Copper-Catalyzed [3+2] Annulation of O-Acyl Ketoximes with 2-Aryl Malonates for the Synthesis of 3-Aryl-4-Pyrrolin-2-Ones

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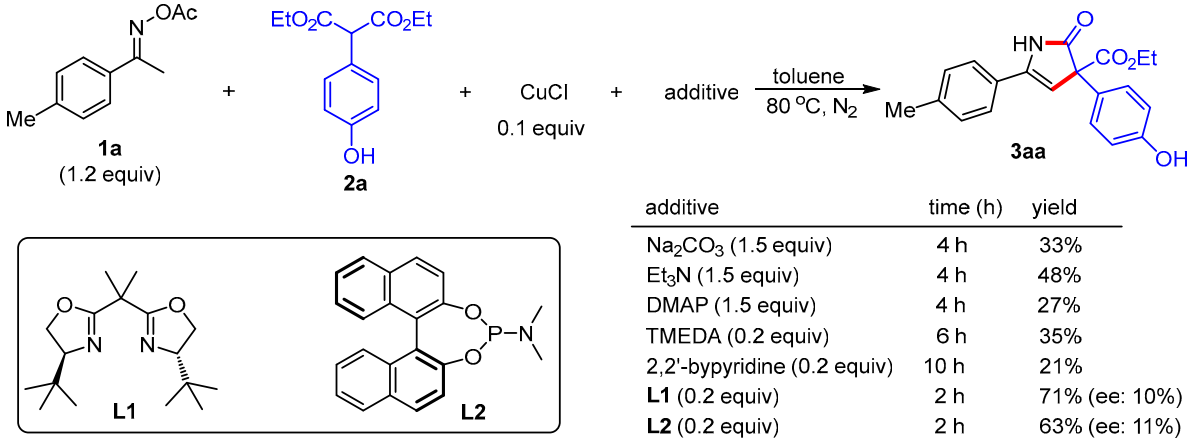
General Information

^{1}H and ^{13}C NMR (proton broadband decoupling) spectra were recorded on Bruker Avance 300 and 400 MHz (75 and 100 MHz for ^{13}C NMR) spectrometer at ambient temperature. The ^{1}H and the ^{13}C chemical shifts are given in ppm. The peak calibration was as follow: $CDCl_3$ as the solvent (^{1}H NMR: $CHCl_3$ = 7.26 ppm; ^{13}C NMR: $CDCl_3$ = 77.16 ppm), d_6-DMSO as the solvent (1H NMR: d_6-DMSO = 2.50 ppm; ^{13}C NMR: d_6-DMSO = 39.52 ppm). Flash column chromatography was performed over silica gel (200-300 mesh); HRMS was obtained on QTOF mass spectrometer. The melting point of those solids obtained through column chromatography was not provided because they were not a crystalline state and most of the purity did not reach 99%. Compounds **7**, **11a**, **11b**, and **13** were purchased commercially.

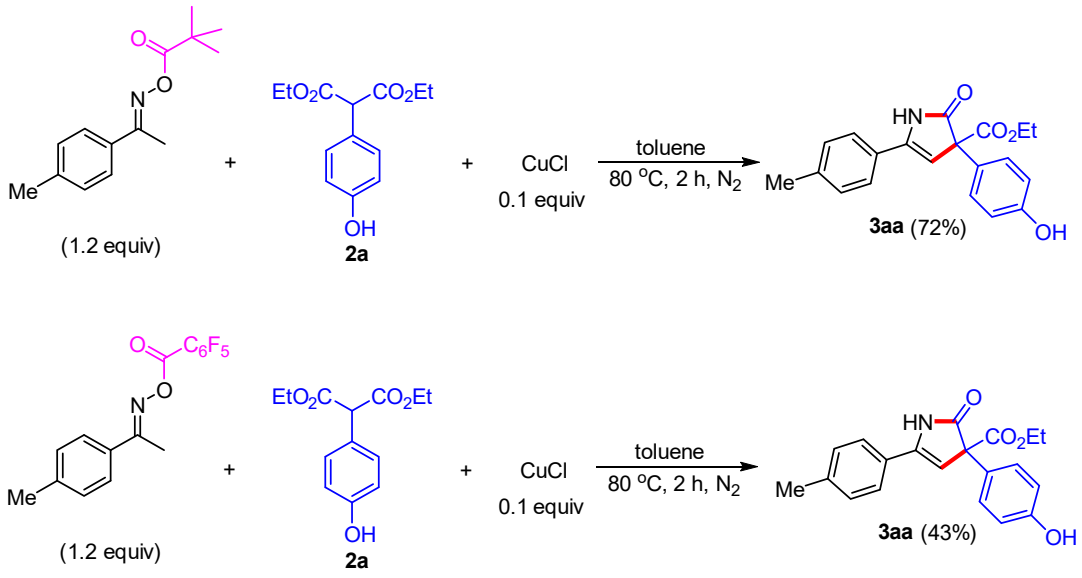
The influence of bases and ligands was showed in Scheme S1. Although one molecule of acetic acid was released in the reaction of **1a** with **2a**, addition of bases such as Na_2CO_3, Et_3N, and DMAP had no improvement in the yield. On the contrary, the reaction speed was significantly slowed down and a considerable decrease in the yield was observed. The addition of TMEDA and 2,2'-bypyridine as a ligand also resulted in decrease of the yield. However, the addition of oxazoline and phosphoramidite ligand gave a comparable yield with that of no addition of ligand. The addition of chiral oxazoline ligand **L1** and phosphoramidite ligand **L2** afforded **3aa** in 71% (10 % ee) and 63% yield (11% ee), respectively.

The influence of other *O*-protecting groups was also evaluated (Scheme S2). *O*-pivaloyl oxime had a similar reactivity with *O*-acetyl oxime. However, the *O*-pentafluorobenzoyl oxime gave a low yield of **3aa** because a large decomposition to ketone was observed.



additive	time (h)	yield
Na_2CO_3 (1.5 equiv)	4 h	33%
Et_3N (1.5 equiv)	4 h	48%
DMAP (1.5 equiv)	4 h	27%
TMEDA (0.2 equiv)	6 h	35%
2,2'-bypyridine (0.2 equiv)	10 h	21%
L1 (0.2 equiv)	2 h	71% (ee: 10%)
L2 (0.2 equiv)	2 h	63% (ee: 11%)

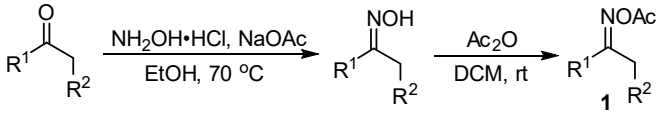
Scheme S1 The influence of bases and ligands on the reaction.



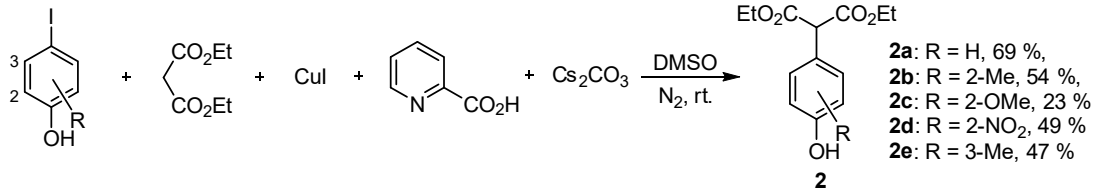
Scheme S2 The influence of acyl groups on the reaction.

Preparation of *O*-Acyl Oximes 1

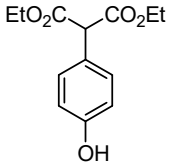
O-Acetyl oximes **1** were prepared according to our previously reported procedures.[1]



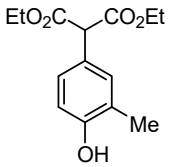
Preparation of of Diethyl 2-(4-Hydroxyaryl)malonates 2.



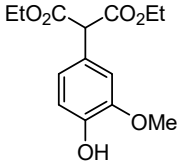
A mixture of iodinated phenols (3 mmol), 2-picolinic acid (73.8 mg, 0.6 mmol), Cs_2CO_3 (2.9340 g, 9 mmol), and diethyl malonate (960.0 mg, 6 mmol) in DMSO (3 mL) was stirred at room temperature for 5 minutes. Then, CuI (57.0 mg, 0.2 mmol) was added and the mixture stirred at room temperature under N_2 atmosphere until the full conversion of iodinated phenol as determined by TLC. Water (30 mL) and ethyl acetate (30 mL) was added and pH value was adjusted to 4-5 with dilute hydrochloric acid. The organic phase was separated and the aqueous phase was further extracted with ethyl acetate (2 × 30 mL). The combined organic phase was washed with aqueous $NaHCO_3$, saturated brine, and dried over anhydrous Na_2SO_4. After filtering and removing the solvent under reduced pressure, the residue was purified by column chromatography (ethyl acetate: petroleum ether = 1 : 10 to 1 : 3) to give the products **2**. (for **2b** and **2c**, the reaction was stirred in a 60 °C oil bath; for **2e**, the reaction was stirred in a 50 °C oil bath).



