Heteropoly acid (PW/SiO_2) Catalyzed Environmentally Benign Synthesis of 4-Thiazolidinone Derivatives

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Abstract:

A silica-supported phosphotungstic heteropoly acid (PW/SiO_2) promoted cyclocondensation-cyclization pathway has been established using one pot reaction of anilines, aldehydes and mercaptoacetic acid to give 4-thiazolidinone derivatives in good to promising yields using microwave irradiation. Application for this protocol easy workup, high yields, short reaction times, variability of functional groups, recyclability and solvent-free conditions.

Keywords: Heteropoly acid (PW/SiO_2), Environmentally benign, Multicomponent reactions, 4-Thiazolidinones,

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1. Introduction

Heteropoly acids (HPAs) with Keggin structure possess special characteristics that allow their use as catalysts in acid reactions, as they have a very high intrinsic acidity [1]. However, due to the low surface area of the bulk HPA, it is advisable to support them on a carrier with high surface area such as silica, activated carbon, alumina, or clays [2-7]. The use of a support that leads to good dispersion of the HPA on a high surface area can result in an increase of the catalytic activity [8]. In the design of this type of supported catalyst, the porous structure is an aspect to be taken into account. The pore size must be adequate in order that the molecule transport to or from the active sites can be made easier. Besides, good HPA immobilization in the support is a subject to be carefully considered for the use of the catalysts in liquid-phase reactions. In our previous studies [9,10], it was proved that silica is a support with suitable properties to obtain HPA-based catalysts for acid reactions. The aim of the present work is to study the use of an efficient catalyst based on heteropoly acid supported on silica, particularly dodecatungestophosphoric acid (PW), and its comparison with molybdophosphoric acid (PMo), supported on different solids in preparation of mandelates. Also, efficacy of $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ (CsPW) as a heterogeneous catalyst has been checked.

Multicomponent reactions (MCRs) have been widely used for the synthesis of a wide range of heterocycles. As heterocyclic fragments are present in the majority of natural products and drug-like compounds, efficient synthesis of diverse heterocyclic compounds remains a key issue until now. MCR is one of the most effective synthetic techniques for the development of various heterocyclic compounds, applying subsequent transformation, cyclization and functionalization, leading to a diversity-oriented synthesis [11]. Thus, various medical chemists have been attracted by the development of multi-component reaction protocols for the synthesis of heterocyclic compounds.

4-Thiazolidinones and its derivatives have drawn considerable attention of the researchers in the recent years due to their medicinal properties. 4-Thiazolidinones is a medicinally significant pharmacophore with wide range of remarkable pharmacological activity such as anti-convulsant [12], anti-inflammatory [13], antimicrobial [14], anti-viral [15], antitumor [16], antidiabetic [17], antituberculosis [18], antiparasitic [19], analgesic [20], antidiarrhoeal [20], antiarthritic [21], cardiovascular activity [22], anti-HIV [23] and FSH agonist [24]. Furthermore, 4-

thiazolidinones conjugates are also exhibits prominent cancer activity against several cancer cell line such as antiproliferative activity against Reh and Nalm6 cells [25], antiapoptotic biocomplex (Bcl-XL-BH3) [26], breast cancer JSP-1 inhibitor [27], Cyclin B/CDK1 inhibitor [28], MCF-7 [29], integrin avb3 receptor [30], HT29 colon cancer cell line [31] and tumor necrosis factor (TNFα) [32]. Structure of representative bio-active 4-thiazolidinone motifs are disclose in **Fig. 1**.

