Synthesis of the Precursor of Anti-Inflammatory Agents by Cross-Coupling Using Electrogenerated Highly Reactive Zinc

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Abstract: Highly reactive zinc metal was readily prepared by electrolysis of a DMF solution containing naphthalene and a supporting electrolyte in a one-compartment cell fitted with a platinum cathode and a zinc anode. This reactive zinc was used for efficient transformation of ethyl 2-bromoacrylate into the corresponding organozinc compound, which was reacted with various aryl iodides in the presence of palladium catalyst to give the corresponding cross-coupling products, ethyl 2-arylpropenoates, in high yields. These cross-coupling reactions were successfully applied to a synthesis of the precursors of non-steroidal anti-inflammatory agents such as ibuprofen, naproxen, ketoprofen, loxoprofen, indoprofen, suprofen, cicloprofen, and flurbiprofen.

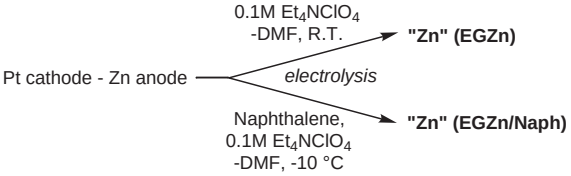
Key words: anti-inflammatory agents, cross-coupling, reactive zinc, organometallic reagents, electrolysis

2-Arylpropanoic acids are well-known as the lead structure of non-steroidal anti-inflammatory agents represented by ibuprofen.[1] Many synthetic strategies have been developed for the preparation of these acids, especially for their derivatives: e.g. methylation of arylacetic acids,[2] cyanation of 1-aryl-1-haloethanes,[3] introduction of aryl group into the α-position of propanoic acids,[4] rearrangement of propiophenones or their derivatives,[5] and others.[6] However, most of these synthetic approaches give *racemic* 2-arylpropanoic acids, whereas anti-inflammatory active compounds are (*S*)-2-arylpropanoic acids. Most useful method for the synthesis of (*S*)-2-arylpropanoic acids would be the preparation of 2-arylpropenoic acids followed by enantioselective hydrogenation with Ru-(*S*)-BINAP catalyst.[7] Therefore, our attention has been directed to an efficient preparation of 2-arylpropenoic acids or their derivatives.

We have already reported the preparation of 2-phenylpropenoic acid by electrochemical carboxylation of α-bromostyrene and its application to efficient synthesis of the precursor of ibuprofen, 2-(*p*-isobutylphenyl)propenoic acid.[8] On the other hand, we recently examined the preparation of 2-arylpropenoic acid esters by using a cross-coupling reaction of ethyl 2-bromoacrylate with aryl halides. We developed very efficient method for the synthesis of ethyl 2-arylpropenoates by cross-coupling reaction of organozinc compound, derived from ethyl 2-bromoacrylate and electrogenerated highly reactive zinc, with aryl iodides[9] or bromides[10] in the presence of a Pd(II) catalyst. In this paper we report a successful application of these cross-coupling reactions to an efficient synthesis of the precursor of various anti-inflammatory agents such as ibuprofen, naproxen, ketoprofen, loxoprofen, indoprofen, suprofen, flurbiprofen, and cicloprofen. Similar cross-coupling of α-stannyl acrylate with aryl iodides or triflates has been reported to give methyl 2-arylpropenoates in moderate yields and was found to be applicable to the synthesis of the precursor of naproxen in 71% yield.[11]

We have earlier reported a new method for the preparation of reactive zinc (EGZn) by electrolysis (Scheme 1) and its use in facile isoprenylation[12] and allylation[13,14] of aldehydes and ketones. We have also reported a facile preparation of organozinc compounds from functionalized alkyl iodides by using EGZn and their cross-couplings with aryl halides.[15] However, organozinc bromides were rarely obtained or were only obtained in very low yields from the corresponding organic bromides, even if the reactive EGZn was used. Therefore, we developed a new electrochemical method for preparation of more highly reactive zinc (EGZn/Naph) by using naphthalene as a mediator.[9]

Highly reactive zinc was readily prepared by constant-current electrolysis of a DMF solution containing 0.1 M Et_4NClO_4 in the presence of naphthalene. Electrolysis was carried out at –10 °C in a one-compartment cell fitted with a platinum plate cathode and a zinc plate anode.[9] In this electrolysis, a one-electron reduction of naphthalene molecule gives naphthalene radical anions, which reduce zinc ions, generated by anodic dissolution of the zinc metal, to give zero-valent highly reactive zinc (EGZn/Naph) (Scheme 1).



