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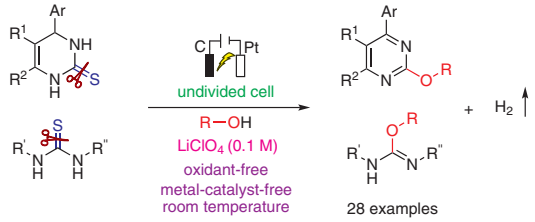
Metal- and Oxidant-Free Electrochemical Oxidative Desulfurization C–O Coupling of Thiourea-Type Compounds with Alcohols

Zheng-He Zhu
Ming-Zhe Ren
Bao-Qian Cao
Zheng-Jun Quan*
Xi-Cun Wang*

Gansu International Scientific and Technological Cooperation Base of Water-Retention Chemical Functional Materials, College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou, Gansu 730070, P. R. of China
quanzhengjun@hotmail.com
wangxicun@nwnu.edu.cn



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Abstract An efficient desulfurization C–O coupling reaction of 3,4-dihydropyrimidine-2(1*H*)-thiones (including thioureas) with alcohols was developed under electrochemical oxidation conditions. Herein, transition-metal catalysts and additives are not required and the alcohol is both the solvent and the alkoxy donor.

Key words electrochemical oxidation, alkoxylation, alcohols, thioureas, desulfurization

Recently, electrochemistry has been increasingly used in organic synthesis. It can be used to substitute poisonous or dangerous oxidizing or reducing agents.[1] Electrochemical oxidations have been successfully used for sulfur (SH)-containing compounds to give disulfides[1c,d] or sulfonyl compounds.[1h] However, desulfurization reactions of sulfur compounds are still uncommon under electrochemical conditions. Sulfur-containing compounds are widely found in natural products, pesticides, proteins[2] and functional materials.[3] Their biological activities[4] or reactivities[5] play a unique role in organic chemistry. Because the C–S bond is relatively easier to activate and functionalize than other carbon–heteroatom bonds (e.g., C–O, C–N),[6] activation of C–S bonds is important in organic chemistry.[7] Generally, transition metals have been used to catalyze C–S bond activation to construct new chemical bonds.[8] Great progress has been developed in this field, and some typical examples are cited herein. In 2000, Liebeskind and Srogl first reported a desulfurization C–C coupling reaction of thiol esters and boric acids in the presence of copper(I) thiophene-2-carboxylate (CuTC) (1.5–3.0 equiv) and $Pd_2(dba)_3$.[9] In 2009, Knochel and co-workers reported the use of Pd-catalyzed C–S bond cleavage of thiomethyl-substituted N-heterocyclic compounds.[10] In 2014, Osuka and co-workers reported the Pd-catalyzed C–N bond formation between aryl sulfides and aromatic amines.[11] In 2017, Morandi and co-workers used a Pd-catalyzed desulfurization of arylthiophenols with mercaptans or thiophenols to form C–S bonds.[12] In some cases of transition-metal-activated C–S bonds,[13] sulfur atoms can bind tightly to the transition metal, resulting in permanent deactivation of the transition metal, thus hindering the reaction.[14] To overcome these difficulties, an active Grignard reagent was used as a nucleophile[15] or an aryl sulfide having a specific structure to promote efficient conversion was employed.[16,17] More recently, a gold-catalyzed desulfurization of mercaptans with olefins to form C–C bonds under photochemical conditions has been reported.[18] Pyrithione including *pyrimidinethione* entered our field of view because of its special structure and as it is a major component of many natural products and drugs, such as the current cholesterol-lowering drug rosuvastatin (Crestor)[19] and the potent anticancer drug imatinib (Gleevec).[20] The main part of the compound is a pyrimidine structure. Our group has reported a series of desulfurization C–X (X = C, N) coupling reactions of 3,4-dihydropyrimidine-2(1*H*)-thiones (DHPMs) or their disulfides in a Pd–Cu reaction system (Schemes 1A and 1B).[21] Subsequently, Sohn and co-workers reported the C–S bond activation/cleavage of DHPMs to form C–C (Scheme 1A)[22a] and C–O bonds (Scheme 1C)[22b] in a stoichiometric Cu system. These reported methods have provided great progress for C–S bond activation/cleavage; however, some drawbacks are obvious. For example, they need stoichiometric Cu reagent and transition-metal catalyst with/without the presence of stoichiometric oxidant. Furthermore, the reaction times are long and temperatures are high.[22c,d]

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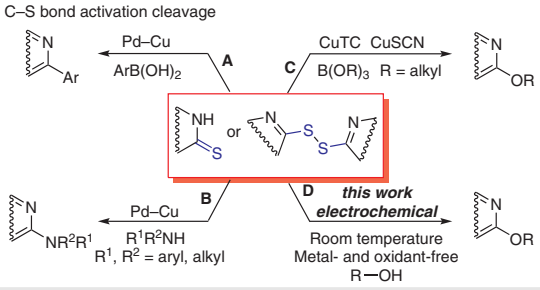


