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C–H Thiolation

Copper-Catalyzed Regioselective Direct C–H Thiolation and Thiocyanation of Uracils

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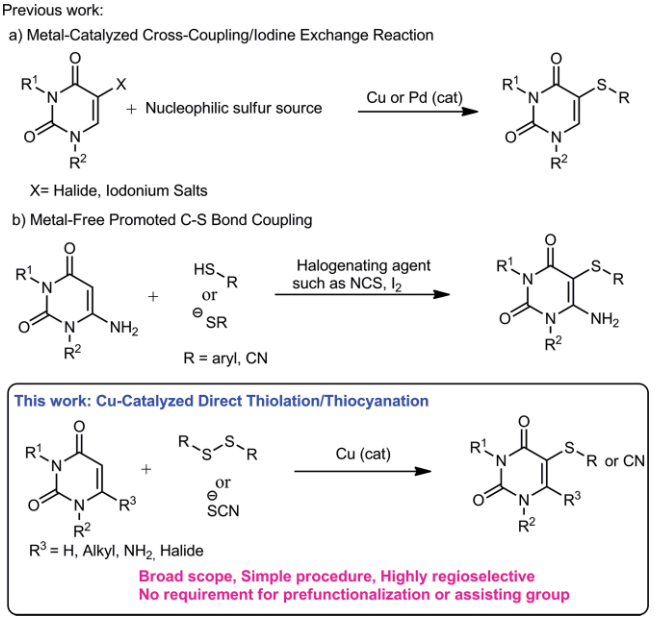
Abstract: A novel copper-catalyzed direct C–H thiolation and thiocyanation of uracils using disulfides and thiocyanate salts respectively as coupling partners are described. These reactions enable the C–H bond cleavage and C–S bond formation to proceed efficiently under relatively mild conditions, providing useful methods for a preparation of a series of thio-substituted at the *C5* position of uracil derivatives. These protocols exhibit several merits including simple experimental procedures, readily accessible substrates and reagents, broad scopes, high yields, and excellent regioselectivity. Preliminary mechanistic studies revealed that a radical pathway is likely to be involved.

Introduction

Uracils represent ubiquitous structural motifs found in a number of natural products, agrochemicals and pharmaceuticals.[1] A number of uracil analogues possess antiviral, antitumor, antibacterial as well as herbicidal and insecticidal properties.[2] Due to their wide array of biological and pharmacological activities as well as their synthetic accessibility, they have attracted considerable attention as important lead pharmacophores in drug discovery and other related applications.[3] Over the past two decades, many researchers have devoted their efforts to develop efficient methods for preparations and manipulations of functionalized uracil ring.[4]

Sulfur atom containing compounds are significant oriented targets in synthesis, medicinal chemistry, and material science.[5] The incorporation of sulfur moiety into organic molecules can partially modify the physical and biological properties of the parent compounds.[6] Despite the high impact to many research areas, a few strategies for introducing sulfur moiety into uracil cores were found in literature, including the transition metal-catalyzed C–S cross coupling reactions of arylthiols or other nucleophilic sulfur sources with halides or iodonium salts (Scheme 1a),[7] as well as the metal-free (I_2 or NCS)-promoted C–S bond formation (Scheme 1b),[8] which requires for pre-functionalization of substrates or the presence of an adjacent nucleophilic assisting group (such as NH_2 group).

Besides, these existing approaches also suffer from other limitations, such as the need for odorous, expensive and/or toxic reagents, harsh conditions under inert atmosphere and tedious reaction procedures, which could greatly reduce their scope, structural diversity and further utilization. Thus, developing facile and efficient methods for the direct construction of C–S bond of uracil derivatives is still highly desirable.



Scheme 1. Approaches for installation of sulfur moiety into uracil cores.

Our group have been focused on the oxidative C–H functionalization strategies to manipulate various *N*-heterocycles.[9] In continuation of our recent research interest, we aim to accomplish the direct C–S coupling of uracils with commercially available and easy-to-handle sulfur precursors. Herein, we disclose a highly efficient, convenient and regioselective copper-catalyzed direct C–H thiolation and thiocyanation of uracil derivatives with disulfides and thiocyanate salts to access a good range of products in moderate to excellent yields. In addition, these oxidative coupling reactions proceed very well under relatively mild and air-tolerant conditions, which makes these protocols useful for the preparation of a series of 5-thio-substituted

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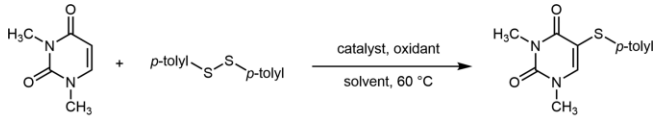
uracils which can be further exploited in a number of applications.

Results and Discussion

Optimization of Reaction Conditions

Our initial studies on direct C–H functionalization/C–S bond coupling were performed with an extensive screening of reaction conditions,[10] and we found that a reaction of uracil (**1a**) and *p*-tolyl disulfide (**2a**) in the presence of CuBr (10 mol-%) and $K_2S_2O_8$ (2 equiv.) in DMSO at 60 °C under atmospheric air produced a 14 % yield of the 5-thio-substituted product **3a** (Table 1, entry 1). We next proceeded to conduct a solvent screening,[10] and pleasingly a reaction in CH_3CN solvent gave the desired product in 74 % (entry 4). Subsequent optimization of a catalytic source (entries 4–10) revealed that $Cu(OTf)_2$ could successfully delivered a complete conversion, affording a maximum 89 % yield of **3a** (entry 10). Additional investigation on the effect of an oxidant led to a further improvement of yield to 96 % as 1.5 equiv. of $K_2S_2O_8$ was employed (entry 13). Unfortunately, only trace amount of product was detected when conducting a reaction at room temperature. Finally, we carried out reactions in the absence of copper or persulfate and the outcomes indicated a necessity of both $Cu(OTf)_2$ and $K_2S_2O_8$ in this transformation (entries 15–16).

Table 1. Optimization of reaction conditions.[a]