Scheme 1

The reaction of EGZn/Naph with ethyl 2-bromoacrylate (**1**) gave efficiently the corresponding organozinc bromide **2** and subsequent cross-coupling reaction with various aryl iodides **3** in the presence of palladium catalyst proceeded efficiently to give ethyl 2-arylpropenoates **4** in

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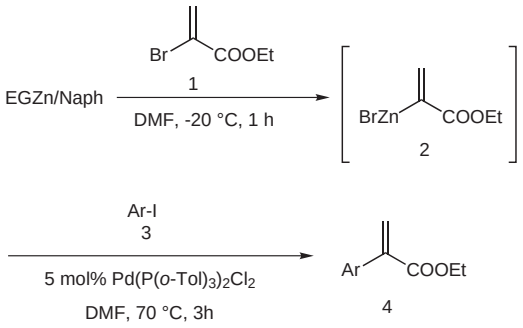
almost quantitative yields (Scheme 2).[9] All of the steps involving the electrochemical preparation of highly reactive EGZn/Naph, the transformation of **1** to the corresponding organozinc **2**, and the cross-coupling reaction of **2** with aryl iodides **3** were carried out in a one-pot.

We applied these efficient cross-coupling reactions to a synthesis of the precursor of anti-inflammatory agents. Cross-coupling reaction of organozinc bromide **2** with 4-isobutyliodobenzene (**3a**) gave the precursor of ibuprofen (**4a**) in 93% yield. Similar one-pot reactions of **2** with aryl iodides **3b**–**h** afforded the precursor of ketoprofen (**4b**) cicloprofen (**4c**), loxoprofen (**4d**), indoprofen (**4e**), naproxen (**4f**), suprofen (**4g**), and flurbiprofen (**4h**) in high yields, respectively. Results are summarized in Table 1.



Scheme 2

IR spectra were recorded on a Jasco IR-810 IR spectrometer. ^{1}H NMR spectra were recorded on a Jeol JNM-EX270 FT NMR spectrometer operated at 270 MHz (solvent $CDCl_3$). Proton-decoupled ^{13}C NMR spectra were recorded at 67.5 MHz on a Jeol JNM-EX270 spectrometer. ^{1}H and ^{13}C chemical shifts are reported in ppm (δ) using $SiMe_4$ as an internal standard. High and low resolution mass spectra were determined with a Jeol JMS-AX500 or Jeol JMS-SX102A spectrometer. TLC and column chromatography were carried out on Merck silica gel (60 PF-254). Commercially available anhyd DMF packed under N_2 (Kanto Chemical) was used without further purification. Et_4NClO_4 was prepared according to the previously reported method.[15] Zinc plate is commercially available in more than 99.9% purities, and they were washed with 2 N HCl before electrolysis. Commercially available naphthalene (Junsei Chemical, 99%) was used after recrystallization from MeOH. Iodobenzene is commercially available and was purified by distillation prior to use.

Ethyl 2-bromoacrylate,[16] and 1-iodo-4-isobutylbenzene (**3a**)[17] were prepared according to the procedure reported in the literature. 3-Iodobenzophenone (**3b**), 2-iodofluorene (**3c**), 2-iodo-6-methoxynaphthalene (**3f**), 2-(4-iodobenzoyl)thiophene (**3g**),[18] 2-fluoro-4-iodobiphenyl (**3h**) were prepared by iodination of the corresponding aryl bromides according to the literature.[19] 2-(4-Iodobenzyl)cyclopentanone (**3d**) and 2-(4-iodophenyl)-2,3-dihydroisoindol-1-one (**3e**) were prepared by the following procedures described below.

