Article

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Silica gel-Mediated Friedel-Crafts Reaction of Indoles with Functionalized Nitroallylic Acetates via an S_N1 Process

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An environmentally friendly Friedel-Crafts reaction was demonstrated between indoles and functionalized nitroallylic acetates in the presence of silica gel, providing the corresponding C-3-selective regioisomers in good to high overall chemical yields (70-93%).

Keywords: Friedel-Crafts reaction; Indole; Nitroallylic acetate; Electrophile; S_N1.

INTRODUCTION

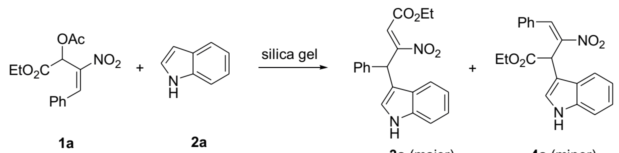
The Friedel-Crafts reaction is an electrophilic aromatic substitution reaction typically catalyzed by a Lewis acid or Brønsted acid to derivatize the starting aromatic compounds.[1] In recent years, considerable attention has been directed towards performing the Friedel-Crafts reaction in an environmentally friendly manner by utilizing various heterogeneous catalysts such as graphite,[2] zeolites,[3] clays,[4] and heteropoly acids.[5] Ionic liquids have also been effectively employed to minimize the corrosive wastes.[6]

Indole derivatives constitute an important class of structural frameworks that encompass various biologically active natural products and pharmaceuticals.[7] Indoles have been found to be successful in Friedel-Crafts reactions as it is a strong nucleophile. In general, the Friedel-Crafts alkylation of indole leads to the C-3-substituted product,[8] but there are reports of such reaction yielding the C-2-substituted product.[9] Furthermore, *N*-alkylation becomes unavoidable in some instances.[10] Recently, the allylic alkylation of indoles has met with some success in the presence of metal complexes acting as catalysts.[7a,c-e,h,j] Herein, we report functionalized nitroallylic acetates (**1a**-**j**) as effective electrophilic components of the Friedel-Crafts reaction with indoles. The silica gel-mediated reaction proceeded smoothly to provide the corresponding C-3-alkylated products under neat conditions.

RESULTS AND DISCUSSION

During optimization we chose ethyl 2-acetoxy-3-nitro-4-phenylbut-3-enoate (**1a**)[11] and indole (**2a**) as reaction partners and scrutinized the silica gel-mediated reaction between them under various reaction conditions (Table 1).

Table 1. Standardization of silica gel-mediated Friedel-Crafts reaction[a]



Entry	**1a**:**2a**	**1a**:silica gel[b]	T (°C)	t (h)	**3a** (% yield)[c]	**4a** (% yield)[c]
1	1.0:1.5	1:3	rt	2.5	66	9
2	1.0:1.5	1:5	rt	2.5	70	12
3	1.0:1.5	1:8	rt	2	79	11
4	1.0:1.5	1:10	rt	2	80	11
5	1.0:1.5	1:8	0	6	75	11
6	1.0:1.5	1:8	40	1	80	13
7	1.0:2.0	1:8	40	1	75	15
8	1.0:1.5	1:8	40	1	80	13
9	**1.0:1.0**	**1:8**	**40**	**1**	**82**	**11**
10	1.5:1.0	1:8	40	1	76	15

[a] All reactions were performed on a 0.13 mmol scale. [b] By weight. [c] Isolated yields after flash column chromatography.

We have found that 1.0 equiv of nitroallylic acetate (**1a**) and 1.5 equiv of indole afforded the desired **3a** in 79% isolated yield in the presence of silica gel at ambient temperature for 2 h (Table 1, entry 3). The minor product **4a** was isolated with 11% yield. We have also observed that reaction rates accelerated in warmer conditions (40 °C) and took only 1 h to give comparable yields (Table 1, entry 6). Later studies with different ratios of substrates revealed that equal amounts of indole and nitroallylic acetate are sufficient to obtain the best chemical yield (Table 1, entry 9).

