Tetrahedron 75 (2019) 130537

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Iodine/persulfate-promoted site-selective direct thiolation of quinolones and uracils

Danupat Beukeaw, Medena Noikham, Sirilata Yotphan*

Department of Chemistry and Center of Excellence for Innovation in Chemistry, Faculty of Science, Mahidol University, Rama VI Road, Bangkok 10400, Thailand

ARTICLE INFO

Article history:
Received 5 July 2019
Received in revised form
9 August 2019
Accepted 19 August 2019
Available online 22 August 2019

Keywords:
Iodine
Direct thiolation
Quinolone
Uracil
Sulfone

ABSTRACT

A simple and general method for direct thiolation of 4-quinolones with disulfides or thiols under I_2/$K_2S_2O_8$ system has been developed. Under the optimal conditions, the C–S bond coupling can take place effectively with good to decent yields and excellent regioselectivity of the *S*-linked products. The established metal-free site-selective approach was also applicable to transform a range of uracil substrates to the thio-substituted products under mild conditions. Further transformation to the sulfone derivatives can be conveniently performed in one-pot. These easy-to-handle protocols represent a useful and interesting synthetic alternative with good substrate scope and functional group compatibility.

1. Introduction

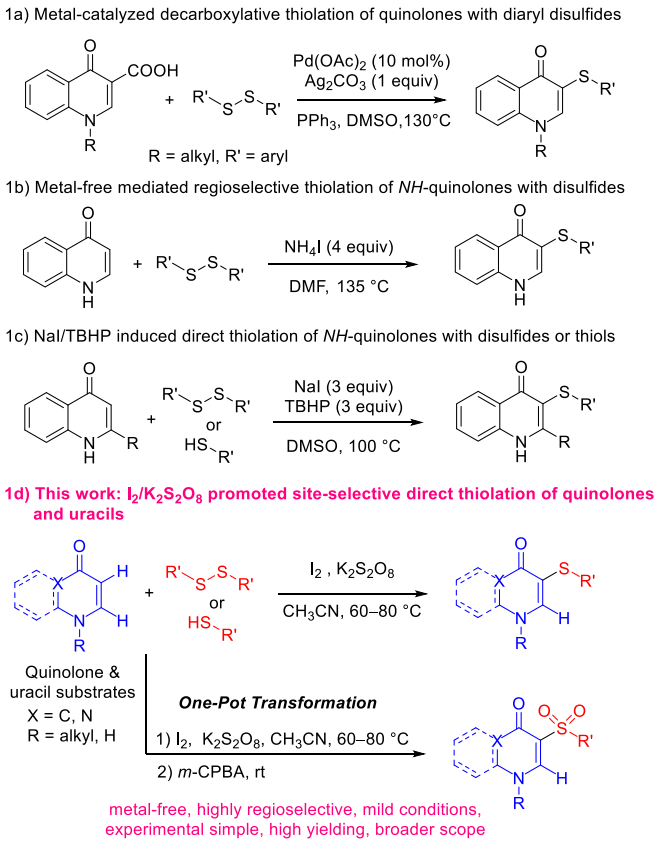
Organic sulfur-containing compounds are widely present in a large number of bioactive natural products, synthetic drugs, agrochemicals and functional materials [1]. Among various organosulfur compounds, thioethers (sulfide group) had found extensive applications in the field of medicine, biology, organic synthesis, catalysis, coordination chemistry, polymers, and other related applications, as they can serve as an important auxiliary function in molecules [2]. The incorporation of thioether moieties into the organic compounds through C–S bond forming reactions has always been an attractive interest to researchers. Much of the early work on C–S bond construction involved a classical cross-coupling of organic halides with thiols or metal thiolates [3]. With substantial progress in a field of C–H bond functionalization, a direct formation of C–S bond through C–H functionalization reactions have recently received considerable attention [4]. Despite several examples of metal-catalyzed or metal-free transformations have been reported, the site-selective transformations still remain open to study.

Quinolones and uracils are privileged classes of *N*-heterocyclic enones found in a number of bioactive compounds and pharmaceutical agents. Many of these quinolone and uracil analogues are also known to display a broad spectrum of activities such as antibacterial, antiviral, antitumor, antimalarial as well as herbicidal and insecticidal properties [5,6]. Owing to their fascinating profiles, they have been extensively manipulated in several areas including organic synthesis, medicinal and pharmacological chemistry, agricultural science and material chemistry [7]. In recent years, tremendous efforts have been devoted to the site-selective synthesis and modification of these heterocycles in order to increase their structural diversity and utilization. Particularly, incorporation of bioactive moieties or functional groups into their skeletons could modify their reactivity, thereby leading to further applications.

In the context of direct construction of C–S bond linkage, the thioether functionality can be directly introduced into the 4-quinolone core *via* Pd-catalyzed decarboxylative C–S bond coupling reaction (Scheme 1a) [8]. In addition, the metal-free systems to mediate thiolation process (using NH_4I or NaI/TBHP) were subsequently reported (Schemes 1b and 1c) [9,10]. Despite their usefulness in forming C–S bonds, these methods still have some limitations, such as high temperature, toxic solvent, using a large excess of halogen, a requirement of a blocking or directing group and narrow substrate scope. Therefore, alternative protocols to access these compounds efficiently under mild conditions are highly desirable.

* Corresponding author.
E-mail address: sirilata.yot@mahidol.ac.th (S. Yotphan).

https://doi.org/10.1016/j.tet.2019.130537
0040-4020/



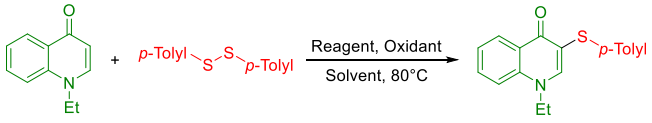
Scheme 1. Synthesis of thioether derivatives of 4-quinolone.

With our interests toward the development of improved synthetic routes to chemically modify various *N*-heterocyclic compounds [11], herein, we disclose a convenient metal-free approach for site-selective direct thiolation of quinolones with disulfides or thiols using iodine/persulfate-promoted C–S bond coupling reaction. This metal-free method offers a very simple and general protocol to access the *S*-linked products of 4-quinolone compounds regioselectively under relatively mild conditions. The established thiolation method is also applicable to deliver the sulfide moiety to uracil substrates effectively (Scheme 1d) [12,13]. In addition, the optimized conditions are compatible with further oxidation reaction, resulting in a conversion to sulfone derivatives in one-pot. Other benefits of our strategies are air-tolerant, employing readily accessible starting materials, giving high yields of products, and avoiding the use of expensive or a large excess amount of halogen inducing reagents.

2. Results and discussion

We began our study on the direct thiolation of quinolone with optimization of reaction conditions between *N*-ethyl 4-quinolone (**1a**) and *p*-tolyl disulfide (**2a**). Upon testing a reaction in acetonitrile (CH_3CN) solvent, the presence of halogen source and potassium persulfate ($K_2S_2O_8$) as the oxidant allowed the direct C–S bond coupling to occur and only 3-thiosubstituted product was formed in this reaction at 80 °C (Table 1). Among various choices of halogen inducers, molecular iodine (I_2) delivered the highest amount of the corresponding 3-thio substituted product (entry 4), while other halogen sources provided lower quantities (entries 1–3 and 5–8). In addition, replacing $K_2S_2O_8$ by other persulfate salts (entries 9 and 10) or peroxide oxidants resulted in a reduction of

Table 1
Optimization of reaction conditions.[a]



1a **2a** **3a**

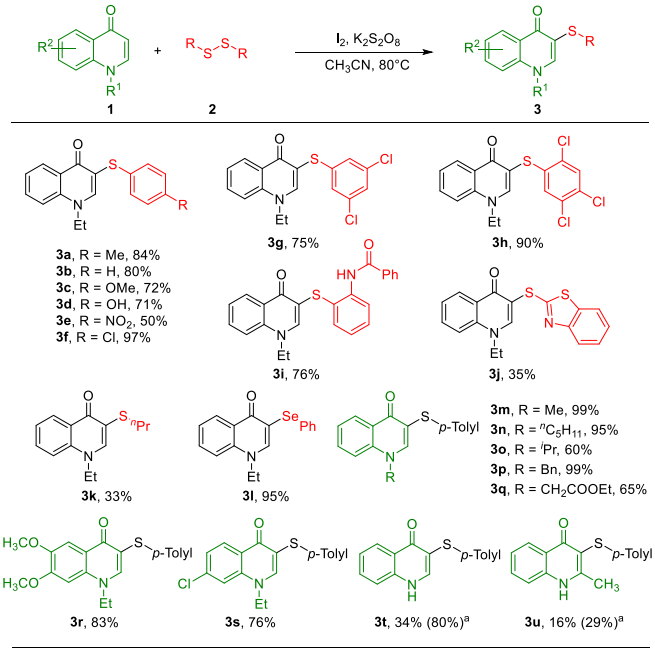
Entry	Reagent	Oxidant	Solvent	Yield[b]
1	NCS	$K_2S_2O_8$	CH_3CN	21
2	NBS	$K_2S_2O_8$	CH_3CN	47
3	NIS	$K_2S_2O_8$	CH_3CN	42
4	**I_2**	**$K_2S_2O_8$**	**CH_3CN**	**84 (84[c])**
5	NaCl	$K_2S_2O_8$	CH_3CN	57
6	NaBr	$K_2S_2O_8$	CH_3CN	60
7	NaI	$K_2S_2O_8$	CH_3CN	78
8	NH_4I	$K_2S_2O_8$	CH_3CN	76
9	I_2	$Na_2S_2O_8$	CH_3CN	34
10	I_2	$(NH_4)_2S_2O_8$	CH_3CN	60
11	I_2	$K_2S_2O_8$	Toluene	66
12	I_2	$K_2S_2O_8$	MeOH	20
13	I_2	$K_2S_2O_8$	H_2O	32
14	I_2	$K_2S_2O_8$	DMSO	6
15	I_2 (50%)	$K_2S_2O_8$	CH_3CN	49
16	I_2 (20%)	$K_2S_2O_8$	CH_3CN	23
17	–	$K_2S_2O_8$	CH_3CN	no reaction
18	I_2	–	CH_3CN	28

