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# Hydrogen Peroxide-Mediated Rapid Room Temperature Metal-Free C(sp$^2$)-H Thiocyanation of Amino Pyrazoles, Amino Uracils, and Enamines

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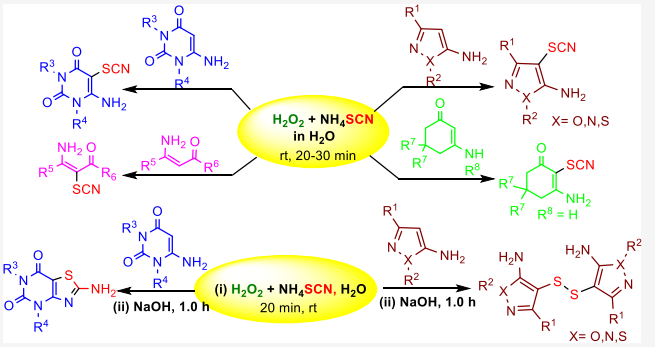
**ABSTRACT:** A rapid metal- and additive-free room temperature method for C(sp$^2$)-H thiocyanation of aminopyrazoles, aminoisoxazole, aminoisothiazole, amino uracils, and aliphatic enamines has been developed in an aqueous medium using hydrogen peroxide as a benign oxidant and ammonium thiocyanate as a thiocyanating agent. On the other hand, the reaction of hydrogen peroxide and ammonium thiocyanate followed by one-pot addition of NaOH provides the corresponding disulfides in the case of amino azoles, and pyrimidine-fused 2-amino thiazoles were observed in the case of aminouracils. The salient features of this method are the use of an eco-friendly oxidant, reaction tunability to access different products, wide substrate scope, and good to very good yields.




## INTRODUCTION

Thiocyanation is one of the popular and very useful transformations for the incorporation of C−S bonds in organic synthesis.[1] Organic thiocyanates can be easily transformed into various thiol derivatives such as thiols, disulfides, thioethers, thiocarbamates, and phosphonothioates and for diverse sulfur-containing heterocycles.[2] In addition to these, organic thiocyanates possess diverse medicinal properties such as antiparasitic, antifungal, and antibacterial.[3] Considering their enormous applications, over the years, numerous methods for the formation of the C−SCN bond have been developed.[4] Recently, thiocyanation of C(sp$^2$)-H bond has gained considerable attention, and different catalysts and thiocyanating agents are being used for this purpose.[5] As for example, Jiang and Wu et al. reported an oxidative thiocyanation method for aromatic and heteroaromatic compounds using KSCN and molecular oxygen in the presence of $Cu(OTf)_2$ as the catalyst (Scheme 1a).[6] Wan et al. reported thiocyanation of C−H bonds of enaminones using $NH_4SCN$ and visible light in the presence of rose bengal or $Ru(bpy)_3Cl_2·6H_2O$ as photocatalysts (Scheme 1b).[7] Chen and Liu et al. developed an NBS-mediated synthesis of 2-aminothiazole derivatives from the reaction of enaminones with KSCN (Scheme 1c).[8] Subsequently, Duan et al. reported thiocyanation reaction of enaminones using NBS and KSCN either in DMF or ethanol medium to prepare thiocyanated products and aminothiazoles, as shown in Scheme 1d.[9] Recently, $K_2S_2O_8$ in combination with $NH_4SCN$ has been explored for the thiocyanation of N-substituted pyrazolone (Scheme 1e)[10] and pyrazolin-5-ones (Scheme 1f).[11] Similarly, molecular oxygen in the TFA medium has been used for thiocyanation of 4-aminocoumarins in the presence of visible light.[12] Despite these useful methods for thiocyanation, very few methods are known in the literature for the C(sp$^2$)-H thiocyanation of heterocycles using readily available and environmentally benign reagents.

Aminopyrazole and aminouracils are found in diverse drugs and bioactive molecules, and they act as valuable starting materials for the construction of fused *N*-heterocycles.[13] Although a plethora of methods are known in the literature for thiocyanation of arenes, indoles, carbazoles, pyrroles, and imidazopyridines, however, till now, only limited methods are known for the thiocyanation of the pyrazole moiety.[14] Hydrogen peroxide is a popular and benign oxidizing agent used in various organic transformations.[15] Recently, Cheng et al. have reported hydrogen peroxide-mediated iodide-catalyzed sulfenylation and selenylation of unprotected uracil derivatives.[16] To the best of our knowledge, $H_2O_2$ has not been used under additive- and metal-free conditions for the thiocyanation reactions. In continuation of our work on new methodology development,[17] we wanted to develop a metal-free thiocyana-

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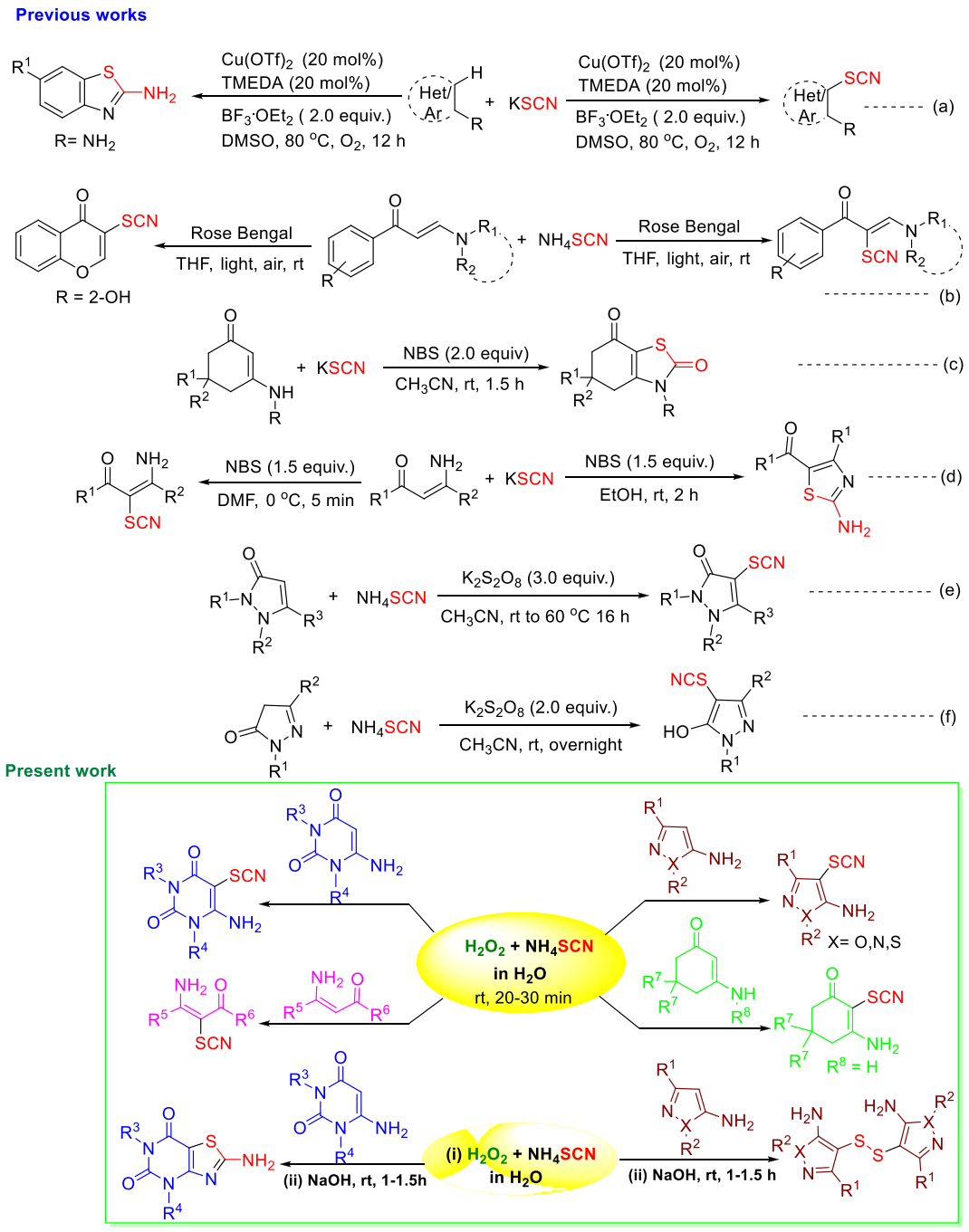
**Scheme 1. Few Recent Methods for Thiocyanation and Our Work**




tion method for the $sp^2$(C–H) bond using readily available $H_2O_2$ as a benign oxidizing agent.

## RESULTS AND DISCUSSION

We started our preliminary investigation on thiocyanation by taking 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**1e**) and $NH_4SCN$ (**2**) as model substrates. The reaction of **1e** with **2** in acetonitrile medium in the absence of any catalyst or oxidizing agent did not provide our expected product **3e** even after 12 h of room temperature stirring. Interestingly, when we performed the same reaction in the presence of 2 equiv of $H_2O_2$ within 2 h, the corresponding thiocyanated product **3e** was obtained in 35% yield (Table 1, entry 2). With this encouraging result, next, we focused on the optimization of the reaction conditions by screening this reaction in different solvents such as THF, DMF, MeOH, EtOH, and $H_2O$ (Table 1, entries 3–7). From this screening, we observed that the water medium provided the highest yield among all the screened solvents (Table 1, entry 7). Considering this outcome, then we tried to improve the yield of the reaction by increasing the amount of $H_2O_2$ and thiocyanating agent $NH_4SCN$. Interestingly, using 4.0 equiv of $H_2O_2$ and 3.0 equiv of $NH_4SCN$, 65% yield of **3e** was observed within 30 min. The best result was obtained using 8.0 equiv of $H_2O_2$ and 3.0 equiv of $NH_4SCN$ within 15 min (Table 1, entry 10). We also screened NaSCN and KSCN as thiocyanating agents under


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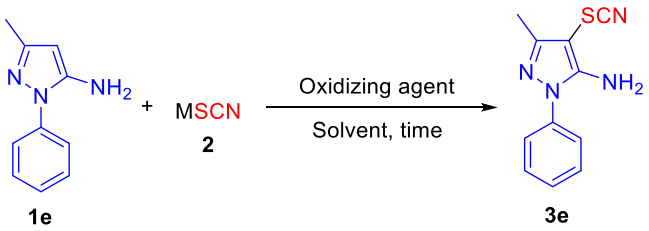
**Table 1. Optimization of Reaction Conditions**[a]




