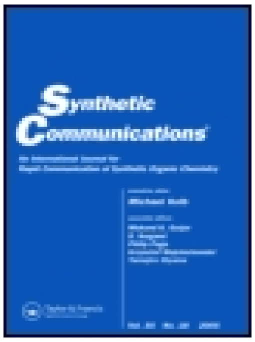

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Silica chloride (SiO_2-Cl) catalyzed one pot synthesis of 2,3-disubstituted-thiazolidin-4-one

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ABSTRACT
In this paper, we report one-pot, three-component cyclo condensation of an aldehyde, an amine and thioglycolic acid to form 2,3-disubstituted-thiazolidin-4-one by using supported protic acid (Silica Chloride: SiO_2-Cl) catalyst. The catalyst SiO_2-Cl is compatible with a variety of aldehydes (aryl/heteroaryl) and the aromatic amines affording 2,3-disubstituted-thiazolidin-4-one analogs in 72–89% yields. Moreover, the supported catalyst was recycled several times without significant loss of catalytical activity

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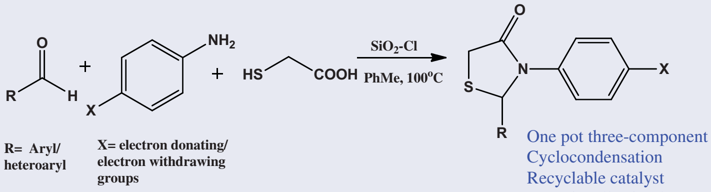
KEYWORDS
Cyclocondensation; 2,3-disubstituted-thiazolidin-4-one; one-pot reaction; recycle; supported SiO_2-Cl catalyst; three-component

GRAPHICAL ABSTRACT



One pot three-component
Cyclocondensation
Recyclable catalyst
operationally simple

Introduction

Chemically functionalized thiazolidinones are the most extensively studied class of compounds with a wide range of biological activities.[1] 4-Thiazolidinones are considered as privileged pharmacophores with vibrant activities like antibacterial, antiviral, anticancer, anticonvulsant, anti-inflammatory.[2–6] Numerous reports highlighting 4-thiazoliodinones as a precursor for the synthesis of different pharmaceutically important substances like monohalogenated β-lactam, a polymethine cyanine dye, and pyrazolothiazole derivative are available.[7–9] Consequently, there has been continuous interest in the development of new synthetic protocols for the construction of thiazolidin-4-one. General methods employ reaction between aldehyde, amine and thioglycolic acid or a two-step condensation involving imine synthesis and treatment of imine with thioglycolic acid. It was proposed that the reaction may proceed either *via*-imine formation followed by an attack of sulfur atom of thioglycolic acid on imine carbon involving

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intermolecular cyclization and expulsion of water or *via*-initial condensation of the amine and thioacid to form amide followed by condensation and cyclization with an aldehyde. The drawback of these methods is they require an efficient water removable system/dehydrating agent to forward the reaction.[10–13] Protocols in presence of Lewis acid like anhydrous $ZnCl_2$[14,15], solid acid catalyst, activated fly ash by using sealed vessels were also available.[16–17] An alternative greener method making the use of the microwave for the synthesis of thiazolidinone with improved yield was also reported.[18]

However, most of these methods suffer from disadvantages such as the use of special apparatus/reactor, use of the stoichiometric amount of hazardous catalyst, auxiliary substances, condensing agents, harsh reaction conditions, the formation of toxic byproducts, tedious workup procedures, an inert, anhydrous atmosphere and long reaction time.

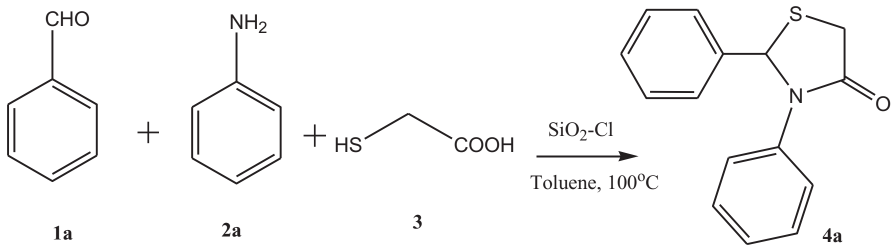
In recent years, the use of the immobilized or supported acid catalyst in a chemical reaction is receiving much attention due to ease of preparation, recyclability, high utilization efficiency, and less toxicity. Silica Chloride (SiO_2-Cl) is one such good solid acid catalyst in terms of convenience, easy preparation and insolubility in organic solvents. It is also considered as an excellent in-situ proton generating agent known for accepting a wide variety of nucleophiles.[19] Homogenous catalysts are often destroyed during isolation of the product. Also, these “single-use” catalyst utilization leads to high manufacturing costs. SiO_2-Cl decreases the production of toxic wastes, at the same time it can act as lewis acid center on silica, this increases the selectivity with respect to desired product formation.[20] SiO_2-Cl also has high thermal and mechanical stability offering substituted-3,4-dihydropyrimidinone synthesis, facile tosylation of alcohol, C–C bond formation, pyrano or furanoquinoline synthesis.[20–23] Ring expansion chlorination of 1,3-dithiolane and 1,3-dithianes with SiO_2-Cl as catalyst was also reported.[24] Most interestingly, SiO_2-Cl works better in water as solvent giving higher yields of 2,3-dihydroquinazoline-4(1H)-one compounds.[25] Synthesis of 3-hydroxy-1H-indazole in presence of SiO_2-Cl and ultrasound is also high yielding.[26]