1a = quinolone, 2a = disulfide, entry 4 = optimal condition.
[a] Conditions: **1a** (0.25 mmol), **2a** (0.38 mmol, 1.5 equiv), reagent (0.25 mmol, 1 equiv), oxidant (0.5 mmol, 2 equiv), solvent (0.5 mL), 70 °C, 12 h.
[b] GC yield.
[c] Isolated yield.

yield. We also found that the thiolation was much less effective as carrying out this reaction in other solvents (entries 11–14). Employing catalytic amounts of I_2 resulted in lower yields and conversions (entries 15 and 16) [14]. Lastly, no reaction was observed in the absence of I_2 (entry 17), and only 28% yield of the product **3a** was obtained when the oxidant was omitted from the reaction (entry 18). These results highlight the importance of both I_2 and $K_2S_2O_8$ in this transformation. Overall, the optimal conditions for the metal-free regioselective direct thiolation was established (Table 1, entry 4; 1 equiv of quinolone, 1.5 equiv of disulfide, 1 equiv of I_2, 3 equiv of $K_2S_2O_8$, CH_3CN, 80 °C, 12 h).

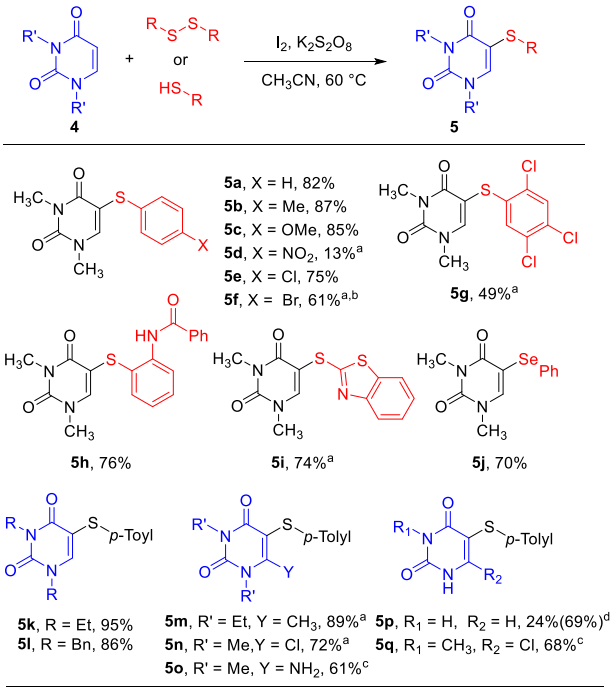
Next, the scope of this transformation was examined in detail under the optimized conditions. As shown in Table 2, several diaryl disulfides could react with quinolone **1a** smoothly to produce the desired products (**3a**–**3i**) in good to excellent yields. In general, aryl disulfides with electron-donating groups (–Me, –OMe, –OH) proceeded very well, and high yields of the products were obtained (**3a**, **3c** and **3d**). Disulfides bearing electron-withdrawing group ($-NO_2$) is also suitable for this transformation (**3e**, 50%). Pleasingly, the chloro substituents on the phenyl ring of disulfides are well tolerated, which enable a potential application in further functionalization (**3f**–**3h**). The amide group (CO–NH) on diaryl disulfide was also a viable coupling partner for this C–S cross-coupling reaction. Meanwhile, heteroaromatic disulfide as well as dialkyl disulfide was less effective in this transformation and quite low yields of products (**3j** and **3k**) were found, indicating a less stability of the sulfur intermediate species. Nevertheless, upon switching to diphenyl diselenide, the direct C–Se bond formation was achieved in decent quantity under the established conditions (**3l**, 95%). We next turned our attention toward the reactions of other quinolone substrates. For other *N*-alkylated 4-quinolones substrates, good to excellent amounts of products were isolated from the reactions. In particular, the *N*-2-ethoxy-2-oxoethyl (with ester functionality) 4-

Table 2
Substrate scope of $I_2/K_2S_2O_8$-promoted site-selective direct thiolation of quinolone.



Conditions: **1** (0.5 mmol, 1 equiv), **2** (0.75 mmol, 1.5 equiv), I_2 (0.5 mmol, 1 equiv), $K_2S_2O_8$ (1 mmol, 2 equiv), CH_3CN (1 mL), 80 °C, 12–16 h, as monitored by TLC. Isolated yields after chromatography.
[a] Employing 1.5 equiv of iodine.

Table 3
Direct thiolation of uracils.

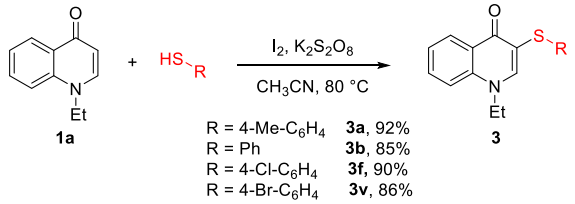


Conditions: **4** (0.5 mmol, 1 equiv), disulfide or thiol (0.75 mmol, 1.5 equiv), I_2 (0.1 mmol, 0.2 equiv), $K_2S_2O_8$ (1 mmol, 2 equiv), CH_3CN (1 mL), 60 °C, 12–16 h, as monitored by TLC. Isolated yields after chromatography.
[a] Employing 1 equiv of I_2.
[b] Using 4-bromothiophenol as a thiolating reagent.
[c] Using NaI (1 equiv) instead of I_2.
[d] Employing 1.5 equiv of I_2.

quinolone was compatible and afforded the product **3q** in gratified quantities. Furthermore, quinolone substrates bearing the methoxy or chloro substituted on benzene ring worked well and provided the desired compounds (**3r** and **3s**) in high yields. On the other hand, a somewhat smaller amount of product **3t** was observed in case of *NH*-quinolone, though using 1.5 equivalent of iodine could help to enhance the yield from this transformation. Nonetheless, the presence of the methyl substitution at *C3* position showed a deleterious effect on the conversion, and much lower yield of coupling product **3u** was found, suggesting that the steric hindrance from the substituent at the *C3* position of quinolone is likely to impede with the product formation.

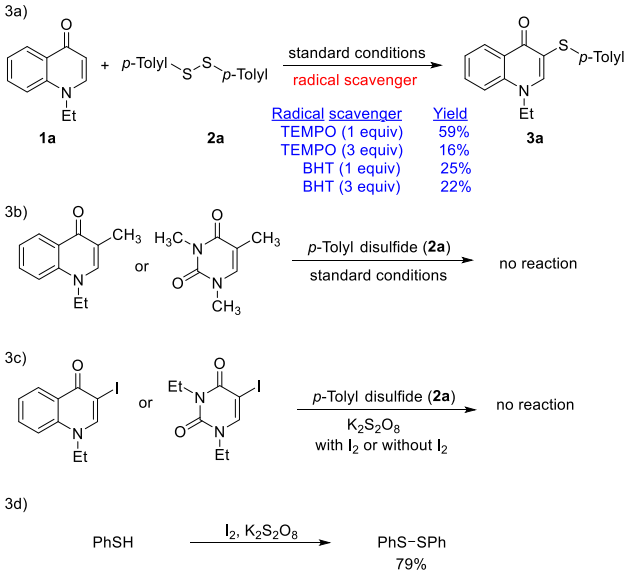
For this present strategy, thiophenols could also be employed as an alternate sulfur precursor instead of disulfides in the direct thiolation reaction. As shown in Scheme 2, comparable yields with excellent site-selectivity of the products were accomplished in all cases. Other regioisomers of products were not detected under standard conditions.

With the success of direct C–S bond coupling of quinolones, we extended this protocol to uracil substrates, and we found that they also underwent thiolation with no difficulty and produced the uracil derivatives under similar conditions [15]. As shown in Table 3, the thiol moieties were installed exclusively at the α position to the amide carbonyl group of uracil (*C5* position) in all cases. Various aryldisulfides and thiols including electron-rich, halogen, amide or heteroaryl substitution reacted readily with 1,3-dimethyluracil under the $I_2/K_2S_2O_8$-promoted system and gave the products in good to excellent yields (**5a**–**5i**), with the exception of the nitro substitution (**5d**) which exhibited a considerably decreased reactivity toward this reaction. Similar to quinolone substrate, direct selenylation of uracil with diphenyl diselenide was achievable under the standard conditions (70%). Apart from 1.3-dimethyluracil, other *N*-protect uracils were feasible, and excellent yields of C–S coupling products were obtained (**5k** and **5l**). To our surprise, the uracil substrates with the substitution at *C6* position did not appear to interrupt the incorporation of the thiol moiety, and good to high yields of products were received (**5m**–**5o**). Remarkably, no side reactions due to the presence of the chloro or amino group at *C6* position were detected under the optimal conditions (**5n** and **5o**). Finally, the *NH*-uracil substrates were also amendable to convert to desired products **5p** and **5q** in satisfying quantities.



