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Facile Regiocontrolled Three-Step Synthesis of Poly-Substituted Furans, Pyrroles, and Thiophenes: Consecutive Michael Addition of Methyl Cyanoacetate to α,β-Enone, CuI-Mediated Aerobic Oxidation, and Acid-Catalyzed Paal-Knorr Synthesis

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An efficient synthesis of poly-substituted furans, pyrroles, and thiophenes was carried out in a regiocontrolled manner *via* a three-step process; (i) conjugate addition of methyl cyanoacetate derivatives to α,β-enones, (ii) CuI-mediated aerobic oxidation, and (iii) Paal-Knorr type synthesis of five-membered heterocycles.

Key Words : Furans, Pyrroles, Thiophenes, CuI, Paal-Knorr synthesis

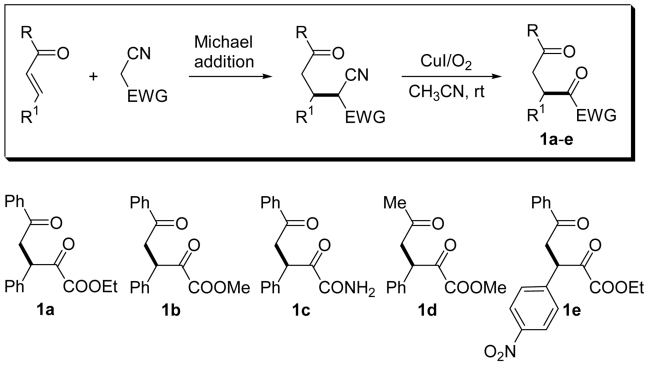
Introduction

Recently, we reported an efficient synthesis of 2,5-diketoesters *via* a conjugate addition of methyl cyanoacetate to α,β-unsaturated ketone and a following CuI-mediated aerobic oxidation.[1] The protocol is a very simple and high-yielding process of 2,5-diketoesters (vide infra, Scheme 1).[1,2] 2,5-Diketoesters could be used for the synthesis of various five-membered heterocyclic compounds such as furans and pyrroles.[2c,d]

Although the Paal-Knorr syntheses of furans and pyrroles from various 1,4-diketones have been used extensively in organic synthesis,[3,4] the use of 2,5-diketoesters has not been reported much,[2c,d] presumably due to the lack of general synthetic methods of 2,5-diketoesters.[1,2] Thus we decided to synthesize poly-substituted furans,[3,5] pyrroles,[4,5] and thiophenes[5,6] in a regioselective manner in order to shed more light on our convenient synthetic protocol of 2,5-diketoesters.

Results and Discussion

The required 2,5-diketoesters were prepared according to our previous paper in two steps; (i) Michael addition of methyl cyanoacetate, ethyl cyanoacetate, and cyanoacetamide to the corresponding α,β-unsaturated ketones and (ii) CuI-mediated aerobic oxidation, as shown in Scheme 1.[1] Five representative starting materials **1a-e** were prepared in good yields (72-90%) and used for the syntheses of furans, pyrroles, and thiophenes.



Scheme 1. Preparation of starting materials (Ref. 1).

Table 1. Synthesis of poly-substituted furans

Entry	Substrate	Conditions[a]	Products (%)	
1	**1a**	60 °C, 60 min	**2a** (78)	**3a** (<5)[b]
2	**1b**	50 °C, 90 min	**2b** (74)	
3	**1c**	60 °C, 60 min	**2c** (31)	**3c** (58)[c]
4	**1d**	50 °C, 30 min	**2d** (68)	
5	**1e**	50 °C, 90 min	**2e** (74)	

[a]Conditions: Substrate **1** (0.5 mmol), benzene, H_2SO_4 (5.0 equiv). [b]Hydrolysis and concomitant decarboxylation was reported (Ref. 7). [c]Hydrolysis of **2c** to **3c** was observed even in AcOH (reflux).