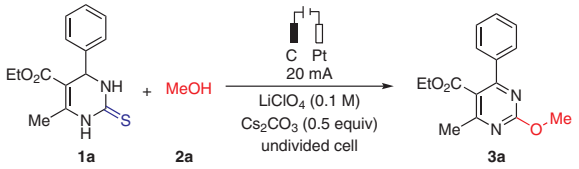
Scheme 1 C–S bond activation/cleavage

Herein, we report a metal- and oxidant-free procedure to activate and cleave the C–S bond. The C–O bond is formed by an electrochemical oxidative desulfurization C–O coupling reaction of thiourea-type compounds with inexpensive and readily available alcohols (Scheme 1D). We have previously developed the C–O cross-coupling reactions of pyrimidin-2-yl sulfonates with phenols[23a] and 2-hydroxypyrimidines with OH nucleophiles.[23b] The current method to form C–O bonds is simpler than the classical Ullmann[24a] and Buchwald–Hartwig coupling reactions.[24b]

We tested our design using DHPM **1a** and methanol (**2a**) as model substrates (Table 1; for details, see Supporting Information, Table S1). The optimal reaction conditions were obtained under a constant current of 20 mA in an undivided, straight reaction tube containing carbon as an anode and platinum as a cathode with reaction for 6 hours, to give the desired product **3a** in 81% yield (entry 1). A series of electrolytes were chosen and found to give lower yields of **3a** than that obtained by using $LiClO_4$ (entry 2). The reaction yield was best when Cs_2CO_3 (0.5 equiv) was used as the base. In the absence of a base, **3a** was obtained in 28% yield. For the electrode material, it was experimentally proven that the selection of carbon rod as anode and platinum as cathode are the best choice (entries 4 and 5). When the operating current was reduced to 15 mA or 10 mA, the yield of **3a** decreased significantly (entries 6 and 7). Further studies showed that when the reaction was carried out in a MeCN/MeOH (1:1) mixture, **3a** was formed in 25% yield (entry 8). No product **3a** was observed in the absence of current (entry 9).

Under the optimal reaction conditions, multiple alcohols (Scheme 2; MeOH, EtOH, *n*-PrOH, *i*-PrOH) were tested and found to give the corresponding products **3a–3d** in moderate to good yields (Scheme 2A). Next, we evaluated the reaction range of the DHPM substrate by changing the aryl substituent at the C4/C6 position. Both the electronic and steric effects of the C4 aryl substituent on the product yields are slight (Scheme 2A, **3e–3n**). When the C4 aryl *para*-substituent was methoxy, the product was obtained in a lower yield (Scheme 2A, **3h**). When C5 was substituted by a methyl ester, isobutyl ester or *tert*-butyl ester group, the desired product **3o–3r** was obtained in moderate yield. The

Table 1 Optimization of the Reaction Conditions[a]



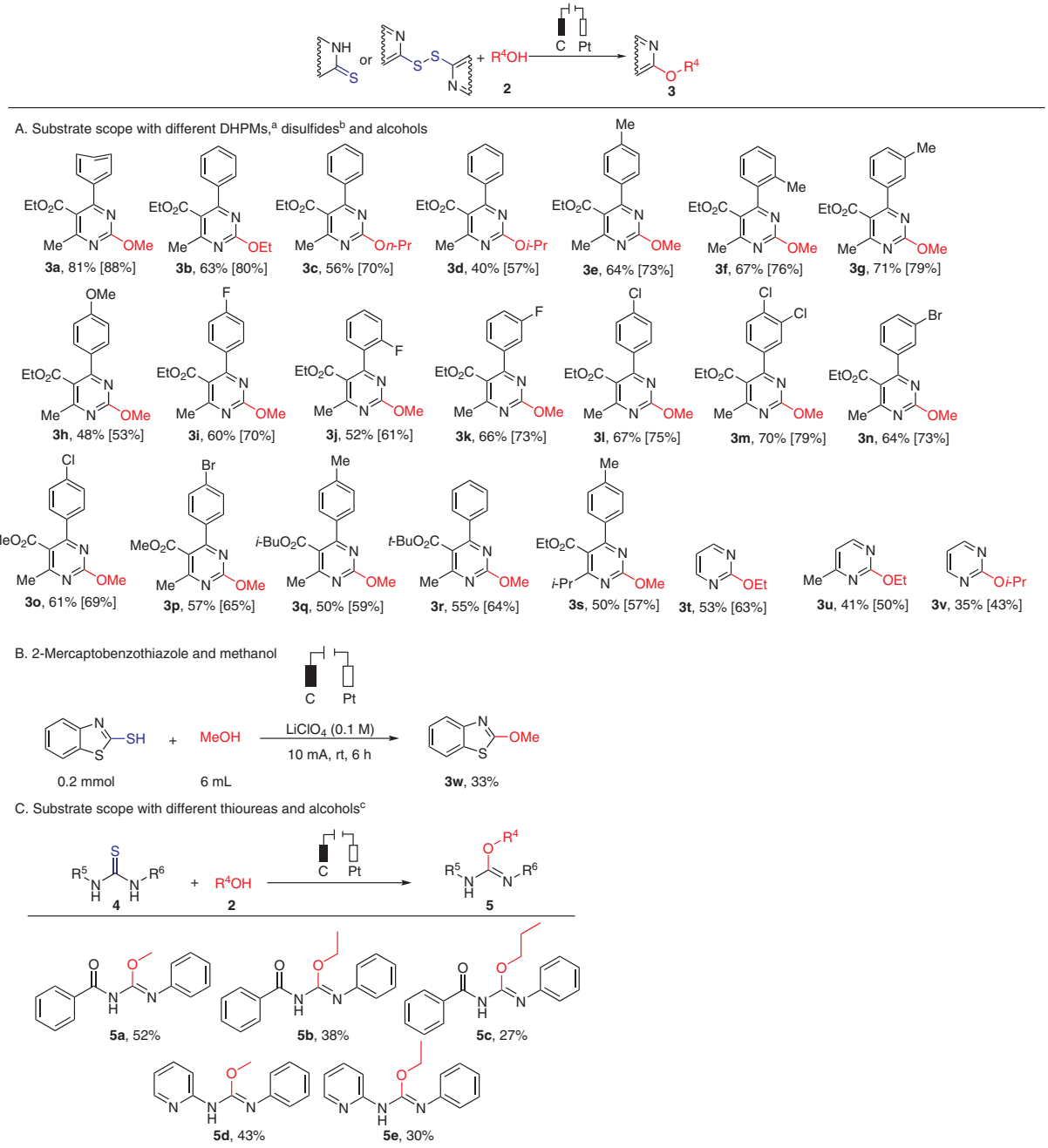
Entry	Variation from the standard reaction conditions	Yield (%)[b]
1	none	81
2	*n*-Bu_4NI, *n*-Bu_4NBF_4, instead of $LiClO_4$	60, 50
3	1.0 equiv, 0.8 equiv, 0.2 equiv of Cs_2CO_3	65, 71, 74
4	C(+)/C(–), instead of C(+)/Pt(–)	20
5	Pt(+)/Pt(–), instead of C(+)/Pt(–)	35
6	15 mA, instead of 20 mA,	64
7	10 mA, instead of 20 mA	51
8	MeCN/MeOH (1:1), instead of MeOH	25
9	no electric current	n.d.[c]

