A Facile, Mechanochemical, Solvent-, and Catalyst-Free Synthesis of Functionalized 4-Thiazolidinones

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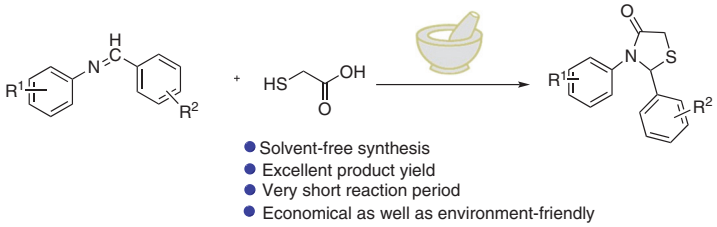


Received: 01.09.2023
Accepted after revision: 12.10.2023
Published online: 12.10.2023 (Accepted Manuscript), 16.11.2023 (Version of Record)
DOI: 10.1055/a-2190-9678; Art ID: SO-2023-09-0069-L

Abstract A highly eco-friendly greener approach based on the mechanochemical method using mortar and pestle is explored for the preparation of a variety of functionalized 4-thiazolidinones. The developed methodology does not require the use of harmful or expensive reagents and organic solvents and requires very less reaction time with easy isolation. The explored greener approach for the synthesis of 4-thiazolidinones is an important in terms of their usefulness for their valuable pharmacological properties.

Key words mechanochemistry, green chemistry, grinding, 4-thiazolidinones, solvent-free synthesis

One of the main challenges for the medicinal chemistry is to develop the useful therapeutic agents for the treatment of various types of infections against increasing multidrug resistant microbial pathogens as well as applications against different disorders. In the literature, there are numerous small-membered biologically active molecules which has druglike properties. Of these, five-membered rings, containing two heteroatoms such as 4-thiazolidinone ring have been observed in the core structure in various biologically active molecules.[1–4] The immense importance of 4-thiazolidinones-based scaffolds in various medications including antitubercular, anticancer, antidiabetic, anti-icrobial, anti-inflammatory, antimalarial, antiviral, aesthetic, etc. has fascinated organic chemists for their synthesis via newer synthetic methods.[5–8]

The conventional methods for the preparation of 4-thiazolidinones involves the high-temperature conditions, the use of organic solvents, expensive catalysts, the use of column chromatography for the separation and purification process (Figure 1).[9,10] The impact of global warming and interest towards the decrease in usage of harmful chemicals have encouraged researchers to revisit and further developing simple, economical, and environment-friendly pathways for the synthesis of the 4-thiazolidinone moiety.

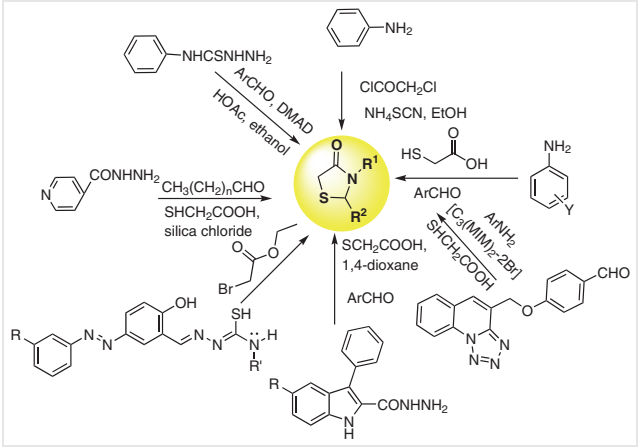


Figure 1 Earlier methods for the formation of functionalized 4-thiazolidinones

Keeping in mind, the biological activities of 4-thiazolidinones[1–8] (Figure 2) and realizing the importance of the green methodologies in organic synthesis, it was thought worthwhile to explore the greener methods for the preparations of functionalized 4-thiazolidinones.