1a 2a 3a

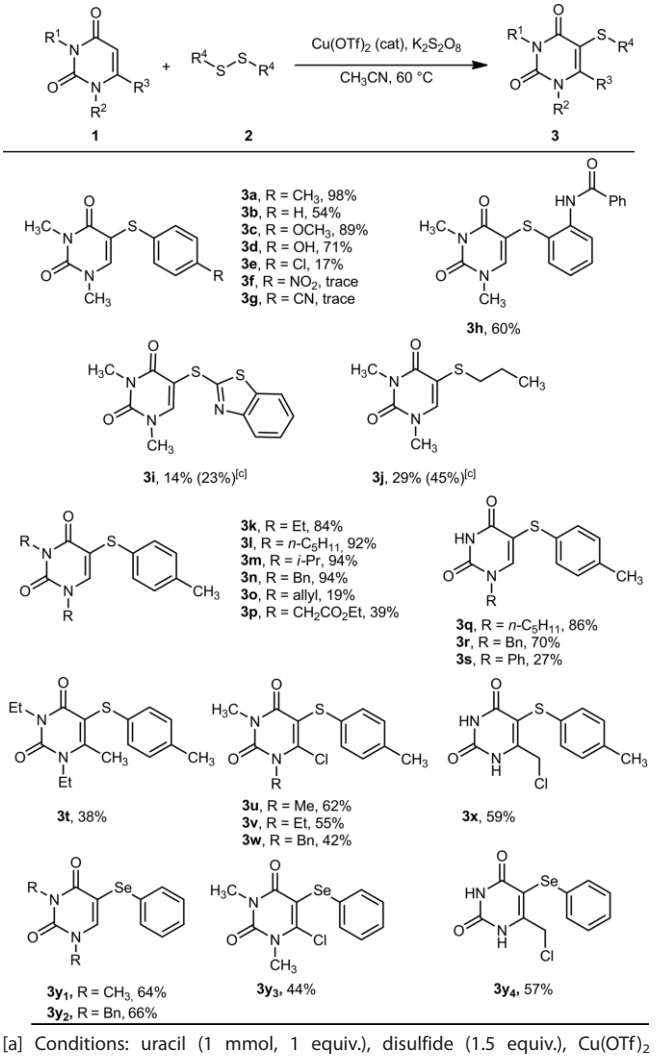
Entry	Catalyst	Oxidant (equiv.)	Solvent	Yield [%][b]
1	CuBr	$K_2S_2O_8$ (2)	DMSO	14
2	CuBr	$K_2S_2O_8$ (2)	THF	Trace
3	CuBr	$K_2S_2O_8$ (2)	MeOH	Trace
4	CuBr	$K_2S_2O_8$ (2)	CH_3CN	74
5	CuCl	$K_2S_2O_8$ (2)	CH_3CN	78
6	CuI	$K_2S_2O_8$ (2)	CH_3CN	32
7	$CuCl_2$	$K_2S_2O_8$ (2)	CH_3CN	74
8	$CuBr_2$	$K_2S_2O_8$ (2)	CH_3CN	65
9	$Cu(OAc)_2$	$K_2S_2O_8$ (2)	CH_3CN	15
10	$Cu(OTf)_2$	$K_2S_2O_8$ (2)	CH_3CN	89
11	$Cu(OTf)_2$	$Na_2S_2O_8$ (2)	CH_3CN	51
12	$Cu(OTf)_2$	$(NH_4)_2S_2O_8$ (2)	CH_3CN	21
13	**$Cu(OTf)_2$**	**$K_2S_2O_8$ (1.5)**	**CH_3CN**	**96 (4 h)**
14	$Cu(OTf)_2$	$K_2S_2O_8$ (1)	CH_3CN	36
15	$Cu(OTf)_2$	–	CH_3CN	Trace
16	–	$K_2S_2O_8$ (1.5)	CH_3CN	Trace

[a] Conditions: **1a** (0.25 mmol, 1 equiv.), **2a** (1.5 equiv.), catalyst (10 mol-%) in 1 mL of solvent at 60 °C under an air atmosphere for 4–16 h, as monitored by TLC. [b] GC yield.

Substrate Scope and Limitation

Under the optimal reaction conditions, we assessed the scope of the direct thiolation with various disulfide and uracil substrates. In general, this reaction is quite versatile and can accommodate a good range of substrates, and both electronic and steric variations exert certain effect on this transformation. As shown in Table 2, thiolation reactions of uracil **1a** with electron rich diaryl disulfides proceeded smoothly, providing 5-thio-substituted uracil products (**3a–3d** and **3h**) in good to excellent yields. It is noteworthy that the hydroxyl and amide functionalities were well tolerated. Meanwhile, low yield of product was obtained with chloro substituted diaryl disulfides (**3e**). In the case of electron deficient diaryl disulfides (such as 4-nitro or 4-cyano phenyl disulfides), only trace amount of products was detected (**3f**–**g**). These outcomes indicate that the electronic effect from disulfides is crucial for the efficiency of the transformation. In addition, we tested the reactions with diheteroaryl and dialkyl disulfides, unfortunately, low to fair extents of the desired products were obtained (**3i** and **3j**). It is likely that the sulfur species generated from heteroaryl or alkyl disulfides are less stable than those sulfur species generated from the diaryl disulfide sources.

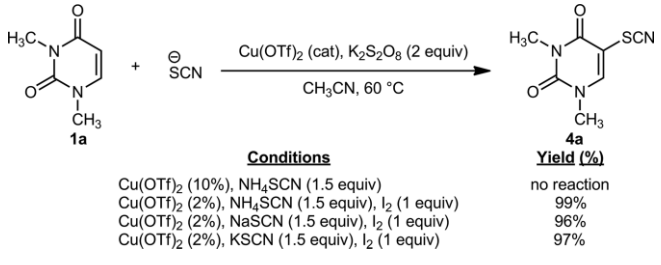
Table 2. Copper-catalyzed direct thiolation of uracils with disulfides.[a,b]



[a] Conditions: uracil (1 mmol, 1 equiv.), disulfide (1.5 equiv.), $Cu(OTf)_2$ (10 mol-%), $K_2S_2O_8$ (1.5 equiv.) in CH_3CN (4 mL) at 60 °C under an air atmosphere for 4–16 h, as monitored by TLC. [b] Isolated yields. [c] Reaction was conducted using $Cu(OTf)_2$ (20 mol-%) for 48 h.

Next, the effect of substituents on the nitrogen atoms of uracil substrates was examined, and the results revealed that no substantial impact was observed upon increasing a steric hindrance of alkyl substituents on nitrogen atoms (**3k**–**3n**). Nonetheless, the presence of *N*-allyl or *N*-alkyl ester groups (**3o** and **3p**) showed a deleterious effect on this C–H thiolation reaction and they delivered the corresponding products in somewhat lower yields, suggesting a possible interruption of these functional groups in the catalytic oxidative coupling process. The copper-catalyzed thiolation was also readily amenable to the synthesis of 5-thiolated products from non-protected *NH*-uracil substrates (**3q–3r** and **3x**). Thus, these outcomes implied that the presence of imide or amide hydrogen (R^1 or R^2 = H) would not impede the direct C–S bond coupling in this transformation. However, due to a poor nucleophilicity, low yield was obtained for the *N*-phenyl uracil (**3s**). On the other hand, uracil substrates bearing a substitution on the *C6* position (R^3 group) exhibited a decreased reactivity towards the reaction, and only fair yield of product (**3t**) was obtained, indicative of a possible steric interference from R^3 group in thiolation process. However, we were delighted to observe that uracils with a chloro or a chloromethyl substituent proved to be a viable substrate, providing an opportunity for further functionalization (**3u**–**3x**). Other side reactions such as coupling reaction or dehalogenation were not detected under the optimal conditions. Lastly, the optimized system also proved applicable to the C–H selenylation of uracils with diphenyl diselenide, affording the corresponding product **3y$_1$**–**3y$_4$** in satisfied quantities.

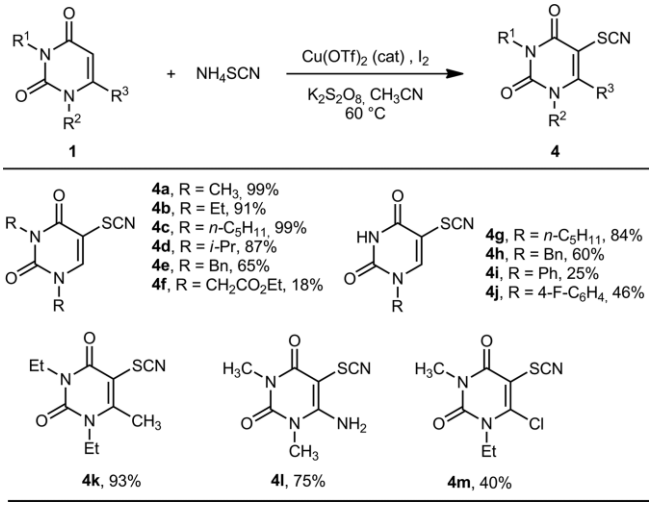
After having the encouraging results for the copper-catalyzed direct C–S bond coupling of uracil with disulfide, we then turned our interest toward the direct thiocyanation, which could lead to a useful building block and a pivotal synthetic intermediate to a variety of sulfur containing compounds.[11] Under the previously established conditions, however, no reaction between uracil and NH_4SCN occurred (Scheme 2). As we screened a set of additives,[10] we found that the direct C–H thiocyanation could be fruitfully accomplished upon adding a molecular iodine (I_2, 1equiv.) into the reaction, and the uracil **1a** was completely converted into the corresponding product **4a** (99 %) with thiocyanate group installed exclusively at the 5-position. Gratifyingly, other thiocyanate salts such as NaSCN and KSCN were also very well effective, giving excellent yields of product under the newly optimized conditions.