With suitable reaction conditions realized, we extended our methodology and various nitroallylic acetates

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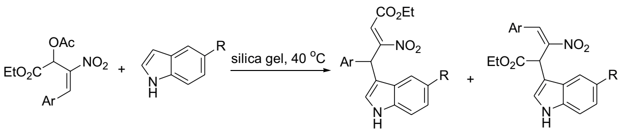
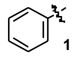
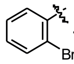
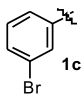
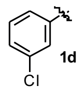
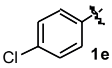
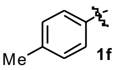
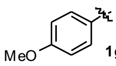
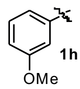
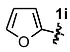
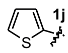
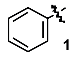
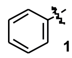
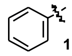
Table 2. Silica gel-mediated Friedel-Crafts reaction of nitroallylic acetates with indoles[a]



1a-j **2a-d** **3a-m** **4a-m**

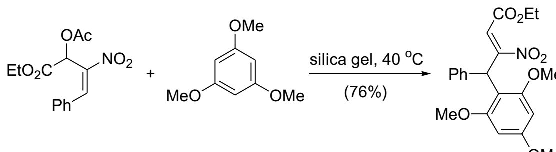
Entry	Ar	R =	t (h)	**3** (% yield)[b]	**4** (% yield)[b]
1	 **1a**	H	1	**3a** (82)	**4a** (11)
2	 **1b**	H	1.5	**3b** (70)	**4b** (<5)
3	 **1c**	H	1.5	**3c** (75)	**4c** (10)
4	 **1d**	H	2	**3d** (76)	**4d** (14)
5	 **1e**	H	2	**3e** (74)	**4e** (14)
6	 **1f**	H	2	**3f** (73)	**4f** (8)
7	 **1g**	H	3	**3g** (65)	**4g** (18)
8	 **1h**	H	2.5	**3h** (75)	**4h** (12)
9	 **1i**	H	2	**3i** (70)	**4i** (10)
10	 **1j**	H	3	**3j** (57)	**4j** (34)
11	 **1a**	Me (**2b**)	1	**3k** (78)	**4k** (15)
12	 **1a**	Ome (**2c**)	1	**3l** (78)	**4l** (11)
13	 **1a**	Cl (**2d**)	8	**3m** (70)	**4m** (16)

[a] All reactions were carried out on a 0.13 mmol scale of nitroallylic acetates (**1a**-**j**) with 0.13 mmol indoles (**2a**-**d**) in the presence of silica gel (304 mg) at 40 °C. [b] Isolated yields after flash column chromatography.

(**1a-j**) with different substitution profiles and subject to the Friedel-Crafts reaction with indoles (**2a-d**) (Table 2). The corresponding products **3a-m** and the minor regioisomers **4a-m** were obtained in 57-82% and 34-<5% isolated yields, respectively. These two products were readily separable by flash column chromatography. We have also carried out reactions using furyl and thiophenyl derived nitroallylic acetates as the electrophilic partners, and found that the latter afforded the products with less selectivity (major:minor = 57:34) (Table 2, entry 10). Other substituted indoles (**2b-d**) have also been successfully brought into the scope of this reaction (Table 2, entries 11-13). However, the reaction with 5-chloro substituted indole (**2d**) took a longer time to yield the corresponding products in good yields (Table 2, entry 13).

A scaled up reaction was performed to demonstrate the utility of this synthetic protocol. Treatment of the indole (0.8 g, 7.0 mmol) with nitroallylic acetate **1a** (2.0 g, 7.0 mmol) at 40 °C for 1.5 h provided **3a** and **4a** with 77% and 8% isolated yields, respectively.

In addition, various aromatic/heteroaromatic substrates (benzene and benzene derivatives, pyridine, etc) were tested under optimum conditions. Most failed the electrophilic aromatic substitution, while the reaction of 1,3,5-trimoethoxybenzene with **1a** proceeded smoothly to give **6a** with a 76% chemical yield (eq 1).



eq 1

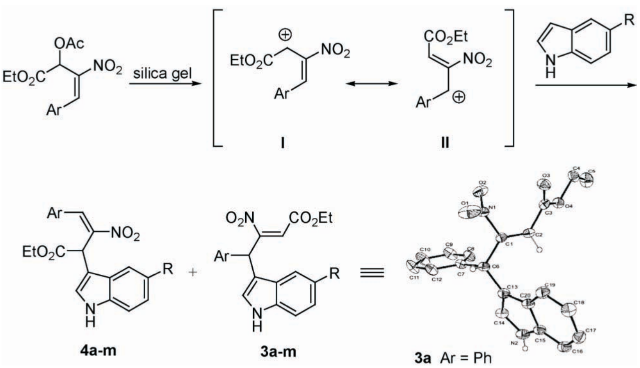
1a **5** **6a**

The reaction is believed to proceed through an S_N1 process. The hydrogen bonding activation between the silica gel and the acetate group of the nitroallylic acetate led to the formation carbocation intermediates (**I** and **II**). The indole derivatives then reacted with the silica gel-induced species. This is in agreement with previously reported work that demonstrated the formation of carbocataion intermediate in the silica gel-mediated rearrangement of allylic acetates under microwave irradiation.[12] The formation of the two regioisomers can be rationalized by the energy difference of the two optimized intermediates **I** (minor) and **II** (major, benzylic carbocation) (Scheme I). It is worth noting that the Z-geometry (**II**) dominated when double bond migration occurred.