Ethyl 2-Bromoacrylate (1)[16]
Yield: 82%; colorless oil; bp 80 °C/69 mmHg.

IR (neat): 1725, 1605, 1259, 1102 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 6.96 (d, 1 H, *J* = 1.7 Hz), 6.27 (d, 1 H, *J* = 1.7 Hz), 4.29 (q, 2 H, *J* = 7.3 Hz), 1.34 (t, 3 H, *J* = 7.3 Hz).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 161.72, 130.26, 121.47, 62.57, 13.93.

EIMS: *m*/*z* (%) = 180 (18), 178 (18), 150 (19), 133 (40), 105 (49), 99 (65), 45 (100).

HRMS: *m*/*z* calcd for $C_5H_7BrO_2$: 177.9629. Found: 177.9622.

1-Iodo-4-isobutylbenzene (3a)[19]
Yield: 61%; bp 120–122 °C/16 mmHg.

IR (neat): 1484, 1465, 1401, 1384, 1007 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.58 (dd, 2 H, *J* = 2.0 6.6 Hz), 6.90 (dd, 2 H, *J* = 2.0, 6.6 Hz), 2.41 (d, 2 H, *J* = 7.26 Hz), 1.82 (m, 1 H), 0.88 (d, 6 H, *J* = 6.6 Hz).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 141.22, 137.07, 131.20, 90.66, 44.84, 30.08, 22.25.

EIMS: *m*/*z* (%) = 260 (73), 232 (68), 217 (100), 203 (18), 128 (17), 89 (27), 77 (14).

HRMS: *m*/*z* calcd for $C_{10}H_{13}I$: 260.0062. Found: 260.0066.

3-Iodobenzophenone (3b)[20]
IR (neat): 3058, 1663, 1447, 1270, 715, 658 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 8.13 (t, 1 H, *J* = 1.7 Hz), 7.92 (dd, 1 H, *J* = 1.0, 7.9 Hz), 7.75 (m, 3 H), 7.60 (d, 2 H, *J* = 7.3 Hz), 7.53 (m, 1 H), 7.23 (t, 1 H, *J* = 7.9 Hz).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 194.95, 141.06, 139.41, 138.51, 136.78, 132.76, 129.94, 129.88, 129.06, 128.37, 93.99.

EIMS: *m*/*z* (%) = 308 (69), 231 (23), 203 (10), 181 (8), 105 (100), 77 (39).

HRMS: *m*/*z* calcd for $C_{13}H_9IO$: 307.9698. Found: 307.9699.

2-Iodofluorene (3c)[21]
Yield: 53%; light yellow crystals; mp 123–125 °C (Lit.[21] mp 124–126 °C).

IR (nujol): 3130, 1465, 1377, 821, 762, 729 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.89 (s, 1 H), 7.76 (d, 1 H, *J* = 7.9 Hz), 7.70 (d, 1 H, *J* = 7.9 Hz), 7.53 (d, 2 H, *J* = 7.9 Hz), 7.36 (m, 2 H), 3.87 (s, 2 H).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 145.34, 142.55, 141.17, 140.63, 135.60, 134.02, 127.21, 126.83, 124.91, 121.38, 119.91, 91.81, 36.52.

