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Tromethamine organocatalyzed efficient tandem-multicomponent synthesis of new thiazolyl-4-thiazolidinones in aqueous medium

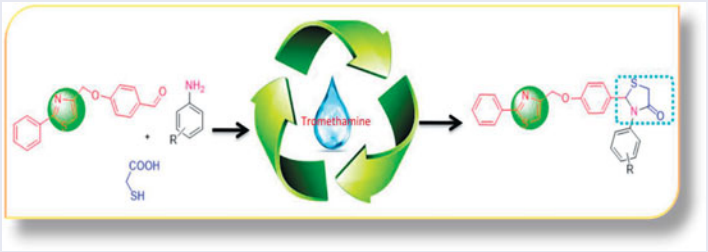
Manisha R. Bhosle[a], Sayali A. Kharote[a], Giribala M. Bondle[a], and Jyotirling R. Mali[b]

[a]Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, Maharashtra, 431004, India; [b]College of Pharmacy, Dongguk University-Seoul, Goyang, 10326, Republic of Korea

ABSTRACT

The catalytic potential of tris(hydroxymethyl)aminomethane (Tromethamine) has been assessed for the one pot three component tandem reaction involving a thiazolylmethoxy phenyl/aromatic carboxaldehyde, substituted amines and thioglycolic acid to form new thiazolyl-4-thiazolidinones and known substituted-4-thiazolidinones. This strategy involves the use of tromethamine as a reusable promoter and water as an eco-friendly reaction medium. The merits of this protocol are high atom economy, mild reaction conditions, good yields of desired products in short reaction times, and reusable reaction medium. The generality and functional tolerance of this convergent and environmentally benign method is demonstrated.

GRAPHICAL ABSTRACT



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KEYWORDS
4-Thiazolidinone; multicomponent; organocatalysis; tromethamine

Introduction

Functionalized thiazolidinones are one of the most extensively investigated class of compounds because of their broad range of pharmacological profiles. Compounds containing 4-thiazolidinone moiety possessing an assortment of pharmacological activities such as antibacterial,[1] anticancer,[2] antitubercular,[3] antioxidant,[4] anti-inflammatory,[5] COX-1 inhibitor,[6] anti HIV,[7] and anti-histaminic agents.[8] Further, the presence of

CONTACT Manisha R. Bhosle d.manisha11@gmail.com Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, Maharashtra, 431004, India.
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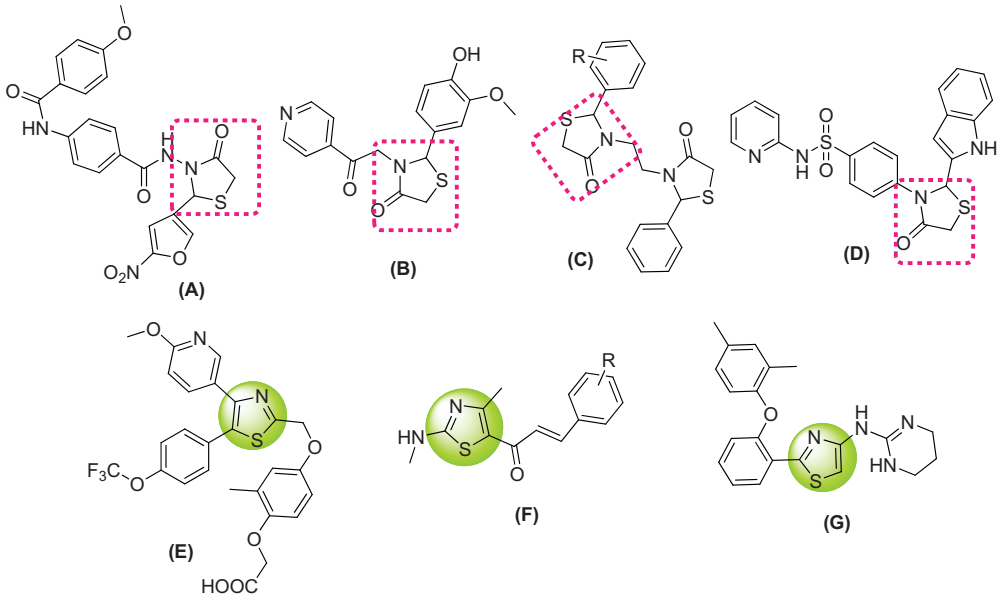