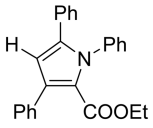
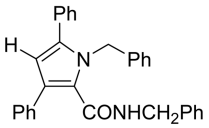
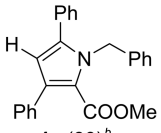
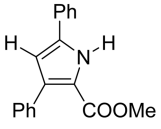
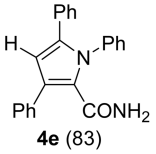
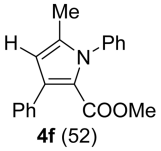
Initially, we examined a synthesis of ethyl 3,5-diphenylfuran-2-carboxylate (**2a**) by acid-catalyzed Paal-Knorr synthesis of **1a**, as a model compound. The reaction of **1a** in CH_3CN (reflux, 3 h) in the presence of AcOH showed almost no reaction. The reaction was very slow even in refluxing AcOH solvent, and more than the half of **1a** remained after 15 h. Thus we examined the use of H_2SO_4 as an acid catalyst. After some trials we could obtain **2a** in a reasonable yield (78%) in the presence of H_2SO_4 (5.0 equiv) in benzene (60 °C) in short time (60 min). The reaction at room temperature required longer reaction time while the amounts of side products such as **3a**[7] increased when the reaction was performed at refluxing temperature. Thus we carried out the synthesis of furan derivatives **2b-e** under the optimized conditions (50-60 °C in the presence of 5.0 equiv of H_2SO_4), and the results are summarized in Table 1. Furans **2b**, **2d**, and **2e** were obtained in moderate yields (entries 2, 4 and 5). However, when we used the amide derivative **1c** as a starting material (entry 3), furan **2c** was obtained in low yield (31%). Instead, a carboxylic acid derivative **3c** was obtained as a major product (58%).

As a next experiment, we examined the synthesis of poly-substituted pyrrole derivatives, as summarized in Table 2. The reaction of **1a** and aniline was performed in the presence of sulfamic acid (NH_2SO_3H) as a catalyst.[8] Pyrrole derivative **4a** was isolated in good yield (84%) at room temperature (entry 1). When we carried out the reaction at elevated temperature (50 °C) the reaction was completed in short time (5 h) to provide **4a** in a slightly lower yield (78%). The reaction of **1b** and benzylamine (2.0 equiv) was not completed even after 24 h at room temperature. When we increased the amounts of benzylamine (4.0 equiv, entry 2), *N*-benzylamide derivative **4b** was obtained in moderate yield (55%). The ester group was completely converted to *N*-benzylamide group under the reaction conditions. Thus we carried out the reaction of **1b** and benzylamine in refluxing AcOH (entry 3), and compound **4c** was obtained as a major product (80%) along with a low yield of **4b** (11%). The synthesis of *N*-unsubstituted pyrrole could be carried out using NH_4OAc as an ammonia source. Actually, the reaction of **1b** produced **4d** in good yield (94%), and AcOH was used as a solvent in this case (entry 4). Similarly, the reactions of **1c** and **1d** with aniline gave **4e** and **4f** in good to moderate yields (entries 5 and 6).

Poly-substituted thiophenes were also synthesized using Lawesson's reagent as a thionation reagent.[6] As shown in Table 3, we synthesized three thiophenes **5a-c** in reasonable yields (41-81%). Trace amounts (< 5%) of the corresponding furan derivatives were isolated in some entries. Thiophene **5b** was obtained as its thioamide derivative.

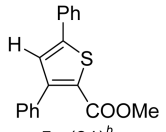
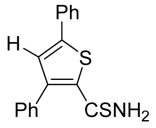
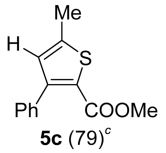
In order to show one of the advantages of our synthetic protocol, we examined the synthesis of 5-unsubstituted pyrrole **6a** from **4a** by removal of the ester moiety. In general, the synthesis of pyrrole derivatives bearing a hydro-

