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# Base Controlled Three-Component Regioselective Synthesis of 2-Imino Thiazolines and 2-Thioxoimidazolin-4-ones

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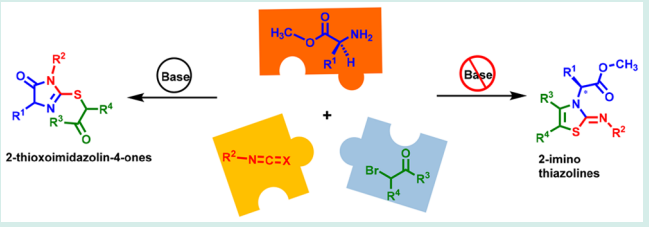
Supporting Information

**ABSTRACT:** Base-controlled regioselective synthesis of 2-imino thiazolines and 2-thioxoimidazolin-4-ones was achieved to use a one-pot reaction between chiral amino esters, isothiocyanates, and α-bromoketones/alkyl halides. This three-component coupling reaction in acetonitrile provides 2-imino thiazolines, whereas the formation of 2-thioxoimidazolin-4-ones was observed under basic conditions at ambient temperature. The corresponding products were obtained in good to excellent yield with broad substrate scope. Isolation of thiourea and thiohydantoin intermediates disclosed the course of the reaction mechanism.




**KEYWORDS:** *2-imino thiazoline, multicomponent reaction, regioselective synthesis, single reactant replacement, 2-thioxoimidazolin-4-one*

## INTRODUCTION

The 2-imino thiazole moiety is a core component of various heterocycles with interesting biological activities. For example, TS-943 has antithrombotic activity toward platelet glycoprotein-IIb/IIIa receptors in humans.[1] Moreover, coumarinyl thiazoline has potential anticonvulsant activity,[2] whereas neonicotinoid shows insecticidal activity preferentially having high affinity at the insect *Drosophila* nicotinic acetylcholine receptor.[3] In addition, 3,4-diarylthiazol-2(3*H*)-one exhibits an anticancer effect against human CEM leukemia cells[4] (Figure 1).

Hydantoin is a privileged scaffold found in various natural products and pharmaceutical agents, and modification of this class of compounds has led to interesting bioactive molecules. For instance, fenamidone shows fungicidal activity by acting as a quinone outside inhibitor.[5] In addition, 2-thioxoimidazolin-4-one possesses anticancer activity against human prostate cancer cell lines LNCaP.[6]

To achieve high structural diversity during the synthesis of biologically interesting molecules, various synthetic methods have been developed in the past. Multicomponent reactions (MCRs) are a one-pot reaction strategy where multiple bond-forming processes occur between three or more substrates in a cascade manner to afford a product.[7] Owing to their synthetic advantages in terms of efficiency and atom economy, this approach has been employed to generate libraries of small molecules and became an important tool in the drug discovery process.[8] Despite being an expedient strategy, MCR suffers from the key issue regarding limited scaffold diversity and complexity due to the availability of a handful of MCRs which were mostly discovered in a serendipitous way.[9]

In this context, intense research efforts started toward rational design of novel MCRs. Single reactant replacement (SRR) and condition-based divergence (CBD) are between the two logic-based approaches implemented for the enhancement of the molecular diversity. SRR strategy consists of replacement of a reactant (C) for another reactant (D) comprising comparable reactivity based on the analysis of the role of each reactant mechanistically in known MCRs.[10] However, CBD involves generation of structurally diverse scaffolds from the same starting materials via different reaction pathways by varying reaction conditions such as bases, catalysts, solvents. and additives.[11]

In light of the strategies reported for the improvement of MCRs, we were intrigued to combine SRR and CBD approaches in one single reaction, thereby both scaffold diversification and complexity could be addressed.

To the best of our knowledge, this is the first example where the combination of SRR with CBD is utilized in a single MCR.

An extensive literature survey had revealed that there were few reports on the synthesis of substituted 2-imino thiazoles via multicomponent reaction between isothiocyanates, amines,

