Suzuki Coupling at the 2-Position of Densely Functionalized Pyrimidones

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Abstract: A variety of ethyl 1-substituted 2-aryl-5-ethoxy-6-oxo-1,6-dihydropyrimidine-4-carboxylates were synthesized by efficient thermal or microwave-promoted Suzuki coupling of 2-chloro-N1-substituted precursors.

Key words: antiviral agents, pyrimidones, cross-coupling

A recent research project revealed 1-substituted 2-aryl-5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxylic acids (pyrimidones, **1**) as a novel class of Hepatitis C virus (HCV) RNA-dependent RNA polymerase inhibitors[1,2] (Figure 1).

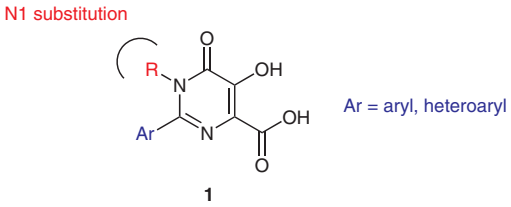

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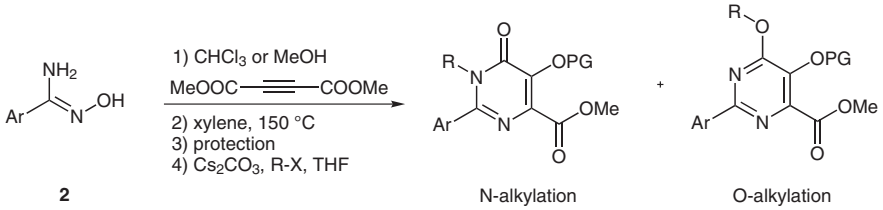
Figure 1 1-Substituted 2-aryl-5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxylic acids **1**

For a rapid exploration of the SAR (structure–activity relationship) in the series, we were targeting an efficient methodology to insert aryl groups in position 2 of the pyrimidone in the presence of different groups on the N1 nitrogen. The remaining substitution pattern of the pyrimidone scaffold, which has been shown to be essential for biological activity,[1,2] was kept fixed. The route typically used[1] for the synthesis of the pyrimidone scaffold was not very efficient for a combined SAR in positions 1 and 2, since the aryl group was introduced early in the synthesis from the amidoxime **2** (Scheme 1) and the alkylation of N1 nitrogen proceeded with low selectivity for the desired N-alkylated product, being furthermore limited to the more reactive electrophiles, and hence to a small number of substituents.

Carbon–carbon bond formation in position 2 of the pyrimidone scaffold having the appropriate N1 substituent already in place was an attractive route for our purposes. From a survey of the literature it was found that carbon–carbon bond formation on 2-halopyrimidines via transition-metal-catalyzed[3] cross-coupling reactions is well documented. The analogous reaction on N1-substituted pyrimidones has very little precedent[4] despite the interest in this class of compounds related to their wide range of biological activities[5].

Herein we report the Suzuki cross-coupling of densely functionalized ethyl 1-substituted 2-chloro-5-ethoxy-6-oxo-1,6-dihydropyrimidine-4-carboxylates with a variety of boronic acids. For an easy access to the desired target structures, it is mandatory that the N1-substituted pyrimidones are readily accessible. Sochilin[6] and co-workers had described the synthesis of pyrimidone **5a**. We applied their methodology to access 2-chloropyrimidone **3a**, as well as the benzyl and phenyl analogues **3b** and **3c**, which we needed to explore the scope and limitations of the methodology.

All three compounds were accessible in multigram quantities by the four-step route shown in Scheme 2. Condensation of commercially available N-substituted ureas with diethyl 2-ethoxy-3-oxosuccinate[6,7] afforded hydantoins **4a–c** which underwent a base-promoted ring expansion to the corresponding 2-hydroxypyrimidones **5a–c**. Esterification and reaction with phosphorous oxychloride afforded the chlorides **3a–c** which were obtained pure with only one column chromatographic purification after the last step.



2 N-alkylation O-alkylation

Scheme 1 Typical synthetic route to pyrimidones[1]

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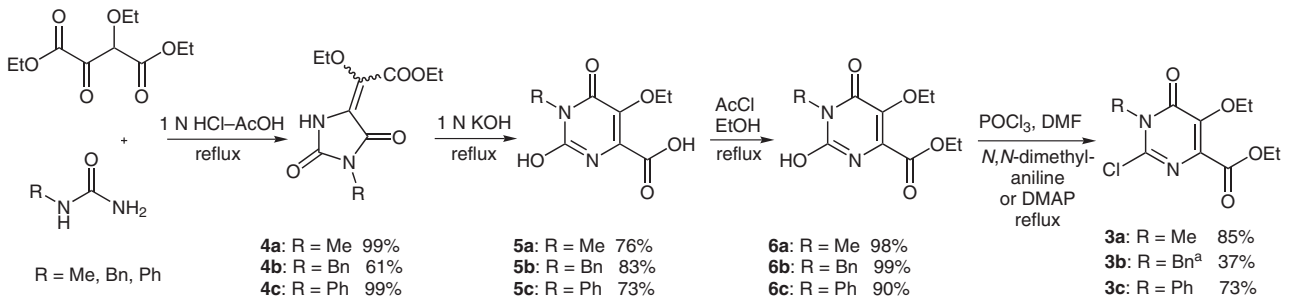

Scheme 2 Synthesis of ethyl 1-substituted 2-chloro-5-ethoxy-6-oxo-1,6-dihydropyrimidine-4-carboxylates **3a–c**. [a] DMAP was used as catalyst and the reaction was performed in a microwave apparatus at 200 °C.

We chose chloride **3a** as initial substrate for the optimization of the reaction conditions, using 3-methoxyphenylboronic acid as the coupling counterpart[1] for the optimization. The results obtained are reported in Table 1. We initially cross-coupled **3a** using the 'classical' tetrakis(triphenylphosphine)palladium(0) and 1,2-bis(diphenylphosphinoethane)palladium(II) chloride. In both cases complete consumption of **3a** was observed in about four hours and we were able to isolate **7a** in 50% and 45% yield, respectively (Table 1, entries 1 and 2).