1e 3e

| entry | oxidizing agent (equiv) | MSCN (equiv) | solvent | time | yield[b] (%) |
|---|---|---|---|---|---|
| 1 | | $NH_4SCN$ (1) | MeCN | 12 h | NR |
| 2 | $H_2O_2$ (2) | $NH_4SCN$ (2) | MeCN | 2 h | 35 |
| 3 | $H_2O_2$ (2) | $NH_4SCN$ (2) | THF | 2 h | 40 |
| 4 | $H_2O_2$ (2) | $NH_4SCN$ (2) | DMF | 2 h | 30 |
| 5 | $H_2O_2$ (2) | $NH_4SCN$ (2) | MeOH | 2 h | 45 |
| 6 | $H_2O_2$ (2) | $NH_4SCN$ (2) | EtOH | 2 h | 52 |
| 7 | $H_2O_2$ (2) | $NH_4SCN$ (2) | $H_2O$ | 2 h | 58 |
| 8 | $H_2O_2$ (4) | $NH_4SCN$ (3) | $H_2O$ | 30 min | 65 |
| 9 | $H_2O_2$ (6) | $NH_4SCN$ (3) | $H_2O$ | 20 min | 70 |
| **10** | **$H_2O_2$ (8)** | **$NH_4SCN$ (3)** | **$H_2O$** | **15 min** | **81** |
| 11 | $H_2O_2$ (8) | NaSCN (3) | $H_2O$ | 20 min | 78 |
| 12 | $H_2O_2$ (8) | KSCN (3) | $H_2O$ | 20 min | 75 |
| 13 | $K_2S_2O_8$ (8) | $NH_4SCN$ (3) | $H_2O$ | 15 min | 77 |
| 14 | $Na_2S_2O_8$ (8) | $NH_4SCN$ (3) | $H_2O$ | 15 min | 74 |
| 15 | oxone (8) | $NH_4SCN$ (3) | $H_2O$ | 15 min | 72 |
| 16 | TBHP (8) | $NH_4SCN$ (3) | $H_2O$ | 15 min | 75 |
| 17 | $O_2$ | $NH_4SCN$ (3) | $H_2O$ | 6 h | trace |

[a]Reactions were carried out using 0.5 mmol (1.0 equiv) of **1e** at room temperature. [b]Yield of the isolated product.

similar reaction conditions, and relatively lower yields were observed than those of $NH_4SCN$ (Table 1, entries 11−12).

Next, various oxidants such as $K_2S_2O_8$, $Na_2S_2O_8$, oxone, and TBHP were screened in the presence of 3.0 equiv of $NH_4SCN$ at room temperature. In all these cases, the observed yield was lower than that of entry 10. We also tried a reaction using molecular oxygen as the oxidant, keeping all other parameters constant, and to our surprise, only a trace amount of our desired product **3e** was observed even after 6 h of reaction time (Table 1, entry 17). Thus, considering all these, 3.0 equiv of $NH_4SCN$ and 8.0 equiv of $H_2O_2$ in water as a reaction medium were chosen as the optimum reaction conditions for this transformation (Table 1, entry 10).

With these optimized reaction conditions at hand, we then turned our attention to check the generality and scope of this method. A wide variety of aminopyrazole derivatives with $R^1$ = methyl, tertiary butyl, phenyl, and *p*-tolyl groups and $R^2$ = H, Me, and Ph were found suitable for thiocyanation by this method, and the corresponding thiocyanated products were obtained in good to very good yields (Table 2). Then, we tried to explore 5-amino-3-methylisoxazole and 5-amino-3-methylisothiazole under similar reaction conditions, and the corresponding products **3i** and **3j** were obtained with 85 and 78% yields, respectively. We also tried thiocyanation of 3,5-dimethyl-1-phenyl-1*H*-pyrazole, a pyrazole derivative without having any amino substituent under similar reaction conditions. To our surprise, the reaction was very slow, and only 20% yield of **3k** was obtained even after 6 h of stirring. Similar to aminopyrazoles, 6-aminouracil also provided the corresponding thiocyanation product **5a** in very good yield under the standard reaction conditions. Likewise, monosubstituted and disubstituted 6-aminouracils with alkyl groups such as methyl, ethyl, and propyl were reacted, and the corresponding products **5b**−**5e** were prepared in good to very good yields. This method is also applicable to electron-rich pyrimidine-like 2,4,6-triaminopyrimidine, and the corresponding product **5f** was obtained with relatively lower yield (60%). It is noteworthy to mention that all these reactions were completed within 15−20 min time. All the products were fully characterized by $^1H$ & $^{13}C$ NMR and by recording HRMS. Next, we tried this methodology to acyclic enamine derivatives having the ketone or ester functionality. Under the standard reaction conditions, 4-amino-3-penten-2-one provided the corresponding product **7a** in 81% yield within 20 min. The scope of acyclic enamine derivatives was studied by preparing **7b**−**7e**, and the results are summarized in Table 3. Cyclic enamines such as 3-aminocyclohex-2-en-1-one and 3-amino-5,5-dimethyl cyclohex-2-en-1-one were reacted under the standard reaction conditions, and the corresponding products **7f** (78%) and **7g** (76%), respectively, were obtained. Likewise, 5,5-dimethyl-3-morpholinocyclohex-2-en-1-one, a cyclic enamine derivative having the tertiary amine functionality, provided the corresponding product **7h** in 73% yield. Interestingly, in all the cases, we did not observe any intramolecular cyclization product. However, when cyclic enaminone, 3-(cyclohexylamino)-5,5-dimethylcyclohex-2-en-1-one, having a secondary amine group was treated with $NH_4SCN$ under the standard reaction conditions, we observed thiocyanation followed by intramolecular cyclized product **9a**.

Next, the feasibility of gram-scale synthesis of thiocyanated products was checked. For this purpose, we took aminopyrazole **1e** in 8.0 mmol and 3.0 equiv of $NH_4SCN$ and 8.0 equiv of $H_2O_2$ in 40 mL of water and kept under room temperature stirring for 20 min. After completion of the reaction, the corresponding thiocyanated product **3e** was obtained in 78% yield (Scheme 2a). Similarly, aminouracil **4c**


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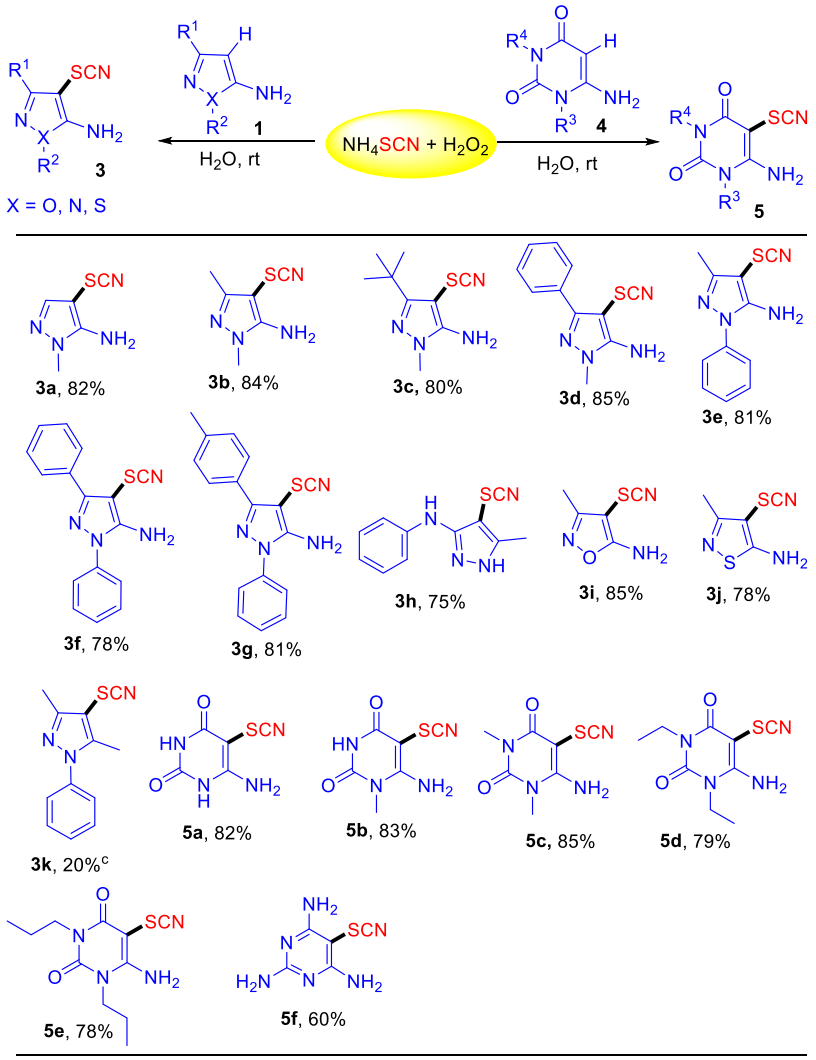
Table 2. Substrate Scope for the $H_2O_2$-Mediated Thiocyanation of Aminopyrazole and Amino Uracils[a,b]




[a]Reaction conditions: $NH_4SCN$ (1.5 mmol), **1** or **4** (0.5 mmol), and 30% $H_2O_2$ (4.0 mmol) in $H_2O$ (3.0 mL), rt, 15−20 min. [b]Yield of the isolated product. [c]For **3k**, the reaction time was 6 h.

also provided 79% yield of **5c** when performed in 8.0 mmol scale reaction, as shown in Scheme 2b.

After developing this methodology for thiocyanation of diverse aminopyrazole, aminouracil, and enamine derivatives, next, we wanted to examine the outcome of a one-pot reaction of aminopyrazole with $NH_4SCN$ in the presence of $H_2O_2$ followed by treatment with NaOH solution. For this purpose, we initially took 5-amino-1,3-dimethyl-1*H*-pyrazole (0.5 mmol), $H_2O_2$ (4.0 mmol), and $NH_4SCN$ (1.5 mmol) in 3.0 mL of water, and the resultant reaction mixture was stirred for 20 min at room temperature; to this solution, 5.0% (w/v) NaOH solution (0.3 mL) was added, and the resultant solution was kept under room temperature stirring for another 1.0 h.

