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Silica chloride catalyzed one-pot synthesis of fully substituted pyrazoles

Dhanaji V. Jawale, Umesh R. Pratap, Jyotirling R. Mali, Ramrao A. Mane *

Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad (M.S.) 431 004, India

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Abstract

Silica chloride catalysted one pot cyclocondensation of aldehydes, ethyl acetoacetate and phenyl hydrazine leading to substituted pyrazoles has been reported.

Keywords: One-pot synthesis; Silica chloride; Solvent free; Fully substituted pyrazoles

Pyrazoles are the privileged scaffold and show promising biological activities. Pyrazole is an important core nucleus of various drugs viz. PNU-32945, Zoniporide and Celecoxib (Fig. 1). These drugs act as HIV-reverse transcriptase inhibitors [1], sodium hydrogen ion exchanger inhibitors [2] and COX-2 inhibitors [3]. Pyrazoles are also emerged as potential antihyperglycemic agents [4]. A number of pyrazole compounds specially, 1,3-disubstituted pyrazoles [5] and 1,3,5-trisubstituted pyrazoles [6,7] have been cited in the literature and are found to elicit anti-hyperglycemic activity (Fig. 1).

Owing to the important features of pyrazoles, various synthetic methods are reported for the pyrazoles. Condensation of hydrazonyl halides with β-dicarbonyl compounds and 1,3-dipolar cycloaddition of diazo compounds with alkynes [8–10] are found to yield pyrazoles. 1,3,5-Trisubstituted pyrazolines have been synthesized by condensing chalcones with hydrazines. The pyrazolines on aromatization using various oxidants, $PhI(OAc)_2$ [11], MnO_2 [12] and PBr_3 [13] are found to give pyrazoles.

The most widely used synthetic protocol for obtaining polysubstituted pyrazoles is by condensing 1,3-dicarbonyl compounds with hydrazines using acid catalysts like sulphuric acid [14], polystyrensulphonic acid [15] and hydrochloric acid [16]. To provide an efficient multicomponent one-pot synthesis for polysubstituted pyrazoles L. Shen et al. have recently reported the cyclocondensation of aldehydes, 1,3-dicarbonyl compounds and phenyl hydrazines using ytterbium perfluorooctanoate as rare earth condensing catalyst and IBX as an oxidant for obtaining good to moderate yields of polysubstituted pyrazoles [17,18]. This is a unique report however it has certain limitations as it needs non readily available and costly rare earth catalyst, ytterbium perfluorobutanoate. It has been revealed that silica chloride is gaining importance as catalyst in accelerating various organic transformations [19–23] and cyclocondensations leading of bioactive heterocycles [19–23,27]. Multicomponent reactions are convenient and are found in use in various organic transformations because of their several advantages [24–26].

* Corresponding author.
E-mail address: manera2011@gmail.com (R.A. Mane).

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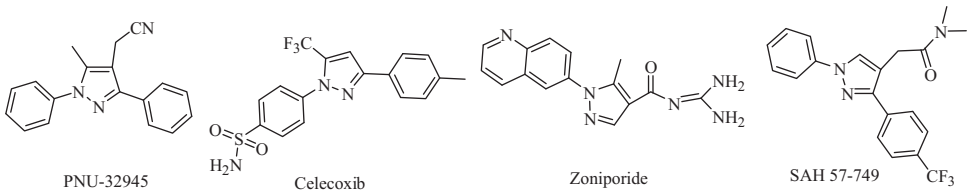


Fig. 1. Biologically active substituted pyrazoles.

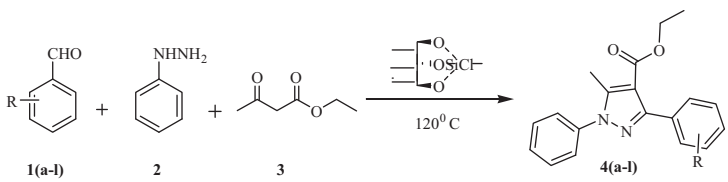
In continuation of our earlier work on the development of the convenient synthetic protocols for bioactive molecules [27–30] using some of the green tools and considering the above urgent need here it was thought worthwhile to develop better synthetic protocol by carrying the cyclocondensation of multicomponents, aromatic aldehydes, ethylacetoacetate and phenyl hydrazine under neat condition or in organic medium using freshly prepared silica chloride as catalyst to obtain better yields of the desired polysubstituted pyrazoles.

We have developed one-pot three component convenient synthesis for fully substituted pyrazoles (**4a-l**). Aromatic aldehydes (**1a-l**), phenyl hydrazine (**2**) and ethyl acetoacetate (**3**) were allowed to react under solvent free condition at 120 °C in presence of dry silica chloride and obtained high yields of the titled pyrazoles (Scheme 1), detail information are put in supplementary file.

To investigate the choice of catalyst, the cyclocondensation of 4-bromobenzaldehyde (**1b**), phenyl hydrazine (**2**) and ethyl acetoacetate (**3**), was carried as a model reaction to afford the pyrazole (**4b**). Initially the reaction was run in the absence of catalyst and was observed that after prolonged heating also the cyclocondensation did not run satisfactorily. Then the above model reaction was performed separately in the presence of various catalysts like acetic acid, $ZnCl_2$, molecular iodine and silica chloride and the results are summarized in Table 1.

