An Environmentally Benign Water Promoted Catalyst Free Highly Efficient, One-pot Synthesis of 2-Imino-4-thiazolidinone

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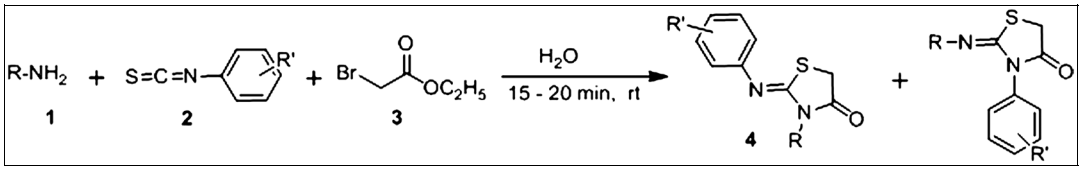

A practical and efficient protocol has been developed for the synthesis of 2-imino-4-thiazolidinone through a unique one pot three-component reaction of variety of amines, isothiocyanate and ethylbromoacetate in water. The method is free of catalyst and other toxic solvents, has shorter reaction times, high-yielding, effortlessness in isolation of product, making it more eco-friendly process, and suitable for large scale operation.

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INTRODUCTION

In recent years, multicomponent reactions (MCRs), have received considerable attention compared with conventional multistep methods that involves several bond formations in one step producing a complex molecule, economically viable, eco-friendly process, with reduced amount of waste products and their wide range of applications in pharmaceutical chemistry for generation of structural diversity and combinatorial libraries for drug discovery [1]. The use of water as reaction medium is an important challenge for organic chemist because it is non-flammable, non-toxic, non-volatile and inexpensive "green solvent". Recently, water has been employed as a solvent in many organic reactions [2].

The synthesis of 2-imino-4-thiazolidinone has gained considerable significance as an important intermediate for many heterocycles [3] and also demonstrates diverse biological activities such as tuberculostatic [4], antidiabetic [5], antihistaminic [6], and antifungal activity [7]. Interestingly, 4-thiazolidinone is an important group of heterocycles found in numerous natural products and pharmaceuticals such as Cox inhibition [8], anti-HIV [9], and human chondrocyte anti-degenerative [10] properties. Some thiazolidin-4-one derivatives are known to exhibit diverse bioactivities such as Ca^{2+} channel blocker [11], PAF antagonist [12], cardioprotective [13], and cyclooxygenase inhibitory [14]. Moreover, existing literature reveals that there are several substituted thiazolidinones derivatives that show potent anti-inflammatory activity [15] (1, Fig. 1), and compound 2 (Fig. 1) affects the growth of colorectal cancer cells and acts as diverse integrin $\alpha_v\beta_3$ antagonists [16].

A review of the literature illustrated that the reported method for the synthesis of 2-imino-4-thiazolidinone [17] is having some limitations such as harsh reaction conditions, long reaction times, and using volatile solvents resulting in lesser yield. Yella *et al*. [18] have also reported the synthesis of these compounds but in two steps, that is, first synthesis of thiourea followed by synthesis of iminothiazolidinone. The efficient synthetic method to prepare 2-imino-4-thiazolidinone, in particular with green solvent and different substitution patterns on each of the nitrogen atoms is still lacking. Therefore, the development of simple, convenient, and environmentally benign approaches for the synthesis of 2-imino-4-thiazolidinone is still desirable. In continuation of our efforts to develop new synthetic methods for important organic products [19], herein we report one pot, regioselective synthesis of 2-imino-4-thiazolidinone. We recently have been trying to develop approaches to carry out this reaction without any catalyst. Fortunately, we revealed that the one-pot three-component reaction of a various amines, isothiocyanates, and ethylbromoacetate proceeded smoothly at room temperature in water as solvent under catalyst-free condition; and this approach provide access to a wide range of 2-imino-4-thiazolidinone derivatives in excellent yields. To the best of our knowledge, there are no existing precedent protocols for the synthesis of 2-imino-4-thiazolidinone using water as medium through one pot, three-component reaction at room temperature.

RESULT AND DISCUSSION

Initially, we studied the impact of *N*,*N*-dimethylformamide (DMF) on the model reaction between aniline **1a** (1 mmol), phenylisothiocyanate **2a** (1 mmol), and ethylbromoacetate **3** (1 mmol) (Table 1) at room temperature, reaction proceeded smoothly affording product **4a** in 80% yield. Later on, we started the optimization of reaction in volume ratio of DMF-water as solvent at room temperature. We observed that, upon changing the volume ratio of DMF to water from 2:1 to 1:2, the yield of the product increases from 84 to 90%.