Interestingly, in this reaction, we observed product **10a**, a disulfide of an aminopyrazole derivative, in good yield. Next, with this interesting observation, we focused to generalize this one-pot method for the formation of disulfides by varying aminopyrazole derivatives under similar reaction conditions. Different aminopyrazole derivatives with alkyl or aryl substitutes were found suitable for this one-pot disulfide formation reaction. Next, using this one-pot two-step process, a set of disulfides of aminopyrazoles such as **10b**−**10d** were prepared, and the results are summarized in Table 4. Similar to aminopyrazoles, 5-amino-3-methyl-isothiozole also provided the corresponding disulfide **10e** in good yield. All the products were fully characterized by $^1H$ & $^{13}C$ NMR and HRMS. In addition to these, for the unambiguous structure determination, we recorded single-crystal XRD of **10d**.

After having these interesting observations, next we tried to see the outcome of our one-pot two-step procedure in amino uracils. To our surprise, when 6-amino-1,3-dimethyluracil was taken as a substrate and the same reaction procedure was followed, we observed the corresponding fused aminothiazole derivative **11a** in very good yield instead of any disulfide. Similar to 6-amino-1,3-dimethyluracil, other aminouracil derivatives also provided the corresponding uracil-fused 2-aminobenzothiazoles **11b** and **11c** in good yields (Table 5). Six-membered cyclic enaminone, 3-aminocyclohex-2-enone, also behaved similar to aminouracils and provided the corresponding fused 2-aminothiazole **11d** in good yield.

Finally, we tried to utilize our thiocyanated products for the preparation of various sulfur-containing products. Thus, first, we took compound **3e** and reacted with an excess amount of phenyl magnesium bromide, and the corresponding phenyl


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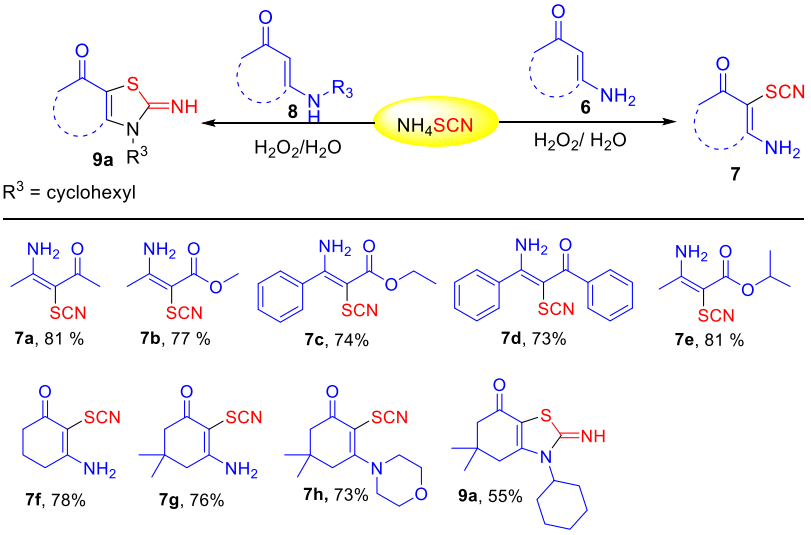
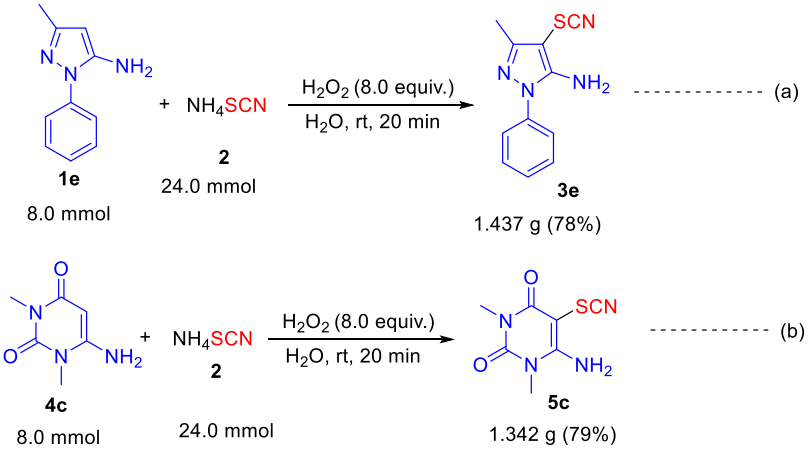
**Table 3. Substrate Scope for Thiocyanation of Enamine Derivatives**[a,b]




[a]Reaction conditions: $NH_4SCN$ (1.5 mmol), **6** or **8** (0.5 mmol), and 30% $H_2O_2$ (8.0 equiv) in $H_2O$ (3.0 mL), rt, 15−20 min. [b]Yield of the isolated product.

**Scheme 2. Controlled Experiment for Gram-Scale Synthesis of 3e and 5b**




thioether of aminopyrazole **13** was obtained in 65% yield (Scheme 3a). Then, we performed a reaction of **3e** with sodium azide in the presence of $ZnCl_2$ to prepare a hybrid thioether having aminopyrazole linked with tetrazole (**14**), as shown in Scheme 3a. Next, we have used acyclic enamine derivative **7a** to prepare cyclic product **15a** in the presence of sulfuric acid in the water medium. Likewise, **7b** was treated with sulfuric acid in the water medium, and within 3 h, the corresponding thiazolone **15b** was obtained in 72% yield.

Mechanistically, we believe that $H_2O_2$-mediated thiocyanation can go through either path I or path II, as shown in Scheme 4a. The hydroxyl radical ($HO^{\bullet}$) generated from $H_2O_2$ can abstract one electron from the −SCN anion to form the SCN radical (**I**) or dimerized intermediate (**II**). In the case of path I, 3-position of aminopyrazole, which acts as a C-nucleophilic site, attacks intermediate **II** to form intermediate **III**. Finally, a hydroxide ion (generated from abstracting one electron from the reaction of thiocyanate anion by the hydroxyl radical) abstracts one $H^+$ from **III** to provide our desired product **3e**. On the other hand, reaction can also follow path II. In this case, reaction goes via intermediates **IV** and **V** to provide the desired product **3e**. Synthesis of symmetrical disulfides from the organic thiocyanates in the presence of bases is known in the literature.[18] Based on the literature reports,[18,19] we propose that disulfide formation in the case of amino pyrazoles takes place by the nucleophilic attack of the hydroxide ion on the CN functionality of SCN in **3e**, which will provide the thiolate anion. This resultant thiolate anion subsequently attacks another molecule of thiocyanate to form an S−S bond, as shown in Scheme 4b.

## CONCLUSIONS

In summary, we have developed an efficient rapid room temperature additive- and metal-free methodology for the C−H thiocyanation of diverse amino (pyrazoles, isothaizole, isoxazole, and aminouracils) and enamine derivatives using $H_2O_2$ as a benign oxidizing agent. Interestingly, one-pot two-step reaction of $NH_4SCN$ and $H_2O_2$ followed by NaOH addition provides the corresponding disulfides by amino-pyrazoles, whereas aminouracil and cyclic enamines provide the corresponding fused 2-aminothiazole derivatives. The salient features of this work are simple procedure, short


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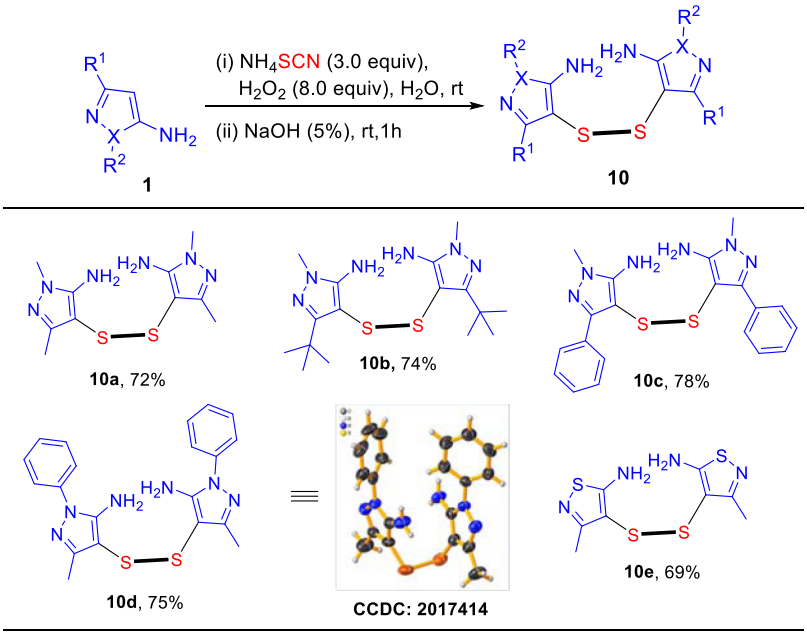
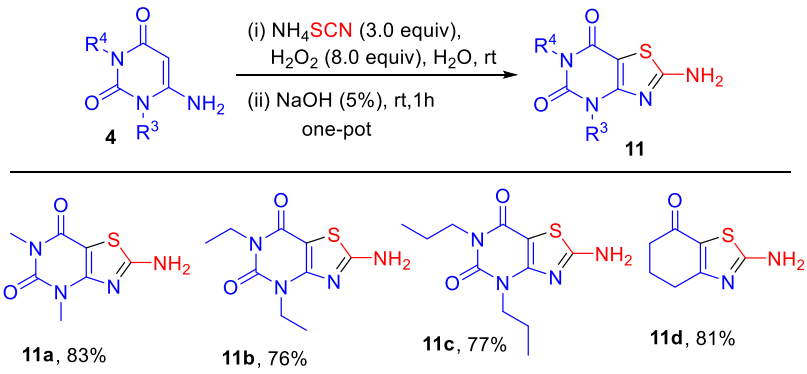
**Table 4. One-Pot Two-Step Synthesis of Disulfides**[a,b]



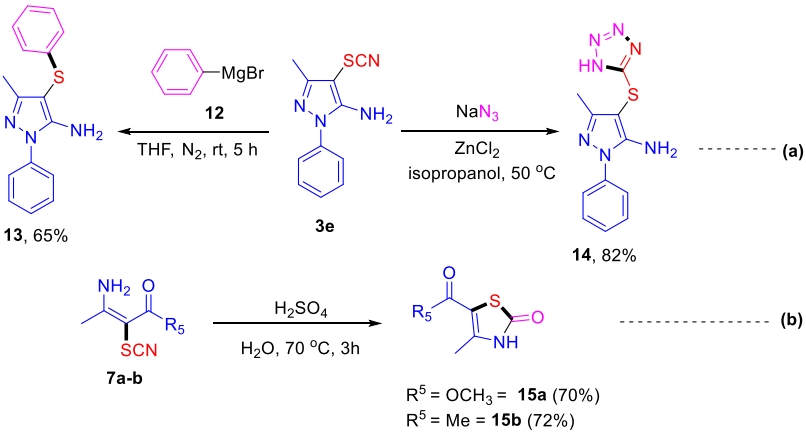

[a]Reaction conditions: **1** (0.5 mmol), $NH_4SCN$ (1.5 mmol) (i) 30% $H_2O_2$ (8.0 equiv) in $H_2O$ (3.0 mL), rt, 20−30 min. (ii) NaOH (5%) rt, 1 h. [b]Yield of the isolated product.

