PAPER

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A sustainable strategy for the synthesis of bis-2-iminothiazolidin-4-ones utilizing novel series of asymmetrically substituted bis-thioureas as viable precursors†

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A novel series of asymmetrically substituted bis-thioureas has been synthesized in an effective pattern *via* the reaction of diamines with isothiocyanates utilizing the ultrasonic irradiation as a sustainable energy source. This reaction performs well at mild conditions to give the products in quantitative yields for a broad scope of substrates. The bis-thiourea derivatives are used for the design of unprecedented series of bis-2-iminothiazolidin-4-ones promoted by the ultrasonic irradiation. The reaction affords the formation of regioselective products, which depends on the pK_as of the diamines. The diamine linked to the thiourea possessing lower pK_a is involved in the imino part, and the diamine having higher pK_a is a part of the other heterocyclic nitrogen. Moreover, this new strategy has excellent environmental parameters, demonstrating that this protocol is a green and sustainable process.

Introduction

Both symmetrical and asymmetrical thiourea derivatives represent a class of significant compounds in drug design.[1] These derivatives have been utilized in many therapeutics such as anti-bacterial,[2] anti-HIV,[3] anti-inflammatory,[4] anti-cancer,[5] antioxidant,[6] anti-tubercular,[7] anti-parasitic,[8] antifungal[9] and rodenticide agents.[10] Furthermore, the thiourea derivatives have been utilized as agrochemicals, such as herbicides,[11] and as a regulator for the growth of insects.[12] They have additionally wide applications in the preparation of heterocyclic compounds and other organic molecules.[13] Recently, thioureas have been employed as ligands and organocatalysts in a diversity of asymmetric organic syntheses.[14] Moreover, they have been used in the manufacture of polymer[15] and as sensors for heavy metal detection.[16] In addition, the applications of thiourea derivatives have been extended to analytical chemistry; they are used for the metal ions preconcentration.[17] These fundamental characteristics of thiourea derivatives make them versatile building blocks in synthetic organic chemistry.[18] Thus, great endeavors have been directed to the evolution of novel synthetic protocols for these important building blocks.[19] These reported strategies have some disadvantages comprising the requirements of harsh

reaction conditions, poisonous reagents, and the fact that these strategies are mainly restricted to prepare symmetrically substituted thioureas.

As a privileged moiety, thiazole is an important structural motif that has acquired an important standing in newfangled heterocyclic chemistry essentially because of its presence in a broad variety of biologically active compounds.[20] Due to the high degree of biological activity of thiazole derivatives, numerous procedures of their preparation have been reported.[21] In spite of these methods, newer protocols for the generation of thiazole derivatives remain in demand.

Recently, focusing on green chemistry utilizing eco-friendly chemicals and reaction conditions is a standout among the most intriguing advancements in the preparation of broadly utilized organic compounds.[22] The ultrasound-assisted organic reactions have attracted much attention due to the greater selectivity, simplicity of procedure, repression of the generation of by-product, and fast preparation of different organic compounds when compared with traditional thermal heating.[23] Solvent, the main contributor of the ecological performance of the reaction, is another factor that ought to be taken into consideration in a green methodology.[24] Despite water being a predominantly attractive solvent, most organic compounds do not adequately dissolve in it.[25] Alternatively, ethanol performs well as the reaction medium since it is comparatively non-hazardous to the environment.[24] Motivated by the previously mentioned actualities and as a part of our interest in developing economic and simple reactions promoted by ultrasound to synthesize bis-heterocyclic compounds,[22] herein, we wish to report a facile strategy for the fast preparation of new and

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asymmetrically substituted bis-thioureas as building blocks for the synthesis of bis-2-imino-4-thiazolinone derivatives in superb yields mediated by the ultrasonic irradiation.

