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Nano copper oxide mediated ligand-free C–S cross-coupling and concomitant oxidative aromatization of 4-aryl-3,4-dihydropyrimidin-2(1*H*)-thione with diaryliodonium salts

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ABSTRACT

A wide range of Biginelli 4-aryl-3,4-dihydropyrimidin-2(1*H*)-thiones undergo ligand-free C–S cross-coupling with diaryliodonium triflates in the presence of CuO nanoparticles with the concomitant oxidative aromatization to form highly substituted 2-(thioaryl)pyrimidine. The nano CuO catalyst can be recycled and reused three times without any significant loss of catalytic activity.

Aryl sulfides are structural motifs found in many biological and pharmaceutically active compounds and have been used as important intermediates in several organic transformations.[1] The transition metal (Pd, Cu, Ni, Co, and Fe) catalyzed cross-coupling reactions of aryl halides with appropriate thiols are generally a method of choice for the construction of a C(aryl)–S bond.[2] Recently, the advent of nanostructured transition metals has been considered as a sustainable and competitive alternative to conventional catalysis.[3] This is due to the high surface areas and rich exposed active sites of the nano-catalysts which enhance catalytic efficiency, thereby requiring lower loading of catalyst. Additionally, the insolubility of nano-catalysts in reaction solvents imparts the advantages of heterogeneous catalysis such as simplified isolation of the product along with easy recovery and recyclability of the catalysts. As a result, intensive work has recently been reported for the C(aryl)–S cross-coupling reactions of iodoarenes with thiols to form diaryl sulfides using various nanoparticle size catalysts such as CuI,[4] $CuFe_2O_4$,[5] and CuO[6] and In_2O_3.[7]

Biginelli 3,4-dihydropyrimidine-2(1*H*)-one (DHPM) is a privileged heterocyclic scaffold exhibiting a wide range of pharmacological properties such as calcium channel blockers, hepatitis B virus replication inhibitors, mitotic kinesin inhibitors, and α_{1a}-adrenergic receptor antagonists.[8] Owing to this remarkable pharmacological profile, the recent decade has witnessed a considerable growth in the decoration of all the six positions of DHPMs (N1, C2, N3, C4, C5, and C6) to produce low molecular weight 'drug like' compounds.[9] As the original Biginelli reaction is carried out by a three-component condensation of ethyl acetoacetate, aldehyde, and urea or thiourea, the C2 position of DHPMs is always either with carbonyl or thiocarbonyl functional groups. The C2 position of DHPMs with thiocarbonyl functional group has been synthetically manipulated (Fig. 1) by (i) reaction with alkyl halide to produce 1,4-dihydropyrimidine[10] followed by oxidative aromatization using (diacetoxyiodo)benzene, CAN, $Mn(OAc)_3$, and MnO_2 to form pyrimidine,[11] (ii) reaction of alkyne or doubly electrophilic building block like α-halo ketone to furnish fused pyrimidines,[12] (iii) oxidative aromatization to form disulfide,[13] and (iv) desulfitative Liebeskind–Srogl coupling of arylboronic acid or aryltributyltin to form 2-arylation product.[14] The C–S cross-coupling of 3,4-dihydropyrimidin-2(1*H*)-thione with aryl halide is a relatively less investigated reaction in the literature.

Among the various cross-coupling reactions, there is a great synthetic challenge for C–S bond formation due to the susceptibility of sulfur for oxidative dimerization and its tendency to bind with metal which causes the modification or deactivation of the catalyst.[15] In contrast to aryl sulfides, the methods for the synthesis of heterocyclic sulfides including pyrimidine moiety are very limited. The 3,4-dihydropyrimidine-2(1*H*)-thione can be considered as the structural analog of cyclic thiourea and therefore, we were intrigued with the possibility of C–S cross-coupling reaction with a suitable arylating agent. Moreover, only a few reports have

