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Silica gel promoted environment-friendly synthesis of 2,3-disubstituted 4-thiazolidinones

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ABSTRACT

Three-component one pot silica gel promoted synthesis of 2,3-disubstituted 4-thiazolidinones is described. The method provides rapid and easy access to thiazolidinone compounds in good to excellent yields.

Thiazolidinones are extensively investigated compounds in the recent years and have fascinated organic and medicinal chemists. Thiazolidinones have emerged as an important class of compound because of their biological importance and have shown interesting biological activity profiles such as antibacterial,[1] anticancer,[2] antitubercular,[3] antioxidant,[4] anti-inflammatory,[5] COX-1 inhibitor,[6] anti HIV,[7] and anti-histaminic[8] agents. Figure 1 shows a few important compounds having thiazolidinones moieties.

Several methods have been described in the literature for the synthesis of thiazolidinones which include one pot three-component condensation of amine, carbonyl compound, and thioglycolic acid or two-step synthesis.[9] The three-component condensation involves loss of water in the final step which is critical to obtain in high yields of thiazolidinones. Different desiccants have been used to affect the dehydration such as molecular sieves,[10] trimethylorthoformate,[11] sodium sulfate,[12] $ZnCl_2$,[13] and azeotropic distillation with benzene or toluene.[14] The most recently used methods for the synthesis of thiazolidinones include DCC,[15] *Saccharomyces cerevisiae*,[16] HBTU,[17] [bmim][PF6],[18] $Bi(SCH_2COOH)_3$,[19] and silica chloride.[20] However, the use of these reagents has some limitations such as high temperature, longer reaction time, corrosive, expensive, hazardous reaction condition, and purification issues due to the formation of by-products. Therefore, it is desired to develop a new method which can eliminate these difficulties.

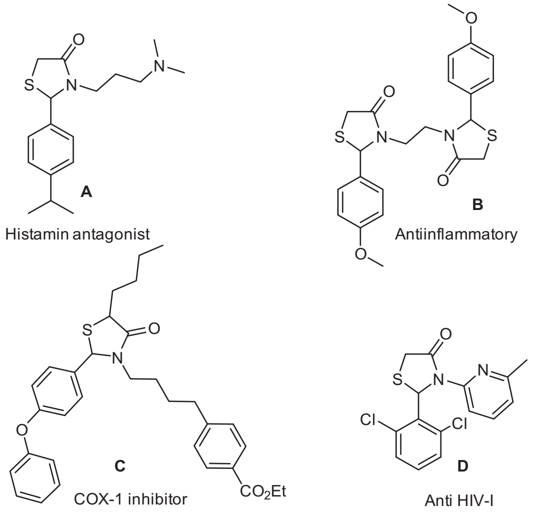

Figure 1. Some biologically important thiazolidinone compounds.

There is always a need for greener alternative to any reaction where formation of by-products can be avoided by using reagents which are non-reactive in the reaction medium and are easily separable from the product. Silica gel is one such green alternative as it is insoluble in most organic solvents and no by-product is formed when used in reactions. Silica gel has been used as a reagent or promoter for the synthesis[21–24] because it is easily available, nontoxic, cheap, and can be separated easily from the product. While

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0040-4039/

working on the synthesis of thiazolidinones, we encountered some difficulties that encouraged us to develop a new method to eliminate these difficulties. In this Letter, we report silica gel as environment friendly and benign reagent for the synthesis of thiazolidinones via three-component one pot condensation of aldehyde, amine, and thioglycolic acid. Slightly acidic and mild desiccant[25] nature of silica gel is being utilized for this reaction. To the best of our knowledge silica gel has not been used as promoter for the synthesis of thiazolidinones. The reactions are quick and no work-up procedure[26] is involved which make it clean and green alternative to other reported procedures and is feasible for parallel synthesis of a large number of compounds.