Scheme 2. Copper-catalyzed direct thiocyanation of uracil with thiocyanate salt.

Having affirmed the optimal conditions for the copper-catalyzed regioselective direct thiocyanation, the scope was then explored using NH_4SCN with various uracils (Table 3). In general, the thiocyanation reaction tolerated a diverse range of *N*-alkylated uracil substrates (**4a–4e**), providing the expected products in good to excellent yields, with the exception of the uracil substrate with an alkyl ester on nitrogen (**4f**). The *NH* uracils were also feasible substrates, affording the products in moderate to decent quantities (**4g** and **4h**). Similarly to the direct thiolation, thiocyanation reactions of *N*-phenyl protected uracils resulted in lower yields (**4i–4j**) due to their poor nucleophilicity. In the case of the uracil bearing a methyl group at *C6*, no significant reduction of product yield was found (**4k**). Strikingly, uracils possessing functional group such as amino (NH_2) and chloro at 6-position were also compatible to the direct C–H thiocynation, furnishing the corresponding products (**4l–4m**) in moderate to good yields. Other possible side reactions such as dechlorination or competitive coupling at 6 position were not observed.

Table 3. Substrate Scope of the Direct Thiocyanation.[a,b]

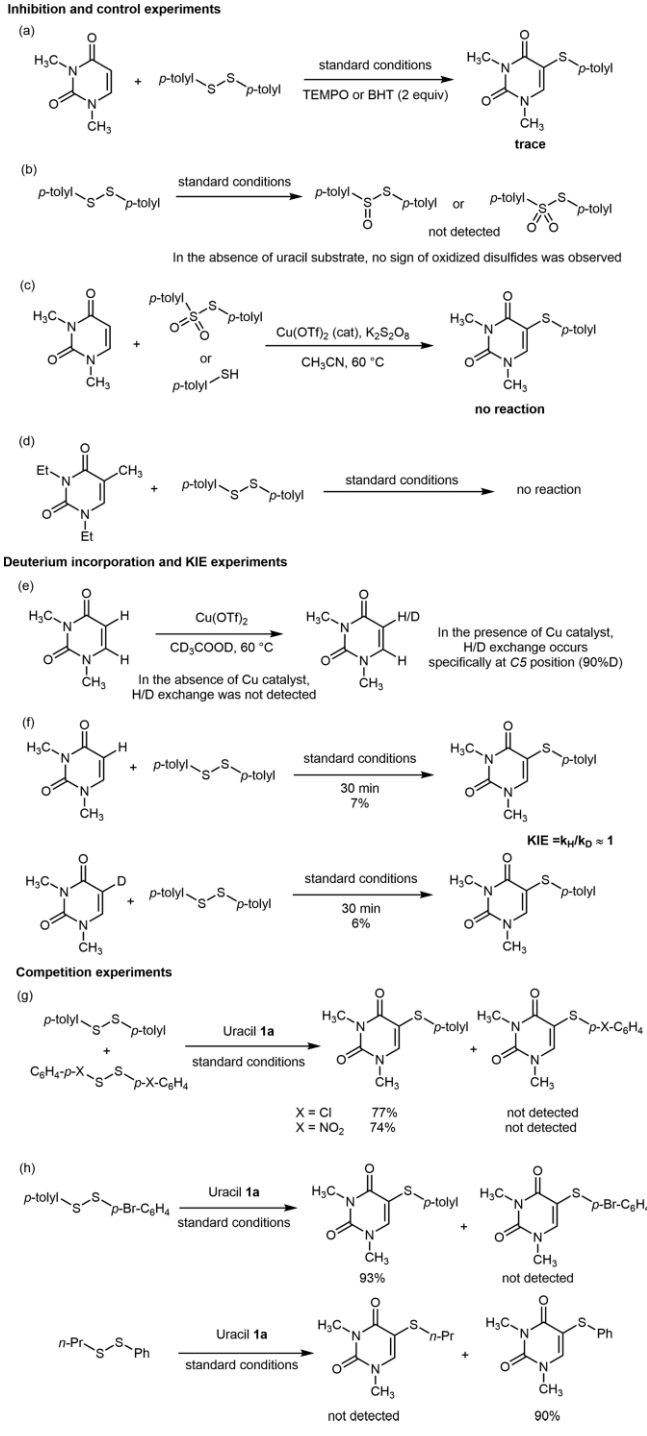


[a] Conditions: uracil (1 mmol, 1 equiv.), NH_4SCN (1.5 equiv.), $Cu(OTf)_2$ (2 mol-%), I_2 (1 equiv.), $K_2S_2O_8$ (2 equiv.) in CH_3CN (4 mL) at 60 °C under an air atmosphere, 4 h. [b] Isolated yield.

Reaction Mechanism

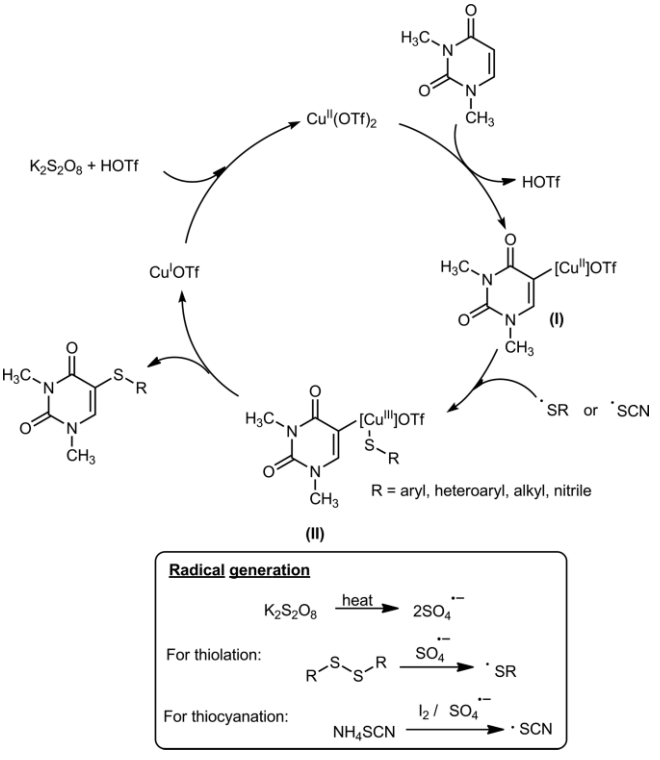
To investigate the reaction mechanism, several control experiments were performed. In the case of the direct thiolation, no reaction was observed when adding a radical scavenger (such as TEMPO or BHT) to the standard conditions (Scheme 3a), which is indicative of a radical process. Besides, the sulfur species such as thiol or oxidized disulfide should not be an intermediate involved in this transformation (Scheme 3b and 3c). Moreover, no reaction was observed when employing 5-methyl-substituted uracil, suggesting that the copper-catalyzed thiolation takes place solely at the 5-position of uracil substrate (Scheme 3d). The regiocontrol of this transformation was also explained by the deuterium incorporation experiment, in which the C–H bond metallation occurred at the most electron-rich *C5* position of uracil substrate (Scheme 3e). Additionally, upon evaluating two parallel reactions (Scheme 3f), no kinetic isotope effect (KIE) was observed (KIE ≈ 1). Thus, the C–H bond

cleavage under this copper catalysis might not be a rate-determining step. Lastly, competition experiments showed that this thiolation reaction favored to form the product with more electron rich aryl sulfide (Scheme 3g and 3h). These results could be a consequence of a stability of the radical intermediate that was generated during the course of reaction. For the direct thiocyanation, the control experiments also suggested a possible involvement of a radical process with no kinetic isotope effect (KIE ≈ 1), and I_2 is likely to play a vital role in a radical generation.[10]



Scheme 3. Control experiments for the direct thiolation.