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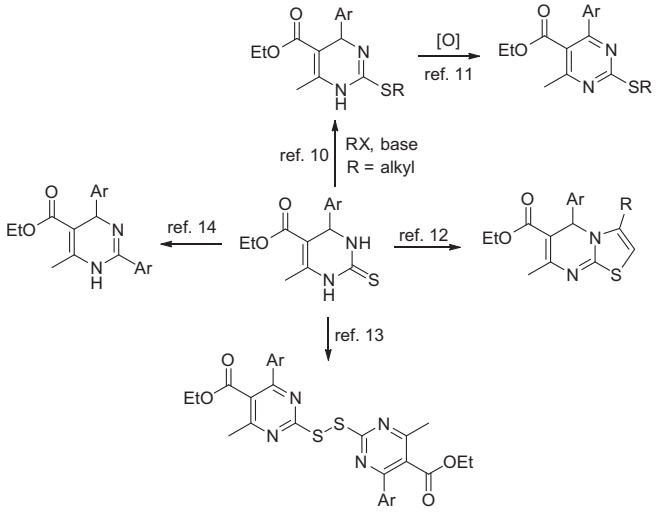
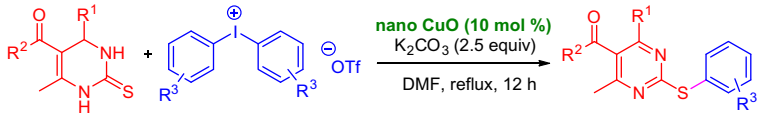


Figure 1. Decoration of 3,4-dihydropyrimidine-2(1*H*)-thione via functionalization at the C-2 position.

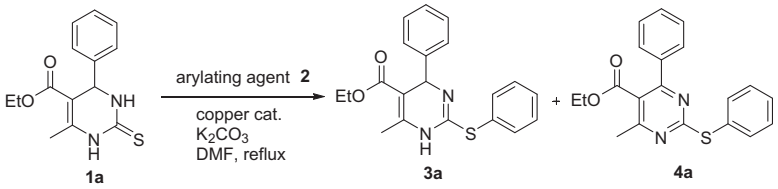
appeared describing the coupling of thiocarbonyl functional groups with aryl halides.[16] To date, there is only one example in the literature for C–S cross-coupling of 3,4-dihydropyrimidine-2(1*H*)-thione with phenylboronic acid using stoichiometric $Cu(OAc)_2$ under microwave conditions (45 min) to form 2-thiophenyl-1,4-dihydropyrimidine.[14a] Recently, a diaryliodonium salt has gained a renewed interest in various C–C, C–N, C–O, and C–S coupling reactions as a more reactive version of iodobenzene.[17] It has been explored in the C–S cross-coupling reactions of aromatic and aliphatic thiols using $Pd(PPh_3)_4$.[18] Here, we report our studies on the C–S cross-coupling reaction of 3,4-dihydropyrimidine-2(1*H*)-thione with a diaryliodonium salt using CuO nano-catalyst under ligand-free conditions. It was observed that 3,4-dihydropyrimidine-2(1*H*)-thione undergoes C–S cross-coupling with a symmetrical diaryliodonium salt with concomitant oxidative aromatization to form highly functionalized 2-thioarylpyrimidine derivatives (Scheme 1).

The optimum conditions for the S-arylation of 4-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione (**1a**) were investigated by screening of appropriate arylating agents and copper catalysts in DMF using K_2CO_3 as the base. The results are summarized in Table 1. The initial attempts of utilizing iodobenzene for arylation of **1a** using various copper catalysts such as $Cu(OAc)_2$, $CuCl_2$, CuI, and nano CuO (entries 1–6) resulted in poor yields (0–27%) of 2-phenylthio-1,4-dihydropyrimidine **3a**. Therefore, we used diphenyliodonium salts as arylating agents for the tentative C–S cross-coupling using different copper catalysts (entries 7–15). In the absence of copper catalyst, C(aryl)–S coupling of **1a** with diphenyliodonium salts did not take place (entries 7 and 12). When the same coupling reaction was examined with diphenyliodonium chloride (entry 8) using CuI (10 mol %), the formation of **3a** and aromatized 2-(phenylthio)pyrimidine **4a**, respectively, took place in 17% and 46% yields. Other catalysts such as $Cu(OAc)_2$ and $CuCl_2$ were found to be inferior for the C–S cross-coupling of diphenyliodonium chloride with **1a** (entries 9 and 10). Screening of nano CuO as a catalyst revealed that the yield of aromatized pyrimidine **4a** was much higher than CuI with negligible formation of **3a** (entry 11). Further



Scheme 1. C–S cross-coupling and concomitant oxidative aromatization of 4-aryl-3,4-dihydropyrimidine-2(1*H*)-thione.