The major side-reactions, as judged by LC-MS, were hydrolysis of **3a** to the corresponding 2-hydroxy pyrimidone **6a** and reduction of **3a** to ethyl 5-ethoxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxylate. When we used K_3PO_4 as a base in the absence of water, the hydrolysis of the chloride was suppressed and **7a** was isolated in 80% yield (Table 1, entry 3).

Table 1 Suzuki Coupling of **3a** under Thermal Conditions

Entry	Boronic acid	Conditions[a]	Product	Yield (%)[b]
1	3-methoxyphenyl	A	**7a**	50[c]
2	3-methoxyphenyl	B	**7a**	45[c]
3	3-methoxyphenyl	C	**7a**	80[c]
4	3-methoxyphenyl	D	**7a**	92[c]
5	phenyl	D	**7b**	86[c]
6	4-acetoxyphenyl	D	**7c**	75
7	3-thienyl	D	**7d**	99
8	2-thienyl	D	**7e**	79
9	4-methoxyphenyl	D	**7f**	58
10	2-methoxyphenyl	D	**7k**	40[d]
11	1-naphthyl	D	**7g**	10[d]
12	*o*-tolyl	D	**7h**	0[d]

[a] Conditions A: $Pd(PPh_3)_4$ (10%), Na_2CO_3 (3.0 equiv), boronic acid (1.5 equiv), DME–EtOH–H_2O, 80 °C, 4 h; Conditions B: $Pd(dppe)Cl_2$ (10%), Na_2CO_3 (3.0 equiv), boronic acid (1.3 equiv), toluene–H_2O, 100 °C; Conditions C: $Pd(PPh_3)_4$ (10%), K_3PO_4 (3.0 equiv), boronic acid (1.1 equiv), toluene, 100 °C, 16 h; Conditions D: $Pd_2(dba)_3$ (6%), [(*t*-Bu)$_3$PH]BF_4 (12%), KF (3.3 equiv), boronic acid (1.1 equiv), dioxane, 85 °C, 16 h.
[b] Isolated yields.
[c] Average of two independent experiments.
[d] Isolated yield after 48 h, incomplete conversion of **3a**.

We were pleased to find that the reaction of **3a** with 1.1 equivalents of 3-methoxyphenylboronic acid proceeded with very high yield in the presence of Pd_2dba_3 (6 mol%) and the air-stable [(*t*-Bu)$_3$ PH]BF_4 ligand[9] (12 mol%) in dioxane at 85 °C (Table 1, entry 4). With respect to condition C (Table 1), which also gave a high isolated yield of **7a**, the Fu catalyst allowed an easier isolation of the coupling product from the reaction by-products. These conditions were then used to determine the scope and limitations of the boronic acid partner (Scheme 3).

Scheme 3 Suzuki cross-coupling of 2-chloropyrimidones

As shown by the data reported in Table 1, the reaction proceeds smoothly with aryl- and heteroarylboronic acids (entries 5–8), tolerating the presence of reactive functional groups and of electron-donating substituents (entries 6 and 9), with yields varying from moderate to high. In the case of increased steric demand of the boronic acid counterpart lower yields were observed, as for the coupling of **3a** with 2-methoxyphenyl- and 1-naphthylboronic acids (entry 10 and 11). In both cases, a considerable amount of unreacted **3a** was detected by LC-MS even after two days. In the case of *o*-tolylboronic acid formation of product was observable only in traces by LC-MS (entry 12) with mostly unreacted starting material present.

To achieve good conversion also in the case of increased steric hindrance in the boronic acid component, we decided to investigate the reaction under controlled microwave acceleration.[10] High-speed synthesis using microwaves has received great attention in the recent years.[11] In the pharmaceutical industry, the drug discovery process gained considerable benefit from the use of microwave synthesis due to its ability of greatly reduce reaction times, which concomitantly diminishes or suppresses the occurrence of side reactions and consequently increases chemical yields.

When we performed the Suzuki coupling of **3a** with *o*-tolylboronic acid under microwave irradiation, we observed complete conversion of **3a** with the formation of **7h** in 86% isolated yield using $Pd_2(dba)_3$/[(*t*-Bu)$_3$PH]BF_4 in dioxane at 135 °C for 10 minutes (Table 2, entry 1). These conditions did not tolerate further steric hindrance. The 2,6-dimethylphenylboronic acid gave low conversion. No improvement was observed upon increasing the temperature and/or the reaction times, presumably due to decomposition of the $Pd_2(dba)_3$/[(*t*-Bu)$_3$PH]BF_4 catalyst. We decided to test $Pd(PPh_3)_4$ which had given good results in the thermal reaction (Table 1, entry 3) and whose use in microwave-accelerated chemistry has already been well documented.[10,11]

Irridiation of **3a** and 2,6-dimethylphenylboronic acid in the presence of 10% of $Pd(PPh_3)_4$ in toluene–DMF (5:1) at 200 °C for five minutes gave the coupling product **7i** in 67% isolated yield (Table 2, entry 3). As the results in Table 2 show, the microwave-accelerated methodology with $Pd(PPh_3)_4$ as the catalyst is not only effective in the case of increased steric hindrance, but also compatible with the presence of sensitive functional groups (entries 4–8). Furthermore, the catalyst loading can be reduced to 1%, at least in simple coupling reactions, as entry 9 shows. On the other hand, alkylboronic acids {which are reported to react in the presence of the $Pd_2(dba)_3$/[(*t*-Bu)$_3$PH]BF_4 catalyst[8b]} are completely unreactive towards our substrate under both of the above-described reaction conditions (entry 10).

Table 2 Suzuki Coupling of **3a** under Microwave Heating

Entry	Boronic acid	Method[a]	Product	Yield (%)
1	*o*-tolyl	A	**7h**	77
2	2,6-dimethylphenyl	A	**7i**	traces
3	2,6-dimethylphenyl	B	**7i**	67
4	1-naphthyl	B	**7g**	81
5	2-naphthyl	B	**7j**	82
6	2-methoxyphenyl	B	**7k**	84
7	4-formylphenyl	B	**7l**	65
8	styryl	B	**7m**	70
9	phenyl	C	**7b**	88
10	cyclohexyl	A, B	**7n**	0

[a] Method A: $Pd_2(dba)_3$ (6%), [(*t*-Bu)$_3$PH]BF_4 (12%), KF, dioxane, 135 °C, 10 min; Method B: $Pd(PPh_3)_4$ (10%), K_3PO_4, toluene–DMF (5:1), 200 °C, 10 min; Method C: $Pd(PPh_3)_4$ (1%), K_3PO_4, toluene–DMF (5:1), 200 °C, 10 min.