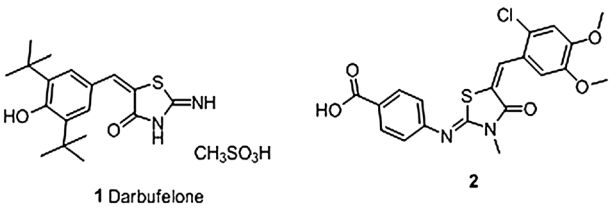


Figure 1. Medicinally important iminothiazolidinones.

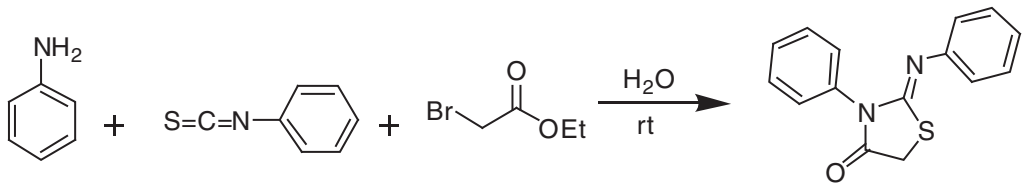
From the previous result, we found that upon increasing the water content, yield of the product increases. Hence, we performed the reaction in clean water, and the resulting product was obtained in maximum yield (98%). So, water was selected as the best choice for the reaction.

To realize the efficiency and scope of the reaction for the synthesis of 2-imino-4-thiazolidinone, ethylbromoacetate was reacted with various amines and isothiocyanates under optimized reaction condition (Scheme 1).The results are displayed in Table 2. As per Table 2, aromatic and aliphatic amines efficiently react with substituted phenylisothiocyanates, experienced by exothermic reaction at room temperature to afford the *in situ* formation of thiourea, and followed by reaction with ethylbromoacetate, resulting in the formation of product **4**.

A highly efficient method for the preparation of 2-imino-4-thiazolidinone has been achieved from both symmetrical and unsymmetrical thiourea in the absence of base. This reaction gives regio-selective product for unsymmetrical thiourea, which is dependent on pK_a of amines. Its formation takes place with amine attached to thiourea having lower pK_a as a part of imino component and amine having higher p*K*a contributes to other heterocyclic nitrogen. The measured p*K*a of aniline and *p*-methoxyaniline is 4.63 and 5.34, respectively. Hence, aniline forms a part of imino component, and *p*-methoxyaniline contributes to the other heterocyclic nitrogen in the 2-imino-4-thiazolidinone skeleton. The structures of all compounds were characterized by ^1H and ^{13}C NMR, IR and mass spectrometry, and elemental analysis. Proton NMR of product showed doublet at $\delta = 3.92$ ppm ($J = 0.8$ Hz) corresponding to two protons adjacent to sulfur atom, an observation that is also found in the earlier literature [20]. IR spectra of all compounds show characteristics peak for carbonyl group in the range of 1627–1646 cm^{-1}. HPLC analysis of the compounds **4c**, **4d**, **4g**, and **4i** shows regioisomers in the ratio 63:37, 62:38, 60:40, and 66:34, respectively. To verify the skeletal structure of product 2-imino-4-thiazolidinone, compound **4a** was selected and characterized by X-ray crystallography (CCDC 833911) as shown in Figure 2 [21].

Table 1

Solvent effect on the reaction.[a]



Entry	Solvent	Reaction time (min)	Yield[b] (%)
1	DMF	15	80
2	DMF-H_2O (2:1)	15	84
3	DMF-H_2O (1:1)	15	86
4	DMF-H_2O (1:2)	15	90
5	H_2O	15	98

[a]Reaction condition: aniline (1 mmol), phenylisothiocyanate (1 mmol), and ethylbromoacetate (1 mmol), room temperature. The reaction was monitored by TLC.
[b]Isolated yields.

Scheme 1. Synthesis of 2-imino-4-thiazolidinone.