The model reaction was performed using benzaldehyde, benzylamine, and thioglycolic acid keeping in mind that mild dehydrating nature of silica gel may provide assistance in removal of water in the final step of the condensation to afford thiazolidinone compound. Benzylamine (1.0 mmol) was added to a stirred solution of benzaldehyde (1.05 mmol) in THF (10 mL) at 0 °C and the mixture was stirred for 5 min. Thioglycolic acid (2.0 mmol) was then added to the above reaction and stirring was continued for another 5 min followed by addition of silica gel (0.5 g). The reaction was stirred for 4 h where upon the solvent was removed under reduced pressure and the slurry was purified by flash column chromatography to afford the pure product in 52% yield (Scheme 1).

After the initial success in THF, we screened various solvents and the results are shown in Table 1. The reaction was sluggish when diethyl ether was used as solvent and only 15% product formation was observed although the intermediate imine could be isolated. This suggests that diethyl ether is not a suitable solvent for the conversion of Schiff base to the desired thiazolidinone. A lower yield of the product (48%) was obtained when acetonitrile was used as solvent. The reaction yields were the best when dichloromethane or 1,2-dichloroethane was used as solvent. The easy availability, low cost, and easy evaporation of dichloromethane added advantage and was the solvent of choice for further reactions.

Encouraged by the result, we explored the scope and generality of the reaction using different amines and aldehydes and observed the corresponding products in good to excellent yields (Tables 2 and 3). First the scope of the reaction was tested by treating benzaldehyde, thioglycolic acid with various amines (Scheme 2) and the results are presented in Table 2.

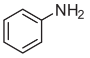
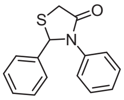
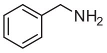
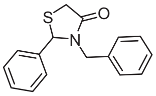
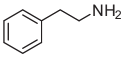
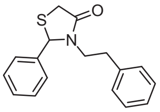
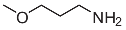
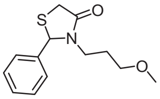
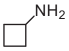
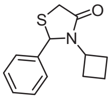
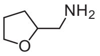
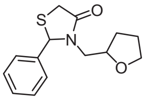
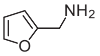
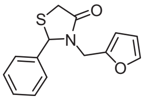
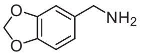
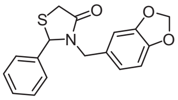
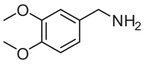
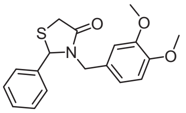
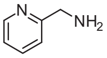
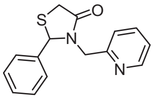
Aliphatic and aromatic amines reacted smoothly to afford the products in excellent yields, while aniline (Table 2, entry 1) gave 78% yield, benzylamine (Table 2, entry 2) and 2-phenylethylamine (Table 2, entry 3) afforded respective thiazolidinones in 87% and 93% yields. The furan-2-ylmethanamine (Table 2, entry 7) and (tetrahydrofuran-2-yl)methanamine (Table 2, entry 6) which are sensitive to acidic condition afforded the product in 83% and 77% yields respectively. Aliphatic amines like 3-methoxypropan-1-amine and cyclobutylamine (Table 2, entries 4 and 5) also reacted smoothly to afford the product in 78% and 93% yields respectively. Substituted aromatic methanamines (Table 2, entries 8 and 9) reacted in a similar fashion to give the required products in excellent yields. Pyridine amine such as 2-picolylamine (Table 2, entry 10) afforded the product in 86% yield after flash column chromatography.

Table 1
Effect of solvent on silica gel mediated thiazolidinone synthesis

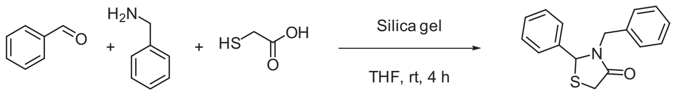
Entry	Solvent	Yield (%)
1	THF	52[a]
2	Et_2O	15[b]
3	Acetonitrile	48[a]
4	**Dichloromethane**	**87**[a]
5	1,2-Dichloroethane	84[a]

[a] Yields are after purification of the compounds.
[b] Imine was isolated in 48% yield.

