c*]pyrazole system was performed. This detailed study with the support of literature revealed that the first two steps involved in the reaction path *i.e.* formation of Knoevenagel condensation product (Figure 1(a)) and pyrazolone (Figure 1(b)) can be achieved either under solvent-free condition or using water as a reaction medium, that even in the absence of catalyst. The only challenge was to achieve the desired product (Figure 1(c)) by cycloaddition of (a) and (b).

Therefore, to accomplish this goal and considering the significance of green chemistry concept, model reaction was carried out initially under solvent-free and catalyst-free conditions at room temperature and higher temperature (100 °C) for 60 min. But, formation of the desired product was not observed (Table 1, entries 1-2). In subsequent optimization experiments, efforts were directed towards the use of water as a reaction medium. Increasing interest of organic chemists for the use of water as a solvent of choice and its unique properties²⁷ turned our attention to examine it for the present reaction. During the study, model reaction was performed using water as a reaction medium at different temperatures. To our surprise, reaction in aqueous media at reflux conditions only was observed to proceed towards the

desired product in satisfactory yield (74 %) (Table 1, entry 4).

With these results in hand, our next objective was to increase the product yield obtained in the earlier study. The only way in mind was the addition of a suitable catalyst which could enhance efficiency of the present method in terms of product yield as well as reaction time. In consideration of this basis and having the knowledge of recently investigated silica-water reaction medium,¹⁰ it was decided to utilize this system for our reaction. When actually this reaction medium was applied for the model reaction, we were delighted to know that the reaction was completing within only 30 min and that too at room temperature affording the product in good yield (83%) (Table 1, entry 6).

Additionally, some more trials were taken with varying quantities of silica and water to know their proper amount to be utilized for the reaction in an order to attain the best experimental conditions. Above investigation emphasized that the presence of 300 mg of silica gel 60 in combination with 5 mL water for the reaction of 1 mmol of substrate affords the highest yield of the product (94%) (Table 1, entry 11). This may be due to the achievement of best concentration of reaction mixture, since lowering or increasing the volume of silica/water leads to decreased rate of reaction (Table 1, entries 5-12).

Reason behind the success of water bringing the reaction in its favor may be hydrophobic interactions which induce favorable aggregation of organic substrates in water. Due to this the organic substrates aggregate and result in their increased concentration which leads to fast collisions of the reactants thus leading to the formation of desired product in very short reaction times. Furthermore, exceptional performance of silica as an effective organic reaction medium in water could be attributed to the fact that the organic substrates get adsorbed to the silica by hydrophobic interactions between the surface of the silica and the organic molecule. In addition, the surface area available for a reaction (surface area of the silica) in such a system is quite large compared with that of the interface in a conventional liquid-liquid biphasic system.

Diagrammatic representation depicting possible mechanism for silica catalyzed synthesis of pyrano[2,3-*c*]pyrazoles is shown with the help of Figure 1.

Based on the heterogeneous nature of the silica, some additional studies were performed to test the reusability of the catalytic system. Model reaction was carried out over four cycles using the same catalytic system, which was recovered simply by extracting the product from aqueous reaction mixture with ethyl acetate. Reused catalytic system was found to be efficient, for every cycle without much loss in product yield. Practically observed fall in yield after successive runs may be due to little bit loss of catalyst during each recovery process (Table 2).

To demonstrate the efficiency and the applicability of the developed method, reaction was performed with variety of electronically divergent aryl aldehydes under optimized reaction conditions and no obvious electronic effects of the substituent present on the aromatic ring of aldehyde was

Table 1. Screening of catalysts^a

Entry	Silica gel 60 (mg)	Water (mL)	Temp (°C)	Time (min)	Yield ^b (%)
1	–	–	RT	60	No Reaction
2	–	–	100	60	Trace
3	–	10	RT	60	Trace
4	–	10	Reflux	60	74
5	100	10	RT	30	74
6	200	10	RT	30	83
7	300	10	RT	30	84
8	400	10	RT	30	89
9	500	10	RT	30	91
10	300	2	RT	20	85
11	300	5	RT	20	94
12	300	5	Reflux	20	91

^aReaction conditions: **1a** (1 mmol), **2** (1 mmol), **3** (1 mmol) and **4** (1 mmol). ^bIsolated Yields.