[a] Standard reaction conditions: **1a** (0.2 mmol), **2a** (6 mL), $LiClO_4$ (0.1 M), Cs_2CO_3 (0.5 equiv), carbon rod anode, platinum cathode, undivided cell, 20 mA constant current, rt, 6 h, under air.
[b] Isolated yields.
[c] Not detected.

substrate with an isopropyl substituent at the C6 position afforded the desired product **3s** in a moderate yield of 50%. Simple pyrimidinethiones also reacted with alcohols to give the desired products **3t**, **3u** and **3v** in 53%, 41% and 35% yield, respectively. When 2-mercaptobenzothiazole was used as a substrate, reaction with methanol provided 2-methoxybenzothiazole (**3w**) in 33% yield (Scheme 2B). In comparison, the yields of products **3a–3v** obtained by using the corresponding disulfides as substrates were higher (Scheme 2A, yields in square brackets). When simple 4-methylthiophenol was used as a substrate, no desulfurization product was obtained, rather methyl 4-methylbenzenesulfinate was obtained.[25]

Guanidine compounds are widely used in medicine, chemistry and other industries due to their strong basicity, high stability and good biological activity.[26] Generally, guanidines are prepared by the addition of amines to cyanamide and iso(thio)urea. Therefore, we selected *N*-benzoyl-*N*′-phenylthiourea and *N*-phenyl-*N*′-(pyridin-2-yl)thiourea as substrates for the reaction with alcohols (MeOH, EtOH, *n*-PrOH) to synthesize alkoxy products. Fortunately, the corresponding isourea compounds **5a–5e** were obtained in fair yields (Scheme 2C).

To gain insight into the details of electrocatalytic desulfurization of pyrimidinethiones, control experiments were performed. In the first place, cyclic voltammetry experiments with **1a**, and with **1a** and base in argon, were carried out separately (Figure 1). An oxidation peak of **1a** was observed at 1.55 V (blue line), and at 1.63 V (red line) for **1a** in



Scheme 2 Substrate expansion of the desulfurization C–O coupling reaction of thiones and disulfides with alcohols **2**. [a] *Reagents and conditions*: DHPM (0.2 mmol), **2** (6 mL), $LiClO_4$ (0.1 M), Cs_2CO_3 (0.5 equiv), carbon rod anode, platinum cathode, undivided cell, 20 mA constant current, rt, 6 h; isolated yields. [b] *Reagents and conditions*: disulfide (0.1 mmol), **2** (6 mL), $LiClO_4$ (0.1 M), carbon rod anode, platinum cathode, undivided cell, 20 mA constant current, rt, 6 h; isolated yields in square brackets. [c] *Reagents and conditions*: **4** (0.2 mmol), **2** (6 mL), $LiClO_4$ (0.1 M), carbon rod anode, platinum cathode, undivided cell, 8 mA constant current, rt, 6 h; isolated yields.

the presence of base. Next, when **1a** and base were exposed to air, oxidation peaks of **1a** were observed at 1.21 and 1.42 V (green line). Therefore, DHPMs are more susceptible to oxidize in the presence of air.