Thus, convenient, versatile, high yielding SiO_2-Cl attracted us in the search for improved methods for synthesis of title compounds. The multicomponent, one-pot strategy was under consideration instead of stepwise imine formation, and condensation of the preformed imine with thioglycolic acid as to avoid purification procedures. Keeping mechanism in mind, SiO_2-Cl having strong electrophilic activation potential was considered as an ideal reagent for our novel, one-pot, multicomponent protocol for the synthesis of 2,3-disubstituted-thaizolidin-4-one. We have used a wide variety of aldehydes, amines with thioglycolic acid.

Result and discussion

The model reaction (Scheme 1) involving an equimolar mixture of benzaldehyde **1a**, aniline **2a** and thioglycolic acid **3** was carried out in toluene at 100 °C with and without SiO_2-Cl. It was noticed that in the presence of SiO_2-Cl expected product **4a** affords in significant yield, whereas no product was obtained in the absence of SiO_2-Cl.

Considering the basic fact that as the surface area available for the reaction increases reaction rate also increases; the activity of reagent adsorbed on solid support will also get improved due to an increase in the effective surface area of the reagent. In the literature, it



Scheme 1. Synthesis of 2,3-diphenyl-thiazolidine-4-one **4a** using silica chloride (SiO_2-Cl).

Table 1. Effect of surface area of silica supported SiO_2-Cl on synthesis of 2,3-diphenyl-thiazolidine-4-one (**4a**)[a].

Entry	Mesh size of silica gel supported with SiO_2-Cl	Yield[b]
1	230–400	82
2	100–120	75
3	60–120	72
4	SiO_2	No yield

[a] Reaction conditions: 1 mmol of benzaldehyde (**1a**), 1 mmol of aniline (**2a**), 1 mmol of thioglycolic acid (**3**) in presence of 1 mmol of SiO_2-Cl immobilized on silica gel of different mesh size heated in toluene (10 ml) at 100 °C for 3 h.

[b] Isolated yield of **4a**.

Table 2. Optimization of 2,3-diphenyl-thiazolidine-4-one (**4a**)[a].

Entry	Amount of SiO_2-Cl[b]	Solvent	Time (h)	Temp (°C)	Yield[c] (%)
1	0.5	Toluene	3	100	30
2	1.0	Toluene	3	100	50
3	2.0	Toluene	3	100	62
4	2.5	Toluene	2	100	63
5	**2.5**	**Toluene**	**3**	**100**	**82**
6	4.0	Toluene	3	100	84
7	2.5	Toluene	4	100	84
8	2.5	Toluene	3	80	75
9	2.5	Toluene	3	110	82
10	2.5	Benzene	3	100	79
11	2.5	1,4-Dioxane	3	100	80
12	2.5	THF	3	Reflux	14
13	2.5	DMF	3	100	23
14	2.5	Ethanol	3	Reflux	42

[a] Reaction conditions: 1 mmol of benzaldehyde (**1a**), 1 mmol of aniline (**2a**), 1 mmol of thioglycolic acid (**3**) in presence of various solvents (10 ml) heated at different temperatures for the indicated time period.

[b] The molar equivalents of SiO_2-Cl used with respect to aldehyde **1**.

[c] Isolated yield.

was reported that silica chloride (SiO_2-Cl) was prepared by using silica gel and thionyl chloride.[27] For our experiment, we prepared varieties of silica gel with mesh size 230–400, 100–120, 60–120 by using the reported procedure. The model reaction to yield **4a** was further carried out using SiO_2-Cl of different mesh size and results were incorporated in Table 1. Silica gel with mesh size 230–400 was found suitable for our reaction (Table 1, entry 1).