**Table 5. One-Pot Two-Step Synthesis of Fused 2-Aminothiazoles**[a,b]




[a]Reaction conditions: $NH_4SCN$ (1.5 mmol, 3.0 equiv), **4** (0.5 mmol, 1.0 equiv), (i) $H_2O_2$ (8.0 equiv) in $H_2O$ (3.0 mL), rt, 20−30 min. (ii) NaOH (5%) rt, 1 h. [b]Yield of the isolated product.

**Scheme 3. Synthetic Utility of Thiocyanated Products**





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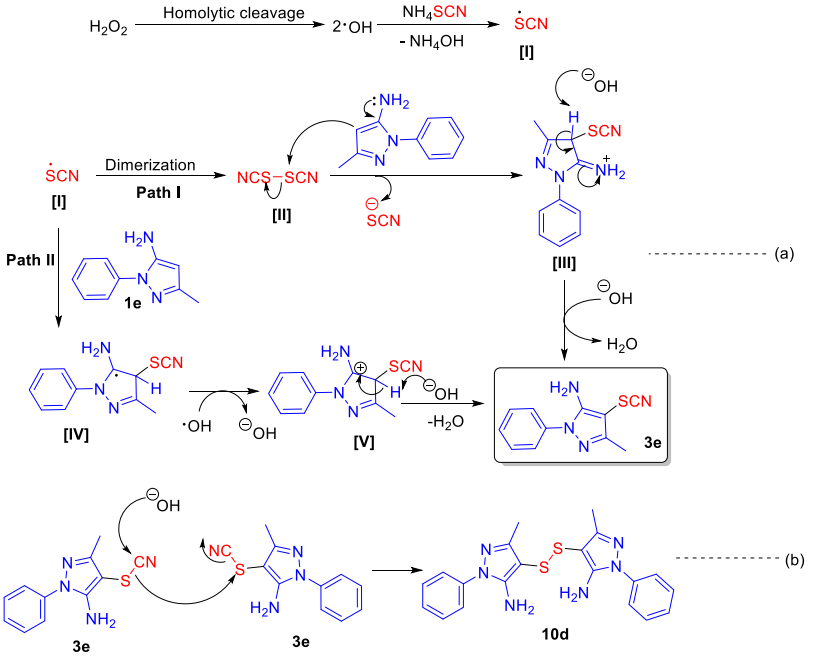
**Scheme 4. Plausible Reaction Mechanism for Thiocyanation and Disulfide Formation**




reaction time, wide substrate scope with good to very good yields, use of $H_2O_2$ as a readily available eco-friendly oxidizing agent, and tunability of the method for the one-pot preparation of disulfides and aminothiazoles. Gram-scale thiocyanation is also possible by this method.

## EXPERIMENTAL SECTION

**General Information.** All the reagents were procured from commercial sources (Sigma-Aldrich, Merck, and Alfa-Aesar) and used as such without further purification. Organic extracts were dried over anhydrous sodium sulfate. Solvents were removed using a rotary evaporator under reduced pressure. Reactions were monitored by TLC. Column chromatographic separations were performed using Merck silica gel (60−120 mesh). Melting points were recorded using an SRS EZ-Melt automated melting point apparatus by capillary methods and uncorrected. NMR spectra were recorded in a Bruker 400 MHz spectrometer in $CDCl_3$ or DMSO-$d_6$ with tetramethylsilane as the internal standard. Chemical shift values are reported in $\delta$ values (ppm) downfield from tetramethylsilane. HRMS analysis was carried out using a Bruker Impact HD mass spectrometer (Impact HD UHR-TOF, ESI with positive mode), Agilent 6520 Q-TOF, and XEVO G2-XS QTOF mass spectrometer. Single-crystal XRD was recorded in a Bruker AXS (D8 Quest system) X-ray diffractometer.

**Experimental Procedure.** *General Procedure for the Synthesis of **3a**−**3j** and **5a**−**5f**.* In a 10.0 mL round-bottom flask, 0.5 mmol of aminopyrazole/isoxazole/isothiazole or amino uracil, 1.5 mmol of $NH_4SCN$, and 3.0 mL of $H_2O$ were transferred. To this mixture, 4.0 mmol of 30% $H_2O_2$ was added, and the resultant mixture was kept under constant stirring at ambient temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was transferred to a separating funnel, and 10.0 mL of water was added and extracted three times with dichloromethane (3 × 10.0 mL) for **3a**−**3j**, and for **5a**−**5f**, 3 × 10.0 mL of ethyl acetate was used. The resultant organic layer was dried over anhydrous sodium sulfate and concentrated using a rotavap. The crude product was purified by silica gel column chromatography using a mixture of hexane−ethyl acetate as the eluent.

*1-Methyl-4-thiocyanato-1H-pyrazol-5-amine (**3a**).* It was purified by column chromatography [eluent hexane/ethyl acetate = 17:3 (v/v)]. White solid; yield 63 mg (82%); mp 105−107 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.87 (s, 1H), 5.28 (s, 2H), 3.60 (s, 3H). $^{13}$C {$^1$H} NMR (100 MHz, DMSO-$d_6$): $\delta$ 156.9, 136.3, 112.3, 78.9, 38.6. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_5H_7N_4S$, 155.0386; found, 155.0381.

*1,3-Dimethyl-4-thiocyanato-1H-pyrazol-5-amine (**3b**).* It was purified by column chromatography [eluent hexane/ethyl acetate = 17:3 (v/v)]. Yield 71 mg (84%); white solid; mp 180−182 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 6.14 (s, 2H), 3.47 (s, 3H), 2.07 (s, 3H). $^{13}$C {$^1$H} NMR (100 MHz, DMSO-$d_6$): $\delta$ 150.6, 148.5, 112.5, 72.8, 34.6, 11.8. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_6H_9N_4S$, 169.0542; found, 169.0545.

*3-(tert-Butyl)-1-methyl-4-thiocyanato-1H-pyrazol-5-amine (**3c**).* It was purified by column chromatography [eluent hexane/ethyl acetate = 9:1 (v/v)]. White solid; yield 84 mg (80%); mp 101−103 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 6.11 (s, 2H), 3.49 (s, 3H), 1.32 (s, 9H). $^{13}$C {$^1$H} NMR (100 MHz, DMSO-$d_6$): $\delta$ 158.5, 152.3, 113.3, 70.8, 35.2, 33.3, 29.6. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_9H_{15}N_4S$, 211.1012; found, 211.1014.

*1-Methyl-3-phenyl-4-thiocyanato-1H-pyrazol-5-amine (**3d**).* It was purified by column chromatography [eluent hexane/ethyl acetate = 9:1 (v/v)]. Brown solid; yield 98 mg (85%); mp 124−126 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.76 (d, $J$ = 8.0 Hz, 2H), 7.47 (t, $J$ = 8.0, 2H), 7.40 (t, $J$ = 8.0 Hz, 1H), 6.36 (s, 2H), 3.62 (s, 3H). $^{13}$C {$^1$H} NMR (100 MHz, DMSO-$d_6$): $\delta$ 151.8, 149.7, 132.2, 128.5, 128.2, 127.2, 112.8, 71.9, 35.2. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_{11}H_{11}N_4S$, 231.0699; found, 231.0695.

*3-Methyl-1-phenyl-4-thiocyanato-1H-pyrazol-5-amine (**3e**).* It was purified by column chromatography [eluent hexane/ethyl acetate = 9:1 (v/v)]. White solid; yield 93 mg (81%); mp 108−110 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.51−7.48 (m, 4H), 7.40−7.34 (m, 1H), 6.32 (s, 2H), 2.19 (s, 3H). $^{13}$C {$^1$H} NMR (100 MHz, DMSO-$d_6$): $\delta$ 150.5, 150.3, 138.3, 129.3, 127.1, 123.4, 112.3, 75.1, 11.9. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_{11}H_{11}N_4S$, 231.0699; found, 231.0706.

*1,3-Diphenyl-4-thiocyanato-1H-pyrazol-5-amine (**3f**).* It was purified by column chromatography [eluent hexane/ethyl acetate = 19:1 (v/v)]. Saddle brown solid; yield 114 mg (78%) mp 80−82 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.89 (d, $J$ = 8.0 Hz, 2H), 7.58−7.41 (m, 8H), 4.56 (s, 2H). $^{13}$C {$^1$H} NMR (100 MHz, $CDCl_3$): $\delta$ 152.9, 149.6, 137.8, 131.4, 129.9, 129.1, 128.7, 128.1, 124.2, 111.3,76.2. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_{16}H_{13}N_4S$, 293.0855; found, 293.0857.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*1-Phenyl-4-thiocyanato-3-(p-tolyl)-1H-pyrazol-5-amine (**3g**).* It was purified by column chromatography [eluent hexane/ethyl acetate = 19:1(v/v)]. Saddle brown semisolid; yield 124 mg (81%). $^1$H NMR (400 MHz, DMSO- $d_6$): δ 7.79 (d, $J$ = 8.0 Hz, 2H), 7.54 (d, $J$ = 8.0 Hz, 2H), 7.49 (t, $J$ = 8.0 Hz, 2H), 7.40 (t, $J$ = 8.0 Hz, 1H), 7.29 (d, $J$ = 8.0 Hz, 2H), 4.56 (s, 2H), 2.39 (s, 3H). $^{13}$C {$^1$H} NMR (100 MHz, $CDCl_3$): δ 152.8, 149.6, 138.9, 137.8, 129.8, 129.3, 128.5, 128.4, 127.9, 124.1, 111.4, 75.9, 21.4. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_{17}H_{15}N_4S$, 307.1012; found, 307.1014.