To further study the reaction mechanism, a series of control experiments was carried out (Scheme 3). When the radical-trapping agent TEMPO or BHT was added to the reaction of **1a** with methanol, only a trace or 20% yield of **3a** was obtained (Scheme 3a). Further, after the addition of

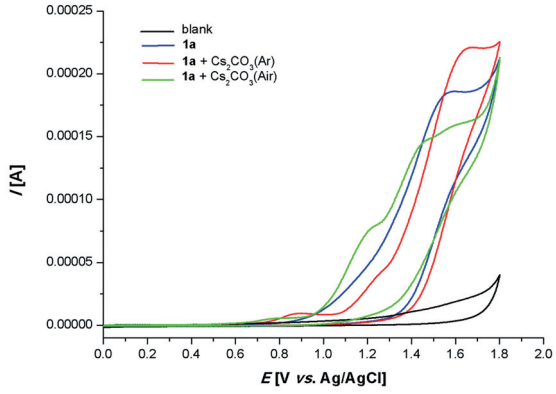


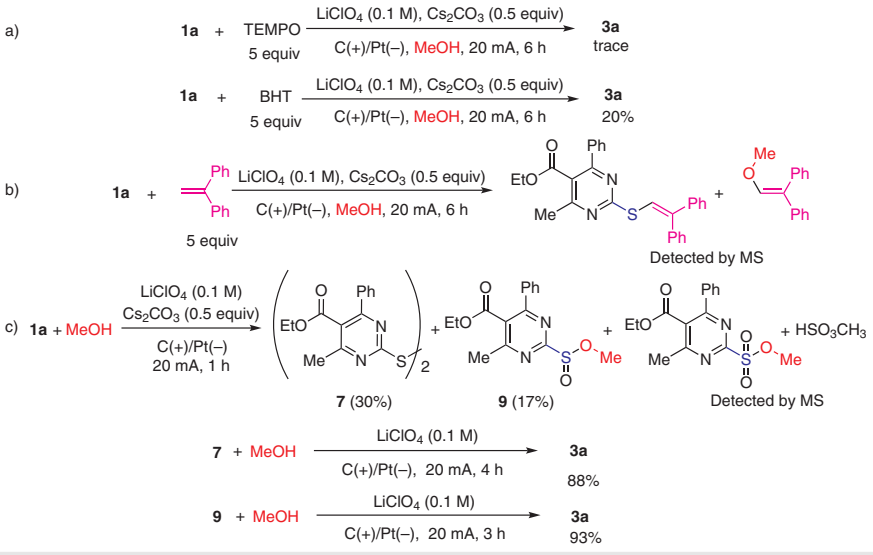
Figure 1 Cyclic voltammograms of **1a**

1,1-diphenylethylene (Scheme 3b), the corresponding sulfur radical and methoxy product were detected by mass spectrometry (see Supporting Information); thus, the formation of radicals in the reaction is presumed. These observations indicate the presence of an S radical in intermediate **6** (see Scheme 4).[1c,d,h,27] Meanwhile, the possibility of an SET process forming disulfide **7** cannot be ruled out, because TEMPO can be oxidized at a potential lower than substrates **1**. The lack of product formation could be a result of preferential oxidation of these radical inhibitors. Methoxy radicals are difficult to produce, so it is presumed that a methoxy anion is formed. When the reaction of **1a** with methanol was carried out for 1 hour, the dimerized product **7** and methyl pyrimidinesulfinate **9** were isolated (Scheme 3c), and methyl pyrimidinesulfonate and methyl sulfonate were detected by mass spectrometry (see Supporting Information). At the same time, the desired product **3a** was obtained in 88% and 93% yield by using **7** and **9**, respectively, as substrate (Scheme 3c). Therefore, it is speculated that **7** and **9** are intermediates of the reaction.

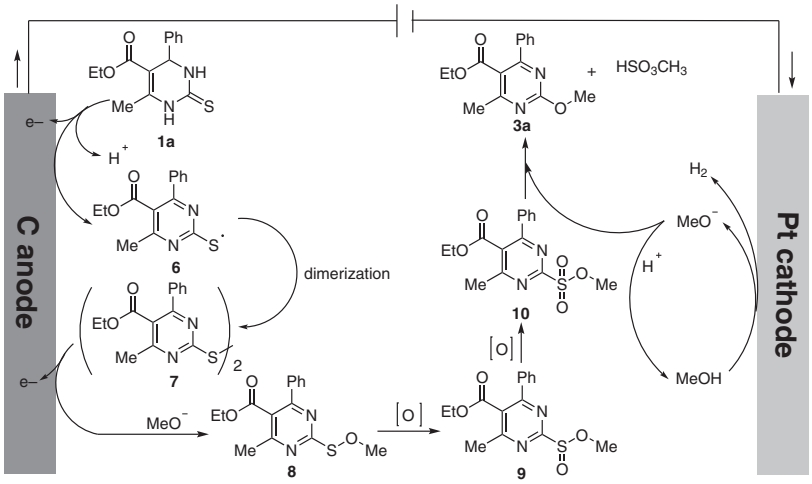
According to the literature and our experimental results, a C–O cross-coupling mechanism of electrochemical oxidative desulfurization is proposed in Scheme 4. First, **1a** is deprotonated by the action of the base, and further oxidized at the anode to form disulfide **7** by dimerization of the sulfur radical **6**.[28] At the same time, on the cathode, methanol (**2a**) is reduced to produce H_2 and methoxy anion. Then, a nucleophilic attack of compound **7** by methoxy anion occurs to form **8**. By two consecutive oxidation steps, **8** is further oxidized to methyl pyrimidinesulfonate **10**. Then, **9** or **10** reacts with methoxide anion to obtain product **3a** and methyl sulfonate.