In order to study the effect of different substituents on the N1 nitrogen, we then performed the Suzuki coupling under the optimized microwave conditions with 2-chloropyrimidones **3b** and **3c** (Scheme 3). As shown by the results presented in Table 3, the *N*-benzyl derivative **3b** underwent Suzuki coupling in the presence of 10% Pd $(PPh_3)_4$ in high isolated yields both with phenyl- and 3-thienylboronic acids (entries 1 and 3). The reaction tolerates the presence of steric hindrance on the boronic acid counterpart as shown by the coupling with *o*-tolylboronic acid (entry 2) which proceeded in 74% isolated yield. The overall reactivity of **3b** in the microwave-accelerated Suzuki coupling is substantially similar to the one of the *N*-methyl derivative **3a**. In the case of the *N*-phenyl derivative **3c**, reactions were considerably slower, requiring 20 minutes of microwave heating in order to achieve complete conversion (or not further progression in the case of incomplete reaction).

For **3c**, the $Pd_2(dba)_3$/[(*t*-Bu)$_3$PH]BF_4 catalyst proved to be superior to $Pd(PPh_3)_4$, this being consistent with the reported higher efficiency of the former in the presence of increased steric hindrance on the aryl chloride, but the yields were substantially lower than in previous cases. As summarized by the results reported in Table 3, **3c** coupled to phenylboronic acid in 84% yield (entry 4), to 4-methoxyphenylboronic acid in 50% yield (entry 6), to *o*-tolylboronic acid in 34% yield (entry 5) and only in trace amount to 2,6-dimethylphenylboronic acid (entry 7). In the last example, apart from incomplete conversion, a major side reaction was the reduction of **3c**. For this particular example, the use of the S-PHOS/$Pd_2(dba)_3$ catalyst[12] partially suppressed reduction but gave only a slightly increase in yield of **9d** (20% isolated). We are currently investigating whether this reaction can be further improved.

In summary, we have reported the Suzuki coupling of densely functionalized N1-substituted 2-chloropyrimidones with a variety of boronic acids, which was virtually unprecedented in the literature for such systems. A proper choice of the reaction conditions (i.e. thermal or microwave heating, use of different catalysts) allowed us to couple sterically demanding as well as electronically deactivated and heterocyclic boronic acids with isolated yields ranging from moderate to excellent. We believe that this methodology can be applied also to similar heterocyclic systems of potential interest in medicinal chemistry.

In terms of the advantage offered to our drug discovery process, the methodology represents a very important tool to rapidly explore the structure–activity relationship in position 2 of the pyrimidone ring while having a different

Table 3 Suzuki Coupling of **3b** and **3c** under Microwave Heating

Entry	Boronic acid	Chloride	Method[a]	Product	Yield (%)
1	phenyl	**3b**	B	**8a**	82
2	*o*-tolyl	**3b**	B	**8b**	74
3	3-thienyl	**3b**	D	**8c**	78
4	phenyl	**3c**	D	**9a**	84
5	*o*-tolyl	**3c**	D	**9b**	34
6	4-methoxyphenyl	**3c**	D	**9c**	50
7	2,6-dimethylphenyl	**3c**	D	**9d**	traces

[a] Method B (see Table 2): $Pd(PPh_3)_4$ (10%), K_3PO_4 (3.0 equiv), boronic acid (1.1 equiv), toluene–DMF (5:1), 200 °C, 15 min; Method D: $Pd_2(dba)_3$ (6%), $[(t\text{-}Bu)_3PH]BF_4$ (12%), KF (3.3 equiv), boronic acid (1.1 equiv), dioxane, 135 °C, 20 min.

substituent on the N1 nitrogen. This provided the opportunity to synthesize derivatives which we were not able to obtain by other routes.

Reagents and anhydrous solvents were obtained from commercial sources and were used without further purification unless otherwise noted. Petroleum ether (PE) used refers to the fraction boiling in the range 40–65 °C.

Nuclear magnetic resonance (^{1}H NMR, ^{13}C NMR) spectra were obtained on Bruker AMX 400 (400 MHz) or AMX 300 (300 MHz) spectrometer. For ^{1}H spectra chemical shifts are reported in ppm relative to internal TMS or the residual solvent peak. Data are reported as follows: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; qui, quintet; m, multiplet; br, broad; app, apparent), coupling constants and integration. Low-resolution mass spectra (*m*/*z*) were recorded on a Perkin-Elmer API 100 (electrospray ionization) mass spectrometer; only molecular and isotopic ions are reported. High-resolution mass measurements were performed on a Finnigan TSQ Quantum Ultra AM in Selected Ion Monitoring Mode (SIM). Elemental analyses were performed on an Elemental Analyzer EA1108 (Carlo Erba Strumentazione). Microwave heating was performed using a Smith Creator™ microvawe reactor (supplied by Personal Chemistry/Biotage).

Caution (!) The palladium catalysts tend to decompose under microwave heating with formation of a precipitate, presumably consisting of palladium black, which can result in considerable overheating. The sealed vials used for the microwave reactions should therefore **not** be used for a second run of heating in the case of incomplete reactions.

Flash Chromatography was performed either using 230–400 mesh silica gel 60 (Merck) as stationary phase or by Jones Flashmaster II™ and Flashmaster Personal purification systems, using prepacked Isolute™ Si cartridges.

Compounds 4a–c; Ethyl 2-Ethoxy(1-methyl-2, 5-dioxoimidazolidin-4-ylidene)ethanoate (4a); Typical Procedure

A mixture of diethyl 2-ethoxy-3-oxosuccinate[6] (3 g, 12.9 mmol) and *N*-methylurea (0.960 g, 12.9 mmol) was refluxed for 2 h in 1 M HCl–AcOH (65 mL). The cooled reaction mixture was evaporated to dryness and the residue co-evaporated with toluene and dried in vacuo to afford **4a** (3.12 g, 99%) as an off-white solid, which was carried through without further purification.