Table 2
Synthesis of 4-thiazolidines using benzaldehyde, thioglycolic, and different amines

Entry	Amines	Time (h)	Product	Yield[a] (%)
1		7		78[b]
2		4		87[b]
3		3		93
4		4		78
5		6		93
6		3		77[c]
7		6		83
8		4		90
9		6		96
10		7		86

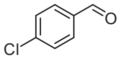
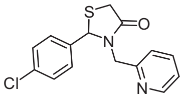
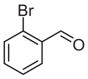
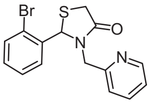
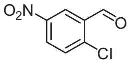
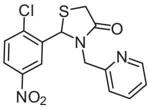
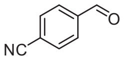
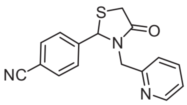
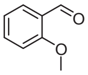
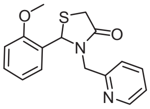
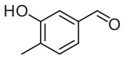
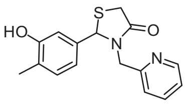
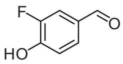
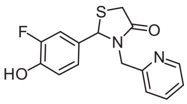
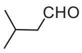
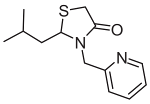
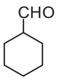
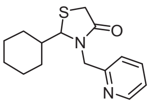
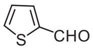
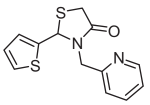
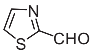
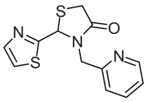
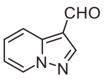
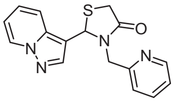
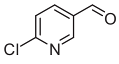
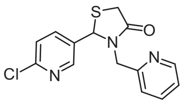
[a] Isolated yields obtained using 1.0 mmol of amine, 1.05 mmol of aldehyde, 2.0 mmol of thioglycolic acid, and 0.5 g of silica gel (100–200 mesh) in dichloromethane at room temperature.
[b] Ref. 15.
[c] Mixture of diastereomers.



Scheme 1. Reagent and condition: benzaldehyde (1.05 equiv), benzylamine (1.0 equiv), thioglycolic acid (2.0 equiv), THF, silica gel (0.5 g), rt, 4 h, 52% yield.

Furthermore to evaluate the scope of the reaction, different aldehydes were reacted with 2-picolylamine and thioglycolic acid under the same reaction condition (Scheme 3) and the results are presented in Table 3. Aldehydes having electron withdrawing groups (Table 3, entries 1–4) reacted smoothly in 3–6 h and the products were obtained in excellent yields ranging from 83% to 93%. Electron donating group such as OMe present in the aldehyde (Table 3, entry 5) afforded excellent yields of the product. Presence

Table 3
Synthesis of 4-thiazolidine using 2-picolylamine, thioglycolic acid, and various aldehydes

Entry	Aldehydes	Time (h)	Product	Yield[a] (%)
1		4		93
2		5		91
3		6		83
4		6		86
5		4		92
6		5		82
7		6		85
8		3		95
9		4		96
10		4		88
11		5		78
12		7		72
13		7		85

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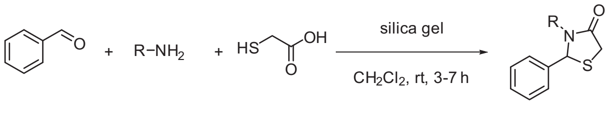
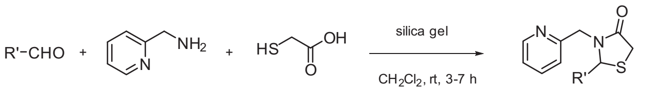
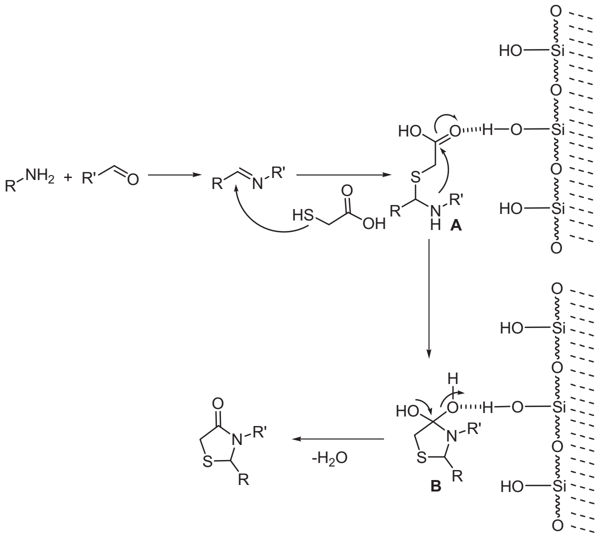
[a] Isolated yields obtained using amine (1.0 mmol), aldehyde (1.05 mmol), thioglycolic acid (2.0 mmol). and silica gel (0.5 g, 100–200 mesh) in dichloromethane at room temperature.