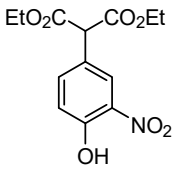
2a[2] (eluent : ethyl acetate / petroleum ether = 1 / 6, white solid, 521.6 mg, 69%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.6 Hz, 2H), 6.77 (d, *J* = 8.7 Hz, 2H), 5.46 (br, 1H), 4.54 (s, 1H), 4.14-4.28 (m, 4H), 1.26 (t, *J* = 7.1 Hz, 6H).



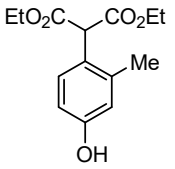
2b (eluent : ethyl acetate / petroleum ether = 1 / 3, yellow liquid, 427.5 mg, 54%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, *J* = 2.2 Hz, 1H), 7.08 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.69 (d, *J* = 8.3 Hz, 1H), 5.11 (br, 1H), 4.51 (s, 1H), 4.09-4.29 (m, 4H), 2.22 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 154.1, 131.9, 128.0, 124.7, 124.3, 115.2, 62.0, 57.3, 16.0, 14.2; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{14}H_{19}O_5$ 267.1227, found 267.1222.



2c (eluent : ethyl acetate / petroleum ether = 1 / 3, yellow liquid, 195.5 mg, 23%): ^{1}HNMR (300 MHz, $CDCl_3$) δ 6.98 (d, *J* = 1.6 Hz, 1H), 6.80-6.91 (m, 2H), 5.64 (br, 1H), 4.52 (s, 1H), 4.10-4.31 (m, 4H), 3.90 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 146.6, 145.8, 124.6, 122.7, 114.4, 111.6, 61.9, 57.5, 56.1, 14.2; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{14}H_{19}O_6$ 283.1176, found 283.1179.

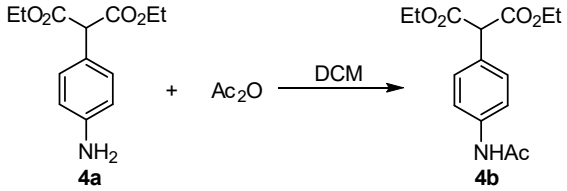


2d (eluent : ethyl acetate / petroleum ether = 1 / 10, yellow liquid, 435.3 mg, 49%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.59 (s, 1H), 8.15 (d, *J* = 2.2 Hz, 1H), 7.69 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.16 (d, *J* = 8.7 Hz, 1H), 4.59 (s, 1H), 4.15-4.31 (m, 4H), 1.27 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 155.1, 138.6, 133.4, 126.0, 125.3, 120.4, 62.4, 56.7, 14.1; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{13}H_{16}NO_7$ 298.0921, found 298.0914.



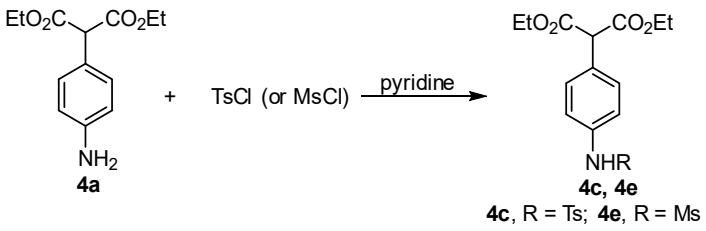
2e (eluent : ethyl acetate / petroleum ether = 1 / 6, yellow liquid, 371.5 mg, 47%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.9 Hz, 1H), 6.55-6.63 (m, 2H), 4.79 (s, 1H), 4.17-4.28 (m, 4H), 2.24 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 155.7, 138.2, 130.1, 123.4, 117.5, 113.5, 62.0, 53.8, 19.9, 14.1; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{14}H_{19}O_5$ 267.1227, found 267.1224.

Preparation of 4b.



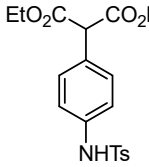
A mixture of **4a** (502 mg, 2 mmol, which was prepared according to the reported procedure[4]) and triethylamine (303 mg, 3.0 mmol) in dry dichloromethane (10 mL) was cooled to 0 ºC and then acetic anhydride (244.8 mg, 2.4 mmol) was added dropwise under stirring. After full conversion of **4a**, water (25 mL) was added and the mixture was extracted three times with dichloromethane (3 × 30 mL). The combined organic phase was wash with aqueous sodium bicarbonate, saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate : petroleum ether = 1 : 4 to 1 : 2) to give the product **4b**[3] (white solid, 476 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.43 (br, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 4.57 (s, 1H), 4.14-4.27 (m, 4H), 2.15 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 6H).

Preparation of 4c and 4e.

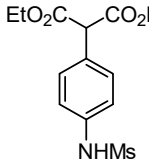


A solution of **4a** (502 mg, 2 mmol) in pyridine (3 mL) was cooled to 0 ºC and then TsCl or MsCl (2.4 mmol) was added in portions or dropwise under stirring. After the addition, the mixture was stirred at room temperature until no change was observed as determined by TLC. Water (30 mL)

was added and the mixture was extracted with dichloromethane (3 × 30 mL). The combined organic phase was wash with diluted hydrochloric acid, water, aqueous sodium bicarbonate, saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate : petroleum ether = 1 : 4 to 1 : 2) to give the product **4c** or **4e**.

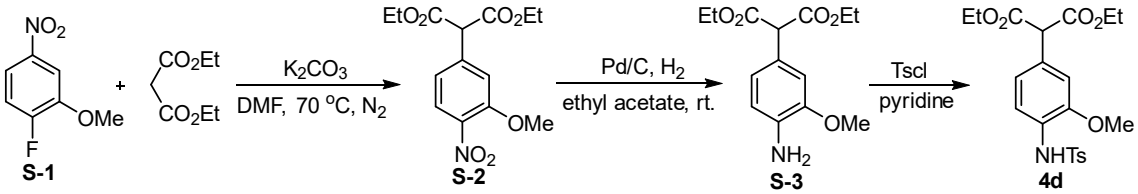


4c (white solid, 586 mg, 72%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.5 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 7.04 (d, J = 8.6 Hz, 2H), 6.81 (br, 1H), 4.55 (s, 1H), 4.12-4.26 (m, 4H), 2.40 (s, 3H), 1.24 (t, J = 7.2 Hz, 6H); 13C NMR (100 MHz, $CDCl_3$) δ 168.2, 144.1, 136.8, 136.3, 130.4, 129.8, 129.4, 127.4, 121.0, 62.0, 57.3, 21.6, 14.1; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{20}H_{24}NO_6S$ 406.1319, found 406.1314.



4e (white solid, 436 mg, 66%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 8.5 Hz, 2H), 7.20 (d, J = 8.6 Hz, 2H), 6.70 (br, 1H), 4.59 (s, 1H), 4.14-4.29 (m, 4H), 3.02 (s, 3H), 1.27 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 137.0, 130.7, 129.7, 120.5, 62.2, 57.3, 39.5, 14.1 HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{14}H_{20}NO_6S$ 330.1006, found 330.1002.

Preparation of 4d.



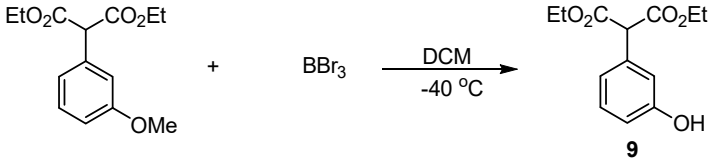
A mixture of 1-fluoro-2-methoxy-4-nitrobenzene (342 mg, 2 mmol), diethyl malonate (480 mg, 3 mmol), and K_2CO_3 (552 mg, 4 mmol) in DMF (8 mL) was stirred at 70 °C under N_2 atmosphere until the full conversion of **S-1** as determined by TLC. The reaction was cooled to room temperature. Water (80 mL) and ethyl acetate (40 mL) was added and pH value was adjusted to 4-5 with dilute hydrochloric acid. The organic phase was separated and the aqueous phase was further extracted with ethyl acetate (2 × 40 mL). The combined organic phases were washed with water (40 mL) and saturated brine (20 mL). After drying over Na_2SO_4 and filtering, the solvent was removed under reduced pressure to give a residue, which was used directly for the next step reaction without further purification.

Palladium/carbon (10% on carbon, 60 mg) and ethyl acetate (15 mL) was added to the above residue. The atmosphere was removed and nitrogen was backfilled (3 times). At the last time, hydrogen was backfilled and the mixture was stirred at room temperature under hydrogen atmosphere (baloon) until the full conversion as determined by TLC. The mixture was filtered to

remove palladium/carbon and the filtrate was concentrated under reduced pressure to obtain a crude product **S-3**, which was used directly for the next step reaction without further purification.

Pyridine (3 mL) was added to the obtained crude product and the mixture was cooled to 0 ºC. tosyl chloride (457 mg, 2.4 mmol) was added in portions under stirring. After addition, the mixture was stirred at room temperature until no change was observed as determined by TLC. Water (30 mL) was added and the mixture was extracted three times with dichloromethane (3 × 40 mL). The combined organic phase was wash with diluted hydrochloric acid, water, aqueous sodium bicarbonate, saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate: petroleum ether = 1 : 4 to 1 : 2) to give the product **4d** (white solid, 264 mg, 30% yield for the three step reaction from **S1** to **4d**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 8.3 Hz, 2H), 7.06 (s, 1H), 4.84-4.89 (m, 2H), 4.50 (s, 1H), 4.10-4.25 (m, 4H), 3.69 (s, 3H), 2.36 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 149.0, 143.9, 136.4, 129.6, 129.4, 127.4, 126.3, 122.3, 119.7, 111.5, 62.0, 57.6, 55.9, 21.6, 14.1; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{21}H_{26}NO_7S$ 436.1424, found 436.1416.