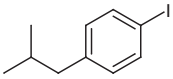
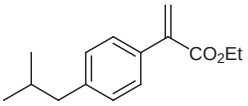
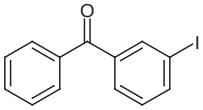
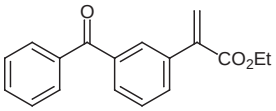
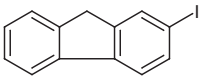
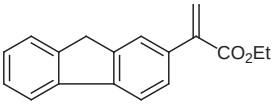
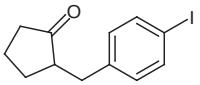
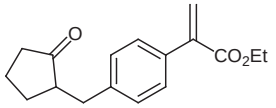
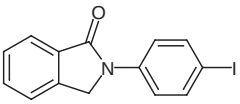
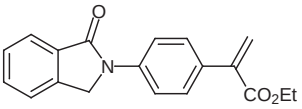
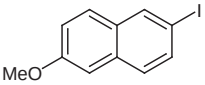
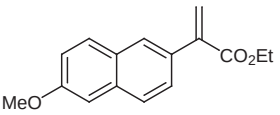
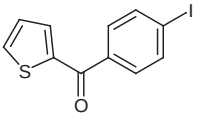
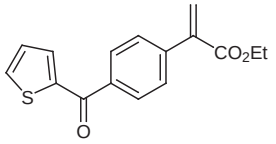
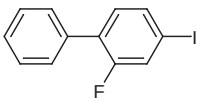
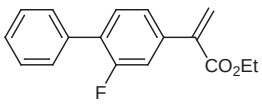
EIMS: *m*/*z* (%) = 292 (67), 165 (100), 83 (12).

HRMS: *m*/*z* calcd for $C_{13}H_9I$: 291.9749. Found: 291.9749.

2-(4-Iodobenzyl)cyclopentanone (3d)
To a mixture of NaH (2.0 g, 26 mmol) and anhyd DMF (170 mL) in a 200 mL side-arm flask fitted with a reflux condenser and a N_2-inlet system, was added methyl cyclopentanone-2-carboxylate (6.2 mL, 50 mmol) via syringe and the mixture was stirred for 3 h. A DMF (20 ml) solution of 4-bromobenzyl chloride (12.5 g, 26 mmol) was added and the mixture was stirred for 4 d at r.t. The mixture was extracted with Et_2O (3 × 100 mL), and the Et_2O layer was washed with brine (4 × 100 mL), and dried ($MgSO_4$). Evaporation of the solvent gave methyl 1-(4-bromobenzyl)-2-oxocyclopentanecarboxylate as a yellow oil, which was used directly in the following reaction. A mixture of the crude product and 48% HBr (25 mL) in a 100 mL flask fitted with a reflux condenser and N_2-inlet system was refluxed for 22 h. The mixture was cooled and poured into ice-water and extracted with Et_2O. The combined organic solutions were washed with sat. aq Na_2CO_3 (2 × 100 mL), brine (100 mL) and dried ($MgSO_4$ Evaporation of the solvent gave the crude product 2-(4-bromobenzyl)cyclopentanone in 82% yield. Iodination of the product according to the literature[19] gave **3d** as a crystalline solid in 64% yield; mp 83–84 °C.

IR (neat): 1721, 1460, 1378, 1154, 854 cm^{-1}.

Table 1 Synthesis of the Precursors of Anti-Inflammatory Agents[a]

Entry	Aryl Iodide **3**	Product **4**	Yield (%)[b]
1	 **3a**	 **4a**	93
2	 **3b**	 **4b**	92
3	 **3c**	 **4c**	87
4	 **3d**	 **4d**	96
5	 **3e**	 **4e**	94
6	 **3f**	 **4f**	95
7	 **3g**	 **4g**	72
8	 **3h**	 **4h**	84

[a] Organozinc bromide **2**, prepared from ethyl 2-bromoacrylate (**1**) (3 mmol) and EGZn/Naph (6 mmol) in DMF was reacted at 70 °C for 3 h with aryl iodides **3** (2 mmol) in the presence of 5 mol% of $Pd[P(o\text{-}Tol)_3]_2Cl_2$.
[b] Isolated yields based on aryl iodides.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.60 (dd, 2 H, *J* = 2.0, 8.3 Hz), 6.92 (dd, 2 H, *J* = 2.0, 8.3 Hz), 3.07 (d, 1 H, *J* = 13.2 Hz), 2.55–2.47 (m, 1 H), 2.40–2.25 (m, 2 H), 2.16–1.91 (m, 4 H), 1.82–1.61 (m, 1 H).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 219.71, 139.59, 137.43, 131.00, 91.30, 50.73, 38.10, 35.01, 29.00, 20.49.

EIMS: *m*/*z* (%) = 300 (100), 217 (80), 204 (14), 145 (9), 116 (11), 90 (14).