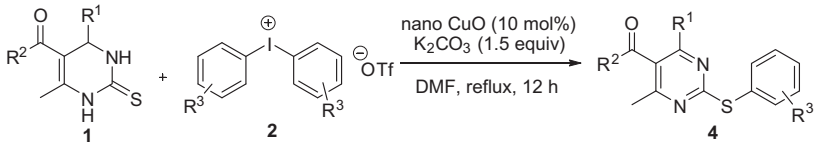
Table 1
Optimization of reaction conditions for C–S cross-coupling of 4-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione with arylating agents[a]

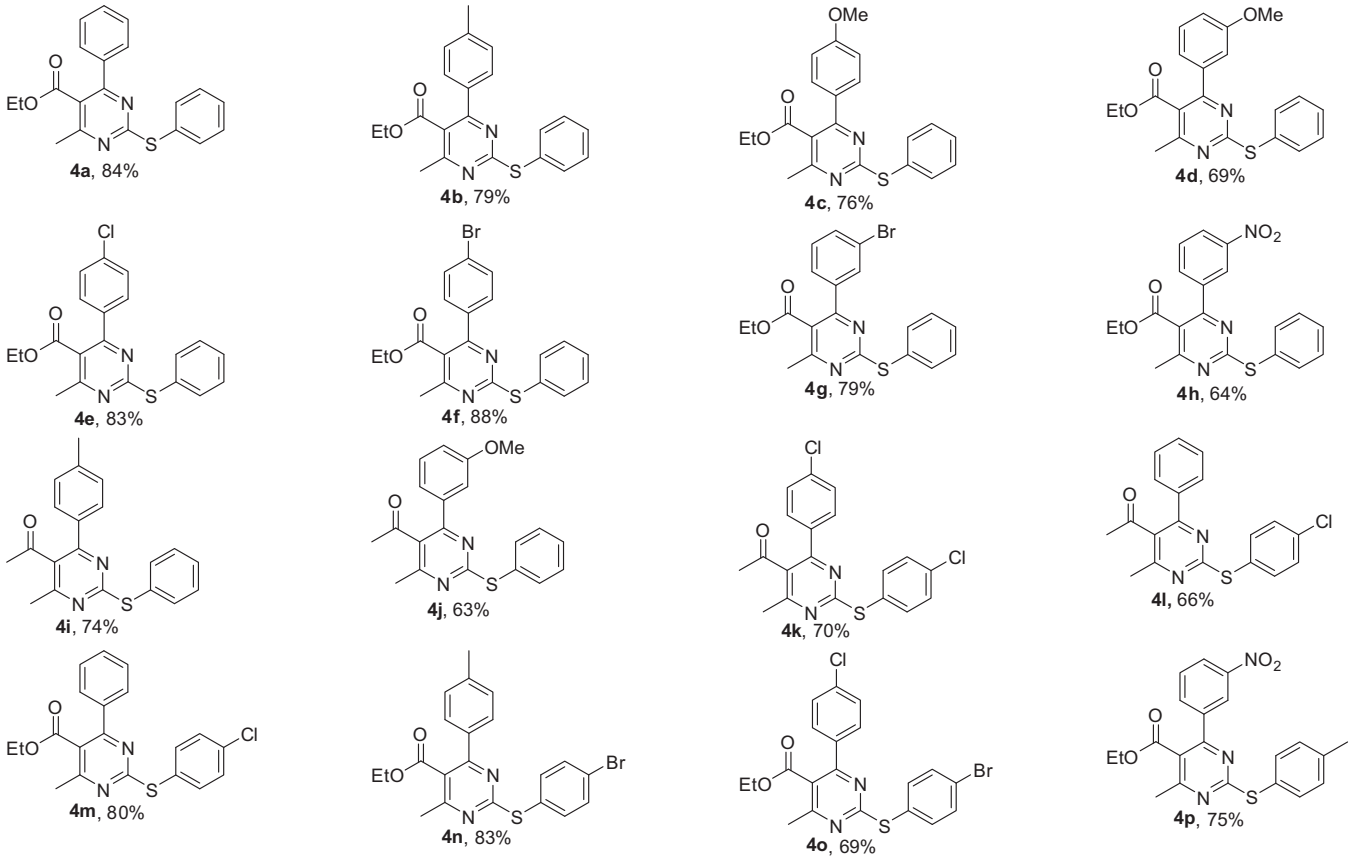


Entry	Arylating agent	Copper catalyst (mol %)	Yield **3a** (%)	Yield **4a** (%)	Time (h)
1	PhI	$Cu(OAc)_2$ (10 mol %)	00	00	24
2	PhI	$CuCl_2$ (10 mol %)	00	00	24
3	PhI	CuI (10 mol %)	14	00	24
4	PhI	CuI (20 mol %)	23	00	24
5	PhI	CuO nano (10 mol %)	18	00	24
6	PhI	CuO nano (20 mol %)	27	00	24
7	Ph_2ICl	—	00	00	24
8	Ph_2ICl	CuI (10 mol %)	17	46	12
9	Ph_2ICl	$Cu(OAc)_2$ (10 mol %)	21	00	24
10	Ph_2ICl	$CuCl_2$ (10 mol %)	00	00	24
11	Ph_2ICl	CuO nano (10 mol %)	14	58	24
12	Ph_2IOTf	—			08
13	Ph_2IOTf	CuO nano (10 mol %)	12	67	12
14[b]	Ph_2IOTf	CuO nano (10 mol %)	00	84	08
15	Ph_2IBF_4	CuO nano (10 mol %)	16	63	12