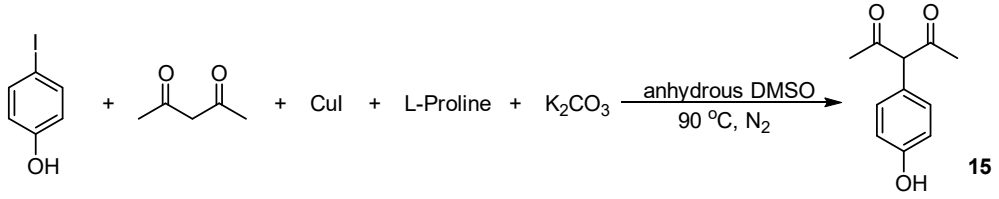
Preparation of 9.



9

Diethyl 2-(3-methoxyphenyl)malonate (399.0 mg, 1.5 mmol) was dissolved in 4 mL of dichloromethane. After cooling to -40 °C, boron tribromide (2.0 mol/L solution in dichloromethane, 4.5 mL, 9 mmol) was added dropwise. Two hours later, water (30 mL) was added and the mixture was extracted with dichloromethane (3 × 30 mL). The combined organic phase was wash with water, saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate: petroleum ether = 1 : 3) to give the product **9** (white solid, 282.6 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (t, *J* = 7.9 Hz, 1H), 6.92 (t, *J* = 2.0 Hz, 1H), 6.89 (d, *J* = 7.7 Hz, 1H), 6.79 (ddd, *J* = 8.2, 2.4, 0.7 Hz, 1H), 6.35 (br, 1H), 4.58 (s, 1H), 4.14-4.28 (m, 4H), 1.25 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 156.3, 134.0, 129.9, 121.5, 116.2, 115.7, 62.2, 57.8, 14.1; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{13}H_{17}O_5$ 253.1071, found 253.1076.

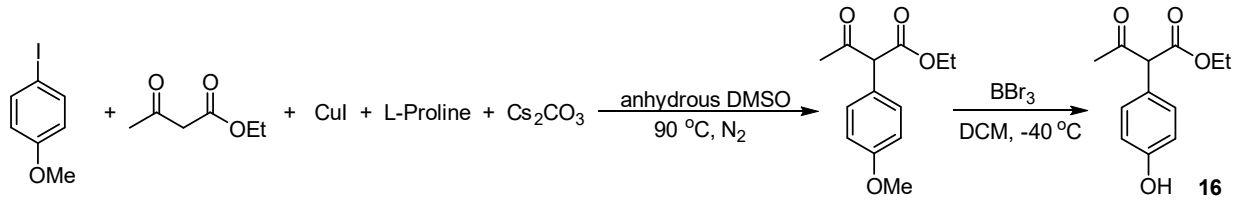
Preparation of 15



15

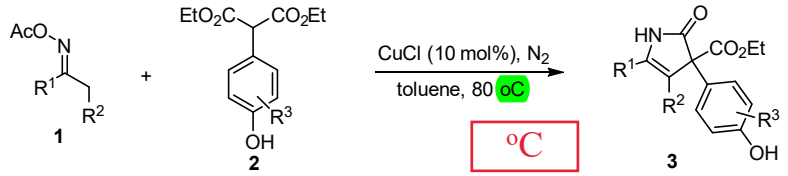
A mixture of 4-iodophenol (220 mg, 1 mmol), acetylacetone (300 mg, 3 mmol), CuI (19.1 mg, 0.1 mmol), L-proline (23 mg, 0.2 mmol), and K_2CO_3 (414 mg, 3 mmol) in anhydrous DMSO (4 mL) was stirred at 90 °C for 16 h. After cooling to room temperature, 40 mL of water and 20 mL of ethyl acetate was added and the pH value was adjusted to 4-5 with dilute hydrochloric acid. The organic phase was separated and the aqueous phase was further extracted two times with ethyl acetate (2 × 20 mL). The combined organic phase was washed with saturated brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate: petroleum ether = 1 : 3) to give the product **15**[5] (79.3 mg, 41%, existed in the enolic form). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.40 (br, 1H), 1.90 (s, 6H).

Preparation of 16

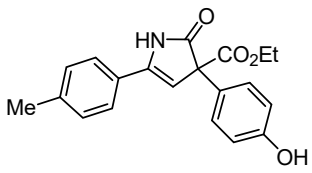


A mixture of 1-iodo-4-methoxybenzene (702 mg, 3 mmol), ethyl acetoacetate (585 mg, 4.5 mmol), CuI (115 mg, 0.6 mmol), L-proline (138 mg, 1.2 mmol), and Cs_2CO_3 (3.90 g, 12 mmol) in anhydrous DMSO (10 mL) was stirred at 50 °C for 12 h. After cooling to room temperature, 100 mL of water and 30 mL of ethyl acetate was added and the pH value was adjusted to 4-5 with dilute hydrochloric acid. The organic phase was separated and the aqueous phase was further extracted with ethyl acetate (2 × 30 mL). The combined organic phase was washed with saturated brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate: petroleum ether = 1 : 20) to give the product ethyl α-(4-methoxyphenyl)acetoacetate, which was then dissolved in 6 mL of anhydrous dichloromethane. After cooling to -40 °C, boron tribromide (2 mol/L solution in dichloromethane, 3 mL, 6 mmol) was added slowly. Upon completion of the reaction (1 h) as determined by TLC, 30 mL of water was added to quench the reaction. The mixture was extracted with dichloromethane (3 × 20 mL). The combined organic phase was washed with saturated brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate: petroleum ether = 1 : 6) to give the product ethyl α-(4-hydroxyphenyl)acetoacetate **16**[6] (168.7 mg, 25% for two step of reaction, keto : enol = 8 : 1). ^{1}H NMR (400 MHz, $CDCl_3$, only the data of keto form was presented) δ 7.17 (d, J = 8.6 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 5.89 (br, 1H), 4.63 (s, 1 H), 4.10-4.31 (m, 2H), 2.17 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, only the data of keto form was presented) δ 202.7, 169.3, 156.1, 130.7, 124.5, 116.0, 65.0, 61.9, 28.9, 14.2.

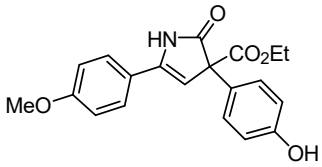
General Procedure for the Preparation of 3.



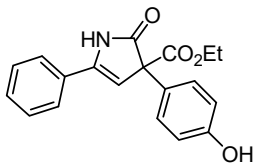
A mixture of *O*-acetyl oximes **1** (0.48 mmol), diethyl 2-(4-hydroxyaryl)malonates **2** (0.4 mmol), and CuCl (4.0 mg, 0.04 mmol) in toluene (2 mL) was stirred at 80 °C under N_2 atmosphere until the full conversion of **2** as determined by TLC. The reaction was cooled to room temperature. Water (25 mL) was added and the mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic phases was washed with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (acetone: petroleum ether = 1 : 3 to 1 : 1) to give the products **3.**



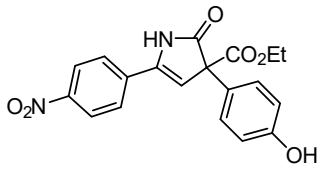
3aa (eluent : acetone / petroleum ether = 1 / 2, white solid, 97.1 mg, 72%): ^{1}H NMR (300 MHz, d$_6$-DMSO) δ 10.33 (d, *J*= 1.6 Hz, 1H), 9.47 (s, 1H), 7.64 (d, *J* = 8.1 Hz, 2H), 7.19-7.32 (m, 4H), 6.74 (d, *J* = 8.7 Hz, 2H), 6.13 (d, *J* = 1.7 Hz, 1H), 4.07-4.16 (m, 2H), 2.33 (s, 3H), 1.12 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, d$_6$-DMSO) δ 176.2, 169.2, 157.0, 142.9, 139.1, 129.3, 128.7, 126.8, 126.5, 125.2, 115.0, 103.0, 64.3, 61.4, 20.9, 14.0; HRMS (ESI)m/z $[M+H]^+$ Calcd for $C_{20}H_{20}NO_4$ 338.1387, found 338.1383.



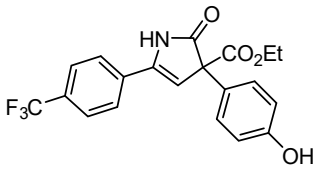
3ba (eluent :acetone / petroleum ether = 1 / 1, yellow solid, 99.5 mg, 70%): ^{1}H NMR (300 MHz, d$_6$-DMSO) δ 10.31 (d, *J* = 1.8 Hz, 1H), 9.46 (s, 1H), 7.70 (d, *J* = 8.9 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H), 7.00 (d, *J* = 8.9 Hz, 2H), 6.74 (d, *J* = 8.7 Hz, 2H), 6.04 (d, *J* = 1.8 Hz, 1H), 4.07-4.16 (m, 2H), 3.79 (s, 3H), 1.12 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, d$_6$-DMSO) δ 176.3, 169.3, 160.1, 156.9, 142.6, 128.7, 126.9, 126.8, 121.8, 115.0, 114.2, 101.7, 64.3, 61.3, 55.3, 14.0; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{20}H_{20}NO_5$ 354.1336, found 354.1330.