Figure 1. 4-Thiazolidinone and thiazole containing bioactive molecules.

the N-C-S linkage in the thiazolidinone is also responsible for the treatment of diabetic neuropathy, an aldose reductase inhibitor.[9] These have given the 4-thiazolidinone framework the status of a privileged pharmacophore that makes the functionalized thiazolidinones highly sought for compounds for medicinal chemists toward the generation of new therapeutic leads. Figure 1 shows molecules having 4-thiazolidinone as pharmacophore.[10]

The thiazoles are also important pharmacophores found in a wide variety of bioactive molecules and natural products (Fig. 1).[11] Thiazole derivatives are associated with a broad spectrum of biological properties, including antitumor,[12] antiparasitic,[13] antifungal,[14] antimicrobial,[15] antiproliferative,[16] antihypertension,[17] anti-inflammation,[18] oxidase inhibitors, and free radical scavengers.[19] Some novel thiazole derivatives[20] especially BILS 179 BS8 were reported to exhibit a high antiviral activity against hepatitis C virus (HCV) and HSV, respectively. Considering the above significance of both molecules we decided to combine 4-thiazolidinone and thiazole in one molecular framework to obtain new hybrids, thiazolyl-4-thiazolidinones.

The relevance of these structural motifs has constituted the focus of many investigations regarding improved strategies for their synthesis. In the literature, several campaigns for the synthesis of thiazolidinones are known either via multicomponent tandem reaction or two-step process.[21] However, the most commonly used protocol is multicomponent tandem reaction between a primary amine, aldehyde, and thioglycolic acid. There are reports of acceleration of the above cyclocondensation using catalysts and coupling agents such as DCC,[22] HBTU[23] or metal Lewis acid catalysts,[24] solid acid catalysts,[25] activated fly ash,[26] ionic liquids,[27] silica gel[28] and nano-Fe3O4@SiO2.[29] However, some of these methods suffer from at least one of the following disadvantages: longer reaction time, corrosive nature, hazardous reaction conditions, tedious work-up procedures, unsatisfactory yields, and use of non-recyclable reagents. Thus, a convenient, versatile, rapid and high

yielding synthetic method is needed to fulfill the timely supply of the designed molecules and enrichment of medicinal chemists' tool box.

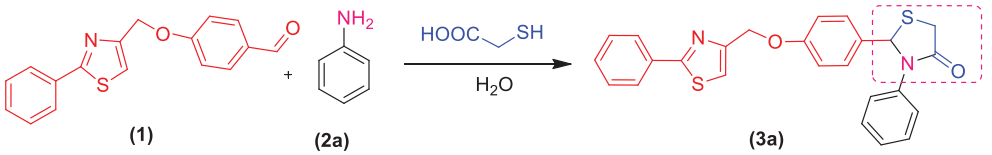
Finding novel synthetic procedures for a variety of attractive compounds that can be considered as pharmaceutics has been investigated over the last decades. Catalysis plays a central role in chemical processes and lies at the heart of countless chemical transformations, from academic research at laboratories level to the chemical industry level. By using catalytic systems, one can reduce the temperature of a chemical reaction, reduce reagent-based waste, and enhance the yield of a transformation that potentially avoids the unwanted side reactions leading to a green technology.[30] The introduction of new methodologies in recent years based on environmentally friendly conditions using the efficient and reusable catalyst as well as water-mediated procedures has gained significant attention among the researchers.[31] Excipients are widely used as drug delivery systems and biopharmaceuticals. However, when they are introduced into organic synthesis they act as a catalyst and some as a reaction medium.[32] For decades, various excipients, including chitosan,[33] meglumine,[34] PEG-400[35] have been developed and reported as catalyst and medium. Tromethamine (Tris(hydroxymethyl) aminomethane) is excipient used as organocatalyst by Desai and Kim *et al.* for the efficient synthesis of pyran-annulated heterocycles and β-phosphonomalonates respectively.[36] Tromethamine, which contains an amino and three alcoholic groups, it is physiologically inert, biodegradable, noncorrosive, and is available commercially at extremely low cost.[37]

As part of our continuing efforts to synthesize new heterocyclic scaffolds in an environmentally benign fashion,[38] we have applied developing organocatalysis in combination with water for the efficient preparation of the desired hybrids, thiazolyl-4-thiazolidinones. Considering the use of excepients to be an effective catalyst for various transformations, herein we report tromethamine in water as green catalytic system which makes the synthetic process more applicable. To the best of our knowledge, this type of catalytic system has not been documented for the present transformation.