HRMS: *m*/*z* calcd for $C_{12}H_{13}IO$: 300.0011. Found: 300.0009.

Anal. Calcd for $C_{12}H_{13}IO$: C, 48.02; H, 4.37; I, 42.28. Found: C, 48.21; H, 4.57; I, 42.32.

2-(4-Iodophenyl)-2,3-dihydroisoindol-1-one (3e)

To a mixture of *o*-formylphthalic acid (3.76 g, 25 mmol) and anhyd DMF (150 mL) in a 300 mL three-necked flask, were added MeI (15.6 g, 250 mmol) and $NaHCO_3$ (8.4 g, 100 mmol) and stirred for 66 h at r.t. The mixture was extracted with EtOAc (3 × 100 mL) and washed with H_2O (3 × 100 mL), brine (100 mL), and dried ($MgSO_4$). Evaporation of the solvent gave a colorless oil, which was used in the following reaction. A mixture of the crude product, 4-iodoaniline (7.0 g, 32 mmol), AcOH (1.4 mL), and triacetoxy boro-

hydride (9.8 g, 46 mmol) in anhyd CH_2Cl_2 (250 mL) was stirred for 47 h at r.t. The mixture was extracted with CH_2Cl_2 (2 × 100 mL), and the combined organic layers were washed with aq 2 N NaOH (100 mL), H_2O (2 × 100 mL), brine, and dried ($MgSO_4$). Evaporation of the solvent gave a crystalline solid, which was filtered to give **3e** in 83% yield; mp 200–203 °C.

IR (neat): 1686, 1465, 1377, 826, 731 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.93 (d, 1 H, *J* = 7.3 Hz), 7.72–7.50 (m, 7 H), 4.84 (s, 2 H).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 167.51, 139.80, 139.28, 138.02, 132.90, 132.33, 128.50, 124.19, 122.64, 120.88, 87.85, 50.41.

EIMS: *m*/*z* (%) = 335 (100), 307 (15), 208 (7), 179 (7), 104 (10), 90 (12), 76 (16).

HRMS: *m*/*z* calcd for $C_{14}H_{10}INO$: 334.9807. Found: 334.9798.

Anal. Calcd for $C_{14}H_{10}INO$: C, 50.17; H, 3.01; N, 4.18; I, 37.87. Found: C, 49.91; H, 3.10; N, 4.05; I, 38.16.

2-Iodo-6-methoxynaphthalene (3f)[19]
Yield: 38%; mp 145–146 °C (Lit.[19] mp 146–147 °C).

^1H NMR (270 MHz, $CDCl_3$): δ = 8.14 (s, 1 H), 7.68–7.46 (m, 3 H), 7.25–7.07 (m, 2 H), 3.92 (s, 3 H).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 157.93, 136.19, 134.68, 133.30, 130.55, 128.34, 128.30, 119.52, 105.63, 88.05, 55.28.

EIMS: *m*/*z* (%) = 284 (100), 269 (18), 236 (56), 223 (13), 193 (27), 114 (44).

HRMS: *m*/*z* calcd for $C_{11}H_9OI$: 283.9698. Found: 283.9688.

2-(4-Iodobenzoyl)thiophene (3g)[22]
Yield: 60%; mp 107–108 °C (Lit.[22] mp 106.5 °C).

IR (nujol): 1625, 1460, 1377, 849 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.87 (dd, 2 H, *J* = 2.0, 6.6 Hz), 7.75 (dd, 1 H, *J* = 1.0, 4.6 Hz), 7.62 (dd, 1 H, *J* = 1.0, 3.6 Hz), 7.59 (dd, 2 H, *J* = 2.0, 6.6 Hz), 7.17 (dd, 1 H, *J* = 3.6, 4.6 Hz).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 187.28, 143.11, 137.68, 137.38, 134.79, 134.59, 130.60, 128.07, 99.75.

EIMS: *m*/*z* (%) = 314 (82), 231 (25), 203 (14), 187 (22), 111 (100), 76 (30).

HRMS: *m*/*z* calcd for $C_{11}H_7IOS$: 313.9263. Found: 313.9263.