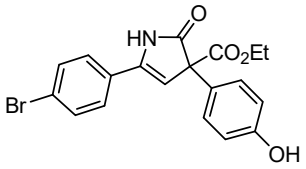
3ca (eluent : acetone / petroleum ether = 1 / 1, yellow solid, 90.4 mg, 70%): ^{1}H NMR (300 MHz, d$_6$-DMSO) δ 10.40 (d, *J* = 1.6 Hz, 1H), 9.48 (s, 1H), 7.71-7.80 (m, 2H), 7.37-7.50 (m, 3H), 7.2 (d, *J* = 8.7 Hz, 2H), 6.75 (d, *J* = 8.7 Hz, 2H), 6.22 (d, *J* = 1.9 Hz, 1H), 4.06-4.17 (m, 2H), 1.13 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, d$_6$-DMSO) δ 176.2, 169.1, 157.0, 142.9, 129.4, 129.2, 128.8, 128.7, 126.7, 125.2, 115.1, 104.0, 64.3, 61.4, 14.0; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{19}H_{18}NO_4$ 324.1230, found 324.1222.



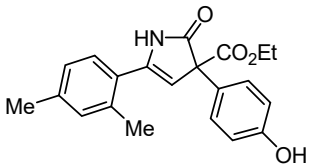
3da (eluent : acetone / petroleum ether = 1 / 2, yellow solid, 112.1 mg, 76%): ^{1}H NMR (300 MHz, d$_6$-DMSO) δ 10.64 (d, *J* = 1.6 Hz, 1H), 9.51 (s, 1H), 8.30 (d, *J* = 8.9 Hz, 2H), 8.03 (d, *J* = 8.9 Hz, 2H), 7.29 (d, *J* = 8.7 Hz, 2H), 6.76 (d, *J* = 8.7 Hz, 2H), 6.59 (d, *J* = 1.8 Hz, 1H), 4.09-4.17 (m, 2H), 1.13 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, d$_6$-DMSO) δ 175.9, 168.5,157.1, 147.5, 141.3, 135.3, 128.7, 126.4, 126.2, 124.1, 115.2, 108.9, 64.6, 61.6, 14.0; HRMS (ESI) m/z [M+H]$^+$ Calcd for $C_{19}H_{17}N_2O_6$ 369.1081, found 369.1086.



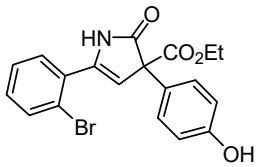
3ea (eluent : acetone / petroleum ether = 1 / 2, white solid, 97.8 mg, 63%): ^{1}H NMR (300 MHz, d$_6$-DMSO) δ 10.56 (s, 1H), 9.50 (s, 1H), 7.98 (d, *J* = 7.7 Hz, 2H), 7.98 (d, *J* = 7.7 Hz, 2H), 7.28 (d, *J* = 7.8 Hz, 2H), 6.75 (d, *J* = 7.8 Hz, 2H), 6.46 (s, 1H), 4.04-4.20 (m, 2H), 1.13 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, d$_6$-DMSO) δ 175.5, 169.0, 157.0, 144.8, 144.5, 134.3, 128.7, 126.4, 115.1, 111.9, 110.0, 101.6, 64.0, 61.5, 14.0; HRMS (ESI) m/z [M+H]$^+$ Calcd for $C_{20}H_{17}F_3NO_4$ 392.1104, found 392.1100.



3fa (eluent : acetone / petroleum ether = 1 / 2, white solid, 114.0 mg, 71%): ^{1}H NMR (400 MHz, d$_6$-DMSO) δ 10.43 (s, 1H), 9.49 (s, 1H), 7.71 (d, *J* = 8.6 Hz, 2H), 7.66 (d, *J* = 8.6 Hz, 2H), 7.26 (d, *J* = 8.6 Hz, 2H), 6.74 (d, *J* = 8.6 Hz, 2H), 6.30 (d, *J* = 1.4 Hz, 1H), 4.08-4.15 (m, 2H), 1.12 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, d$_6$-DMSO) δ 176.1, 168.9, 157.0, 142.0, 131.8, 128.7, 128.5, 127.3, 126.5, 122.7, 115.1, 105.0, 64.4, 61.5, 14.0; HRMS (ESI) m/z [M+H]$^+$ Calcd for $C_{19}H_{17}BrNO_4$ 402.0335, found 402.0339.

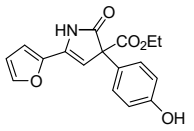


3ga (eluent : acetone / petroleum ether = 1 / 2, white solid, 102.4mg, 73%): ^{1}H NMR (300 MHz, d$_6$-DMSO) δ 10.02 (d, *J*= 1.6 Hz, 1H), 9.47 (s, 1H), 7.29 (d, *J* = 8.7 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.12 (s, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 8.7 Hz, 2H), 5.63 (d, *J* = 1.9 Hz, 1H), 4.08-4.19 (m, 2H), 2.38 (s, 3H), 2.30 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 3H);^{13}C NMR (75 MHz, d$_6$-DMSO) δ 175.7, 169.2, 157.0, 143.4, 138.6, 135.9, 131.4, 128.8, 128.2, 127.3, 126.6, 126.5, 115.0, 106.8, 64.5, 61.3, 20.8, 20.3, 14.0; HRMS (ESI) m/z [M+H]$^+$ Calcd for $C_{21}H_{22}NO_4$ 352.1543, found 352.1538.

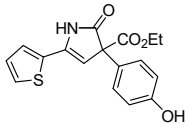


3ha (eluent : acetone / petroleum ether = 1 / 2, yellow solid, 118.9 mg, 74%): ^{1}H NMR (400 MHz, d$_6$-DMSO) δ 10.12 (d, *J* = 1.7 Hz, 1H), 9.49 (s, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.45-7.54 (m, 2H), 7.36-7.41 (m, 1H), 7.29 (d, *J* =8.7 Hz, 2H), 6.76 (d, *J* = 8.7 Hz, 2H), 5.84 (d, *J* =1.9 Hz, 1H), 4.09-4.19 (m, 2H), 1.15 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, d$_6$-DMSO) δ 175.3, 168.8, 157.0, 142.5, 133.5, 131.5, 131.2, 130.7, 128.7, 128.0, 126.3, 121.5, 115.1, 108.4, 64.5, 61.4, 14.0; HRMS (ESI) m/z

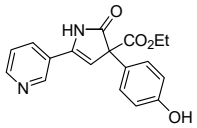
[M+H]$^+$ Calcd for $C_{19}H_{17}BrNO_4$ 402.0335, found 402.0332.



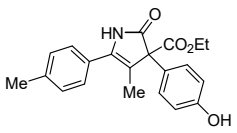
3ia (eluent : acetone / petroleum ether = 1 / 2, white solid, 76.2 mg, 61%): ^{1}H NMR (300 MHz, d$_6$-DMSO) δ 10.43 (s, 1H), 9.49 (s, 1H), 7.84 (d, *J* = 1.7 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 3.3 Hz, 1H), 6.74 (d, *J* = 8.6 Hz, 2H), 6.64 (dd, *J* = 3.2, 1.7 Hz, 1H), 5.86 (d, *J* = 1.8 Hz, 1H), 4.05-4.18 (m, 2H), 1.13 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, d$_6$-DMSO) δ 175.5, 168.9, 157.0, 144.8, 144.5, 134.3, 128.7, 126.4, 115.1, 111.9, 109.9, 101.6, 63.9, 61.5, 14.0; HRMS (ESI) m/z [M+H]$^+$ Calcd for $C_{17}H_{16}NO_5$ 314.1023, found 314.1020.



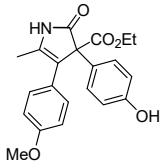
3ja (eluent : acetone / petroleum ether = 1 / 2, white solid, 59.2 mg, 45%): ^{1}H NMR (300 MHz, d$_6$-DMSO) δ 10.51 (s, 1H), 9.49 (s,1H), 7.67 (br, 1H), 7.47 (br, 1H), 7.24 (d, *J* = 8.6 Hz, 2H), 7.14 (br, 1H), 6.75 (d, *J* = 8.6 Hz, 2H), 7.08-7.33 (m, 5H), 6.75 (d, *J* = 7.6 Hz, 2H), 5.91 (s, 1H), 3.96-4.26 (m, 2H), 1.13 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, d$_6$-DMSO) δ 175.7, 168.9, 157.0, 137.8, 132.4, 128.7, 128.0, 127.8, 126.6, 126.5, 115.1, 102.6, 64.3, 61.5, 14.0; HRMS (ESI) m/z [M+H]$^+$ Calcd for $C_{17}H_{16}NO_4S$ 330.0795, found 330.0788.