Results and discussion

In our initial studies based on the preparation of asymmetrically substituted bis-thioureas, benzyl isothiocyanate **1a** and *trans*-1,4-diaminocyclohexane **2a** were chosen as the model reagents for the optimization of the reaction conditions. To test the possibility of our envisioned protocol, in a model reaction, to a solution of benzyl isothiocyanate **1a** (1 mmol) in acetonitrile (MeCN, 10 mL), *trans*-1,4-diaminocyclohexane **2a** (0.5 mmol) was added pinch wise over a period of 5 min under stirring at ambient temperature (23 °C). The stirring process was continued for 120 min until a sticky solid was formed. MeOH (2 mL) was added to this mixture with continuous stirring for another 15 min. The formation of a novel product along with other minor side products was observed together with the retention of some starting materials. Isolation by a usual workup procedure was followed by purification (45% isolated yield, Table 1, entry 1), and the characterization revealed the product to be 1,1′-[(1R,4R)-cyclohexane-1,4-diyl]bis(3-benzylthiourea) **3a**. Further optimization such as increasing the amount of benzyl isothiocyanate to 2.5 equiv. ameliorated the isolated yield (**3a**) up to 58%. Next, the above-mentioned model reaction was carried out under ultrasonic irradiation (40 MHz) for 5 min at ambient temperature (23 °C). Thin layer chromatography displayed the complete transformation of the starting materials to the product **3a**. Interestingly, the obtained bis-thiourea derivative **3a** was isolated instantly after the substrates were mixed, and it recrystallized from EtOH in an excellent yield (92%, Table 1, entry 3). Screening of some other solvents all afforded inferior outcomes except dichloromethane (DCM), which afforded **3a** in 88% yield (Table 1, entry 4). For instance, EtOH and water delivered **3a** in only 21% and 25% yields, respectively (Table 1, entries 5 and 6). A polar aprotic solvent such as acetone also afforded a poor reaction yield (Table 1, entry 7). Interestingly, performing the aforesaid model reaction under a solvent-free condition furnished the required product **3a** in 97% yield (Table 1, entry 8). Reducing the reaction time to 3 min led to the incomplete conversion to product **3a** (Table 1, entry 9). Consequently, the ultrasonic irradiation of **1a** (1 mmol) and **2a** (0.50 mmol) at room temperature for 5 min were selected as the optimum conditions to produce the derivative **3a** in 97% yield (Table 1, entry 8).

After verifying the practicality of the protocol, the generality and scope of this reaction were assessed by using different types of isothiocyanates (**1a**, **b**) and diamines (**2a**, **b**) (Scheme 1). Better yields were observed in the case of *trans*-1,4-diaminocyclohexane (**2a**), for example, **3a** (97%) and **3b** (96%). The suggested structures of the derivatives **3a–d** were deduced from their satisfactory spectral data. The IR spectra of the compounds **3a–d** displayed the characteristic stretching bands of NH and C=S groups at 3271–3207 and 1262–1250 cm^{-1}, respectively. The ^{1}H NMR spectra of the derivatives **3a–d** showed the NH protons of the thiourea functionality (S=CNHR) at the region δ = 7.89–7.25 ppm. The other protons showed up at the expected chemical shifts (ESI†).
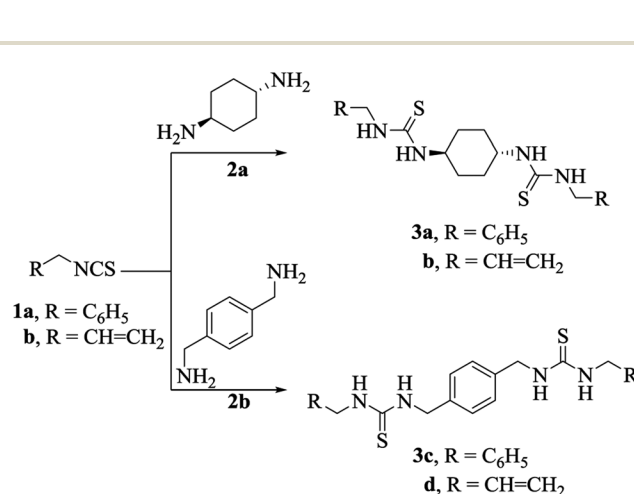
The asymmetrically substituted thiourea frameworks have been demonstrated to be advantageous precursors for diversified functional compounds including thiazoles, imidazoles and pyrimidines. Thus, bis-thioureas **3a–d** represent versatile building blocks for the preparation of various bis-heterocycles such as bis-thiazolidines. For our initial investigation that aimed to synthesize bis-thiazolidines, asymmetrically substituted bis-thiourea **3a** and dimethyl acetylenedicarboxylate (DMAD, **4a**) were taken as the model substrates. We commenced this study by conducting the reaction in EtOH at room temperature under ultrasonic irradiation, which exclusively produced the compound **5a** within 7 min (Table 2, entry 1). The obtained results encouraged us to further investigate the influence of the solvent and temperature on the model reaction. As displayed in Table 2, different outcomes of the target product