2-Fluoro-4-iodobiphenyl (3h)
Yield: 40%.

IR (neat) : 1205, 1158, 859, 764, 697 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.27–7.58 (m, 6 H), 7.19–7.13 (t, 2 H, *J* = 8.3 Hz).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 160.97, 133.53, 131.81, 128.66, 128.45, 127.92, 125.45, 125.07, 92.08.

EIMS: *m*/*z* (%) = 298 (100), 170 (97), 151 (20), 144 (7), 99 (5), 85 (23), 75 (10), 51 (8).

HRMS: *m*/*z* calcd for $C_{12}H_8FI$: 297.9655. Found: 297.9654.

Electrogenerated Highly Reactive Zinc (EGZn/Naph)
A normal one-compartment cell equipped with a magnetic stirrer and a serum cap was used. Electrogenerated highly reactive zinc (EGZn/Naph) (6 mmol) was prepared by the electrolysis of a DMF solution (10 mL) containing 0.1 M Et_4NClO_4 (230 mg) and naphthalene (12 mmol) in a one-compartment cell fitted with a platinum plate cathode (2 × 2 cm^2) and a zinc plate anode (2 × 2 cm^2). Electrolysis was carried out at –10 °C at a constant current of 60 mA/cm^2 under N_2. The quantity of electricity passed was 0.012 Faradays, which corresponded to 2 Faradays per mol of zinc. The amount of EGZn/Naph was calculated from the weight of dissolved zinc anode. A solution containing EGZn/Naph was directly used for the preparation of organozinc compounds after the zinc anode was removed from the electrolysis cell.

Cross-Coupling Reaction Using EGZn/Naph; General Procedure
To the DMF solution containing EGZn/Naph was added ethyl 2-bromoacrylate (**1**; 537 mg, 3 mmol) and the mixture was stirred at –20 °C under N_2 for 1 h. The appropriate aryl iodide **3** (2 mmol) and $Pd[P(o\text{-}Tol)_3]_2Cl_2$ (0.11 mmol) were added, and the reaction mixture was stirred at 70 °C for 3 h. The resulting mixture was quenched with aq HCl solution and filtered. The filtrate was extracted with Et_2O (3 × 50 mL) and the combined organic layers were washed with H_2O (3 × 100 mL), sat. aq $Na_2S_2O_3$ solution (100 mL) and brine (100 mL), and dried ($MgSO_4$). After evaporation of Et_2O, the crude product was purified by column chromatography on silica gel with EtOAc–hexane to give the ethyl 2-arylpropenoate **4**.

Ethyl 2-(4-Isobutylphenyl)propenoate (4a)
Colorless oil.

IR (neat): 1720, 1615, 1512, 1466, 1367, 1199, 1181, 1089, 850, 806 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.34 (d, 2 H, *J* = 8.3 Hz), 7.13 (d, 2 H, *J* = 8.3 Hz), 6.28 (d, 1 H, *J* = 1.3 Hz), 5.87 (d, 1 H, *J* = 1.3 Hz), 4.29 (q, 2 H, *J* = 7.3 Hz), 2.48 (d, 2 H, *J* = 6.9 Hz), 1.87 (m, 1 H), 1.33 (t, 3 H, *J* = 7.3 Hz), 0.91 (d, 6 H, *J* = 6.9 Hz).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 163.99, 142.41, 141.37, 130.91, 128.75 125.45, 118.98, 60.90, 44.94, 30.01, 22.28, 13.95.

EIMS: *m*/*z* (%) = 232 (63), 189 (100), 161 (16), 145 (15), 115 (28).

HRMS: *m*/*z* calcd for $C_{15}H_{20}O_2$: 232.1463. Found: 232.1472.

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.68; H, 8.83.