Scheme 2. Direct thiolation using thiols.

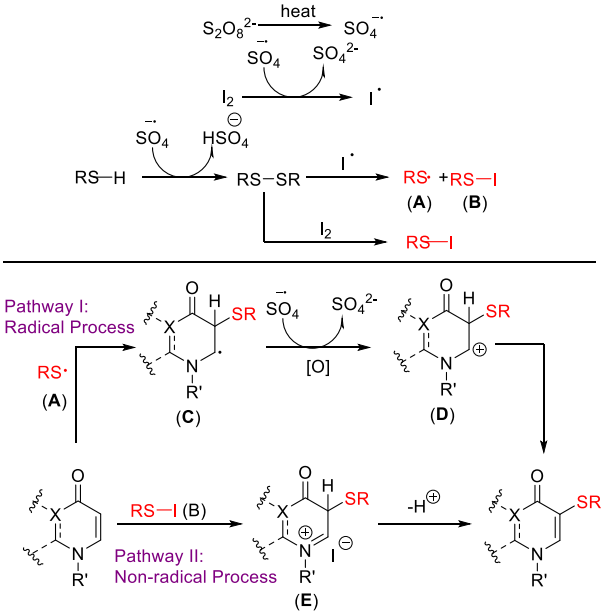
To gain insight into the reaction mechanism, we conducted control experiments as shown in Scheme 3. Adding 1 or 3 equiv of radical inhibitors, such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 2,6-di-*tert*-butylphenol (BHT), to the standard reaction, the yield of the coupled product was decreased (Scheme 3a), which is indicative of partial inhibition of the reaction. These outcomes suggested that the transformation is likely to operate under a radical process. However, these observations cannot completely rule out the possibility of a non-radical pathway. When employing



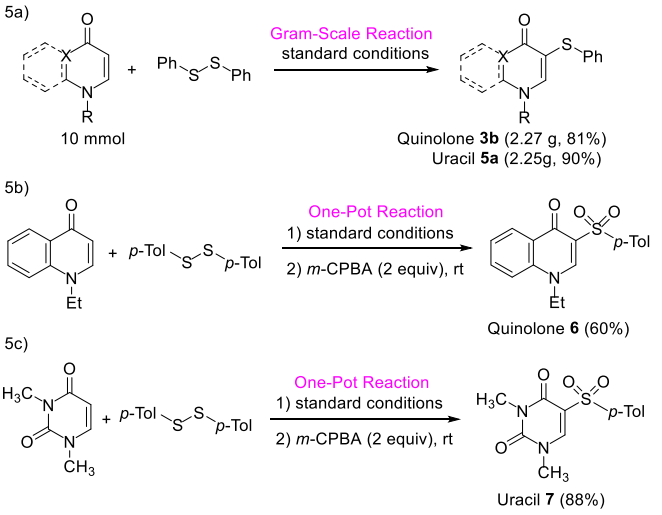
Scheme 3. Control experiments.

3-methyl substituted quinolone or 5-methyl substituted uracil as a substrate of this transformation, no reactions were found (Scheme 3b). These results confirmed the regioselectivity of this metal-free reaction as the direct C−S bond coupling takes place solely at the α position to the carbonyl moiety. Besides, when subjecting the iodo quinolone or iodo uracil substrate to reaction, no reaction was detected (Scheme 3c). Therefore, these iodo species might not be intermediates in this transformation. Nonetheless, we found that the thiol precursor can be converted to the disulfide compound under the standard conditions (Scheme 3d) [16].

Although some detail reaction mechanism is still unclear at this stage, plausible mechanistic processes were proposed as depicted in Scheme 4. Based on our observation and other relevant literature [11h,17,18], we believed that both intermediates **A** (RS•) and **B** (RS−I) are initially generated from a series of reactions of I_2, disulfide (or thiol) and persulfate anion ($S_2O_8^{2-}$) or sulfate radical anion ($SO_4^{\bullet-}$) and the final product could be formed by two possible pathways [11h,18]. In pathway I, a radical triggered process, the RS• radical intermediate reacts with the substrate to form the radical intermediate **C**, in which a thiol group is installed at the α position to the carbonyl moiety. Then, this intermediate is further oxidized by a sulfate radical anion *via* a SET process to form the carbocation intermediate **D**. A subsequent loss of a proton would furnish the final product [19]. In pathway II, a non-radical process, a reaction between RS−I and substrate could result in a formation of iminium intermediate **E**, which can undergo elimination to deliver the product [9,10,20].



Scheme 4. Possible reaction mechanism.



Scheme 5. Gram-scale reaction and further transformation to sulfones in one-pot.

Furthermore, it is noteworthy that this $I_2/K_2S_2O_8$-mediated direct thiolation protocol could be effectively and practically scaled up to the gram scale (10 mmol) with similar efficacy to the small scale reactions. As shown in Scheme 5a, the *S*-linked products **3b** and **5a** could be conveniently prepared under the standard conditions in high yields, 81% (2.27 g) and 90% (2.25 g), respectively. Lastly, the optimal systems were compatible with further oxidation reaction, resulting in a successful conversion to sulfone analogues in one-pot (Scheme 5b and 5c). These outcomes suggested a useful and promising application in the industry.

3. Conclusion

In summary, a simple and inexpensive $I_2/K_2S_2O_8$-induced system was developed for a direct thiolation of 4-quinolones and uracils. Using disulfides or thiols as a thiolating agent, these metal-free approaches enable the C−S bond coupling to occur effectively under relatively mild conditions. Further transformation to the sulfone derivatives can be conveniently accomplished in one-pot process. Additional advantages of these methods include high regioselectivity, accommodating broad scope, avoiding the requirement of large excess amount of halide reagent, and providing moderate to excellent yields of products with good scalability and simple experimental procedure, which are useful for a modification of *N*- heterocycles for medicinal chemistry, drug discovery research, and other related areas. Further expansion of the synthetic utility and study of potential biological applications of these synthesized compounds are currently in progress in our laboratory.

4. Experimental section

4.1. General methods

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 glasswares were used in all cases. Column chromatography was performed over silica gel (SiO_2; 60 Å silica gel, Merck Grade, 70–230 Mesh). GC experiments were carried out with an Agilent 6890N GC-FID on chromatograph equipped with Agilent column HP-1, dimethylpolysiloxane column (30 m × 0.25 mm ID × 0.25 μm). ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, in DMSO-d_6 and $CDCl_3$ solutions. NMR chemical shifts are reported in ppm and were measured relative to DMSO to DMSO (2.50 ppm for ^{1}H and 39.52 ppm for ^{13}C) and $CHCl_3$ (7.26 ppm for ^{1}H and 77.16 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 ^{1}H NMR, ^{13}C NMR data with those of literature [12e,13,21].

4.2. Preparation of the starting materials

The *N*-alkylated quinolone and uracil substrates were synthesized from the *NH*-quinolones and *NH*-uracils and the corresponding alkylhalides *via* standard alkylation reactions according to the literature procedures [22,23].

4.3. Typical experimental procedure for the $I_2/K_2S_2O_8$-promoted direct thiolation of quinolones and uracils: synthesis of compounds **3a**–**3v** and **5a–5q**

An 8 mL oven-dried scintillation vial equipped with a magnetic stir bar was charged with a mixture of 4-quinolone or uracil (0.50 mmol, 1.0 equiv), disulfide or thiol (0.75 mmol, 1.5 equiv), molecular iodine (I_2) (128 mg, 0.50 mmol, 1.0 equiv), $K_2S_2O_8$ (1.00–1.50 mmol, 2.0–3.0 equiv), and acetonitrile (CH_3CN) (1 mL). The vial was capped, and the reaction mixture was stirred at 60 or 80 °C for 12–16 h. Upon completion, saturated $Na_2S_2O_3$ (5 mL) and distilled deionized H_2O (10 mL) was added, and the mixture was extracted with ethyl acetate (3 × 25 mL). The combined organic layer was washed with saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by SiO_2 column chromatography to afford the desired thioether products.

4.3.1. 1-Ethyl-3-(p-tolylthio)quinolin-4(1H)-one (**3a**)

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a light yellow solid (123 mg, 84% yield); mp = 176.0–177.4 °C; IR (neat): 3032, 2977, 2916, 1598, 1487, 1384, 1181, 1082, 804, 771, 702, 637 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.54 (s, 1H), 8.21 (d, *J* = 7.6 Hz, 1H), 7.83–7.76 (m, 2H), 7.47–7.43 (m, 1H), 7.08–7.01 (m, 4H), 4.37 (q, *J* = 7.2 Hz, 2H), 2.22 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 174.3, 149.3, 139.2, 134.6, 133.7, 132.4, 129.4, 126.9, 126.3, 126.1, 124.2, 116.8, 110.6, 47.3, 20.4, 14.4 ppm; HRMS (ESI): *m*/*z* [M+Na]$^+$ calcd for $C_{18}H_{17}NOSNa$: 318.0923; found: 318.0927.