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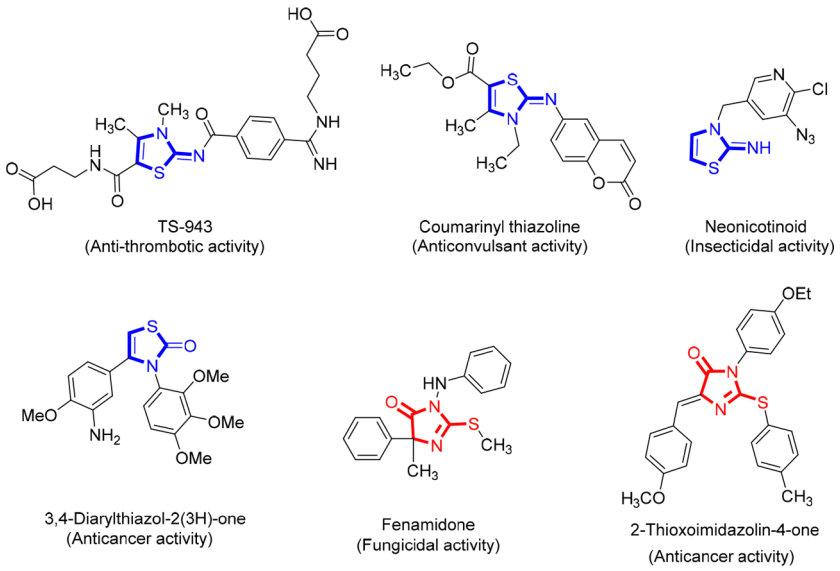


**Figure 1.** Bioactive compounds containing 2-imino thiazole and thioxoimidazolin-4-one motifs.

and $\alpha$-haloketones.[12] In this context, we envisaged that this MCR could be carried out through a single reactant replacement approach (SRR) using chiral amino acid esters in place of amines under different reaction conditions to achieve CBD concomitantly which may lead to biologically interesting chiral heterocycles. (Figure 2)

Herein, we report a novel approach for the synthesis of 2-iminothiazoles and 2-thio imidazol-4-ones in a one-pot, two-step strategy from chiral amino acids, isothiocyanates, and $\alpha$-bromoketones/alkyl halides. The great feature of the current MCR involves selective divergence toward the formation of either thioimidazo-4-ones or 2-iminothiazoles depending on the presence of a base in the reaction.

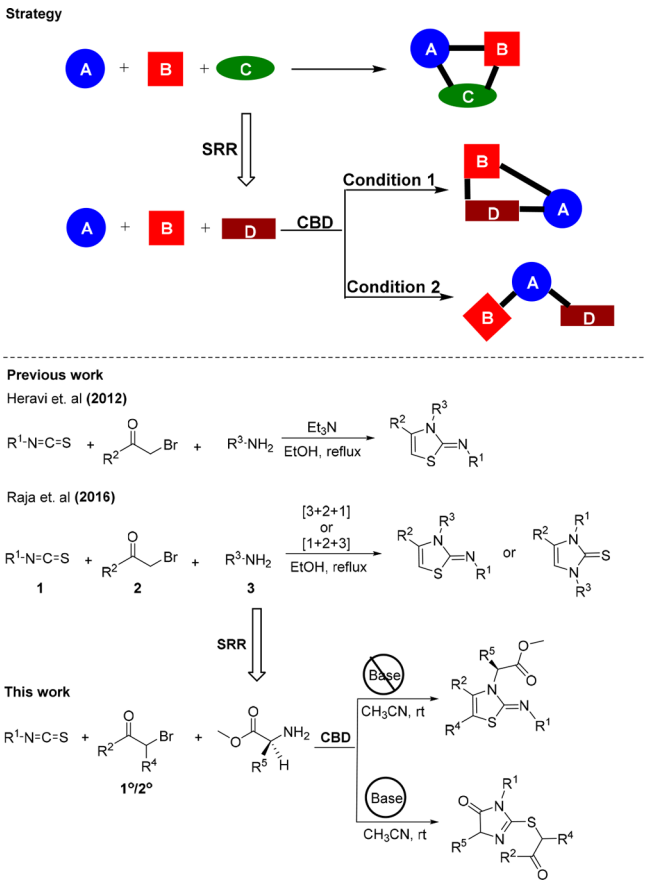


**Figure 2.** Integration of SRR and CBD strategies in a single MCR.

## RESULTS AND DISCUSSION

Initially, when L-phenyl alanine methyl ester **1**{*1*} was treated with phenyl isothiocyanate **2**{*1*} and 2-bromoacetophenone **4**{*1*} in the presence of $NaHCO_3$ in $CH_3CN$ either at −30 or 0 °C for 16 h, thiourea **3**{*1,1*} was obtained as a sole product (Table 1, entries 1−2). When the same reaction was repeated at 10 °C, thiohydantoin intermediate **7**{*1,1*} was obtained through intramolecular cyclization of **3**{*1,1*}, but it failed to further react with 2-bromoacetophenone **4**{*1*} (Table 1, entry 3). Thiohydantoin **7**{*1,1*} obtained from above reaction was analyzed by spectral analysis and unambiguously established by X-ray crystallography (Figure 3).