Scheme 2. Reagents and conditions: Benzaldehyde (1.05 equiv), amine (1.0 equiv), thioglycolic acid (2.0 equiv), CH_2Cl_2, silica gel (0.5 g, 100–200 mesh), rt, 3–7 h.



Scheme 3. Reagents and conditions: aldehyde (1.05 equiv), 2-picolylamine (1.0 equiv), thioglycolic acid (2.0 equiv), CH_2Cl_2, silica gel (0.5 g), rt, 3–7 h.



Scheme 4. Plausible mechanism of the reaction.

of the free hydroxyl group in the aldehydes (Table 3, entries 6 and 7) did not affect the yield to a larger extent and the products were obtained in 82% and 85% yields respectively.

Similarly, more reactive aliphatic aldehydes (Table 3, entries 8 and 9) when reacted with 2-picolylamine and thioglycolic acid afforded higher yields of the products in short reaction time. Finally, to evaluate the significance of the method, reactions were performed using different heterocyclic aldehydes (Table 3, entries 10–13). Thiophene-2-aldehyde and thiazole-2-aldehyde reacted cleanly under the above reaction condition and the products were obtained in 88% and 78% yields without any difficulty. Slightly lower yield of the product was obtained when pyrazolo[1,5-*a*]pyridine-3-carbaldehyde was reacted with 2-picolylamine and the product was obtained in 72% yield after flash column chromatography purification. The substituted pyridine aldehyde such as 6-chloronicotinaldehyde reacted well to afford the product in 85% yield. The reactions are clean and require a short column chromatography purification to get the pure product which makes the procedure useful to run parallel reactions for library synthesis.

We hypothesize that silica gel may activate the acid group thereby generating an electron deficient carbon. This facilitates the intramolecular addition of amine to form intermediate **B**. Finally, the loss of H_2O from intermediate **B** affords thiazolidinones (Scheme 4).

In summary, an efficient synthesis of thiazolidinones derived from diverse aldehydes, amines, and thioglycolic acid is reported. This method avoids the use of toxic, expensive, hazardous chemicals, and provides an easy and rapid access to pharmaceutically important thiazolidinone derivatives. The method offers many advantages over the reported methods such as shorter reaction time, cleaner reaction profile, easy isolation, and excellent yield of the products.

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Supplementary data

Supplementary data (synthesized compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.03.007.

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26. *General experimental procedure:* To a solution of benzylamine (1.0 mmol) in dichloromethane (10 mL) at 0 °C was added benzaldehyde (1.05 mmol) and the mixture was stirred for 5 min. Thioglycolic acid (2.0 mmol) was then added to the above reaction and stirring was continued for another 5 min at 0 °C followed by addition of silica gel (0.5 g, 100–200 mesh). The reaction was stirred for 4 h at room temperature when TLC showed complete conversion of starting amine, the solvent was removed under reduced pressure and the slurry so formed was purified by flash column chromatography over 12 g SNAP cartridge by eluting with gradient of 10–20% ethyl acetate in hexane to afford 3-benzyl-2-phenylthiazolidin-4-one in 87% yield..