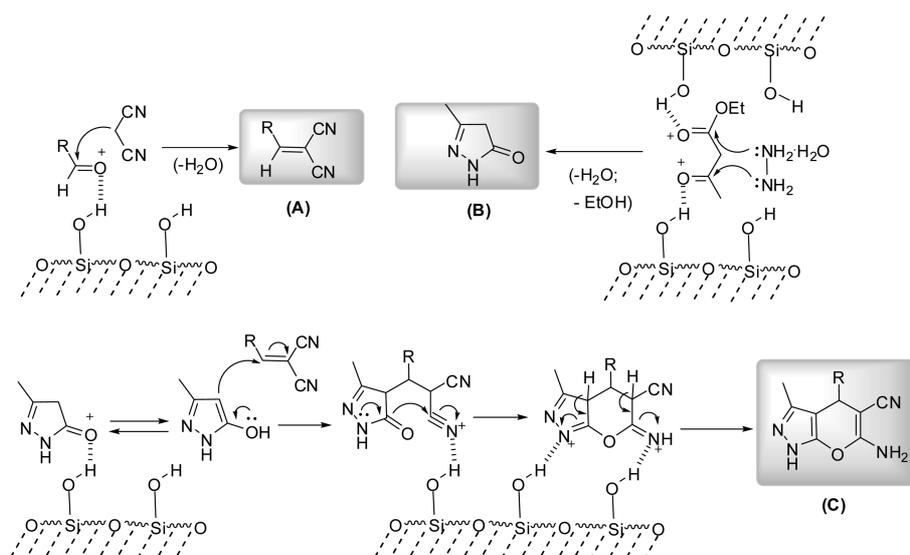


Figure 1. Proposed mechanism for the silica catalyzed synthesis of pyrano[2,3-*c*]pyrazoles.

Table 2. Recycling and reuse of the silica^a

Run	1 (Fresh)	2	3	4
Yield ^b (%)	94	91	87	86

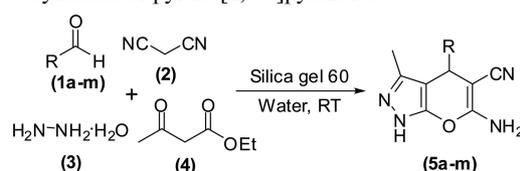
^aReactions of **1a** (1 mmol), **2** (1 mmol), **3** (1 mmol), **4** (1 mmol), silica gel 60 (300 mg) and water (5 mL) at RT were conducted for 20 min. Thereafter, reaction mixture extracted with ethyl acetate (3 × 10 mL) to remove the product from reaction mass. Thus, remaining aqueous suspension with silica gel 60 was reused for next run. ^bIsolated yields.

observed, affording the products in each case with excellent yields. Representative results are summarized in Table 3.

It is generally observed that most of developed synthetic protocols work well on small scale, but does not show satisfactory performance for large scale reactions. In view of the ever growing importance of the scalable reactions, we were keen to know the efficiency of this synthetic strategy on large scale. In this endeavor, model reaction was performed on large scale, *i.e.* 0.1 mole (13.6 gm) with respect to 4-methoxy benzaldehyde by varying the amount of silica/water and it was found that vigorous stirring of the reaction mixture containing 10 gm silica gel 60 and 150 mL water for 40 min at room temperature completes the reaction efficiently in 84% product yield.

In summary, a facile, economic, and green protocol for one-pot multicomponent cyclocondensation of aldehydes, malononitrile, hydrazine hydrate and ethyl acetoacetate is established. Application of silica-water reaction medium for the synthesis of pyrano[2,3-*c*]pyrazoles has been exploited based on the adsorptive nature of silica. The reaction conditions are mild accepting several functional groups present in the molecules and all reactions proceed under essentially neutral conditions, thus reducing the possibility of many unwanted side reactions. In addition, present method offers marked improvements with regard to product yield, reaction time, and greenness of procedure, avoiding hazardous organic solvents/toxic catalysts and provides a better, clean and practical alternative to the existing protocols.