However, when the temperature was elevated to 20 °C, the above reaction proceeded smoothly, and **8**{*1,1,1*} was obtained in 84% yield (Table 1, entry 4). Next, screening of different bases such as DIPEA, $Et_3N$, and $K_2CO_3$ revealed that one equivalent of $K_2CO_3$ was optimal for this transformation, and the desired product **8**{*1,1,1*} was obtained in 92% yield (Table 1, entries 5−7). After that, different solvents such as methanol, dichloromethane, and 1,4-dioxane were screened. When protic solvent such as methanol was employed, carbamate as well as $\beta$-ketoamine were obtained instead of the desired product[13,14] (Table 1, entry 8). The desired product was obtained in 91% yield in dichloromethane (Table 1, entry 9). The efficiency of the reaction was reduced in 1,4-dioxane, albeit the desired product was obtained in 76% yield (Table 1, entry 10). Conversely, when a mixture of L-phenyl alanine methyl ester **1**{*1*}, phenyl isothiocyanate **2**{*1*}, and 2-bromoacetophenone **4**{*1*} was stirred without a base in $CH_3CN$ for 6 h, 2-iminothiazole **5**{*1,1,1*} was obtained in excellent yield (Table 1, entry 11). Total chemocontrol was observed since the formation of regioisomer **5′**{*1,1,1*} was also possible due to the unsymmetrical thiourea **3**{*1,1*}. Moreover, *N,N*-annulated product **6**{*1,1,1*} was not detected due to the sequential addition of reactants used in the same reaction.[15]



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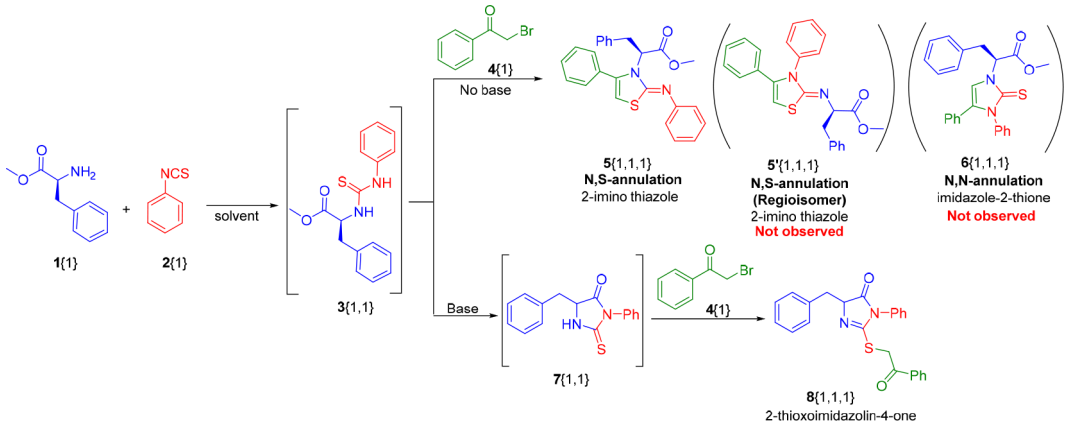
**Table 1. Optimization of One-Pot, Two-Step Synthesis of 2-Imino Thiazoline (5) and 2-Thioxoimidazolin-4-one (8)**[a]




| entry | base | solvent | temp (°C) | time (h) | yield (%)[b] 3{1,1} | 7{1,1} | 5{1,1,1} | 8{1,1,1} |
|---|---|---|---|---|---|---|---|---|
| 1 | $NaHCO_3$ | $CH_3CN$ | −30 | 16 | 80 | | | |
| 2 | $NaHCO_3$ | $CH_3CN$ | 0 | 16 | 88 | | | |
| 3 | $NaHCO_3$ | $CH_3CN$ | 10 | 26 | | 85 | | |
| 4 | $NaHCO_3$ | $CH_3CN$ | 20 | 16 | | | | 84 |
| 5 | DIPEA | $CH_3CN$ | 25 | 16 | | | | 74 |
| 6 | $Et_3N$ | $CH_3CN$ | 25 | 16 | | | | 80 |
| 7 | $K_2CO_3$ | $CH_3CN$ | 25 | 16 | | | | 92 |
| 8 | $K_2CO_3$ | MeOH | 25 | 16 | | | | 0 |
| 9 | $K_2CO_3$ | $CH_2Cl_2$ | 25 | 16 | | | | 91 |
| 10 | $K_2CO_3$ | 1,4-dioxane | 25 | 36 | | | | 76[c] |
| 11 | | $CH_3CN$ | 25 | 6 | | | 88 | |

[a]Reaction conditions: **1**{*1*} (1 mmol), **2**{*1*} (1.5 mmol), **4**{*1*} (1.5 mmol), base (1 mmol), solvent (5 mL). [b]Isolated yield. [c]4 equiv of $K_2CO_3$ used.