CONCLUSION

We have reported silica gel-mediated 'green' Friedel-Crafts reactions between functionalized nitroallylic acetates and indoles to afford C-3 indole derivatives. Depending on the stability of the carbocation intermediate, two functionalized regioisomers were isolated in high to excellent overall chemical yields. The operationally simple, metal-free, ecocompatible and neat conditions make this process attractive.

Scheme I Proposed mechanism of the Friedel-Crafts reaction and the X-ray ORTEP drawing of **3a** (30% probability)[13]



EXPERIMENTAL

Typical procedure

To a solution of nitroallylic acetate **1a** (38 mg, 0.13 mmol) in CH_2Cl_2 (5 mL) was added silica gel (304 mg, Merck silica gel 60, 230-400 mesh) in one portion. This was added indole **2a** (0.13 mmol) and the solvent was removed *in vacuo*. The resulting mixture was stirred at 40 °C for 1 h and purified by flash column chromatography (eluted with hexanes:EtOAc = 6:1) to give the products **3a** (82%) and **4a** (11%).

3a: yield 82%; R_f = 0.13 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.52 (d, J = 7.84 Hz, 1H), 7.29-7.32 (m, 6H), 7.18-7.22 (m, 1H), 7.12 (t, J = 7.92 Hz, 1H), 6.67 (d, J = 2.44 Hz, 1H), 5.67 (s, 2H), 4.15 (q, J = 7.16 Hz, 2H), 1.2 (t, J = 7.16 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.18, 161.41, 136.91, 136.73, 129.14, 128.70, 128.19, 125.88, 124.85, 122.91, 122.53, 120.00, 118.88, 113.06, 111.77, 62.05, 46.34, 13.82; IR (CH_2Cl_2) ν 3424.35, 3070.11, 2996.30, 2922.50, 1727.18, 1539.17, 1458.06, 1369.58, 1266.35, 1200.00, 1096.77, 1026.72, 742.85, 694.93 cm^{-1}; m.p. 97.7-100.3 °C; HRMS $[M+Na]^+$ calcd for $C_{20}H_{18}N_2O_4$ 373.1164. Found 373.1173.

4a: yield 11%; R_f = 0.2 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.47 (d, J = 7.96, 1H), 7.10-7.36 (m, 9H), 6.94 (s, 1H), 6.74 (s, 1H), 3.93-4.02 (m, 2H), 1.11 (t, J = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.66, 162.45, 138.40, 135.85, 128.40, 128.10, 127.07, 126.90, 125.00, 122.35, 122.22, 119.85, 118.73, 112.17, 111.24, 61.82, 40.62, 13.67; IR (CH_2Cl_2) ν 3416.97, 1723.50, 1657.14, 1539.17, 1336.40, 1207.37, 742.85 cm^{-1}; HRMS $[M+Na]^+$ calcd for $C_{20}H_{18}N_2O_4$ 373.1164. Found 373.1180.

3b: Reaction Time: 1.5 h; yield 70%; R_f = 0.13 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.61 (d, J = 7.88 Hz, 1H), 7.52 (d, J = 7.92 Hz, 1H), 7.12-7.37 (m, 6H), 6.78 (s, 1H), 6.23 (s, 1H), 5.67 (s, 1H), 4.19 (q, J = 7.16 Hz, 2H), 1.25 (t, J = 7.16 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.95, 159.70, 136.69, 133.70, 129.63, 129.55, 127.89, 126.01, 125.12, 124.52, 123.03, 120.45, 119.40, 119.40, 118.91, 111.97, 111.59, 62.01, 45.48, 13.75; IR (CH_2Cl_2) ν 3416.97, 3055.35, 2988.92, 1727.18, 1664.51, 1539.17, 1465.43, 1369.58, 1266.35, 1196.31, 1096.77, 1023.04, 746.54 cm^{-1}; HRMS $[M+Na]^+$ calcd for $C_{20}H_{17}BrN_2O_4$ 451.0269. Found 451.0278.

