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RESEARCH ARTICLE

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C-O and C-S coupling reaction of 1,2-di(pyrimidin-2-yl) disulfides with phenols/thiophenols promoted by copper(I) chloride

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Abstract

An efficient protocol for C-O and C-S bonds formation by the cross-coupling reaction of 1,2-di(pyrimidin-2-yl) disulfides with phenols/thiophenols promoted by copper(I) chloride was established. It was discovered that variously substituted di(hetero)aryl disulfides and phenols were well tolerated. This strategy is the conversion of disulfides into hetero-aryl ethers and thioethers by a copper-promoted chemoselective C-S bond cleavage of disulfides.

1 | INTRODUCTION

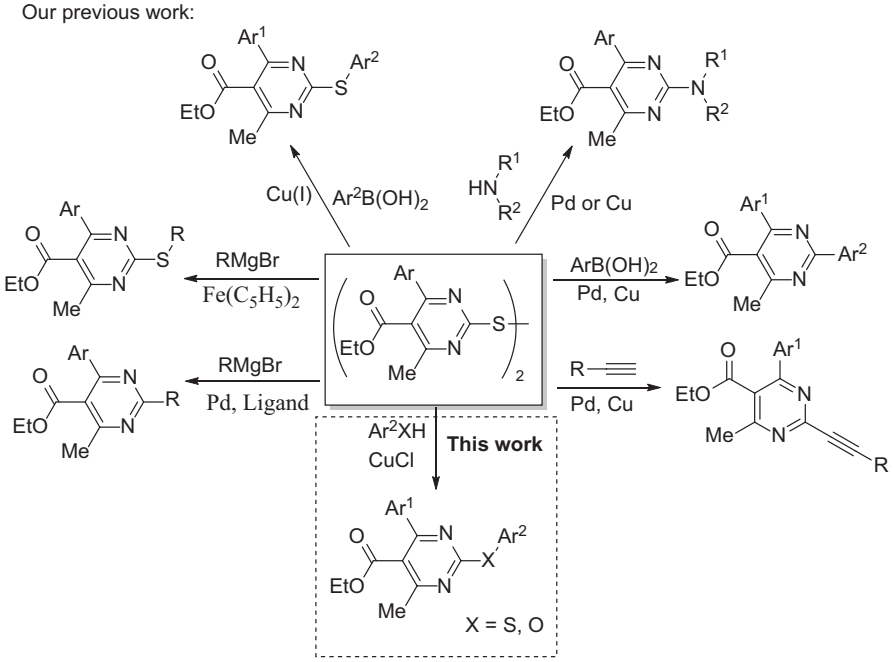
Diaryl ethers and thioethers are the ubiquitous scaffolds in natural, pharmaceutical, agrochemical, and fine organic chemicals, and particularly, heterobiaryl ether frameworks containing a *N*-hetero-ring are found in pharmaceutically relevant compounds such as Sorafenib, XK469, Tafenoquine, and AMG900. [1] It has been informed that one-half of the small molecules approved by the U.S. Food and Drug Administration (FDA) are heterocyclic and contain at least 1 nitrogen. Therefore, the discovery and development of new synthetic methodologies for C-O and C-S bonds formation have played an important role in organic chemistry.[2] Usually, copper-catalyzed Ullmann reaction has been extensively used for the synthesis of ethers involving phenols and aryl halides, it often suffers from harsh reaction conditions such as higher temperatures (>125-220°C), stronger bases.[3]

Transition metal-catalyzed C-O/C-S cross-coupling reaction has become a significant methodology for the formation of ethers and thioethers through the reaction of electrophilic aryl halides with nucleophilic phenols/aryl thiols including the copper-mediated or catalyzed Chan–Lam–Evans type Ar–B/Ar–OH couplings.[4]

In addition to the use of aryl halides, which synthesis often involves tedious steps, harsh reaction conditions, and waste production, sulfonates,[5] nitroarenes[6], aromatic esters,[7] and others as alternative electrophiles were introduced into the C-O cross-coupling chemistry.