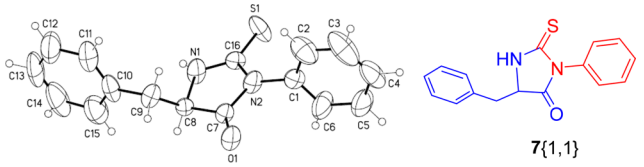



**Figure 3.** ORTEP diagram of 5-benzyl-3-phenyl-2-thioxoimidazolidin-4-one 7{*1,1*} (atomic displacement ellipsoids are drawn at the 50% probability level).

Both products 5{*1,1,3*} and 8{*3,1,8*} as representative examples were determined by spectroscopic analysis and further confirmed by X-ray crystal study. Proton NMR analysis of 5{*1,1,3*} indicated the absence of NH signals and the appearance of a singlet ($\delta$ = 5.52 ppm) for C-5 H of the thiazole ring as well as a signal of C═N at 156.4 ppm in carbon NMR, respectively. Proton NMR of 8{*3,1,8*} exhibited disappearance of the signal of methyl ester and the appearance of isolated doublets at 4.8 and 4.54 ppm for diastereotopic

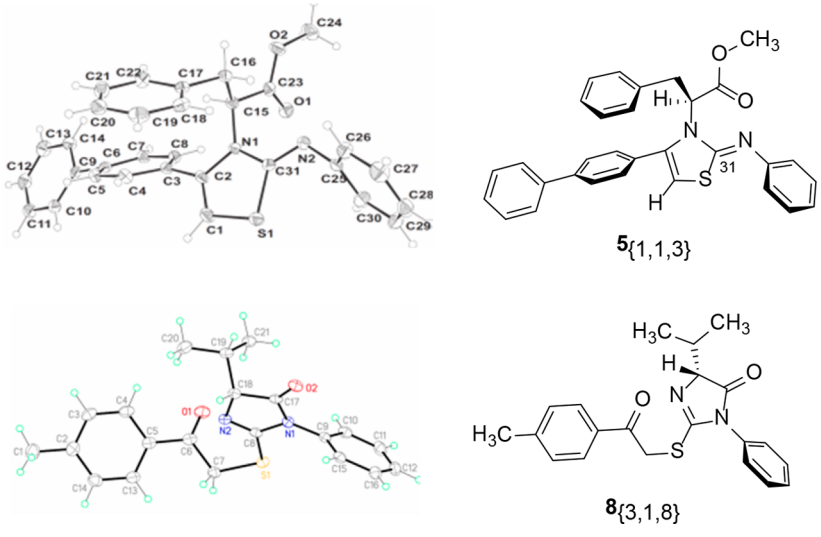



**Figure 4.** ORTEP diagram of 5{*1,1,3*} and 8{*3,1,8*} (atomic displacement ellipsoids are drawn at the 50% probability level).