Table 1 Optimization of the reaction conditions for the preparation of 1,1′-[(1R,4R)-cyclohexane-1,4-diyl]bis(3-benzylthiourea) **3a**^{a}

Entry	Solvent	Method	Time (min)	Yield (%)^b
1	MeCN	Stirring	120	45
2	MeCN	Stirring	120	58^c
3	MeCN	US	5	92
4	DCM	US	5	88
5	EtOH	US	5	21
6	H$_2$O	US	10	25
7	Acetone	US	5	15
8	—	**US**	**5**	**97**
9	—	US	3	82

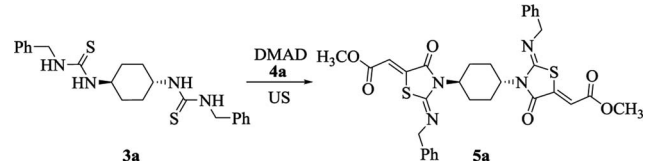^{a} The reaction was conducted with **1a** (1.0 mmol) and **2a** (0.5 mmol). ^{b} Isolated yields. ^{c} The reaction was conducted with **1a** (1.5 mmol) and **2a** (0.5 mmol).

Scheme 1 An ultrasound-assisted protocol for the synthesis of asymmetrically substituted bis-thioureas **3a–d**.[26]

Table 2 Optimization of the reaction conditions for the synthesis of dimethyl 2,2′-[(2Z,2′Z)-((1R,4R)-cyclohexane-1,4-diyl]bis(2-(benzylimino)-4-oxothiazolidin-3-yl-5-ylidene))(2Z,2′Z)-diacetate **5a**

Entry	Solvent	Temp. (°C)	Time (min)	Yield (%)
1	EtOH	23	7	84
2	MeOH	23	7	88
3	H_2O	23	7	86
4	MeCN	23	7	65
5	DCM	23	7	60
6	Dioxane	23	7	46
7	DMF	23	7	55
8	—	23	10	67
9	H_2O	50	7	75
10	H_2O	70	7	63
11	**H_2O**	**23**	**10**	**88**
12	H_2O	23	25	89

5a (46–88%) were obtained when the mixture of **3a** with DMAD was stirred under given conditions in diverse solvents. The reaction using MeOH and water gave the corresponding product **5a** in satisfactory yields (Table 2, entries 2 and 3). In contrast, the results with other solvents such as MeCN and DCM were unsatisfactory (Table 2, entries 4 and 5). Likewise, due to the issue of isolating the solid products, poor yields occurred when dioxane and DMF were employed as solvents in the model reaction (Table 2, entries 6 and 7). From the environmental and economical standpoint and considering the toxicity of MeOH, water was selected as the reaction medium for this series of reactions. Moreover, on performing the corresponding solvent-free reaction, an unfruitful result was obtained (Table 2, entry 8). Similarly, increasing the operation temperature of the reaction did not enhance the reaction yields (Table 2, entries 9 and 10). Nevertheless, slight improvement in the reaction yield was observed when the time was increased to 25 minutes (Table 2, entries 11 and 12). Thus, the best reaction conditions were optimized in water at room temperature under ultrasonic irradiation for 10 min (Table 2, entry 11).