4.3.2. 1-Ethyl-3-(phenylthio)quinolin-4(1H)-one (**3b**)

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a yellow solid (113 mg, 80% yield); mp = 165.5–166.5 °C; IR (neat): 3031, 2978, 1581, 1542, 1487, 1233, 1172, 1083, 804, 771, 703 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.60 (s, 1H), 8.22 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.84–7.78 (m, 2H), 7.48–7.44 (m, 1H), 7.25–7.22 (m, 2H), 7.13–7.09 (m, 3H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 174.4, 150.0, 139.3, 137.6, 132.6, 128.8, 126.4, 126.2, 126.1, 125.1, 124.3, 117.0, 109.5, 47.4, 14.5 ppm; HRMS (ESI): *m*/*z* [M+Na]$^+$ calcd for $C_{17}H_{15}NOSNa$: 304.0767; found: 304.0768.

4.3.3. 1-Ethyl-3-((4-methoxyphenyl)thio)quinolin-4(1H)-one (**3c**)

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a yellow solid in (112 mg, 72% yield); mp = 151.0–152.8 °C; IR (neat): 3023, 2974, 1724, 1581, 1460, 1384, 1241, 1171, 1032, 771, 627 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.47 (s, 1H), 8.20 (d, *J* = 8.4 Hz,1H), 7.81–7.75 (m, 2H), 7.46–7.42 (m, 1H), 7.22–7.18 (m, 2H), 6.87–6.84 (m, 2H), 4.36 (q, *J* = 7.2 Hz, 2H), 3.70 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 174.2, 158.0, 148.2, 139.1, 132.4, 130.1, 127.2, 126.3, 126.0, 124.1, 116.8, 114.7, 112.4, 55.2, 47.3, 14.4 ppm; HRMS (ESI): *m*/*z* [M+Na]$^+$ calcd for $C_{18}H_{17}NO_2SNa$: 334.0872; found: 334.0875.

4.3.4. 1-Ethyl-3-((4-hydroxyphenyl)thio)quinolin-4(1H)-one (**3d**)

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a brown solid in (105 mg, 71% yield); mp = 197.6–199.9 °C; IR (neat): 2921, 1598, 1581, 1488, 1266, 1223, 1168, 1086, 832, 755, 695, 516 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.47 (s, 1H), 8.36 (s, 1H), 8.20 (d, *J* = 7.6 Hz, 1H), 7.80–7.76 (m, 2H), 7.45–7.41 (m, 1H), 7.14 (d, *J* = 8.8 Hz, 2H), 6.69 (d, *J* = 8.4 Hz, 2H), 4.33 (d, *J* = 7.2 Hz, 2H), 1.34 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 174.2, 156.4, 147.5, 139.0, 132.4, 131.0, 126.3, 125.9, 124.6, 124.0, 116.8, 116.0, 113.4, 47.3, 14.4 ppm; HRMS (ESI): *m*/*z* [M+Na]$^+$ calcd for $C_{17}H_{15}NO_2SNa$: 320.0716; found: 320.0720.

4.3.5. 1-Ethyl-3-((4-nitrophenyl)thio)quinolin-4(1H)-one (**3e**)

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a yellow solid (82 mg, 50% yield); mp = 164.5–166.5 °C; IR (neat): 1571, 1543, 1510, 1368, 1330, 1085, 839, 765, 740, 700, 535, 520 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.72 (s, 1H), 8.24 (dd, *J* = 8.1, 1.5 Hz, 1H), 8.09–8.06 (m, 2H), 7.89–7.82 (m, 2H), 7.52–7.49 (m, 1H), 7.30–7.27 (m, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 174.0, 150.5, 148.2, 144.5, 139.3, 132.8, 126.4, 126.2, 125.5, 124.6, 123.8, 117.1, 106.9, 47.5, 14.4 ppm; HRMS (ESI): *m*/*z* [M+H]$^+$ calcd for $C_{17}H_{15}N_2O_3S$, 327.0798; found: 327.0799.

4.3.6. 3-((4-Chlorophenyl)thio)-1-ethylquinolin-4(1H)-one (**3f**)

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a yellow solid (153 mg, 97% yield); mp = 148.8–151.5 °C; IR (neat): 3411, 2924, 1574, 1502, 1331, 1224, 1172, 1086, 853, 759, 737 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.64 (s, 1H), 8.21 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.85–7.79 (m, 2H), 7.49–7.45 (m, 1H), 7.31–7.28 (m, 2H), 7.15–7.11 (m, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 174.1, 150.6, 148.2, 144.5, 139.4, 132.9, 126.5, 126.3, 125.5, 124.7, 123.9, 117.2, 106.9, 47.6, 14.5 ppm; HRMS (ESI): *m*/*z* [M+Na]$^+$ calcd for $C_{17}H_{14}ClNOSNa$: 338.0377; found: 338.0372.

4.3.7. 3-((3,5-Dichlorophenyl)thio)-1-ethylquinolin-4(1H)-one (**3g**)

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a white solid (130 mg, 75% yield); mp = 174.0–175.8 °C; IR (neat): 3064, 3017, 1587, 1580, 1542, 1401, 1365, 1228, 757 cm^{-1}.^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.67 (s, 1H), 8.23 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.87–7.80 (m, 2H), 7.51–7.47 (m, 1H), 7.34–7.33 (m, 1H), 7.12 (d, *J* = 2.0 Hz, 2H), 4.39 (q, *J* = 7.2 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 174.1, 150.6, 142.5, 139.4, 134.3,

132.8, 126.4, 126.2, 124.7, 124.6, 123.9, 117.2, 107.2, 47.6, 14.4 ppm; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{17}H_{13}Cl_2NOSNa$: 371.9987; found: 371.9988.

4.3.8. 1-Ethyl-3-((2,4,5-trichlorophenyl)thio)quinolin-4(1H)-one (**3h**)

Purification by column chromatography (Hexanes/EtOAc, 1/1) as an orange solid (174 mg, 90% yield); mp = 193.3–194.9 °C; IR (neat): 3045, 2980, 2930, 1599, 1427, 1221, 1109, 1051, 918, 906, 757, 639 cm^{-1}.^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.70 (s, 1H), 8.25 (d, J = 8.0 Hz, 1H), 7.90–7.83 (m, 3H), 7.54–7.50 (m, 1H), 6.90 (s, 1H), 4.40 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H) ppm.^{13}C NMR (DMSO-d_6, 100 MHz) δ 174.0, 150.9, 139.4, 137.9, 132.9, 130.5, 130.4, 128.6, 127.8, 127.0, 126.4, 126.2, 124.8, 117.3, 105.9, 47.7, 14.4 ppm; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{17}H_{12}Cl_3NOSNa$: 405.9597; found: 405.9592.

4.3.9. N-(2-((1-Ethyl-4-oxo-1,4-dihydroquinolin-3-yl)thio)phenyl) benzamide (**3i**)

Purification by column chromatography (Hexanes/EtOAc, 1/1) as an orange solid (152 mg, 76% yield); mp = 203.1–204.6 °C; IR (neat): 3058, 2978, 1665, 1598, 1567, 1518, 1486, 1432, 1308, 763, 688 cm^{-1}.^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.41 (s, 1H), 8.82 (s, 1H), 8.28–8.24 (m, 3H), 7.91–7.89 (m, 1H), 7.84–7.78 (m, 2H), 7.66–7.58 (m, 4H), 7.48–7.45 (m, 1H), 7.38–7.34 (m, 1H), 7.14 (td, J = 7.6, 1.4 Hz, 1H), 4.42 (q, J = 7.1 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 175.6, 164.7, 149.3, 139.4 (2C), 139.1, 134.8, 134.4, 132.8, 131.8, 128.9, 128.6, 127.9, 127.6, 126.4, 125.4, 124.6, 124.4, 117.0, 113.4, 47.6, 14.4 ppm; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{24}H_{21}N_2O_2S$: 401.1318; found: 401.1314.

4.3.10. 3-(Benzo[d]thiazol-2-ylthio)-1-ethylquinolin-4(1H)-one (**3j**)

Purification by column chromatography (Hexanes/EtOAc, 1/1) as an orange solid (60 mg, 35% yield); mp = 118.3–120.5 °C; IR (neat): 3358, 3030, 2920, 1600, 1580, 1459, 1424, 1009, 760, 698 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.91 (s, 1H), 8.29 (dd, J = 8.0, 1.5 Hz, 1H), 7.92–7.84 (m, 3H), 7.82–7.80 (m, 1H), 7.55–7.51 (m, 1H), 7.45–7.41 (m, 1H), 7.32–7.27 (m, 1H), 4.45 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.8, 170.9, 153.9, 151.4, 139.3, 134.8, 133.0, 126.5, 126.5, 126.2, 124.9, 124.0, 121.5, 121.1, 117.2, 107.3, 47.6, 14.5 ppm; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{18}H_{15}N_2OS_2$: 339.0620; found: 339.0619.

4.3.11. 1-Ethyl-3-(propylthio)quinolin-4(1H)-one (**3k**)

Purification by column chromatography (Hexanes/EtOAc,1/1) as a yellow oil (41 mg, 33% yield); IR (neat): 3437, 2960, 2927, 1596, 1581, 1483, 1223, 1169, 868, 757, 698 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.27 (s, 1H), 8.21 (d, J = 8.0 Hz, 1H), 7.76–7.73 (m, 2H), 7.43–7.39 (m, 1H), 4.35 (q, J = 7.1 Hz, 2H), 2.78 (t, J = 7.1 Hz, 2H), 1.54–1.45 (m, 2H), 1.34 (t, J = 7.1 Hz, 3H), 0.94 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 174.5, 145.3, 138.8, 132.1, 126.1, 125.2, 123.7, 116.6, 113.4, 47.1, 33.6, 22.0, 14.4, 13.2 ppm; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{18}NOS$: 248.1104; found: 248.1102.