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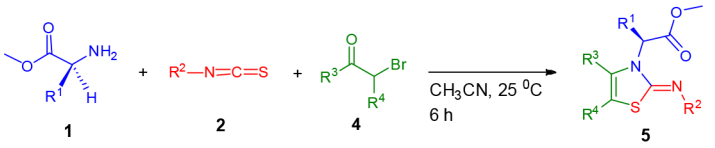
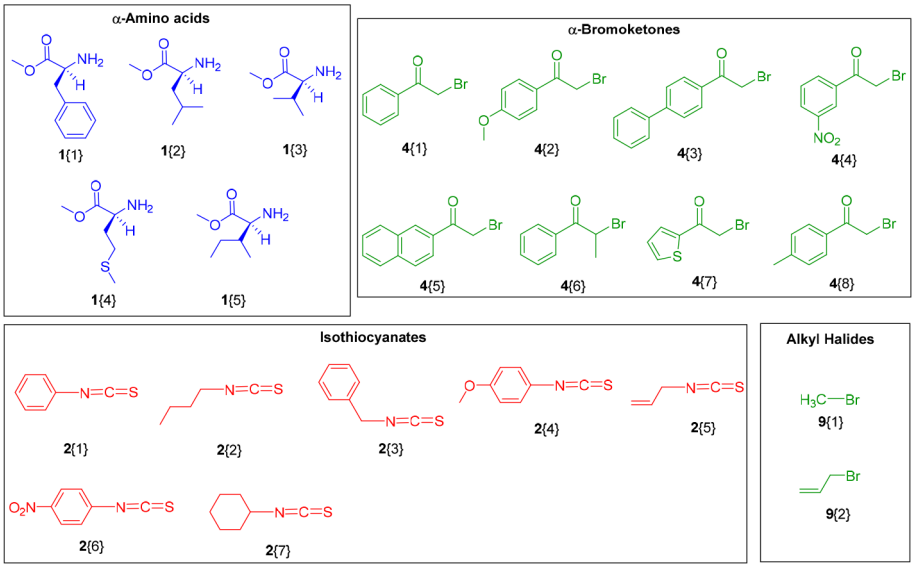
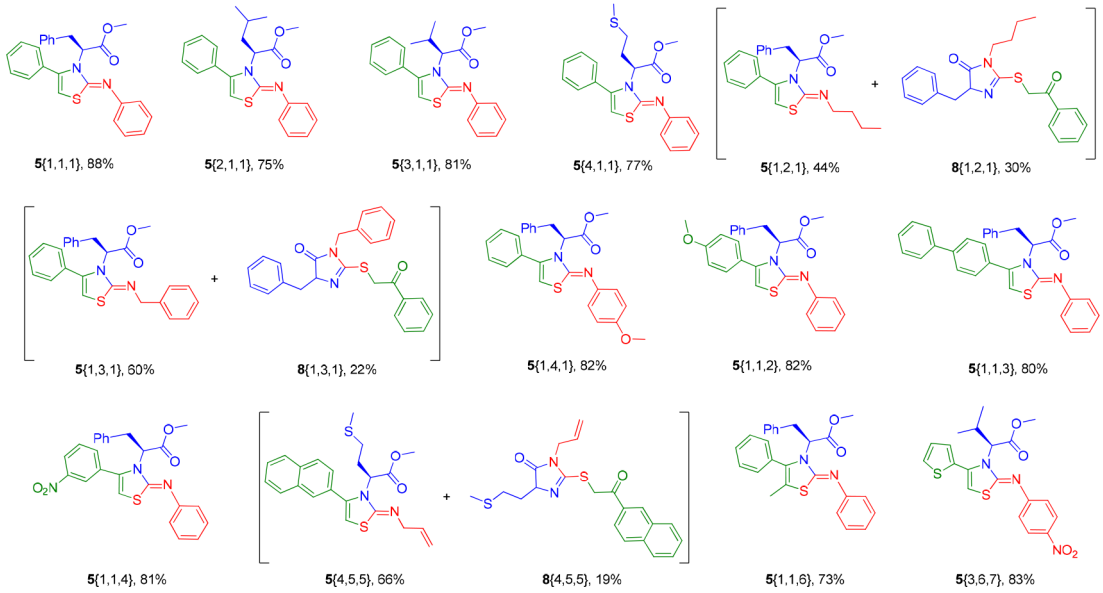
**Table 2. Substrate Scope for the Synthesis of 2-Iminothiazoles (5)**[a]




[a]Reaction conditions: **1** (1 mmol), **2** (1.5 mmol), **4** (1.5 mmol), $CH_3CN$ (5 mL).

protons of the $CH_2$ group. It is evident from the X-ray structure of **5**{*1,1,3*} that the phenyl moiety of the C═N bond is oriented toward sulfur, adopting a Z-configuration of the exocyclic azomethine linkage at C-31. The two phenyl rings of the diphenyl moiety are perpendicular to each other. X-ray crystallography revealed the absolute structure of the product **8**{*3,1,8*} having an isopropyl group at an axial position and the five-member ring in a half-chair form (Figure 4). Chiral HPLC analysis of representative compound **5**{*1,1,2*} showed that the current reaction afforded only one enantiomer. Additionally, compound **5**{*1,1,2*} was prepared from D-phenylalanine methyl ester, and the coinjections of both isomers confirmed the formation of enantiopure **5**{*1,1,2*} (SI, pp 33−35). Conversely, racemization was observed in the case of S-alkylated product **8**{*1,1,2*}.

Having optimized conditions, the scope of this strategy for the synthesis of 2-iminothiazoles **5** and 2-thioxoimidazolin-4-ones **8** was investigated (Tables 2 and 3). The reaction proceeded smoothly when various isothiocyanates and alkyl halides/α-bromoketones were used. Under neutral conditions, aromatic isothiocyanates bearing electron donating or electron withdrawing groups afforded corresponding products in good to excellent yield, whereas aliphatic isothiocyanates furnished the desired products (**5**{*1,2,1*}, **5**{*1,3,1*}, and **5**{*4,5,5*}) in



