The First Solvent-Free, Microwave-Accelerated, Three-Component Synthesis of Thiazolidin-4-ones via One-Pot Tandem Staudinger/aza-Wittig Reaction

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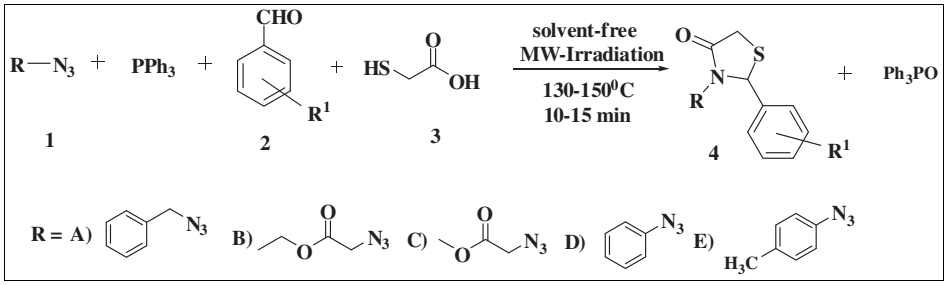

An efficient and rapid, solvent-free, microwave-accelerated, one-pot, three-component protocol for thiazolidin-4-ones synthesis from organic azides has been reported for the first time via Staudinger/aza-Wittig reaction. The microwave-accelerated, solvent-free approach overcomes the limitations associated with the prevailing solution phase methodologies. In particular, its novelty is that it eradicates the vital limitation, that is, accumulation of water (byproduct) that is known to affect the yield and rate of the reaction. Thus, a library of thiazolidin-4-ones has been synthesized in short time in excellent yields (92–96%).

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INTRODUCTION

Thiazolidin-4-ones are important group of heterocycles found in numerous natural products and pharmaceuticals [1]. They exhibit diversified pharmacological activities such as platelet activating factor (PAF) antagonist [2], antifungal activity [3], cardioprotective [4], antihistaminic [5], anti-HIV [6], analgesic [7], cytotoxic [8], COX-1 inhibitors [9], and nonnucleoside inhibitors of HIV-RT [10]. Therefore, the synthesis of thiazolidin-4-ones is of considerable interest. Consequently, focus is directed more towards the development of elegant and eco-friendly protocols for their synthesis.

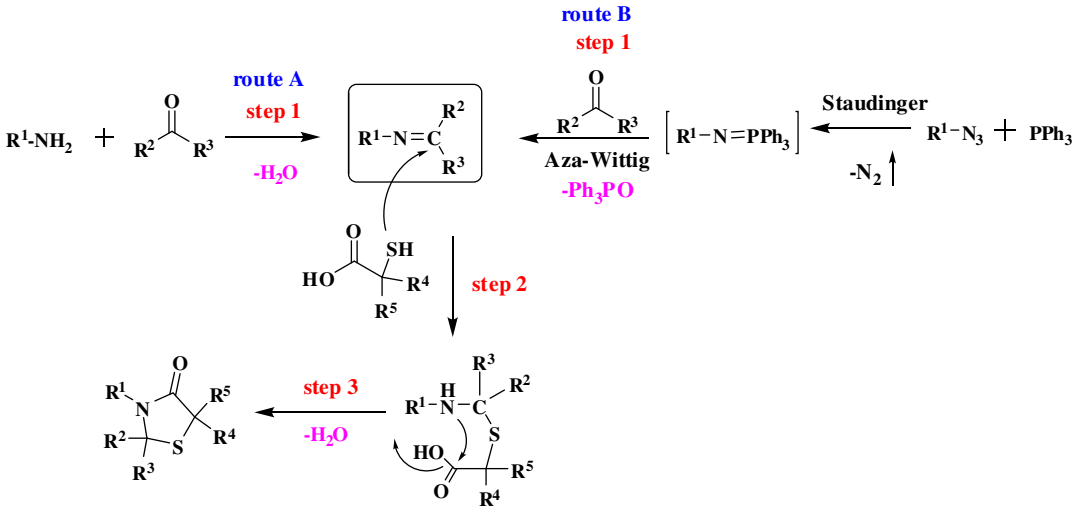
RESULTS AND DISCUSSION

Of the most frequently used methodologies for thiazolidin-4-ones, the three-component reactions involving an amine, a carbonyl compound, and mercaptoacetic acid have been well documented [11,12], wherein condensation of amines with aldehydes afford the imines that react with mercaptoacetic acid to afford thiazolidin-4-ones. The vital limitation of this method is the accumulation of water that is eliminated in steps 1 and 3 (Scheme 1, route A) that decreases both the rate of the reaction and yield of the product.