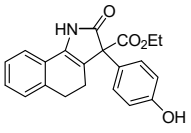
3ka (eluent : acetone / petroleum ether = 1 / 1, white solid, 68.9 mg, 53%): ^{1}H NMR (400 MHz, d$_6$-DMSO) δ 10.52 (s, 1H), 9.53 (br,1H), 8.99 (d, *J* = 1.3 Hz, 1H), 8.60 (d, *J* = 4.8 Hz, 1H), 8.14 (d, *J* = 8.1 Hz, 1H), 7.49 (dd, *J* = 8.1, 4.9 Hz, 1H), 7.28 (d, *J* = 8.7 Hz, 2H), 6.75(d, *J* = 8.6 Hz, 2H), 6.42 (s, 1H), 4.08-4.17 (m, 2H), 1.13 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100MHz, d$_6$-DMSO) δ 176.1, 168.8, 157.1, 150.2, 146.4, 140.5, 132.6, 128.7, 126.4, 125.2, 123.8, 115.1, 105.9, 64.3, 61.5, 14.0; HRMS (ESI) m/z [M+H]$^+$ Calcd for $C_{18}H_{17}N_2O_4$ 325.1183, found 325.1186.



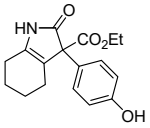
3la (eluent:acetone / petroleum ether = 1 / 2, yellow solid, 95.3 mg, 68%): ^{1}H NMR (300 MHz, d$_6$-DMSO) δ 9.98 (s, 1H), 9.49 (s, 1H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 8.6 Hz, 2H), 6.76 (d, *J* = 8.7 Hz, 2H), 4.13-4.25 (m, 2H), 2.35 (s, 3H), 1.83 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, d$_6$-DMSO) δ 175.8, 168.9, 156.9, 138.4, 137.9, 129.2, 127.6, 127.2, 125.9, 115.2, 111.3, 68.4, 61.2, 59.8, 20.9, 14.1, 11.1; HRMS (ESI) m/z [M+H]$^+$ Calcd for $C_{21}H_{22}NO_4$ 352.1543, found 352.1541.



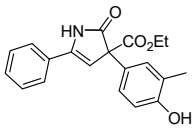
3ma (eluent : acetone / petroleum ether = 1 / 1, red solid, 76.6 mg, 52%):^{1}H NMR (400 MHz, d$_6$-DMSO) δ 9.86 (s, 1H), 9.43 (s, 1H), 7.11 (d, *J* = 8.5 Hz, 2H), 7.04 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.68 (d, *J* = 8.5 Hz, 2H), 4.04-4.14 (m, 2H), 3.69 (s, 3H), 2.11 (s, 3H), 1.01 (t, *J*= 7.1 Hz, 3H); ^{13}C NMR (100 MHz, d$_6$-DMSO) δ 175.6, 169.3, 157.5, 156.7, 136.9, 129.7, 129.1, 125.9, 125.8, 115.6, 114.8, 113.6, 67.2, 61.0, 55.0, 13.9, 12.9; HRMS (ESI) m/z [M+H]$^+$ Calcd for $C_{21}H_{22}NO_5$ 368.1492, found 368.1486.



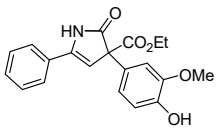
3na (eluent : acetone / petroleumether = 1 / 1, yellow solid, 99.4 mg, 71%): ^{1}H NMR (400 MHz, d$_6$-DMSO) δ 10.42 (s, 1H), 9.50 (s, 1H), 7.37-7.42 (m, 1H), 7.22-7.31 (m, 3H), 7.09 (d, *J* = 8.7 Hz, 2H), 6.77 (d, *J* = 8.6 Hz, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.03 (dt, *J* = 15.9, 9.0 Hz, 1H), 2.92 (dt, *J* = 15.9, 7.2 Hz, 1H), 2.34 (dd, *J* = 9.0, 7.2 Hz, 2H), 1.14 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, d$_6$-DMSO) δ 176.3, 168.4, 157.0, 137.6, 135.8, 128.9, 128.4, 128.2, 126.6, 126.1, 125.9, 121.7, 115.3, 114.6, 66.7, 61.4, 27.7, 20.1, 14.1; HRMS (ESI) m/z [M+H]$^+$ Calcd for $C_{21}H_{20}NO_4$ 350.1387, found 350.1378.



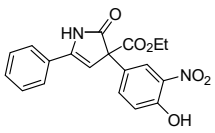
3qa (eluent : acetone / petroleum ether = 1 /1, yellow waxy solid, 37.1 mg, 31%): ^{1}H NMR (400 MHz, d$_6$-DMSO) δ 9.46 (d, *J* = 15.5 Hz, 2H), 6.94 (d, *J* = 8.6 Hz, 2H), 6.73 (d, *J* = 8.7 Hz, 2H), 4.09-4.19 (m, 2H), 2.13-2.26 (m, 2H), 1.85-1.97 (m, 2H), 1.60-1.80 (m, 4H), 1.14 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, d$_6$-DMSO) δ 176.0, 169.0, 156.7, 139.0, 128.8, 126.1, 115.1, 112.3, 66.2, 60.9, 22.4, 21.9, 21.8, 21.1, 14.1; HRMS (ESI) m/z [M+H]$^+$ Calcd for $C_{17}H_{20}NO_4$ 302.1387, found 302.1382.



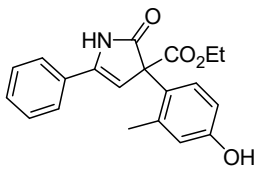
3cb (eluent : acetone / petroleum ether = 1 / 1, white solid, 96.5 mg, 72%): ^{1}H NMR (400 MHz, d$_6$-DMSO) δ 10.37 (d, *J* = 1.8 Hz, 1H), 9.36 (s, 1H), 7.72-7.79 (m, 2H), 7.38-7.49 (m, 3H), 7.15 (d, *J*= 2.1 Hz, 2H), 7.08 (dd, *J*= 8.4, 2.1 Hz, 2H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.20 (d, *J* = 1.8 Hz, 1H), 4.07-4.16 (m, 2H), 2.11 (s, 3H), 1.13 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, d$_6$-DMSO) δ 176.2, 169.1, 155.1, 142.8, 129.8, 129.4, 129.3, 128.8, 126.5, 125.9, 125.2, 123.6, 114.3, 104.1, 64.4, 61.3, 16.2, 14.0; HRMS (ESI) m/z [M+H]$^+$ Calcd for $C_{20}H_{20}NO_4$ 338.1387, found 338.1382.



3cc (eluent : acetone / petroleum ether = 1 / 1, yellow solid, 74.4 mg, 53%): ^{1}H NMR (400 MHz, d$_6$-DMSO) δ 10.42 (s, 1H), 9.08 (s, 1H), 7.76 (d, *J* = 7.1 Hz, 2H), 7.38-7.49 (m, 3H), 7.04 (d, *J* = 1.6 Hz, 1H), 6.89 (dd, *J* = 8.2, 1.7 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 6.26 (d, *J* = 1.8 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.75 (s, 3H), 1.13 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, d$_6$-DMSO) δ 176.1, 169.0, 147.3, 146.4, 142.9, 129.5, 129.3, 128.8, 127.1, 125.3, 120.2, 115.1, 112.0, 104.1, 64.5, 61.4, 55.7, 14.0; HRMS (ESI) m/z [M+H]$^+$ Calcd for $C_{20}H_{20}NO_5$ 354.1336, found 354.1333.

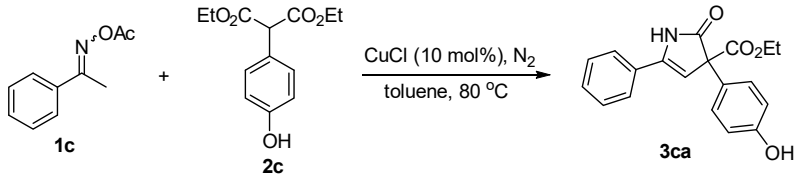


3cd (eluent : acetone / petroleum ether = 1 / 2, yellow solid, 74.6 mg, 51%): ^{1}H NMR (300 MHz, d$_6$-DMSO) δ 11.13 (s, 1H), 10.63 (d, *J* = 1.5 Hz, 1H), 8.00 (d, *J* =2.3 Hz, 1H), 7.74-7.81 (m, 2H), 7.71 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.39-7.51 (m, 3H), 7.19 (d, *J* = 8.8 Hz, 1H), 6.36 (d, *J* = 1.9 Hz, 1H), 4.10-4.20 (m, 2H), 1.13 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, d$_6$-DMSO) δ 175.6, 168.5, 151.9, 144.0, 136.4, 134.9, 129.7, 129.0, 128.9, 127.2, 125.4, 124.0, 119.2, 103.0, 63.8, 61.9, 13.9; HRMS (ESI) m/z [M+H]$^+$ Calcd for $C_{19}H_{17}N_2O_6$ 369.1081, found 369.1086.