*5-Methyl-N-phenyl-4-thiocyanato-1H-pyrazol-3-amine (**3h**).* It was purified by column chromatography [eluent hexane/ethyl acetate = 4:1 (v/v)]. Yield 86 mg (75%), white solid; mp 171−173 °C. $^1$H NMR (400 MHz, DMSO- $d_6$): δ 12.60 (s, 1H), 8.25 (s, 1H), 7.54 (d, $J$ = 8.0 Hz, 2H), 7.20 (t, $J$ = 8.0 Hz, 2H), 6.79 (t, $J$ = 8.0 Hz, 1H), 2.33 (s, 3H). $^{13}$C {$^1$H} NMR (100 MHz, DMSO- $d_6$): δ 152.3, 146.8, 144.2, 142.7, 128.5, 119.1, 116.0, 112.1, 81.6, 40.2, 9.7. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_{11}H_{11}N_4S$, 231.0699; found, 231.0693.

*3-Methyl-4-thiocyanatoisoxazol-5-amine (**3i**).* It was purified by column chromatography [eluent hexane/ethyl acetate = 9:1(v/v)]. Yield 66 mg (85%), white solid; mp 160−162 °C; $^1$H NMR (400 MHz, $CDCl_3$): δ 5.29 (br s, 2H), 2.29 (s, 3H). $^{13}$C {$^1$H} NMR (100 MHz, $CDCl_3$): δ 170.4, 162.2, 109.9, 70.1, 10.5 ppm. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_5H_6N_3OS$, 156.0226; found, 156.0228.

*3-Methyl-4-thiocyanatoisothiazol-5-amine (**3j**).* It was purified by column chromatography [eluent hexane/ethyl acetate = 9:1 (v/v)]. Yield 67 mg (78%) brownish solid; mp 104−106 °C. $^1$H NMR (400 MHz, $CDCl_3$ + DMSO-$d_6$): δ 6.58 (br s, 2H), 2.32 (s, 3H). $^{13}$C {$^1$H} NMR (100 MHz, $CDCl_3$ + DMSO-$d_6$): δ 175.6, 166.1, 109.8, 88.6, 18.2. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_5H_6N_3S_2$, 171.9998; found, 172.0002.

*3,5-Dimethyl-1-phenyl-4-thiocyanato-1H-pyrazole (**3k**).* It was purified by column chromatography [eluent hexane/ethyl acetate = 32:1 (v/v)]. Yield 23 mg (20%) white solid; mp 96−98 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ (7.52−7.39 m, 5H), 2.44 (s, 3H), 2.43 (s, 3H). $^{13}$C {$^1$H} NMR (100 MHz, $CDCl_3$): δ 152.1, 144.5, 139.2, 129.5, 128.8, 125.1, 110.9, 96.7, 12.1, 11.6. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_{12}H_{12}N_3S$, 230.0746; found, 230.0755.

*6-Amino-5-thiocyanatopyrimidine-2,4(1H,3H)-dione (**5a**).* It was purified by washing with methanol. Yield 76 mg (82%) white solid; mp 358−360 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 10.85 (s, 1H), 10.68 (s, 1H), 7.25 (br s, 2H). $^{13}$C {$^1$H} NMR (100 MHz, DMSO-$d_6$): δ 162.1, 157.6, 149.5, 112.5, 65.8. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_5H_5N_4O_2S$, 185.0128; found, 185.0122.

*6-Amino-1-methyl-5-thiocyanatopyrimidine-2,4(1H,3H)-dione (**5b**).* It was purified by column chromatography [eluent hexane/ethyl acetate = 7:3 (v/v)]. Yield 83 mg (83%) white solid; mp 312−314 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 11.03 (s, 1H), 7.86 (s, 2H), 3.27 (s, 3H). $^{13}$C {$^1$H} NMR (100 MHz, DMSO-$d_6$): δ 160.6, 158.6, 149.9, 112.5, 66.2, 30.0. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_6H_7N_4O_2S$, 199.0284; found, 199.0287.

*6-Amino-1,3-dimethyl-5-thiocyanatopyrimidine-2,4(1H,3H)-dione (**5c**).* It was purified by column chromatography [eluent hexane/ethyl acetate = 7:3 (v/v)]. Yield 90 mg (85%) white solid; mp 302−304 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 7.88 (s, 2H), 3.34 (s, 3H), 3.15 (s, 3H). $^{13}$C {$^1$H} NMR (100 MHz, DMSO-$d_6$): δ 160.2, 157.3, 150.3, 112.4, 66.2, 31.0, 28.3. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_7H_9N_4O_2S$, 213.0441; found, 213.0446.

*6-Amino-1,3-diethyl-5-thiocyanatopyrimidine-2,4(1H,3H)-dione (**5d**).* It was purified by column chromatography [eluent hexane/ethyl acetate = 8:2 (v/v)]. Yield 95 mg (79%) white solid; mp 172−174 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 7.91 (s, 2H), 3.95 (q, $J$ = 8.0 Hz, 2H), 3.81 (q, $J$ = 8.0 Hz, 2H), 1.12 (t, $J$ = 8.0 Hz, 3H), 1.07 (t, $J$ = 8.0 Hz, 3H). $^{13}$C {$^1$H} NMR (100 MHz, DMSO-$d_6$): δ 159.8, 156.4, 149.7, 112.6, 66.6, 38.9, 36.5, 13.1, 12.9. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_9H_{13}N_4O_2S$, 241.0754; found, 241.0756.

*6-Amino-1,3-dipropyl-5-thiocyanatopyrimidine-2,4(1H,3H)-dione (**5e**).* It was purified by column chromatography [eluent hexane/ethyl acetate = 8:2 (v/v)]. Yield 105 mg (78%) white solid; mp 152−154 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 8.52 (s, 2H), 3.92 (t, $J$ = 8.0 Hz, 2H), 3.77 (m, 2H), 1.66−1.58 (m, 7.5 Hz, 2H), 1.57−1.48 (m, 2H), 0.84 (q, $J$ = 8 Hz, 6H). $^{13}$C {$^1$H} NMR (100 MHz, DMSO-$d_6$): δ 173.3, 156.7, 155.9, 151.4, 92.7, 46.4, 42.6, 21.4, 21.2, 11.6, 11.3. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_{11}H_{17}N_4O_2S$, 269.1067; found, 269.1075.

*5-Thiocyanatopyrimidine-2,4,6-triamine (**5f**).* It was purified by just washing with methanol. Yield 55 mg (60%) white solid; mp 208−210 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 6.55 (br s, 4H), 6.02 (br s, 2H). $^{13}$C {$^1$H} NMR (100 MHz, DMSO-$d_6$): δ 163.2, 159.6, 111.8, 63.5 ppm. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_5H_7N_6S$, 183.0447; found, 183.04454.

*General Procedure for the Synthesis of **7a**−**h** and **9a**.* In a 10.0 mL round-bottom flask, 0.5 mmol of enamine derivatives (**6**), 1.5 mmol of $NH_4SCN$, and 3.0 mL of $H_2O$ were transferred. To this mixture, 4.0 mmol of 30% $H_2O_2$ was added, and the resultant mixture was kept under constant stirring at ambient temperature. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was transferred to a separating funnel, and 10.0 mL of water was added and extracted with 3 × 10.0 mL of ethyl acetate. The resultant organic layer was dried over anhydrous sodium sulfate and concentrated using rotavap. Finally, the crude product was purified by silica gel column chromatography using a mixture of hexane and ethyl acetate as the eluent.

*(E)-4-Amino-3-thiocyanatopent-3-en-2-one (**7a**).* It was purified by column chromatography [eluent hexane/ethyl acetate = 9:1 (v/v)]. White solid. Yield 115 mg (81%), mp 152−154 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 10.56 (br s, 1H), 8.92 (br s, 1H), 2.34 (s, 3H), 2.30 (s, 3H). $^{13}$C {$^1$H} NMR (100 MHz, DMSO-$d_6$): δ 195.7, 170.3, 113.8, 84.8, 28.7, 22.4. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_6H_9N_2OS$, 157.0430; found, 157.0433.

*(E)-Methyl 3-Amino-2-thiocyanatobut-2-enoate (**7b**).* It was purified by column chromatography [eluent hexane/ethyl acetate = 9:1 (v/v)]. Yield 66 mg (77%); white solid; mp 101−103 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 9.27 (br s, 1H), 5.72 (br s, 1H), 3.78 (s, 3H), 2.39 (s, 3H). $^{13}$C {$^1$H} NMR (100 MHz, $CDCl_3$): δ 168.9, 168.7, 113.5, 75.9, 52.1, 23.5. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_6H_9N_2O_2S$, 173.0379; found, 173.0378.

*Ethyl 3-Amino-3-phenyl-2-thiocyanatoacrylate (**7c**).* It was purified by column chromatography [eluent hexane/ethyl acetate = 19:1 (v/v)]. Yield 92 mg (74%), white solid; mp 98−100 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 9.34 (br s, 1H), 7.51−7.46 (m, 3H), 7.43−741 (m, 2H), 5.61 (br s, 1H), 4.30 (q, $J$ = 8.0 Hz, 2H), 1.39 (t, $J$ = 8.0 Hz, 3H). $^{13}$C {$^1$H} NMR (100 MHz, $CDCl_3$): δ 169.7, 168.8, 136.9, 130.5, 128.9, 127.4, 114.1, 77.5, 61.3, 14.5. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_{12}H_{13}N_2O_2S$, 249.0692; found, 249.0693.