Table 3. Synthesis of pyrano[2,3-*c*]pyrazoles^a



Entry	Compound	R	Yield ^b (%)	mp (°C)
1	5a	4-OCH ₃ -C ₆ H ₄	94	208-210 ^[18]
2	5b	C ₆ H ₅	91	242-244 ^[18]
3	5c	4-Cl-C ₆ H ₄	96	230-232 ^[18]
4	5d	2-Cl-C ₆ H ₄	89	243-244 ^[18]
5	5e	4-F-C ₆ H ₄	93	171-172 ^[21]
6	5f	3-Br-C ₆ H ₄	87	222-224 ^[18]
7	5g	4-OH-C ₆ H ₄	92	221-223 ^[18]
8	5h	2-NO ₂ -C ₆ H ₄	93	223-224 ^[23a]
9	5i	3-NO ₂ -C ₆ H ₄	89	189-191 ^[21]
10	5j	4-NO ₂ -C ₆ H ₄	90	255-257 ^[18]
11	5k	3,4-(OCH ₃) ₂ -C ₆ H ₃	84	190-191 ^[23a]
12	5l	4-OH-3-OCH ₃ -C ₆ H ₃	88	233-235 ^[18]
13	5m	4-CH ₃ -C ₆ H ₄	91	174-176 ^[21]

^aReaction conditions: **1** (1 mmol), **2** (1 mmol), **3** (1 mmol), **4** (1 mmol) and silica gel 60 (300 mg) in water (5 mL) at RT for 20 min. ^bIsolated Yields.

Experimental

All chemicals were purchased and used without any further purification. Melting points were recorded on a Veego apparatus and are uncorrected. ¹H NMR and ¹³C NMR spectra were recorded on Varian AS 400 MHz spectrometer in DMSO-*d*₆ or CDCl₃. Chemical shifts (δ) are in ppm (parts per million) relative to TMS. Mass spectra were recorded on a macro mass spectrometer (waters) by electro-spray (ES) method.

Typical Experimental Procedure for the Synthesis of 6-Amino-1,4-dihydro-4-(4-methoxyphenyl)-3-methyl-

pyrano[2,3-*c*]pyrazole-5-carbonitrile (5a): A mixture of 4-methoxy benzaldehyde **1a** (1 mmol), malononitrile **2** (1 mmol), hydrazine hydrate **3** (1 mmol), ethyl acetoacetate **4** (1 mmol) and silica gel 60 (0.3 gm) in water (5 mL) was stirred at rt for 20 min. Progress of the reaction was monitored by TLC (ethyl acetate:*n*-hexane = 1:9). After completion of the reaction, reaction mixture was subjected for solvent-extraction using ethyl acetate (3 × 10 mL). Thus obtained portion of organic layer (ethyl acetate) was concentrated on rotary evaporator under reduced pressure to achieve the desired product. This crude product (**5a**) was purified by recrystallization technique from 10% aqueous ethanol as a solvent.

6-Amino-1,4-dihydro-4-(4-methoxyphenyl)-3-methyl-pyrano[2,3-*c*]pyrazole-5-carbonitrile (5a): ¹H NMR (DMSO-*d*₆, 400 MHz) δ 1.76 (s, 3H, -CH₃), 3.71 (s, 3H, -OCH₃), 4.51 (s, 1H), 6.79 (s, 2H, -NH₂), 6.84 (d, 2H, *J* = 8.0 Hz), 7.04 (d, 2H, *J* = 8.0 Hz), 12.04 (s, 1H, -NH); ¹³C NMR (DMSO-*d*₆, 100 MHz) δ 11.1, 24.6, 56.2, 62.0, 114.4, 114.9, 127.5, 128.7, 140.0, 143.4, 152.9, 158.8, 166.3; ES-MS: *m/z* 283.2 [M+H]⁺. (Similar procedure was used for the synthesis of compounds **5(a-m)**).

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