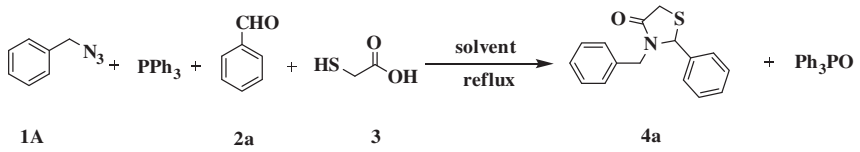
Thus, the azeotropic removal of water has been reported to be crucial for obtaining high yields of thiazolidin-4-ones in short time. Alternatively, desiccants such as molecular sieves, anhydrous $ZnCl_2$ [13], sodium sulfate [14], N, N-dicyclohexyl carbodiimide (DCC) [15], or 2-(1*H*-benzotriazo-1-yl)-1,1,3,3-tetramethyl uraniumhexafluorophospate (HBTU) [16] have been used as the dehydrating agents to accelerate the intramolecular cyclization resulting in shortening the reaction time and improved yields. On the other hand, usage of condensation agents [15–17], microwaves [18a], Lewis acids or bases [18b], and ionic liquids [18b] had resulted in improved yields of thiazolidin-4-ones. Thus, the main drawback in the existing solution phase protocols is the accumulation of water eliminated during the course of the reaction that either forms an azeotrope with the solvent or becomes collected in the reaction mixture.

Alternatively, Staudinger/aza-Wittig reactions are a powerful tool in organic synthetic strategies towards constructing nitrogen containing heterocycles [19], that is, azides are employed as an alternative to amines. With regard to thiazolidin-4-one synthesis, to the best of our knowledge, there is only a couple of recent reports [20,21] that utilizes Staudinger/aza-Wittig reactions to afford imine intermediate that with mercaptoacetic acid affords the product (Scheme 1, route B). However, these are also solution phase protocols. The advantage of these protocols using azides in the place of amines is that they involve elimination of nitrogen instead of water in step 1 (Scheme 1, route B). However, water elimination in step 3 and its azeotrope formation is unavoidable that affects the reaction rate and/or yield of thiazolidin-4-ones [20,21]. Thus, from the discussion *vide supra*, it is understood that solution phase methodologies for thiazolidin-4-one synthesis is unhealthy as they are associated with

Scheme 1. Mechanistic pathway in thiazolidin-4-ones synthesis starting from amines and azides.



Scheme 2. Tandem one-pot synthesis of thiazolidin-4-one (**4a**) in solvent.



many limitations such as toxicity of the solvents, usage of condensation agents, and desiccants, the vital being accumulation of water that would restrict their broad scope and question their eco-friendliness. Thus, search for newer protocols overcoming the limitations is worth the attempt.

In this regard, we have recently reported for the first time the advantages of switching over from a solution phase to a solvent-free methodology by achieving the efficient and rapid syntheses of amides [22], thioamides [23], and cyclic imides [24], under solvent-free condition overcoming the limitations associated with the solution phase protocols. In continuation of this, we were tempted to attend the three-component synthesis of thiazolidin-4ones via microwave-accelerated, solvent-free condition with added advantage, that is, the change from the solution phase protocol to microwave-accelerated, solvent-free condition would decrease the accumulation of water (eliminated during the course of the reaction) in two ways, viz. (1) no azeotrope formation and (2) the microwave-accelerated rate of heating leading to spontaneous vaporization of water. With this objective, it was envisaged that an environmentally benign synthesis of thiazolidin-4ones could be accomplished. Thus, we herein submit the first report on solvent-free, microwave-accelerated, one-pot, three-component synthesis of thiazoldin-4-ones by tandem Staudinger/aza-Wittig coupling/cyclization. Interestingly, the present study is characterized by very short reaction time affording excellent yield, the details of which are discussed *vide infra*.