Table 2. Synthesis of poly-substituted pyrroles

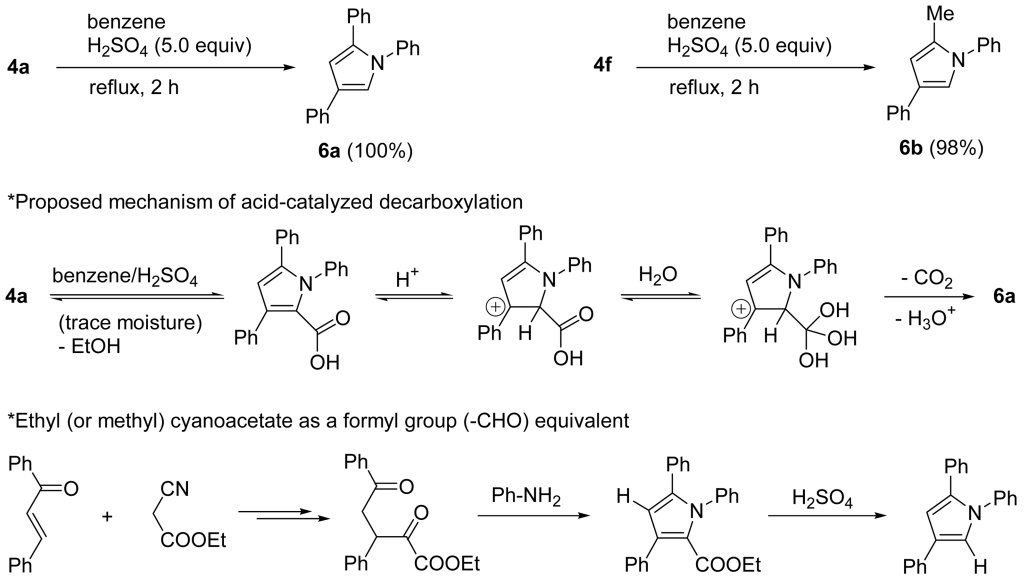
Entry	Substrate	Conditions[a]	Products (%)
1	**1a**	aniline (2.0 equiv) NH_2SO_3H (0.1 equiv) rt, 24 h	 **4a** (84)
2	**1b**	benzylamine (4.0 equiv) NH_2SO_3H (0.1 equiv) rt, 24 h	 **4b** (55)
3	**1b**	benzylamine (2.0 equiv) AcOH, reflux, 1 h	 **4c** (80)[b]
4	**1b**	NH_4OAc (2.0 equiv) NH_2SO_3H (0.1 equiv) AcOH, 50 °C, 1 h	 **4d** (94)
5	**1c**	aniline (2.0 equiv) NH_2SO_3H (0.1 equiv) rt, 48 h	 **4e** (83)
6	**1d**	aniline (2.0 equiv) NH_2SO_3H (0.1 equiv) rt, 24 h	 **4f** (52)

[a]Conditions: Substrate **1** (0.5 mmol). [b]Compound **4b** was isolated in low yield (11%).

Table 3. Synthesis of poly-substituted thiophenes[a]

Entry	Substrate	Products (%)
1	**1b**	 **5a** (81)[b]
2	**1c**	 **5b** (41)
3	**1d**	 **5c** (79)[c]

[a]Conditions: Substrate **1** (0.5 mmol), Lawesson's reagent (1.2 equiv), benzene, 50-60 °C, 3 h. [b]Compound **2b** was isolated in 5%. [c]Compound **2d** was isolated in 4%.



Scheme 2. Synthesis of 5-*H*-pyrrole derivatives *via* acid-catalyzed decarboxylation.

gen atom either at 2- or 5-positions has been known as somewhat difficult.[9,10] The Paal-Knorr synthesis using γ-ketoaldehyde could be used;[9] however, the synthesis of γ-ketoaldehyde is somewhat tedious.[9a] Thus, an indirect method has been used in some cases; namely, a synthesis of pyrrole-2-carboxylic acid and a subsequent decarboxylation process.[10] With these points in mind, we examined the conversion of **4a** and **4f** to the corresponding 5-*H*-pyrrole derivatives **6a** and **6b**, as shown in Scheme 2. The reactions provided **6a** and **6b** in quantitative yields under the influence of H_2SO_4 in refluxing benzene. The plausible mechanism is suggested in Scheme 2 based on the reported decarboxylation of pyrrole-2-carboxylic acid.[11] The results stated that 2,5-diketoesters could be used efficiently for the synthesis of 5-unsubstituted pyrroles, and eventually methyl cyanoacetate as a formyl group equivalent, as also shown in Scheme 2.