[a] Reaction conditions unless otherwise stated: Arylating agent (1 equiv), K_2CO_3 (1.5 equiv), catalyst, DMF (10 mL).
[b] Ar_2IOTf (1.5 equiv), K_2CO_3 (2.5 equiv), catalyst, DMF (10 mL).

Table 2
Cross-coupling of 3,4-dihydropyrimidine-2(1*H*)-thione with diphenyl iodonium triflates[a]





[a] Reaction conditions: 3,4-Dihydropyrimidine-2(1*H*)-thione (1 mmol), diaryliodonium triflate (1.5 mmol), CuO nanoparticle (0.025 mmol), and K_2CO_3 (2.5 mmol) in 10 mL DMF under reflux for 12 h.

studies were also carried out about the influence of different counter anions of diphenyliodonium salts (entries 12–15), which showed that satisfactory results could be obtained with diphenyliodonium triflates, resulting in the formation of aromatized pyrimidine **4a** in good yields. However, 1.5 equiv of diphenyliodonium triflates with respect to **1a** were required for the exclusive formation of aromatized **4a** in 84% excellent yield (entry 14). Therefore, the optimized conditions for C–S cross-coupling of **1a** employed nano CuO (10 mol %), diphenyliodonium triflate (1.5 equiv), and K_2CO_3 (2.5 equiv) in DMF for the exclusive formation of aromatized **4a**.[19]

With the successful optimization results in hand, we moved on to investigate the scope of the process in terms of the reaction of various 4-aryl-3,4-dihydropyrimidine-2(1*H*)-thiones with diphenyliodonium triflates (Table 2). A wide variety of 4-aryl-3,4-dihydropyrimidine-2(1*H*)-thiones derived from ethyl acetoacetate (entries **4a**–**h** and **4m**–**p**) and acetyl acetone (entries **4i**–**l**) with differently substituted aromatic ring at the C4 position were employed for C–S cross-coupling reaction with diphenyliodonium triflates. As can be seen, in all the cases excellent yields of highly functionalized 2-(thioaryl)pyrimidine were obtained and all the products were characterized by IR, NMR and mass spectrometry.[20]

To the best of our knowledge, this is the first kind of report on the one-pot synthesis of biologically and synthetically important 2-(thioaryl)pyrimidine from readily accessible 4-aryl-3,4-dihydropyrimidine-2(1*H*)-thione.

Various symmetrical diaryliodonium salts were also examined in C–S cross-coupling with 4-aryl-3,4-dihydropyrimidine-2(1*H*)-thione (entries **4k**–**p**). The protocol is tolerant to the presence of electron-donating and withdrawing functional groups of symmetrical diaryliodonium salts. The reaction of unsymmetrical iodonium salts with **1** resulted in a mixture of 2-(thioaryl)pyrimidines due to the transfer of both the aryl groups on sulfur (Supplementary data).

As nano CuO is a heterogeneous catalyst, the recyclability of the catalyst in this coupling reaction was examined. To facilitate the catalyst recovery, the model C–S cross-coupling reaction of diphenyliodonium triflate with 4-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione was carried out on 5 mmol scale. After each cycle, the catalyst was recovered by simple centrifugation, washing with deionized water and ethanol, and then drying in vacuo. The separated catalyst was again reused for C–S cross-coupling and this was repeated three times. In these cases, the yield of **4a** was found to be 87%, 79%, and 73% in successive three times use.

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In summary, we have developed a facile one-pot CuO nanoparticle catalyzed ligand-free C–S cross-coupling of diaryliodonium salts with 4-aryl-3,4-dihydropyrimidine-2(1*H*)-thione to furnish highly functionalized 2-(phenylthio)pyrimidine which are biologically and synthetically important scaffolds. It is a unique example of CuO nanoparticle catalysis for a C–S cross-coupling reaction of thiocarbonyl functional groups of DHPMs with concomitant oxidative aromatization to produce pyrimidine. This method also offers significant advantages such as operational simplicity with a recyclable catalytic system. This is also a first report of a C–S cross-coupling reaction of diaryliodonium salts using a copper based catalytic system.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.131.