Di(hetero)aryl disulfides are widely used as electrophiles instead of aryl halides for the construction of C-S bond through S-S bond cleavage,[8] because that disulfides are structurally symmetrical, air stable, and easy to handle.[9] Recently, we developed a series of method to construct C-C, C-N, and C-S bonds through C-S and S-S bonds cleavage of di(hetero)aryl disulfides with various nucleophiles including aryl boronic acids, alkynes, Grignard reagents, and amines.[10] The obtained products tetra-substituted pyrimidines display wide pharmacological and biological properties[11] In continuation of our work in the formation of the C-C and C-Z (Z = O, N, S) bond utilizing 1,2-di(pyrimidin-2-yl) disulfide as an electrophile, we investigated the C-O and C-S coupling of the di(hetero)aryl disulfides with phenol and aryl thiol using CuCl to obtain oxylated and sulfenylated pyrimidines (Scheme 1).

We have reported the synthesis of 2-phenolic pyrimidines by C-S and C-O cross-coupling reaction of pyrimidin-2-yl sulfonates with aryl thiols and phenols.[12] Alternatively, we have developed an efficient preparation of 2-arylated pyrimidines by the Mitsunobu reaction between 2-hydroxypyrimidine and phenols. [12b] Compared pyrimidin-2-yl sulfonates from Biginelli 3,4-dihydropyrimidine-2(1H)-ones *via* 2-step procedures of oxidation/esterification, di(hetero)aryl disulfides were easily available from Biginelli 3,4-dihydropyrimidine-2(1H)-thiones by one-step reaction.

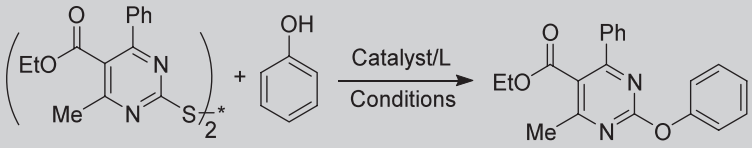


SCHEME 1 Synthesis of the tetra-substituted pyrimidines from 1,2-di(pyrimidin-2-yl) disulfides

2 | RESULT AND DISCUSSION

Recently, we reported that CuCl[10e] and $Cu(OAc)_2{\cdot}H_2O$ (20 mol%)/NaAsc (30 mol%)[13] catalyst systems promoted the C-N cross-coupling reaction of di(hetero)aryl disulfides and aryl halides with amines or amides. So, we tested the CuCl and $CuSO_4{\cdot}H_2O$ (100 mol%)/NaAsc (200 mol%) promoter systems in the C-O coupling of 1,2-di(pyrimidin-2-yl) disulfides **1a** and phenol **2a** (Table 1). We found that CuCl gave a good yield of the product **3a** (61%) in the presence of K_3PO_4 as a base; however, $CuSO_4{\cdot}H_2O$/NaAsc system only obtained **3a** in a yield of 35%. Other tested conditions could not obviously improve the reaction yield (entries 3-8). For examples, CuI and 2-OHPhCOOCu facilitated the formation of product **3a** albeit with low yield, respectively (entries 3-4). No desired product was detected in the

TABLE 1 Optimization of reaction conditions for the C-O coupling of di(pyrimidin-2-yl) disulfide and phenol[a]



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

Entry	Cat. (eq.)	Base (equiv)	Temp. (°C)	Time (h)	Solvent	Yield[b] (%)
1	$CuSO_4$ (1.0)/NaAsc (2.0)	K_3PO_4 (3.0)	80	12	Xylene	35
2	CuCl (1.0)	K_3PO_4 (3.0)	80	12	Xylene	61
3	CuI (1.0)	K_3PO_4 (3.0)	80	12	Xylene	56
4	*o*-OHC_6H_4COOCu (1.0)	K_3PO_4 (3.0)	80	12	Xylene	38
5	-	K_3PO_4 (3.0)	80	12	Xylene	-
6	CuCl (1.0)	K_3PO_4 (3.0)	80	24	Dioxane	28
7	CuCl (0.5)	K_3PO_4 (3.0)	80	12	Xylene	45
8	CuCl (1.5)	K_3PO_4 (3.0)	80	12	Xylene	65
9	CuCl (1.0)	K_3PO_4 (3.0)	140	12	Xylene	76
10	CuCl (1.0)	K_3PO_4 (3.0)	140	24	Xylene	77

NaAsc = L-ascorbic acid sodium salt.