In summary, we have reported the reaction of thiourea-type compounds with alcohols to form ether compounds by electrochemical oxidative cleavage of C–S bonds. The reaction can perform well using various thioureas and primary alcohols (MeOH, EtOH, *n*-PrOH) and *i*-PrOH as coupling agents. It does not require transition-metal catalysis or oxidant. Mechanism studies have confirmed that the oxidation of the thiourea to disulfide is important.

Reactions were carried out in a constant current mode using a potentiostat from Xiamen Bodong Biotechnology Co., Ltd. Cyclic voltammograms were recorded on a CHI 660E workstation. Column chromatography was carried out on silica gel (200–300 mesh) and TLC analysis was performed on silica gel GF254 plates. ^{1}H NMR and ^{13}C NMR data were recorded using Varian Mercury plus-400 and Agilent 600 MHz



Scheme 3 Control experiments



Scheme 4 Proposed mechanism

DD2 instruments, with $CDCl_3$ as solvent and TMS as an internal standard. Chemical shifts are reported in δ units (ppm), with the TMS resonance in the ^1H NMR spectra specified as 0.00 ppm. ^1H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant in Hz (*J* value) and integration. Chemical shifts of the ^{13}C NMR spectra from TMS were recorded using the central peak of $CDCl_3$ (77.0 ppm) as an internal standard. Melting points were measured using an XT-4 apparatus. High-resolution mass spectrometry (ESI) was obtained using a Thermo Scientific Q Exactive mass spectrometer to record the exact mass of the molecular ion + hydrogen ($[M + H]^+$).

Ethyl 2-Methoxy-4-methyl-6-phenylpyrimidine-5-carboxylate (3a);[22b] Typical Procedure

1a (55.2 mg, 0.2 mmol), Cs_2CO_3 (32.6 mg, 0.1 mmol, 0.5 equiv), $LiClO_4$ (63.8 mg, 0.6 mmol) and MeOH (6 mL) were added to a straight reaction tube, which was equipped with a graphite rod (Ø 6 mm) as an anode and a platinum plate (10 × 10 × 2 mm) as a cathode. Electrolysis was performed using a constant current of 20 mA, with stirring at room temperature under an air atmosphere until the substrate was completely consumed (detected by TLC). Then, silica gel was added and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether, 1:20) to give pure product **3a** as a colorless oil; yield: 44.1 mg (81%). All products **3** and **5** were synthesized according to this procedure.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.64–7.63 (m, 2 H), 7.45–7.40 (m, 3 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 4.06 (s, 3 H), 2.56 (s, 3 H), 1.02 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.7, 168.3, 166.5, 164.5, 137.8, 130.0, 128.4, 128.3, 119.9, 61.6, 55.0, 22.8, 13.6.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{16}N_2O_3$: 273.1234; found: 273.1232.

Ethyl 2-Ethoxy-4-methyl-6-phenylpyrimidine-5-carboxylate (3b)[22b]

Yield: 36.1 mg (63%); colorless oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.60 (m, 2 H), 7.45–7.40 (m, 3 H), 4.49 (q, *J* = 6.8 Hz, 2 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 2.56 (s, 3 H), 1.43 (t, *J* = 7.2 Hz, 3 H), 1.01 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.6, 168.3, 166.4, 164.1, 137.9, 130.0, 128.3, 128.2, 119.7, 63.7, 61.5, 22.7, 14.4, 13.6.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{18}N_2O_3$: 287.1390; found: 287.1392.

Ethyl 4-Methyl-6-phenyl-2-propoxypyrimidine-5-carboxylate (3c)[22b]

Yield: 33.6 mg (56%); colorless oil.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.63–7.60 (m, 2 H), 7.45–7.39 (m, 3 H), 4.38 (t, *J* = 6.6 Hz, 2 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 2.55 (s, 3 H), 1.87–1.80 (m, 2 H), 1.04–0.99 (m, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.6, 168.3, 166.4, 164.3, 137.9, 130.0, 128.3, 128.2, 119.7, 69.5, 61.5, 22.7, 22.2, 13.6, 10.5.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{20}N_2O_3$: 301.1547; found: 301.1546.

Ethyl 2-Isopropoxy-4-methyl-6-phenylpyrimidine-5-carboxylate (3d)[22b]

Yield: 24.0 mg (40%); colorless oil.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.64–7.61 (m, 2 H), 7.46–7.40 (m, 3 H), 5.44–5.37 (m, 1 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 2.55 (s, 3 H), 1.41 (d, *J* = 6.0 Hz, 6 H), 1.02 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.7, 168.4, 166.4, 163.7, 138.0, 129.9, 128.3, 128.2, 119.4, 70.6, 61.5, 22.8, 21.9, 13.6.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{20}N_2O_3$: 301.1547; found: 301.1544.