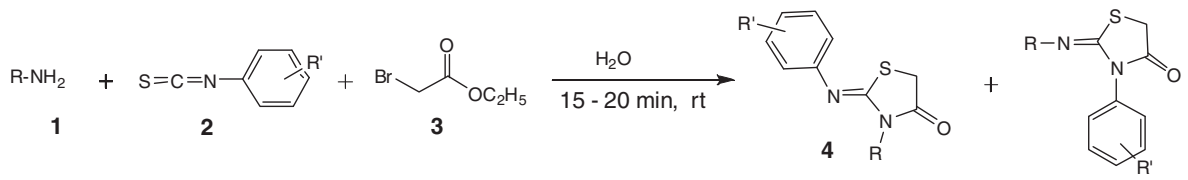
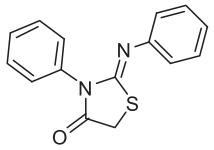
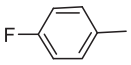
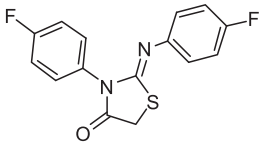
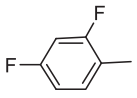
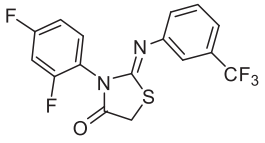
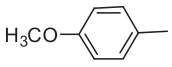
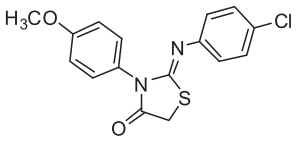
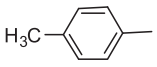
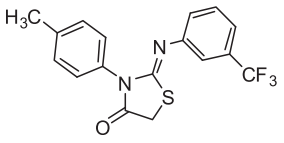
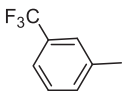
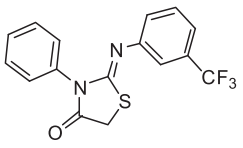
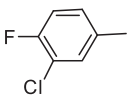
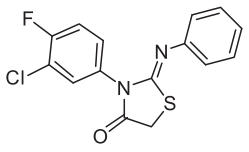
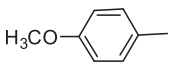
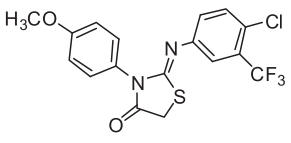
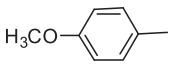
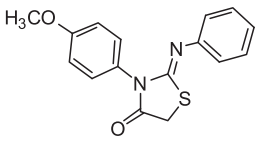


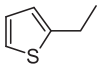
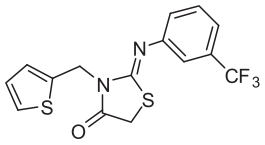
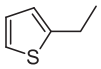
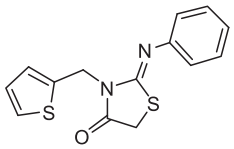
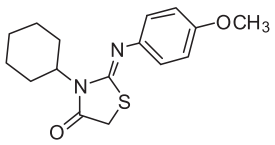
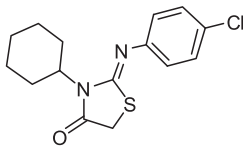
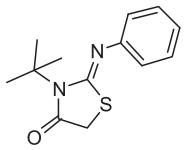
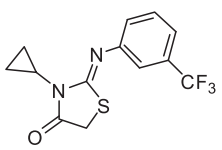
Table 2

Regioselective synthesis of 2-imino-4-thiazolidinone in water as solvent under catalyst free condition.

Entry	R	R′	Product (**4**)	Ratio[a]	Time (min)	Yield[b] (%)
a		H			15	98
b		4-F			15	96
c		3-CF_3		63:37	15	94
d		4-Cl		62:38	15	95
e		3-CF_3			15	96
f		H			20	94
g		H		60:40	15	95
h		3-CF_3,4-Cl			15	94
i		H		66:34	15	95

(*Continued*)

Table 2
(*Continued*)

Entry	R	R′	Product (**4**)	Ratio[a]	Time (min)	Yield[b] (%)
j		3-CF_3			15	94
k		H			20	93
l		4-OCH_3			15	94
m		4-Cl			15	95
n	*t*-Butyl	H			15	96
o		3-CF_3			20	96

[a]Ratio of regioisomers as measured by HPLC analysis.
[b]Isolated yield after purification.