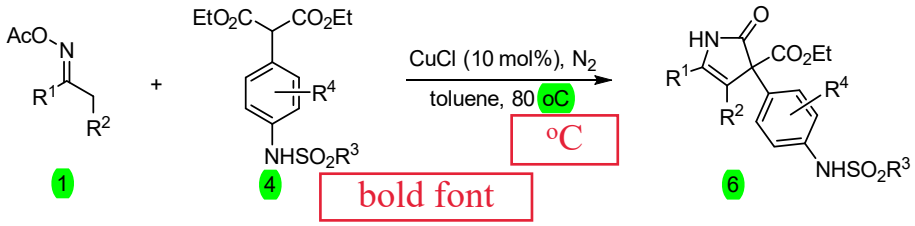
3ce (eluent : acetone / dichloromethane = 1 / 8, yellow solid, 55.1 mg, 41%): ^{1}H NMR (400 MHz, d$_6$-DMSO) δ 10.40 (d, *J* = 1.8Hz, 1H), 9.38 (s, 1H), 7.31-7.80 (m, 2H), 7.38-7.48 (m, 3H), 7.02 (d, *J*= 8.5 Hz, 1H), 6.64 (d, *J* = 2.5 Hz, 1H), 6.52 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.03(d, *J* = 2.0 Hz, 1H), 4.09-4.21 (m, 2H), 2.31 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, d$_6$-DMSO) δ 176.4, 169.3, 156.8, 142.7, 138.9, 129.5, 129.1, 128.8, 128.7, 126.0, 125.3, 118.7, 112.3, 104.6, 65.4, 61.5, 20.4, 14.0; HRMS (ESI) m/z [M+H]$^+$ Calcd for $C_{20}H_{20}NO_4$ 338.1387, found 338.1383.

4 mol Scale Reaction for the Preparation 3ca.

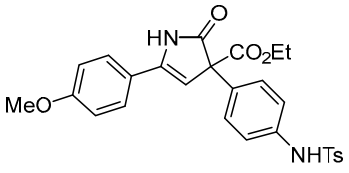


A mixture of *O*-acetyl acetophenone oxime **1c** (850 mg, 4.8 mmol), diethyl 2-(4-hydroxyphenyl)malonate **2c** (1.01 g, 4 mmol), and CuCl (39.6 mg, 0.4 mmol) in toluene (20 mL) was stirred at 80 °C under N_2 atmosphere for 3 h. The solvent was removed under reduced pressure. Water (50 mL) was added and the mixture was extracted three times with ethyl acetate (3 × 60 mL). The combined organic phases was washed with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (acetone: petroleum ether = 1 : 3 to 1 : 1) to give the product **3ca** (751 mg, 58%).

General Procedure for the Preparation of 6.

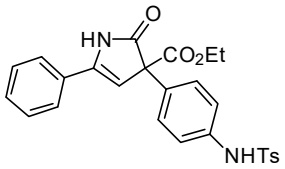


A mixture of *O*-acyl oximes **1** (0.48 mmol), diethyl 2-(4-sulfonamidoaryl)malonates **4** (0.4 mmol), and CuCl (4.0 mg, 0.04 mmol) in toluene (2 mL) was stirred at 80 °C under N_2 atmosphere no change was observed as determined by TLC. The reaction was cooled to room temperature. Water (25 mL) was added and the mixture was extracted three times with ethyl acetate (3 × 30 mL). The combined organic phases was wash with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to give the products **6.**

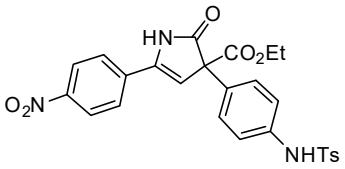


6bc (eluent : acetone / dichloromethane = 1 / 5, white solid, 125.7 mg, 62%): ^{1}H NMR (400 MHz, d$_6$-DMSO) δ 10.36 (s, 1H), 10.32 (s, 1H), 7.67 (d, *J* = 8.9 Hz, 2H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.3 Hz,

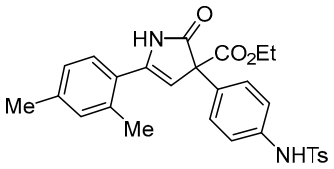
2H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.07 (d, *J* = 8.6 Hz, 2H), 7.00 (d, *J* = 8.9 Hz, 2H), 6.01 (d, *J* = 1.7 Hz, 1H), 4.04-4.13 (m, 2H), 3.79 (s, 3H), 2.32 (s, 3H), 1.09 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, d$_6$-DMSO) δ 175.8, 168.9, 160.2, 143.4, 143.0, 137.3, 136.8, 131.9, 129.8, 128.5, 126.9, 126.7, 121.6, 119.3, 114.2, 101.2, 64.4, 61.5, 55.3, 21.0, 13.9; HRMS (ESI) m/z [M+H]$^+$ Calcd for $C_{27}H_{27}N_2O_6S$ 507.1584, found 507.1587.



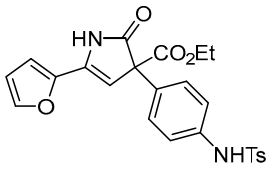
6cc (eluent : acetone / dichloromethane = 1 / 25, white solid, 133.2 mg, 68%): ^{1}H NMR (400 MHz, d$_6$-DMSO) δ 10.44 (s, 1H), 10.33 (s, 1H), 7.70-7.75 (m, 2H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.39-7.48 (m, 3H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.07 (d, *J* = 8.5 Hz, 2H), 6.20 (d, *J* = 1.8 Hz, 1H), 4.05-4.14 (m, 2H), 2.32 (s, 3H), 1.09 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, d$_6$-DMSO) δ 175.7, 168.7, 143.4, 143.3, 137.4, 136.7, 131.6, 129.8, 129.5, 129.1, 128.8, 128.5, 126.7, 125.3, 119.3, 103.5, 64.5, 61.6, 30.0, 13.9; HRMS (ESI) m/z [M+H]$^+$ Calcd for $C_{26}H_{25}N_2O_5S$ 477.1479, found 477.1485.



6dc (eluent : acetone / dichloromethane = 1 / 8, yellow solid, 134.2 mg, 64%): ^{1}H NMR (400 MHz, d$_6$-DMSO) δ 10.68 (s, 1H), 10.36 (s, 1H), 8.30 (d, *J* = 8.8 Hz, 2H), 8.00 (d, *J* = 8.7 Hz, 2H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.28-7.40 (m, 4H), 7.08 (d, *J* = 8.6 Hz, 2H), 6.56 (s, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 2.32 (s, 3H), 1.09 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, d$_6$-DMSO) δ 175.4, 168.1, 147.5, 143.4, 141.7, 137.5, 136.7, 135.1, 131.1, 129.8, 128.5, 126.7, 126.5, 124.0, 119.3, 108.3, 64.7, 61.8, 21.0, 13.9; HRMS (ESI) m/z [M+H]$^+$ Calcd for$C_{26}H_{24}N_3O_7S$ 522.1329, found 522.1326.

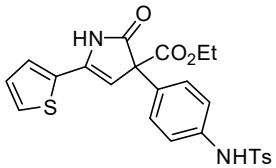


6gc (eluent : acetone / dichloromethane = 1 / 15, yellow solid, 151.9 mg, 75%): ^{1}H NMR (400 MHz, d$_6$-DMSO) δ 10.35 (br, 1H), 10.07 (s, 1H), 7.66-7.73 (m, 2H), 7.31-7.38 (m, 4H), 7.26 (dd, *J* = 8.0, 2.1 Hz, 1H), 7.03-7.14 (m, 4H), 5.61 (br, 1H), 4.06-4.17 (m, 2H), 2.35 (s, 3H), 2.32 (s, 3H), 2.29 (s, 3H), 1.11 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, d$_6$-DMSO) δ 175.2, 168.8, 143.8, 143.4, 138.7, 137.4, 136.8, 135.9, 131.6, 131.4, 129.8, 128.6, 128.2, 127.2, 126.7, 126.5, 119.3, 106.3, 64.6, 61.5, 21.0, 20.8, 20.3, 13.9; HRMS (ESI) m/z [M+H]$^+$ Calcd for $C_{28}H_{29}N_2O_5S$ 505.1792, found 505.1796.

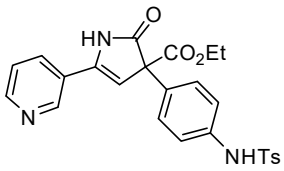


6ic (eluent : acetone / dichloromethane = 1 / 15, yellow solid, 124.9 mg, 67%): ^{1}H NMR (400 MHz, d$_6$-DMSO) δ 10.49 (s, 1H), 10.34 (s, 1H), 7.83 (s, 1H), 7.67 (d, *J*= 7.8 Hz, 2H), 7.28-7.36 (m, 4H), 7.05-7.13 (m, 2H), 6.88 (d, *J* = 3.1 Hz, 1H), 6.62 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.86 (s, 1H), 4.06-4.15 (m, 2H), 2.31 (s, 3H), 1.09 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100MHz, d$_6$-DMSO) δ 175.0, 168.5, 144.8, 144.3, 143.4, 137.4, 136.8, 134.6, 131.4, 129.8, 128.5, 126.7, 119.3, 111.9, 110.1, 101.1,

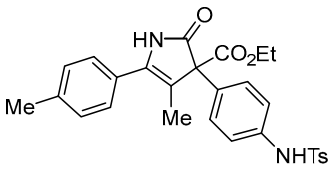
64.1, 61.7, 21.0, 13.9; HRMS (ESI) m/z $[M+Na]^+$ Calcd for $C_{24}H_{23}N_2O_6S$ 467.1271, found 467.1266.