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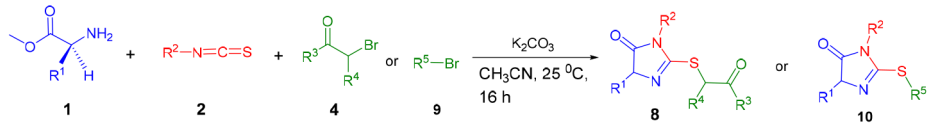
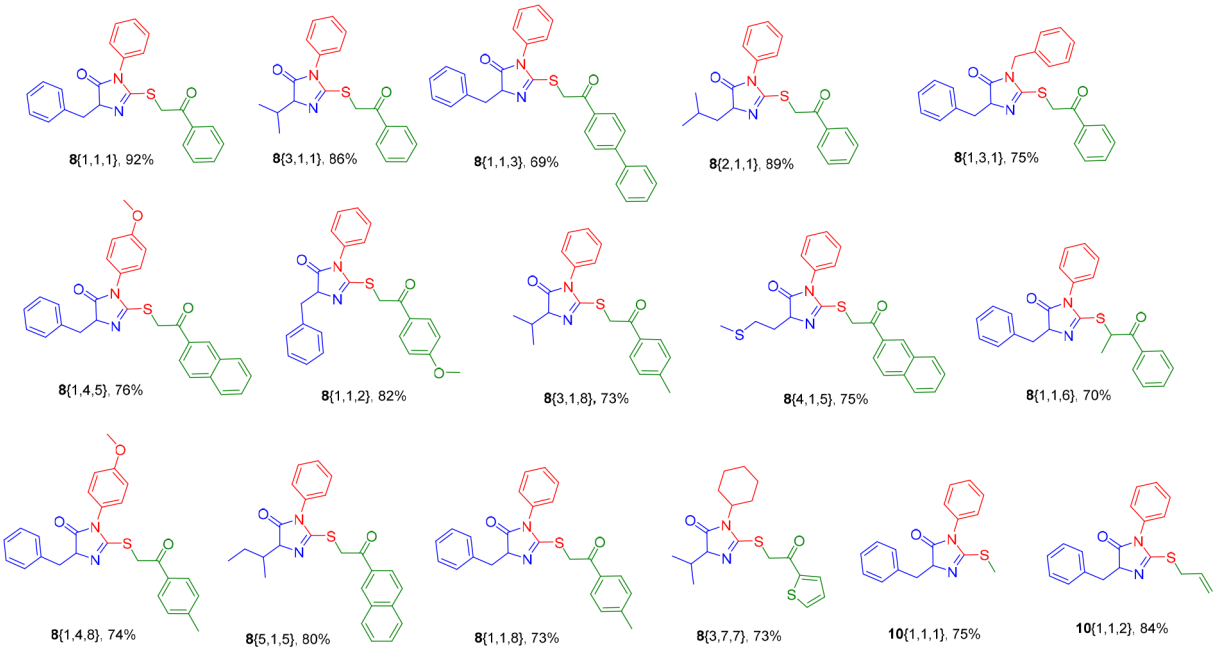
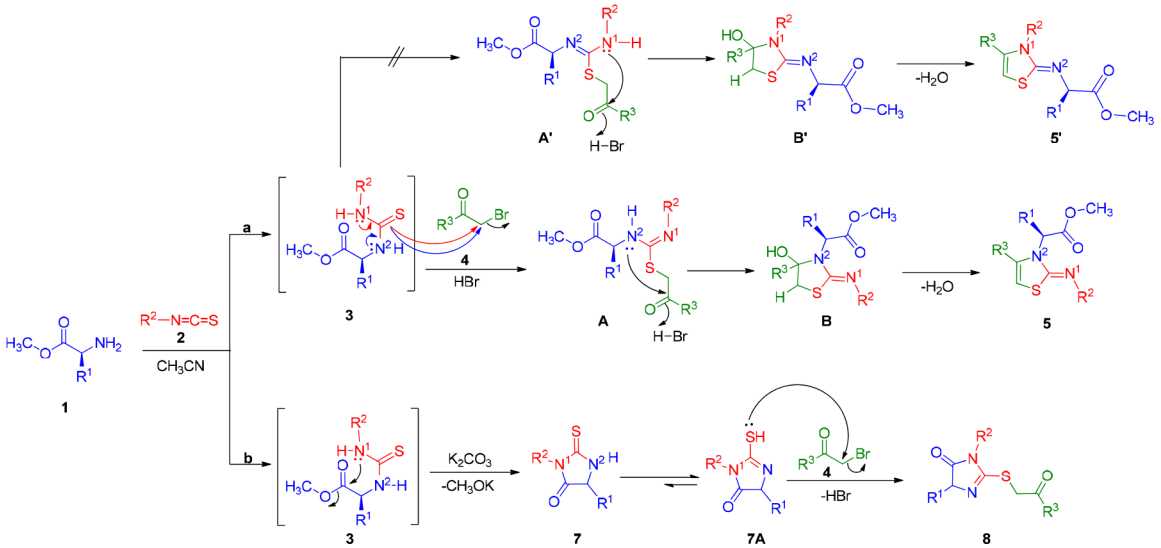
**Table 3. Substrate Scope for the Synthesis of 2-Thioxoimidazolin-4-ones (8)**[a]




[a]Reaction conditions: **1** (1 mmol), **2** (1.5 mmol), **4** (1.5 mmol), base (1 equiv), $CH_3CN$ (5 mL).