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19. *General procedure for C–S cross-coupling of 4-aryl-3,4-dihydropyrimidin-2(1H)-thione with symmetrical diaryliodonium triflates*: CuO nano particles (mean particle size, 33 nm, surface area, 29 m^2/g, and purity, 99.99%) were purchased from Sigma Aldrich. A mixture of 4-aryl-3,4-dihydropyrimidin-2(1*H*)-thione (1.5 mmol), diaryliodonium triflates (2.25 mmol), K_2CO_3 (2.5 mmol), nano CuO (10 mol %) was refluxed in DMF (10 mL) for the appropriate time (8–12 h) till the consumption of starting material took place. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. After completion of reaction, water (10 mL) and EtOAc (10 mL) were added and the organic layers were separated. The combined organic layers were dried on anhydrous Na_2SO_4 followed by the evaporation of the solvent to obtain the crude product, which was purified by column chromatography on silica gel using petroleum ether/EtOAc 9:1 as eluent to give desired products in excellent purity.
20. *Spectral data for all the compounds: Ethyl 4-methyl-6-phenyl-2-(phenylthio)pyrimidine-5-carboxylate* (***4a***): Yellow solid, mp 87–88 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 1.06 (3H, t, J = 6.8 Hz, CH_3), 2.51 (3H, s, CH_3), 4.16 (2H, q, J = 7.2 Hz, CH_2), 7.38–7.43 (4H, m, ArH), 7.51 (2H, d, J = 8 Hz, ArH), 7.65 (2H, d, J = 7.2 Hz, ArH). ^{13}C NMR 100 MHz ($CDCl_3$): δ 13.63, 22.62, 61.80, 121.49, 128.39, 128.42, 128.95, 129.10, 129.46, 130.21, 135.22, 137.34, 163.57, 165.95, 168.12, 172.10. IR (cm^{-1}): 3059, 2980, 1718, 1524, 1215, 686. HRMS (ESI) Calcd for $C_{20}H_{18}N_2O_2S$ (M+H) 351.10890. Found: 351.19550.
Ethyl 4-methyl-2-(phenylthio)-6-p-tolylpyrimidine-5-carboxylate (***4b***): White solid, mp 62–63 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 1.10 (3H, t, J = 7.12 Hz, CH_3), 2.35 (3H, s, CH_3), 2.49 (3H, s, CH_3), 4.20 (2H, q, J = 7.12 Hz, CH_2), 7.16 (2H, d, J = 8 Hz), 7.38–7.43 (5H, m, ArH), 7.63–7.65 (2H, m, ArH). ^{13}C NMR 100 MHz ($CDCl_3$): δ 13.74, 21.41, 22.61, 61.80, 121.26, 128.42, 128.92, 129.05, 129.14, 129.54, 134.40, 135.26, 140.63, 163.30, 165.75, 168.36, 171.94. IR (cm^{-1}): 3058, 2922, 1715, 1609, 1524, 1222, 832, 687. HRMS (ESI) Calcd for $C_{21}H_{20}N_2O_2S$ (M+H) 365.12455. Found: 365.24188.
Ethyl 4-(4-methoxyphenyl)-6-methyl-2-(phenylthio)pyrimidine-5-carboxylate (***4c***): White solid, mp 78–80 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 1.05 (3H, t, J = 7.16 Hz, CH_3), 2.40 (3H, s, CH_3), 3.73 (3H, s, CH_3), 4.14 (2H, q, J = 7.16 Hz,CH_2), 6.78 (2H, d, J = 8 Hz, ArH), 7.32–7.34 (3H, m, ArH), 7.41 (2H, d, J = 8 Hz, ArH), 7.55–7.57 (2H, m, ArH). ^{13}C NMR 100 MHz ($CDCl_3$): δ 13.83, 22.58, 29.72, 61.82, 113.84, 120.84, 128.93, 129.06, 129.52, 129.59, 130.17, 135.28, 161.49, 162.58, 165.66, 168.55, 171.80. IR (cm^{-1}): 3063, 2918, 1714, 1605, 1526, 1224, 841, 687. HRMS (ESI) Calcd for $C_{21}H_{20}N_2O_3S$ (M+H) 381.11946. Found: 381.17743.