CONCLUSION

In conclusion, we have developed a novel protocol of three component reaction for the synthesis of 2-imino-4-thiazolidinone at room temperature, in less time and in excellent yield. Regioselective formations of 2-imino-4-thiazolidinones were observed from unsymmetrical thiourea. Different substitution pattern on 2-imino-4-thiazolidinone does not affect the yield of reaction. Major advantage is that the reaction is carried out in water as a green solvent. The procedure is extremely useful in synthetic and medicinal chemistry.

EXPERIMENTAL

All chemicals and reagents were purchased from Aldrich (Sigma–Aldrich, St. Louis, MO, USA), Lancaster (Alfa Aesar, Johnson Matthey Company, Ward Hill, MA, USA) or Spectrochem Pvt. Ltd (Mumbai, India) and were used without further purification. Reactions were monitored by TLC, performed on silica gel glass plates containing 60 GF-254, and visualization on TLC was achieved by UV light or iodine indicator. ^1H and ^{13}C spectra were recorded on Bruker UXNMR/XWIN-NMR (300 MHz) instruments. Chemical shifts (δ) are reported in ppm downfield from internal TMS standard. IR spectra were recorded on Thermo Nicolet Nexus 670 FTIR spectrometer. ESI spectra were recorded on Micro

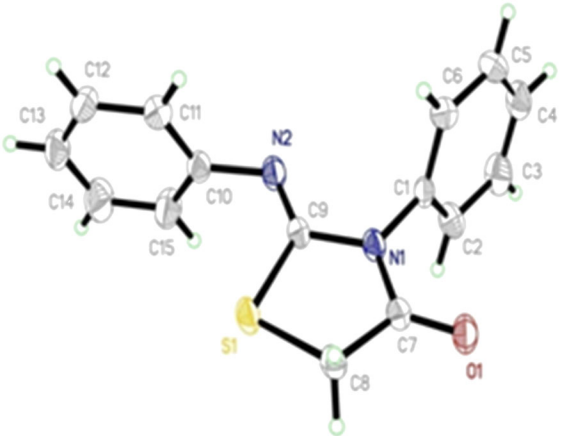


Figure 2. ORTEP molecular diagram of **4a** with thermal ellipsoid at 30% probability.

mass, Quattro LC using ESI + software with capillary voltage 3.98 kV and ESI mode positive ion trap detector. HPLC was performed with spectra system (Shimadzu, Kyoto, Japan) using analytical column (water-Xterra®, 5 µm, 4.6 × 250 mm).The flow was 1 mL/min, with mobile phase of 10 mµ ammonium acetate/acetonitrile = 50:50 (v/v). Melting points were determined with an Electro thermal melting point apparatus and are uncorrected.

General procedure for the synthesis of 3-phenyl-2-(phenylimino)thiazolidin-4-one (4a). A mixture of aniline (0.093 g, 1 mmol) and phenylisothiocyanate (0.135 g, 1 mmol) was stirred at room temperature for 5 min; then to this mixture, water (5 mL) was added. Ethylbromoacetate (0.167 g, 1 mmol) was added dropwise, and the mixture stirred at room temperature for 10 min. After completion of reaction monitored by TLC, reaction mixture extracted with ethyl acetate and saturated $NaHCO_3$. Organic layer was dried over anhydrous $NaSO_4$ and crystallized from chloroform/hexane (6:4) to afford the pure product **4a** (0.263 g).

3-Phenyl-2-(phenylimino)thiazolidin-4-one (4a). White solid. Mp 176–178°C. IR (KBr): 1724, 1636, 1371, 1152. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.95 (d, *J* = 0.8 Hz, 2H), 6.85 (d, *J* = 7.6 Hz, 2H), 7.07 (t, *J* = 7.6 Hz, 1H), 7.23–7.55 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.8, 120.8, 124.5, 127.9, 128.9, 129.1, 129.3, 134.6, 148, 154.8, 171.3. ESI–MS [M + H$^+$]: *m/z* = 269. *Anal*. Calcd for $C_{15}H_{12}N_2OS$: C 66.91, H 4.70, N 10.41; Found: C 66.87, H 4.67, N 10.37.

(Z)-3-(4-fluorophenyl)-2-(4-fluorophenylimino)thiazolidin-4-one (4b). White solid. Mp 120–122°C. IR (KBr): 1731, 1642, 1378, 1160. ^{1}H NMR (75 MHz, $CDCl_3$): δ = 3.88–4.00 (m, 2H), 6.74–6.89 (m, 2H), 6.92–7.07 (m, 2H), 7.11–7.42 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.7, 115.8, 116.6, 122.3, 129.8, 130.4, 143.8, 155.4, 161.6, 164.0, 171.2. ESI–MS [M + H$^+$]: *m/z* = 305. *Anal*. Calcd for $C_{15}H_{10}F_2N_2OS$: C 59.21, H 3.29, N 9.21; Found: C 59.16, H 3.24, N 9.17.