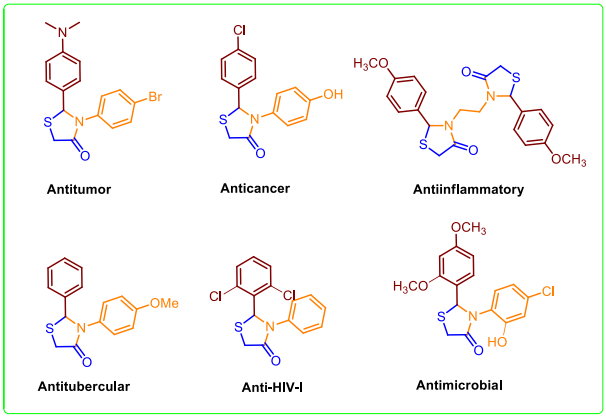


Fig. 1. Structure of bio-active 4-thiazolidinones conjugates

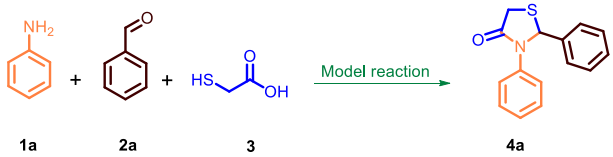
Due to the wide range of biological activities of 4-thiazolidinones, several synthesis pathway have been established for the synthesis of 4-thiazolidinone conjugates. Because of wide range of pharmacological activity numerous catalytic route have been established including, acetic acid [33], ammonium persulfate [34], acid catalysed [35], $Bi[SCH_2COOH]_3$ [36], Cd-Zr_4- $[PO_4]_6$ [37], DIPEA [38], DBSA [39], montmorillonite K-10 [40], *N*-methyl pyridinium tosylate [41], nano-Fe_3O_4@SiO_2 [42], silica gel [43], silica supported $CoFe_2O_4$@SiO_2/$PrNH_2$ [44], $SnCl_2$ [45], ionic liquid [bmim]OH [46] and $Y[OTf]_3$ [47]. However, the above well developed protocol some drawbacks such as hazardous solvent, extended heating, separation, recycling of catalyst and tedious work-up procedure.

As per our study, the existential of this work is to begin efficient and rapid synthetic protocol for the synthesis of 4-thiazolidinone derivatives under ecofriendly conditions. As an extension of emerging efficient and economic strategy to expand biologically considerable active compounds, herein, we disclose first time microwave assisted solvent free synthesis of 4-thiazolidinone derivatives using silica-supported phosphotungstic heteropoly acid (PW/SiO_2) as a catalyst to give good to prominent yields.

RESULTS AND DISCUSSION

Chemistry

To attain optimized reaction conditions procedure based on the reaction of aniline (**1a**), benzaldehyde (**2a**) (1 mmol) and mercaptoacetic acid (**3**) (1 mmol) as representative reaction (**Scheme 1**), we screened solvents, catalyst loading, temperatures and the details of this study are illustrated in **Table 1**.



Scheme 1. Model reaction

First, we performed the model reaction using 40 wt% of PW/SiO_2 (12 mol%, 0.2 g) as the catalyst under reflux conditions in different solvents, but in all cases yields were considerably lower than when the model reaction was carried out under solvent free conditions (**entries 1-15**).

Table 1. Optimization of the reaction conditions for the synthesis of 4-thiazolidinone[a]

Entries	Solvent	PW/SiO_2 mol %	Time (min)	Temp (°C)	Yield[b] (%)
1	EtOH	40 wt% (12 mol %)	40	Reflux	58
2	MeOH	40 wt% (12 mol %)	40	Reflux	60
3	*tert*-BuOH	40 wt% (12 mol %)	40	Reflux	65
4	H_2O	40 wt% (12 mol %)	40	Reflux	38
5	CH_3CN	40 wt% (12 mol %)	40	Reflux	40
6	THF	40 wt% (12 mol %)	40	Reflux	44
7	$PhCH_3$	40 wt% (12 mol %)	40	Reflux	50
8	DMF	40 wt% (12 mol %)	40	Reflux	60
9	**Solvent-free**	**40 wt% (12 mol %)**	**40**	**80**	**95**
10	Solvent-free	40 wt% (12 mol %)	40	60	63
11	Solvent-free	40 wt% (12 mol %)	40	70	72
12	Solvent-free	40 wt% (12 mol %)	40	90	91
13	Solvent-free	40 wt% (12 mol %)	40	100	82
14	Solvent-free	20 wt% (12 mol %)	40	80	59
15	Solvent-free	60 wt% (12 mol %)	40	80	94

[a]Reaction conditions: aniline (**1a**), benzaldehyde (**2a**) (1 mmol) and mercaptoacetic acid (**3**) (1 mmol) and PW/SiO_2 (0.2 g). [b]Isolated yield.