At the outset, for the purpose of optimization, the one-pot, three-component synthesis of thiazolidin-4-one was attempted (Scheme 2) in various solvents and solvent-free conditions. That is, a mixture of benzyl azide (**1A**, 1 eq), triphenylphosphine (1.1 eq), benzaldehyde (**2a**, 1 eq), and mercaptoacetic acid (**3**, 1.1 eq) was refluxed in various solvents that took around 2–6 h (Table 1, entry 1–5) for completion affording 75–82% of thiazolidin-4-one (**4a**).

From the aforementioned solvent screening, it could be inferred that the rate of the reaction is temperature dependent. That is, in high boiling solvents with relatively lower polarity, viz. toluene and xylene (Table 1, entry 4 and 5), the reaction is fast and completed within 2–2.5 h. On the

Table 1

Optimization for the synthesis of the thiazolidin-4-one (**4a**).

Entry	Reaction condition		
	Solvent	Time (h)	Yield[a] (%)
1	THF	6	77
2	Acetonitrile	5	75
3	Benzene	5	76
4	Toluene	2.5	82
5	Xylene	2.0	80
6	Solvent-free	10 min[b]	94

[a]Isolated yield.
[b]Microwave-irradiation (temperature 150°C, power 80 W).

basis of this, it was envisaged that higher reaction temperatures could be obtained in absence of solvent and the rate of heating may be further accelerated using microwave irradiation. To our delight, as expected, under microwave assisted (CEM DISCOVER, Benchmate model, single-mode design with inbuilt IR sensor) solvent-free condition, accumulation of water is avoided thus resulting in a prominent increase in the rate of the reaction affording excellent yield (94%) of the product (**4a**) in just 10 min (Table 1, entry 6).

Having optimized the reaction conditions, the broad scope of the eco-friendly protocol has been established by the convenient synthesis of a library of compounds (20 examples). This resulted in the rapid synthesis of thiazolidin-4-ones in just 10–15 min by microwave-accelerated one-pot, solvent-free three-component methodology. That is, *in situ* formation of imines by aza-Wittig reaction of nascent phosphazenes (generated from azides and triphenylphosphine) with aldehydes followed by the instantaneous reaction of the imine with mercaptoacetic acid at 130–150°C (Scheme 3) to afford thiazolidin-4-ones (**4a–t**) in excellent yields (92–96%, Table 2).

Subsequently, the reason for the high rate of thiazolidin-4-one formation under solvent-free condition was sought for. In this regard, it was envisaged that the conversion of azide to phosphazene in the first step of the reaction (Scheme 1, route B) might have been enhanced. As an attempt to understand this prediction, the consumption of the azide in the reaction of benzyl azide with triphenylphosphine at room temperature under solvent-free condition was monitored by FTIR (FTIR monitoring of the consumption of azide in the reaction under microwave irradiation involving higher temperature was not attempted based on the safety ground). That is, the intensity of the band because of the azido group around 2100 cm^{-1} was examined at varying time intervals (Fig. 1). It was observed that the intensity of the band decreased (Fig. 1a–f) as the time progressed and disappeared in 2.5 h (Fig. 1f). This clearly indicates that the conversion of the azide to the phosphazene is accelerated as envisaged.

This is also supported by a recent report [21] that discloses that phosphazene formation in THF occurs just in 5 min under microwave irradiation. On a similar ground, in the present study, it is understood that phosphazene formation is accelerated by microwave irradiation under solvent-free condition. Further, the rate enhancement may also be due to the high collision between the polar components in the intimacy generated in the fused molten phase at higher temperature under solvent-free condition.

All the synthesized compounds were completely characterized by NMR (1D and 2D), IR, and mass spectral techniques. Recently, we have published the X-ray crystal structure of **4a** [25], which prove its structure unequivocally.

CONCLUSION

In conclusion, we have described a rapid and environmentally benign synthesis of the thiazolidin-4-ones in excellent yields from organic azides, triphenylphosphine, aldehydes with mercaptoacetic acid by a tandem one-pot, solvent-free, microwave-accelerated, three-component protocol. The tandem reaction is initiated by the *in situ* generation of nascent phosphazenes that with aldehydes afford the imines that is trapped by intermolecular nucleophilic attack of mercaptoacetic acid followed by intramolecular cyclization to afford the thiazolidin-4-ones. This solvent-free protocol overcomes most of the limitations associated with the solution phase methods, the vital limitation being the water accumulation in the course of the reaction resulting in an efficient and rapid synthesis.