3c: Reaction Time: 1.5 h; yield 75%; R_f = 0.16 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.46-7.54 (m, 3H), 7.39 (d, J = 8.16 Hz, 1H), 7.25-7.28 (m, 3H), 7.16 (t, J = 7.68 Hz, 1H), 6.77 (d, J = 2.4 Hz, 1H), 5.69 (s, 2H), 4.19 (q, J = 7.16 Hz, 2H), 1.25 (t, J = 7.16 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.72, 160.22, 139.34, 136.67, 131.68, 131.35, 130.56, 127.19, 125.73, 124.51, 123.13, 120.57, 120.57, 118.91, 118.80, 112.76, 111.60, 61.99, 45.73, 13.73; IR (CH_2Cl_2) ν 3424.35, 2981.54, 2922.50, 2856.08, 1727.18, 1660.82, 1542.85, 1461.75, 1369.58, 1262.67, 1196.31, 1096.77, 1026.72, 742.85 cm^{-1}; HRMS $[M+Na]^+$ calcd for $C_{20}H_{17}BrN_2O_4$ 451.0269. Found 451.0283.

4c: yield 10%; R_f = 0.2 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.48-7.52 (m, 2H), 7.37-7.40 (m, 2H), 7.12-7.28 (m, 6H), 7.06 (d, J = 2.48 Hz, 1H), 6.80 (s, 1H), 4.03-4.15 (m, 2H), 1.20 (t, J = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.64, 161.93, 141.01, 135.86, 131.07, 130.29, 129.96, 126.89, 126.79, 124.99, 124.99, 122.68, 122.61, 120.17, 118.69, 111.62, 111.30, 62.04, 39.96, 13.81; IR (CH_2Cl_2) ν 3424.35, 2922.50, 2848.70, 1723.50, 1539.17, 1472.81, 1458.06, 1336.40, 1211.05, 742.85 cm^{-1}; HRMS $[M+Na]^+$ calcd for $C_{20}H_{17}BrN_2O_4$ 451.0269. Found 451.0291.

3d: Reaction Time: 2 h; yield 76%; R_f = 0.17 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.51 (d, J = 7.84 Hz, 1H), 7.15-7.39 (m, 7H), 6.76 (s, 1H), 5.69 (s, 2H), 4.19 (q, J = 7.08 Hz, 2H), 1.25 (t, J = 7.08 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.77, 160.27, 139.07, 136.68, 134.99, 130.31, 128.78, 128.42, 126.78, 125.73, 124.53, 123.12, 120.56, 118.90, 118.79, 112.70, 111.63, 62.02, 45.78, 13.74; IR (CH_2Cl_2) ν 3424.35, 2922.50, 1638.70, 1539.17, 1465.43, 1376.95, 1196.31, 1093.08, 1023.04, 742.85 cm^{-1}; HRMS $[M+Na]^+$ calcd for $C_{20}H_{17}ClN_2O_4$ 407.0775. Found 407.0783.

4d: yield 14%; R_f = 0.2 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.36-7.40 (m, 2H), 7.12-7.24 (m, 7H), 7.06 (d, *J* = 2.40 Hz, 1H), 6.80 (s, 1H), 4.03-4.15 (m, 2H), 1.20 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.64, 162.00, 140.74, 135.87, 134.42, 129.66, 128.22, 127.36, 126.92, 126.31, 124.97, 122.69, 122.58, 120.17, 118.71, 111.68, 111.29, 62.03, 40.01, 13.81; IR (CH_2Cl_2) ν 3416.97, 2988.92, 1719.81, 1657.14, 1535.48, 1340.09, 1207.37, 742.85 cm^{-1}; HRMS $[M+Na]^+$ calcd for $C_{20}H_{17}ClN_2O_4$ 407.0775. Found 407.0783.

3e: Reaction Time: 2 h; yield 74%; R_f = 0.18 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.50 (d, *J* = 7.92 Hz, 1H), 7.15-7.38 (m, 7H), 6.74 (s, 1H), 5.68 (s, 2H), 4.18 (q, *J* = 7.00 Hz, 2H), 1.24 (t, *J* = 7.00 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.78, 160.53, 136.69, 135.53, 134.09, 129.97, 129.29, 125.73, 124.48, 123.11, 120.54, 118.85, 118.68, 112.98, 111.61, 61.99, 45.59, 13.74; IR (CH_2Cl_2) ν 3409.59, 2988.92, 2937.26, 1723.50, 1664.51, 1539.17, 1369.58, 1196.31, 1093.08, 1015.66, 746.54 cm^{-1}; m.p. 115.1-116.0 °C; HRMS $[M+Na]^+$ calcd for $C_{20}H_{17}ClN_2O_4$ 407.0775. Found 407.0784.