Result and discussion

In the present work initially, to get 4-((2-Phenylthiazol-4-yl)methoxy)benzaldehyde (**1**) as required precursor, we performed the reaction sequence starting from thiobenzamide.[39] Thiobenzamide cyclocondensed with 1,3-dicloro acetone in ethanol at 80 °C to obtain chloromethyl thiazole. Chloromethyl thiazole further condensed with 4-hydroxy benzaldehyde in the presence of K_2CO_3/DMF at room temperature to get desired starting 4-((2-Phenylthiazol-4-yl)methoxy)benzaldehyde (**1**) in excellent yield.

Water is a very attractive solvent for a number of efficient organic reactions at different temperature. The use of water in multicomponent reactions offers significant environment advantages and has attracted a great deal of interest in recent years.[40] Water promotes or accelerates an excellent supporting medium with numerous advantages including the ease of product isolation, non-toxicity, non-flammability, high heat capacity and redox stability. Many organic transformations were known to promote by water.[41] Therefore, We commenced our investigation with a reaction using an equimolar ratio of freshly prepared 4-((2-Phenylthiazol-4-yl)methoxy)benzaldehyde (**1**), aniline (**2a**) and thioglycolic acid (**3**) as model substrates in water (Scheme 1). To solublize the



Scheme 1. 2-(4-((2-Phenylthiazol-4-yl)methoxy)phenyl)-3-phenylthiazolidin-4-one (**3a**).

Table 1. Formation of 2-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)-3-phenylthiazolidin-4-one (**3a**) using different catalyst in aqueous medium.

Entry	Catalyst/Solvent	Catalyst Loading (mol%)	Time (h)	Yield (%)[b]
1	H_2O	—	15	27
2	CTAB/H_2O	20	1	64
3	TTAB/H_2O	20	1	59
4	p-TSA/H_2O	20	1	48
5	α-Cyclodextrin/H_2O	20	1	45
6	β-Cyclodextrin/H_2O	20	1	76
7	γ-Cyclodextrin/H_2O	20	1	42
8	Taurine/H_2O	20	1	51
9	Tromethamine/H_2O	10, 20, 30, 40	1	43, 71, 82and 83
10	Tromethamine/H_2O (rt, 60, 80, 100 °C)	20	1	32, 56, 81, 83
11	Tromethamine/EtOH	20	1	79
12	Tromethamine/EtOH:H_2O (1:1)	20	1	80
13	Tromethamine/MeOH	20	1	74
14	Tromethamine/CH_3CN	20	1	51

[a]Reaction conditions: 4-((2-Phenylthiazol-4-yl)methoxy)benzaldehyde (**1**) (4 mmol), aniline (4 mmol), thioglycolic acid (8 mmol), water (15 mL), 80 °C.
[b]Isolated yield.

organic reactants in water various catalysts such as CTAB, TTAB, p-TSA, β-Cyclodextrin, Taurine, and Tromethamine were screened for the model reaction (Table 1, entries 1–9) at 80 °C for 1 h. Amongst them, tromethamine were found to be an excellent catalyst, furnishing the product in excellent yield of 82% (Table 1, entry 9). In the absence of catalyst, the one-pot multicomponent cyclocondensation at reflux temperature in water did not exhibit similar reaction condensations (Table 1, entry 1).

To derive the superlative reaction parameters such as the amount of the catalyst required and temperature, and the influence of the solvent for the tromethamine catalyzed 4-thiazolidinone formation, the model reaction (Scheme 1) was performed under different variations of these parameters. The use of 30 mol% of load of catalyst tromethmine afforded the compound **3a** in 82% yields (Table 1, entry 9) within 1 h under aqueous conditions. However, an increase in the amount of catalyst did not result in any improvement in the yield of the product. Temperature plays an important role to carry out the cyclocondensation. Consequently, the effect of temperature on the test reaction was investigated by carrying out the reaction at rt, 60, 80, and 100 °C in water (Table 1, entry 10). It was observed that at a temperature lower than 80 °C, the reaction did not proceed efficiently and, at higher temperatures, only a marginal increase in the product yield was observed. Thus, 80 °C was chosen as the optimum reaction temperature for the synthesis of 4-thiazolidinones.