This is the first report on the solvent-free synthesis of thiazolidin-4-ones by microwave-accelerated, one-pot, three-component strategy.

EXPERIMENTAL

General. All chemicals, reagents, and solvents were of commercially high purity grade purchased from Avra Synthesis Pvt. Ltd. and Merck Ltd. India. Silica gel (60–120 mesh) was used for column chromatographic isolation and purification of the compounds synthesized. Organic azides used in the investigation were prepared according to the literature procedures. Melting points were obtained on electro-thermal apparatus and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ on Bruker Avance 300 MHz spectrometer and the chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane, with coupling constant (*J*) values in Hertz (Hz). The splitting

Scheme 3. Tandem one-pot solvent-free, microwave-accelerated synthesis of thiazolidin-4-ones (**4**).

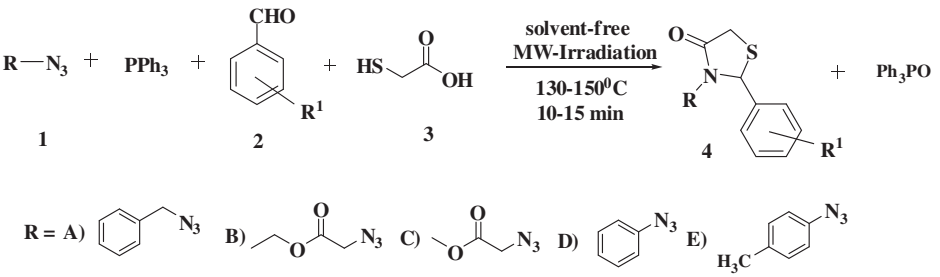
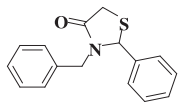
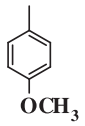
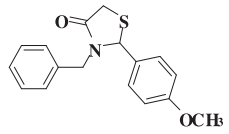
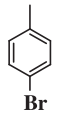
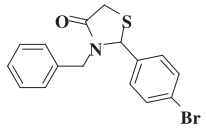
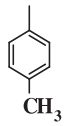
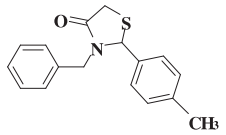
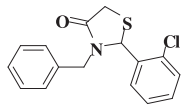
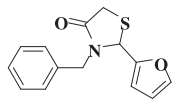
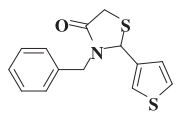
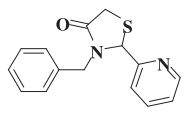
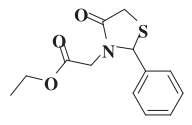


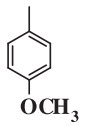
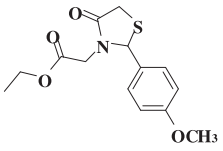
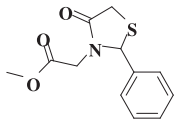
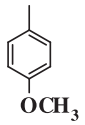
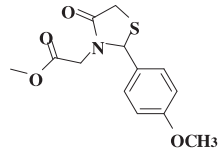
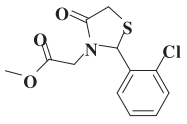
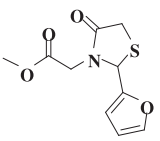
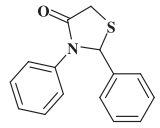
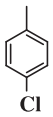
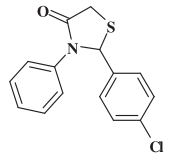
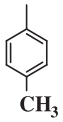
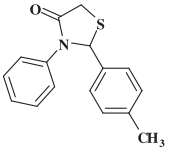
Table 2

Solvent-free, microwave-accelerated, one-pot synthesis of the thiazolidin-4-ones (**4a–t**).

