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Silica gel an Efficient Catalyst for One-pot Synthesis of Pyrazines from Ethylenediamine and 1, 2-Diketones and their Analogs

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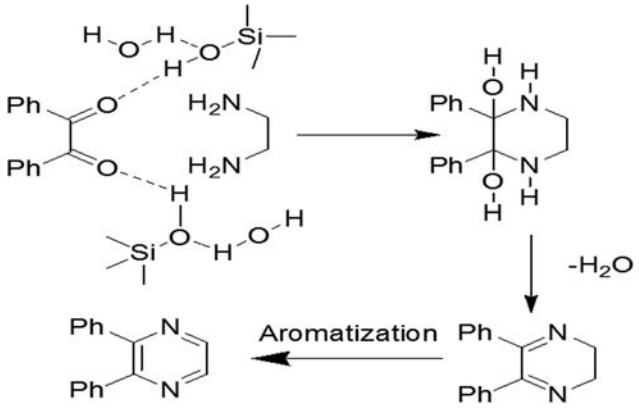
ABSTRACT A straightforward one-pot synthesis of pyrazines from ethylenediamine and 1, 2-diketones/ α-hydroxy ketone/α-bromo ketone under solvent-free conditions at room temperature is described. This environmentally benign process has the edge on previous methods in respect of workup procedure, ease and cost of reaction, and use and generation of hazardous substances. The catalyst is recovered, characterized, and proved to be recyclable for successive four runs examined with appreciable conversions.



KEYWORDS: Ethylenediamine, Environmentally Benign, 1, 2-Diketone, Pyrazine, Silica gel.

INTRODUCTION

Heterocyclic compounds are widespread in nature,[1] and compounds containing *N*-heterocyclic moieties are of immense importance in pharmaceuticals as well as in medicines.[2] Likewise, pyrazine is a class of privileged *N*-heterocycle that is vital component of aroma fragrances[3] and forms the active core of large number of biologically active substances.[4-6] Pyrazinamide is used against *Mycobacterium tuberculosis* to treat tuberculosis.[7] Despite their wide agrochemical uses,[8] pyrazine derivatives have broad spectrum of biological activities[9] such as relaxing cardiovascular and uterine smooth muscle, anti-aggregation, antithrombotic, COX-2 inhibiting and analgesic effects,[10] anticancer,[11] antimycobacterial, antimalarial, anti-HIV activity, and cytotoxicity.[12] It also plays an important role in making flavor ingredient in food and pheromones in various insect.[13,14] It also acts as versatile synthetic intermediate.[15] Due to these wide applications of pyrazine derivatives, their synthesis has always been important for organic chemists. Several synthetic strategies have been developed so far for their synthesis over the years.[16]

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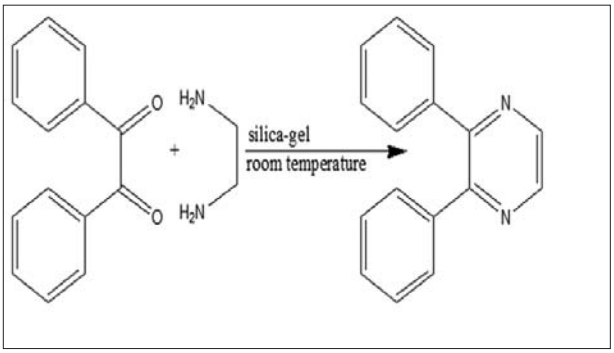
Pyrazines were formed through catalytic dehydrogenation of ethanolamine vapor. The catalysts used were copper oxide, zinc oxide, copper, and sodium carbonate.[17] Condensation of α-amino ketone,[18] Pd-catalyzed cross-coupling reaction also produced pyrazine derivatives.[19] Further, pyrazine compounds were prepared by the reaction of diamine with diol in vapor phase, catalyzed by granular alumina.[20] Catalytic system such as copper-zinc-chromium,[21] zinc-phosphoric acid-manganese,[22] copper-chromium,[23] and silver[24] were also used for the preparation of 2-methyl pyrazine from propylene glycol and ethylenediamine. Pyrazines were also synthesized from the condensation of epoxides and diamines using copper-chromium catalyst.[25] Piperazines get dehydrogenated in the presence of palladium catalyst to produce pyrazines in high yield.[26] α-hydroxy ketones and 1, 2-diamine also produce pyrazines through MnO_2-catalyzed tandem oxidation reaction under refluxing conditions, but the yields were not so encouraging;[27] moreover, this reaction requires an excess amount of MnO_2 catalyst that detracts from the commercial point of view and green condition.[28] Direct condensation of 1, 2-diketones with 1,2-diamine has so far been the better procedure of pyrazine synthesis through dihydropyrazine.[29] Although there are several methods of pyrazine synthesis in literature, most of them are regarded as ineffective because of poor yield, long reaction time, tedious workup process, and drastic reaction condition.[30] Therefore, the development of efficient, mild, and environmental-friendly method for pyrazine synthesis has been a long-cherished goal for organic chemists.