Ethyl 2-Methoxy-4-methyl-6-(*p*-tolyl)pyrimidine-5-carboxylate (3e)

Yield: 36.6 mg (64%); colorless oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 8.4 Hz, 2 H), 7.23 (d, *J* = 8.0 Hz, 2 H), 4.17 (q, *J* = 6.8 Hz, 2 H), 4.06 (s, 3 H), 2.55 (s, 3 H), 2.39 (s, 3 H), 1.08 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.8, 168.7, 166.5, 164.7, 140.7, 135.1, 129.3, 128.5, 119.9, 61.9, 55.2, 23.0, 21.6, 13.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{18}N_2O_3$: 287.1390; found: 287.1392.

Ethyl 2-Methoxy-4-methyl-6-(*o*-tolyl)pyrimidine-5-carboxylate (3f)

Yield: 38.3 mg (67%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (s, 1 H), 7.41 (d, *J* = 7.6 Hz, 1 H), 7.33–7.25 (m, 2 H), 4.15 (q, *J* = 7.2 Hz, 2 H), 4.06 (s, 3 H), 2.56 (s, 3 H), 2.39 (s, 3 H), 1.05 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.5, 168.3, 166.6, 164.5, 138.1, 137.7, 130.8, 128.9, 128.2, 125.3, 119.9, 61.6, 55.0, 22.7, 21.4, 13.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{18}N_2O_3$: 287.1390; found: 287.1391.

Ethyl 2-Methoxy-4-methyl-6-(*m*-tolyl)pyrimidine-5-carboxylate (3g)

Yield: 40.6 mg (71%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.47 (m, 1 H), 7.44–7.41 (m, 1 H), 7.34–7.27 (m, 2 H), 4.16 (q, *J* = 7.2 Hz, 2 H), 4.08 (s, 3 H), 2.57 (s, 3 H), 2.40 (s, 3 H), 1.06 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.5, 168.3, 166.6, 164.5, 138.1, 137.7, 130.8, 128.9, 128.2, 125.3, 119.9, 61.6, 55.0, 22.7, 21.4, 13.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{18}N_2O_3$: 287.1390; found: 287.1391.

Ethyl 2-Methoxy-4-(4-methoxyphenyl)-6-methylpyrimidine-5-carboxylate (3h)[29]

Yield: 29.0 mg (48%); colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.66–7.63 (m, 2 H), 6.95–6.92 (m, 2 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 4.06 (s, 3 H), 3.84 (s, 3 H), 2.54 (s, 3 H), 1.12 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.7, 168.3, 165.5, 164.4, 161.4, 130.1, 130.0, 119.4, 113.8, 61.6, 55.4, 54.9, 22.7, 13.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{18}N_2O_4$: 303.1339; found: 303.1337.

Ethyl 4-(4-Fluorophenyl)-2-methoxy-6-methylpyrimidine-5-carboxylate (3i)

Yield: 34.8 mg (60%); colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.67–7.60 (m, 2 H), 7.12–7.07 (m, 2 H), 4.16 (q, *J* = 7.2 Hz, 2 H), 4.04 (s, 3 H), 2.54 (s, 3 H), 1.07 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.8, 168.2, 165.1, 164.8, 164.4, 163.1, 133.9 (d, *J* = 3.0 Hz), 130.4 (d, *J* = 7.5 Hz), 119.7, 115.5, 115.4, 61.7, 55.0, 22.7, 13.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{15}FN_2O_3$: 291.1139; found: 291.1136.

Ethyl 4-(2-Fluorophenyl)-2-methoxy-6-methylpyrimidine-5-carboxylate (3j)

Yield: 30.2 mg (52%); colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.59–7.56 (m, 1 H), 7.44–7.39 (m, 1 H), 7.25–7.21 (m, 1 H), 7.10–7.06 (m, 1 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 4.05 (s, 3 H), 2.65 (s, 3 H), 1.01 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.9, 166.7, 164.6, 163.3, 160.5, 158.8, 131.4, 131.4, 130.8, 130.8, 126.4 (d, *J* = 15.0 Hz), 124.3, 124.3, 120.4, 115.4, 115.2, 61.3, 55.1, 23.7, 13.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{15}FN_2O_3$: 291.1139; found: 291.1137.

Ethyl 4-(3-Fluorophenyl)-2-methoxy-6-methylpyrimidine-5-carboxylate (3k)

Yield: 38.3 mg (66%); colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.40–7.37 (m, 3 H), 7.17–7.13 (m, 1 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 4.06 (s, 3 H), 2.56 (s, 3 H), 1.07 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.0, 167.9, 164.9 (d, *J* = 3.0 Hz), 164.5, 163.4, 161.8, 139.9 (d, *J* = 7.5 Hz), 129.9 (d, *J* = 9.0 Hz), 124.0 (d, *J* = 3.0 Hz), 119.9, 117.0, 116.9, 115.5, 115.4, 61.7, 55.1, 22.8, 13.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{15}FN_2O_3$: 291.1139; found: 291.1137.

Ethyl 4-(4-Chlorophenyl)-2-methoxy-6-methylpyrimidine-5-carboxylate (3l)[29]

Yield: 41.0 mg (67%); colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.58–7.56 (m, 2 H), 7.40–7.37 (m, 2 H), 4.16 (q, *J* = 7.2 Hz, 2 H), 4.04 (s, 3 H), 2.55 (s, 3 H), 1.08 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.9, 168.0, 165.1, 164.5, 136.4, 136.2, 129.7, 128.6, 119.7, 61.7, 55.1, 22.8, 13.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{15}ClN_2O_3$: 307.0844; found: 307.0841.