Entry	Azides	Aldehydes	Thiazolidin-4-ones		MW-irradiation		
	1 R=	**2** R^1=	**4a–t**		Temp. (°C)	Time (min)	Yield[a] (%)
1	A			**a**	150	10	94
2	A			**b**	150	10	96
3	A			**c**	150	10	94
4	A			**d**	150	10	93
5	A			**e**	150	10	92
6	A			**f**	150	10	94
7	A			**g**	150	10	94
8	A			**h**	150	10	95
9	B			**i**	150	15	94

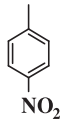
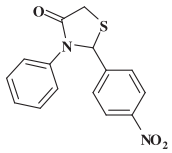
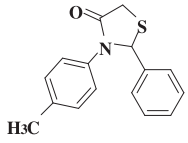
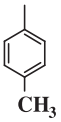
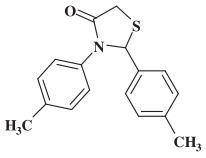
(*Continued*)

Table 2
(Continued)

Entry	Azides	Aldehydes	Thiazolidin-4-ones	MW-irradiation		
	1 R=	**2** R^1=	**4a–t**	Temp. (°C)	Time (min)	Yield[a] (%)
10	B		 **j**	150	15	96
11	C		 **k**	140	15	95
12	C		 **l**	140	15	96
13	C		 **m**	140	15	93
14	C		 **n**	140	15	94
15	D		 **o**	130	10	94
16	D		 **p**	130	10	94
17	D		 **q**	130	10	93

(*Continued*)

Table 2
(Continued)

Entry	Azides	Aldehydes	Thiazolidin-4-ones	MW-irradiation		
	1 R=	**2** R^1=	**4a–t**	Temp. (°C)	Time (min)	Yield[a] (%)
18	D		 **r**	130	10	93
19	E		 **s**	130	10	95
20	E		 **t**	130	10	94

[a]Isolated yield.

patterns in ^{1}H NMR spectra are reported as follows: m, multiplet; s, singlet; d, doublet; and t, triplet. ^{13}C NMR data are reported with the solvent peak ($CDCl_3$ = 77.00) as the internal standard. Elemental analyses were performed and were found to be in agreement, that is, within ±0.4% of the calculated values. Compounds **4a** [15], (**4b**, **4c**, **4d**) [26], **4e** [27], (**4k**, **4l**) [12a], (**4o**, **4p**, **4q**) [28], and (**4r**, **4s**, **4t**) [29] are known, and their ^{1}H and ^{13}C NMR spectra are identical to the reported values.

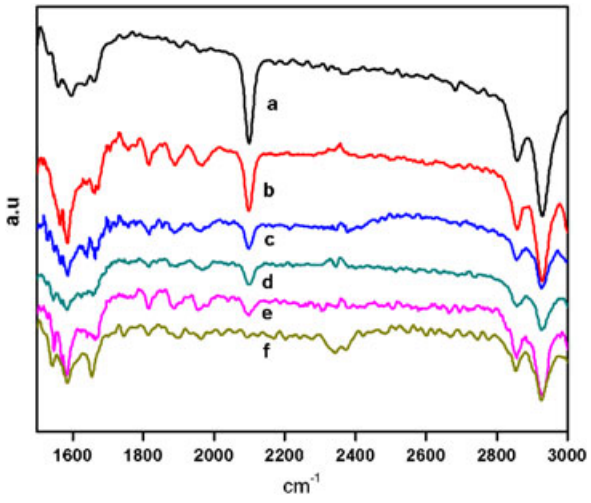


Figure 1. Phosphazene ($C_6H_5CH_2N{=}PPh_3$) formation under solvent-free condition from benzyl azide and triphenyl phosphine at room temperature: (a) 0 min, (b) 30 min, (c) 1 h, (d) 1.5 h, (e) 2 h, and (f) 2.5 h.