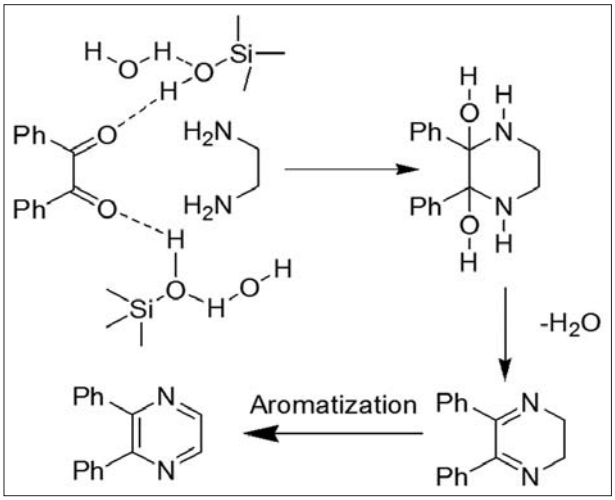
Since the primary demands of green synthesis include minimization of steps, that is, one-pot tandem reactions as well as catalytic processes under metal-free conditions,[31] we explored a greener process for the synthesis of pyrazines directly from simple synthons such as ethylenediamine and 1, 2-dicarbonyl compounds or α-hydroxy or α-bromo ketone at room temperature. In recent days, solvent-free synthesis has attracted the attention of chemists because they are environmentally benign processes. In continuation of our interest in the development of solvent-free synthesis,[32] herein, we report a new synthetic strategy for the preparation of pyrazine derivatives catalyzed by silica gel under solvent-free condition. Silica gel has been effectively used in organic synthesis not only as a simple medium but also as a mild acid catalyst or as an accelerator. It is easily separable from the product because of its insolubility in organic solvents. Silica gel supported catalysts such as SiO_2/BF_3, $SiO_2/NaHSO_4$, $SiO_2/FeCl_3$, and SiO_2/H_2SO_4[33] have also been used in various types of organic transformations. With this background of silica gel and in connection with our present interest, we envisioned that silica gel itself could serve as an eco-friendly, easily available, and cheap alternative catalyst for the synthesis of pyrazines through the metal-free, solvent-free tandem reduction condensation in one-pot protocol (**Scheme 1**).

RESULTS AND DISCUSSION

In our present investigation, we have selected ethylenediamine and benzil for synthesizing 2,3-dihenylpyrazine. We mixed benzil (1 mmol) and ethylenediamine (2 mmol) into silica gel (2 g) at 100°C under magnetic stirrer for 12 h and found no product (**entry 1, Table 1**). Then, we took ethylenediamine (1.5 mmol), benzyl (1.5 mmol), and silica gel (1.5 g) at 50°C for 5 h and got 42% desired product. The reaction conditions were optimized and are summarized in **Table 1**. Finally, it was found that the optimum condition for obtaining the desired product involves - ethylenediamine (1 mmol), benzil (1 mmol), and silica gel (1 g) with few drops of water at room temperature (**entry 5, Table 1**). To show the general applicability, we attempted the developed optimized protocol to a number of chemically diversified ketone and ethylenediamine to synthesize a library of pyrazine derivatives (**Table 2**). The same protocol also gave excellent result (**entry 20, Table 2**) when applied on 1, 2-diketo derivative of pentacyclic triterpenoids of lupane or friedelin skeleton (A, B, or C). Moreover, it was found that silica gel was recyclable and only 1 g moistened silica gel is much