*(E)-3-Amino-1,3-diphenyl-2-thiocyanatoprop-2-en-1-one (**7d**).* It was purified by column chromatography [eluent hexane/ethyl acetate = 9:1 (v/v)]. Yield 103 mg (73%), white solid; mp 94−96 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 11.18 (br s, 1H), 7.61−7.59 (m, 2H), 7.55−7.52 (m, 5H), 7.46−7.44 (m, 3H), 6.23 (s, 1H). $^{13}$C {$^1$H} NMR (100 MHz, $CDCl_3$): δ 197.7, 172.9, 141.1, 136.8, 130.8, 130.2, 129.1, 128.2, 127.4, 127.1, 114.5, 87.2. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_{16}H_{13}N_2OS$, 281.0743; found, 281.0745.

*(E)-Isopropyl 3-Amino-2-thiocyanatobut-2-enoate (**7e**).* It was purified by column chromatography [eluent hexane/ethyl acetate = 19:1 (v/v)]. Yield 81 mg (81%), white solid; mp 100−102 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 9.27 (br s, 1H), 5.62 (br s, 1H), 5.03 (sep, $J$ = 8.0 Hz, 1H), 2.37 (s, 3H), 1.32 (d, $J$ = 8.0 Hz, 6H). $^{13}$C {$^1$H} NMR (100 MHz, $CDCl_3$): δ 168.14, 168.10, 113.6, 76.5, 68.4, 23.5, 22.1. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_8H_{13}N_2O_2S$, 201.0692; found, 201.0693.

*3-Amino-2-thiocyanatocyclohex-2-enone (**7f**).* It was purified by column chromatography [eluent hexane/ethyl acetate = 1:1 (v/v)]. Yield 66 mg (78%) white solid; mp 188−190 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 8.20 (s, 1H), 7.80 (s, 1H), 2.60 (t, $J$ = 8.0 Hz, 2H), 2.30 (t, $J$ = 8.0 Hz, 2H), 1.83−1.77 (m, 2H). $^{13}$C {$^1$H} NMR (100 MHz, DMSO-$d_6$): δ 189.9, 171.2, 112.5, 86.3, 36.7, 29.9, 20.1. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_7H_9N_2OS$, 169.0430; found, 169.0429.

*3-Amino-5,5-dimethyl-2-thiocyanatocyclohex-2-enone (**7g**).* It was purified by column chromatography [eluent hexane/ethyl acetate


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= 1:1(v/v)]. Yield 75 mg (76%), white solid; mp 180−182 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.91 (br s, 1H), 7.03 (br s, 1H), 2.42 (s, 2H), 2.21 (s, 2H), 0.96 (s, 6H). $^{13}$C {$^1$H} NMR (100 MHz, DMSO-$d_6$): $\delta$ 189.8, 168.8, 111.3, 85.9, 50.1, 42.9, 31.1, 27.3. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_9H_{13}N_2OS$, 197.0743; found, 197.0754.

*5,5-Dimethyl-3-morpholino-2-thiocyanatocyclohex-2-enone (**7h**).* It was purified by column chromatography [eluent hexane/ethyl acetate = 1:1 (v/v)]. Yield 97 mg (73%), white solid; mp 105−107 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.83 (t, $J$ = 4.0 Hz, 4H), 3.72 (t, $J$ = 4.0 Hz, 4H), 2.47 (s, 2H), 2.36 (s, 2H), 1.07 (s, 6H). $^{13}$C {$^1$H} NMR (100 MHz, $CDCl_3$): $\delta$ 192.0, 168.2, 112.1, 92.9, 67.1, 50.7, 50.1, 44.8, 31.7, 28.5. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_{13}H_{19}N_2O_2S$, 267.1162; found, 267.1169.

*3-Cyclohexyl-2-imino-5,5-dimethyl-2,3,5,6-tetrahydrobenzo[d]-thiazol-7(4H)-one (**9a**).* It was purified by column chromatography [eluent hexane/ethyl acetate = 1:1 (v/v)]. Yield 77 mg (55%), yellow solid; mp 198−200 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.61 (br s, 2H), 2.34 (s, 2H), 1.90−1.69 (m, 6H), 1.43−1.34 (m, 2H), 1.26−1.19 (m, 3H), 1.15 (s, 6H). $^{13}$C {$^1$H} NMR (100 MHz, $CDCl_3$): $\delta$ 188.2, 164.3, 153.2, 109.3, 60.5, 50.3, 39.4, 34.8, 29.8, 28.7, 26.4, 25.3. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_{15}H_{23}N_2OS$, 279.1526; found, 279.1534.

*General Procedure for the Synthesis of **10a**−**10e**.* A mixture of aminopyrazole/isothiazole (0.5 mmol), $NH_4SCN$ (1.5 mmol), and 3.0 mL of water was transferred to a 15 mL round-bottom flask. To this mixture, 4.0 mmol of 30% $H_2O_2$ was added, and the resultant mixture was stirred for 20 min. Then, 5% sodium hydroxide solution (0.3 mL) was added to the reaction mixture and stirred for another 1.0 h. After the completion of the reaction, as monitored by the TLC, the reaction mixture was filtered off and washed with 5.0 × 2 mL of water followed by 10.0 mL of methanol. All the compounds were purified by silica gel column chromatography.

*4,4′-Disulfanediylbis(1,3-dimethyl-1H-pyrazol-5-amine) (**10a**).* It was purified by column chromatography [eluent hexane/ethyl acetate = 17:3 (v/v)]. Yield 103 mg (72%); saddle brown solid; mp 140−142 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 5.51 (s, 4H), 3.44 (s, 6H), 1.70 (s, 6H). $^{13}$C {$^1$H} NMR (125 MHz, DMSO-$d_6$): $\delta$ 149.9, 149.1, 90.3, 34.5, 11.4. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_{10}H_{17}N_6S_2$, 285.0951; found, 285.0947.

*4,4′-Disulfanediylbis(3-(tert-butyl)-1-methyl-1H-pyrazol-5-amine) (**10b**).* It was purified by column chromatography [eluent hexane/ethyl acetate = 17:3 (v/v)]. Yield 68 mg (74%); reddish solid; mp 155−157 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.70 (br s, 4H), 3.56 (s, 6H), 1.37 (s, 18H). $^{13}$C {$^1$H} NMR (100 MHz, $CDCl_3$): $\delta$ 160.7, 150.2, 92.2, 34.7, 33.8, 29.9 ppm. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_{16}H_{29}N_6S_2$, 369.1890; found, 369.1891.

*4,4′-Disulfanediylbis(1-methyl-3-phenyl-1H-pyrazol-5-amine) (**10c**).* It was purified by column chromatography [eluent hexane/ethyl acetate = 17:3 (v/v)]. Yield 80 mg (78%); saddle brown solid; mp 176−178 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.49−7.43 (m, 8H), 7.34 (t, $J$ = 8.0 Hz, 2H), 4.20 (s, 4H), 2.17 (s, 6H). $^{13}$C {$^1$H} NMR (100 MHz, $CDCl_3$): $\delta$ 152.7, 148.7, 138.5, 129.8, 127.7, 123.5, 94.2, 12.1. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_{20}H_{21}N_6S_2$, 409.1264; found, 409.1278.

*4,4′-Disulfanediylbis(3-methyl-1-phenyl-1H-pyrazol-5-amine) (**10d**).* It was purified by column chromatography [eluent hexane/ethyl acetate = 17:3 (v/v)]. Yield 77 mg (75%); saddle brown solid; mp 140−142 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.50−7.43 (m, 8H), 7.34 (t, $J$ = 8.0 Hz, 2H), 4.19 (s, 4H), 2.18 (s, 6H). $^{13}$C {$^1$H} NMR (100 MHz, $CDCl_3$): $\delta$ 152.7, 148.8, 138.5, 129.8, 127.7, 123.5, 94.21, 12.11 ppm. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_{20}H_{21}N_6S_2$, 409.1264; found, 409.1276.

*4,4′-Disulfanediylbis(3-methylisothiazol-5-amine) (**10e**).* It was purified by column chromatography [eluent hexane/ethyl acetate = 17:3 (v/v)] yield 50 mg (69%); yellow solid; mp 222−224 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.16 (s, 4H), 1.82 (s, 6H). $^{13}$C {$^1$H} NMR (100 MHz, DMSO-$d_6$): $\delta$ 175.4, 167.4, 103.6, 17.7 ppm. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_8H_{11}N_4S_4$, 290.9861; found, 290.9867.

*General Procedure for the Synthesis of **11a**−**11d**.* A mixture of the 6-amino uracil derivative (0.5 mmol), $NH_4SCN$ (1.5 mmol), and 3.0 mL of water was transferred to a 25 mL round-bottom flask. To this mixture, 4.0 mmol of 30% $H_2O_2$ was added, and the resultant mixture was stirred for 20 min. Then, 5% sodium hydroxide solution (0.3 mL) was added to the reaction mixture and stirred for another 1.0 h. After the completion of the reaction, as monitored by the TLC, the reaction mixture was filtered off, and the residue was washed with 5.0 × 2.0 mL of water, followed by washing with 2.0 mL of methanol. Compound **11d** was also prepared by the same method just by replacing 6-aminouracil with 3-aminocyclohex-2-enone.

*2-Amino-4,6-dimethylthiazolo[4,5-d]pyrimidine-5,7(4H,6H)-dione (**11a**).* It was purified by filtration, and the residue was washed with 5.0 × 2 mL of water, followed by washing with 2.0 mL of methanol. Yield 88 mg (83%); white solid; mp 362−364 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.50 (s, 2H), 3.42 (s, 3H), 3.18 (s, 3H). $^{13}$C {$^1$H} NMR (100 MHz, DMSO-$d_6$): $\delta$ 172.6, 156.4, 155.6, 151.5, 91.9, 31.5, 27.7. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_7H_9N_4O_2S$, 213.0441; found, 213.0446.