Ethyl 2-(3-Benzoylphenyl)propenoate (4b)
IR (neat): 1720, 1663, 1618, 1448, 1200, 1026, 710 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.86–7.76 (m, 3 H), 7.75–7.57 (m, 3 H), 7.52–7.45 (m, 3 H), 6.43 (d, 1 H, *J* = 1.0 Hz), 5.96 (d, 1 H, *J* = 1.0 Hz), 4.30 (q, 2 H, *J* = 7.3 Hz), 1.33 (t, 3 H, *J* = 7.3 Hz).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 196.37, 166.31, 140.67, 137.45, 137.39, 136.96, 132.51, 132.33, 130.08, 129.92, 129.72, 128.30, 128.05, 127.71, 61.28, 14.18.

EIMS: *m*/*z* (%) = 280 (45), 203 (69), 105 (100), 77 (52).

HRMS: *m*/*z* calcd for $C_{18}H_{16}O_3$: 280.1099. Found: 280.1094.

Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 76.78; H, 5.85.

Ethyl 2-(2-Fluorenyl)propenoate (4c)
IR (neat): 1720, 1610, 1457, 1401, 1209, 1025, 738 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.80–7.62 (m, 2 H), 7.62 (d, 1 H, *J* = 0.7 Hz), 7.53 (d, 1 H, *J* = 0.7 Hz), 7.46–7.31 (m, 3 H), 6.35 (d, 1 H, *J* = 1.3 Hz), 5.95 (d, 1 H, *J* = 1.3 Hz), 4.32 (q, 2 H, *J* = 7.3 Hz), 3.92 (s, 2 H), 1.35 (t, 3 H, *J* = 7.3 Hz).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 167.08, 143.52, 143.31, 143.02, 141.74, 141.22, 135.20, 127.04, 126.85, 126.76, 125.89, 125.01, 124.91, 120.02, 119.43, 61.12, 36.88, 14.22.

EIMS: *m*/*z* (%) = 264 (85), 235 (22), 190 (100), 165 (16).

HRMS: *m*/*z* calcd for $C_{18}H_{16}O_2$: 264.1150. Found: 264.1162.

Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.84; H, 5.92.

Ethyl 2-[4-(2-Oxocyclopentylmethyl)phenyl]propenoate (4d)
IR (neat): 2962, 1741, 1719, 1615, 1514, 1455, 1405, 1199, 1183, 1023, 863, 702 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.35 (dd, 2 H, *J* = 2.0, 8.3 Hz), 7.15 (dd, 2 H, *J* = 2.0, 8.3 Hz), 6.31 (d, 1 H, *J* = 1.0 Hz), 5.87 (d, 1 H, *J* = 1.0 Hz), 4.29 (q, 2 H, *J* = 7.3 Hz), 3.16 (dd, 1 H, *J* = 4.0, 13.5 Hz), 2.54 (dd, 1 H, *J* = 9.6, 13.5 Hz), 2.35 (m, 2 H), 2.05 (m, 4 H), 1.73 (m, 1 H), 1.34 (t, 3 H, *J* = 7.3 Hz).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 219.68, 166.52, 140.90, 139.82, 134.32, 128.34, 128.00, 125.59, 60.76, 50.57, 37.81, 34.95, 28.86, 20.24, 13.91.

EIMS: *m*/*z* (%) = 272 (83), 198 (46), 189 (100), 141 (26), 115 (48), 91 (25).

HRMS: *m*/*z* calcd for $C_{17}H_{20}O_3$: 272.1412. Found: 272.1418.

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.66; H, 7.43.

Ethyl 2-[4-(1-Oxo-1,3-dihydroisoindol-2-yl)phenyl]propenoate (4e)
Mp 110–111 °C.

IR (nujol): 2854, 1721, 1687, 1467, 1154, 735 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.95–7.87 (m, 3 H), 7.61–7.58 (m, 1 H), 7.54–7.49 (m, 4 H), 6.34 (d, 1 H, *J* = 1.0 Hz), 5.92 (d, 1 H, *J* = 1.0 Hz), 4.88 (s, 2 H), 4.31 (q, 2 H, *J* = 7.3 Hz), 1.35 (t, 3 H, *J* = 7.3 Hz).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 167.49, 166.76, 140.70, 140.02, 139.35, 133.08, 132.65, 132.15, 129.04, 128.39, 126.00, 124.13, 122.61, 118.74, 61.12, 50.59, 14.20.