The effect of temperature was also studied by carrying out the model reaction at different temperatures under solvent free conditions, and the best results were obtained at 80 ºC (**entry 9**). Increasing the weight percentage of silica supported PW did not meaningfully increase in yield of final product, but lowering the weight percentage did (**entries 14-15**). On balance, the conditions shown in entry 9 represented the best yields in terms of temperature, weight percentage of catalyst and solvent.

Further, the model reaction was tested with 4, 8, 12 and 16 mol% of the catalyst at 80 ºC (**Table 2, entries 1-4**). The maximum yield (95%) of the reaction was obtained in 30 min with 12 mol% of the catalyst (**entry 3**). A further increase in the mol% of catalyst did not meaningfully affect the yield (**entry 4**). These results were supportive of the conclusion that solvent free conditions at 80 ºC with 12 mol% of the catalyst supplied at 40 wt% is the best choice for these reactions.

Table 2. Optimization of catalyst concentration[a]

Entries	Catalyst Mol %	Solvent	Time (min)	Temp (°C)	Yield[b] (%)
1	4	solvent free	40	80	58
2	8	solvent free	40	80	79
3	12	solvent free	40	80	95
4	16	solvent free	40	80	94

[a]Reaction conditions: aniline (**1a**), benzaldehyde (**2a**) (1 mmol) and mercaptoacetic acid (**3**) (1 mmol) at 80 °C for 30 min. [b]Isolated yield.

We have also studied the recyclability and reusability of the silica supported PW catalyst for subsequent reaction runs done under the same reaction conditions.

Table 3. Recycling of the catalyst[a]

Entry	Run	Time (min)	Yield (%)[b]
1	Fresh	30	95
2	I	30	92
2	II	30	87
3	III	30	84
4	IV	30	80

[a]Reaction conditions: aniline (**1a**), benzaldehyde (**2a**) (1 mmol) and mercaptoacetic acid (**3**) (1 mmol) and 12 mol% PW/SiO_2at 80 °C. [b]Isolated yield.

The product **3a** was obtained in 91, 88, 85 and 83% yields after four successive cycles. See the Experimental section for details of catalyst isolation from the reaction mixture.