[a]Catalytic conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), solvent (3 mL), under a N_2 atmosphere.

[b]Isolated yield based on disulfide **1a** (based on both pyrimidine groups from one molecule).

absence of promoter, but the starting material **1a** was recovered (entry 5). Lowering or enhancing the loading of CuCl could not improve the obtained product (entries 7-8). Notably, when the reaction was carried out at a high temperature 140°C, the product **3a** was isolated in 76%-77% yield (entries 9-10).

To test the scope of the C-O coupling reaction, the phenols **2a-h** were reacted with **1a** under the optimized conditions (Scheme 2) and the yields of the obtained products are shown in Scheme 2. In general, good yields (67%-75%) of the desired products **3a-g** were obtained from phenols when the aryl group containing either an electron-withdrawing (Cl, Br) or an electron-donating (Me) group. However, moderate yield (37%) of the desired ether derivative **3h** was obtained when employed 2,4-dichlorophenol **2h**.

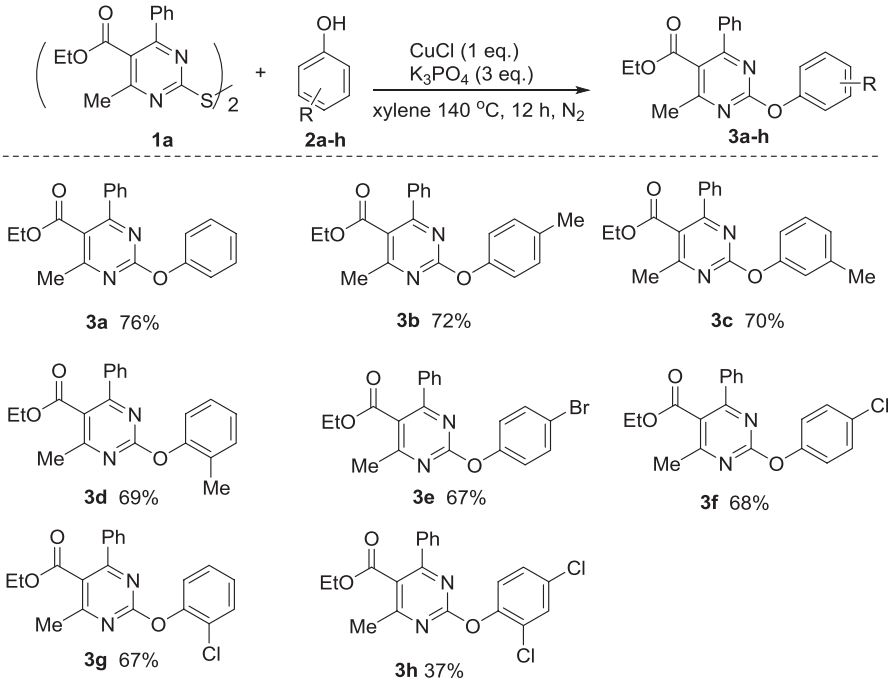
To further expand the scope of the nucleophilic coupling partners, we explored the C-S couplings of the disulfides **1** with 4-methoxybenzenethiol **4a**. These C-S coupling reactions smoothly proceeded under the optimal reaction conditions to give the desired products (Scheme 3). Various pyrimidine functionalized-disulfides (**1a-f**) were suitable partners for the coupling reaction giving the C-S cross-coupling products (**5a-g**) in good yields. Notably, couplings of 4-fluoro-, 4-chloro-, 4-bromo-, 4-methyl-, and 4-nitrophenyl substituted disulfides proceeded with **4a** to yield the C-S coupling products in good yields (**5a-g**). The process also tolerated a variety of steric and electronic changes to thiophenols such as 4-chloro-, 4-bromo-, and 4-methyl-substituted thiophenols to deliver the products **5h-i** in good yields of 52%-59%.