To derive the optimal reaction parameters such as the amount of SiO_2-Cl required, time, temperature, and influence of solvent for the synthesis of substituted thiazolidin-4-one formation; the model reaction was performed using different variations of these parameters and results are incorporated in Table 2. The use of 2.5 mol% of SiO_2-Cl afforded **4a** in 82% yield (Table 2, entry 5). The influence of the solvent was also evaluated for the model reaction. The reaction was performed using hydrocarbon, halogenated hydrocarbon, ethereal, protic polar and aprotic polar solvents in the presence of SiO_2-Cl. The best results were obtained in toluene (82%, Table 2, entry 5), benzene (79%, Table 2, entry 10) and 1,4-dioxane (80%, Table 2, entry 11). Based on Pfizer solvent selection guidelines,[28] toluene was preferred over benzene and 1,4-dioxane for further reaction. The use of azeotropic distillation using the Dean–Stark apparatus was also evaluated, and it was found that removal of the calculated amount of water using the Dean–Stark apparatus is utmost necessary as the reaction carried out without using azeotropic distillation assembly failed to offer a significant yield of **4a**.

The optimum reaction temperature was found to be 100 °C as an increase in temperature to 110 °C did not offer a high yield of **4a** (Table 2, entry 9). The yield decreases to 75% when the reaction was performed at 80 °C (Table 2, entry 8).

The optimized reaction conditions were used to synthesize varieties of 2,3-disubstituted-thaizolidin-4-one derivatives and the results are summarized in Table 3.

It was observed that SiO_2-Cl is an excellent catalyst in synthesizing substituted thaizolidin-4-one. The formation of thaizolidinone was influenced by the electronic nature of the substituent on aromatic aldehyde and the amine. Almost all electron-withdrawing and donating substituted aromatic aldehydes and aromatic amines are suitable for this reaction and converted into the desired product in satisfactory yields (**4a–4h**). For this reaction, heteroaromatic substituted aldehydes are good substrates and gave a good yield of the corresponding disubstituted thiazolidinone (**4i–4k).**

Recyclability is one of the ideal characteristics of the heterogeneous catalyst; therefore, the recyclability of the catalyst was tested using benzaldehyde, aniline and thioglycolic acid as substrate. After completion of the reaction, the mixture was filtered and the catalyst was separated and washed with EtOAc (3 × 20 ml). The recovered catalyst was dried and activated by heating at 80 °C for 24 h. and used for the next reaction. It was observed that SiO_2-Cl was active even after 5 recycles (Fig. 1).

Conclusion

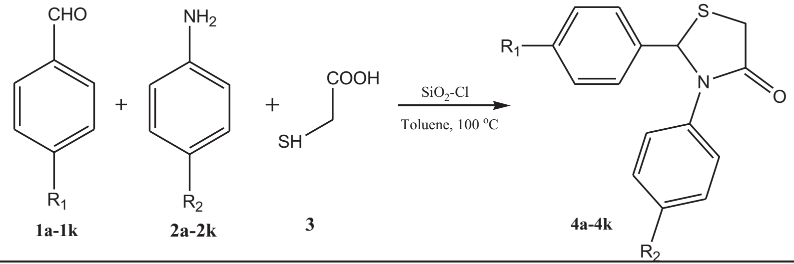
A convenient protocol for the synthesis of 2,3-disubstituted-thiazolidin-4-one analogs has been developed under one-pot, three-component SiO_2-Cl catalyzed cyclo condensation involving a variety of aldehydes, amines, and thioglycolic acid. In conclusion, we have shown the potential of SiO_2-Cl for synthesizing thiazolidine-4-one with good to excellent yields. The new catalytic method offers distinct advantages such as one-pot, three-component synthesis with broad substrate scope, high yield, less reaction time, ease of product isolation, and ease of catalyst preparation, recovery, reusability without loss of catalytic potential.

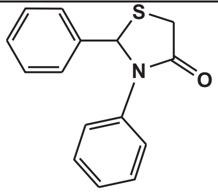
Experimental

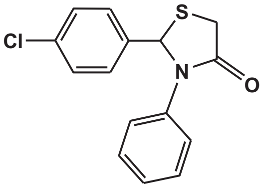
General procedure for preparation of silica chloride

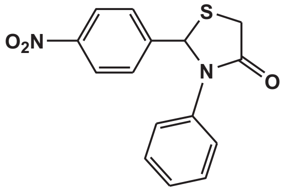
10 g of silica gel (Mesh size 230–400) placed in 250 ml round bottom flask was refluxed with thionyl chloride (40 ml) for 2 h[27]. The reaction was quenched by the addition of

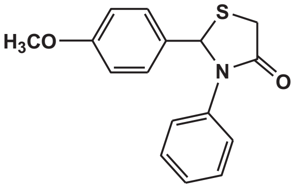
Table 3. SiO_2-Cl catalyzed synthesis of 2,3-disubstituted-thiazolidin-4-one analogues[a].