Having successfully achieved an optimized procedure for this new protocol, we moved to establish the generality of the abovementioned reaction. The developed protocol operated effectively with a broad range of substrates, tolerating a variety of bis-thioureas (**3a–d**, Scheme 2) and dialkyl acetylenedicarboxylates (**4a, b**). It was noticed that the derivatives **5a–d** comprising cyclohexyl moiety participated in the reaction smoothly with higher yields when compared with the derivatives **6** and **7** comprising *p*-xylenyl moiety. Interestingly, the derivatives **5–7** could also be acquired by one-pot synthesis without the isolation of the intermediates **3a–d**. Hence, upon the completion of the reaction between alkyl isothiocyanates
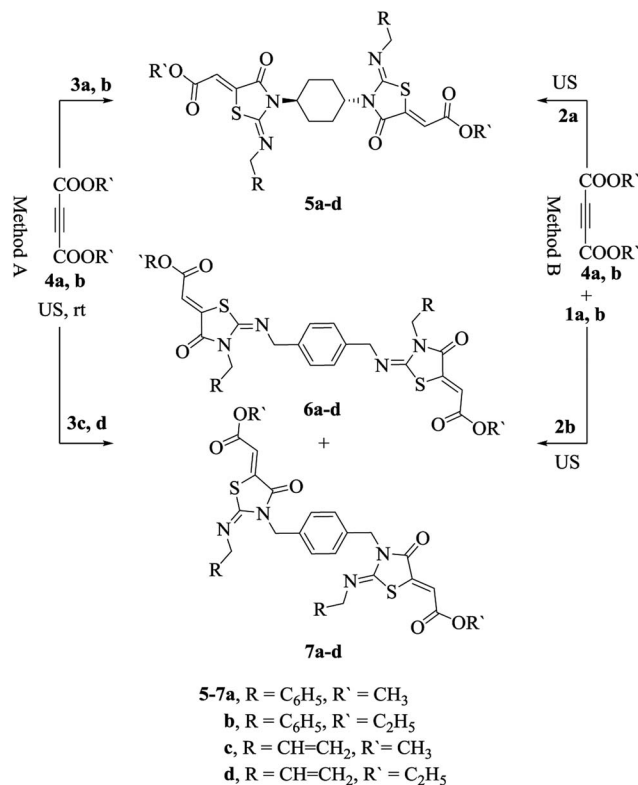
Scheme 2 An ultrasound-assisted protocol for the synthesis of **5–7**.[27]

(**1a, b**) and diamines (**2a, b**) under ultrasonic irradiation (monitored by TLC), the bis-thioureas **3a–d** produced were suspended in water followed by the addition of dialkyl acetylenedicarboxylates (**4a, b**), and the resulting mixture was sonicated at room temperature for additional 10 min to give the desired products (**5–7**, Scheme 2, method B).

The formation of 2-imino-4-oxothiazolidin-5-ylidene acetates (**5–7**) proceeded *via* an addition reaction followed by cyclization and hence, the amine substituent on both sides of thiourea moiety was anticipated to play a significant role on the regioselectivity of the products. Singh and his co-workers[28] found an acceptable correlation between the regioselectivity of the N-acylation pathway and the pK_a values of the precursor amines in thiourea. The greater the difference between the pK_a values of the precursor amines linked to thiourea, the higher is the regioselectivity of N-acylation with the preferential acylation occurring to the amine with a lower pK_a. An analogous result was also obtained during the preparation of both 2-iminothiazolines and thiazole-2-imines.[29]

When asymmetrical thioureas **3c** and **3d** (Scheme 2) containing benzyl and allyl moieties, respectively, linked to the thiourea reacted with dialkyl acetylenedicarboxylates (**4a, b**), a mixture of bis-2-imino-4-oxothiazolidines **6a–d** and **7a–d**, respectively, were obtained (**6a, b** : **7a, b** = 48 : 52 and **6c, d** : **7c, d** = 50 : 50). The measured pK_a values of *p*-xylylenediamine, benzyl amine and allyl amine were 9.46, 9.34 and 9.49, respectively. The ^{1}H NMR spectra of these products displayed two sets of peaks corresponding to the methylene and methine groups and multiple peaks for aromatic protons (see ESI†). While

a larger difference in the pK_as of the precursor amines linked to thiourea was observed, one product was exclusively formed as demonstrated in the derivatives **5a** and **5b** having *trans*-1,4-diaminocyclohexane (pK_a 10.80) and benzyl amine (pK_a 9.34). This was further demonstrated with other derivatives **5c** and **5d** having *trans*-1,4-diaminocyclohexane (pK_a 10.80) attached to one side and allyl amine (pK_a 9.49) attached to the other side in thioureas. The ^{1}H NMR spectra of these products (**5a–d**) displayed only one peak corresponding to the methylene and methine protons (see ESI†). Consequently, we could deduce that in asymmetrical bis-thioureas, the amine having a higher value of pK_a was a part of the heterocyclic nitrogen of the five-membered ring, and the amine linked to the thiourea possessing a lower value of pK_a was a part of the imino component.