^{1}H NMR (400 MHz, $CDCl_3$, 3:1 *E*/*Z** ratio): δ = 10.46* (s, 1 H), 10.03 (s, 1 H), 4.28 (q, *J* = 7.2 Hz, 2 H), 3.94* (q, *J* = 7.2 Hz, 2 H), 3.87 (q, *J* = 6.8 Hz, 2 H), 2.91 (s, 3 H), 2.86* (s, 3 H), 1.29–1.22 (m, 3 H).

Ethyl 2-Ethoxy(1-benzyl-2,5-dioxoimidazolidin-4-ylidene)-ethanoate (4b)

The title compound was obtained analogously from 2-ethoxy-3-oxosuccinate and *N*-benzylurea as an off-white solid (61%).

^{1}H NMR (300 MHz, DMSO-d_6, 5:1 *E*/*Z** ratio): δ = 7.36–7.27 (m, 5 H), 4.62 (s, 2 H), 4.28 (q, *J* = 7.2 Hz, 2 H), 4.20* (q, *J* = 7.2 Hz, 2 H), 3.95* (q, *J* = 6.8 Hz, 2 H), 3.87 (q, *J* = 6.8 Hz, 2 H), 1.29–1.23 (m, 6 H).

Ethyl 2-Ethoxy(1-phenyl-2,5-dioxoimidazolidin-4-ylidene)-ethanoate (4c)

The title compound was obtained analogously from 2-ethoxy-3-oxosuccinate and *N*-phenylurea as a white solid (99%).

^{1}H NMR (400 MHz, DMSO-d_6, 3:1 *E*/*Z** ratio): δ = 7.50–7.39 (m, 5 H), 4.32 (q, *J* = 6.8 Hz, 2 H), 4.30* (q, *J* = 6.8 Hz, 2 H), 4.05* (q, *J* = 6.8 Hz, 2 H), 3.90 (q, *J* = 6.8 Hz, 2 H), 1.28–1.23 (m, 6 H).

Compounds 5a-c; 5-Ethoxy-2-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxylic Acid (5a); Typical Procedure

Compound **4a** (3.12 g, 12.9 mmol) was dissolved in aq 1 N KOH (51.6 mL) and refluxed for 3 h. The mixture was cooled to 0 °C and carefully acidified with conc. HCl. After overnight cooling (+4 °C) led to the formation of a white precipitate, the mixture was filtered and the precipitate was dried in vacuo. Product **5a** was obtained as a white solid (1.74 g, 63%).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 14.2 (br s, 1 H), 10.89 (s, 1 H), 3.93 (q, *J* = 6.8 Hz, 2 H), 3.13 (s, 3 H), 1.20 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 162.2, 161.3, 149.7, 132.4, 132.0, 69.3, 27.6, 15.4.

MS (ES^-): *m*/*z* = 213 (M – H).

Anal. Calcd for $C_8H_{10}N_2O_5 \cdot H_2O$: C, 41.38; H, 5.20; N, 12.13. Found: C, 41.79; H, 5.15; N, 12.13.

1-Benzyl-5-ethoxy-2-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxylic Acid (5b)

This compound was obtained analogously from **4b**; white solid; yield: 83%.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.04 (s, 1 H), 7.34–7.22 (m, 5 H), 4.95 (s, 2 H), 3.93 (q, 2 H, *J* = 6.8 Hz), 1.20 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 161.7, 160.8, 149.2, 136.8, 132.7, 131.6, 128.3, 127.5, 127.2, 69.0, 43.5, 15.0.

MS (ES$^+$): m/z = 291 (M + H).

Anal. Calcd for $C_{14}H_{14}N_2O_5$: C, 57.93; H, 4.86; N, 9.65. Found: C, 58.34; H, 4.90; N, 9.62.

5-Ethoxy-2-hydroxy-6-oxo-1-phenyl-1,6-dihydropyrimidine-4-carboxylic Acid (5c)

This compound was obtained analogously from **4c**; off-white solid; yield: 73%.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.03 (s, 1 H), 7.49–7.40 (m, 3 H), 7.26 (d, J = 7.2 Hz, 2 H), 3.95 (q, J = 7.1 Hz, 2 H), 1.21 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 161.7, 160.9, 149.2, 135.2, 132.8, 132.6, 128.9, 128.7, 128.3, 69.0, 15.1.

MS (ES$^+$): m/z = 277 (M + H).

Anal. Calcd for $C_{13}H_{12}N_2O_5$: C, 56.52; H, 4.38; N, 10.14. Found: C, 56.53; H, 4.35; N, 10.01.

Compounds 6a–c; Ethyl 5-Ethoxy-2-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxylate (6a); Typical Procedure

Acetyl chloride (9.41 mL, 132. 3 mmol) was added dropwise to absolute EtOH (110 mL) at 0 °C. After stirring the resulting solution for 20 min at r.t., **5a** (1.42 g, 6.6.2 mmol) was added in one portion and the mixture was refluxed overnight. The volatiles were evaporated in vacuo and the residue was co-evaporated with toluene and dried to give **6a** (1.57g, 98%) as an off-white solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.03 (br s, 1 H), 4.30 (q, J = 7.1 Hz, 2 H), 3.95 (q, J = 7.1 Hz, 2 H), 3.14 (s, 3 H), 1.30 (t, J = 7.1 Hz, 3 H), 1.22 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 160.8, 160.3, 149.3, 132.5, 130.6, 69.0, 62.3, 27.3, 15.0, 13.8.

MS (ES$^+$): m/z = 243 (M + H).

Anal. Calcd for $C_{10}H_{14}N_2O_5$: C, 49.58; H, 5.83; N, 11.56. Found: C, 49.65; H, 5.44; N, 11.02.