Subsequently, different solvents were screened to test the efficiency of the catalyst in different reaction media, and the results are presented in Table 1. The polar protic solvents (EtOH, EtOH:H_2O (1:1), MeOH), afforded higher yields 79, 80, 74% than the polar aprotic (CH_3CN) ones and water showed superiority among the different polar solvents investigated (Table 1, entry 11–14).

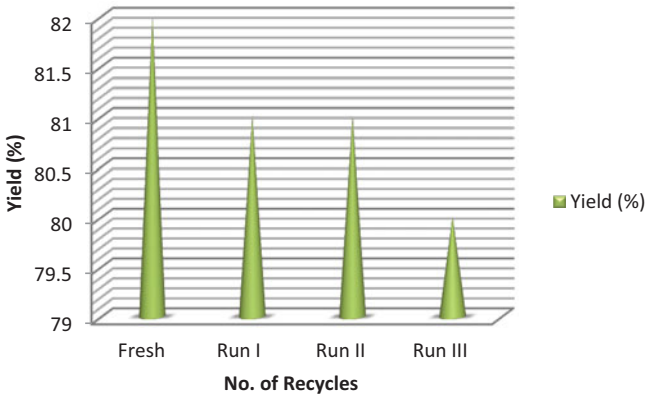
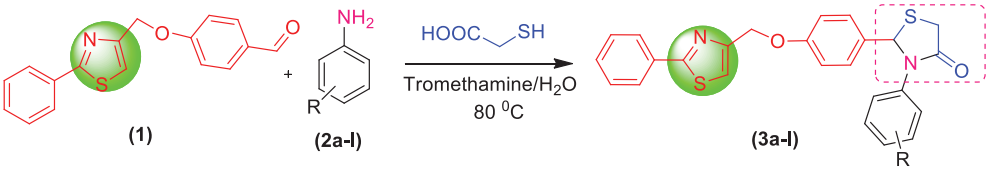


Figure 2. Reuse of tromethamine/water and its effect on yield (%).



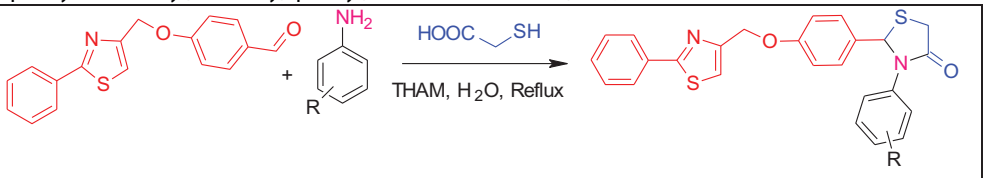
Scheme 2. Synthesis of 3-(substituted phenyl)-2-(4-((2-phenylthiazol-4-yl)methoxy)phenyl) thiazolidin-4-ones (**3a-l**).

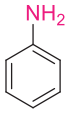
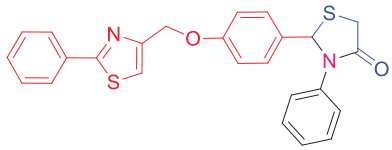
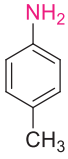
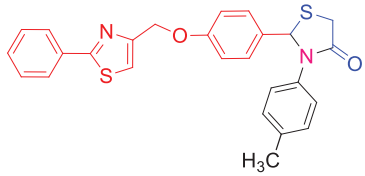
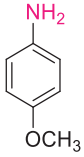
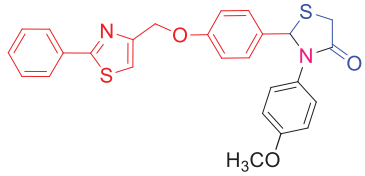
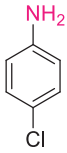
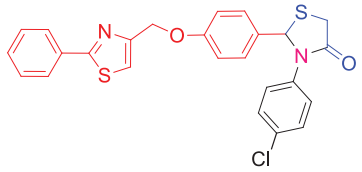
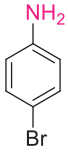
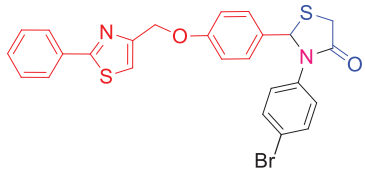
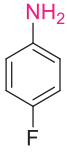
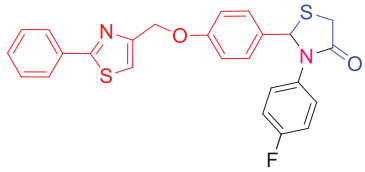
The reusability of catalysts is valuable advantages in modern catalysis research and commercial uses as well as in green chemistry. In this respect, the recovery and reusability of tromethamine were investigated for the model reaction. Tromethamine is completely soluble in reaction media water therefore its isolation and reuse is tedious and expensive.[36a] In this circumstance, we authenticated reusability of the reaction medium. Consequently, the model reaction was performed. The resultant product was isolated by extraction, and the filtrate obtained was reused for the synthesis of **3a**. The reaction media and tromethamine was studied for three successive cycles, showing without an appreciable reduction in catalytic activity. Only a slight decrease in the yield of the desired product, **3a**, was noticed (Fig. 2).