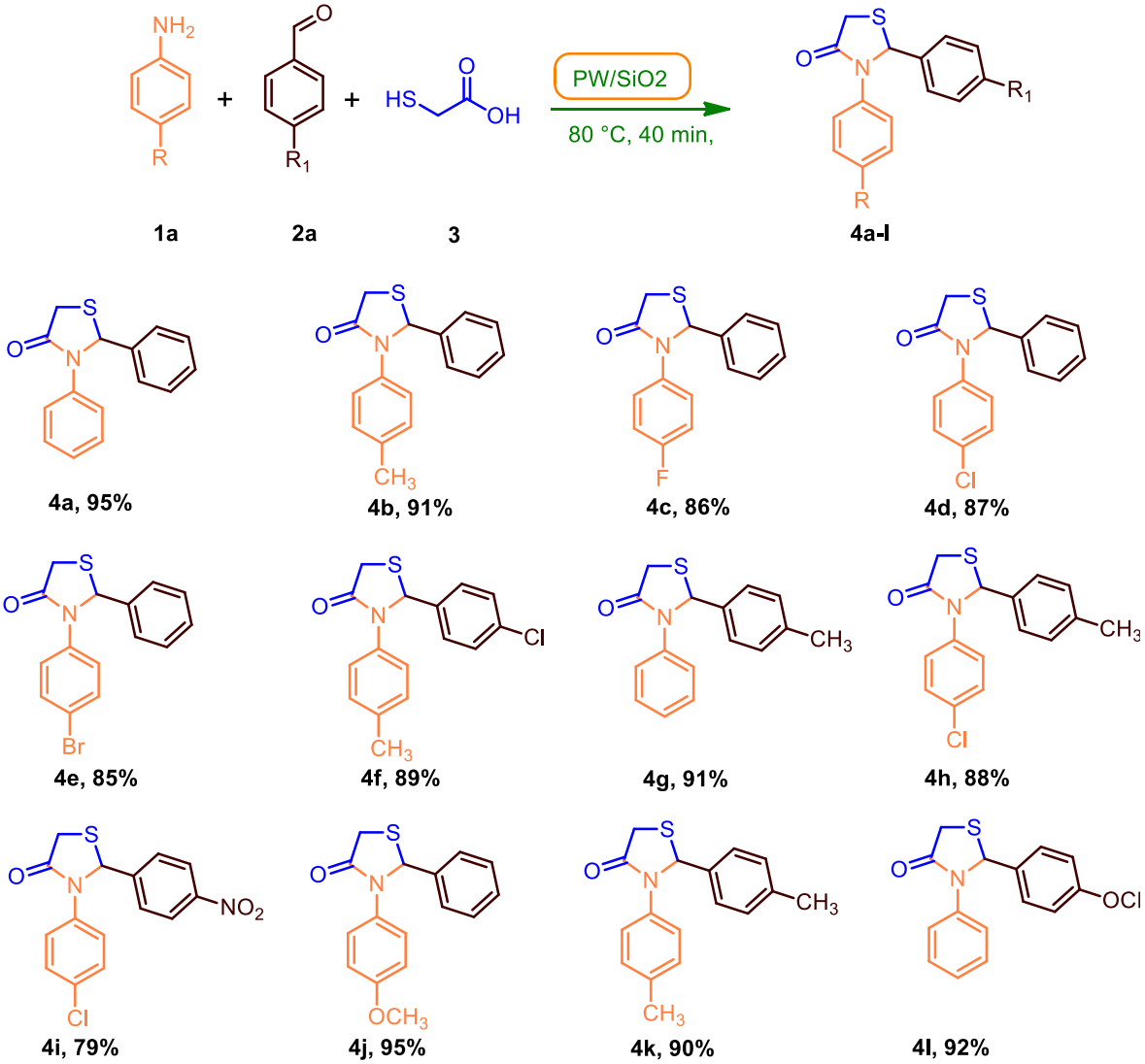
Table 4. **Comparative study for the bronsted acidic PW/SiO_2 catalyst with previous reported catalyst**

We also examine the comparative study PW/SiO_2 catalyst with other reported protocol for the synthesis of 4-thiazolidinones. According to study suggests that PW/SiO_2 is prominent catalyst for the efficient and facile synthesis of 4-thiazolidnones and results are disclose in (**Table 4**, **entry 9**).

Table 4. Comparative study of PW/SiO_2 with Reported Catalysts

Entry	Catalyst	Time (min)	Yield (%)	condition	Ref.
1	[bmim][PF_6]	9 h	80	80 °C	[48]
2	[bmim][BF_4]	1.7 h	82	80 °C	[48]
3	[MOEMIM]TFA	9 h	90	80 °C	[48]
4	$HClO_4$-SiO_2	5 h	85	PhMe/100	[49]
5	TfOH-SiO_2	5 h	72	PhMe/100	[49]
6	H_2SO_4-SiO_2	5 h	55	PhMe/100	[49]
7	Silica gel, DCM	6 h	96	DCM/RT	[43]
8	$Bi(SCH_2COOH)_3$	2 h	90	70 °C	[46]
9	PW/SiO_2	40 min	95	80 °C	Present work