Scheme 1: One-pot condensation of ethylenediamine with 1, 2-diketones resulting pyrazines



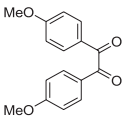
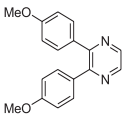
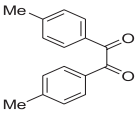
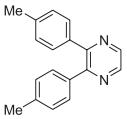
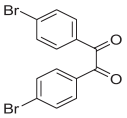
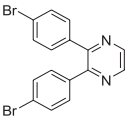
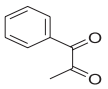
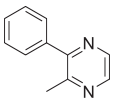
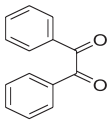
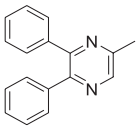
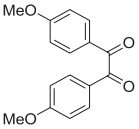
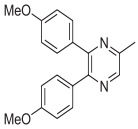
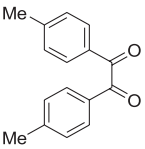
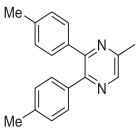
Scheme 2: Plausible mechanism for the synthesis of pyrazine derivatives using moistened silica gel

Table 1: Optimization of reaction conditions for silica-gel catalyzed one-pot condensation of ethylenediamine with benzil[a]

Entry	Silica-gel (gm)	Temp (°C)	Solvent	Ethylene diamine (mmol)	Benzil (mmol)	Time (h)	Conversion(%)[b]
1	2	100	No	2	1	12	Nil
2	1.5	50	No	1.5	1.5	5	42
3	1.0	RT[d]	No	1.0	1.0	7	75
4	0.5	RT	No	1.0	1.0	8	62
5	1.0	RT	water	1.0	1.0	6	87[c]

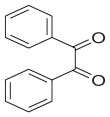
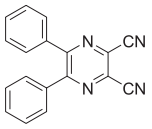
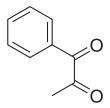
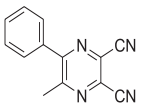
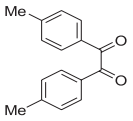
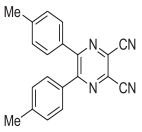
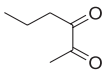
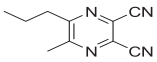
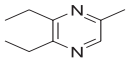
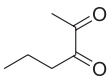
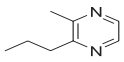
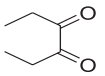
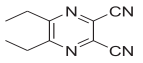
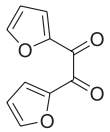
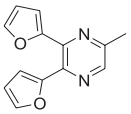
[a]Rection of benzil with ethylenediamine in silica-gel(60-120mesh). [b]Isolated yield. [c]Optimized condition. [d]Room temperature

Table 2: Silica-gel catalyzed condensation of ethylenediamine with 1, 2-dicarbonyl compounds or with α-hydroxy ketones or with α-bromo ketone

Entry no	Ethylene diamine	1,2-dicarbonyl compound/ analogues	Temp (°C)	Time (h)	Product	%Yield
1			RT	6		87
2			RT	6		75
3			RT	6		68
4			RT	10		76
5			RT	8		81
6			RT	7		80
7			RT	6.5		75
8			RT	5		73
9			RT	5.5		73
10			RT	6		85

(contd...)