To account for the transformation, a plausible reaction mechanism for the direct thiolation and thiocyanation is proposed as shown in Scheme 4. We believed that a radical pathway is likely to be involved. First, the Cu^{II} species initially interacts with uracil substrate leading to a facile C–H bond metallation to produce the Cu^{II} uracil complex (intermediate **I**).[9b,12] Then, this copper intermediate **I** is subsequently attacked by sulfide radical (•SR) or thiocyanate radical (•SCN), which is generated from a reaction of disulfide with $K_2S_2O_8$[13] or a reaction of thiocyanate salt with $I_2/K_2S_2O_8$, respectively,[14] to form the Cu^{III} intermediate (**II**), which simultaneously undergoes reductive elimination to furnish the corresponding 5-thio-substituted uracil product and release Cu^{I} species.[15] Finally, oxidation of Cu^{I} would regenerate the Cu^{II} species to resume the cycle.



Scheme 4. Plausible reaction mechanism.

Conclusions

In summary, we have successfully established a novel and highly efficient Cu-catalyzed regioselective direct C–S bond formation of uracils with disulfides and thiocyanate salts through C–H functionalization. Both thiolation and thiocyanation approaches were applicable to a broad range of substrates, providing a series of 5-thio-substituted uracil compounds in moderate to excellent yields. The notable features included using readily available starting materials, bypassing the requirement for pre-functionalization or the presence of the nearby assisting group, employing catalytic amounts of low-cost transition metal catalyst, working very well with simple experimental proce-

dures under relatively mild conditions, good functional group tolerance, and robustness of reactions under air atmosphere, which render these protocols attractive and applicational potential for further utilization in organic synthesis, discovery research and other related fields.

Experimental Section

General Information: Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. All experiments were carried out under air atmosphere, and oven-dried glassware were used in all cases. Column chromatography was performed over silica gel (SiO_2; 60 Å silica gel, Merck Grade, 70–230 Mesh). ^1H and ^{13}C NMR spectra were recorded on Bruker-AV400 spectrometers in $CDCl_3$ or [D_6]DMSO solution, at 400 and 100 MHz, respectively. NMR chemical shifts are reported in ppm, and were measured relative to $CHCl_3$ (7.26 ppm for ^1H and 77.16 ppm for ^{13}C) or DMSO (2.50 ppm for ^1H and 39.52 ppm for ^{13}C). IR spectra were recorded on Bruker FT-IR Spectrometer Model ALPHA by neat method, and only partial data are listed. Melting points were determined on Buchi Melting Point M-565 apparatus. High resolution mass spectroscopy (HRMS) data were analyzed by a high-resolution micrOTOF instrument with electrospray ionization (ESI). The structures of known compounds were corroborated by comparing their ^1H NMR, ^{13}C NMR data with those of literature.[7e,7f,8a]

General Procedure for the Copper-Catalyzed Direct Thiolation of Uracils with Disulfides: To a 20 mL scintillation vial equipped with a magnetic stir bar, uracil **1** (1 mmol, 1.0 equiv.), disulfide **2** (1.5 mmol, 1.5 equiv.), copper(II)trifate [$Cu(OTf)_2$] (0.10 mmol, 10 mol-%), potassium persulfate ($K_2S_2O_8$) (1.5 mmol, 1.5 equiv.) and acetonitrile (CH_3CN) (4 mL) were added, respectively. The reaction mixture was stirred at 60 °C for 4–16 h. Upon completion (monitored by TLC), distilled deionized H_2O (20 mL) was added, and the mixture was extracted with ethyl acetate (EtOAc) (2 × 40 mL). The combined organic layer was washed with saturated NaCl, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by SiO_2 column chromatography to afford the 5-thiolated uracil product **3**.

General Procedure for the Copper-Catalyzed Direct Thiocyanation of Uracils with Ammoniumthiocyanate: To a 20 mL scintillation vial equipped with a magnetic stir bar, uracil **1** (1 mmol, 1 equiv.), ammonium thiocyanate (NH_4SCN) (1.5 mmol, 1.5 equiv.), copper(II)trifate [$Cu(OTf)_2$] (0.02 mmol, 2 mol-%), Iodine (I_2) (1 mmol, 1 equiv.), potassium persulfate ($K_2S_2O_8$) (2 mmol, 2 equiv.) and acetonitrile (CH_3CN) (4 mL) were added, respectively. The reaction mixture was stirred at 60 °C for 4 h. Upon completion, distilled deionized H_2O (20 mL) and sat. $Na_2S_2O_3$ (10 mL) was added, and the mixture was extracted with ethyl acetate (EtOAc) (2 × 40 mL). The combined organic layer was washed with saturated NaCl, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by SiO_2 column chromatography to afford the 5-thiocyanated uracil product **4**.

1,3-Dimethyl-5-(*p*-tolylthio)pyrimidine-2,4(1*H*,3*H*)-dione (3a): White solid (257 mg, 98 % yield); m.p. 124.1– 125.0 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.51 (s, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 3.40 (s, 3H), 3.35 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.9, 151.6, 146.5, 137.4, 131.2, 130.1, 130.0, 107.4, 37.3, 28.7, 21.1; IR (neat, cm^{-1}): $\tilde{\nu}$ = 3045, 2945, 1707, 1652, 1510, 1435, 1340, 1113, 1011, 947, 837, 766, 539; HRMS (ESI): calcd. for $C_{13}H_{14}N_2O_2SNa$ $[M + Na]^+$ 285.0668, found 285.0673.

1,3-Dimethyl-5-(phenylthio)pyrimidine-2,4(1*H*,3*H*)-dione (3b):[7e] Yellow solid (134 mg, 54 % yield); m.p. 123.8– 124.7 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.60 (s, 1H), 7.33–7.28 (m, 4H), 7.21 (t, *J* = 6.9 Hz, 1H), 3.44 (s, 3H), 3.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.9, 151.7, 147.7, 135.3, 129.2, 128.9, 126.9, 106.2, 37.4, 28.8; IR (neat, cm^{-1}): $\tilde{\nu}$ = 3067, 2921, 1706, 1537, 1510, 1433, 1338, 1230, 1150, 1023, 769, 735, 548; HRMS (ESI): calcd. for $C_{12}H_{12}N_2O_2SNa$ $[M + Na]^+$ 271.0512, found 271.0515.

5-[(4-Methoxyphenyl)thio]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (3c): Yellow solid (247 mg, 89 % yield); m.p. 101.7– 102.6 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 8.8 Hz, 2H), 7.38 (s, 1H), 6.84 (d, *J* = 8.4 Hz, 2H), 3.78 (s, 3H), 3.38 (s, 3H), 3.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.9, 159.9, 151.7, 144.9, 133.6, 124.6, 115.1, 109.3, 55.5, 37.3, 28.7; IR (neat, cm^{-1}): $\tilde{\nu}$ = 3061, 2923, 1708, 1659, 1589, 1433, 1288, 1242, 1172, 1025, 838, 766, 528; HRMS (ESI): calcd. for $C_{13}H_{14}N_2O_3SNa$ $[M + Na]^+$ 301.0617, found 301.0614.

5-[(4-Hydroxyphenyl)thio]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (3d): Brown solid (187 mg, 71 % yield); m.p. 180.0 °C (decomposed); ^1H NMR (400 MHz, [D_6]DMSO): δ = 8.28 (s, 1H), 7.36 (d, *J* = 7.2 Hz, 2H), 7.28–7.21 (m, 3H), 3.34 (s, 3H), 3.20 (s, 3H); ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 161.5, 151.5, 151.1, 131.5, 129.5, 129.3, 126.5, 98.2, 36.6, 28.4; IR (neat, cm^{-1}): $\tilde{\nu}$ = 3266, 2923, 1706, 1632, 1581, 1492, 1434, 1222, 1022, 998, 820, 768, 633, 516; HRMS (ESI): calcd. for $C_{12}H_{12}N_2O_3SNa$ $[M + Na]^+$ 287.0461, found 287.0458.