4e: yield 14%; R_f = 0.2 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.45 (d, *J* = 8 Hz, 1H), 7.38 (d, *J* = 8 Hz, 1H), 7.22-7.32 (m, 5H), 7.10-7.13 (m, 2H), 7.03 (d, *J* = 2.40 Hz, 1H), 6.75 (s, 1H), 4.00-4.13 (m, 2H), 1.20 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.65, 162.24, 137.07, 135.92, 133.05, 129.62, 128.61, 126.83, 124.82, 122.67, 122.43, 120.14, 118.79, 112.09, 111.29, 62.00, 40.03, 13.80; IR (CH_2Cl_2) ν 3424.35, 3062.73, 2922.50, 2848.70, 1727.18, 1535.48, 1336.40, 1203.68, 1089.40, 1011.98, 746.54 cm^{-1}; HRMS $[M+Na]^+$ calcd for $C_{20}H_{17}ClN_2O_4$ 407.0775. Found 407.0780.

3f: Reaction Time: 2 h; yield 73%; R_f = 0.14 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.54 (d, *J* = 7.88 Hz, 1H), 7.35 (d, *J* = 8.12 Hz, 1H), 7.12-7.24 (m, 6H), 6.74 (d, *J* = 2.32 Hz, 1H), 5.66 (s, 2H), 4.17 (q, *J* = 7.12 Hz, 2H), 2.34 (s, 3H), 1.23 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.93, 161.43, 137.79, 136.59, 133.75, 129.69, 128.46, 125.85, 124.49, 122.83, 120.29, 118.92, 117.87, 113.48, 111.45, 61.80, 45.86, 21.07, 13.70; IR (CH_2Cl_2) ν 3416.97, 3062.73, 2981.54, 1730.87, 1542.85, 1373.27, 1270.04, 1203.68, 1093.08, 1023.04, 742.85 cm^{-1}; m.p. 117.0-119.4 °C; HRMS $[M+H]^+$ calcd for $C_{21}H_{20}N_2O_4$ 365.1501. Found 365.1515.

4f: yield 8%; R_f = 0.18 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.48 (d, *J* = 8 Hz, 1H), 7.37 (d, *J* = 8 Hz, 1H), 7.04-7.25 (m, 8H), 6.70 (s, 1H), 3.94-4.09 (m, 2H), 2.32 (s, 3H), 1.15 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.70, 162.76, 136.79, 135.94, 135.34, 129.17, 128.14, 127.03, 124.89, 122.45, 122.03, 119.96, 118.94, 112.79, 111.16, 61.80, 40.41, 21.02, 13.76; IR (CH_2Cl_2) ν 3416.97, 3055.35, 2988.92, 2929.88, 2863.46, 1723.50, 1535.48, 1458.06, 1340.09, 1203.68, 1100.46, 1037.78, 857.14, 742.85 cm^{-1}; HRMS $[M+Na]^+$ calcd for $C_{21}H_{20}N_2O_4$ 387.1321. Found 387.1330.

3g: Reaction Time: 3 h; yield 65%; R_f = 0.13 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.53 (d, *J* = 7.88 Hz, 1H), 7.36 (d, *J* = 8.12 Hz, 1H), 7.13-7.25 (m, 4H), 6.87-6.90 (m, 2H), 6.76 (s, 1H), 5.65 (s, 2H), 4.17 (q, *J* = 7.12 Hz, 2H), 3.80 (s, 3H), 1.23 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.93, 161.61, 159.27, 136.60, 129.69, 128.71, 125.79, 124.46, 122.80, 120.25, 118.90, 117.65, 114.37, 113.53, 111.47, 61.81, 55.25, 45.50, 13.69; IR (CH_2Cl_2) ν 3409.59, 3055.35, 2988.92, 2848.70, 1727.18, 1664.51, 1535.48, 1513.36, 1458.06, 1369.58, 1251.61, 1192.62, 1030.41, 742.85 cm^{-1}; m.p. 143.6-148.3 °C; HRMS $[M+H]^+$ calcd for $C_{21}H_{20}N_2O_5$ 381.1459. Found 381.1468.

4g: yield 18%; R_f = 0.18 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.03-7.47 (m, 8H), 6.84 (d, *J* = 8.68 Hz, 2H), 6.66 (s, 1H), 3.96-4.08 (m, 2H), 3.79 (s, 3H), 1.14 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.70, 162.76, 158.71, 135.96, 130.23, 129.52, 126.89, 124.76, 122.47, 121.91, 119.95, 118.96, 113.84, 113.01, 111.17, 61.81, 55.24, 40.15, 13.76; IR (CH_2Cl_2) ν 3416.97, 3055.35, 2937.26, 2848.70, 1727.18, 1601.84, 1539.17, 1513.36, 1458.06, 1332.71, 1306.91, 1251.61, 1211.05, 1177.88, 1026.72, 857.14, 742.85 cm^{-1}; HRMS $[M+Na]^+$ calcd for $C_{21}H_{20}N_2O_5$ 403.1270. Found 403.1281.