Ethyl 4-(3,4-Dichlorophenyl)-2-methoxy-6-methylpyrimidine-5-carboxylate (3m)

Yield: 47.6 mg (70%); colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 1.8 Hz, 1 H), 7.49 (d, *J* = 8.4 Hz, 1 H), 7.45 (dd, *J* = 8.4, 1.8 Hz, 1 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 4.05 (s, 3 H), 2.55 (s, 3 H), 1.13 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.2, 167.7, 164.5, 163.7, 137.5, 134.5, 132.8, 130.4, 130.3, 127.5, 119.8, 61.9, 55.2, 22.9, 13.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{14}Cl_2N_2O_3$: 341.0454; found: 341.0456.

Ethyl 4-(3-Bromophenyl)-2-methoxy-6-methylpyrimidine-5-carboxylate (3n)

Yield: 44.8 mg (64%); colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 1.8 Hz, 1 H), 7.59–7.56 (m, 1 H), 7.55–7.53 (m, 1 H), 7.29 (t, *J* = 7.8 Hz, 1 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 4.06 (s, 3 H), 2.56 (s, 3 H), 1.08 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.1, 167.8, 164.8, 164.5, 139.7, 133.0, 131.3, 129.8, 126.9, 122.4, 119.9, 61.8, 55.1, 22.8, 13.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{15}BrN_2O_3$: 351.0339; found: 351.0336.

Methyl 4-(4-Chlorophenyl)-2-methoxy-6-methylpyrimidine-5-carboxylate (3o)

Yield: 35.6 mg (61%); white solid; mp 85–87 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.59–7.57 (m, 2 H), 7.42–7.39 (m, 2 H), 4.06 (s, 3 H), 3.69 (s, 3 H), 2.55 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.0, 168.6, 165.0, 164.6, 136.5, 136.1, 129.6, 128.7, 119.4, 55.1, 52.5, 22.8.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{13}ClN_2O_3$: 293.0687; found: 293.0685.

Methyl 4-(4-Bromophenyl)-2-methoxy-6-methylpyrimidine-5-carboxylate (3p)

Yield: 38.3 mg (57%); white solid; mp 88–89 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.57–7.55 (m, 2 H), 7.51–7.49 (m, 2 H), 4.05 (s, 3 H), 3.68 (s, 3 H), 2.54 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.1, 168.6, 165.1, 164.6, 136.5, 131.7, 129.8, 124.9, 119.3, 55.1, 52.6, 22.8.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{13}BrN_2O_3$: 337.0182; found: 337.0185.

Isobutyl 2-Methoxy-4-methyl-6-(*p*-tolyl)pyrimidine-5-carboxylate (3q)

Yield: 31.4 mg (50%); colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.57–7.55 (m, 2 H), 7.24–7.21 (m, 2 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 4.06 (s, 3 H), 3.22–3.15 (m, 1 H), 2.39 (s, 3 H), 1.31 (s, 3 H), 1.30 (s, 3 H), 1.09 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 176.2, 168.7, 166.1, 164.9, 140.3, 135.0, 129.1, 128.2, 119.2, 61.6, 54.8, 33.1, 21.6, 21.4, 13.7.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{22}N_2O_3$: 315.1703; found: 315.1701.

***tert*-Butyl 2-Methoxy-4-methyl-6-phenylpyrimidine-5-carboxylate (3r)**

Yield: 33.0 mg (55%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.64 (m, 2 H), 7.47–7.42 (m, 3 H), 4.05 (s, 3 H), 2.57 (s, 3 H), 1.35 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.2, 167.2, 166.0, 164.2, 137.9, 129.9, 128.5, 128.3, 121.5, 82.6, 54.9, 27.6, 22.7.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{20}N_2O_3$: 301.1547; found: 301.1546.

Ethyl 4-Isopropyl-2-methoxy-6-(*p*-tolyl)pyrimidine-5-carboxylate (3s)

Yield: 31.4 mg (50%); colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 8.4 Hz, 2 H), 7.22 (d, *J* = 7.8 Hz, 2 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 4.06 (s, 3 H), 3.22–3.17 (m, 1 H), 2.39 (s, 3 H), 1.31 (d, *J* = 6.6 Hz, 6 H), 1.09 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 176.2, 168.7, 166.1, 164.9, 140.3, 135.1, 129.1, 128.2, 119.2, 61.6, 54.8, 33.1, 21.6, 21.4, 13.7.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{22}N_2O_3$: 315.1703; found: 315.1705.

2-Ethoxypyrimidine (3t)[22b]

Yield: 13.2 mg (53%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (d, *J* = 4.8 Hz, 2 H), 6.91 (t, *J* = 4.8 Hz, 1 H), 4.41 (q, *J* = 7.2 Hz, 2 H), 1.43 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 165.2, 159.2, 114.7, 63.3, 14.4.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_6H_8N_2O$: 125.0709; found: 125.0708.

2-Ethoxy-4-methylpyrimidine (3u)[22b]

Yield: 11.3 mg (41%); colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 4.8 Hz, 1 H), 6.73 (d, *J* = 4.8 Hz, 1 H), 4.36 (q, *J* = 7.2 Hz, 2 H), 2.41 (s, 3 H), 1.38 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.9, 165.0, 158.4, 114.3, 63.1, 24.0, 14.4.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_7H_{10}N_2O$: 139.0866; found: 139.0864.