5-[(4-Chlorophenyl)thio]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (3e): Orange solid (48 mg, 17 % yield); m.p. 121.7– 122.1 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.66 (s, 1H), 7.28–7.24 (m, 4H), 3.46 (s, 3H), 3.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.8, 151.6, 147.9, 133.9, 133.1, 130.2, 129.4, 105.7, 37.5, 28.9; IR (neat, cm^{-1}): $\tilde{\nu}$ = 2922, 2852, 1712, 1659, 1511, 1471, 1337, 1142, 1089, 1005, 811, 765, 542; HRMS (ESI): calcd. for $C_{12}H_{11}ClN_2O_2SNa$ $[M + Na]^+$ 305.0122, found 305.0125.

***N*-{2-[(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)thio]phenyl}benzamide (3h):** White solid (220 mg, 60 % yield); m.p. 222.6– 223.2 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 10.54 (s, 1H), 8.29 (d, *J* = 8.4 Hz, 1H), 8.22 (d, *J* = 7.6 Hz, 2H), 7.72 (s, 1H), 7.58–7.50 (m, 4H), 7.44–7.40 (m, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 3.42 (s, 3H), 3.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 163.3, 151.3, 147.0, 140.8 (2C), 136.5, 134.9, 131.9, 130.9, 128.7, 127.9, 125.1, 123.7, 108.7, 37.5, 29.0; IR (neat, cm^{-1}): $\tilde{\nu}$ = 3306, 2923, 1701, 1637, 1578, 1492, 1433, 1305, 1073, 1019, 755, 704, 607; HRMS (ESI): calcd. for $C_{19}H_{17}N_3O_3SNa$ $[M + Na]^+$ 390.0883, found 390.0885.

5-(Benzo[*d*]thiazol-2-ylthio)-1,3-dimethylpyrimidine-2,4-(1*H*,3*H*)-dione (3i): Brown solid (70 mg, 23 % yield); m.p. 185.4–186.0 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.89 (s, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.28 (t, *J* = 7.2 Hz, 1H), 3.47 (s, 3H), 3.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8, 161.2, 153.7, 151.4, 150.4, 135.7, 126.3, 124.7, 122.1, 121.1, 102.2, 37.7, 29.0; IR (neat, cm^{-1}): $\tilde{\nu}$ = 3057, 2923, 1714, 1651, 1608, 1456, 1332, 1274, 1123, 1009, 941, 760, 666, 535; HRMS (ESI): calcd. for $C_{13}H_{11}N_3O_2S_2Na$ $[M + Na]^+$ 328.0185, found 328.0183.

1,3-Dimethyl-5-(propylthio)pyrimidine-2,4(1*H*,3*H*)-dione (3j): Yellow solid (96 mg, 45 % yield); m.p. 63.6– 64.5 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.48 (s, 1H), 3.40 (s, 3H), 3.37 (s, 3H), 2.73 (t, *J* = 7.2 Hz, 2H), 1.60–1.51 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.4, 151.8, 145.7, 106.9, 37.2, 35.6, 28.6, 22.7, 13.3; IR (neat, cm^{-1}): $\tilde{\nu}$ = 3063, 2929, 1695, 1637, 1615, 1430, 1388, 1340, 1228, 1149, 1019, 964, 768, 755, 537; HRMS (ESI): calcd. for $C_9H_{14}N_2O_2SNa$ $[M + Na]^+$ 237.0668, found 237.0670.

1,3-Diethyl-5-(*p*-tolylthio)pyrimidine-2,4(1*H*,3*H*)-dione (3k): Yellow oil (244 mg, 84 % yield); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.54 (s,

1H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 4.02 (q, *J* = 7.0 Hz, 2H), 3.81 (q, *J* = 7.2 Hz, 2H), 2.30 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.3, 150.6, 145.6, 137.0, 131.2, 129.9, 129.6, 107.3, 45.1, 37.3, 21.0, 14.4, 12.7; IR (neat, cm^{-1}): $\tilde{\nu}$ = 3055, 2977, 1702, 1611, 1491, 1437, 1326, 1260, 1206, 1086, 1015, 802, 770, 562, 511; HRMS (ESI): calcd. for $C_{15}H_{18}N_2O_2SNa$ [M + Na]$^+$ 313.0981, found 313.0979.

1,3-Dipentyl-5-(*p*-tolylthio)pyrimidine-2,4(1*H*,3*H*)-dione (3l): Orange oil (344 mg, 92 % yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (s, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 3.97 (t, *J* = 7.4 Hz, 2H), 3.77 (t, *J* = 7.4 Hz, 2H), 2.33 (s, 3H), 1.75–1.61 (m, 4H), 1.41–1.30 (m, 8H), 0.95–0.89 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.4, 151.0, 146.0, 137.1, 131.4, 129.9, 129.7, 107.2, 50.1, 42.2, 29.0, 28.7, 28.6, 27.1, 22.3, 22.2, 21.0, 14.0, 13.9; IR (neat, cm^{-1}): $\tilde{\nu}$ = 2955, 2925, 1706, 1655, 1614, 1492, 1438, 1331, 1216, 1144, 803, 770, 654, 584, 509; HRMS (ESI): calcd. for $C_{21}H_{31}N_2O_2S$ [M + H]$^+$ 375.2101, found 375.2108.

1,3-Diisopropyl-5-(*p*-tolylthio)pyrimidine-2,4(1*H*,3*H*)-dithione (3m): Yellow solid (299 mg, 94 % yield); m.p. 110.5– 111.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (s, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 5.20 (sep, *J* = 6.8 Hz, 1H), 4.86 (sep, *J* = 6.8 Hz, 1H), 2.30 (s, 3H), 1.44 (d, *J* = 6.8 Hz, 6H), 1.30 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.5, 150.9, 141.7, 137.1, 131.5, 130.0, 129.6, 107.6, 48.3, 47.0, 21.6, 21.1, 19.2; IR (neat, cm^{-1}): $\tilde{\nu}$ = 2974, 2922, 1698, 1650, 1613, 1492, 1432, 1331, 1270, 1083, 1051, 802, 772, 554; HRMS (ESI): calcd. for $C_{17}H_{22}N_2O_2SNa$ [M + Na]$^+$ 341.1294, found 341.1299.

1,3-Dibenzyl-5-(*p*-tolylthio)pyrimidine-2,4(1*H*,3*H*)-dithione (3n): Brown solid (389 mg, 94 % yield); m.p. 133.6– 134.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 7.2 Hz, 2H), 7.42 (s, 1H), 7.33–7.21 (m, 8H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 7.6 Hz, 2H), 5.12 (s, 2H), 4.85 (s, 2H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.3, 151.3, 145.1, 137.2, 136.5, 134.9, 130.7, 130.0, 129.8, 129.3, 129.2, 128.6, 128.4, 128.2, 127.8, 108.2, 52.6, 45.4, 21.1; IR (neat, cm^{-1}): $\tilde{\nu}$ = 3063, 2921, 1713, 1652, 1606, 1492, 1434, 1320, 1076, 805, 744, 687, 598, 525; HRMS (ESI): calcd. for $C_{25}H_{23}N_2O_2S$ [M + H]$^+$ 415.1475, found 415.1483.

1,3-Diallyl-5-(*p*-tolylthio)pyrimidine-2,4(1*H*,3*H*)-dithione (3o): Yellow oil (60 mg, 19 % yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (s, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 5.93– 5.82 (m, 2H), 5.34– 5.17 (m, 4H), 4.56 (d, *J* = 5.6 Hz, 2H), 4.38 (d, *J* = 5.6 Hz, 2H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1, 150.9, 145.3, 137.4, 131.4, 131.3, 131.0, 130.1, 130.0, 120.1, 118.6, 108.1, 51.4, 44.3, 21.2; IR (neat, cm^{-1}): $\tilde{\nu}$ = 3070, 2923, 1708, 1656, 1613, 1492, 1433, 1327, 1231, 990, 927, 803, 772, 511; HRMS (ESI): calcd. for $C_{17}H_{18}N_2O_2SNa$ [M + Na]$^+$ 337.0981, found 337.0985.