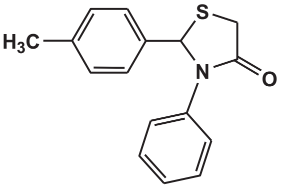


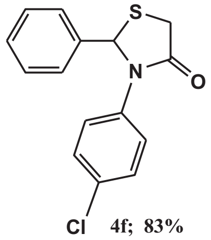

4a; 82%

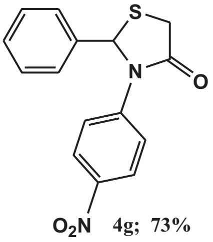

4b; 86%

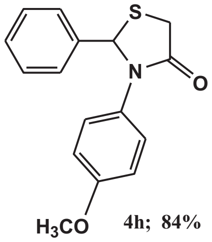

4c; 89%

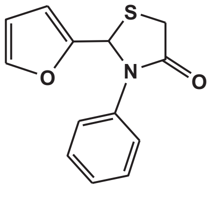

4d; 75%

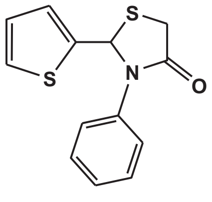

4e; 78%

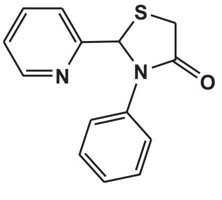

4f; 83%


4g; 73%


4h; 84%


4i; 73%


4j; 77%


4k; 73%

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[a] Reaction conditions: 1 mmol of aromatic aldehyde, 1 mmol of aromatic amine, 1 mmol of thioglycolic acid and SiO_2-Cl (2.5 mol%) stirred in 10 ml of toluene at 100 °C for 3 h.

[b] Isolated yield.

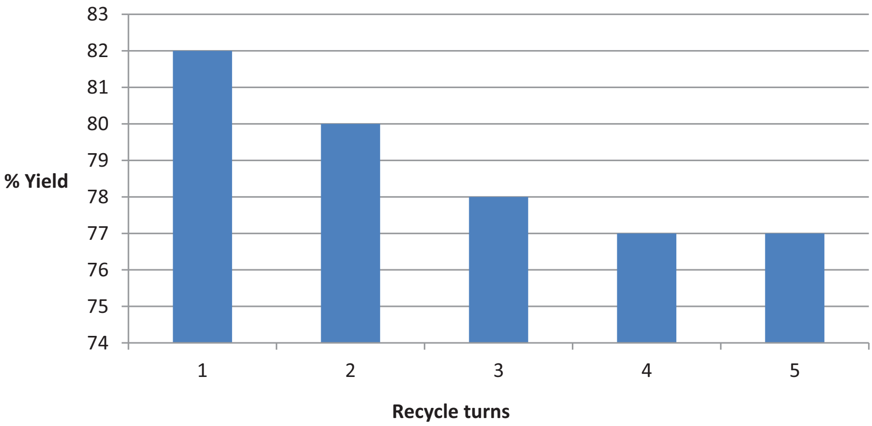

Figure 1. Recycle study of SiO_2-Cl.

toluene (50 ml) and unreacted thionyl chloride was removed by vacuum distillation. The resulting grayish-white powder was flame dried and stored in sealed glass vial without loss of activity.

General procedure for the synthesis of 2,3-disubstituted-thiazolidin-4-one (4a–4k)

To a magnetically stirred mixture of aromatic aldehyde **1a–1k** (1 equiv.), aromatic amine **2a–2k** (1 equiv.) and thioglycolic acid **3** (1 equiv.) in toluene (10 ml) 2.5 mol % of SiO_2-Cl was added. The reaction mixture was heated at 100 °C using Dean–Stark apparatus. The reaction was continued till water ceased to separate and the progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was filtered to separate the catalyst. The filtrate was evaporated under reduced pressure to get the crude product. The crude product thus obtained was washed with sodium bicarbonate, sodium bisulfite solution, water and finally dried to get the pure product.

General procedure for recyclability of catalyst

The catalyst which was separated from the reaction mixture was washed with ethyl acetate and dried under the reduced pressure to evaporate traces of solvent. It was further activated by heating at 80 °C for 24 h. and used for the next reaction.

2,3-diphenyl-thiazolidin-4 one (**4a**):[10,29] White solid; mp 130–131 °C (lit. 131–132 °C), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.21–7.01 (m, $J = 5.84$ Hz, 10H), 6.05 (s, 1H), 3.91–3.86 (d, $J = 15.8$ Hz, 1H), 3.78–3.74 (d, $J = 15.8$ Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 171.08, 139.55, 137.54, 129.12, 128.93, 129.91, 127.08, 126.96, 125. 63, 65.62, 33.51.

The supporting material contains the spectral characterization data. This material can be found via the "Supplementary Content" section of this article's webpage.

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