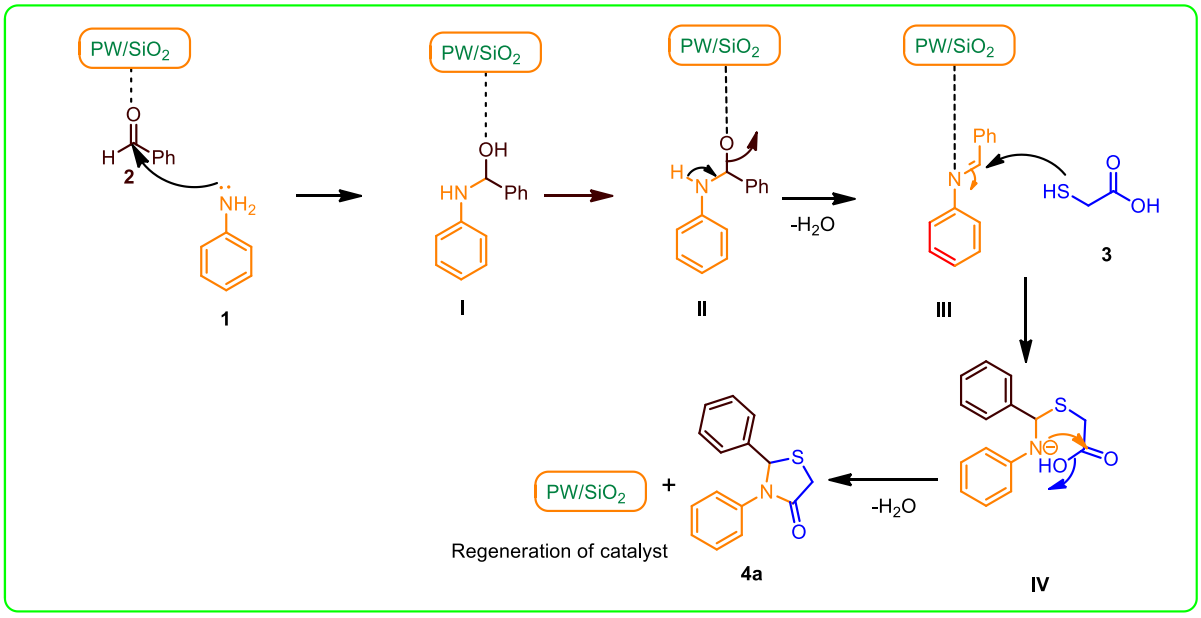
The structural elucidation of synthesize **4f** compound was confirmed by ^1H and ^{13}C NMR analysis. ^1H NMR spectra the peak observed at 2.28 δ ppm for the CH_3 group. The peak observed at doublet of a doublet 4.00-3.86 ppm due to the presence of -CH_2 protons in titled compound. The C-H proton of the 4-thiazolidinone ring observed at singlet at δ 6.04 ppm. In ^{13}C NMR spectra peak observed at 32.70, 64.30 and 170.1 ppm for the CH, CH_2 and C=O bond present in synthesized compounds.



Scheme 2. Substrate scope for the synthesis of 4-Thiazolidinones using PW/SiO_2 catalyst.

Plausible Reaction Mechanism

Reaction mechanism for the synthesis of 4-thiazolidinones employing PW/SiO_2 is catalyst. In first step benzaldehyde activated by followed by nucleophilic substitution of aniline results formation **I** intermediate. In next step removal of water molecules from intermediates **I** with the help of PW/SiO_2 to give imine product **II**. In the third step intermediate **III** react with **3** afforded cycloaddition product **IV**. Further intramolecular cyclization to form final product **4a** *via* removal of H_2O molecule and regeneration of catalyst. Details reaction mechanism is disclose in **Scheme 3.**



Scheme 3. Reaction mechanism for the synthesis of compound **4a**.

2. Experimental section

2.1. Materials and methods

Experimental section and NMR files are incorporated in supporting information.

Preparation of PW/SiO_2

Experimental protocol for the Synthesis of PW/SiO_2 are given in supporting information.

General Procedure for Synthesis of 4-thiazolidinone derivatives (4a-l)

A mixture of anilines (**1a**) (1 mmol), aryl aldehyde (**2a**) (1 mmol), mercaptoacetic acid (**3**) (1 mmol) and PW/SiO_2 20 mol% at 80 °C for 40 min. The progress of the reaction was monitored by thin layer chromatography (*n*-Hexane/EtOAc 8:2). Further, addition of ice cold water (10 mL) was added to it and stirred for 10 min and filtered. The obtained solid was filtered, washed with cold water to remove the ionic liquid. The obtained crude compounds were recrystallized using ethanol. The synthesized compound is confirmed by MP, ^{1}H NMR and ^{13}C NMR spectra.