Diethyl 2,4-dithioxo-5-(*p*-tolylthio)pyrimidine-1,3(2*H*,4*H*)-dicarboxylate (3p): Brown oil (158 mg, 39 % yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (s, 1H), 7.25 (d, *J* = 7.2 Hz, 2H), 7.09 (d, *J* = 7.6 Hz, 2H), 4.68 (s, 2H), 4.47 (s, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.30 (s, 3H), 1.29 (t, *J* = 7.0 Hz, 3H), 1.24 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 167.1, 160.9, 151.0, 146.1, 145.4, 137.5, 130.6, 130.2, 129.9, 108.5, 62.5, 61.8, 50.1, 42.9, 21.2, 14.2; IR (neat, cm^{-1}): $\tilde{\nu}$ = 2920, 2851, 1745, 1716, 1663, 1617, 1492, 1348, 1275, 1199, 1016, 805, 774, 542; HRMS (ESI): calcd. for $C_{19}H_{22}N_2O_6SNa$ [M + Na]$^+$ 429.1091, found 429.1088.

1-Pentyl-5-(*p*-tolylthio)pyrimidine-2,4(1*H*,3*H*)-dione (3q): Yellow solid (262 mg, 86 % yield); m.p. 188.5– 189.4 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.59 (s, 1H), 8.23 (s, 1H), 7.11 (d, *J* = 8.8 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 3.71 (t, *J* = 7.2 Hz, 2H), 2.23 (s, 3H), 1.63–1.56 (m, 2H), 1.31–1.22 (m, 4H), 0.85 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 161.9, 151.8, 150.8, 135.2, 133.0, 129.6, 127.0, 103.2, 48.0, 28.1, 28.0, 21.8, 20.5, 13.8; IR (neat, cm^{-1}): $\tilde{\nu}$ = 3400, 3016, 2850, 1698, 1650, 1607, 1456, 1425, 1359, 1024, 949, 795, 564; HRMS (ESI): calcd. for $C_{16}H_{20}N_2O_2SNa$ [M + Na]$^+$ 327.1138, found 327.1137.

1-Benzyl-5-(*p*-tolylthio)pyrimidine-2,4(1*H*,3*H*)-dione (3r): Yellow solid (227 mg, 70 % yield); m.p. 215.3– 216.2 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.72 (s, 1H), 8.38 (s, 1H), 7.39–7.28 (m, 5H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.8 Hz, 2H), 4.96 (s, 2H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 161.8, 151.4, 150.9, 136.5, 135.3, 132.7, 129.7, 128.7, 127.8, 127.6, 127.1, 103.9, 50.8, 20.5; IR (neat, cm^{-1}): $\tilde{\nu}$ = 3400, 2955, 2848, 1648, 1602, 1488, 1427, 1333, 1239, 1137, 1027, 796, 754, 694, 601, 534; HRMS (ESI): calcd. for $C_{18}H_{16}N_2O_2SNa$ [M + Na]$^+$ 347.0825, found 347.0830.

1-Phenyl-5-(*p*-tolylthio)pyrimidine-2,4(1*H*,3*H*)-dione (3s): Yellow solid (84 mg, 27 % yield); m.p. 186.2– 187.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.56 (s, 1H), 7.68 (s, 1H), 7.52– 7.43 (m, 3H), 7.37– 7.31 (m, 4H), 7.12 (d, *J* = 8.0 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.4, 149.8, 147.8, 138.1, 137.9, 130.6, 130.2, 129.9, 129.4, 126.4, 125.2, 109.7, 29.8; IR (neat, cm^{-1}): $\tilde{\nu}$ = 2921, 2851, 1712, 1654, 1590, 1490, 1412, 1305, 1277, 795, 758, 694, 576, 515; HRMS (ESI): calcd. for $C_{17}H_{14}N_2O_2SNa$ [M + Na]$^+$ 333.0668, found 333.0665.

1,3-Diethyl-6-methyl-5-(*p*-tolylthio)pyrimidine-2,4(1*H*,3*H*)-dione (3t): Yellow solid (116 mg, 38 % yield); m.p. 87.7– 88.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 7.6 Hz, 2H), 4.04–3.97 (m, 4H), 2.65 (s, 3H), 2.26 (s, 3H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.20 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1, 157.1, 150.9, 136.0, 132.9, 129.8, 127.8, 105.7, 41.9, 37.6, 21.0, 18.4, 14.1, 12.8; IR (neat, cm^{-1}): $\tilde{\nu}$ = 2983, 2853, 1699, 1642, 1572, 1491, 1440, 1332, 1181, 1016, 801, 771, 642, 547; HRMS (ESI): calcd. for $C_{16}H_{21}N_2O_2S$ [M + H]$^+$ 305.1318, found 305.1315.

6-Chloro-1,3-dimethyl-5-(*p*-tolylthio)pyrimidine-2,4(1*H*,3*H*)-dione (3u): Yellow solid (184 mg, 62 % yield); m.p. 123.0– 123.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.4 Hz, 2H), 7.04 (d, *J* = 7.6 Hz, 2H), 3.61 (s, 3H), 3.32 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.1, 151.9, 150.4, 137.1, 131.1, 129.8, 129.6, 107.2, 35.4, 29.3, 21.0; IR (neat, cm^{-1}): $\tilde{\nu}$ = 2921, 2852, 1706, 1650, 1562, 1413, 1376, 1340, 1182, 1029, 995, 801, 759, 594; HRMS (ESI): calcd. for $C_{13}H_{13}ClN_2O_2SNa$ [M + Na]$^+$ 319.0278, found 319.0275.

6-Chloro-1-ethyl-3-methyl-5-(*p*-tolylthio)pyrimidine-2,4(1*H*,3*H*)-dione (3v): Brown solid (171 mg, 55 % yield); m.p. 88.6– 89.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 7.6 Hz, 2H), 4.22 (q, *J* = 7.0 Hz, 2H), 3.34 (s, 3H), 2.28 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.2, 151.4, 150.1, 137.1, 131.2, 129.9, 129.6, 107.3, 44.5, 29.3, 21.1, 13.9; IR (neat, cm^{-1}): $\tilde{\nu}$ = 2982, 2918, 1708, 1652, 1556, 1424, 1206, 1084, 1000, 859, 795, 760, 595; HRMS (ESI): calcd. for $C_{14}H_{15}ClN_2O_2SNa$ [M + Na]$^+$ 333.0435, found 333.0439.

1-Benzyl-6-chloro-3-methyl-5-(*p*-tolylthio)pyrimidine-2,4-(1*H*,3*H*)-dione (3w): Yellow solid (156 mg, 42 % yield); m.p. 103.3–104.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.31 (m, 5H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 5.38 (s, 2H), 3.39 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.1, 151.5, 150.7, 137.3, 135.2, 131.0, 129.9, 129.7, 128.9, 128.3, 127.5, 108.0, 51.7, 29.6, 21.1; IR (neat, cm^{-1}): $\tilde{\nu}$ = 2921, 2855, 1704, 1656, 1555, 1423, 1384, 1203, 996, 963, 804, 760, 732, 545; HRMS (ESI): calcd. for $C_{19}H_{17}ClN_2O_2SNa$ [M + Na]$^+$ 395.0591, found 395.0592.