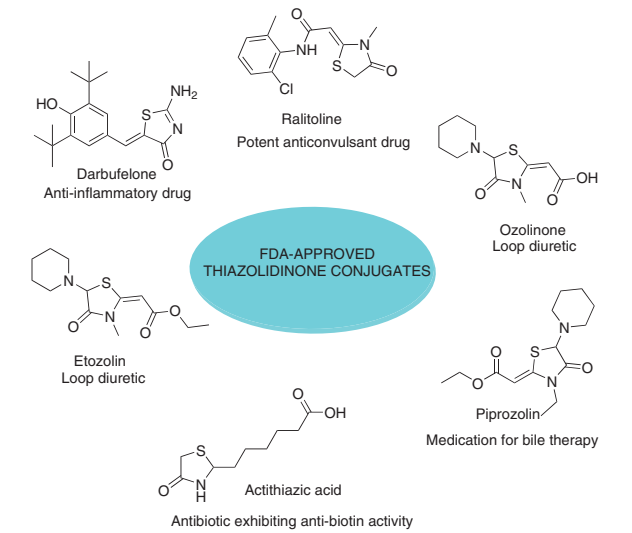


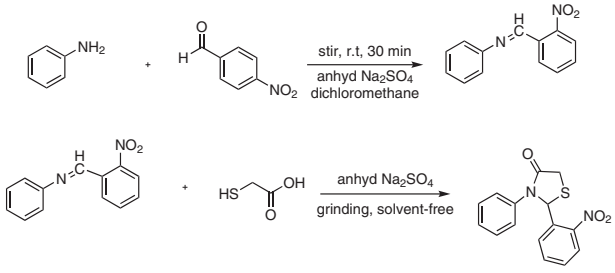
Figure 2 Functionalized 4-thiazolidinones-based FDA-approved drugs

On the other hand, mechanochemical synthesis is emerging as new green method for the preparation of various heterocycles via C–O, C–N, and C–S bond formation through methods like grinding and sonication.[11–18] The simple economical method offers several benefits such as less use of harmful toxic solvents, use of eco-friendly chemicals, less use of toxic and expensive metal-based catalyst, lesser release of harmful wastes and no or negligible byproduct formation.[19–21] Since the reaction does not result in the formation of any byproduct, the yield of the reaction is also remarkably higher as compared to conventional methods employed.

Keeping in view of the diverse pharmacological profile of functionalized 4-thiazolidinones and the upsurge in their synthetic developments,[22–27] we have explored the facile and greener approach for the synthesis of functionalized thiazolidin-4-ones. The current methodology involved the simple grinding method using mortar and pestle. The developed methodology did not involve the use of any expensive catalyst, solvent, or high-temperature conditions, and the reaction completed within few minutes. Moreover, the reaction did not result in the formation of any byproduct and afforded a variety of 4-thiazolidinone derivatives **1a–k** in high yield.

The starting materials were procured commercially. The variety of functionalized amines and aldehydes were explored in the initial synthesis of the functionalized imines by traditional methods.[28] The functionalized imines **4a–j** were explored in the synthesis of functionalized thiazolidin-4-ones. The optimizations of the employed methodology were performed based on achieving better yields of the desired product as well as the time required to complete the reactions with varying the reaction conditions based on the amount of thioglycolic acid and anhydrous sodium sulfate (dehydrating agent). The investigated reaction model obtained after optimization of the model reaction for the synthesis of 2-(2-nitrophenyl)-3-phenylthiazolidin-4-one is represented in Table 1. It is evident that without the use of dehydrating agent the reaction was quite slow and resulted in poor yield (Table 1, entry 1). Further, the addition of sodium sulfate to the reaction mixture during grinding not only increased but also enhanced the product yield (Table 1, entry 2). It is evident that on further grinding the product yield was found to be marginally improved (Table 1, entry 3). Increasing the amount of thioglycolic acid and the dehydrating agent a maximum product yield was reported (Table 1, entry 4). At last (Table 1, entry 5), grinding time-period was recorded and a maximum product yield of 95% was obtained after 12 min of grinding.

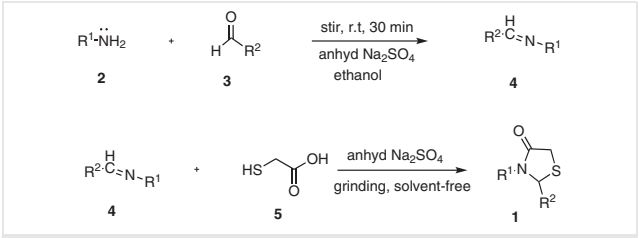
Table 1 Optimization of the Reaction Conditions for the Synthesis of Functionalized Thiazolidin-4-ones



Entry	Imine (equiv)	Thioglycolic acid (equiv)	Dehydrating agent (equiv)	Time (min)	Yield (%)[a]
1	1.0	1.0	–	15	48
2	1.0	1.0	Na_2SO_4 (1)	15	80
3	1.0	1.2	Na_2SO_4 (1)	5	83
4	1.0	1.0	Na_2SO_4 (2)	8	88
5	1.0	1.2	Na_2SO_4 (2)	8	95

[a] Isolated yields.