Inspired by these observations and to generalize the synthetic procedure, a variety of electronically divergent aromatic amines were treated with 4-((2-Phenylthiazol-4-yl)methoxy)benzaldehyde and mercaptoacetic acid in presence of tromethamine in water (Scheme 2). Aromatic amines with several functionalities such as Cl, OH, CH_3, OCH_3 and NO_2 were found to be compatible under the optimized reaction condition (Table 2).

After our initial success, the general applicability of the newly developed protocol is demonstrated through the reaction of various aryl aldehydes reacted elegantly with substituted anilines and thioglycolic acid to form the corresponding 1,3-disubstituted-4-thiazolidinones in excellent yields (Scheme 3). The reactions proceeded well with electron donating and withdrawing substituted aromatic aldehydes, as well as different variations of the amines affording the respective thiazolidinone in very good to excellent (84–93%) yields (Table 3).

Table 2. Substrate scope of the present tandem MCR for synthesis of 3-(substituted phenyl)-2-(4-((2-phenylthiazol-4-yl)methoxy) phenyl) thiazolidin-4-ones (**3a–l**).



Sr. No.	Aniline	Compound	Yield (%)
1		 **3a**	82
2			79
3			81
4			89
5			80
6			76

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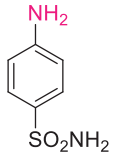
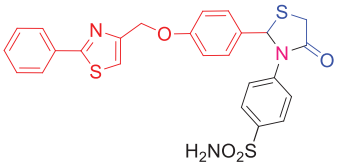
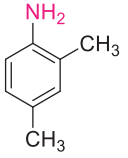
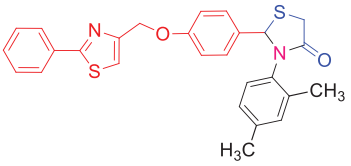
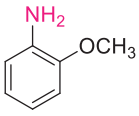
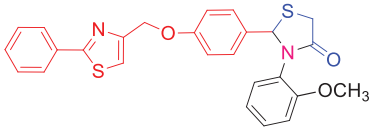
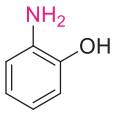
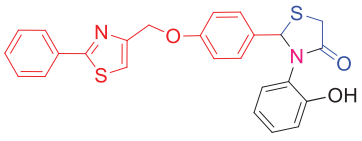
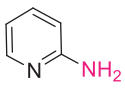
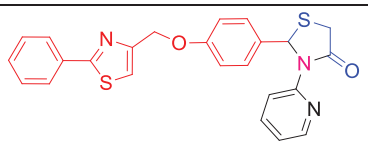
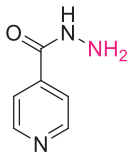
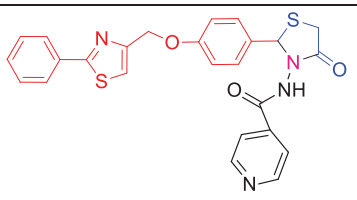
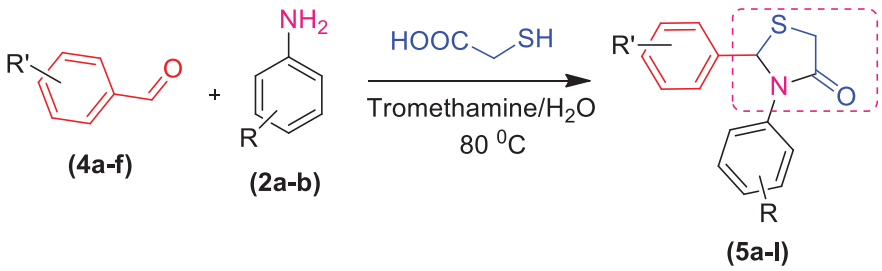
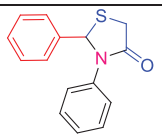
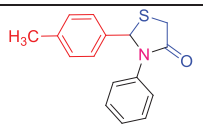
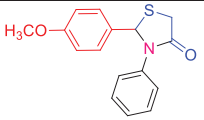
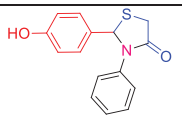
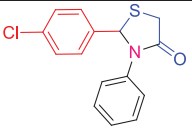
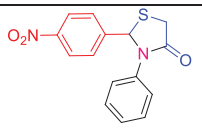
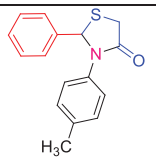
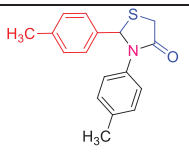
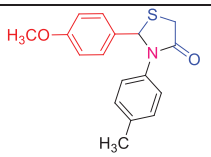
7			86
8			80
9			86
10			89
11			82
12			87