Ethyl 4-(3-methoxyphenyl)-6-methyl-2-(phenylthio)pyrimidine-5-carboxylate (***4d***): White solid, mp 69–70 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 1.08 (3H, t, J = 7.2 Hz, CH_3), 2.51 (3H. s, CH_3), 3.72 (3H, s, OCH_3), 4.19 (2H, q, J = 7.2 Hz, CH_2), 6.93 (1H, d, J = 7.6 Hz, ArH), 7.07 (2H, d, J = 7.2 Hz, ArH), 7.23 (1H, s, ArH), 7.40 (3H, d, J = 6 Hz, ArH), 7.64 (2H, d, J = 7.6 Hz, ArH). ^{13}C NMR 100 MHz ($CDCl_3$): δ 13.70, 22.59, 55.28, 61.86, 113.07, 117.02, 120.72, 121.49, 128.96, 129.09, 129.34, 129,53, 135.37, 138.52, 159.64, 163.10, 165.90, 168.13, 172.11. IR (cm^{-1}): 3074, 2922, 1714, 1597, 1524, 1223, 778, 686. HRMS (ESI) Calcd for $C_{20}H_{17}N_3O_4S$ (M+H) 381.11946. Found: 381.22009.
Ethyl 4-(4-chlolophenyl)-6-methyl-2-(phenylthio)pyrimidine-5-carboxylate (***4e***): White Solid, mp 87–89 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 1.04 (3H, t, J = 7.2 Hz, CH_3), 2.43 (3H, s, CH_3), 4.13 (2H, q, J = 7.48 Hz, CH_2), 7.21 (2H, d, J = 6.6 Hz), 7.33–7.38 (5H, m, ArH), 7.56 (2H, d, J = 6.84 Hz, ArH). ^{13}C NMR 100 MHz ($CDCl_3$): δ 13.74, 22.67, 61.96, 99.99, 121.25, 128.67, 128.99, 129.22, 129.26, 129.79, 135.30, 135.72, 136.59, 162.17, 166.16, 167.94, 172.32. IR (cm^{-1}): 3072, 2922, 1719, 1605, 1523, 1219, 841, 687. HRMS (ESI) Calcd for $C_{20}H_{17}ClN_2O_2S$ (M+H) 384.06993. Found: 384.17688.
Ethyl 4-(4-bromophenyl)-6-methyl-2-(phenylthio)pyrimidine-5-carboxylate (***4f***): White solid, mp 82–84 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 1.11 (3H, t, J = 7.16 Hz, CH_3), 2.50 (3H, s, CH_3), 4.20 (2H, q, J = 7.12 Hz, CH_2), 7.36–7.42 (5H, m, ArH), 7.50 (2H, d, J = 8.48 Hz), 7.60 (2H, d, J = 8.68 Hz). ^{13}C NMR 100 MHz ($CDCl_3$): δ 13.75, 22.68, 61.98, 121.23, 125, 129, 129.23, 130.01, 130.06, 131.64, 135.30, 136.19, 137.59, 162.24, 166.19, 167.91, 172.36. IR (cm^{-1}): 3071, 2920, 1718, 1588, 1523, 1224, 839, 698. HRMS (ESI) Calcd for $C_{20}H_{17}BrN_2O_2S$ (M+H) 430.01941. Found: 431.16266.
Ethyl 4-(3-bromophenyl)-6-methyl-2-(phenylthio)pyrimidine-5-carboxylate (***4g***): White solid, mp 88–90 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 1.04 (3H, t, CH_3, J = 7.16 Hz), 2.47 (3H, s, CH_3), 4.14 (2H, q, CH_2, J = 7.2 Hz), 7.33–7.37 (5H, m, ArH), 7.45 (1H, d, ArH, J = 7 Hz), 7.54–7.59 (3H, m, ArH). ^{13}C NMR 100 MHz ($CDCl_3$): δ 13.80, 22.68, 62.00, 121.29, 122.50, 129.02, 129.25, 129.27, 129.85, 129.92, 131.59, 133.12, 135.30, 139.03, 139.18, 161.57, 161.73, 166.31, 172.42. IR (cm^{-1}): 3061, 2980, 1712, 1604, 1519, 1225, 780, 687. HRMS (ESI) Calcd for $C_{20}H_{17}BrN_2O_2S$ (M+H) 428.01941. Found: 429.11279.
Ethyl 4-methyl-6-(3-nitrophenyl)-2-(phenylthio)pyrimidine-5-carboxylate (***4h***): White Solid, mp 98–99 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 1.17 (3H, t, J = 7.2 Hz,