4.3.12. 1-Ethyl-3-(phenylselanyl)quinolin-4(1H)-one (**3l**)

Purification by column chromatography (Hexanes/EtOAc,3/2) as a white solid (155 mg, 95% yield); mp = 177.8–179.3 °C; IR (neat): 3032, 2980, 1617, 1598, 1579, 1471, 1366, 1171, 1087, 910, 770, 702 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.63 (s, 1H), 8.23–8.21 (m, 1H), 7.85–7.78 (m, 2H), 7.47 (ddd, J = 8.0, 6.2, 1.7 Hz, 1H), 7.31–7.27 (m, 2H), 7.15–7.11 (m, 2H), 4.39 (q, J = 7.1 Hz, 2H), 1.38 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 174.2, 150.0, 139.3, 136.7, 132.6, 129.6, 128.7, 127.8, 126.4, 126.2, 124.4, 117.0, 109.0, 47.4, 14.4 ppm; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{17}H_{15}NOSeNa$: 352.0211; found: 352.0212.

4.3.13. 1-Methyl-3-(p-tolylthio)quinolin-4(1H)-one (**3m**)

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a brown solid (140 mg, 99% yield); mp = 164.7–166.1 °C; IR (neat):2917, 2855, 1722, 1592,1469, 1279, 1154, 787, 756, 693 cm^{-1}.^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.53 (s, 1H), 8.20 (dd, J = 8.0, 1.6 Hz, 1H), 7.83–7.78 (m, 1H), 7.72 (d, J = 8.5 Hz, 1H), 7.49–7.45 (m, 1H), 7.08–7.03 (m, 4H), 3.89 (s, 3H), 2.22 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 174.4, 150.5, 140.4, 134.6, 133.9, 132.4, 129.4, 126.8, 126.0, 125.8, 124.3, 117.1, 110.0, 40.2, 20.5 ppm; HRMS (ESI): *m/z* [M+Na]+ calcd for C17H15NOSNa: 304.0767; found: 304.0770.

4.3.14. 1-Pentyl-3-(p-tolylthio)quinolin-4(1H)-one (**3n**)

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a brown solid (160 mg, 95% yield); mp = 83.1–85.9 °C; IR (neat): 2954, 2919, 2854, 1598, 1484, 1222, 1083, 847, 760, 697 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.51 (s, 1H), 8.22–8.20 (m, 1H), 7.81–7.75 (m, 2H), 7.46–7.42 (m, 1H), 7.07–7.03 (m, 4H), 4.32 (t, J = 7.2 Hz, 2H), 2.22 (s, 3H), 1.78–1.71 (m, 2H), 1.31–1.25 (m, 4H), 0.83 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 174.3, 149.8, 139.3, 134.7, 133.8, 132.4, 129.5, 126.9, 126.3, 126.1, 124.2, 117.0, 110.3, 52.1, 28.1, 28.0, 21.7, 20.5, 13.9 ppm; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{21}H_{23}NOSNa$: 360.1393; found: 360.1396.

4.3.15. 1-Isopropyl-3-(p-tolylthio)quinolin-4(1H)-one (**3o**)

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a white solid (94 mg, 60% yield); mp = 130.7–132.3 °C; IR (neat): 2976, 2919, 2852, 1574, 1542, 1488, 1463, 761, 695, 507 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.39–8.38 (m, 1H), 8.24 (dd, J = 7.9, 1.7 Hz, 1H), 7.96 (d, J = 7.2 Hz, 1H), 7.79 (ddd, J = 8.7, 6.9, 1.7 Hz, 1H), 7.47–7.44 (m, 1H), 7.08–7.06 (m, 4H), 5.09 (sep, J = 6.6 Hz, 1H), 2.23 (s, 3H), 1.49 (d, J = 6.5 Hz, 6H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 173.9, 144.0, 139.6, 134.8, 133.5, 132.4, 129.5, 127.2, 126.4, 126.0, 124.1, 116.3, 111.4, 50.6, 21.4, 20.4 ppm; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{19}H_{20}NOS$, 310.1260; found: 310.1266.

4.3.16. 1-Benzyl-3-(p-tolylthio)quinolin-4(1H)-one (**3p**)

Purification by column chromatography (Hexanes/EtOAc, 3/2) as a light yellow solid (178 mg, 99% yield); mp = 165.3–166.2 °C; IR (neat): 3031, 2915, 2861, 1622, 1596, 1481, 1227, 757, 693, 541 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.76 (s, 1H), 8.20 (dd, J = 8.0, 1.4 Hz, 1H), 7.69–7.62 (m, 2H), 7.43–7.33 (m, 3H), 7.30–7.24 (m, 3H), 7.12–7.07 (m, 4H), 5.62 (s, 2H), 2.24 (s, 3H) ppm.; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 174.4, 150.3, 139.6, 136.3, 134.8, 133.6, 132.4, 129.5, 128.9, 127.8, 127.0, 126.4, 126.3, 126.2, 124.4, 117.6, 111.0, 55.0, 20.5 ppm; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{23}H_{19}NOSNa$: 380.1080; found: 380.1081.

4.3.17. Ethyl 2-(4-oxo-3-(p-tolylthio)quinolin-1(4H)-yl)acetate (**3q**)

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a dark brown solid (114 mg, 65% yield); mp = 152.0–153.4 °C; IR (neat):3033, 2920, 1736, 1579, 1543, 1235, 796, 762, 691,511 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.53 (s, 1H), 8.21 (dd, J = 8.0, 1.6 Hz, 1H), 7.78–7.74 (m, 1H), 7.55 (d, J = 8.6 Hz, 1H), 7.48–7.44 (m, 1H), 7.09–7.05 (m, 4H), 5.30 (s, 2H), 4.18 (q, J = 7.1 Hz, 2H), 2.23 (s, 3H), 1.21 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 174.5, 168.0, 150.5, 140.1, 134.8, 133.4, 132.6, 129.5, 126.9, 126.2, 125.6, 124.4, 116.6, 110.9, 61.5, 52.7, 20.5, 14.0 ppm; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{20}H_{19}NO_3SNa$: 376.0978; found: 376.0979.

*4.3.18. 1-Ethyl-6,7-dimethoxy-3-(p-tolylthio)quinolin-4(1H)-one (**3r**)*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a brown solid in (147 mg, 83% yield); mp = 167.8–169.7 °C; IR (neat): 3045, 2919, 1723, 1580, 1488, 1254, 1079, 997, 899, 803, 579 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 8.41 (s, 1H), 7.57 (s, 1H), 7.10 (s, 1H), 7.10–7.01 (m, 4H), 4.37 (q, J = 7.1 Hz, 2H), 3.97 (s, 3H), 3.84 (s, 3H), 2.22 (s, 3H), 1.37 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 173.2, 153.2, 147.8, 147.0, 134.8, 134.4, 134.2, 129.4, 126.7, 120.2, 109.6, 105.7, 98.5, 56.2, 55.5, 47.4, 20.5, 14.5 ppm; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{20}H_{21}NO_3SNa$: 378.1134; found: 378.1138.

*4.3.19. 7-Chloro-1-ethyl-3-(p-tolylthio)quinolin-4(1H)-one (**3s**)*

Purification by column chromatography (Hexanes/EtOAc,1/1) as a light yellow solid (126 mg, 76% yield); mp = 150.0–151.0 °C; IR (neat): 3024, 2977, 2921, 1585, 1453, 1221, 1077, 887, 778, 677 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 8.53 (s, 1H), 8.19 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 1.6 Hz, 1H), 7.47 (dd, J = 8.6, 1.8 Hz, 1H), 7.09–7.04 (m, 4H), 4.36 (q, J = 7.1 Hz, 2H), 2.23 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 173.7, 149.6, 140.1, 137.6, 134.8, 133.3, 129.5, 128.5, 127.1, 124.7, 124.6, 116.5, 111.7, 47.4, 20.5, 14.4 ppm; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{18}H_{16}ClNOSNa$: 352.0533; found: 352.0537.

*4.3.20. 3-(p-Tolylthio)quinolin-4(1H)-one (**3t**)*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a light yellow solid (45 mg, 34% yield); mp. = 218.4–220.8 °C; IR (neat): 3055, 2993, 2914, 2858, 1623, 1556, 1502, 1347, 753, 688, 586 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 12.23 (d, J = 6.3 Hz, 1H), 8.30 (d, J = 6.4 Hz, 1H), 8.11 (dd, J = 8.1, 1.4 Hz, 1H), 7.72–7.68 (m, 1H), 7.61–7.59 (m, 1H), 7.40–7.36 (m, 1H), 7.12–7.01 (m, 4H), 2.23 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 174.8, 144.7, 139.7, 134.7, 133.7, 132.1, 129.5, 127.2, 125.4, 125.0, 124.0, 118.6, 110.7, 20.5 ppm; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{16}H_{13}NOSNa$: 290.0610; found: 290.0609.