[a]Reaction Conditions: 4-((2-Phenylthiazol-4-yl)methoxy)benzaldehyde (**4**) (4 mmol), substituted amines (**2a-l**) (4 mmol), Thioglycolic acid (8 mmol), Tromethamine (30 mol%), Water (15 mL) stirred at 80 °C.
[b]Isolated yield.

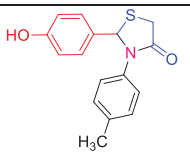
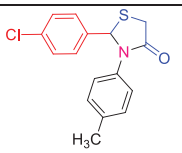
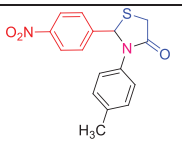


Scheme 3. Synthesis of 1,3-disubstituted-4-thiazolidinones (**5a–l**).

Table 3. Substrate scope for synthesis 2,3-disubstituted 4-thiazolidinones (**5a–l**).

Sr. No.	R'	R	Product	Yield (%)
1	H	H		**93**
2	4-CH_3	H		**89**
3	4-OCH_3	H		**86**
4	4-OH	H		**87**
5	4-Cl	H		**90**
6	4-NO_2	H		**86**
7	H	4-CH_3		**94**
8	4-CH_3	4-CH_3		**84**
9	4-OCH_3	4-CH_3		**87**

(*continued*)

10	4-OH	4-CH_3		**93**
11	4-Cl	4-CH_3		**93**
12	4-NO_2	4-CH_3		**85**

[a]Reaction conditions: Substituted benzaldehydes (**4a-f**) (4 mmol), substituted amines (**2a-b**) (4 mmol), thioglycolic acid (8 mmol), tromethamine (30 mol%), water (15 mL) stirred at 80 °C.
[b]Isolated yield.
[c]Melting points are in good agreement with those reported in the literature.[38a,42].