3h: Reaction Time: 2.5 h; yield 75%; R_f = 0.12 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.54 (d, *J* = 7.92 Hz, 1H), 7.35 (d, *J* = 8.12 Hz, 1H), 7.14-7.27 (m, 3H), 6.92 (d, *J* = 7.68 Hz, 1H), 6.84-6.87 (m, 2H),6.78 (s, 1H), 5.68 (s, 2H), 4.17 (q, *J* = 7.12 Hz, 2H), 3.77 (s, 3H), 1.23 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.90, 160.95, 159.96, 138.31, 136.53, 129.97, 125.77, 124.53, 122.80, 120.82, 120.26, 118.78, 118.23, 114.56, 113.20, 112.98, 111.48, 61.83, 55.20, 46.08, 13.67; IR (CH_2Cl_2) ν 3424.35, 3062.73, 2929.88, 2856.08, 1727.18, 1668.20, 1605.52, 1539.17, 1461.75, 1270.04, 1030.41, 882.94, 746.54 cm^{-1}; m.p. 117.0-119.4 °C; HRMS $[M+H]^+$ calcd for $C_{21}H_{20}N_2O_5$ 381.1450. Found 381.1459.

4h: yield 12%; R_f = 0.18 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.50 (d, *J* = 8 Hz, 1H), 7.36 (d, *J* = 8 Hz, 1H), 7.18-7.25 (m, 2H), 7.09-7.13 (m, 2H), 7.04 (d, *J* = 2.12 Hz, 1H), 6.94-6.96 (m, 2H), 6.78-6.81 (m, 1H), 6.73 (s, 1H), 3.94-4.09 (m, 2H), 3.75 (s, 3H), 1.15 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.69, 162.34, 159.72, 140.06, 135.88, 129.41, 127.05, 125.05, 122.48, 122.29, 120.54, 120.00, 118.84, 114.26, 112.30, 112.30, 111.19, 61.85, 55.19, 40.56, 13.76; IR (CH_2Cl_2) ν 3416.97, 3055.35, 2922.50, 2848.70, 1723.50, 1598.15, 1583.41, 1535.48, 1491.24, 1458.06, 1336.4, 1266.35, 1207.37, 1041.47, 742.85 cm^{-1}; HRMS [M+Na]$^+$ calcd for $C_{21}H_{20}N_2O_5$ 403.1270. Found 403.1279.

3i: Reaction Time: 2 h; yield 70%; R_f = 0.1 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.56 (d, *J* = 7.84 Hz, 1H), 7.43 (d, *J* = 1.36 Hz, 1H), 7.38 (d, *J* = 8.08 Hz, 1H), 7.21-7.25 (m, 1H), 7.13-7.17 (m, 1H), 7.08 (d, *J* = 2 Hz, 1H), 6.33 (q, *J* = 1.96 Hz, 1H), 6.23 (d, *J* = 3.24 Hz, 1H), 5.77 (d, *J* = 9.84 Hz, 2H), 4.19 (q, *J* = 7.16 Hz, 2H), 1.24 (t, *J* = 7.16 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.69, 158.84, 149.94, 143.01, 136.38, 125.68, 124.05, 122.89, 120.41, 118.79, 117.76, 111.51, 110.66, 110.40, 109.33, 61.90, 39.90, 13.71; IR (CH_2Cl_2) ν 3424.35, 2988.92, 1727.18, 1668.20, 1542.85, 1458.06, 1262.67, 1200.00, 1019.35, 742.85 cm^{-1}; HRMS [M+H]$^+$ calcd for $C_{18}H_{16}N_2O_5$ 341.1137. Found 341.1144.

4i: yield 10%; R_f = 0.18 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.61 (d, *J* = 7.92 Hz, 1H), 7.14-7.39 (m, 5H), 7.08 (s, 1H), 6.94 (s, 1H), 6.34 (dd, *J* = 3.24, 1.92 Hz, 1H), 6.18 (d, *J* = 3.28 Hz, 1H), 4.23-4.29 (m, 2H), 1.31 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.77, 160.75, 151.98, 141.76, 135.66, 126.75, 124.95, 122.52, 121.96, 120.11, 118.72, 111.27, 110.61, 110.13, 107.79, 62.07, 31.92, 13.96; IR (CH_2Cl_2) ν 3416.97, 3062.73, 2922.50, 2856.08, 1727.18, 1539.17, 1458.06, 1340.09, 1207.37, 1096.77, 1011.98, 742.85 cm^{-1}; HRMS [M+H]$^+$ calcd for $C_{18}H_{16}N_2O_5$ 341.1137. Found 341.1149.