3-(2,4-Difluorophenyl)-2-(3-(trifluoromethyl)phenylimino) thiazolidin-4-one (4c). Yellow liquid. IR (neat): 1733, 1630, 1364, 1180. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.91–4.07 (m, 4H), 6.78–6.90 (m, 2H), 6.96–7.09 (m, 3H), 7.15 (s, 1H), 7.28–7.46 (m, 3H), 7.56–7.73 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.7, 32.9, 104.7, 105.0, 111.1, 112.3, 117.9, 118.0, 121.3, 121.4, 122.9, 123.0, 124.2, 125.1, 125.8, 129.7, 129.8, 130.9, 131.4, 134.8, 147.9, 151.7, 154.8, 156.4, 159.6, 161.4, 164.9, 170.2, 170.8. ESI–MS [M + H$^+$]: *m/z* = 373. *Anal*. Calcd for $C_{16}H_9F_5N_2OS$: C 51.61, H 2.42, N 7.53; Found: C 51.54, H 2.36, N 7.48.

2-(4-Chlorophenylimino)-3-(4-methoxyphenyl)thiazolidin-4-one (4d). White solid. IR (KBr): 1723, 1643, 1369, 1162. ^{1}H NMR (75 MHz, $CDCl_3$): δ = 3.78 (d, *J* = 0.8 Hz, 2 × 2H), 3.83 (s, 3H), 3.94 (s, 3H), 6.76–6.85 (m, 5H), 6.98 (d, *J* = 8.9 Hz, 2H), 7.18–7.35 (m, 7H), 7.47 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.8, 55.3, 55.4, 114.3, 114.7, 121.9, 122.3, 126.9, 128.9, 129.2, 129.3, 129.5, 129.8, 133.1, 134.7, 140.8, 146.6, 154.3, 155.9, 156.8, 159.7, 171.1, 171.4. ESI–MS [M + H$^+$]: *m/z* = 333. *Anal*. Calcd for $C_{16}H_{13}ClN_2O_2S$: C 57.83, H 3.92, N 8.43; Found: C 57.76, H 3.87, N 8.37.

3-P-tolyl-2-(3-(trifluoromethyl)phenylimino)thiazolidin-4-one (4e). White solid. Mp 108–110°C. IR (KBr): 1734, 1627, 1362, 1172. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.84 (s, 3H), 3.96 (d, *J* = 0.8 Hz, 2H), 6.95–7.09 (m, 3H), 7.16 (s, 1H), 7.24 (d, *J* = 7.6 Hz, 2H,), 7.33–7.46 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.8, 55.4, 114.7, 118.1, 121.1, 124.2, 126.9, 128.9, 129.6, 131.2, 131.7, 148.5, 156.5, 159.8, 171.3. ESI–MS [M + H$^+$]: *m/z* = 351. *Anal*. Calcd. For $C_{17}H_{13}F_3N_2OS$: C 58.29, H 3.71, N 8.0; Found: C 58.21, H 3.66, N 7.96.

3-phenyl-2-(3-(trifluoromethyl)phenylimino)thiazolidin-4-one (4f). White solid. Mp 69–71°C. IR(KBr): 1735, 1632, 1361, 1169. ^{1}H- NMR (75 MHz, $CDCl_3$): δ = 3.98 (d, *J* = 0.9 Hz, 2H), 6.86 (d, *J* = 7.2 Hz, 1H), 6.99-7.74 (m, 8H). ^{13}C- NMR (75 MHz, $CDCl_3$): δ = 32.9, 118.1, 121.2, 124.2, 127.9, 129.1, 129.4, 129.7, 131.3, 131.7, 134.4, 148.4, 156.2, 171.1. ESI–MS [M + H$^+$]: *m/z* = 337. Anal. Calcd for $C_{16}H_{11}F_3N_2OS$: C 57.14, H 3.28, N 8.33; Found: C 57.08, H 3.22, N 8.26.