Table 2: *(Continued)*

Entry no	Ethylene diamine	1,2-dicarbonyl compound/ analogues	Temp (°C)	Time (h)	Product	%Yield
11			RT	5		85
12			RT	7		86
13			RT	6		75
14			RT	6.5		82
15			RT	5.5		75
16			RT	7		73
17			RT	8		76
18			RT	7		72
19			RT	5.6		81
20		A/B/C	RT	6	D/E/F	80

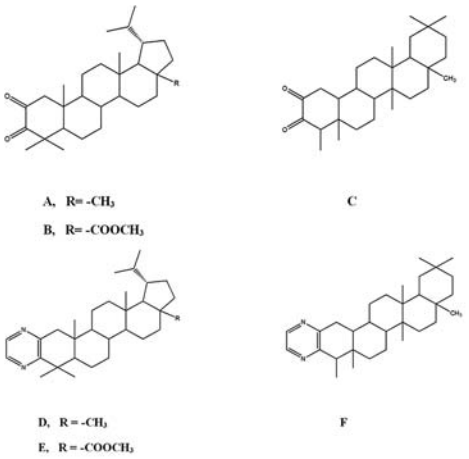
Note: % Yield refers to the isolated yield of all compounds. For known compounds, melting points 34-35 and for rest of the compounds respective characterization data are provided in the supporting information

Table 3: Recycling of the silica-gel tested with ethylenediamine and benzil in one-pot reaction

Entry	Recovered silica-gel (g)	Silica-gel used	Time (h)	Yield(%)
1st run	___	1gm	6	77
2nd run	1gm	1gm	8	75
3rd run	1gm	1gm	7	76

more effective in the shortest time. The progress of reaction was monitored by thin-layer chromatography (TLC). In the present investigation, it is observed that no additional steps required to aromatize the dihydropyrazine derivatives as reported in the earlier methods and this is the main advantage of the present study. The study also indicates that a trace amount of water on silica gel is very much effective and a precalcined silica gel is ineffective to bring about the reaction. A plausible mechanism is depicted in **Scheme 2**.

% Yield refers to the isolated yield of all compounds. For known compounds, melting points[34,35] and for rest of the compounds respective characterization data are provided in the supporting information.



We also tested the reusability of the catalyst silica gel **(Table 3).** The catalyst was recovered from the reaction mixture as follows: The reaction mixture was taken in ethyl acetate (2 mL), subjected to the centrifugation (5000 rpm), and removed the supernatant liquid. The residue was washed with ethyl acetate followed by acetone. Drying under vacuum furnished the powder, which is identical as compared to the first-time used silica gel.

EXPERIMENTAL

Preparation of 2, 3-disubstituted pyrazines

Typical procedure

Ethylenediamine (1 mmol), benzil (1 mmol), and the silica gel (1 g) were mixed in a mortar and the mixture was grinded for a few minutes in the presence of 2–3 drops of water. Finally, the mixture was transferred to a 50 mL round bottom bottle and was kept under magnetic stirrer at room temperature for 6 h. The completion of reaction was monitored by TLC. Ethyl acetate (3×15 ml) was added to the reaction mixture and the extract was filtered through anhydrous Na_2SO_4. Finally, 2,3-diphenylpyrazine was isolated by column chromatography over silica gel (60-120 mesh) where pet ether and ethyl acetate mixture was used as eluent.

Preparation of 2-substituted pyrazines

1-Bromoacetophenone was isolated from the reaction of acetophenone with NBS. Then, 1-bromo acetophenone (1 mmol) was reacted with ethylenediamine (1 mmol) and silica gel (1 g) with 2–3 drops of water to give 2-phenylpyrazine (68%).

The catalyst silica gel was proved to be recyclable for up to four runs (**Table 3**).

CONCLUSION

The present work demonstrates the synthesis of bioactive scaffold pyrazine derivatives directly from ethylenediamine and 1, 2-diketone or with its analogs through one-pot condensation reactions using silica gel as the catalyst under complete metal-free conditions. The conditions are straightforward and mild, and no other side products are obtained. Green process of preparation of pyrazines from ethylenediamine and keto-compounds is developed that could override existing metal-catalyzed reaction conditions.

ACKNOWLEDGMENTS

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