Unfortunately, some limitations were noted in case of diaryl disulfides; such as 2,2′-dithiodipyridine and diphenyl disulfide (treated with phenol **2a**) were unreactive. Likewise, the reaction of **1a** with some strong electron-withdrawing group-substituted phenols (nitrophenol) or alkyl alcohols such as 2-propanol or benzyl alcohol were also failed to achieve the desired product, but the starting materials were recovered (Figure 1). Compared with the active 1,2-di(pyrimidin-2-yl) disulfides, the diaryl disulfides were relatively unactive and failed to coupling with phenol to give the corresponding products.

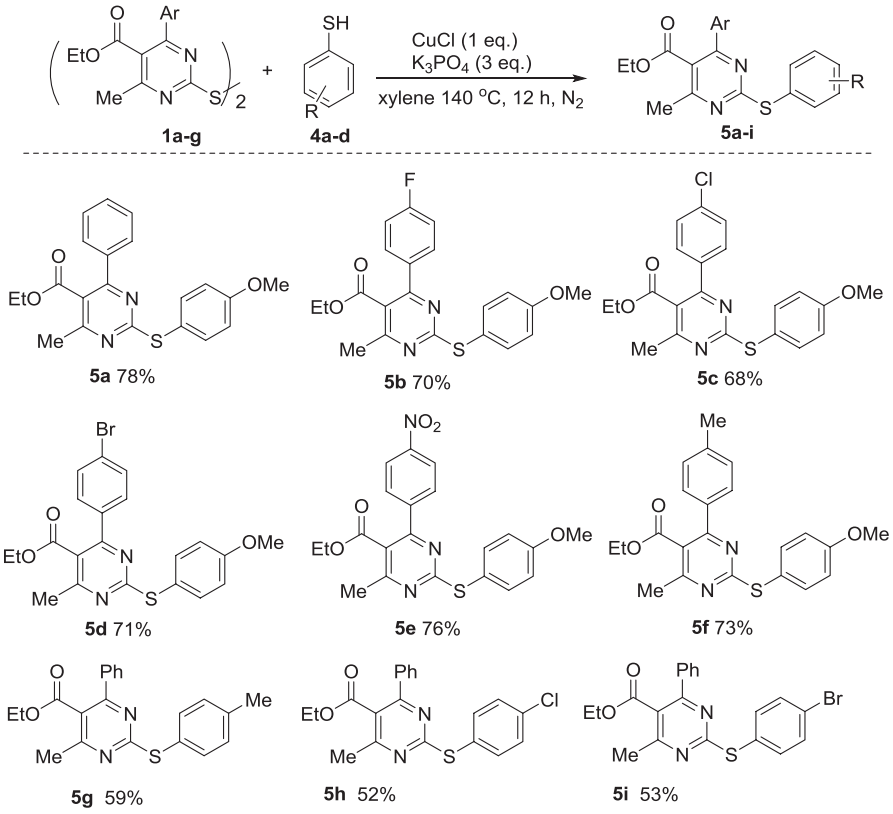
Finally, we proposed a possible mechanism for the C-O/C-S coupling reaction described in Scheme 4. It can be informed that pyrimidine-containing disulfides are more efficient than aryl disulfides in the reaction due to the coordination of a soft basic N-atom to the copper salt promoting C-S activation to give the intermediate **A**. Subsequently, the complex **A** reacts with phenol producing the intermediate species **B**, which subsequently undergoes reductive cleavage of the C-S bond giving the C-O coupling product **3a**. [10b-f]

3 | CONCLUSIONS

In summary, we developed an efficient method for C-O and C-S cross-coupling reaction of 1,2-di(pyrimidin-2-yl) disulfides with phenols and thiophenols via Cu-promoted C-S bond cleavage of disulfides. The use of promoter CuCl was necessary for efficient formation of the C-O and C-S bond in this reaction in a homogeneous system heightens the overall efficiency of the given synthesis.