Cyclization of the asymmetrically substituted bis-thiourea derivatives **3a–d** with ethyl chloroacetate was also studied under ultrasonic irradiation. Initially, the reaction was carried out at a mild temperature of 30 °C for 30 minutes in EtOH containing catalytic amount of NaOAc. Then, the reaction was proceeded with a considerable amount of starting materials remaining unreacted. However, by increasing the operating temperature to 60 °C, the required products **8–10** were obtained in moderate yields (≈60%) with some unconsumed starting materials still present. Next, the reaction was studied at different temperatures, *viz.*, 70 °C, 80 °C and 90 °C for 30 min, affording the products in ≈75%, 88% and 89% yields, respectively. Following this study, the best result was obtained at 90 °C, and this temperature condition yielded the products in ≈90% under sonication for 30 min. Likewise, in the case of the cyclization of asymmetrical bis-thioureas **3c, d**, a mixture of regioisomeric products may be possible. However, with all asymmetrical bis-thioureas **3a, b** used, only one regioisomeric product was obtained in high yields under the present reaction conditions. The formation of the compounds **8–10** was established by the disappearance of the thiourea NHs and C=S absorption bands and the appearance of the characteristic lactam C=O bands at 1720–1716 cm^{-1} in the IR spectra. The ^{1}H NMR spectra of the products displayed the presence of a singlet at $\delta = 4.04$–4.02 (**8a** and **8b**) and a doublet at $\delta = 4.12$–4.07 (**9** and **10**), which was assigned to the methylene protons of the thiazolidinone ring and confirmed the ring closure. The presence of the doublet might have been due to the mixture of regioisomeric products (**9a : 10a** = 49 : 51 and **9b : 10b** = 50 : 50). Condensation of bis-thiazolidin-4-ones **8a, b** with 4-chlorobenzaldehyde in EtOH buffered with NaOAc under ultrasonic irradiation afforded bis-5-arylidene-2-imino-4-thiazolidinones **11a, b** (Scheme 3). The suggested structures of **11a, b** were confirmed by elemental analyses and spectroscopic data. The derivatives **11a, b** existed as *E* and *Z* geometrical isomers, respectively; the *Z* conformation of the exocyclic C=C double bond was assigned on the basis of ^{1}H NMR spectra, which revealed the characterized down-field signals corresponding to their methine-group protons when compared to that of the *E*-isomer.[30] For instance, the ^{1}H NMR spectrum of the derivative **11a** displayed only one type of methine proton that was deshielded by the adjacent C=O and was detected at $\delta = 7.82$ ppm. Then, we investigated a one-pot three-
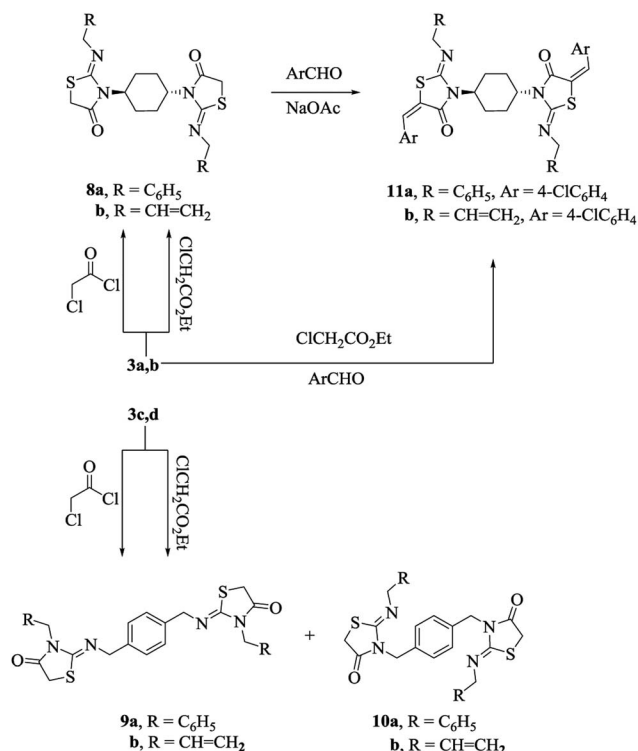