**Scheme 1. A Possible Mechanism for the Synthesis of 5 and 8**




moderate yield accompanied by the formation of 2-thioxoimidazolin-4-ones **8**{*1,2,1*}, **8**{*1,3,1*}, and **8**{*4,5,5*}.

We reasoned that the electron-donating character of alkyl groups renders the NH group more nucleophilic, which consequently reacts with carbonyl carbon in an intramolecular way to form the hydantoin intermediates. Similarly, $\alpha$-bromoketones with electron-withdrawing and electron-donating groups ($R^3$) afforded corresponding products in good yield (**5**{*1,1,2*} and **5**{*1,1,4*}). In addition, the desired product was also obtained when polyaromatic and heteroaromatic $\alpha$-bromoketones were used (**5**{*1,1,3*} and **5**{*3,6,7*}). Notably, sterically hindered $\alpha$-bromoalkylketone gave the product **5**{*1,1,6*} in 73% yield, but **8**{*1,1,6*} was obtained as an inseparable diastereomeric mixture. Additionally, use of alkyl halides **9** provided **10**{*1,1,1*} and **10**{*1,1,2*} in 75% and 84% yields, respectively.

On the basis of intermediate isolation, literature reports, and the obtained results, a possible mechanism for the synthesis of



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**5** and **8** is shown in Scheme 1. In path a, a coupling reaction of α-amino acid methyl ester **1** and isothiocyanate **2** generates thiourea **3** first. In the next step, nucleophilic attack of the sulfur atom (soft nucleophile) at the soft electrophilic carbon of the bromomethyl group affords isothiourea **A**.[16] Intramolecular nucleophilic attack of the $NH_2$ group at carbonyl carbon and the subsequent loss of $H_2O$ from **B** furnishes 2-iminothioazole **5**. In path **b**, a base-promoted intramolecular attack of the $N^1H$ group at the methyl ester moiety generates thiohydantoin **7** with the liberation of methanol. Thiohydntoin intermediate **7** tautomerizes into **7A**, and intermolecular attack of the sulfur atom at the carbon of bromomethyl group subsequently eliminates HBr to yield 2-thioxoimidazolin-4-one **8**.[17]

## CONCLUSION

In conclusion, we have developed a novel protocol for the rapid synthesis of 2-imino thiazolines and 2-thioxoimidazolin-4-ones by a base controlled multicomponent reaction employing chiral amino esters, isothiocyanates, and α-bromoketones/alkyl halides. In this reaction, the absence of a base afforded 2-imino thiazolines, whereas basic conditions delivered 2-thioxoimidazolin-4-ones. Employment of aliphatic isothiocyanates under neutral conditions gave a mixture of 2-imino thiazolines and 2-thioxoimidazolin-4-ones. The isolation of intermediates indicated the formation of 2-imino thiazoline through an isothiourea intermediate. However, the formation of a hydantoin intermediate proceeds through intramolecular cyclization of isothiourea in the presence of a base to deliver 2-thioxoimidazolin-4-one. This methodology comprises the amalgamation of a single reactant replacement and condition-based divergence approach in a multicomponent reaction to achieve skeletal diversity.

## EXPERIMENTAL SECTION

**General Methods.** $^1H$ NMR (400 MHz) and $^{13}C$ NMR (101 MHz) spectra were recorded on 400-MR automated spectrometer. Chemical shifts are reported in parts per million (ppm) on the δ scale from an internal standard (TMS). Analytical thin-layer chromatography (TLC) was performed using 0.25 mm silica-gel-coated Kiselgel 60 $F_{254}$ plates. Flash chromatography was performed using the indicated solvent and silica gel 60 (Merck, 230−400 mesh). High-resolution mass spectra (HRMS) were recorded in ESI mode using a TOF mass spectrometer. All materials were purchased from commercial sources and used without further purification.