*4.3.21. 2-Methyl-3-(p-tolylthio)quinolin-4(1H)-one (**3u**)*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a light yellow solid (22 mg, 16% yield); mp = 218.4–220.8 °C; IR (neat): 2921, 2853, 1724, 1489, 1472, 1342, 1145, 797, 754, 696, 581 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 12.09 (s, 1H), 8.05 (dd, J = 8.1, 1.5 Hz, 1H), 7.70–7.67 (m, 1H), 7.57–7.55 (m, 1H), 7.37–7.34 (m, 1H), 7.03–7.01 (m, 2H), 6.96–6.94 (m, 2H), 2.58 (s, 3H), 2.20 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 174.7, 155.4, 139.1, 134.3, 133.9, 132.0, 129.4, 125.9, 125.5, 124.0, 123.7, 117.9, 109.0, 20.4, 19.9 ppm; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{16}NOS$: 282.0947; found: 282.0945.

*4.3.22. 3-((4-Bromophenyl)thio)-1-ethylquinolin-4(1H)-one (**3v**)*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a yellow solid (154.2 mg, 86% yield); mp = 159.6–162.3 °C; IR (neat): 2918, 1616, 1593, 1485, 1223, 1084, 1006, 810, 756, 695 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 8.63 (s, 1H), 8.23–8.21 (m, 1H), 7.85–7.79 (m, 2H), 7.47 (ddd, J = 8.0, 6.5, 1.5 Hz, 1H), 7.43–7.40 (m, 2H), 7.08–7.05 (m, 2H), 4.39 (q, J = 7.1 Hz, 2H), 1.38 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 174.2, 149.9, 139.3, 137.3, 132.6, 131.5, 128.1, 126.4, 126.2, 124.4, 117.8, 117.0, 109.0, 47.4, 14.4 ppm; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{17}H_{14}BrNOSNa$: 381.9872; found: 381.9873.

*4.3.23. 1,3-Dimethyl-5-(phenylthio)pyrimidine-2,4(1H,3H)-dione (**5a**) [13]*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a white solid (102 mg, 82% yield); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.60 (s, 1H), 7.28–7.24 (m, 4H), 7.20–7.19 (m, 1H), 3.41 (s, 3H), 3.36 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.7, 151.5, 147.5, 135.1, 129.1, 128.7, 126.8, 106.0, 37.2, 28.6 ppm; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{12}H_{12}N_2O_2SNa$: 271.0512; found: 271.0516.

*4.3.24. 1,3-Dimethyl-5-(p-tolylthio)pyrimidine-2,4(1H,3H)-dione (**5b**) [13]*

Purification by column chromatography (Hexanes/EtOAc,1/1) as a yellow solid (115 mg, 87% yield); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.51 (s, 1H), 7.25–7.23 (m, 2H), 7.09–7.07 (m, 2H), 3.39 (s, 3H), 3.35 (s, 3H), 2.29 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.9, 151.6, 146.5, 137.4, 131.2, 130.0, 129.9, 107.4, 37.3, 28.7, 21.1 ppm; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{13}H_{14}N_2O_2SNa$: 285.0668; found: 285.0665.

*4.3.25. 5-((4-Methoxyphenyl)thio)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (**5c**) [13]*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a white solid (118 mg, 85% yield); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.39–7.35 (m, 3H), 6.84–6.80 (m, 2H), 3.76 (s, 3H), 3.37 (s, 3H), 3.33 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.8, 159.7, 151.5, 145.1, 133.3, 124.5, 114.9, 108.9, 55.4, 37.2, 28.6 ppm; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{13}H_{14}N_2O_3SNa$: 301.0617; found: 301.0612.

*4.3.26. 1,3-Dimethyl-5-((4-nitrophenyl)thio)pyrimidine-2,4(1H,3H)-dione (**5d**)*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a yellow solid (19 mg, 13% yield); mp = 185.5–186.4 °C; IR (neat): 3056, 2920, 1708, 1644, 1614, 1434, 1329, 1086, 851, 840, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.12–8.11 (m, 1H), 8.10–8.09 (m, 1H), 7.79 (s, 1H), 7.29–7.28 (m, 1H), 7.27–7.25 (m, 1H), 3.51 (s, 3H), 3.41 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.4, 151.5, 149.7, 146.0, 145.7, 126.5, 124.3, 102.6, 37.7, 29.0 ppm; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{12}H_{11}N_3O_4SNa$: 316.0362; found: 316.0368.

*4.3.27. 5-((4-Chlorophenyl)thio)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (**5e**) [13]*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a yellow solid (106 mg, 75% yield); ^1H NMR (400 MHz, $CDCl_3$):δ 7.65 (s, 1H), 7.24–7.17 (m, 4H), 3.42 (s, 3H), 3.35 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.7, 151.5, 148.0, 133.9, 132.9, 130.1, 129.3, 105.5, 37.4, 28.8 ppm; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{12}H_{11}ClN_2O_2SNa$: 305.0122; found: 305.0121.

*4.3.28. 5-((4-Bromophenyl)thio)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (**5f**)*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a white solid (99 mg, 61% yield); mp = 159.0–159.9 °C; IR (KBr): 3445, 3061, 3042, 1716, 1667, 1614, 1472, 1440,1342, 767 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.65 (s, 1H), 7.38–7.35 (m, 2H), 7.17–7.13 (m, 2H), 3.43 (s, 3H), 3.36 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.7, 151.6, 148.1, 134.7, 132.2, 130.3, 120.9, 105.4, 37.4, 28.8 ppm; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{12}H_{11}BrN_2O_2SNa$: 348.9617; found: 348.9618.

*4.3.29. 1,3-Dimethyl-5-((2,4,5-trichlorophenyl)thio)pyrimidine-2,4(1H,3H)-dione (**5g**)*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a yellow solid (86 mg, 49% yield); mp = 198.3–200.3 °C; IR (KBr): 3451, 3080, 3066, 2920, 1714, 1651, 1431, 1347, 1056, 766 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.76 (s, 1H), 7.44 (s, 1H), 7.07 (s, 1H), 3.49 (s, 3H), 3.40 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.4, 151.5, 149.7, 135.3, 132.4, 131.8, 131.3, 131.0, 129.2, 102.5, 37.7, 29.0 ppm; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{10}Cl_3N_2O_2S$: 350.9523; found: 350.9522.

*4.3.30. N-(2-((1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)thio)phenyl)benzamide (**5h**) [13]*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a white solid (138 mg, 76% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.52 (s, 1H), 8.29 (dd, J = 8.3, 1.3 Hz, 1H), 8.23–8.20 (m, 2H), 7.71 (s, 1H), 7.58–7.50 (m, 4H), 7.44–7.40 (m, 1H), 7.09 (td, J = 7.6, 1.4 Hz, 1H), 3.41 (s, 3H), 3.31 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.8, 163.2, 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 ppm; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{19}H_{17}N_3O_3SNa$: 390.0883; found: 390.0886.

*4.3.31. 5-(Benzo[d]thiazol-2-ylthio)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (**5i**) [13]*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as an orange solid (113 mg, 74% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.90 (s, 1H), 7.87–7.85 (m, 1H), 7.73–7.71 (m, 1H), 7.43–7.39 (m, 1H), 7.32–7.27 (m, 1H), 3.50 (s, 3H), 3.42 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.6, 161.2, 153.8, 151.5, 150.3, 135.8, 126.4, 124.8, 122.3, 121.1, 102.5, 37.7, 29.1 ppm; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{12}N_3O_2S_2$: 306.0365; found: 306.0369.

*4.3.32. 1,3-Dimethyl-5-(phenylselanyl)pyrimidine-2,4(1H,3H)-dione (**5j**) [13]*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a white solid (102 mg, 70% yield); ^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.50–7.47 (m, 2H), 7.41 (s, 1H), 7.27–7.23 (m, 3H), 3.35 (s, 3H), 3.34 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.0, 151.7, 147.5, 146.4, 132.8, 129.5, 127.9, 103.3, 37.2, 28.6 ppm; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{12}H_{12}N_2O_2SeNa$: 318.9956; found: 318.9953.

*4.3.33. 1,3-Diethyl-5-(p-tolylthio)pyrimidine-2,4(1H,3H)-dione (**5k**) [13]*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a yellow oil (139 mg, 95% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49 (s, 1H), 7.25–7.22 (m, 2H), 7.09–7.07 (m, 2H), 4.00 (q, J = 7.1 Hz, 2H), 3.80 (q, J = 7.2 Hz, 2H), 2.29 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.4, 150.8, 145.4, 137.3, 131.2, 130.0, 129.9, 107.7, 45.2, 37.4, 21.1, 14.5, 12.8 ppm; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{15}H_{18}N_2O_2SNa$: 313.0981; found: 313.0987.

*4.3.34. 1,3-Dibenzyl-5-(p-tolylthio)pyrimidine-2,4(1H,3H)-dione (**5l**) [13]*

Purification by column chromatography (Hexanes/EtOAc, 3/2) as a yellow solid (178 mg, 86% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50–7.45 (m, 2H), 7.40 (s, 1H), 7.38–7.32 (m, 3H), 7.31–7.22 (m, 5H), 7.21–7.16 (m, 2H), 7.06 (d, J = 7.9 Hz, 2H), 5.14 (s, 2H), 4.89 (s, 2H), 2.30 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.4, 151.4, 144.9, 137.4, 136.6, 135.0, 130.8, 130.1, 130.0, 129.4, 129.2, 128.7, 128.5, 128.2, 127.8, 108.6, 52.7, 45.5, 21.2 ppm; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{25}H_{22}N_2O_2SNa$: 437.1294; found: 437.1305.