Ethyl 1-Benzyl-5-ethoxy-2-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxylate (6b)

This compound was obtained analogously from **5b**; white solid; yield: 99%.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.17 (br s, 1 H), 7.34–7.22 (m, 5 H), 4.95 (s, 2 H), 4.31(q, J = 7.1 Hz, 2 H), 3.93 (q, J = 7.1 Hz, 2 H), 1.30 (t, J = 7.1 Hz, 3 H), 1.22 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 160.6, 160.2, 149.2, 136.7, 132.5, 131.1, 128.3, 127.5, 127.2, 69.1, 62.4, 43.5, 15.0, 13.7.

MS (ES$^+$): m/z = 319 (M + H).

Anal. Calcd for $C_{16}H_{18}N_2O_5 \cdot 1/2H_2O$: C, 58.71; H, 5.85; N, 8.56. Found: C, 58.78; H, 5.51; N, 8.62.

Ethyl 5-Ethoxy-2-hydroxy-6-oxo-1-phenyl-1,6-dihydropyrimidine-4-carboxylate (6c)

This compound was obtained analogously from **5c**; off-white solid; yield: 90%.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.18 (s, 1 H), 7.49–7.39 (m, 3 H), 7.28–7.26 (d, J = 7.2 Hz, 2 H), 4.34 (d, J = 7.1 Hz, 2 H) 3.98 (q, J = 7.1 Hz, 2 H), 1.32 (t, J = 7.1 Hz, 3 H), 1.22 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 160.7, 160.4, 149.2, 135.2, 132.9, 131.4, 128.8, 128.7, 128.2, 69.1, 62.4, 15.0, 13.8.

MS (ES$^+$): m/z = 305 (M + H).

Anal. Calcd for $C_{15}H_{16}N_2O_5$: C, 59.21; H, 5.30; N, 9.77. Found: C, 59.50; H, 5.31; N, 9.44.

Compounds 3a–c; Ethyl 2-Chloro-5-ethoxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxylate (3a); Typical Procedure

N,*N*-Dimethylaniline (0.856 mL, 6.76 mmol) was added to a stirred solution of **6a** (1.17g, 4.83 mmol) in $POCl_3$ (34.5 mL) and the mixture was refluxed overnight. Excess of $POCl_3$ was evaporated in vacuo and the residue was poured into ice-water and extracted with Et_2O. The combined ethereal layers were washed with brine, dried (Na_2SO_4) and evaporated in vacuo. Purification by flash chromatography (SiO_2, PE–EtOAc, 2:1) gave **3a** (1.07 g, 85%) as a light-yellow oil, which solidified upon standing.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.30 (q, J = 6.8 Hz, 2 H), 4.13 (q, J = 6.8 Hz, 2 H), 3.53 (s, 3 H), 1.28 (t, J = 6.8 Hz, 3 H), 1.24 (t, J = 6.8 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 162.9, 159.2, 143.4, 142.1, 140.0, 68.2, 61.6, 33.78, 15.1, 13.9.

MS (ES$^+$): m/z = 261 (M + H).

Anal. Calcd for $C_{10}H_{13}ClN_2O_4 \cdot H_2O$: C, 46.08; H, 5.03; N, 10.75. Found: C, 45.83; H, 4.89; N, 10.49.

Ethyl 1-Benzyl-2-chloro-5-ethoxy-6-oxo-1,6-dihydropyrimidine-4-carboxylate (3b)

This compound was obtained analogously from **6b** in the presence of catalytic amount of DMAP under microwave irradiation at 200 °C for 15 min; colorless oil; yield: 37%.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.40–7.27 (m, 5 H), 5.32 (s, 2 H), 4.32 (q, J = 6.9 Hz, 2 H), 4.18 (q, J = 6.9 Hz, 2 H), 1.30 (t, J = 6.9 Hz, 3 H), 1.26 (t, J = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 163.3, 160.1, 144.1, 142.8, 140.6, 134.3, 129.1, 128.6, 128.1, 69.6, 62.4, 50.5, 15.6, 14.3.

MS (ES$^+$): m/z = 337 (M + H).

Anal. Calcd for $C_{16}H_{17}ClN_2O_5$: C, 57.06; H, 5.09; N, 8.32. Found: C, 57.33; H, 5.10; N, 8.26.

Ethyl 2-Chloro-5-ethoxy-6-oxo-1-phenyl-1,6-dihydropyrimidine-4-carboxylate (3c)

This compound was obtained similarly from **6c**; light-yellow solid; yield: 73%.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.59–7.48 (m, 5 H), 4.35 (d, J = 7.1 Hz, 2 H) 4.17 (q, J = 7.1 Hz, 2 H), 1.32 (t, J = 7.1 Hz, 3 H), 1.26 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 163.1, 159.3, 143.2, 142.3, 140.0, 137.0, 129.7, 129.4, 128.0, 68.4, 61.7, 15.1, 13.9.

MS (ES$^+$): m/z = 323 (M + H).

Anal. Calcd for $C_{15}H_{15}ClN_2O_4$: C, 55.82; H, 4.68; N, 8.68. Found: C, 55.89; H, 4.72; N, 8.73.

Suzuki Coupling of Chlorides 3a–c; Ethyl 5-Ethoxy-2-(3-methoxyphenyl)-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxylate (7a); Typical Procedure (Thermal Condition D, Table 1)

Ethyl 2-chloro-5-ethoxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxylate (**3a**; 50 mg, 0.192 mmol), 3-methoxyphenylboronic acid (32 mg, 0.211 mmol), $Pd_2(dba)_3$ (10 mg, 0.011 mmol), [(t-Bu)$_3$PH]BF$_4$ (7 mg, 0.0023 mmmol) and spray-dried KF (38 mg, 0.65 mmol) were placed in an oven-dried flask and purged with argon. Anhydrous, degassed dioxane (0.65 mL) was added and the mixture was purged with three vacuum/argon cycles, before being heated at 85 °C in an inert atmosphere for 3 h. The cooled mixture was diluted with EtOAc, filtered over a plug of Celite and the filtrate was evaporated in vacuo. The residue was purified by Flashmaster personal (SiO_2, PE–EtOAc, 3:1) to give **7a** as a colorless oil; yield: 59 mg (92%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.36 (m, 1 H), 7.06–7.02 (m, 3 H), 4.40 (q, *J* = 7.2 Hz, 2 H), 4.32 (q, *J* = 7.2 Hz, 2 H), 3.84 (s, 3 H), 3.45 (s, 3 H), 1.41 (t, *J* = 7.2 Hz, 3 H), 1.39 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.6, 160.4, 160.0, 155.2, 142.5, 141.6, 135.5, 130.1, 120.5, 116.4, 113.9, 69.1, 62.1, 55.6, 34.9, 15.6, 14.3.