3-(3-chloro-4-fluorophenyl)-2-(phenylimino)thiazolidin-4-one (4g). White solid. IR (KBr): 1719, 1631, 1379, 1170. ^{1}H NMR (75 MHz, $CDCl_3$): δ = 3.96 (d, *J* = 0.8 Hz, 2 × 2H), 6.69–6.78 (m, 1H), 6.85 (d, *J* = 7.6 Hz, 2H), 6.96 (dd, J_1 = 6.4 Hz, J_2 = 2.6 Hz, 1H), 7.02–7.15 (m, 2H), 7.22–7.35 (m, 5H), 7.38–7.55 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.7, 32.8, 116.7, 116.9, 120.5, 120.6, 120.7, 122.9, 124.8, 127.8, 129.1, 129.2, 129.3, 130.5, 134.4, 144.6, 147.5, 156.8, 159.5, 170.9, 171.1. ESI–MS [M + H$^+$]: *m/z* = 321. *Anal*. Calcd for $C_{15}H_{10}ClFN_2OS$: C 56.25, H 3.13, N 8.75; Found: C 56.17, H 3.08, N 8.69.

2-(4-chloro-3-(trifluoromethyl)phenylimino)-3-(4-methoxyphenyl)thiazolidin-4-one (4h). White solid. Mp 48–50°C. IR (KBr): 1740, 1646, 1380, 1175. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.84 (s, 3H), 3.96 (d, *J* = 0.9 Hz, 2H), 6.98 (d, *J* = 8.9 Hz, 3H), 7.17–7.28 (m, 3H), 7.42 (d, *J* = 7.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.8, 55.4, 114.8, 120.6, 124.4, 125.3, 126.7, 127.5, 128.7, 128.9, 132.1, 146.8, 157.1, 159.9, 171.2. ESI–MS [M + H$^+$]: *m/z* = 401. *Anal*. Calcd for $C_{17}H_{12}ClF_3N_2O_2S$: C 51.0, H 3.0, N 7.0; Found: C 50.96, H 2.94, N, 6.96.

(Z)-3-(4-methoxyphenyl)-2-(phenylimino)thiazolidin-4-one (4i). White solid. IR (KBr): 1716, 1643, 1368, 1161. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.77 (s, 3H), 3.83 (s, 3H), 3.92 (d, *J* = 0.8 Hz, 2 × 2H), 6.77–6.88 (m, 6H), 6.94–7.11 (m, 3H), 7.21–7.54 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.7, 32.8, 55.3, 55.4, 114.3, 114.7, 120.8, 121.9, 124.5, 127.1, 127.9, 129.1, 129.3, 134.7, 141.1, 148.1, 155.2, 156.7, 159.7, 171.4, 171.6. ESI–MS [M + H$^+$]: *m/z* = 299. *Anal*. Calcd for $C_{16}H_{14}N_2O_2S$: C 64.43, H 4.70, N 9.39; Found: C 64.36, H 4.64, N 9.32.

3-(Thiophen-2-ylmethyl)-2-(3-(trifluoromethyl)phenylimino) thiazolidin-4-one (4j). Yellow liquid. IR (neat): 1721, 1640, 1381, 1135. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.81 (d, *J* = 0.8 Hz, 2H), 5.14 (s, 2H), 6.91–6.97 (m, 1H), 7.12–7.27 (m, 4H), 7.36–7.50 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.8, 40.6, 118.1, 118.2, 121.3. 121.4, 124.4, 126.4, 126.5, 128.6, 129.8, 136.7, 148.2, 154.8, 170.8. ESI–MS [M + H$^+$]:

$m/z = 357$. *Anal*. Calcd for $C_{15}H_{11}F_3N_2OS_2$: C 50.56, H 3.09, N 7.87; Found: C 50.48, H 3.02, N 7.81.

2-(Phenylimino)-3-(thiophen-2-ylmethyl)thiazolidin-4-one (4k). White solid. Mp 88–90°C. IR (KBr): 1722, 1639, 1383, 1137. ^{1}H NMR (75 MHz, $CDCl_3$): $\delta = 3.77$ (d, $J = 0.8$ Hz, 2H), 5.15 (s, 2H), 6.89–7.00 (m, 3H), 7.07–7.25 (m, 3H), 7.32 (t, $J = 7.4$ Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 32.7$, 40.5, 120.9, 124.7, 126.2, 126.4, 128.5, 129.2, 137.0, 147.7, 153.3, 171.0. ESI–MS $[M + H^+]$: $m/z = 289$. *Anal*. Calcd for $C_{14}H_{12}N_2OS_2$: C 58.33, H 4.17, N 9.72; Found: C 58.26, H 4.11, N 9.66.