*2-Amino-4,6-diethylthiazolo[5,4-d]pyrimidine-5,7(4H,6H)-dione (**11b**).* It was purified by filtration, and the residue was washed with 5.0 × 2 mL of water, followed by washing with 2.0 mL of methanol. Yield 92 mg (76%); white solid; mp 172−174 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.50 (s, 2H), 4.00 (q, $J$ = 8.0 Hz, 2H), 3.84 (q, $J$ = 8.0 Hz, 2H), 1.17 (t, $J$ = 8.0 Hz, 3H), 1.08 (t, $J$ = 8.0 Hz, 3H). $^{13}$C {$^1$H} NMR (100 MHz, DMSO-$d_6$): $\delta$ 173.0, 156.2, 155.3, 150.7, 92.5, 39.9, 35.9, 13.41, 13.23. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_9H_{13}N_4O_2S$, 241.0754; found, 241.0760.

*2-Amino-4,6-dipropylthiazolo[5,4-d]pyrimidine-5,7(4H,6H)-dione (**11c**).* It was purified by filtration, and the residue was washed with 5.0 × 2 mL of water, followed by washing with 2.0 mL of methanol. Yield 103 mg (77%); white solid mp 152−154 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.50 (s, 2H), 3.91 (t, $J$ = 8.0 Hz, 2H), 3.77 (t, $J$ = 8.0 Hz, 2H), 1.67−1.58 (m, 2H), 1.57−1.47 (m, 2H), 0.84 (q, $J$ = 8.0 Hz, 6H). $^{13}$C {$^1$H} NMR (100 MHz, DMSO-$d_6$): $\delta$ 172.9, 156.3, 155.5, 151.0, 92.3, 46.0, 42.2, 21.0, 20.8, 11.2, 10.9. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_{11}H_{17}N_4O_2S$, 269.1067; found, 269.1072.

*2-Amino-5,6-dihydrobenzo[d]thiazol-7(4H)-one (**11d**).* It was purified by filtration, and the residue was washed with 5.0 × 2 mL of water, followed by washing with 2.0 mL of methanol. Yield 68 mg (81%); white solid; mp 262−264 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.09 (br s, 2H), 2.66 (t, $J$ = 8.0 Hz, 2H), 2.35 (t, $J$ = 8.0 Hz, 2H), 2.06−1.87 (m, 2H). $^{13}$C {$^1$H} NMR (100 MHz, DMSO-$d_6$): $\delta$ 189.7, 173.6, 168.3, 118.6, 36.8, 26.8, 22.5. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_7H_9N_2OS$, 169.0430; found, 169.0432.

*Procedure for the Synthesis of 3-Methyl-1-phenyl-4-(phenylthio)-1H-pyrazol-5-amine (**13**).* 3-methyl-1-phenyl-4-thiocyanato-1*H*-pyrazol-5-amine **3e** (115 mg, 0.5 mmol) and 3.0 mL of dry THF were transferred to a two-neck 25 mL round-bottom flask fitted with a condenser and airtight septums. The temperature of the reaction mixture was kept as 0 °C using an ice bath. Phenyl magnesium bromide (1.0 M) in THF (1.46 mL, 3.0 equiv) was transferred dropwise using a syringe to the reaction mixture under constant stirring conditions. After addition, the ice bath was removed, and temperature was allowed to reach 25 °C. The mixture was kept under stirring conditions at this temperature for 6.0 h. After completion of the reaction, saturated solution of ammonium chloride (5.0 mL) was added to the reaction mixture and extracted with dichloromethane (3 × 5.0 mL). The combined organic layers were dried over anhydrous sodium sulfate and filtered, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography [eluent hexane/ethyl acetate = 19:1 (v/v)]. Yield 92 mg (65%); dark red semisolid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.60 (d, $J$ = 8.0 Hz, 2H), 7.49 (t, $J$ = 8.0 Hz, 2H), 7.35 (t, $J$ = 8.0 Hz, 1H), 7.24 (t, $J$ = 8.0 Hz, 2H), 7.12−7.10 (m, 3H), 4.22 (s, 2H), 2.24 (s, 3H). $^{13}$C {$^1$H} NMR (100 MHz, $CDCl_3$): $\delta$ 153.3, 148.6, 138.8, 138.4, 129.7, 129.1, 127.6, 125.2, 125.1, 123.5, 87.9, 12.4. HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_{16}H_{16}N_3S$, 282.1059; found, 282.1061.


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*Procedure for the Preparation of 4-((2H-Tetrazol-5-yl)thio)-3-methyl-1-phenyl-1H-pyrazol-5-amine (**14**).* 3-methyl-1-phenyl-4-thiocyanato-1*H*-pyrazol-5-amine **3e** (115 mg, 0.5 mmol), $ZnCl_2$ (0.5 mmol), and $NaN_3$ (0.6 mmol) were taken in an oven-dried 10.0 mL round-bottom flask and flushed with $N_2$ gas. To this mixture, 2.0 mL of isopropanol was then injected using a syringe. The resulting mixture was heated to 50 °C using an oil bath and kept under constant stirring for 3 h. After cooling to room temperature, the solvent was evaporated under reduced pressure. After that, 5% NaOH (5.0 mL) was added, and the mixture was stirred for 20 min, until all the precipitates had dissolved and a suspension of $Zn(OH)_2$ had formed. The suspension was filtered, and the solid was washed with 5% NaOH (5.0 mL). Next, pH of the filtrate was adjusted to 1.0 by adding conc. HCl, which caused the tetrazole product to precipitate. The tetrazole was filtered, washed with 9% HCl (2 × 5.0 mL) followed by 2 × 5.0 mL of water, and dried. Yield 112 mg (82%); white solid, mp 201−203 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.68 (d, $J$ = 8.0 Hz, 2H), 7.37−7.28 (m, 3H), 6.05 (br s, 2H), 3.65 (s, 3H). $^{13}$C {$^1$H} NMR (100 MHz, DMSO-$d_6$): $\delta$ 152.6, 150.3, 133.4, 128.7, 128.3, 127.4 76.3, 35.6. HRMS (ESI) $m/z$: $[M + H]^+$ calcd for $C_{11}H_{12}N_7S$, 274.0869; found, 274.0873.

*Synthesis of Compounds **15a** and **15b**.* Methyl 3-amino-2-thiocyanatobut-2-enoate (**7b**, 86 mg, 0.5 mmol) or 4-amino-3-thiocyanatopent-3-en-2-one (**7a**, 79 mg, 0.5 mmol) was transferred to a 10.0 mL round-bottom flask, and 3.0 mL of 50% $H_2SO_4$ was added to it. The mixture was kept at 70 °C using an oil bath with constant stirring for 3 h. After completion of the reaction, as monitored by TLC, the mixture was neutralized with $NaHCO_3$ solution and extracted with dichloromethane (3 × 5.0 mL). The organic part was dried over anhydrous $Na_2SO_4$ and flittered. The solvent was removed using a rotary evaporator under reduced pressure and finally purified by column chromatography.

*Methyl 4-Methyl-2-oxo-2,3-dihydrothiazole-5-carboxylate (**15a**).* It was purified by column chromatography [eluent hexane/ethyl acetate = 7:3 (v/v)]. Yield 61 mg (70%) white solid, mp 197−199 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 11.98 (br s, 1H), 3.71 (s, 3H), 2.36 (s, 3H). $^{13}$C {$^1$H} NMR (100 MHz, DMSO-$d_6$): $\delta$ 170.2, 161.5, 143.9, 101.6, 51.9, 13.4. HRMS (ESI) $m/z$: $[M + H]^+$ calcd for $C_6H_8NO_3S$, 174.0219, found, 174.0216.

*5-Acetyl-4-methylthiazol-2(3H)-one (**15b**).* It was purified by column chromatography [eluent hexane/ethyl acetate = 7:3 (v/v)]. Yield 57 mg (72%) white solid; mp 211−213 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 11.91 (s, 1H), 2.39 (s, 3H), 2.35 (s, 3H). $^{13}$C {$^1$H} NMR (100 MHz, DMSO-$d_6$): $\delta$ 189.2, 170.2, 142.3, 114.8, 29.2, 14.4. HRMS (ESI) $m/z$: $[M + H]^+$ calcd for $C_6H_8NO_2S$, 158.0270; found, 158.0268.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01738.

NMR spectra for all product compounds and crystal structure information of **10d** (PDF)

Crystal structure information of the products (CIF)

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES


(1) Castanheiro, T.; Suffert, J.; Donnard, M.; Gulea, M. Recent Advances in the Chemistry of Organic Thiocyanates. *Chem. Soc. Rev.* **2016**, *45*, 494−505.

(2) (a) Gulea, M.; Hammerschmidt, F.; Marchand, P.; Masson, S.; Pisljagic, V.; Wuggenig, F. Synthesis of chiral, nonracemic α-sulfanylphosphonates and derivatives. *Tetrahedron: Asymmetry* **2003**, *14*, 1829−1836. (b) Lu, X.; Wang, H.; Gao, R.; Sun, D.; Bi, X. Microwave-assisted synthesis of asymmetric disulfides. *RSC Adv.* **2014**, *4*, 28794−28797. (c) Renard, P.-Y.; Schwebel, H.; Vayron, P.; Josien, L.; Valleix, A.; Mioskowski, C. Easy Access to Phosphonothioates. *Chem.−Eur. J.* **2002**, *8*, 2910−2916. (d) Demko, Z. P.; Sharpless, K. B. An Intramolecular [2 + 3] Cycloaddition Route to Fused 5-Heterosubstituted Tetrazoles. *Org. Lett.* **2001**, *3*, 4091−4094. (e) Riemschneider, R.; Wojahn, F.; Orlick, G. Thiocarbamates. III.1Aryl Thiocarbamates from Aryl Thiocyanates. *J. Am. Chem. Soc.* **1951**, *73*, 5905−5907.

(3) (a) Kokorekin, V. A.; Terent'ev, A. O.; Ramenskaya, G. V.; Grammatikova, N. É.; Rodionova, G. M.; Ilovaiskii, A. I. Synthesis and Antifungal Activity of Arylthiocyanates. *Pharm. Chem. J.* **2013**, *47*, 422−425. (b) Szajnman, S. H.; Yan, W.; Bailey, B. N.; Docampo, R.; Elhalem, E.; Rodriguez, J. B. Design and Synthesis of Aryloxyethyl Thiocyanate Derivatives as Potent Inhibitors ofTrypanosoma cruziProliferation. *J. Med. Chem.* **2000**, *43*, 1826−1840. (c) Elicio, P. D.; Chao, M. N.; Galizzi, M.; Li, C.; Szajnman, S. H.; Docampo, R.; Moreno, S. N. J.; Rodriguez, J. B. Design, Synthesis and Biological Evaluation of WC-9 Analogs as Antiparasitic Agents. *Eur. J. Med. Chem.* **2013**, *69*, 480−489.