6-(Chloromethyl)-5-(*p*-tolylthio)pyrimidine-2,4(1*H*,3*H*)-dione (3x): Brown solid (166 mg, 59 % yield); m.p. 79.5– 80.4 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.71 (s, 1H), 11.49 (s, 1H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 4.63 (s, 2H), 2.23 (s, 3H);

^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 162.1, 155.9, 150.5, 135.3, 132.2, 129.6, 127.1, 103.4, 40.1, 20.5; IR (neat, cm^{-1}): $\tilde{\nu}$ = 3053, 2920, 2260, 1706, 1670, 1604, 1492, 1410, 1321, 1165, 1044, 823, 736, 579; HRMS (ESI): calcd. for $C_{12}H_{11}ClN_2O_2SNa$ [M + Na]$^+$ 305.0122, found 305.0122.

1,3-Dimethyl-5-(phenylselanyl)pyrimidine-2,4(1*H*,3*H*)-dione (3y$_1$):[7f] Yellow solid (189 mg, 64 % yield); m.p. 100.9– 101.3 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.55 (s, 1H), 8.14 (s, 1H), 7.16 (d, *J* = 8.5 Hz, 2H), 6.70 (d, *J* = 8.4 Hz, 2H), 3.32 (s, 3H), 3.16 (s, 3H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 161.5, 156.8, 151.3, 149.2, 131.1, 123.7, 116.1, 104.3, 36.6, 28.2; IR (neat, cm^{-1}): $\tilde{\nu}$ = 3040, 2919, 1703, 1638, 1608, 1433, 1340, 1278, 1146, 1021, 767, 533; HRMS (ESI): calcd. for $C_{12}H_{12}N_2O_2SeNa$ [M + Na]$^+$ 318.9956, found 318.9957.

1,3-Dibenzyl-5-(phenylselanyl)pyrimidine-2,4(1*H*,3*H*)-dione (3y$_2$): Yellow oil (296 mg, 66 % yield); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.47 (d, *J* = 6.8 Hz, 2H), 7.41– 7.39 (m, 2H), 7.32– 7.16 (m, 12H), 5.13 (s, 2H), 4.81 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_6$): δ = 161.4, 151.4, 144.6, 136.6, 135.0, 132.7, 129.5, 129.2, 129.1, 129.0, 128.5, 128.4, 128.1, 127.9, 127.7, 104.3, 52.4, 45.4; IR (neat, cm^{-1}): $\tilde{\nu}$ = 3060, 2927, 1702, 1641, 1612, 1431, 1323, 1218, 1067, 1029, 823, 733, 629, 521; HRMS (ESI): calcd. for $C_{24}H_{20}N_2O_2SeNa$ [M + Na]$^+$ 471.0582, found 471.0583.

6-Chloro-1,3-dimethyl-5-(phenylselanyl)pyrimidine-2,4(1*H*,3*H*)-dione (3y$_3$): Brown solid (145 mg, 44 % yield); m.p. 87.3– 88.1 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.52– 7.49 (m, 2H), 7.28– 7.24 (m, 3H), 3.67 (s, 3H), 3.38 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 160.5, 151.8, 150.9, 132.1, 130.3, 129.4, 127.7, 104.4, 35.8, 29.7; IR (neat, cm^{-1}): $\tilde{\nu}$ = 2952, 2852, 1699, 1643, 1559, 1415, 1370, 1230, 1175, 1022, 986, 863, 756, 735, 686; HRMS (ESI): calcd. for $C_{12}H_{11}ClN_2O_2SeNa$ [M + Na]$^+$ 352.9566, found 352.9561.

6-(Chloromethyl)-5-(phenylselanyl)pyrimidine-2,4(1*H*,3*H*)-dione (3y$_4$): Yellow solid (180 mg, 57 % yield); m.p. 214.7 °C (decomposed); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.69 (s, 1H), 11.48 (s, 1H), 7.35–7.19 (m, 5H), 4.68 (s, 2H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 162.5, 155.9, 150.8, 131.4, 129.5, 129.2, 126.5, 101.6, 42.4; IR (neat, cm^{-1}): $\tilde{\nu}$ = 3138, 2963, 2845, 1722, 1651, 1601, 1417, 1311, 1089, 771, 727, 685, 576. HRMS (ESI): calcd. for $C_{11}H_9ClN_2O_2SeNa$ [M + Na]$^+$ 338.9410, found 338.9407.

1,3-Dimethyl-5-thiocyanatopyrimidine-2,4(1*H*,3*H*)-dione (4a): Yellow solid (195 mg, 99 % yield); m.p. 256.8– 257.3 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.77 (s, 1H), 3.49 (s, 3H), 3.39 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 160.1, 150.9, 147.3, 109.6, 97.2, 38.0, 29.0; IR (neat, cm^{-1}): $\tilde{\nu}$ = 3042, 2950, 2157, 1935, 1699, 1641, 1616, 1487, 1342, 1151, 1019, 765, 540; HRMS (ESI): calcd. for $C_7H_7N_3O_2SNa$ [M + Na]$^+$ 220.0151, found 220.0156.

1,3-Diethyl-5-thiocyanatopyrimidine-2,4(1*H*,3*H*)-dione (4b): Yellow solid (205 mg, 91 % yield); m.p. 130.0– 130.8 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.80 (s, 1H), 3.97 (q, *J* = 7.1 Hz, 2H), 3.86 (d, *J* = 7.2 Hz, 2H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 159.6, 150.0, 147.0, 109.7, 96.8, 45.9, 37.7, 14.4, 12.6; IR (neat, cm^{-1}): $\tilde{\nu}$ = 3049, 2982, 2155, 1703, 1642, 1441, 1268, 1155, 1087, 972, 771, 669, 562, 530; HRMS (ESI): calcd. for $C_9H_{11}N_3O_2SNa$ [M + Na]$^+$ 248.0464, found 248.0460.

1,3-Dipentyl-5-thiocyanatopyrimidine-2,4(1*H*,3*H*)-dione (4c): Orange oil (306 mg, 99 % yield); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.69 (s, 1H), 3.94 (t, *J* = 7.6 Hz, 2H), 3.79 (t, *J* = 7.6 Hz, 2H), 1.74–1.67 (m, 2H), 1.64–1.57 (m, 2H) 1.40– 1.26 (m, 8H), 0.92–0.86 (m, 6H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 159.8, 150.4, 146.4, 109.7, 97.3, 50.9, 42.7, 29.0, 28.9, 28.5, 27.1, 22.3, 22.2, 14.0, 13.9; IR (neat, cm^{-1}): $\tilde{\nu}$ = 3051, 2956, 2159, 1712, 1653, 1617, 1444, 1333, 1216, 1066, 766, 614, 549; HRMS (ESI): calcd. for $C_{15}H_{23}N_3O_2SNa$ [M + Na]$^+$ 332.1403, found 332.1400.

1,3-Diisopropyl-5-thiocyanatopyrimidine-2,4(1*H*,3*H*)-dione (4d): Orange solid (220 mg, 87 % yield); m.p. 97.0– 97.8 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.71 (s, 1H), 5.13 (sep, *J* = 6.9 Hz, 1H), 4.81 (sep, *J* = 6.8 Hz, 1H), 1.40 (d, *J* = 7.0 Hz, 6H), 1.32 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 159.6, 150.0, 143.3, 109.8, 97.0, 49.5, 47.5, 21.4, 18.9; IR (neat, cm^{-1}): $\tilde{\nu}$ = 3047, 2968, 2156, 1701, 1643, 1615, 1435, 1334, 1279, 1052, 965, 770, 669, 553; HRMS (ESI): calcd. for $C_{11}H_{15}N_3O_2SNa$ [M + Na]$^+$ 276.0777, found 276.0776.

1,3-Dibenzyl-5-thiocyanatopyrimidine-2,4(1*H*,3*H*)-dione (4e): Orange oil (227 mg, 65 % yield); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.71(s, 1H), 7.44 (d, *J* = 6.8 Hz, 2H), 7.38–7.32 (m, 3H), 7.28–7.21 (m, 5H), 5.10 (s, 2H), 4.92 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 159.6, 150.7, 146.8, 135.7, 134.2, 129.3, 129.1, 128.9, 128.5, 128.3, 128.0, 109.5, 97.4, 53.1, 45.7; IR (neat, cm^{-1}): $\tilde{\nu}$ = 3033, 2853, 2158, 1711, 1650, 1495, 1438, 1324, 1220, 937, 748, 696, 601, 523; HRMS (ESI): calcd. for $C_{19}H_{15}N_3O_2SNa$ [M + Na]$^+$ 372.0777, found 372.0775.