CH_3), 2.55 (3H, s, CH_3), 4.26 (2H, q, J = 7.6 Hz, CH_2), 7.44 (3H, d, J = 6.4 Hz, ArH), 7.54 (1H, t, J = 8 Hz, ArH), 7.65 (2H, d, J = 7.2 Hz, ArH), 7.84 (1H, d, J = 7.6 Hz, ArH), 8.27 (1H, d, J = 7.6 Hz, ArH), 8.41 (1H, s, ArH). ^{13}C NMR 100 MHz ($CDCl_3$): δ 13.77, 22.81, 62.24, 121.35, 123.73, 124.81, 128.91, 129.15, 129.44, 129.49, 134.21, 135.32, 138.82, 148.23, 160.66, 166.71, 167.43, 172.89. IR (cm^{-1}):3080, 2923, 1724, 1598, 1519, 1218, 772, 688. HRMS (ESI) Calcd for $C_{20}H_{17}N_3O_4S$ (M+H) 396.0933. Found: 396.10890.

1-(4-methyl-2-(phenylthio)-6-p-tolylpyrimidin-5-yl)ethanone (***4i***): White solid, mp 114–116 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 2.03 (3H, s, CH_3), 2.36 (3H, s, CH_3), 2.41 (3H, s, CH_3), 7.19 (2H, d, J = 7.6 Hz, ArH), 7.38–7.42 (5H, m, ArH), 7.64–7.66 (2H, m, ArH). ^{13}C NMR 100 MHz ($CDCl_3$): δ 21.44, 22.49, 32.06, 128.72, 128.93, 129.06, 129.50, 129.59, 134.20, 135.26, 141.22, 162.21, 164.59, 171.51, 204.55. IR (cm^{-1}): 3032, 2919, 1696, 1607, 1518, 1206, 833, 689. HRMS (ESI) Calcd for $C_{20}H_{18}N_2OS$ (M+H) 335.11398. Found: 335.26208.

1-(4-(3-methoxyphenyl)-6-methyl-2-(phenylthio)pyrimidin-5-yl) ethanone (***4j***): White solid, mp 62–63 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 2.05 (3H, s, CH_3), 2.42 (3H, s. CH_3), 3.74 (3H, s, CH_3), 6.97–7.07 (3H, m, ArH), 7.21–7.29 (2H, m, ArH), 7.42 (2H, d, J = 6 Hz, ArH), 7.53 (1H, d, J = 6.8 Hz, ArH), 7.67 (1H, d, J = 7.6 Hz, ArH). ^{13}C NMR 100 MHz ($CDCl_3$): δ 21.36, 29.72, 55.3, 117.60, 121.56, 121.58, 125.91, 128.75, 128.86, 128.96, 129.11, 129.46, 135.36, 135.39, 161.90, 164.68, 164.75, 171.68, 204.35. IR (cm^{-1}): 3056, 2924, 1693, 1598, 1518, 1202, 774, 688. HRMS (ESI) Calcd for $C_{20}H_{18}N_2O_2S$ (M+H) 351.10890. Found: 351.21466.

1-(4-(4-chlorophenyl)-6-methyl-2-(phenylthio)pyrimidin-5-yl) ethanone (***4k***): White solid, mp 95–96 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 1.13 (3H, s, CH_3), 2.50 (3H, s, CH_3), 7.34 (2H, d, J = 8.5 Hz, ArH), 7.41–7.46 (5H, m, ArH), 7.63 (2H, d, J = 6.52 Hz, ArH). ^{13}C NMR 100 MHz ($CDCl_3$): δ 22.66, 29.72, 121.26, 128.67, 128.98, 129.21, 129.79, 135.29, 135.73, 136.59, 162.16, 166.15, 167.93, 172.32, 199.87. IR (cm^{-1}): 3059, 2922, 1708, 1579, 1475, 1237, 830, 685. HRMS (ESI) Calcd for $C_{19}H_{15}ClN_2OS$ (M+H) 355.05936. Found: 355.26031.

1-(2-(4-chlorophenylthio)-4-methyl-6-phenylpyrimidin-5-yl)ethanone (***4l***): White solid, mp 92–94 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 2.02 (3H, s, CH_3), 2.42 (3H, s, CH_3), 7.38–7.51 (7H, m, ArH), 7.58 (2H, d, J = 6.8 Hz, ArH). ^{13}C NMR 100 MHz ($CDCl_3$): δ 22.51, 32.04, 127.92, 128.94, 129.01, 129.17, 130.83, 135.41, 136.92, 162.39, 164.87, 171.04, 204.23. IR (cm^{-1}): 3057, 2923, 1696, 1578, 1519, 1225, 842, 688. HRMS (ESI) Calcd for $C_{19}H_{15}ClN_2OS$ (M+H) 355.05936. Found: 355.28076.