In summary, we disclosed an efficient synthesis of polysubstituted furans, pyrroles, and thiophenes in a regiocontrolled manner *via* a three-step process; (i) conjugate addition of methyl cyanoacetate derivatives to α,β-enones, (ii) CuI-mediated aerobic oxidation, and (iii) Paal-Knorr type synthesis of five-membered heterocycles.

Experimental Section

Preparation of Starting Materials.[1] The starting materials **1a-e** were prepared according to our previous paper.[1]

Typical Procedure for the Synthesis of Furan 2a. To a stirred solution of **1a** (155 mg, 0.5 mmol) in benzene (2.0 mL) was added H_2SO_4 (246 mg, 2.5 mmol), and the reaction mixture was heated to 60 °C for 1 h. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/EtOAc, 20:1) compound **2a** was obtained as a white solid, 114 mg (78%). Other furan derivatives **2b-e** and **3c** were synthesized similarly, and the spectroscopic data are as follows.

Compound 2a:[12a] 78%; white solid, mp 96-97 °C (lit.[12a] 98-99 °C); IR (KBr) 1709, 1482, 1448, 1289 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, J = 7.2 Hz, 3H), 4.33 (q, J = 7.2 Hz, 2H), 6.85 (s, 1H), 7.32-7.48 (m, 6H), 7.60-7.64 (m, 2H), 7.79-7.84 (m, 2H); ESIMS *m/z* 293 $[M+H]^+$.

Compound 2b:[3d] 74%; white solid, mp 69-71 °C; IR (KBr) 1714, 1483, 1449, 1286 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.85 (s, 3H), 6.84 (s, 1H), 7.32-7.45 (m, 6H), 7.60-7.64 (m, 2H), 7.79-7.82 (m, 2H); ESIMS *m/z* 301 $[M+Na]^+$.

Compound 2c: 31%; white solid, mp 143-145 °C; IR (KBr) 3481, 3346, 3281, 3132, 1683, 1609 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.06 (br s, 1H), 6.24 (br s, 1H), 6.85 (s, 1H), 7.32-7.46 (m, 6H), 7.70-7.77 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 109.59, 124.60, 128.29, 128.39, 128.86, 128.91, 129.27 (2C), 131.75, 133.76, 140.04, 154.35, 160.63; ESIMS *m/z* 264 $[M+H]^+$. Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.69; H, 4.71; N, 5.17.

Compound 2d: 68%; white solid, mp 83-85 °C; IR (KBr) 1704, 1548, 1290, 1259 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.82 (s, 3H), 6.26 (s, 1H), 7.28-7.43 (m, 3H), 7.54-7.58 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.85, 51.55, 111.19, 127.94, 128.13, 129.17, 132.10, 136.28, 137.14, 155.71, 159.47; ESIMS *m/z* 217 $[M+H]^+$. Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.43; H, 5.48.

Compound 2e: 74%; pale yellow solid, mp 129-131 °C; IR (KBr) 1708, 1513, 1345, 1298 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (t, J = 7.2 Hz, 3H), 4.35 (q, J = 7.2 Hz, 2H), 6.87 (s, 1H), 7.37-7.49 (m, 3H), 7.78-7.84 (m, 4H), 8.26-8.29 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.18, 61.14, 108.69, 123.18, 124.95, 128.82, 128.93, 129.44, 130.29, 134.10, 138.70, 138.87, 147.49, 156.43, 158.78; ESIMS *m/z* 360 $[M+Na]^+$. Anal. Calcd for $C_{19}H_{15}NO_5$: C, 67.65; H, 4.48; N, 4.15. Found: C, 67.57; H, 4.71; N, 4.08.