General procedure for the synthesis of thiazoldin-4-ones (4a–t). To a well ground intimate mixture of triphenyl phosphine (1.1 eq) and aldehyde, **2** (1.0 eq) in a microwave vial (10 mL) equipped with a magnetic stirring bar, the organic azide, **1** (0.2 g, 1.0 eq) was added in drops while stirring. Stirring was continued until liberation of nitrogen ceased, and the mercaptoacetic acid **3** (1.1 eq) was added to the aforementioned mixture, and the reaction vessel was sealed with a septum. It was then placed into the cavity of a focused monomode microwave reactor (CEM Discover, Benchmate) and operated at 130–150°C (temperature monitored by a built-in IR sensor), power 80 W for 10–15 min. The reaction temperature was maintained by modulating the power level of the reactor. The reaction mixture was allowed to stand at room temperature. Then, the residue was purified by column chromatography on silica (petroleum ether-ethyl acetate, 94:6) to afford the thiazolidin-4-ones (**4a–t**) in 92–96% yield. The obtained results are summarized in Table 2.

3-Benzyl-2-(furan-2-yl)thiazolidin-4-one (4f). Gummy matter. Yield: 94%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17–7.43 (m, 6H, ArH). 6.30 (d, 1H, J = 3.0 Hz, ArH), 6.35 (m, 1H, ArH), 5.43 (s, 1H, NCHS), 5.12 (d, 1H, J = 15.0 Hz, NCH_2), 3.93 (d, 1H, J = 15.3 Hz, NCH_2). 3.69 (d, 1H, J = 6.3 Hz, SCH_2), 3.64 (d, 1H, J = 6.0 Hz, SCH_2); ^{13}C NMR (75 MHz, CDCl3): δ 170.82, 150.84, 143.64, 135.64, 128.76, 128.21, 127.89, 110.49, 109.25, 55.63, 46.48, 32.57; *Anal.* Calcd for $C_{14}H_{13}NO_2S$: C, 64.84; H, 5.05; N, 5.40; S, 12.36. Found: C, 64.86; H, 5.06; N, 5.41; S, 12.37.

3-Benzyl-2-(thiophen-3-yl)thiazolidin-4-one (4g). Gummy matter. Yield: 94%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.03 (d, 1H, J = 5.7 Hz, ArH), 7.14 (m, 3H, ArH), 7.26–7.38 (m, 5H, ArH), 5.53 (s, 1H, NCHS), 5.12 (d, 1H, J = 14.7 Hz, NCH_2), 3.87

(d, 1H, J = 15.6 Hz, SC$\underline{H}_2$), 3.74 (d, 1H, J = 15.6 Hz, SC$\underline{H}_2$), 3.61 (d, 1H, J = 15.0 Hz, NC$\underline{H}_2$); ^{13}C NMR (75 MHz, C$\underline{D}$Cl$_3$): δ 170.76, 140.30, 128.71, 128.26, 127.84, 127.66, 125.79, 124.00, 57.97, 46.19, 32.85; *Anal*. Calcd for $C_{14}H_{13}NOS_2$: C, 61.06; H, 4.76; N, 5.09; S, 23.29. Found: C, 61.07; H, 4.75; N, 5.08; S, 23.28.

3-Benzyl-2-(pyridine-2-yl)thiazolidin-4-one (4h). Gummy matter. Yield: 95%. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.09 (m, 2H, ArH), 7.21–7.38 (m, 7H, ArH), 5.38 (s, 1H, NC$\underline{H}$S), 5.16 (d, 1H, J = 14.7 Hz, NC$\underline{H}_2$), 3.90 (d, 1H, J = 15.3 Hz, SC$\underline{H}_2$), 3.76 (d, 1H, J = 15.6 Hz, SC$\underline{H}_2$), 3.52 (d, 1H, J = 14.7 Hz, NC$\underline{H}_2$); ^{13}C NMR (75 MHz, C$\underline{D}$Cl$_3$): δ 171.18, 139.10, 135.24, 131.04, 129.15, 129.07, 128.71, 128.36, 127.87, 127.10, 62.69, 47.16, 32.96; *Anal*. Calcd for $C_{15}H_{14}N_2OS$: C, 66.64; H, 5.22; N, 10.36; S, 11.86. Found: C, 66.63; H, 5.21; N, 10.35; S, 11.85.