After optimizing the reaction conditions, a variety of arylaldehyde **3** and amines **2** were tested to yield a series of substituted imines **4** which on condensation reaction with thioglycolic acid (1.5 equiv), sodium sulfate (2.0 equiv) using traditional grinding method using mortar and pestle for 8 min afforded 4-thiazolidinone derivatives **1a–k** in high yield (Scheme 1).[29–31] A wide range of electron-withdrawing and electron-donating 2,3-diphenyl-substituted thiazolidin-4-one derivatives were obtained in good yield (Table 2, entries 1–11). However, in the case of glyoxal the desired thiazolidin-4-one derivative was not obtained probably due to steric crowding because of the presence of two thiazolidine-4-one rings (bis-thiazolidin-4-ones).



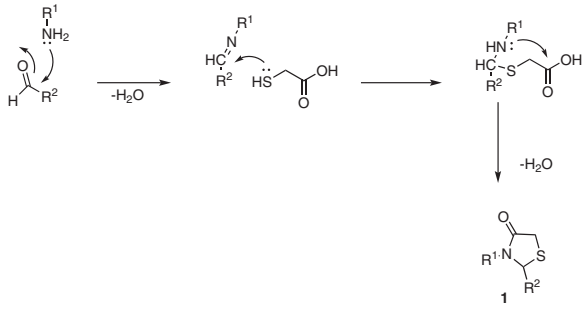
Scheme 1 Synthesis of 2,3-diphenyl-substituted thiazolidin-4-ones

Table 2 Substrate Scope in the Synthesis of 2,3-Diphenyl-Substituted Thiazolidine-4-ones[a]

Entry	R^1	R^2	Product **1**	Time (min)	Yield (%)[b]
1	C_6H_5	C_6H_5	**1a**	8	90 (4.93 g)
2	C_6H_5	2-$NO_2C_6H_4$	**1b**	8	95 (6.12 g)
3	4-ClC_6H_4	C_6H_5	**1c**	8	94 (4.26 g)
4	4-$CH_3C_6H_4$	C_6H_5	**1d**	8	82 (4.12 g)
5	2-$CH_3C_6H_4$	C_6H_5	**1e**	8	90 (4.52 g)
6	2-$CH_3C_6H_4$	2-$NO_2C_6H_4$	**1f**	8	95 (5.57 g)
7	4-FC_6H_4	C_6H_5	**1g**	8	90 (4.42 g)
8	C_6H_5	4-$NO_2C_6H_4$	**1h**	8	92 (5.93 g)
9	C_6H_{11} (cyclohexyl)	C_6H_5	**1i**	8	90 (4.73 g)
10	$C_6H_5CH_2$ (benzyl)	C_6H_5	**1j**	8	85 (4.27 g)
11	C_4H_9 (*n*-butyl)	C_6H_5	**1k**	8	95 (6.11 g)
12	C_6H_5	CHO	–	8	no reaction

[a] Optimized reaction conditions: imine (1.0 equiv), thioglycolic acid (1.5 equiv), Na_2SO_4 (2 equiv), no solvent, grinding (9–12 min).
[b] Isolated percentage yield and mass yield.