Scheme 3 An ultrasound-assisted protocol for the synthesis of the derivatives **8–11**.[31]

component reaction of bis-thioureas **3a, b** with ethyl chloroacetate and 4-chlorobenzaldehyde, respectively, under ultrasonic irradiation; the required products **11a, b**, respectively, were obtained in good yields under irradiation for 30 min at 90 °C. Additionally, the derivatives **8–10** could also be synthesized through the reactions of bis-thioureas **3a–d** (1 mmol) with chloroacetyl chloride (2.1 mmol) under ultrasonic irradiation (Scheme 3, solvent-free and catalyst-free conditions). These products were identical in all respects (IR and NMR) to the products obtained using ethyl chloroacetate. However, this procedure could not be applied as the one-pot protocol for the syntheses of **11a, b** since chloroacetyl chloride is quite reactive towards the base utilized.

From the green chemistry point of view, it would be valuable to estimate the "greenness" of our novel aforementioned protocols. Diverse metrics[32] that have been applied to estimate and compare the 'greenness' of methodologies and products were calculated for some selected compounds (**3a**, **5a** and **8a**). These metrics included Carbon Efficiency (CE), Atom Economy (AE), E-factor, Reaction Mass Efficiency (RME) and Process Mass Intensity (PMI). To assess the possibility of the scale-up of the present strategies, the selected reactions were carried out on gram-scale to afford the required compounds **3a**, **5a** and **8a** in 97.21, 90.19 and 94% yields, respectively (Scheme 4). An excellent combination of green metrics such as higher values of AE (100–75%), CE (100–86.66%) and RME (97.21–70.5%) and lower values of both PMI (1.41–1.03) and E-factor (0.098–0.028) confirmed the eco-friendly nature of the present protocols.
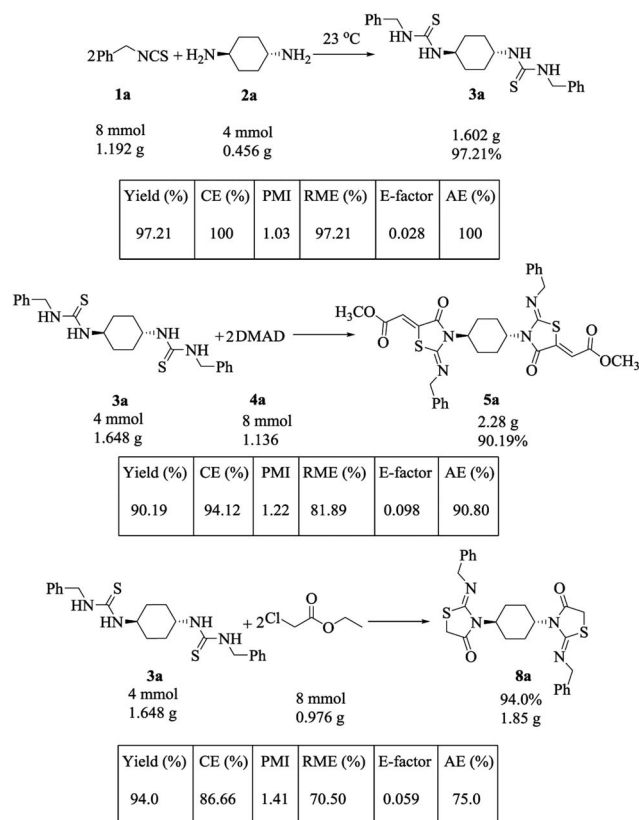
Scheme 4 Scaled-up synthesis of derivatives **3a**, **5a** and **8a**.