Plausible mechanism of reaction

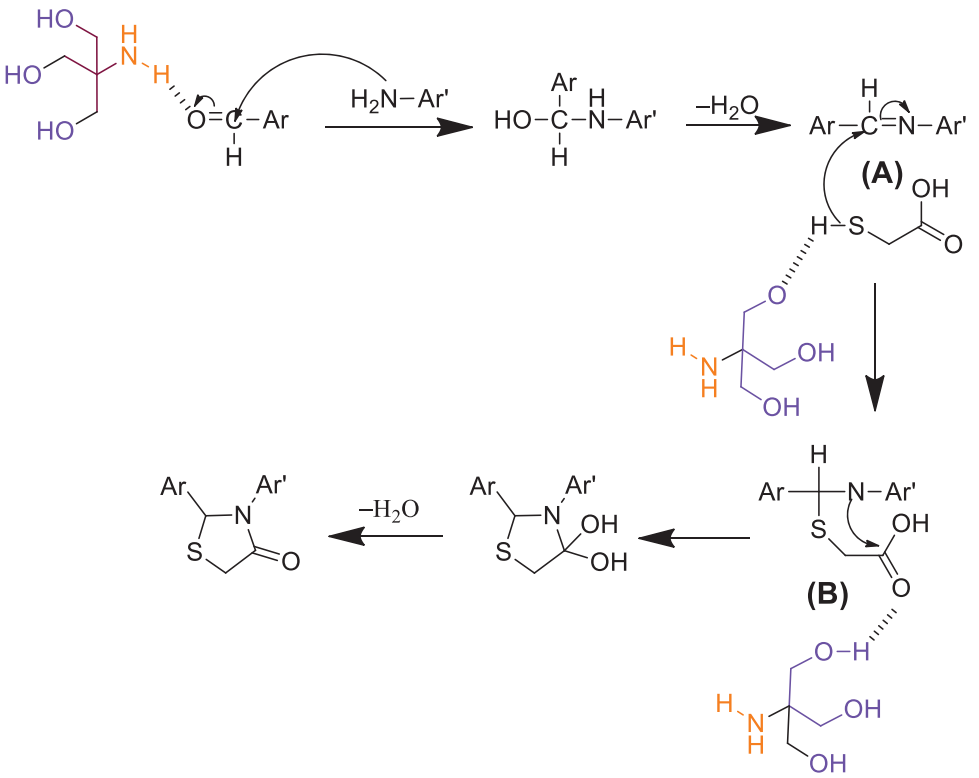
It is known that tromethamine contains an amino and three alcoholic groups and are inert. Amino hydrogen of tromethamine favors interaction with an oxygen atom of the carbonyl group of the aldehyde, followed by nucleophilic attack of substituted amines, leading to the formation of an imine intermediate (A). Then, free hydroxyl group interact with the protons of thioglycolic acid and the sulfur anions of thioglycolic acid attack the activated imine group of the intermediate (A), affording the intermediate (B). Next, the tromethamine again activates the intermediate (B), followed by removal of water, resulting in the final desired 4-thiazolidinones (Scheme 4).

Experimental

General: All the chemicals used were of laboratory grade. Melting points of all the synthesized compounds were determined in open capillary tubes and are uncorrected. ^{1}H NMR spectra were recorded with a Bruker Avance 400 spectrometer operating at 400 MHz using DMSO solvent and tetramethylsilane (TMS) as the internal standard and chemical shift in δ ppm. Mass spectra were recorded on a Sciex, Model; API 3000 LCMS/MS Instrument. The elemental analysis was done on Thermofisher EA1112 series CHNS Elemental Analyzer. The purity of each compound was checked by TLC using silica-gel, 60F_{254} aluminum sheets as adsorbent and visualization was accomplished by iodine/ultraviolet light.

General procedure for the synthesis of 3-(substituted phenyl)-2-(4-((2-phenylthiazol-4-yl)methoxy) phenyl) thiazolidin-4-ones (3a-l)

The mixture of 4-((2-phenylthiazol-4-yl)methoxy)benzaldehyde **(1)** (4 mmol) and substituted anilines (**2a-l)** (4.1 mmol) in water (20 mL) containing tris-hydroxymethylaminomethane



Scheme 4. Plausible mechanism for the synthesis of 4-thiazolidinones.

(Tromethamine) (30 mol%) was stirred at 80 °C for 15 min. Then thioglycolic acid (8 mmol) was added and stirred at 80 °C. Progress of the reaction was monitored by thin layer chromatography ethyl acetate:hexane (3:7) as solvent. After 45 min. of stirring reaction mixture was cooled at room temperature, saturated sodium bicarbonate was added till gate pink color, to remove thioglycolic acid. Sticky compound was extracted with ethyl acetate and evaporated organic layer under reduced pressure. Thus obtained solid was filtered, dried and purified by crystallization using ethanol as solvent.