3j: Reaction Time: 3 h; yield 57%; R_f = 0.13 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.37 (d, *J* = 8.12 Hz, 1H), 7.12-7.27 (m, 3H), 6.97-7.03 (m, 3H), 5.99 (s, 1H), 5.80 (s, 1H), 4.19 (q, *J* = 7.16 Hz, 2H), 1.24 (t, *J* = 7.16 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.84, 160.68, 139.97, 136.49, 127.14, 127.11, 125.94, 125.57, 124.10, 122.93, 120.39, 118.78, 117.97, 112.93, 111.53, 61.94, 40.92, 13.70; IR (CH_2Cl_2) ν 3409.59, 2937.26, 2856.08, 1727.18, 1535.48, 1373.27, 1258.98, 1196.31, 1100.46, 1019.35, 746.54, 709.67 cm^{-1}; HRMS [M+H]$^+$ calcd for $C_{18}H_{16}N_2O_4S$ 357.0909. Found 357.0926.

4j: yield 34%; R_f = 0.18 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.55 (d, *J* = 7.96 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.04-7.29 (m, 7H), 6.96-6.97 (m, 1H), 4.20-4.24 (m, 2H), 1.27 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.70, 162.28, 142.03, 135.69, 126.76, 126.66, 126.36, 125.03, 124.81, 122.54, 121.67, 120.09, 118.57, 112.48, 111.29, 62.09, 35.89, 13.93; IR (CH_2Cl_2) ν 3409.59, 3099.63, 2922.50, 2848.70, 1749.30, 1638.70, 1535.48, 1314.28, 1211.05, 1056.22, 739.17 cm^{-1}; HRMS [M+Na]$^+$ calcd for $C_{18}H_{16}N_2O_4S$ 379.0729. Found 379.0738.

3k: Reaction Time: 1 h; yield 78%; R_f = 0.13 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.24-7.36 (m, 7H), 7.05 (d, *J* = 8.32 Hz, 1H), 6.69 (d, *J* = 2.28 Hz, 1H), 5.67 (s, 2H), 4.18 (q, *J* = 7.12 Hz, 2H), 2.44 (s, 3H), 1.25 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.93, 161.18, 136.90, 134.89, 129.76, 128.98, 128.58, 128.00, 126.08, 124.63, 124.56, 118.38, 118.16, 112.83, 111.11, 61.81, 46.13, 21.49, 13.71; IR (CH_2Cl_2) ν 3431.73, 2988.92, 2922.50, 2863.46, 1727.18, 1539.17, 1369.58, 1270.04, 1192.62, 1096.77, 1026.72, 798.15, 702.30 cm^{-1}; HRMS [M+Na]$^+$ calcd for $C_{21}H_{20}N_2O_4$ 387.1321. Found 387.1332.

4k: yield 15%; R_f = 0.18 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.25-7.37 (m, 7H), 7.14 (s, 1H), 7.03 (d, *J* = 9.28 Hz, 1H), 7.00 (d, *J* = 2.52 Hz, 1H), 6.70 (s, 1H), 3.94-4.09 (m, 2H), 2.41 (s, 3H), 1.19 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.71, 162.51, 138.56, 134.24, 129.28, 128.44, 128.16, 127.28, 127.08, 125.10, 124.15, 122.24, 118.41, 111.93, 110.87, 61.82, 40.65, 21.52, 13.77; IR (CH_2Cl_2) ν 3416.97, 3062.73, 2922.50, 2856.08, 1727.18, 1657.14, 1539.17, 1447.00, 1373.27, 1340.09, 1266.35, 1207.37, 1096.77, 1034.10, 794.47, 739.17, 702.30 cm^{-1}; HRMS [M+Na]$^+$ calcd for $C_{21}H_{20}N_2O_4$ 387.1321. Found 387.1329.