Diethyl 2,2′-[2,4-dioxo-5-thiocyanatopyrimidine-1,3(2*H*,4*H*)-diyl]diacetate (4f): Orange oil (61 mg, 18 % yield); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.73 (s, 1H), 4.70 (s, 2H), 4.55 (s, 2H), 4.29–4.19 (m, 4H), 1.32–1.26 (m, 6H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 166.9, 166.7, 159.2, 150.2, 147.0, 109.1, 98.6, 62.8, 62.1, 50.4, 43.1, 14.2(2C); IR (neat, cm^{-1}): $\tilde{\nu}$ = 3077, 2923, 2161, 1743, 1718, 1662, 1442, 1374, 1200, 1020, 770, 618, 542; HRMS (ESI): calcd. for $C_{13}H_{15}N_3O_6SNa$ [M + Na]$^+$ 364.0574, found 364.0577.

1-Pentyl-5-thiocyanatopyrimidine-2,4(1*H*,3*H*)-dione (4g): White solid (201 mg, 84 % yield); m.p. 159.8– 160.7 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.90 (s, 1H), 8.50 (s, 1H), 3.70 (t, *J* = 7.2 Hz, 2H), 1.62–1.55 (m, 2H), 1.31–1.18 (m, 4H), 0.85 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 160.7, 152.6, 150.4, 111.2, 94.7, 48.5, 28.1, 27.9, 21.8, 13.8; IR (neat, cm^{-1}): $\tilde{\nu}$ = 3031, 2927, 2161, 1653, 1613, 1460, 1430, 1362, 1268, 1025, 871, 757, 556; HRMS (ESI): calcd. for $C_{10}H_{13}N_3O_2SNa$ [M + Na]$^+$ 262.0621, found 262.0625.

1-Benzyl-5-thiocyanatopyrimidine-2,4(1*H*,3*H*)-dione (4h): Yellow solid (155 mg, 60 % yield); m.p. 185.8– 186.2 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.04 (s, 1H), 8.68 (s, 1H), 7.36–7.30 (m, 5H), 4.95 (s, 2H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 160.6, 152.4, 150.4, 136.1, 128.6, 127.9, 127.7, 111.2, 95.7, 51.4; IR (neat, cm^{-1}): $\tilde{\nu}$ = 3410, 3162, 2846, 2156, 1714, 1667, 1425, 1359, 1244, 1026, 867, 739, 598; HRMS (ESI): calcd. for $C_{12}H_9N_3O_2SNa$ [M + Na]$^+$ 282.0308, found 282.0308.

1-Phenyl-5-thiocyanatopyrimidine-2,4(1*H*,3*H*)-dione (4i): Orange solid (61 mg, 25 % yield); m.p. 213.8 °C (decomposed); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.11 (s, 1H), 8.54 (s, 1H), 7.54–7.45 (m, 5H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 160.7, 152.0, 149.9, 138.1, 129.1, 128.8, 127.0, 111.0, 95.9; IR (neat, cm^{-1}): $\tilde{\nu}$ = 3159, 3032, 2848, 2157, 1681, 1590, 1488, 1413, 1349, 1282, 861, 770, 696, 575; HRMS (ESI): calcd. for $C_{11}H_7N_3O_2SNa$ [M + Na]$^+$ 268.0151, found 268.0150.

1-(4-Fluorophenyl)-5-thiocyanatopyrimidine-2,4(1*H*,3*H*)-dione (4j): Orange solid (121 mg, 46 % yield); m.p. 96.2– 97.1 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.17 (s, 1H), 8.37 (s, 1H), 7.38–7.29 (m, 4H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 162.9, 160.6 (d, *J* = 18.8 Hz), 150.8, 148.8, 131.3 (d, *J* = 2.8 Hz), 130.9 (d, *J* = 8.7 Hz), 115.9 (d, *J* = 22.7 Hz), 111.2, 94.7; ^{19}F NMR (376 MHz, [D$_6$]DMSO): δ = –113.6; IR (neat, cm^{-1}): $\tilde{\nu}$ = 3391, 3077, 2159, 1724, 1667, 1506, 1407, 1331, 1218, 1023, 995, 824, 761, 611; HRMS (ESI): calcd. for $C_{11}H_7FN_3O_2S$ [M + H]$^+$ 264.0238, found 264.0230.

1,3-Diethyl-6-methyl-5-thiocyanatopyrimidine-2,4(1*H*,3*H*)-dione (4k): Orange solid (222 mg, 93 % yield); m.p. 76.7– 77.5 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 4.00–3.93 (m, 4H), 2.66 (s, 3H), 1.26 (t,

J = 7.2 Hz, 3H), 1.16 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 158.6, 150.1, 110.0, 96.4, 42.3, 37.9, 18.9, 13.9, 12.5; IR (neat, cm^{-1}): $\tilde{\nu}$ = 3337, 2973, 2932, 2160, 1702, 1644, 1582, 1422, 1333, 1207, 1092, 1054, 770, 590, 545; HRMS (ESI): calcd. for $C_{10}H_{13}N_3O_2SNa$ [M + Na]$^+$ 262.0621, found 262.0625.

6-Amino-1,3-dimethyl-5-thiocyanatopyrimidine-2,4(1*H*,3*H*)-dione (4l):[8a] Brown solid (159 mg, 75 % yield); m.p. 262.5– 263.0 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.86 (s, 2H), 3.36 (s, 3H), 3.14 (s, 3H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 160.2, 157.3, 150.3, 112.4, 66.3, 31.0, 28.3; IR (neat, cm^{-1}): $\tilde{\nu}$ = 3416, 3374, 2926, 2158, 1706, 1611, 1497, 1370, 1222, 1084, 1021, 757, 747, 582, 530; HRMS (ESI): calcd. for $C_7H_8N_4O_2SNa$ [M + Na]$^+$ 235.0260, found 235.0259.

6-Chloro-1-ethyl-3-methyl-5-thiocyanatopyrimidine-2,4(1*H*,3*H*)-dione (4m): Yellow solid (98 mg, 40 % yield); m.p. 141.5– 142.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.25 (q, J = 7.1 Hz, 2H), 3.38 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.5, 153.1, 149.4, 108.7, 97.5, 45.2, 29.6, 13.8; IR (neat, cm^{-1}): $\tilde{\nu}$ = 3346, 2927, 2159, 1704, 1649, 1565, 1425, 1347, 1204, 1086, 1003, 863, 757, 599, 533; HRMS (ESI): calcd. for $C_8H_8ClN_3O_2SNa$ [M + Na]$^+$ 267.9918, found 267.9917.

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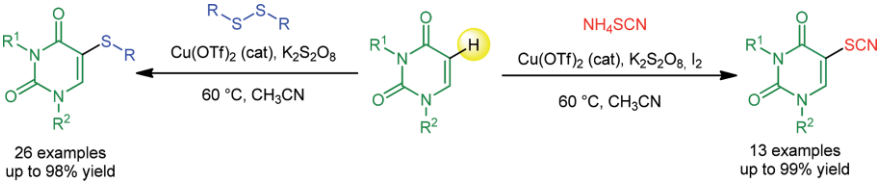
C–H Thiolation



The copper-catalyzed direct C–H thiolation and thiocyanation of uracils using disulfides and thiocyanate salts respectively as coupling partners have been successfully developed. These protocols enable the C–H bond cleavage and C–S bond formation to proceed efficiently, providing useful methods to access of a diverse array of thio-substituted at the 5 position of uracil derivatives in good to excellent yields.

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