SCHEME 2 Scope of disulfides (**1a**) and phenol in the C-O cross-coupling reaction



SCHEME 3 Scope of disulfides (**1a**) and thiophenol in the C-S cross-coupling reaction

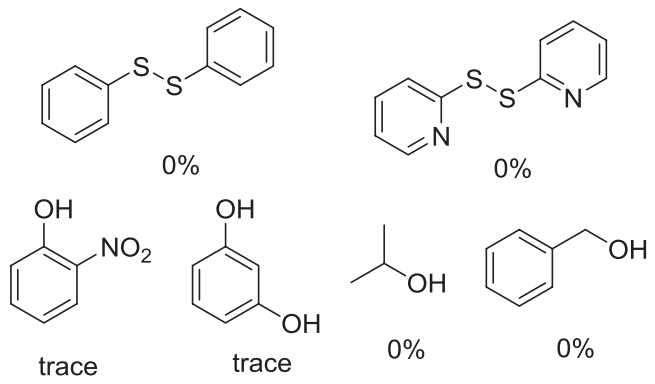


FIGURE 1 Limitations of the C-O coupling of disulfides with alcohols. Reaction conditions are those of Table 1

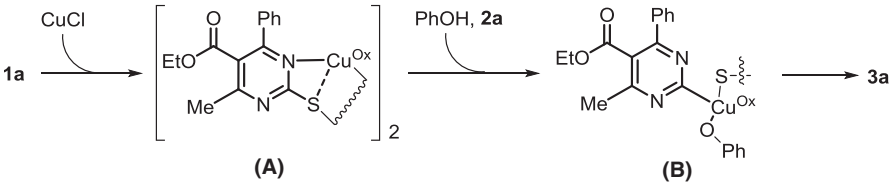
4 | EXPERIMENTAL

4.1 | General procedure for the synthesis of C-S coupling products

Under an atmosphere of nitrogen, disulfide **1a** (0.2 mmol), phenol **2a** (0.6 mmol), CuCl (0.2 mmol), and K_3PO_4 (0.6 mmol) were added to an oven-dried Schlenk tube. The tube was stoppered and degassed with nitrogen 3 times. Water-free xylene (3 mL) was added by syringe, and the mixture was stirred for 12 hours at 140°C, and the reaction was monitored by TLC analysis. Then, the reaction was quenched by adding into NH_4Cl aqueous and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with aqueous NH_4Cl, NaOH (5%), and then brine, dried over $MgSO_4$, filtered, and the volatiles were removed in vacuum. The residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether 1:30) to give the corresponding products.

4.2 | Ethyl 4-methyl-2-phenoxy-6-phenylpyrimidine-5-carboxylate (3a)

Colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.59 (d, J = 7.2 Hz, 2H), 7.46-7.36 (m, 5H), 7.27-7.20 (m, 3H), 4.18 (q, J = 7.2 Hz, 2H), 2.57 (s, 3H), 1.06 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ = 169.14, 168.05, 166.59, 163.94, 152.82, 137.30, 130.26, 129.33, 128.39,



SCHEME 4 Possible mechanism for the C-O coupling reaction of disulfide **1a** with phenol **2a**

128.35, 125.17, 121.56, 121.04, 77.24, 77.03, 76.82, 61.77, 22.73, 13.60 ppm. EI-MS: *m/z* = 334 (M^+).

4.3 | Ethyl 4-methyl-6-phenyl-2-(4-tolyloxy) pyrimidine-5-carboxylate (3b)

Colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.59 (d, *J* = 7.2 Hz, 2H), 7.45-7.39 (m, 3H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 2.56 (s, 3H), 2.37 (s, 3H), 1.06 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ = 169.07, 168.10, 166.61, 164.06, 150.57, 137.37, 134.68, 130.21, 129.83, 128.37, 128.35, 121.21, 120.92, 77.20, 76.98, 76.77, 61.74, 22.73, 20.88, 13.59 ppm. EI-MS: *m/z* = 348 (M^+).

4.4 | Ethyl 4-methyl-6-phenyl-2-(3-tolyloxy) pyrimidine-5-carboxylate (3c)

Colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.61-7.59 (m, 2H), 7.44-7.39 (m, 3H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 7.8 Hz, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 2.57 (s, 3H), 2.38 (s, 3H), 1.06 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ = 169.11, 168.10, 166.63, 164.01, 152.76, 139.50, 137.32, 130.25, 129.00, 128.39, 128.35, 125.97, 122.04, 120.98, 118.52, 77.21, 77.00, 76.79, 61.79, 22.71, 21.38, 13.60 ppm. EI-MS: *m/z* = 348 (M^+).