2,3-Diphenylthiazolidin-4-one (4a): The **4a** was observed *via* cyclocondensation of **1a**, **2a** and **3** as white solid; Mp: 130-132 °C (lit.[50] 128-130 °C); Yield: 91%; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.83 (d, 1H, *J* = 16 Hz), 3.97 (d, 1H, *J* = 16 Hz), 6.09 (s, 1H, S-CH-N), 7.20 (d, *J* = 7.9 Hz, 3H) and 7.22 (dd, *J* = 9.6, 4.9 Hz, 7H).

2-phenyl-3-(*p*-tolyl)thiazolidin-4-one (4b): The **4b** was observed *via* cyclocondensation of **1b**, **2a** and **3** as white solid; Mp: 110-112 °C (lit.[51] 110-112 °C); Yield: 89%; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.27 (s, 3H, CH_3), 3.89 (d, 1H, *J* = 16 Hz), 3.99 (d, 1H, CH_2, *J* = 16 Hz), 6.05 (s, 1H, S-CH-N), 7.16 (m, 2H), 7.23 (d, *J* = 8.3 Hz, 2H) and 7.38-7.26 (m, 5H).

3-(4-fluorophenyl)-2-phenyl thiazolidin-4-one (4c): The **4c** was observed *via* oxidative cyclocondensation of **1c**, **2a** and **3** as white solid; Mp: 115-116 °C (lit.[52] 115-116 °C); Yield: 84%; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.72 (d, 1H, *J* = 16 Hz), 3.82 (d, 1H, CH_2, *J* = 16 Hz), 6.05 (s, 1H, S-CH-N), 6.96 (dd, *J* = 24.1, 6.9 Hz, 2H) and 7.21-7.04 (m, 7H).

3-(4-Chlorophenyl)-2-phenylthiazolidin-4-one (4d): The **4d** was observed *via* cyclocondensation of **1d**, **2a** and **3** as white solid; Mp: 110-112 °C (lit.[52] 110-112 °C); Yield: 86%; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.82 (d, 1H, *J* = 16 Hz), 3.89 (d, 1H, CH_2, *J* = 16 Hz), 5.98 (s, 1H, S-CH-N), 7.17-7.02 (m, 5H), 7.31-7.27 (m, 2H) and 7.41-7.26 (m, 2H).

3-(4-bromophenyl)-2-phenylthiazolidin-4-one (4e): The **4e** was observed *via* cyclocondensation of **1e**, **2a** and **3** as white solid; Mp: 114-115 °C (lit.[52] 115-116 °C); Yield: 85%; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.86 (d, 1H, *J* = 16 Hz), 3.97 (d, 1H, CH_2, *J* = 16 Hz), 6.07 (s, 1H, S-CH-N), 7.12 (dd, *J* = 6.6, 4.7 Hz, 2H) and 7.38-7.18 (m, 7H).

2-(4-chlorophenyl)-3-(*p*-tolyl)thiazolidin-4-one (4f): The **4f** was observed *via* cyclocondensation of **1f**, **2b** and **3** as yellow solid; Mp: 164-166 °C; Yield: 88%; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.28 (s, 3H, CH_3), 3.84 (d, 1H, *J* = 16 Hz), 3.98 (d, 1H, CH_2, *J* = 16 Hz), 6.04 (s, 1H, S-CH-N), 7.01 (dd, *J* = 8.2, 2.8 Hz, 2H), 7.09 (d, *J* = 6.2 Hz, 2H) and 7.26 (dd, *J* = 8.0, 4.4 Hz, 4H); ^{13}C NMR (101 MHz, $cdcl_3$) δ 20.31, 32.70, 64.30, 124.95, 128.37, 129.19, 133.88, 134.00, 136.11, 137.44 and 170.16.