3-Cyclohexyl-2-(4-methoxyphenylimino)thiazolidin-4-one (4l). White solid. Mp 138–140°C. IR (KBr): 1720, 1646, 1370, 1168. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.13$–1.44 (m, 5H), 1.54–1.83 (m, 5H), 3.13 (s, 1H), 3.84 (s, 3H), 3.92 (d, $J = 0.9$ Hz, 2H), 6.94 (d, $J = 8.6$ Hz, 2H), 7.15 (d, $J = 8.6$ Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 24.5$, 25.5, 32.4, 33.2, 55.3, 61.6, 114.2, 127.9, 128.9, 149.3, 159.1, 171.6. ESI–MS $[M + H^+]$: $m/z = 305$. *Anal*. Calcd for $C_{16}H_{20}N_2O_2S$: C 63.16, H 6.57, N 9.21; Found: C 63.08, H 6.49, N 9.16.

2-(4-Chlorophenylimino)-3-cyclohexylthiazolidin-4-one (4m). White solid; Mp 147–149°C. IR (KBr): 1718, 1644, 1366, 1164. ^{1}H NMR (75 MHz, $CDCl_3$): $\delta = 1.16$–1.42 (m, 5H), 1.51–1.79 (m, 5H), 3.11(s, 1H), 3.92 (s, 2H), 7.16–7.26 (m, 2H), 7.40 (d, $J = 8.7$ Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 24.4$, 25.5, 32.5, 33.1, 61.5, 129.0, 129.2, 133.6, 134.0, 148.8, 171.1. ESI–MS $[M + H^+]$: $m/z = 309$. *Anal*. Calcd for $C_{15}H_{17}ClN_2OS$: C 58.44, H 5.52, N 9.10; Found: C 58.36, H 5.48, N 9.04.

(Z)-3-tert-butyl-2-(phenylimino)thiazolidin-4-one (4n). White solid. Mp 108–110°C. IR (KBr): 1726, 1634, 1374, 1155. ^{1}H NMR (75 MHz, $CDCl_3$): $\delta = 1.24$ (s, 9H), 3.93 (d, $J = 0.8$ Hz, 2H), 7.18 (d, $J = 7.4$ Hz, 2H), 7.29–7.47 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 29.7$, 33.9, 55.0, 128.4, 128.7, 129.0, 136.3, 145.2, 170.9. ESI–MS $[M + H^+]$: $m/z = 249$. *Anal*. Calcd for $C_{13}H_{16}N_2OS$: C 62.90, H 6.46, N 11.29; Found: C 62.82, H 6.38, N 11.21.

3-Cyclopropyl-2-(3-(trifluoromethyl)phenylimino)thiazolidin-4-one (4o). Yellow liquid. IR (neat): 1730, 1637, 1372, 1171, 697. ^{1}H NMR (75 MHz, $CDCl_3$): $\delta = 0.70$–1.15 (m, 4H), 2.71–2.83 (m, 1H), 3.74 (d, $J = 0.8$ Hz, 2H), 7.07 (d, $J = 7.6$ Hz, 1H), 7.33–7.49 (m, 2H). ^{13}C NMR (300 MHz, $CDCl_3$): $\delta = 6.6$, 25.8, 32.4, 118.1, 121.1, 124.2, 125.2, 129.6, 131.3, 148.9, 156.5, 171.8. ESI–MS $[M + H^+]$: $m/z = 301$. *Anal*. Calcd for $C_{13}H_{11}F_3N_2OS$: C 52.0, H 3.67, N 9.33; Found: C 51.94, H 3.61, N 9.26.

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[21] *Crystal data*: for **4a**: $C_{15}H_{12}N_2OS$, M = 268.33, orthorhombic, space group Pbca, a = 10.8879(9) Å, b = 10.0574(8) Å, c = 24.2525(19) Å, V = 2655.7(4) Å^3, Z = 8, D_c = 1.342 Mg m-3, λ = 0.71073 Å, μ(Mo Kα) = 0.236 mm-1, F000 = 1120, T = 294(2) K. Total number of measured reflections is 12413. Final refinement to convergence on F^2 gave R = 0.0604 (2192 obs. data only) and Rw = 0.1304, GOF = 1.246. CCDC # 833911.