3l: Reaction Time: 1 h; yield 78%; R_f = 0.13 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.24-7.36 (m, 7H), 6.94 (d, *J* = 2.28 Hz, 1H), 6.87-6.89 (m, 1H), 6.69 (d, *J* = 2.44 Hz, 1H), 5.69 (s, 1H), 5.65 (s, 1H), 4.18 (q, *J* = 7.12 Hz, 2H), 3.82 (s, 3H), 1.25 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.93, 160.85, 154.52, 136.82, 131.65, 128.99, 128.56, 128.02, 126.27, 125.19, 118.36, 113.07, 112.99, 112.28, 100.59, 61.84, 55.88, 46.18, 13.70; IR (CH_2Cl_2) ν 3416.97, 2996.30, 2937.26, 1727.18, 1539.17, 1487.55, 1266.35, 1207.37, 1026.72, 798.15, 698.61 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{20}N_2O_5$ 403.1270. Found 403.1277.

4l: yield 11%; R_f = 0.18 (4:1 Hex/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.25-7.37 (m, 6H), 7.14 (s, 1H), 7.04 (d, *J* = 2.52 Hz, 1H), 6.93 (d, *J* = 2.24 Hz, 1H), 6.85-6.88 (m, 1H), 6.72 (s, 1H), 3.97-4.09 (m, 2H), 3.78 (s, 3H), 1.17 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.76, 162.49, 154.32, 138.44, 130.98, 128.44, 128.06, 127.55, 127.08, 125.76, 122.17, 112.67, 111.98, 111.91, 100.85, 61.84, 55.80, 40.56, 13.79; IR (CH_2Cl_2) ν 3424.35, 3062.73, 2922.50, 2848.70, 1723.50, 1539.17, 1487.55, 1340.09, 1211.05, 1026.72, 798.15, 698.61 cm^{-1}; HRMS $[M+Na]^+$ calcd for $C_{21}H_{20}N_2O_5$ 403.1270. Found 403.1281.

3m: Reaction Time: 8 h; yield 70%; R_f = 0.13 (4:1 Hex/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.48 (d, *J* = 1.84 Hz, 1H), 7.26-7.38 (m, 6H), 7.19 (d, *J* = 1.92 Hz, 1H), 6.83 (d, *J* = 2.48 Hz, 1H), 5.63-5.65 (m, 2H), 4.20 (q, *J* = 7.12 Hz, 2H), 1.25 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.75, 160.86, 136.50, 134.92, 129.13, 128.56, 128.24, 126.95, 126.19, 125.75, 123.39, 118.32, 118.32, 112.99, 112.56, 61.97, 45.91, 13.70; IR (CH_2Cl_2) ν 3424.35, 2929.88, 2856.08, 1727.18, 1671.88, 1542.85, 1458.06, 1200.00, 1030.41, 801.84, 702.30 cm^{-1}; HRMS $[M+Na]^+$ calcd for $C_{20}H_{17}ClN_2O_4$ 407.0775. Found 407.0782.

4m: yield 16%; R_f = 0.19 (4:1 Hex/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.45 (d, *J* = 1.88, 1H), 7.26-7.32 (m, 6H), 7.11-7.18 (m, 3H), 6.70 (s, 1H), 4.00-4.14 (m, 2H), 1.19 (t, *J* = 7.12 Hz, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.65, 162.29, 138.02, 134.25, 128.55, 128.14, 128.08, 127.29, 126.38, 125.87, 122.90, 122.44, 118.45, 112.36, 112.25, 62.01, 40.42, 13.81; IR (CH_2Cl_2) ν 3424.35, 3055.35, 2922.50, 2856.08, 1723.50, 1539.17, 1465.43, 1336.40, 1203.68, 1104.14, 1030.41, 894.00, 739.17, 698.61 cm^{-1}; RMS $[M+Na]^+$ calcd for $C_{20}H_{17}ClN_2O_4$ 407.0775. Found 407.0782.

6a: Reaction Time: 8 h; yield 76%; R_f = 0.2 (4:1 Hex/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 7.24-7.36 (m, 5H), 6.11 (s, 2H), 5.97 (d, *J* = 1.84 Hz, 1H), 5.53 (d, *J* = 2 Hz, 1H), 4.17 (q, *J* = 7.12 Hz, 2H), 3.79 (s, 3H), 3.75 (s, 6H), 1.24 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.54, 163.32, 161.23, 159.04, 137.69, 129.27, 128.51, 127.31, 115.85, 106.06, 91.29, 61.40, 55.77, 55.25, 43.95, 13.76; IR (CH_2Cl_2) ν 3446.49, 2944.64, 2841.32, 1727.18, 1605.52, 1542.85, 1458.06, 1200.00, 1118.89, 1026.72, 816.58, 702.30 cm^{-1}; HRMS $[M+Na]^+$ calcd for $C_{21}H_{23}NO_7$ 424.1372. Found 424.1380.

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