Ethyl 2-(4-chlorophenylthio)-4-methyl-6-phenylpyrimidine-5-carboxylate (***4m***): Yellow solid, mp 42–44 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 1.04 (3H, t, J = 7.2 Hz, CH_3), 2.50 (3H, s, CH_3), 4.17 (2H, q, J = 7.2 Hz, CH_2), 7.35–7.44 (5H, m, ArH), 7.52 (2H, d, J = 6.8 Hz, ArH), 7.57 (2H, d, J = 8 Hz, ArH). ^{13}C NMR 100 MHz ($CDCl_3$): δ 13.64, 22.63, 61.85, 121.76, 127.98, 128.36, 128.48, 129.16, 130.30, 135.38, 136.48, 137.24, 163.70, 166.08, 167.98, 171.46. IR (cm^{-1}): 3062, 2923, 1719, 1601, 1524, 1215, 817, 694. HRMS (ESI) Calcd for $C_{20}H_{17}ClN_2O_2S$ (M+H) 385.06993. Found: 385.17963.

Ethyl 2-(4-bromophenylthio)-4-methyl-6-p-tolylpyrimidin-5-carboxylate (***4n***): Yellow solid, mp 74–76 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 1.09 (3H, t, J = 7.2 Hz, CH_3), 2.36 (3H, s, CH_3), 2.49 (3H, s, CH_3), 4.20 (2H, q, J = 7.2 Hz, CH_2), 7.19 (2H, d, J = 7.6 Hz, ArH), 7.43 (2H, d, J = 8.4 Hz, ArH), 7.51 (4H, d, J = 7.2 Hz, ArH). ^{13}C NMR 100 MHz ($CDCl_3$): δ 13.75, 21.43, 22.60, 61.85, 121.55, 123.57, 128.38, 128.75, 129.23, 132.07, 134.29, 136.69, 138.02, 140.75, 163.46, 165.88, 168.19, 171.15. IR (cm^{-1}): 3011, 2921, 1713, 1609, 1507, 1218, 813, 688. HRMS (ESI) Calcd for $C_{21}H_{19}BrN_2O_2S$ (M+H) 443.03506. Found: 443.13110.

Ethyl 2-(4-bromophenyl)-4-(4-chlorophenyl)-6-methylpyrimidine-5-carboxylate (***4o***): White solid, mp 102–104 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 1.11 (3H, t, J = 7.12 Hz, CH_3), 2.50 (3H, s, CH_3), 4.20 (2H, q, J = 7.08 Hz, CH_2), 7.34–7.37 (2H, m, ArH), 7.44–7.50 (4H, m, ArH), 7.52–7.55 (2H, m, ArH). ^{13}C NMR 100 MHz ($CDCl_3$): δ 13.73, 22.64, 61.99, 121.59, 123.76, 128.47, 128.76, 129.74, 132.15, 135.61, 136.71, 138.11, 162.34, 166.28, 167.76, 171.52. IR (cm^{-1}): 3074, 2984, 2925, 1730, 1593, 1524,1214, 816, 659, 840. HRMS (ESI) Calcd for $C_{20}H_{16}BrClN_2O_2S$ (M+H) 464.77524. Found: 465.12543.

Ethyl 4-methyl-6-(3-nitrophenyl)-2-(p-tolylthio)pyrimidine-5-carboxylate (***4p***): Yellow solid, mp 82–84 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 1.08 (3H, t, J = 7.2 Hz), 2.33 (3H, s, CH_3), 2.47 (3H, s, CH_3), 4.18 (2H, q, J = 7.2 Hz, CH_3), 7.18 (2H, d, J = 7.16 Hz, ArH), 7.43–7.52 (3H, m, ArH), 7.75 (2H, d, J = 6.28 Hz, ArH), 8.21 (2H, d, J = 6 Hz, ArH), 8.33 (1H, s, ArH). ^{13}C NMR 100 MHz ($CDCl_3$): δ 12.72, 20.36, 21.77, 61.16, 120.17, 122.78, 123.75, 124.31, 128.34, 128.93, 133.14, 134.21, 137.87, 138.76, 140.44, 147.24, 159.55, 165.60, 172.23. IR (cm^{-1}): 3057, 2922,2852, 1703, 1565, 1515, 1217, 690, 805. HRMS (ESI) CalCd for $C_{21}H_{19}N_3O_4S$ (M+H) 410.10963. Found: 410.19470.