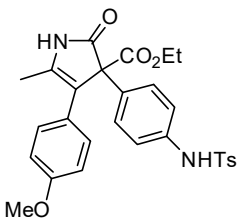
6jc (eluent : acetone / dichloromethane = 1 / 8, yellow solid, 138.2 mg, 72%): ^{1}H NMR (400 MHz, d$_6$-DMSO) δ 10.57 (s, 1H), 10.34 (s, 1H), 7.63-7.72 (m, 3H), 7.47 (d, *J* = 3.5 Hz, 1H), 7.31-7.37 (m, 3H), 7.30 (d, *J* = 1.9 Hz, 1H), 7.05-7.15 (m, 3H), 5.90 (s, 1H), 4.05-4.14 (m, 2H), 2.31 (s, 3H), 1.09 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, 126.75, 126.72, 168.5, 143.4, 138.2, 137.4, 136.8, 132.3, 131.5, 129.8, 128.5, 128.0, 127.9, 126.7, 126.7, 119.3, 102.1, 64.5, 61.7, 21.0, 13.9; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{24}H_{23}N_2O_5S_2$ 483.1043, found 483.1038.



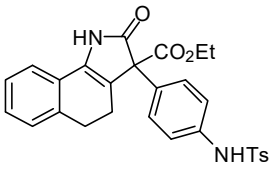
6kc (eluent : methanol / dichloromethane = 1 / 20, white solid, 98.8 mg, 52%):^{1}H NMR (400 MHz, d$_6$-DMSO) δ 10.56 (d, *J* = 1.8 Hz, 1H), 10.34 (s, 1H), 8.96 (d, *J* =1.8 Hz, 1H), 8.60 (dd, *J* = 4.7, 1.3 Hz, 1H), 8.11 (dt, *J* = 8.3, 1.9 Hz, 1H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.49 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.8 Hz, 2H), 7.08 (d, *J* = 8.6 Hz, 2H), 6.38 (d, *J* = 1.8 Hz, 1H), 4.06-4.14 (m, 2H), 2.32 (s, 3H), 1.10 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100MHz, d$_6$-DMSO) δ 175.6, 168.4, 150.2, 146.5, 143.4, 140.8, 137.5, 136.8, 132.6, 131.4, 129.8, 128.5, 126.7, 125.1, 123.7, 119.3, 105.3, 64.4, 61.7, 21.0, 13.9; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{25}H_{24}N_3O_5S$ 478.1431, found 478.1440.



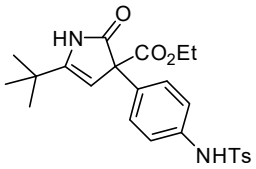
6lc (eluent : acetone / dichloromethane = 1 / 15, yellow solid, 117.2 mg, 58%): ^{1}H NMR (400 MHz, d$_6$-DMSO) δ 10.37 (s, 1H), 10.01 (s, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.06-7.14 (m, 4H), 4.13-4.22 (m, 2H), 2.34 (s, 3H), 2.33 (s, 3H), 1.78 (s, 3H), 1.14 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, d$_6$-DMSO) δ 175.2, 168.5, 143.4, 138.4, 138.2, 137.2, 136.9, 130.9, 129.8, 129.1, 128.9, 127.6, 127.1, 126.7, 119.3, 110.9, 68.4, 61.4, 21.0, 20.9, 14.0, 11.0; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{28}H_{29}N_2O_5S$ 505.1792, found 505.1789.



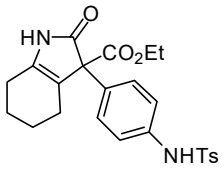
6mc (eluent : acetone / dichloromethane = 1 / 12, yellow solid, 98.9 mg, 48%): ^{1}H NMR (400 MHz, d$_6$-DMSO) δ 10.33 (s, 1H), 9.93 (s, 1H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.7 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.9 Hz, 2H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.69 (s, 3H), 2.32 (s, 3H), 2.08 (s, 3H), 1.01 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, d$_6$-DMSO) δ 175.0, 168.9, 157.6, 143.4, 137.3, 137.1, 136.9, 130.9, 129.8, 129.4, 129.1, 126.7, 125.6, 118.9, 115.4, 113.7, 67.2, 61.2, 55.0, 21.0,13.9, 12.8; HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{28}H_{29}N_2O_6S$ 521.1741, found 521.1733.



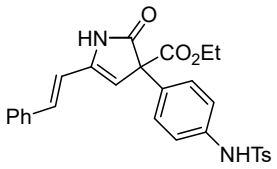
6nc (eluent : acetone / dichloromethane = 1 / 12, brown solid, 88.4 mg, 44%): ^{1}H NMR (400 MHz, d$_6$-DMSO) δ 10.47 (s, 1H), 10.39 (s, 1H), 7.70 (d, *J* = 7.7 Hz, 2H), 7.35-7.42 (m, 1H), 7.34 (d, *J* = 7.7 Hz, 2H), 7.22-7.29 (m, 3H), 7.16 (d, *J* = 8.2 Hz, 2H), 7.11 (d, *J* = 8.2 Hz, 2H), 4.14 (q, *J*= 7.1 Hz, 2H), 3.02 (dt, *J* = 15.8, 9.3 Hz, 1H), 3.02 (dt, *J* = 15.8, 7.1 Hz, 1H), 2.25-2.35 (m, 5H), 1.11 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, d$_6$-DMSO) δ 175.8, 168.0, 143.4, 137.9, 137.4, 136.9, 135.8, 130.8, 129.8, 128.7, 128.5, 128.2, 126.7, 126.6, 126.0, 121.7, 119.4, 114.1, 66.8, 61.5, 27.6, 21.0, 20.0, 14.0; HRMS (ESI) m/z [M+H]$^+$ Calcd for $C_{28}H_{27}N_2O_5S$ 503.1635, found 503.1630.



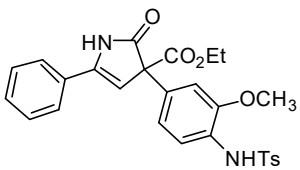
6pc (eluent : methanol / dichloromethane = 1 / 120, white solid, 64.9 mg, 36%): ^{1}H NMR (400 MHz, d$_6$-DMSO) δ 10.34 (s, 1H), 9.83 (d, *J* = 1.7 Hz, 1H), 7.68 (d, *J* =8.3Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 2H), 5.16 (d, *J* = 2.0 Hz, 1H), 3.98-4.14 (m, 2H), 2.32 (s, 3H), 1.13 (s, 9H), 1.06 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, d$_6$-DMSO) δ 175.9, 169.2, 154.7, 143.4, 137.2, 136.9, 131.9, 129.8, 128.4, 126.8, 119.2, 99.7, 63.8, 61.2, 31.7, 27.4, 21.0, 13.8; HRMS (ESI) m/z [M+H]$^+$ Calcd for $C_{24}H_{29}N_2O_5S$ 457.1792, found 457.1797.



6qc (eluent : acetone / dichloromethane = 1 / 15, yellow solid, 75.0 mg, 41%): ^{1}H NMR (400 MHz, d$_6$-DMSO) δ 10.37 (s, 1H), 9.54 (s, 1H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.07 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 4.07-4.17 (m, 2H), 2.32 (s, 3H), 2.11-2.24 (m, 2H), 1.82-1.93 (m, 2H), 1.58-1.78 (m, 4H), 1.11 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, d$_6$-DMSO) δ 175.5, 168.7, 143.4, 139.4, 137.1, 136.9, 131.1, 129.8, 128.7, 126.8, 119.3, 112.0, 66.3, 61.1, 22.3, 21.9, 21.7, 21.00, 21.02, 14.1; HRMS (ESI) m/z [M+H]$^+$ Calcd for $C_{24}H_{27}N_2O_5S$ 455.1635, found 455.1631.

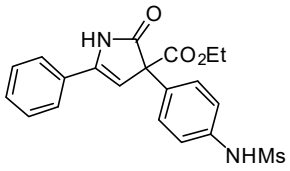


6rc (eluent : acetone / dichloromethane = 1 / 15, yellow solid, 127.1 mg, 61%): ^{1}H NMR (400 MHz, d$_6$-DMSO) δ 10.36 (d, *J* = 3.3 Hz, 1H), 10.34 (s, 1H), 7.68 (dd, *J* = 8.1, 1.9 Hz, 2H), 7.49 (d, *J* = 7.4 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.30-7.36 (m, 3H), 7.23-7.29 (m, 2H), 7.06-7.12 (m, 2H), 7.03 (dd, *J* = 16.5, 2.0 Hz, 1H), 6.1 (d, *J* = 16.5 Hz, 1H), 5.77 (s, 1H), 4.05-4.14 (m, 2H), 2.32 (s, 3H), 1.09 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, d$_6$-DMSO) δ 175.1, 168.6, 143.4, 142.8, 137.4, 136.7, 135.9, 131.8, 131.6, 129.8, 129.0, 128.6, 128.4, 126.78, 126.76, 119.4, 117.5, 108.4, 64.4, 61.6, 21.0, 13.9; HRMS (ESI) m/z [M+Na]$^+$ Calcd for $C_{28}H_{27}N_2O_5S$ 503.1635, found 503.1629.