MS (ES^+): *m*/*z* = 333 (M + H).

Anal. Calcd for $C_{17}H_{20}N_2O_5$: C, 61.44; H, 6.07; N, 8.43. Found: C, 60.96; H, 6.01; N, 8.29.

7b

White solid; yield: 86%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.9 (m, 5 H), 4.40 (q, *J* = 7.2 Hz, 2 H), 4.34 (q, *J* = 7.2 Hz, 2 H), 3.46 (s, 3 H), 1.41 (t, *J* = 7.2 Hz, 3 H), 1.36 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.6, 160.4, 155.3, 142.5, 141.6, 134.3, 130.5, 128.9, 128.4, 69.0, 62.0, 34.9, 15.6, 14.3.

MS (ES^+): *m*/*z* = 303 (M + H).

Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.39; H, 5.94; N, 9.21.

7c

White solid; yield: 75%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 8.1 Hz, 2 H), 7.63 (d, *J* = 8.1 Hz, 2 H), 4.41 (q, *J* = 7.2 Hz, 2 H), 4.36 (q, *J* = 7.2 Hz, 2 H), 3.45 (s, 3 H), 2.65 (s, 3 H), 1.43 (t, *J* = 7.2 Hz, 3 H), 1.38 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.3, 164.5, 160.3, 154.1, 143.0, 141.4, 138.5, 138.4, 129.0, 128.8, 69.2, 62.2, 34.9, 26.9, 15.7, 14.3.

MS (ES^+): *m*/*z* = 345 (M + H).

Anal. Calcd for $C_{18}H_{20}N_2O_5 \cdot 1/2\ H_2O$: C, 61.18; H, 6.00; N, 7.93. Found: C, 61.41; H, 5.98; N, 7.90.

7d

Light-pink oil; yield: 99%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 1.2 Hz, 1 H), 7.43 (dd, *J* = 5.1, 3.0 Hz, 1 H), 7.31 (dd, *J* = 3.0, 1.2 Hz, 1 H), 4.41 (q, *J* = 7.2 Hz, 2 H), 4.35 (q, *J* = 7.2 Hz, 2 H), 3.55 (s, 3 H), 1.41 (t, *J* = 7.2 Hz, 3 H), 1.38 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.64, 160.5, 151.1, 142.5, 141.7, 134.9, 128.6, 127.6, 126.8, 69.1, 62.1, 34.7, 15.7, 14.3.

MS (ES^+): *m*/*z* = 309 (M + H).

Anal. Calcd for $C_{14}H_{16}N_2O_4S$: C, 54.53; H, 5.23; N, 9.08. Found: C, 54.33; H, 5.19; N, 9.00.

7e

Beige oil; yield: 79%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 5.1 Hz, 1 H), 7.47 (d, *J* = 3.0 Hz, 1 H), 7.12 (m, 1 H), 4.41 (q, *J* = 7.2 Hz, 2 H), 4.34 (q, *J* = 7.2 Hz, 2 H), 3.72 (s, 3 H), 1.40 (t, *J* = 7.2 Hz, 3 H), 1.40 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.4, 160.5, 149.3, 142.2, 141.7, 136.2, 130.4, 130.3, 127.7, 69.2, 62.1, 34.7, 15.6, 14.4.

MS (ES^+): *m*/*z* = 309 (M + H).

Anal. Calcd for $C_{14}H_{16}N_2O_4S$: C, 54.53; H, 5.23; N, 9.08. Found: C, 54.32; H, 5.20; N, 9.07.

7f

White solid; yield: 58%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 8.7 Hz, 2 H), 6.98 (d, *J* = 8.7 Hz, 2 H), 4.40 (q, *J* = 7.2 Hz, 2 H), 4.35 (q, *J* = 7.2 Hz, 2 H), 3.86 (s, 3 H), 3.49 (s, 3 H), 1.40 (t, *J* = 7.2 Hz, 3 H), 1.37 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.8, 161.4, 160.7, 155.4, 142.2, 141.8, 130.3, 126.7, 114.3, 69.1, 62.1, 55.6, 35.3, 15.7, 14.3.

MS (ES^+): *m*/*z* = 333 (M + H).

Anal. Calcd for $C_{17}H_{20}N_2O_5$: C, 61.44; H, 6.07; N, 8.43. Found: C, 61.23; H, 6.14; N, 8.50.

Suzuki Coupling of Chlorides 3a–c; Ethyl 5-Ethoxy-1-methyl-2-(2-methylphenyl)-6-oxo-1,6-dihydropyrimidine-4-carboxylate (7h) and Ethyl 5-Ethoxy-2-(2,6-dimethylphenyl)-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxylate (7i); Typical Procedures (Microwave Conditions, Tables 2 and 3)

Method A: Ethyl 2-chloro-5-ethoxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxylate (**3a**; 50 mg, 0.19 mmol), *o*-tolylboronic acid (32 mg, 0.21 mmol), $Pd_2(dba)_3$ (10 mg, 0.011 mmol), $[(t\text{-}Bu)_3PH]BF_4$ (7 mg, 0.023 mmol) and spray-dried KF (38 mg, 0.65 mmol) were placed in an Smith Creator Microwave vial which was sealed and flushed with argon. Anhydrous, degassed dioxane (0.65 mL) was added and the mixture was heated at 135 °C in the Smith Creator apparatus for 10 min. The cooled mixture was diluted with EtOAc, filtered over a plug of Celite and the filtrate was evaporated in vacuo. The residue was purified by Flashmaster Personal (SiO_2; PE–EtOAc, 3:1) to give **7h** as a white solid; yield: 46 mg (77%) (Table 2).

7h

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.24 (m, 4 H), 4.40 (q, *J* = 7.2 Hz, 2 H), 4.35 (q, *J* = 7.2 Hz, 2 H), 3.28 (s, 3 H), 2.21 (s, 3 H), 1.44 (t, *J* = 7.2 Hz, 3 H), 1.38 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.6, 160.3, 155.3, 142.6, 141.7, 135.7, 134.2, 130.9, 130.3, 127.9, 126.6, 69.1, 62.1, 33.5, 19.3, 15.7, 14.3.