**Representative Procedure for the Synthesis of Methyl (S,Z)-3-Phenyl-2-(4-phenyl-2-(phenylimino)-thiazol-3(2H)-yl)propanoate (5{*1,1,1*}).** To the stirred solution of phenyl isothiocyanate **2**{*1*} (113 mg, 1.5 mmol) in acetonitrile (10 mL) was added L-phenylalanine methyl ester **1**{*1*} (100 mg, 1 mmol) dropwise, and the reaction mixture was stirred at 25 °C for 2 h. 2-Bromoacetophenone **4**{*1*} (166 mg, 1.5 mmol) was added to the above reaction mixture, and the reaction was stirred for 4 h. After completion of the reaction, the solvent was removed. The residue was diluted with water (15 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (2−5% ethyl acetate in hexanes) to afford methyl (*S,Z*)-3-phenyl-2-(4-phenyl-2-(phenylimino)-thiazol-3(2*H*)-yl)propanoate **5**{*1,1,1*} (150 mg, 88%).

**Methyl (*Z*)-3-Phenyl-2-(4-phenyl-2-(phenylimino)-thiazol-3(2*H*)-yl)propanoate (5{*1,1,1*}).** $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.41−7.28 (m, 3H), 7.25−7.16 (m, 5H), 7.15−7.10 (m, 2H), 7.08−7.03 (m, 1H), 6.94−6.90 (m, 2H), 6.70 (d, *J* = 7.3 Hz, 2H), 5.52 (s, 1H), 4.53 (dd, *J* = 11.1, 4.0 Hz, 1H), 3.95 (dd, *J* = 14.0, 11.1 Hz, 1H), 3.84 (s, 3H), 3.23 (dd, *J* = 14.0, 4.0 Hz, 1H). $^{13}C$ NMR (101 MHz, $CDCl_3$): δ 170.4, 156.4, 150.5, 140.2, 137.6, 130.9, 129.4, 129.3, 129.1, 129.0, 128.4, 128.3, 126.6, 123.0, 121.3, 95.1, 60.1, 52.6, 32.9. HRMS calcd for $C_{25}H_{23}N_2O_2S$: *m/z* 415.1483. Found: 415.1483 $(M+H)^+$. $[\alpha]_D^{27}$ = −269.20 (*c* = 0.005, $CH_2Cl_2$). HPLC analysis (2% *i*-PrOH/hexane, 0.3 mL $min^{-1}$, 254 nm): 92% ee, $t_R$ = 19.1

**Representative Procedure for the Synthesis of 5-Benzyl-2-((2-oxo-2-phenylethyl)thio)-3-phenyl-3,5-dihydro-4*H*-imidazol-4-one (8{*1,1,1*}).** To the stirred solution of phenyl isothiocyanate **2**{*1*} (113 mg, 1.5 mmol) in acetonitrile (10 mL) was added $K_2CO_3$ (77 mg, 1 mmol) and *L*-phenylalanine methyl ester **1**{*1*} (100 mg, 1 mmol), and the reaction mixture was stirred at 25 °C for 2 h. To the above reaction mixture, 2-bromoacetophenone **4**{*1*} (166 mg, 1.5 mmol) was added, and the reaction was stirred at the same temperature for 14 h. After completion of the reaction, the solvent was evaporated. The residue was diluted with water (15 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (8−15% ethyl acetate in hexanes) to afford 5-benzyl-2-((2-oxo-2-phenylethyl)thio)-3-phenyl-3,5-dihydro-4*H*-imidazol-4-one **8**{*1,1,1*} (205 mg, 92%).

$^1H$ NMR (400 MHz, $CDCl_3$): δ 8.05 (d, *J* = 7.1 Hz, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.35−7.42 (m, 3H), 7.15−7.25 (m, 5H), 6.93−6.84 (m, 2H), 4.70 (d, *J* = 16.7 Hz, 1H), 4.62 (d, *J* = 16.7 Hz, 1H), 4.50 (dd, *J* = 6.1, 4.4 Hz, 1H), 3.31 (dd, *J* = 13.5, 4.4 Hz, 1H), 3.14 (dd, *J* = 13.5, 6.1 Hz, 1H). $^{13}C$ NMR (101 MHz, $CDCl_3$): δ 192.8, 180.1, 161.0, 135.6, 135.6, 133.9, 131.8, 129.8, 129.4, 129.2, 128.8, 128.5, 128.0, 127.3, 126.9, 69.7, 38.5, 37.4. HRMS calcd for $C_{24}H_{21}N_2O_2S$: *m/z* 401.1318. Found: 401.1323 $(M+H)^+$.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.8b00152.

Full spectroscopic data ($^1H$, $^{13}C$ NMR, HRMS and HPLC) of compounds **5**{*1,1,1*}−**5n** and **8**{*1,1,1*}−**8**{*3,7,7*} (PDF)

X-ray crystallographic data of compound **5**{*1,1,3*} (CIF)

X-ray crystallographic data of compound **8**{*3,1,8*}(CIF)

X-ray crystallographic data of compound **7**{*1,1*} (CIF)

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### Notes

The authors declare no competing financial interest.



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