2-Isopropoxypyrimidine (3v)[22b]

Yield: 9.7 mg (35%); colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.46 (d, *J* = 4.8 Hz, 2 H), 6.85 (t, *J* = 4.8 Hz, 1 H), 5.28–5.21 (m, 1 H), 1.37 (d, *J* = 6.0 Hz, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.8, 159.2, 114.4, 70.2, 21.8.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_7H_{10}N_2O$: 139.0866; found: 139.0867.

2-Methoxybenzo[*d*]thiazole (3w)[30]

Yield: 10.9 mg (33%); white solid; mp 68–70 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 8.0 Hz, 1 H), 8.01 (d, *J* = 8.4 Hz, 1 H), 7.63–7.51 (m, 2 H), 3.74 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.1, 153.8, 136.3, 127.4, 127.4, 125.2, 122.6, 51.6.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for C_8H_7NOS: 166.0321; found: 166.0320.

Methyl (*Z*)-*N*-Benzoyl-*N*′-phenylcarbamimidate (5a)[31]

Yield: 26.4 mg (52%); colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 12.05 (s, 1 H), 8.32–8.29 (m, 2 H), 7.54–7.51 (m, 1 H), 7.47–7.43 (m, 2 H), 7.36 (d, *J* = 2.4 Hz, 2 H), 7.35 (s, 2 H), 7.20–7.16 (m, 1 H), 4.13 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 177.8, 161.1, 137.3, 136.2, 132.0, 129.4, 129.1, 128.0, 125.2, 122.3, 55.0.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{14}N_2O_2$: 255.1128; found: 255.1129.

Ethyl (*Z*)-*N*-Benzoyl-*N*′-phenylcarbamimidate (5b)

Yield: 20.4 mg (38%); colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 12.12 (s, 1 H), 8.29–8.26 (m, 2 H), 7.53–7.49 (m, 1 H), 7.46–7.42 (m, 2 H), 7.37–7.33 (m, 4 H), 7.18–7.14 (m, 1 H), 4.66 (q, *J* = 7.2 Hz, 2 H), 1.47 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 177.8, 160.6, 137.5, 136.5, 132.0, 129.3, 129.0, 128.0, 125.0, 122.1, 64.3, 14.5.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{16}N_2O_2$: 269.1285; found: 269.1283.

Propyl (*Z*)-*N*-Benzoyl-*N*′-phenylcarbamimidate (5c)

Yield: 15.2 mg (27%); colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 12.12 (s, 1 H), 8.29–8.27 (m, 2 H), 7.53–7.50 (m, 1 H), 7.46–7.42 (m, 2 H), 7.38–7.33 (m, 4 H), 7.18–7.15 (m, 1 H), 4.56 (t, *J* = 6.6 Hz, 2 H), 1.89–1.83 (m, 2 H), 1.05 (t, *J* = 7.8 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 177.8, 160.8, 137.5, 136.5, 131.9, 129.3, 129.0, 128.0, 125.0, 122.1, 70.0, 22.1, 10.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}N_2O_2$: 283.1441; found: 283.1443.

Methyl (*Z*)-*N*′-Phenyl-*N*-(pyridin-2-yl)carbamimidate (5d)

Yield: 19.5 mg (43%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.28 (s, 1 H), 8.27 (dd, *J* = 4.8, 2.0 Hz, 1 H), 7.62–7.56 (m, 1 H), 7.32 (d, *J* = 4.4 Hz, 4 H), 7.10–7.04 (m, 2 H), 6.90–6.85 (m, 1 H), 3.99 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 160.3, 154.3, 145.6, 138.3, 137.6, 128.8, 123.4, 121.6, 121.2, 116.9, 53.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{13}N_3O$: 228.1131; found: 228.1130.

Ethyl (*Z*)-*N*′-Phenyl-*N*-(pyridin-2-yl)carbamimidate (5e)

Yield: 14.5 mg (30%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.34 (s, 1 H), 8.29–8.25 (m, 1 H), 7.62–7.57 (m, 1 H), 7.37–7.30 (m, 4 H), 7.10–7.02 (m, 2 H), 6.90–6.84 (m, 1 H), 4.50 (q, *J* = 7.2 Hz, 2 H), 1.42 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 153.8, 145.6, 138.5, 137.5, 128.9, 128.8, 123.1, 121.3, 121.2, 116.7, 62.6, 14.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{15}N_3O$: 242.1288; found: 242.1289.

Ethyl 2-(Methoxysulfinyl)-4-methyl-6-phenylpyrimidine-5-carboxylate (9)

Yield: 10.9 mg (17%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 7.6 Hz, 2 H), 7.56–7.46 (m, 3 H), 4.26 (q, *J* = 7.2 Hz, 2 H), 3.79 (s, 3 H), 2.75 (s, 3 H), 1.12 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.7, 167.5, 166.9, 164.7, 136.2, 130.9, 128.7, 128.6, 127.3, 62.4, 52.5, 22.7, 13.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{16}N_2O_4S$: 321.0904; found: 321.0903.

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Supporting Information

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