MS (ES^+): *m*/*z* = 317 (M + H).

Anal. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.86. Found: C, 64.22; H, 6.28; N, 8.75.

Method B: Ethyl 2-chloro-5-ethoxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxylate (**3a**; 50 mg, 0.192 mmol), 2,6-dimethylphenylboronic acid (32 mg, 0.211 mmol), $Pd(PPh_3)_4$ (22 mg, 0.019 mmol) and K_3PO_4 (122 mg, 0.576 mmol) were placed in a Smith Creator microwave vial which was sealed and flushed with argon. Anhydrous toluene (1.6 mL) and DMF (0.3 mL) were added and the mixture was heated at 200 °C in the microwave apparatus for 10 min. The cooled mixture was diluted with EtOAc, filtered over a plug of Celite and the filtrate was evaporated in vacuo. The residue was purified by Flashmaster Personal (SiO_2; PE–EtOAc, 3:1) to give **7i** as a light-yellow oil; yield: 42 mg (67%) (Table 2).

7i

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.26 (m, 1 H), 7.12–7.10 (m, 2 H), 4.40 (q, *J* = 7.2 Hz, 2 H), 4.34 (q, *J* = 7.2 Hz, 2 H), 3.24 (s, 3 H), 2.12 (s, 6 H), 1.42 (t, *J* = 7.2 Hz, 3 H), 1.38 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.6, 160.4, 155.0, 142.4, 142.0, 135.6, 134.0, 130.0, 128.2, 69.2, 62.1, 32.5, 19.5, 15.7, 14.3.

MS (ES^+): *m*/*z* = 331 (M + H).

Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.02. Found: C, 65.3; H, 6.69; N, 8.02.

The following compounds were obtained by microwave-assisted Method B (Tables 2 and 3).

7g
White solid; yield: 81%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00–7.91 (m, 5 H), 4.42 (q, *J* = 7.2 Hz, 2 H), 4.40 (q, *J* = 7.2 Hz, 2 H), 3.24 (s, 3 H), 1.46 (t, *J* = 7.2 Hz, 3 H), 1.38 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.3, 160.0, 154.4, 142.7, 141.6, 133.3, 131.5, 130.5, 130.1, 128.7, 127.6, 126.7, 126.5, 125.2, 124.0, 68.9, 61.9, 33.7, 15.5, 14.0.

MS (ES^+): *m*/*z* = 353 (M + H).

Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 67.93; H, 5.67; N, 7.90.

7j
White crystalline solid; yield: 82%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (s, 1 H), 7.96–7.88 (m, 3 H), 7.62–7.53 (m, 3 H), 4.42 (q, *J* = 7.2 Hz, 2 H), 4.37 (q, *J* = 7.2 Hz, 2 H), 3.51 (s, 3 H), 1.43 (t, *J* = 7.2 Hz, 3 H), 1.40 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.2, 159.3, 155.5, 141.4, 140.8, 133.2, 132.1, 131.6, 128.5, 128.4, 128.0, 127.7, 127.6, 127.0, 125.3, 68.0, 61.4, 34.6, 15.2, 14.0.

MS (ES^+): *m*/*z* = 353 (M + H).

Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 67.87; H, 5.62; N, 7.80.

7k
White solid yield: 84%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (td, *J* = 8.4, 1.6 Hz, 1 H), 7.39 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.07 (t, *J* = 7.6 Hz, 1 H), 7.96 (d, *J* = 8.4 Hz, 1 H), 4.45–4.31 (m, 4 H), 3.82 (s, 3 H), 3.35 (s, 3 H), 1.44–1.36 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.8, 160.3, 156.5, 153.9, 142.7, 141.9, 132.1, 130.3, 123.9, 121.4, 111.0, 69.0, 62.0, 55.7, 33.3, 15.7, 14.3.

MS (ES^+): *m*/*z* = 333 (M + H).

Anal. Calcd for $C_{17}H_{20}N_2O_5 \cdot 1/2H_2O$: C, 59.81; H, 6.20; N, 8.21. Found: C, 59.48; H, 6.01; N, 8.29.

7l
White solid; yield: 65%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.09 (s, 1 H), 8.02 (d, *J* = 8.1 Hz, 2 H), 7.71 (d, 2 H, *J* = 8.1 Hz), 4.41 (q, *J* = 6.9 Hz, 2 H), 4.37 (q, *J* = 6.9 Hz, 2 H), 3.46 (s, 3 H), 1.43 (t, *J* = 6.9 Hz, 3 H), 1.38 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.4, 164.5, 160.3, 153.8, 143.2, 141.4, 139.6, 137.6, 130.2, 129.4, 69.3, 62.3, 35.0, 15.7, 14.4.

MS (ES^+): *m*/*z* = 331 (M + H).

Anal. Calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found: C, 61.65; H, 5.44; N, 8.32.

7m
Yellow solid; yield: 70%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 15.3 Hz, 1 H), 7.71 (d, *J* = 8.1 Hz, 2 H), 7.57 (m, 2 H), 7.40 (m, 3 H), 6.96 (d, *J* = 15.3 Hz, 2 H), 4.44 (q, *J* = 7.2 Hz, 2 H), 4.29 (q, *J* = 7.2 Hz, 2 H), 3.68 (s, 3 H), 1.44 (t, *J* = 7.2 Hz, 3 H), 1.38 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.0, 160.1, 151.9, 142.5, 142.2, 142.0, 135.3, 130.2, 129.1, 128.1, 117.7, 69.1, 62.1, 31.2, 15.6, 14.4.

MS (ES^+): *m*/*z* = 329 (M + H).

Anal. Calcd for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53. Found: C, 65.70; H, 6.12; N, 8.40.

8a
White solid; yield: 82%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.21 (m, 8 H), 6.90–6.88 (m, 2 H), 5.19 (m, 2 H), 4.40 (q, *J* = 6.9 Hz, 2 H), 4.36 (q, *J* = 6.9 Hz, 2 H), 1.41 (t, *J* = 6.9 Hz, 3 H), 1.39 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.7, 160.3, 155.7, 143.1, 141.7, 135.8, 134.4, 130.4, 128.83, 128.76, 128.5, 128.0, 127.3, 69.2, 62.2, 49.7, 15.7, 14.4.