4.5 | Ethyl 4-methyl-6-phenyl-2-(2-tolyloxy) pyrimidine-5-carboxylate (3d)

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57 (d, *J* = 8.0 Hz, 2H, ArH), 7.46-7.37 (m, 2H, ArH), 7.28-7.22 (m, 2H, ArH), 7.18-7.11 (m, 2H, ArH), 4.18 (q, *J* = 8.0 Hz, 2H, CH_2), 2.55 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 1.06 (t, *J* = 8.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.14, 168.15, 166.62, 163.87, 151.35, 137.34, 131.10, 130.55, 130.21, 128.37, 128.35, 126.80, 125.44, 121.86, 120.82, 61.76, 22.74, 16.44, 13.61; EI-MS: *m/z* = 348 (M^+); Anal. Calcd for $C_{21}H_{20}N_2O_3$: C, 72.40; H, 5.79; N, 8.04. Found: C, 72.37; H, 5.75; N, 8. 02.

4.6 | Ethyl 2-(4-bromophenoxy)-4-methyl-6-phenylpyrimidine-5-carboxylate (3e)

Colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.58 (d, *J* = 7.2 Hz, 2H), 7.50 (d, *J* = 9.0 Hz, 2H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 2.57 (s, 3H), 1.06 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ = 169.28, 167.92, 166.73, 163.52, 151.79, 137.04, 132.35 (d, *J* = 19.7 Hz), 130.45, 128.49, 128.31, 123.41, 121.38, 118.19, 117.29, 61.92, 22.67, 13.60. EI-MS: *m/z* = 412 (M^+), 414 (M + 2).

4.7 | Ethyl 2-(4-chlorophenoxy)-4-methyl-6-phenylpyrimidine-5-carboxylate (3f)

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.58 (d, *J* = 8.0 Hz, 2H, ArH), 7.44-7.34 (m, 5H, ArH), 7.18 (d, *J* = 8.0 Hz, 2H, ArH), 4.17 (q, *J* = 8.0 Hz, 2H, CH_2), 2.56 (s, 3H, CH_3), 1.05 (t, *J* = 8.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.05, 167.68, 166.48, 163.43, 151.10, 136.92, 130.26, 130.19, 129.20, 129.07, 128.25, 128.12, 122.77, 121.15, 116.57, 61.65, 22.47, 13.39. EI-MS: *m/z* = 368 (M^+); Anal. Calcd for $C_{20}H_{17}ClN_2O_3$: C, 65.13; H, 4.65; N, 7.60. Found: C, 65.07; H, 4.60; N, 7. 61.

4.8 | Ethyl 2-(2-chlorophenoxy)-4-methyl-6-phenylpyrimidine-5-carboxylate (3g)

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.49 (d, *J* = 4.0 Hz, 2H, ArH), 7.38-7.27 (m, 4H, ArH), 7.20-7.06 (m, 2H, ArH), 7.11-7.07 (m, 1H, ArH), 4.09 (q, *J* = 8.0 Hz, 2H, CH_2), 2.47 (s, 3H, CH_3), 0.97 (t, *J* = 8.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.21, 167.91, 166.50, 163.27, 148.88, 137.15, 130.28, 128.32, 128.30, 127.70, 127.33, 126.44, 123.70, 121.24, 61.73, 22.64, 13.55. EI-MS: *m/z* = 368 (M^+); Anal. Calcd for $C_{20}H_{17}ClN_2O_3$: C, 65.13; H, 4.65; N, 7.60. Found: C, 65.08; H, 4.61; N, 7.62. HRMS (ESI): calculated for $C_{20}H_{17}ClN_2O_3$: $[M+H]^+$ 369.1000; found: 369.0998.