Encouraged by these results an attempt was made to optimize the reaction conditions. The condensation was performed separately in presence of medium like toluene, acetonitrile, methanol and ethanol. Attempt was made to carry the condensation in the absence of medium/diluent. It was recorded that when the condensation was run in the presence of silica chloride using various solvents/diluents like toluene, acetonitrile, methanol and ethanol they were not found to undergo completion even after prolonged heating. It was recorded that the above model reaction when carried under solvent free condition at 120 °C, using silica chloride gave high yield of the pyrazole (**4b**) in short reaction time (Table 1).

To determine the amount of silica chloride required for the formation of pyrazoles (**4b**), the reactions were attempted by varying the amount of silica chloride in the range of 0–35 mol%. It was observed that with increase in



Scheme 1. Silica chloride catalyzed synthesis of fully substituted synthesis of pyrazoles.

Table 1
Optimization of catalysts.

Catalysts[a,b]	Reaction time (h)	Yield[c] (%)
None	>24	Trace
AcOH	8	56
$ZnCl_2$	5	58
I_2	3	62
SiO_2Cl	2	80

[a] Amount of the catalyst 30 mol%.
[b] Reaction was carried at 120 °C.
[c] Isolated yield of pyrazole (**4b**).

Table 2
Optimization of amount of catalyst.

Catalyst (mol%)[a]	Reaction time (h)	Yield (%)[b]	Catalyst (mol%)[a]	Reaction time (h)	Yield (%)[b]
0	24	Trace	20	3	63
5	10	36	25	2	75
10	8	48	30	2	80
15	5	55	35	2	80

[a] Reaction was carried at 120 °C.
[b] Isolated yield of pyrazoles (**4b**).

concentration of silica chloride the yields of pyrazoles were increased. The optimum concentration of silica chloride was found to be 30 mol%. With increase in the amount of silica chloride above 30 mol% there was no any substantial change in the yield and the reaction time (Table 2).

The fascinating scope of this synthetic strategy to afford the fully substituted pyrazoles alleviates the use of toxic and hazardous organic solvents and non readily available catalysts. This method is useful for both electron donating as well as electron withdrawing substituent on the aromatic ring of the aldehydes (Table 3).

It was also noted that the heterogeneous catalyst, silica chloride can be recycled and reused in the cyclo-condensations without any activation for the same reactions and gave better yields of the pyrazoles (**4b**, Table 4).

The silica chloride has labile chlorine and therefore is known as Lewis acid and also acts as dehydrating agent [26]. In this condensation it might be enhancing electrophilic character of aldehydic carbon and hence would have expedited the formation of the intermediates, hydrazones. The addition of the hydrazones and enolate, generated from ethyl acetoacetate might be undergoing rapid cyclization to pyrazolines in presence of silica chloride. The role of silica chloride as catalyst in the cyclocondensation has presented in Scheme 2.

In conclusion a simple, convenient one-pot synthetic protocol has been developed for the synthesis of fully substituted pyrazoles. This new synthetic strategy markedly improve the synthetic efficiency, decreases the production

Table 3
Silica chloride catalyzed one-pot synthesis of fully substituted pyrazoles under solvent free condition.

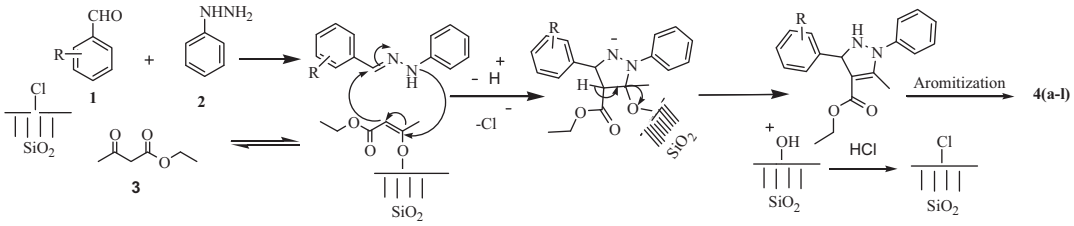
Products[b]	R	Yield[a] (%)	Melting point (°C)
4a	H	76	143–144
4b	4-Br	80	178–179
4c	4-F	78	110–111
4d	4-Cl	79	176–177
4e	3,4-OCH_3	74	140–141
4f	3-Cl	77	162–163
4g	4-OH	75	178–179
4h	2-Cl	78	138–139
4i	4-OCH_3	73	124–125
4j	4-CH_3	74	175–176
4k	3-OH-4-OCH_3	73	158–159
4l	3-OH-4-OCH_2CH_3	72	161–162

[a] Isolated yield.
[b] All the products are characterized by ^1H NMR and mass spectral analyses.

Table 4
Recycling and reusability of silica chloride.

Run	Time (h)[a]	Yield[b] (%)
Ist	2	80
IInd	2	76
IIIrd	2	73
IVth	2	70

[a] Reaction was carried at 120 °C.
[b] Isolated yield of pyrazoles (**4b**).



Scheme 2. Plausible mechanism for the formation of fully substituted pyrazoles using silica chloride.

of chemical waste without the use of highly toxic reagents and gives fully substituted pyrazoles for making the library of new pyrazoles.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2011.05.016.

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