Conclusions

In summary, we have successfully developed an operational and convenient protocol for the effective sonochemical syntheses of asymmetrical bis-thioureas. These synthesized compounds are subjected to a variety of reagents for the preparation of a novel series of regioselective bis-iminothiazolines. We have found a correlation between the regioselectivity and pK_a of the amine. In comparison with the existing arduous protocols for the preparation of iminothiazolines,[21] our methodology is superior in terms of simplicity, environmental friendliness, convenience, and applicability on a gram-scale.

Conflicts of interest

There are no conflicts to declare.

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26 General procedure for the synthesis of bis-thioureas (**3a–d**). Isothiocyanates (**1a, b**, 0.5 mmol) and diamines (**2a, b**, 1.0 mmol) were mixed in a 25 mL round-bottomed flask. The reaction mixture was sonicated in water bath (23 °C) of an ultrasonic cleaner for 5 min as indicated in Table 1. After completion of the reaction (the reaction was monitored by TLC, silica gel; DCM : petroleum ether = 5 : 2 v/v), the reaction mixture was triturated with 2 mL chilled EtOH, and the precipitate was filtered, affording the crude product, which was purified by recrystallization from EtOH (95–97%).

27 General methods for the synthesis of derivatives **5–7**. Method A: to a solution of 1 mmol of bis-thioureas **3a–d** and 10 mL of deionized water in a 50 mL round-bottom flask, 2 mmol of dialkyl acetylenedicarboxylate (DAADs, **4a, b**) was added dropwise at room temperature with continuous stirring. After the complete addition of DAADs, the reaction mixture was sonicated for 10 min (TLC, DCM : MeOH = 9 : 1 v/v); during the reaction, a solid appeared in the solution. After completion of the reaction, excess solvent was removed by filtration, and the residue was recrystallized from ethanol, affording the desired product as colorless to light yellow crystals. Method B: isothiocyanates (**1a, b**, 0.5 mmol) were added dropwise to diamines (**2a, b**, 1.0 mmol) under ultrasonic irradiation for 5 min. To the resulting residue, 10 mL of water was added followed by dropwise addition of 2 mmol of dialkyl acetylenedicarboxylate (DAADs, **4a, b**) at room temperature. After the complete addition of DAADs, the

reaction mixture was sonicated for 10 min (TLC, DCM : MeOH = 9 : 1 v/v); during the reaction, a solid appeared in the solution. After completion of the reaction, the excess solvent was removed by filtration, and the residue was recrystallized from ethanol, affording the desired product as colorless to light yellow crystals (88–92%).

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31 General procedures for the preparation of compounds **8–10**. Method A; from ethyl chloroacetate: the appropriate bis-thioureas **3a–d** (1 mmol), ethyl chloroacetate (2 mmol) and sodium acetate (0.16 g, 2 mmol) were irradiated under ultrasonic conditions in ethanol (25 mL) at 90 °C for 30 min (TLC, DCM : MeOH = 9 : 1 v/v). The resulting solid was filtered, dried and recrystallized from ethanol containing few drops of dioxane to afford the corresponding bis-thiazolidine derivatives **8–10**. Method B; from chloroacetyl chloride: To bis-thioureas **3a–d** (1 mmol) placed in a 10 mL round bottom flask, chloroacetyl chloride (1.2 mmol) was added drop wise under ultrasonic irradiation. After complete addition of chloroacetylchloride, acetonitrile (5 mL) was added to the reaction mixture, and the mixture was stirred continuously for 5 min (TLC, DCM : MeOH = 9 : 1 v/v). The resulting solid was filtered, dried and recrystallized from ethanol containing few drops of dioxane to afford the corresponding bis-thiazolidine derivatives **8–10** (93–88%). Syntheses of derivatives **11a, b**. A one-pot three component mixture of the appropriate bis-thioureas **3a, b** (1 mmol), ethyl chloroacetate (2 mmol), 4-chlorobenzaldehyde (2 mmol) and sodium acetate (5 mmol) were mixed in ethanol (15 mL). The reaction mixture was sonicated at 90 °C for 30 min (TLC, DCM : MeOH = 8 : 2 v/v). The resulting residue was filtered and recrystallized from dioxane to afford the corresponding bis-thiazolidine derivatives **11a, b** in 86–90% yield.

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