4.9 | Ethyl 2-(2,4-dichlorophenoxy)-4-methyl-6-phenylpyrimidine-5-carboxylate (3h)

White solid, m.p. = 88-89°C. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.56 (d, *J* = 7.8 Hz, 2H), 7.47 (s, 1H), 7.44 (t, *J* = 6.8 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.27 (d, *J* = 9.0 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 2.55 (s, 3H), 1.05 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ = 169.40, 167.86, 166.63, 163.02, 147.64, 137.01, 131.28, 130.38, 130.13, 128.43, 128.33, 127.96, 124.60, 121.52, 77.21, 77.00, 76.79, 61.87, 22.70, 13.60 ppm. EI-MS: *m/z* = 402 (M^+), 404 (M + 2).

4.10 | Ethyl 2-(4-methoxyphenylthio)-4-methyl-6-phenylpyrimidine-5-carboxylate (5a)

Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.46 (q, *J* = 8.0 Hz, 4H, ArH), 7.29 (t, *J* = 8.0 Hz, 3H, ArH), 6.87 (d, *J* = 12.0 Hz, 2H, ArH), 4.05 (q, *J* = 8.0 Hz, 2H, CH_2), 3.76 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 0.96 (t, *J* = 8.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.67, 168.09, 165.78, 163.46, 160.41, 137.37, 136.91, 130.06, 128.34, 128.29, 121.27, 121.27, 114.48, 109.71, 61.67, 55.30, 22.57, 13.56. EI-MS: *m/z* = 380 (M^+); Anal. Calcd for $C_{21}H_{20}N_2O_3S$: C, 66.29; H, 5.30; N, 7.36. Found: C, 66.22; H, 5.28; N, 7. 33.

4.11 | Ethyl 4-(4-fluorophenyl)-2-(4-methoxyphenylthio)-6-methylpyrimidine-5-carboxylate (5b)

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.54 (t, *J* = 8.0 Hz, 4H, ArH), 7.05 (t, *J* = 8.0 Hz, 2H, ArH), 6.95 (d, *J* = 8.0 Hz, 2H, ArH), 4.19 (q, *J* = 8.0 Hz, 2H, CH_2), 3.84 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 1.10 (t, *J* = 8.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.78, 168.04, 165.88, 162.15, 160.51, 136.96, 130.55, 130.46, 121.06, 115.53, 115.32, 114.52, 61.77, 55.32, 31.89, 22.57, 13.67. EI-MS: *m/z* = 398 (M^+); Anal. Calcd for $C_{21}H_{19}FN_2O_3S$: C, 63.30; H, 4.81; N, 7.03. Found: C, 63.27; H, 4.79; N, 7.01.

4.12 | Ethyl 4-(4-chlorophenyl)-2-(4-methoxyphenylthio)-6-methylpyrimidine-5-carboxylate (5c)

White solid, m.p. 35-37°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.53 (d, *J* = 8.0 Hz, 2H, ArH), 7.46 (d, *J* = 8.0 Hz, 2H, ArH), 7.34 (d, *J* = 8.0 Hz, 2H, ArH), 6.95 (d, *J* = 12.0 Hz, 2H, ArH), 4.19 (q, *J* = 8.0 Hz, 2H, CH_2), 3.85 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 1.11 (t, *J* = 8.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.89, 167.90, 165.98, 162.08, 160.50, 136.95, 136.44, 129.73, 128.57, 121.06, 119.89, 114.50, 61.81, 55.31, 31.88, 22.59, 13.66. EI-MS: *m/z* = 414 (M^+); Anal. Calcd for $C_{21}H_{19}ClN_2O_3S$: C, 60.79; H, 4.62; N, 6.75. Found: C, 60.73; H, 4.58; N, 6. 69.

4.13 | Ethyl 4-(4-bromophenyl)-2-(4-methoxyphenylthio)-6-methylpyrimidine-5-carboxylate (5d)

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55-7.44 (m, 6H, ArH), 6.73 (d, *J* = 8.0 Hz, 2H, ArH), 4.13 (q, *J* = 8.0 Hz, 2H, CH_2), 3.69 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 1.04 (t, *J* = 8.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.10, 167.54, 166.43, 162.83, 160.27, 136.11, 133.69, 131.69, 130.02, 127.20, 125.04, 122.25, 114.51, 61.97, 55.30, 22.59, 13.65. EI-MS: *m/z* = 458 (M^+); Anal. Calcd for $C_{21}H_{19}BrN_2O_3S$: C, 54.91; H, 4.17; N, 6.10. Found: C, 54.87; H, 4.12; N, 5.98.