MS (ES^+): *m*/*z* = 379 (M + H).

Anal. Calcd for $C_{22}H_{22}N_2O_4$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.86; H, 5.87; N, 7.35.

8b
Yellow oil; yield: 74%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (t, *J* = 1.2 Hz, 1 H), 7.22–7.14 (m, 5 H), 7.08 (d, *J* = 3.6 Hz, 1 H), 6.81 (d, *J* = 6.8 Hz, 1 H), 5.12 (d, *J* = 14.4 Hz, 1 H), 5.02 (d, *J* = 14.4 Hz, 1 H), 4.39 (q, *J* = 7.2 Hz, 4 H), 1.90 (s, 3 H), 1.43 (t, *J* = 7.2 Hz, 3 H), 1.38 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.6, 160.4, 155.3, 143.1, 141.7, 136.5, 135.4, 133.9, 130.8, 130.3, 128.6, 128.3, 128.14, 128.06, 126.1, 69.3, 62.2, 49.0, 19.2, 15.7, 14.3.

MS (ES^+): *m*/*z* = 393 (M + H).

Anal. Calcd for $C_{23}H_{24}N_2O_4 \cdot 1/2H_2O$: C, 68.81; H, 6.28; N, 6.98. Found: C, 68.33; H, 6.03; N, 6.88.

8c
Light-yellow solid, yield: 78%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43 (m, 1 H), 7.42–7.27 (m, 4 H), 7.12 (d, *J* = 5.1 Hz, 1 H), 6.99–6.98 (m, 2 H), 5.27 (s, 2 H), 4.42 (q, *J* = 7.2 Hz, 2 H), 4.35 (q, *J* = 7.2 Hz, 2 H), 1.40 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.7, 160.2, 151.6, 143.0, 141.8, 141.6, 135.9, 134.7, 129.1, 128.3, 128.0, 127.8, 126.7, 69.3, 62.2, 49.8, 15.7, 14.4.

MS (ES^+): *m*/*z* = 385 (M + H).

Anal. Calcd for $C_{20}H_{20}N_2O_4S$: C, 62.48; H, 5.24; N, 7.29. Found: C, 61.98; H, 5.31; N, 7.09.

Method C: This procedure is the same as Method B, except that 1% of catalyst loading was used.

Compound **7b** (see above for characterization) was obtained in 88% isolated yield using this procedure.

Method D: This procedure is the same as Method A (Table 2), however, with a prolonged reaction time of 20 min. The following compounds were obtained by this method:

9a
Yellow solid; yield: 84%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.08 (m, 10 H), 4.44 (q, *J* = 7.2 Hz, 2 H), 4.38 (q, *J* = 7.2 Hz, 2 H), 1.42 (t, *J* = 7.2 Hz, 3 H), 1.41 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.7, 160.0, 154.5, 143.1, 141.8, 136.9, 134.4, 129.8, 129.4, 129.3, 129.1, 128.7, 128.1, 69.2, 62.2, 15.7, 14.3.

MS (ES^+): *m*/*z* = 365 (M + H).

Anal. Calcd for $C_{21}H_{20}N_2O_4$: C, 69.22; H, 5.53; N, 7.69. Found: C, 69.27; H, 5.53; N, 7.76.

9b
White solid; yield: 34%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27–7.22 (m, 3 H), 7.07–7.02 (m, 6 H), 4.43 (q, *J* = 7.2 Hz, 2 H), 4.39 (q, *J* = 7.2 Hz, 2 H), 2.26 (s, 3 H), 1.42 (t, *J* = 7.2 Hz, 3 H), 1.41 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.1, 159.0, 154.3, 141.8, 140.9, 136.4, 135.0, 133.9, 129.5, 129.0, 128.9, 128.6, 128.5, 124.7, 75.0, 68.1, 61.3, 19.1, 15.2, 13.9.

MS (ES$^+$): *m*/*z* = 379 (M + H).

HRMS: *m*/*z* calcd for $C_{22}H_{23}N_2O_4$: 379.1658; found: 379.1657.

9c
White solid; yield: 49%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.31 (m, 3 H), 7.20 (d, *J* = 8.7 Hz, 2 H), 7.10 (d, *J* = 6.3 Hz, 2 H), 6.67 (d, *J* = 8.7 Hz, 2 H), 4.44 (q, *J* = 6.9 Hz, 2 H), 4.33 (q, *J* = 6.9 Hz, 2 H), 1.42 (t, *J* = 6.9 Hz, 3 H), 1.40 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.8, 160.7, 160.2, 154.3, 142.7, 142.0, 137.2, 131.2, 129.4, 129.0, 128.7, 126.7, 113.5, 69.2, 62.2, 55.4, 15.7, 14.4.

MS (ES$^+$): *m*/*z* = 395 (M + H).

Anal. Calcd for $C_{22}H_{22}N_2O_5$: C, 66.99; H, 5.62; N, 7.10. Found: C, 66.98; H, 5.64; N, 7.16.

9d
This compound was obtained by the reaction of **3c** with 2,6-dimethylphenylboronic acid using the conditions described.[12]

White solid; yield: 20%.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.27 (m, 5 H), 7.04 (t, *J* = 7.6 Hz, 1 H), 6.88 (d, *J* = 7.6 Hz, 2 H), 4.33 (q, *J* = 7.0 Hz, 2 H), 4.25 (q, *J* = 7.0 Hz, 2 H), 2.11 (s, 6 H), 1.31 (t, *J* = 7.0 Hz, 3 H), 1.30 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 163.96, 159.1, 154.0, 142.0, 141.3, 140.8, 135.8, 134.9, 133.7, 129.0, 128.9, 128.5, 126.9, 68.1, 61.4, 19.6, 15.2, 13.9.

MS (ES$^+$): *m*/*z* = 393 (M + H).

HRMS: *m*/*z* calcd for $C_{23}H_{24}N_2O_4$: 392.4587; found: 392.4584.

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