*4.3.35. 1,3-Diethyl-6-methyl-5-(p-tolylthio)pyrimidine-2,4(1H,3H)-dione (**5m**)*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a light yellow solid (135 mg, 89% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.12–7.10 (m, 2H), 7.05–7.03 (m, 2H), 4.04–3.98 (m, 4H), 2.66 (s, 3H), 2.27 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H), 1.20 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.1, 157.1, 151.0, 136.1, 132.9, 129.9, 127.8, 105.7, 42.0, 37.7, 21.0, 18.5, 14.2, 12.8 ppm; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{16}H_{21}N_2O_2S$: 305.1318; found: 305.1321.

*4.3.36. 6-Chloro-1,3-dimethyl-5-(p-tolylthio)pyrimidine-2,4(1H,3H)-dione (**5n**) [13]*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a yellow solid (106 mg, 72% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27–7.25 (m, 2H), 7.07 (d, J = 8.0 Hz, 2H), 3.65 (s, 3H), 3.36 (s, 3H), 2.29 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.3, 152.0, 150.6, 137.3, 131.2, 130.0, 129.8, 107.5, 35.5, 29.5, 21.2; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{13}H_{13}ClN_2O_2SNa$: 319.0278; found: 319.0277.

*4.3.37. 6-Amino-1,3-dimethyl-5-(p-tolylthio)pyrimidine-2,4(1H,3H)-dione (**5o**) [12e]*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a white solid (169 mg, 61% yield); ^{1}H (DMSO-d_6, 400 MHz): δ 7.26 (s, 2H), 7.07–7.00 (m, 4H), 3.36 (s, 3H), 3.32 (s, 3H), 2.23 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 161.1, 157.6, 150.8, 134.4, 134.1, 129.4, 125.5, 74.9, 28.2, 20.4 ppm; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{16}N_3O_2S$, 278.0958; found: 278.0958.

*4.3.38. 5-(p-Tolylthio)pyrimidine-2,4(1H,3H)-dione (**5p**) [21]*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a light yellow solid (28 mg, 24% yield); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.36 (s, 1H), 11.32 (d, J = 6.0 Hz, 1H), 7.84 (d, J = 6.0 Hz, 1H), 7.16–7.01 (m, 4H), 2.24 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 162.2, 151.2, 148.1, 135.2, 132.8, 129.6, 127.1, 103.0, 20.4 ppm; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{11}H_{10}N_2O_2SNa$: 257.0355; found: 257.0359.

*4.3.39. 6-Chloro-3-methyl-5-(p-tolylthio)pyrimidine-2,4(1H,3H)-dione (**5q**)*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a light yellow solid (96 mg, 68% yield); mp = 218.0–220.8 °C; IR (KBr): 3448, 3042, 2917, 2895, 1717, 1654, 1588, 1012, 759, 452 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.88 (s, 1H),7.14–7.09 (m, 4H), 3.15 (s, 3H), 2.26 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 160.8, 150.5, 149.8, 135.2, 132.0, 129.6, 126.7, 101.9, 27.8, 20.4 ppm; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{12}H_{11}ClN_2O_2SNa$: 305.0122; found: 305.0124.

*4.4. Typical experimental procedure for the one-pot conversion to sulfones: synthesis of compounds **6** and **7***

Following the typical procedure for the synthesis of compounds **3** and **5**, after the reaction mixture was stirred at 60 or 80 °C for 12–16 h, the resulting mixture was cooled down to room temperature and *m*-CPBA (172 mg, 1.0 mmol, 2 equiv) was added. The reaction mixture was stirred for an additional 2–6 h. Upon completion, saturated $Na_2S_2O_3$ (5 mL) and distilled deionized H_2O (10 mL) was added, and the mixture was extracted with ethyl acetate (3 × 25 mL). The combined organic layer was washed with saturated NaCl, saturated $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by SiO_2 column chromatography to afford the desired thioether products.

*4.4.1. 1-Ethyl-3-tosylquinolin-4(1H)-one (**6**)*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a white solid (98 mg, 60% yield); mp = 145.4–147.5 °C; IR (KBr): 3417, 3071, 3051, 2972, 1631, 1609, 1289, 1140, 698, 667, 543 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.88 (s, 1H), 8.14 (dd, J = 8.0, 1.5 Hz, 1H), 7.92–7.81 (m, 4H), 7.52–7.48 (m, 1H), 7.37 (d, J = 8.1 Hz, 2H), 4.51 (q, J = 7.1 Hz, 2H), 2.36 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.3, 147.4, 143.9, 139.6, 138.9, 134.0, 129.6, 128.4, 128.2, 126.4, 125.9, 119.5, 118.1, 48.9, 21.5, 14.8 ppm; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{18}H_{17}NO_3SNa$: 328.1002; found: 328.1015.

*4.4.2. 1,3-Dimethyl-5-tosylpyrimidine-2,4(1H,3H)-dione (**7**)*

Purification by column chromatography (Hexanes/EtOAc, 1/1) white solid (130 mg, 88% yield); mp = 132.4–134.9 °C; IR (KBr):

3414, 3289, 3068, 2952, 1725, 1672, 1660, 1627, 1303, 608 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.70 (s, 1H), 7.84 (d, $J = 8.3$ Hz, 2H), 7.40 (d, $J = 8.0$ Hz, 2H), 3.44 (s, 3H), 3.06 (s, 3H), 2.38 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.3, 150.7, 150.2, 144.0, 137.5, 129.3, 127.9, 111.9, 37.4, 27.5, 21.0 ppm; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{13}H_{14}N_2O_4SNa$: 317.0566; found: 317.0568.

Acknowledgments

This work was supported by Thailand Research Fund (RSA6280024 and DBG6080007), the Center of Excellence for Innovation in Chemistry (PERCH-CIC), Ministry of Higher Education, Science, Research and Innovation, Central Instrument Facility (CIF), Faculty of Science, Mahidol University, and the Royal Golden Jubilee Ph.D. Program for supporting student scholarship to D.B. (Grant No. PHD/0141/2560).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2019.130537.

References

[1] For selected references, see: (a) Organosulfur chemistry I, in: P.C.B. Page (Ed.), Topics in Current Chemistry, vol. 204, Springer, Berlin, 1999;
(b) Organosulfur chemistry II, in: P.C.B. Page (Ed.), Topics in Current Chemistry, vol. 205, Springer, Berlin, 1999;
(c) L.A. Damani (Ed.), Sulphur-containing Drugs and Related Organic Compounds, Wiley, New York, 1989;
(d) J. Clayden, P. MacLellan, Beilstein J. Org. Chem. 7 (2011) 582;
(e) A. Casini, J.-Y. Winum, J.-L. Montero, A. Scozzafava, C.T. Supuran, Bioorg. Med. Chem. Lett 13 (2003) 837;
(f) M. Mellah, A. Voituriez, E. Schulz, Chem. Rev. 107 (2007) 5133;
(g) A.R. Murphy, J.M. Fréchet, Chem. Rev. 107 (2007) 1066;
(h) J.O. Jeppesen, M.B. Nielsen, J. Becher, Chem. Rev. 104 (2004) 5115.

[2] For selected reviews and examples, see: (a) M.E. Peach, in: S. Patai (Ed.), The Chemistry of the Thiol Group, John Wiley & Sons, London, 1979, pp. 721–756;
(b) L.A. Damani, in: Sulfur-Containing Drugs and Related Organic Compounds: Chemistry, Biochemistry, and Toxicology, vol. 1, Ellis Horwood Ltd., Chichester, UK, 1989. Part B: Metabolism of Sulfur Functional Groups;
(c) S. Oae (Ed.), Organic Sulfur Chemistry: Structure and Mechanism, CRC Press, Boca Raton, 1991;
(d) R.J. Cremlyn, in: An Introduction to Organosulfur Chemistry, Wiley & Sons, New York, 1996;
(e) M.D. McReynolds, J.M. Doughtery, P.R. Hanson, Chem. Rev. 104 (2004) 2239;
(f) J. Zhao, X. Jiang, Chin. Chem. Lett. 29 (2018) 1079;
(g) P. Chauhan, S. Mahajan, D. Enders, Chem. Rev. 114 (2014) 8807.

[3] For selected references, see: (a) T. Kondo, T. Mitsudo, Chem. Rev. 100 (2000) 3205;
(b) F.J.A. Hundscheid, V.K. Tandon, P.H.A.M. Rouwette, A.M. van Leusen, Tetrahedron 43 (1987) 5073;
(c) J. Malmstrom, V. Gupta, L. Engman, J. Org. Chem. 63 (1998) 3318;
(d) P. Blanchard, B. Jousselme, P. Frere, J. Roncali, J. Org. Chem. 67 (2002) 3961;
(e) B.C. Ranu, R. Jana, Adv. Synth. Catal. 347 (2005) 1811;
(f) Y. Nishimoto, A. Okita, M. Yasuda, A. Baba, Org. Lett. 14 (2012) 1846;
(g) J.T. Reeves, K. Camara, Z.S. Han, Y. Xu, H. Lee, C.A. Busacca, C.H. Senanayaka, Org. Lett. 16 (2014) 1196;
(h) I.P. Beletskaya, V.P. Ananikov, Chem. Rev. 111 (2011) 1596.