4.14 | Ethyl 2-(4-methoxyphenylthio)-4-methyl-6-(4-nitrophenyl)pyrimidine-5-carboxylate (5e)

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.23 (d, *J* = 8.0 Hz, 2H, ArH), 7.67 (d, *J* = 8.0 Hz, 2H, ArH), 7.53 (d, *J* = 8.0 Hz, 2H, ArH), 6.96 (d, *J* = 8.0 Hz, 2H, ArH), 4.19 (q, *J* = 8.0 Hz, 2H, CH_2), 3.86 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 1.09 (t, *J* = 8.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.45, 167.26, 166.56, 161.25, 160.64, 148.60, 143.48, 136.95, 129.39, 123.42, 121.36, 119.50, 114.60, 62.00, 55.33, 22.76, 13.66; EI-MS: *m/z* = 425 (M^+); Anal. Calcd for $C_{21}H_{19}N_3O_5S$: C, 59.28; H, 4.50; N, 9.88. Found: C, 59.22; H, 4.47; N, 9. 86.

4.15 | Ethyl 2-(4-methoxyphenylthio)-4-methyl-6-*p*-tolylpyrimidine-5-carboxylate (5f)

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55 (d, *J* = 12.0 Hz, 2H, ArH), 7.42 (d, *J* = 8.0 Hz, 2H, ArH), 7.16 (d, *J* = 8.0 Hz, 2H, ArH), 6.94 (d, *J* = 8.0 Hz, 2H, ArH), 4.19 (q, *J* = 8.0 Hz, 2H, CH_2), 3.85 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 1.10 (t, *J* = 8.0 Hz, 3H, CH_3); EI-MS: *m/z* = 394 (M^+); Anal. Calcd for $C_{22}H_{22}N_2O_3S$: C, 66.98; H, 5.62; N, 7.10. Found: C, 66.96; H, 5.60; N, 7.08.

4.16 | Ethyl 4-methyl-6-phenyl-2-(4-tolylthio)pyrimidine-5-carboxylate (5g)

White solid, m.p. = 64-66°C. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.52 (d, *J* = 8.0 Hz, 4H), 7.41 (t, *J* = 7.2 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 2.49 (s, 3H), 2.39 (s, 3H), 1.04 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.33, 168.04, 165.76, 163.46, 139.10, 137.37, 135.03, 130.02, 129.6, 128.30, 125.88, 121.34, 61.64, 22.54, 21.28, 13.55 ppm. EI-MS: *m/z* = 364 (M^+).

4.17 | Ethyl 2-((4-chlorophenyl)thio)-4-methyl-6-phenylpyrimidine-5-carboxylate (5h)

White solid, m.p. = 41-43°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 7.6 Hz, 2H), 7.35-7.30 (m, 5H), 4.08 (q, *J* = 7.2 Hz, 2H), 2.43 (s, 3H), 0.97 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.66, 168.14, 166.26, 163.90, 137.47, 136.66, 135.58, 130.47, 129.34, 128.64, 128.57, 128.27, 121.98, 77.58, 77.27, 76.95, 62.02, 22.80, 13.84 ppm. EI-MS: *m/z* = 384 (M^+), 386 (M + 2).

4.18 | Ethyl 2-((4-bromophenyl)thio)-4-methyl-6-phenylpyrimidine-5-carboxylate (5i)

White solid, m.p. = 59-61°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 5.6 Hz, 6H), 7.28 (d, *J* = 7.2 Hz, 3H), 4.05 (d, *J* = 7.2 Hz, 2H), 2.40 (s, 3H), 0.93 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.24, 167.86, 166.00, 163.63, 137.20, 136.58, 136.39, 132.02, 130.20, 129.07, 128.67, 128.38, 128.31, 123.53, 121.75, 77.32, 77.00, 76.68, 61.74, 22.53, 13.57 ppm. EI-MS: *m/z* = 428 (M^+), 430 (M + 2).

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