EIMS: *m*/*z* (%) = 307 (100), 234 (64), 209 (9), 103 (8), 90 (6), 77 (6).

HRMS: *m*/*z* calcd for $C_{19}H_{17}NO_3$: 307.1208. Found: 307.1210.

Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.09; H, 5.74; N, 4.27.

Ethyl 2-(6-Methoxynaphthalen-2-yl)propenoate (4f)
IR (neat): 1711, 1605, 1459, 1262, 1196, 1030, 859, 829, 813 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.84 (s, 1 H), 7.73 (t, 2 H, *J* = 8.3 Hz), 7.50 (dd, 1 H, *J* = 2.0, 8.3 Hz), 7.14 (d, 2 H, *J* = 8.3 Hz), 6.38 (d, 1 H, *J* = 1.0 Hz), 5.98 (d, 1 H, *J* = 1.0 Hz), 4.32 (q, 2 H, *J* = 7.3 Hz), 3.91 (s, 3 H), 1.35 (t, 3 H, *J* = 7.3 Hz).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 166.72, 157.81, 141.22, 134.00, 131.70, 129.52, 128.27, 126.99, 126.34, 126.16, 125.61, 118.78, 105.27, 60.83, 54.92, 13.95.

EIMS: *m*/*z* (%) = 256 (100), 228 (14), 183 (71), 168 (15), 139 (19).

HRMS: *m*/*z* calcd for $C_{16}H_{16}O_3$: 256.1099. Found: 256.1097.

Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.24; H, 6.39.

Ethyl 2-[4-(2-Thiophenecarbonyl)phenyl]propenoate (4g)
IR (neat): 1720, 1636, 1414, 1294, 1198, 1086, 1019, 845, 722 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.87 (dd, 2 H, *J* = 2.0, 6.6 Hz), 7.74 (dd, 1 H, *J* = 1.0, 5.0 Hz), 7.68 (dd, 1 H, *J* = 1.0, 4.0 Hz), 7.56 (dd, 2 H, *J* = 2.0, 6.6 Hz), 7.18 (dd, 1 H, *J* = 4.0, 5.0 Hz), 6.47 (d, 1 H, *J* = 1.0 Hz), 6.00 (d, 1 H, *J* = 1.0 Hz), 4.32 (q, 2 H, *J* = 7.3 Hz), 1.35 (t, 3 H, *J* = 7.3 Hz).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 187.47, 166.02, 143.32, 140.47, 137.36, 134.72, 134.18, 128.84, 128.25, 127.94, 127.89, 61.19, 14.04.

EIMS: *m*/*z* (%) = 286 (72), 213 (29), 203 (33), 111 (100).

HRMS: *m*/*z* calcd for $C_{16}H_{14}O_3S$: 286.0663. Found: 286.0670.

Anal. Calcd for $C_{16}H_{14}O_3S$: C, 67.11; H, 4.93; S, 11.20. Found: C, 67.17; H, 4.99; 10.89.

Ethyl 2-[4-(2-Fluoro)biphenyl]propenoate (4h)
IR (neat): 1721, 1616, 1486, 1413, 1220, 1171, 835, 769, 698 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.58–7.55 (m, 2 H), 7.48-7.37 (m, 5 H), 7.31–7.27 (m, 1 H), 6.41 (s, 1 H), 5.98 (s, 1 H), 4.33 (q, 2 H, *J* = 7.3 Hz), 1.36 (t, 3 H, *J* = 7.3 Hz).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 166.33, 161.19, 140.18, 135.45, 130.37, 129.06, 129.02, 128.57, 127.30, 124.40, 116.37, 116.01, 61.39, 14.27.

EIMS: *m*/*z* (%) = 270 (100), 197 (76).

HRMS: *m*/*z* calcd for $C_{17}H_{15}FO_2$: 270.1056. Found: 270.1054.

Anal. Calcd for $C_{17}H_{15}FO_2$: C, 75.54; H, 5.59; F, 7.03. Found: C, 75.71; H, 5.35; F, 6.68.

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