The imines derived from aliphatic amine afforded better yield of thiazolidin-4-ones **1a–k** (Table 2, entries 9-11). However, the imines with aryl substituents afforded slightly low yield of thiazolidin-4-ones **1** (Table 2, entries 1–8). However, the formation of thiazolidin-4-ones **1** did not occur using glyoxaldehyde as aldehyde counterpart of imine (Table 2; entry 12). All the prepared 2,3-diphenyl-substituted thiazolidin-4-ones **1a–k** were characterized with the help of spectroscopic evidences. The ^{1}H NMR spectra of all prepared thiazolidin-4-ones **1a–k** were confirmed by the presence of singlet peak of CH-bonded to substituted phenyl ring in the range of δ = 6.14–6.44 ppm and a double-doublet due to methylene hydrogens at δ = 3.80–4.00 ppm.[32] The probable mechanism for the solvent-free synthesis of 2,3-diphenyl-substituted thiazolidin-4-one derivatives in illustrated in Scheme 2. The mechanism involved initial attack of nucleophilic nitrogen of amines to electrophilic carbonyl carbon of benzaldehydes with the release of a water molecule and the formation of a double bond. Further, nucleophilic sulfur of thioglycolic acid attacks the iminic carbon with the shifting of electrons followed by an attack of the nucleophilic nitrogen on the carboxylic carbon resulting in the formation of a thiazolidinone ring with release of a water molecule. Hence, the use of anhydrous sodium sulfate as mediator in the reaction absorbs the released water molecules thereby enhances and shifts the reaction in the forward direction.



Scheme 2 Proposed mechanism for the synthesis of 2,3-diphenyl-substituted thiazolidin-4-one derivatives

In conclusion, the current manuscript describes the facile solvent-free and green mechanochemical approach for the synthesis of functionalized thiazolidin-4-ones. The employed green approach has a broader substrate scope and afforded the thiazolidin-4-ones in good yields in comparatively short reaction time with easy isolation. The current approach is also an important in terms of the diverse pharmacological profile of functionalized thiazolidin-4-ones.

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

Simranpreet K. Wahan is highly thankful to the Department of Science and Technology, Ministry of Science and Technology, India (DST Inspire) for providing financial support for her research work.

Acknowledgment

IK Gujral Punjab Technical University, Kapurthala, 144601, Punjab is acknowledged for providing research facilities.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-2190-9678.

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(29) **General Procedure for the Synthesis of 2,3-Diphenyl-Substituted Thiazolidin-4-one Derivatives 1a–k**
The reaction involved the preparation of series of imines **4a–k** by stirring the mixture of various aliphatic and aromatic amines **2** (1 equiv) and various substituted benzaldehydes **3a–k** (1.1 equiv) in dichloromethane as solvent at room temperature in the presence of sodium sulfate (2 equiv) as dehydrating agent. After isolation, the mixture of prepared series of imines **4a–k** were mixed and grinded using mortar and pestle with thioglycolic acid **5** (1.5 equiv) and Na_2SO_4 (2 equiv) for 9–12 min till the completion of reaction. The reaction was monitored by using TLC. After the reaction was found to be completed, the workup of the reaction was done by using ethyl acetate (2 × 20 mL). the crude product obtained was dried using magnesium sulfate, filtered, and dried to collect the crude product. The impure product was purified by adding the mixture of diethyl ether and hexane in the ratio of 3:1 dropwise with stirring. After keeping the reaction mixture aside for some time, solid precipitates were found at the bottom of the beaker. Mother liquor was decanted off, and the product obtained was dried to obtain pure solid compounds of 2,3-diphenyl-substituted thiazolidin-4-one derivatives. The same process was repeated 2–3 times to obtain the product without any impurities.
(30) **2,3-Diphenylthiazolidin-4-one (1a)**
Yield: 4.93 g (90%); yellow solid; mp 127–129 °C. IR(KBr): ν = 1655 (C = O) cm^{-1}. ^1H NMR (500 MHz, DMSO): δ = 3.98 (dd, 2 H, CH_2), 5.84 (s, 1 H, CH), 7.31 (dd, 1 H, CH), 7.5 (dd, 1 H, CH), 7.8 (dd, 2 H, CH), 7.9 (d, 2 H, CH), 8.0 (dd, 2 H, CH) ppm.
(31) **2-(2-Nitrophenyl)-3-phenylthiazolidin-4-one (1b)**
Yield: 6.12 g (95%); pale yellow solid; mp 136 °C. IR(KBr): ν = 1654 (C=O), 1595–1313 (NO_2) cm^{-1}. ^1H NMR (500 MHz, DMSO): δ = 3.90–4.00 (dd, 2 H, CH_2), 6.44 (s, 1 H, CH), 7.99 (d, 1 H, CH), 7.57 (dd, 1 H, CH), 7.72 (dd, 1 H, CH), 7.54 (d, 1 H, CH), 7.31 (d, 2 H, CH), 7.27 (dd, 2 H, CH), 7.13 (dd, 1 H, CH) ppm.
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