Ethyl 2-(4-oxo-2-phenylthiazolidin-3-yl)acetate (4i). Gummy matter. Yield: 94%. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.32–7.40 (m, 5H, ArH), 5.84 (s, 1H, NC$\underline{H}$S), 4.43 (d, 1H, J = 17.7 Hz, NC$\underline{H}_2$), 4.15 (m, 2H, OC$\underline{H}_2$CH$_3$), 3.80 (s, 2H, SC$\underline{H}_2$), 3.30 (d, 1H, J = 17.4 Hz, NC$\underline{H}_2$), 1.23 (t, 3H, J = 6.9 Hz OC$\underline{H}_3$CH$_2$); ^{13}C NMR (75 MHz, C$\underline{D}$Cl$_3$): δ 171.93, 167.87, 137.77, 129.51, 129.08, 127.60, 63.65, 61.45, 43.81, 32.69, 29.61, 14.00; *Anal*. Calcd for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28; S, 12.09. Found: C, 58.83; H, 5.71; N, 5.28; S, 12.08.

Ethyl 2-(2-(4-methoxyphenyl)4-oxothiazolidin-3-yl)acetate (4j). Gummy matter. Yield: 96%. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.28 (d, 2H, J = 9.6 Hz, ArH), 6.89 (d, 2H, J = 9.6 Hz, ArH), 5.81 (s, 1H, NC$\underline{H}$S), 4.39 (d, 1H, J = 17.7 Hz, NC$\underline{H}_2$), 4.14 (m, 2H, OC$\underline{H}_2$CH$_3$), 3.79 (s, 3H, OC$\underline{H}_3$), 3.78 (s, 2H, SC$\underline{H}_2$), 3.29 (d, 1H, J = 17.7 Hz, NC$\underline{H}_2$), 1.24 (t, 3H, J = 7.2 Hz, OCH$_2$C$\underline{H}_3$); ^{13}C NMR (75 MHz, C$\underline{D}$Cl$_3$): δ 171.80, 167.97, 160.50, 129.19, 114.42, 63.41, 61.43, 55.32, 43.69, 32.83, 29.63, 14.03; *Anal*. Calcd for $C_{14}H_{17}NO_4S$: C, 56.93; H, 5.80; N, 4.74; S, 10.86. Found: C, 56.93; H, 5.81; N, 4.75; S, 10.85.

Methyl 2-(2-(2-chlorophenyl)-4-oxothiazolidin-3-yl)acetate (4m). Gummy matter. Yield 93%. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.28–7.45 (m, 4H, ArH), 6.28 (s, 1H, NC$\underline{H}$S), 4.54 (d, 1H, J = 17.7 Hz, NC$\underline{H}_2$), 3.79 (s, 2H, SC$\underline{H}_2$), 3.72 (s, 3H, OC$\underline{H}_3$), 3.39 (d, 1H, J = 17.7 Hz, NC$\underline{H}_2$); ^{13}C NMR (75 MHz, C$\underline{D}$Cl$_3$): δ 172.44, 168.09, 135.66, 132.04, 131.18, 130.19, 127.72, 126.55, 59.92, 52.45, 44.01, 32.03; *Anal*. Calcd for $C_{12}H_{12}ClNO_3S$: C, 50.44; H, 4.23; N, 4.90; S, 11.22. Found: C, 50.46; H, 4.23; N, 4.90; S, 11.21.

Methyl 2-(2-(furan-2-yl)4-oxothiazolidin-3-yl)acetate (4n). Gummy matter. Yield: 94%. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.45 (s, 1H, ArH), 6.44 (s, 1H, ArH), 6.36 (s, 1H, ArH), 5.88 (s, 1H, NC$\underline{H}$S), 4.45 (d, 1H, J = 17.7 Hz, NC$\underline{H}_2$), 3.81 (d, 1H, J = 15.6 Hz, SC$\underline{H}_2$), 3.70 (s, 3H, OC$\underline{H}_3$), 3.65 (d, 1H, merged with OCH$_3$, SC$\underline{H}_2$), 3.47 (d, 1H, J = 17.7 Hz, NC$\underline{H}_2$); ^{13}C NMR (75 MHz, C$\underline{D}$Cl$_3$): δ 170.54, 167.89, 149.55, 143.54, 110.18, 109.73, 55.70, 51.85, 43.26, 31.51; *Anal*. Calcd for $C_{10}H_{11}NO_4S$: C, 49.78; H, 4.60; N, 5.81; S, 13.29. Found: C, 49.77; H, 4.60; N, 5.80; S, 13.30.

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