Recycling of reaction media

The mixture of 4-((2-phenylthiazol-4-yl)methoxy)benzaldehyde **(1)** (8 mmol) and anilines (**2a)** (8 mmol) in water (40 mL) containing tris-hydroxymethylaminomethane (Tromethamine) (30 mol%) was stirred at 80 °C for 15 min. Then thioglycolic acid (16 mmol) was added and stirred at 80 °C. Progress of the reaction was monitored by thin layer chromatography ethyl acetate:hexane (3:7) as solvent. After 45 min of stirring reaction mixture was cooled at room temperature. Sticky compound was extracted with ethyl acetate and evaporated organic layer under reduced pressure. The aqueous layer having soluble tromethamine was further reused for next cycle.

Spectral analysis of compounds

3-Phenyl-2-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)thiazolidin-4-one (3a)

Yellow solid, yield 82%, melting point 146–148 °C. **IR** (ATR, υ cm^{-1}) characteristic absorptions: 3250, 3193, 3076, 2888, 2343, 1641, 1480, 1490, 1325, 1171, 947, 747. ^{1}H NMR (400 MHz, DMSO δ_{ppm}):4.37–4.43 (dd, 2 H, CH_2), 5.20 (s, 2 H, CH_2), 6.08 (s, 1 H, CH), 7.38–7.51 (m, 2 H, Ar-H), 7.55–7.70 (m, 4 H, Ar-H), 7.77–7.96 (m, 4 H, Ar-H), 8.04–8.46 (m, 5 H, Ar-H). **MS** (Scanning mode, ESI^+) m/z: 445.5 (M^+). Elemental Anal. calcd. for $C_{25}H_{20}N_2O_2S_2$: C: 67.54; H: 4.53; N: 6.30; S: 14.43; Found: C: 67.53; H: 4.55; N: 6.37; S: 14.41.

General procedure for the synthesis of 1,3-disubstituted-4-thiazolidinones (5a-l)

The mixture of substituted aldehydes **(4a-f)** (4 mmol) and substituted anilines (**2a-b)** (4.1 mmol) in water (20 mL) containing tris-hydroxymethylaminomethane (Tromethamine) (30 mol%) was stirred at 80 °C for 15 min. Then thioglycolic acid (8 mmol) was added and stirred at 80 °C. Progress of the reaction was monitored by thin layer chromatography ethyl acetate:hexane (3:7) as solvent. After 45 min. of stirring reaction mixture was cooled at room temperature, saturated sodium bicarbonate was added till gate pink color, to remove thioglycolic acid. Sticky compound was extracted with ethyl acetate and evaporated organic layer under reduced pressure. Thus obtained solid was filtered, dried and purified by crystallization using ethanol as solvent.

Synthesized compounds characterized by IR, ^{1}H NMR and Melting points are in good agreement with those reported in the literature.[38a,42]

3-Phenyl-2-(4-tolyl)thiazolidin-4-one (5b)

White solid, Yield 89%. Melting point 103–105 °C. **IR** (ATR, υ cm^{-1}) characteristic absorptions: 3202, 2975, 2827, 2357, 1725, 1453, 1149, 1008, 857, 759. ^{1}H NMR (400 MHz, DMSO δ_{ppm}): 2.26 (s, 3 H, CH_3), 3.83–4.02 (dd, 2 H, CH_2), 5.99 (s, 1 H, CH), 7.01–7.29 (m, 9 H, Ar-H). **MS** (Scanning mode, ESI^+): m/z (% intensity): 270 (M^+). Elemental Anal. calcd. For $C_{16}H_{15}NOS$: C: 71.34; H: 5.61; N: 5.20; S: 11.90; Found: C: 71.35; H: 5.60; N: 5.25; S: 11.93.

Conclusion

A tromethamine in water was used as an efficient and green catalytic system for the synthesis of new thiazolyl 4-thiazolidinone and known substituted-4-thiazolidinone *via* a one-pot, three-component reaction of an thiazolylmethoxy phenyl/aromatic carboxaldehyde, substituted amines and thioglycolic acid in good to excellent yields at 80 °C in water. The reaction system was considerably affected by catalyst loading, temperature and solvent. The advantages of using of tromethamine as the catalyst are it is environmentally friendly, low cost, commercially available, easy to separate from the reaction mixture, and has high reusability. Use of tromethamine catalyst results in acceptable

reaction time, high yields and high purities of the obtained products. All of these points are in full compliance with the requirements of green chemistry.

Supporting information (SI)

Full experimental detail, IR, ^{1}H and ^{13}C NMR spectra, this material can be found via the "Supplementary Content" section of this article's webpage.'

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