(4) (a) Fan, W.; Yang, Q.; Xu, F.; Li, P. A Visible-Light-Promoted Aerobic Metal-Free C-3 Thiocyanation of Indoles. *J. Org. Chem.* **2014**, *79*, 10588−10592. (b) Hosseini-Sarvari, M.; Hosseinpour, Z.; Koohgard, M. Visible light thiocyanation of N-bearing aromatic and heteroaromatic compounds using $Ag/TiO_2$ nanotube photocatalyst. *New J. Chem.* **2018**, *42*, 19237−19244. (c) Chen, Y.; Wang, S.; Jiang, Q.; Cheng, C.; Xiao, X.; Zhu, G. Palladium-Catalyzed Site-Selective sp3 C-H Bond Thiocyanation of 2-Aminofurans. *J. Org. Chem.* **2018**, *83*, 716−722. (d) Yang, S.-M.; He, T.-J.; Lin, D.-Z.; Huang, J.-M. Electrosynthesis of (E)-Vinyl Thiocyanates from Cinnamic Acids via Decarboxylative Coupling Reaction. *Org. Lett.* **2019**, *21*, 1958−1962.

(5) (a) Chauhan, P.; Ritu; Preeti; Kumar, S.; Jain, N. Metal-Free and Visible-Light-Promoted C-3 Thiocyanation of 2-Arylquinolin-4-ones. *Eur. J. Org. Chem.* **2019**, 4334−4340. (b) Noikham, M.; Yotphan, S. Copper-Catalyzed Regioselective Direct C-H Thiolation and Thiocyanation of Uracils. *Eur. J. Org. Chem.* **2019**, 2759−2766. (c) Zhang, H.; Wei, Q.; Wei, S.; Qu, J.; Wang, B. Highly Efficient and Practical Thiocyanation of Imidazopyridines Using anN-Chlorosuccinimide/NaSCN Combination. *Eur. J. Org. Chem.* **2016**, 3373−3379. (d) Mitra, S.; Ghosh, M.; Mishra, S.; Hajra, A. Metal-Free Thiocyanation of Imidazoheterocycles through Visible Light Photoredox Catalysis. *J. Org. Chem.* **2015**, *80*, 8275−8281.

(6) Jiang, H.; Yu, W.; Tang, X.; Li, J.; Wu, W. Copper-Catalyzed Aerobic Oxidative Regioselective Thiocyanation of Aromatics and Heteroaromatics. *J. Org. Chem.* **2017**, *82*, 9312−9320.
(7) Gao, Y.; Liu, Y.; Wan, J.-P. Visible Light-Induced Thiocyanation of Enaminone C-H Bond to Access Polyfunctionalized Alkenes and Thiocyano Chromones. *J. Org. Chem.* **2019**, *84*, 2243−2251.
(8) Chen, X.-B.; Wang, X.-Q.; Song, J.-N.; Yang, Q.-L.; Huang, C.; Liu, W. Efficient construction of C-N and C-S bonds in 2-iminothiazoles via cascade reaction of enaminones with potassium thiocyanate. *Org. Biomol. Chem.* **2017**, *15*, 3611−3615.
(9) Duan, X.; Liu, X.; Cuan, X.; Wang, L.; Liu, K.; Zhou, H.; Chen, X.; Li, H.; Wang, J. Solvent-Controlled Synthesis of Thiocyanated Enaminones and 2-Aminothiazoles from Enaminones, KSCN, and NBS. *J. Org. Chem.* **2019**, *84*, 12366−12376.
(10) Kittikool, T.; Yotphan, S. Metal-Free Direct C-H Thiolation and Thiocyanation of Pyrazolones. *Eur. J. Org. Chem.* **2020**, 961−970.
(11) Mao, X.; Ni, J.; Xu, B.; Ding, C. $K_2S_2O_8$-promoted direct thiocyanation of pyrazolin-5-ones with ammonium thiocyanate at room temperature. *Org. Chem. Front.* **2020**, *7*, 350−354.
(12) Li, G.; Yan, Q.; Gong, X.; Dou, X.; Yang, D. Photocatalyst-Free Regioselective C-H Thiocyanation of 4-Aminocoumarins under Visible Light. *ACS Sustainable Chem. Eng.* **2019**, *7*, 14009−14015.
(13) (a) Nitulescu, G. M.; Nedelcu, G.; Buzescu, A.; Olaru, O. T. Aminopyrazoles as Privileged Structures in Anticancer Drug Design-An in Silico Study. *Bulg. Chem. Commun.* **2016**, *48*, 55−60. (b) Aggarwal, R.; Kumar, S. 5-Aminopyrazole as Precursor in Design and Synthesis of Fused Pyrazoloazines. *Beilstein J. Org. Chem.* **2018**, *14*, 203−242. (c) Huang, D. S.; LeBlanc, E. V.; Shekhar-Guturja, T.; Robbins, N.; Krysan, D. J.; Pizarro, J.; Whitesell, L.; Cowen, L. E.; Brown, L. E. Design and Synthesis of Fungal-Selective Resorcylate Aminopyrazole Hsp90 Inhibitors. *J. Med. Chem.* **2020**, *63*, 2139−2180. (d) Shaker, R. M.; Elrady, M. A.; Sadek, K. U. Synthesis, Reactivity, and Biological Activity of 5-Aminouracil and Its Derivatives. *Mol. Divers.* **2016**, *20*, 153−183.
(14) (a) Finar, I. L.; Godfrey, K. E. The Preparation and Properties of Some Derivatives of 1-Phenylpyrazole. *J. Chem. Soc.* **1954**, 2293−2298. (b) Thiruvikraman, S. V.; Seshadri, S. Synthesis of Pyrazolo-[3,4-d]thiazoles. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 785−786. (c) Kokorekin, V. A.; Sigacheva, V. L.; Petrosyan, V. A. New data on heteroarene thiocyanation by anodic oxidation of $NH_4SCN$. The processes of electroinduced nucleophilic aromatic substitution of hydrogen. *Tetrahedron Lett.* **2014**, *55*, 4306−4309. (d) Songsichan, T.; Katrun, P.; Khaikate, O.; Soorukram, D.; Pohmakotr, M.; Reutrakul, V.; Kuhakarn, C. Thiocyanation of Pyrazoles Using $KSCN/K_2S_2O_8$ Combination. *SynOpen* **2018**, *2*, 0006−0016.
(15) (a) Doherty, S.; Knight, J. G.; Carroll, M. A.; Ellison, J. R.; Hobson, S. J.; Stevens, S.; Hardacre, C.; Goodrich, P. Efficient and Selective Hydrogen Peroxide-Mediated Oxidation of Sulfides in Batch and Segmented and Continuous Flow using a Peroxometalate-Based Polymer Immobilised Ionic Liquid Phase Catalyst. *Green Chem.* **2015**, *17*, 1559−1571. (b) Yu, W.; Zhao, Z. Catalyst-Free Selective Oxidation of Diverse Olefins to Carbonyls in High Yield Enabled by Light under Mild Conditions. *Org. Lett.* **2019**, *21*, 7726−7730. (c) Khan, A. T.; Parvin, T.; Choudhury, L. H.; Ghosh, S. A simple synthetic protocol for oxidation of alkyl-arenes into ketones using a combination of $HBr-H_2O_2$. *Tetrahedron Lett.* **2007**, *48*, 2271−2274.
(16) Li, X.-D.; Gao, Y.-T.; Sun, Y.-J.; Jin, X.-Y.; Wang, D.; Liu, L.; Cheng, L. A $NaI/H_2O_2$-Mediated Sulfenylation and Selenylation of Unprotected Uracil and Its Derivatives. *Org. Lett.* **2019**, *21*, 6643−6647.
(17) (a) Panday, A. K.; Mishra, R.; Jana, A.; Parvin, T.; Choudhury, L. H. Synthesis of Pyrimidine Fused Quinolines by Ligand-Free Copper-Catalyzed Domino Reactions. *J. Org. Chem.* **2018**, *83*, 3624−3632. (b) Karamthulla, S.; Jana, A.; Choudhury, L. H. Synthesis of Novel 5,6-Disubstituted Pyrrolo [2,3-d]Pyrimidine-2,4-Diones Via One-Pot Three-Component Reactions. *ACS Comb. Sci.* **2017**, *19*, 108−112. (c) Jana, A.; Bhaumick, P.; Panday, A. K.; Mishra, R.; Choudhury, L. H. $I_2$/DMSO Mediated Multicomponent Reaction for the Synthesis of 2-Arylbenzo[D]Imidazo[2,1-B] Thiazole Derivatives. *Org. Biomol. Chem.* **2019**, *17*, 5316−5330. (d) Panday, A. K.; Ali, D.; Choudhury, L. H. $Cs_2CO_3$-Mediated Rapid Room-Temperature Synthesis of 3-Amino-2-aroyl Benzofurans and Their Copper-Catalyzed N-Arylation Reactions. *ACS Omega* **2020**, *5*, 3646−3660.
(18) (a) Guy, R. G. *The Chemistry of Cyanates and Their Thio Derivatives, Part II*; S., Patai, Ed.; Wiley: New York, 2010; p 867. (b) Burns, C. J.; Field, L. D.; Morgan, J.; Ridley, D. D.; Vignevich, V. Preparation of Cyclic Disulfides from Bisthiocyanates. *Tetrahedron Lett.* **1999**, *40*, 6489−6492. (c) Sengupta, D.; Basu, B. An Efficient Metal-free Synthesis of Organic Disulfides from Thiocyanates using Poly-ionic Resin Hydroxide in Aqueous Medium. *Tetrahedron Lett.* **2013**, *54*, 2277−2281.
(19) Chen, C.; Cao, Y.; Wu, X.; Cai, Y.; Liu, J.; Xu, L.; Ding, K.; Yu, L. Energy saving and environment-friendly element-transfer reactions with industrial application potential. *Chem. Lett.* **2020**, *31*, 1078−1082.


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