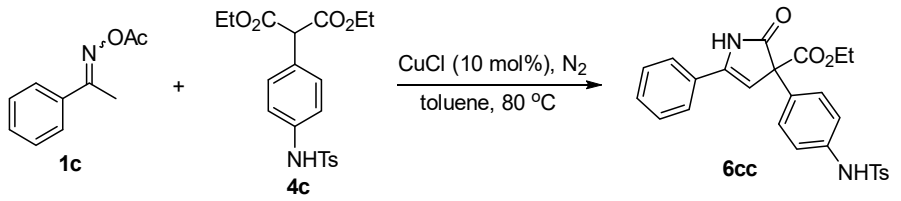
6cd (eluent : acetone / dichloromethane = 1 / 15, white solid, 108.5 mg, 54%): ^{1}H NMR (400 MHz, d$_6$-DMSO) δ 10.48 (s,1H), 9.50 (s, 1H), 7.71-7.77 (m, 2H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.38-7.49 (m, 3H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.18 (dd, *J* = 8.3 Hz, 1H), 7.00 (s, 1H), 6.97 (d, *J* = 8.3 Hz, 1H), 6.26 (d, *J* = 1.8 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.54 (s, 3H), 2.34 (s, 3H), 1.11 (t, *J* = 7.1 Hz,

3H); ^{13}C NMR (100 MHz, d$_6$-DMSO) δ 175.5, 168.5, 151.5, 143.3, 142.9, 137.8, 134.1, 129.6, 129.4, 129.1, 128.8, 126.7, 125.4, 125.3, 123.5, 119.7, 111.2, 103.5, 64.7, 61.6, 55.6, 21.0, 13.9; HRMS (ESI) m/z [M+H]$^+$ Calcd for $C_{27}H_{27}N_2O_6S$ 507.1584, found 507.1577.



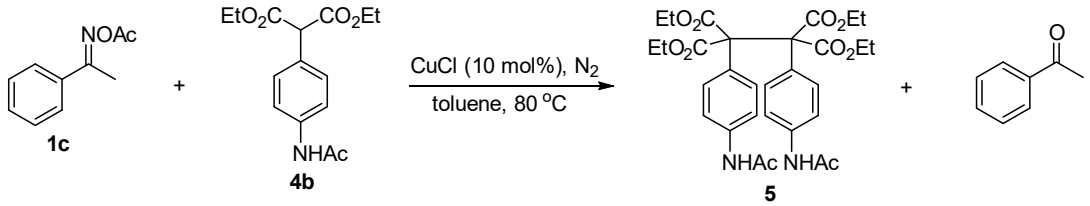
6ce (eluent : acetone / dichloromethane = 1 / 8, yellow solid, 105.8 mg, 66%): ^{1}H NMR (400 MHz, d$_6$-DMSO) δ 10.50 (d, *J* = 1.8 Hz, 1H), 9.82 (s, 1H), 7.77 (d, *J* = 7.4 Hz, 2H), 7.38-7.50 (m, 5H), 7.23 (d, *J* = 8.6 Hz, 2H), 6.25 (d, *J* = 1.7 Hz, 1H), 4.10-4.19 (m, 2H), 3.00 (s, 3H), 1.14 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, d$_6$-DMSO) δ 175.9, 168.8, 143.4, 138.0, 131.8, 129.6, 129.2, 128.8, 128.7, 125.3, 119.6, 103.7, 64.6, 61.7, 39.4, 14.0; HRMS (ESI) m/z [M+H]$^+$ Calcd for $C_{20}H_{21}N_2O_5S$ 401.1166, found 401.1161.

3mol Scale Reaction for the Preparation 6cc.



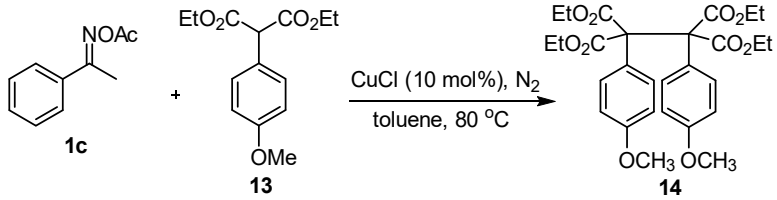
A mixture of *O*-acetyl acetophenone oxime **1c** (637.2 mg, 3.6 mmol), diethyl 2-(4-(*p*-tolylsulfonamido)phenyl)malonate **4c** (1.22 g, 3 mmol), and CuCl (29.7 mg, 0.3 mmol) in toluene (15 mL) was stirred at 80 °C under N_2 atmosphere for 3 h. The solvent was removed under reduced pressure. Water (50 mL) was added and the mixture was extracted four times with ethyl acetate (4 × 60 mL). The combined organic phases was washed with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (acetone / dichloromethane = 1 / 25) to give the product **6cc** (919 mg, 62%).

The Reaction of 1c with diethyl 2-(4-acetamidophenyl)malonate 4b or diethyl 2-(4-methoxyphenyl)malonate 13.



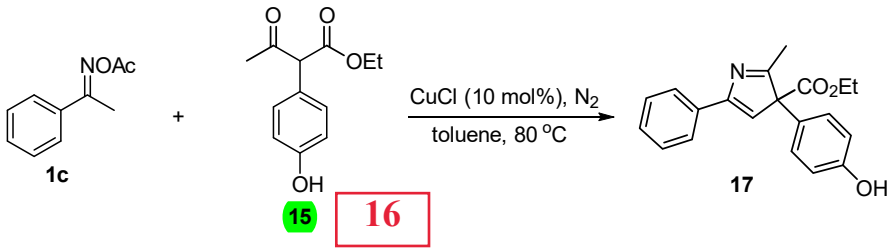
A mixture of *O*-acetyl acetophenone oxime **1c** (85.0 mg, 0.48 mmol), diethyl 2-(4-acetamidophenyl)malonate **4b** (117.2 mg, 0.4 mmol), and CuCl (4.0 mg, 0.04 mmol) in toluene (2 mL) was stirred at 80 °C under N_2 atmosphere until the full conversion as determined by TLC. The reaction was cooled to room temperature. Water (30 mL) was added and the mixture was extracted three times with ethyl acetate (3 × 30 mL). The combined organic phases was wash with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The

residue was purified by column chromatography (eluent : acetone / dichloromethane = 1 / 10 to 1 / 4) to give the acetophenone (28.4 mg, 49%) and product **5** (yellow solid, 53.1 mg, 45%). ^{1}H NMR (400 MHz, d$_6$-DMSO) δ 9.93 (s, 2H), 7.30 (d, *J* = 8.8 Hz, 4H), 6.69 (d, *J* = 8.8 Hz, 4H), 4.16 (br, 8H), 2.02 (s, 6H), 1.15 (br, 12H); ^{13}C NMR (100 MHz, d$_6$-DMSO) δ 168.4, 168.2, 138.5, 131.3, 128.2, 116.7, 69.7, 61.6, 24.0, 13.6; HRMS (ESI) m/z [M+H]$^+$ Calcd for $C_{30}H_{37}N_2O_{10}$ 585.2443, found 585.2447.



A mixture of *O*-acetyl acetophenone oxime **1c** (85.0 mg, 0.48 mmol), diethyl 2-(4-methoxyphenyl)malonate **13** (106.4 mg, 0.4 mmol) and CuCl (4.0 mg, 0.04 mmol) in toluene (2 mL) was stirred at 80 °C under N_2 atmosphere until the full conversion of **13** as determined by TLC. The reaction was cooled to room temperature. Water (30 mL) was added and the mixture was extracted three times with ethyl acetate (3 × 30 mL). The combined organic phases was wash with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent : acetone / petroleum ether = 1 / 6) to give the dimeric product **14** (yellow liquid, 42.0 mg, 40%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (d, *J* = 8.9 Hz, 4H), 6.63 (d, *J* = 9.0 Hz, 4H), 4.14-4.39 (br, 8H), 3.76 (s, 6H), 1.24 (br, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 132.8, 125.6, 111.9, 70.0, 62.1, 55.2, 13.9; HRMS (ESI) m/z [M+H]$^+$ Calcd for $C_{28}H_{35}O_{10}$ 531.2225, found 531.2222.

The Reaction of 1c with Ethyl α-(4-Hydroxyphenyl)acetoacetate 16



A mixture of *O*-acetyl acetophenone oxime **1c** (85.0 mg, 0.48 mmol), ethyl α-(4-hydroxyphenyl)acetoacetate **16** (88.8 mg, 0.4 mmol), and CuCl (4.0 mg, 0.04 mmol) in toluene (2 mL) was stirred at 80 °C under N_2 atmosphere until the full conversion as determined by TLC. The solvent was removed under reduced pressure and the residue was purified by column chromatography (ethyl acetate / petroleum ether = 1 / 6) to give the product **17** (yellow solid, 50.5 mg, 39%). ^{1}H NMR (400 MHz,$CDCl_3$) δ 8.00-8.07 (m, 2H), 7.44-7.54 (m, 3H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.21 (s, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 4.01-4.19 (m, 2H), 1.76 (s, 3H), 1.09 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 170.2, 168.5, 158.8, 132.5, 131.7, 129.1, 129.0, 128.4, 123.3,

119.5, 116.4, 83.7, 62.3, 21.6, 14.0; HRMS (ESI) m/z $[M-H]^-$ Calcd for $C_{20}H_{28}NO_3$ 320.1292, found 320.1295.

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