3-Phenyl-2-(*p*-tolyl)thiazolidin-4-one (4g): The **4g** was observed *via* cyclocondensation of **1a**, **2c** and **3** as brown solid; Mp: 118-120 °C (lit.[50] 116-118 °C); Yield: 91%; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.29 (s, 3H, CH_3), 3.89 (d, 1H, *J* = 16 Hz), 4.02 (d, 1H, CH_2, *J* = 16 Hz), 6.05 (s, 1H, S-CH-N), 7.05 (dt, *J* = 6.4, 5.1 Hz, 4H) and 7.40-7.22 (m, 5H).

3-(4-Chlorophenyl)-2-phenylthiazolidin-4-one (4h): The **4h** was observed *via* cyclocondensation of **1d**, **2c** and **3** as white solid; Mp: 110-112 °C (lit.[50] 110-112 °C); Yield: 88%; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.98 (d, 1H, CH_2, *J* = 16 Hz), 2.25 (s, 3H, CH_3), 3.89 (d, 1H, *J* = 16 Hz), 6.13 (s, 1H, S-CH-N), 7.16-6.93 (m, 4H), 7.45 (d, *J* = 8.2 Hz, 2H), 8.13 (d, *J* = 8.5 Hz, 2H).

3-(4-chlorophenyl)-2-(4-nitrophenyl)thiazolidin-4-one (4i): The **4h** was observed *via* cyclocondensation of **1d**, **2d** and **3** as white solid; Mp: 150-152 °C; Yield: 79%; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.94 (d, 1H, *J* = 16 Hz), 4.04 (d, 1H, CH_2, *J* = 16 Hz), 6.17 (s, 1H, S-CH-N), 7.14 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.55 (d, *J* = 8.6 Hz, 2H) and 8.16 (d, *J* = 8.2 Hz, 2H).

3-(4-methoxyphenyl)-2-phenylthiazolidin-4-one (4j): The **4j** was observed *via* cyclocondensation of **1a**, **2g** and **3** as yellow solid; Mp: 62-64 °C (lit.[52] 61-62 °C); Yield: 95%; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.82 (d, 1H, *J* = 16 Hz), 3.86 (s, 3H, , CH_3), 3.96 (d, 1H, CH_2, *J* = 16 Hz), 6.10 (s, 1H, S-CH-N), 7.24-7.12 (m, 5H), 7.47 (d, *J* = 8.4 Hz, 2H) and 7.82 (d, *J* = 8.2 Hz, 2H).

2,3-di-p-tolylthiazolidin-4-one (4k): The **4k** was observed *via* cyclocondensation of **1b**, **2c** and **3** as white solid; Mp: 122-124 °C (lit.[52] 121-123 °C); Yield: 90%; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.30 (s, 6H, CH_3), 3.84 (d, 1H, *J* = 16 Hz), 3.95 (d, 1H, CH_2, *J* = 16 Hz), 6.14 (s, 1H, S-CH-N), 7.54 (d, *J* = 8.1 Hz, 4H) and 7.84 (d, *J* = 8.2 Hz, 4H).

2-(4-methoxyphenyl)-3-phenylthiazolidin-4-one (4l): The **4l** was observed condensation of **1b**, **2c** and **3** as white solid; Mp: 98-100 °C (lit.[48] 97-99 °C); Yield: 92%; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.83 (s, 3H, -OCH_3), 3.97 (d, 1H, *J* = 16 Hz), 4.12 (d, 1H, CH_2, *J* = 16 Hz), 6.10 (s, 1H, S-CH-N), 7.40-7.26 (m, 5H), 7.64 (d, *J* = 8.3 Hz, 2H) and 7.88 (d, *J* = 8.1 Hz, 2H).

Conclusion

A highly efficient and environmentally benign protocol has been developed for the synthesis of 4-thiazolidinones using an recoverable and inexpensive PW/SiO_2 at 80 °C for 40 min. This reaction protocol many more advantages, such as uniqueness, high atom efficiency, clean reaction profiles, mild reaction condition, ecofriendliness, simple workup and without using any hazardous solvents.

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Availability of Data and Materials

Experimental section and supplementary data (copies of ^{1}H and ^{13}C NMR spectra of represented compounds) associated with this article can be found through the "Supplementary Content" section of this article's webpage.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Consent for publication

No consent for publication was required

Ethics Approval and Consent to Participate

Not applicable.

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