[4] For selected references, see: (a) C. Shen, P. Zhang, Q. Sun, S. Bai, T.S.A. Hor, X. Liu, Chem. Soc. Rev. 44 (2015) 291;
(b) S. Ranjit, R. Lee, D. Heryadi, C. Shen, J.-E. Wu, P. Zhang, K.-W. Huang, X. Liu, J. Org. Chem. 76 (2011) 8999;
(c) T. Gensch, F.J.R. Klauck, F. Glorius, Angew. Chem. Int. Ed. 55 (2016) 11287;
(d) X. Wang, R. Qiu, C. Yan, V.P. Reddy, L. Zhu, X. Xu, S.-F. Yin, Org. Lett. 17 (2015) 1970;
(e) L. Chen, P. Liu, J. Wu, B. Dai, Tetrahedron 74 (2018) 1513;
(f) Y. Ding, W. Wu, W. Zhao, Y. Li, P. Xie, Y. Huang, Y. Liu, A. Zhou, Org. Biomol. Chem. 14 (2016) 1428;
(g) S.K.R. Parumala, R.K. Peddinti, Green Chem. 17 (2015) 4068;
(h) X. Zhu, Y. Yang, G. Xiao, J. Song, Y. Liang, G. Deng, Chem. Commun. 53 (2017) 11917.

[5] For selected examples, see: (a) M. Hadjeri, E.-L. Peiller, C. Beney, N. Deka, M.A. Lawson, C. Dumontet, A. Boumendjel, J. Med. Chem. 47 (2004) 4964;
(b) S. Nakamura, M. Kozuka, K.F. Bastow, H. Tokuda, H. Nishino, M. Suzuki, J. Tatsuzaki, S.M. Natschke, S.-C. Kuo, K.-H. Lee, Bioorg. Med. Chem. 13 (2005) 4396;
(c) V. Cecchetti, C. Parolin, S. Moro, T. Pecere, E. Filipponi, A. Calistri, O. Tabarrini, B. Gatto, M. Palumbo, A. Fravolini, G. Palu, J. Med. Chem. 43 (2000) 3799;
(d) M. Sato, T. Motomura, H. Aramaki, T. Matsuda, M. Yamashita, Y. Ito, H. Kawakami, Y. Matsuzaki, W. Watanabe, K. Yamataka, S. Ikeda, E. Kodama, M. Matsuoka, H. Shinkai, J. Med. Chem. 49 (2006) 1506;
(e) R.M. Cross, A. Monastyrskyi, T.S. Mutka, J.N. Burrows, D.E. Kyle, R. Manetsch, J. Med. Chem. 53 (2010) 7076.

[6] For selected references, see: (a) A. Pałasz, D. Cież, Eur. J. Med. Chem. 97 (2015) 582;
(b) C. Chen, D. Wu, Z. Guo, Q. Xie, G.J. Reinhart, A. Madan, J. Wen, T. Chen, C.Q. Huang, M. Chen, Y. Chen, F.C. Tucci, M. Rowbottom, J. Pontillo, Y.-F. Zhu, W. Wade, J. Saunders, H. Bozigian, R.S. Struthers, J. Med. Chem. 51 (2008) 7478;
(c) W.B. Parker, Chem. Rev. 109 (2009) 2880;
(d) T. Pathak, Chem. Rev. 102 (2002) 1623;
(e) C. Zhi, Z.-Y. Long, A. Manikowski, N.C. Brown, P.M. Tarantino, K. Holm, E.J. Dix, G.E. Wright, K.A. Foster, M.M. Butler, W.A. LaMarr, D.J. Skow, I. Motorina, S. Lamothe, R. Storer, J. Med. Chem. 48 (2005) 7063;
(f) R. Saladino, C. Crestini, A.T. Palamara, M.C. Danti, F. Manetti, F. Corelli, E. Garaci, M. Botta, J. Med. Chem. 44 (2001) 4554;
(g) F. Medda, R.J.M. Russell, M. Higgins, A.R. McCarthy, J. Campbell, A.M.Z. Slawin, D.P. Lane, S. Lain, N.J. Westwood, J. Med. Chem. 52 (2009) 2673.

[7] For selected references, see: (a) G.R. Newkome, W.W. Pandler, in: Contemporary Heterocyclic Chemistry, Wiley, New York, 1982;
(b) G.S. Bisacchi, J. Med. Chem. 58 (2015) 4874;
(c) N.F. Smith, W.D. Figg, A. Sparreboom, Drug Dev. Res. 62 (2004) 233;
(d) L. Wicke, J.W. Engels, Bioconjug. Chem. 23 (2012) 627;
(e) H. Cahová, L. Havran, P. Brázdilová, H. Pivoňková, R. Pohl, M. Fojta, M. Hocek, Angew. Chem. Int. Ed. 47 (2008) 2059.

[8] C. Xia, Z. Wei, Y. Yang, W. Yu, H. Liao, C. Shen, P. Zhang, Chem. Asian J. 11 (2016) 360.

[9] T. Guo, Synth. Commun. 47 (2017) 2053.

[10] P. Ghosh, A.K. Nandi, G. Chhetri, S. Das, J. Org. Chem. 83 (2018) 12411.

[11] For our recent work, see: (a) A. Thupyai, C. Pimpasri, S. Yotphan, Org. Biomol. Chem. 16 (2018) 424;
(b) S. Toonchue, L. Sumunnee, K. Phomphrai, S. Yotphan, Org. Chem. Front. 5 (2018) 1928;
(c) T. Kittikool, A. Thupyai, K. Phomphrai, S. Yotphan, Adv. Synth. Catal. 360 (2018) 3345;
(d) M. Noikham, T. Kittikool, S. Yotphan, Synthesis 50 (2018) 2337;
(e) L. Sumunnee, C. Pimpasri, M. Noikham, S. Yotphan, Org. Biomol. Chem. 16 (2018) 2697;
(f) L. Sumunnee, C. Buathongjan, C. Pimpasri, S. Yotphan, Eur. J. Org. Chem. (2017) 1025;
(g) D. Beukeaw, K. Udomsasporn, S. Yotphan, J. Org. Chem. 80 (2015) 3447;
(h) K. Phakdeeyothin, S. Yotphan, Org. Biomol. Chem. 17 (2019) 6432.

[12] For previous reports on thiolation of uracil, see: (a) N. Probst, R. Lartia, O. Théry, M. Alami, E. Defrancq, S. Messaoudi, Chem. Eur J. 24 (2018) 1795;
(b) F. Botha, M. Slavíčková, R. Pohl, M. Hocek, Org. Biomol. Chem. 14 (2016) 10018;
(c) J.-Y. Lee, P.H. Lee, J. Org. Chem. 73 (2008) 7413;
(d) M. Wang, J. Wei, Q. Fan, X. Jiang, Chem. Commun. 53 (2017) 2918;
(e) A. Jana, A.K. Panday, R. Mishra, T. Parvin, L.H. Choudhury, ChemistrySelect 2 (2017) 9420;
(f) W.-P. Fang, Y.-T. Cheng, Y.-R. Cheng, Y.-J. Cherng, Tetrahedron 61 (2005) 3107.

[13] M. Noikham, S. Yotphan, Eur. J. Org. Chem. (2019) 2759.

[14] For additional screening experiments and substrate preparation, see supplementary data for more information.

[15] For some uracil substrates, a catalytic amount of iodine worked well.

[16] A.D. Hudwekar, P.K. Verma, J. Kour, S. Balgotra, S.D. Sawant, Eur. J. Org. Chem. (2019) 1242.

[17] (a) H. Wang, Y. Li, Q. Lu, M. Yu, X. Bai, S. Wang, H. Cong, H. Zhang, A. Lei, ACS Catal. 9 (2019) 1888;
(b) Y. Liu, Y. Hu, Z. Cao, X. Zhan, W. Luo, Q. Liu, C. Guo, Adv. Synth. Catal. 361 (2019) 1084;
(c) K.D. Mane, A. Mukherjee, K. Vanka, G. Suryavanshi, J. Org. Chem. 84 (2019) 2039;
(d) R. Semwal, C. Ravi, R. Kumar, R. Meena, S. Adimurthy, J. Org. Chem. 84 (2019) 792;
(e) S.A. Rather, A. Kumar, Q.N. Ahmed, Chem. Commun. 55 (2019) 4511.

[18] (a) B. Hu, P. Zhou, Q. Zhang, Y. Wang, S. Zhao, L. Lu, S. Yan, F. Yu, J. Org. Chem. 83 (2018) 14978;
(b) B. Hu, Q. Zhang, S. Zhao, Y. Wang, L. Xu, S. Yan, F. Yu, Adv. Synth. Catal. 361 (2019) 49.

[19] Y. Zheng, Y. He, G. Rong, X. Zhang, Y. Weng, K. Dong, X. Xu, J. Mao, Org. Lett. 17 (2015) 5444.

[20] S.-Y. Zhao, H.-R. Tan, L. Wang, J.-N. Zhu, Z.-H. Yang, Synthesis 50 (2018) 4113.

[21] K. Anzai, J. Heterocycl. Chem. 16 (1979) 567.

[22] P. Bichovski, T.M. Haas, D. Kratzert, J. Streuff, Chem. Eur J. 21 (2015) 2339.

[23] H. Ishiyama, H. Nakajima, H. Nakata, J. Kobayashi, Bioorg. Med. Chem. 17 (2009) 4280.