Compound 3c: 58%; white solid, mp 177-179 °C; IR (KBr) 3135, 1626, 1359, 1249 cm^{-1}; ^1H NMR (300 MHz,

$CDCl_3$) δ 6.64 (s, 1H), 7.30-7.76 (m, 10H), 12.16 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 107.66, 126.05, 128.41, 128.46, 128.67, 128.91, 128.94, 129.22, 133.42, 135.25, 135.46, 141.66, 159.98; ESIMS *m/z* 265 $[M+H]^+$. Anal. Calcd for $C_{17}H_{12}O_3$: C, 77.26; H, 4.58. Found: C, 77.11; H, 4.72.

Typical Procedure for the Synthesis of Pyrrole 4a. A mixture of **1a** (155 mg, 0.5 mmol), aniline (93 mg, 1.0 mmol), and sulfamic acid (5 mg, 0.05 mmol) was stirred at room temperature under solvent-free conditions for 24 h. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/EtOAc, 15:1) compound **4a** was obtained as a white solid, 155 mg (84%). Other pyrrole derivatives **4b-f** were synthesized similarly, and the spectroscopic data are as follows including the data of two pyrrole derivatives **6a** and **6b** in Scheme 2.

Compound 4a: 84%; white solid, mp 129-131 °C; IR (KBr) 1706, 1494, 1455, 1204 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7.2 Hz, 3H), 3.96 (q, *J* = 7.2 Hz, 2H), 6.48 (s, 1H), 7.09-7.42 (m, 13H), 7.52-7.56 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.50, 59.95, 112.08, 121.72, 126.84, 127.35, 127.65, 127.88, 127.99, 128.39, 128.56, 128.92, 129.46, 131.87, 133.39, 135.98, 139.31, 139.51, 161.26; ESIMS *m/z* 368 $[M+H]^+$. Anal. Calcd for $C_{25}H_{21}NO_2$: C, 81.72; H, 5.76; N, 3.81. Found: C, 81.53; H, 5.98; N, 3.79.

Compound 4b: 55%; white solid, mp 122-124 °C; IR (KBr) 3426, 3310, 1646, 1519 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.27 (d, *J* = 6.0 Hz, 2H), 5.62 (s, 2H), 5.64 (br s, 1H), 6.28 (s, 1H), 6.74-6.92 (m, 4H), 7.08-7.46 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.28, 48.87, 110.46, 124.08, 126.23, 126.88, 126.96, 127.04, 127.43, 128.01, 128.10, 128.39 (2C), 128.52, 128.56, 129.00, 129.53, 132.25, 135.32, 137.75, 138.96, 139.35, 162.37; ESIMS *m/z* 443 $[M+H]^+$. Anal. Calcd for $C_{31}H_{26}N_2O$: C, 84.13; H, 5.92; N, 6.33. Found: C, 83.94; H, 6.13; N, 6.07.

Compound 4c: 80%; colorless oil; IR (film) 1698, 1456, 1268, 1202 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.52 (s, 3H), 5.60 (s, 2H), 6.34 (s, 1H), 6.89-6.93 (m, 2H), 7.14-7.48 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.65, 50.75, 112.16, 119.30, 125.65, 126.65, 126.82, 127.59, 128.30, 128.45, 128.50, 129.29, 129.44, 131.91, 134.13, 136.48, 139.29, 140.80, 162.10; ESIMS *m/z* 368 $[M+H]^+$. Anal. Calcd for $C_{25}H_{21}NO_2$: C, 81.72; H, 5.76; N, 3.81. Found: C, 81.59; H, 5.75; N, 3.67.

Compound 4d:[12b] 94%; white solid, mp 175-177 °C (lit.[12b] 179-180 °C); IR (KBr) 3311, 1663, 1453, 1274 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.77 (s, 3H), 6.62 (d, *J* = 3.3 Hz, 1H), 7.28-7.43 (m, 6H), 7.57-7.62 (m, 4H), 9.55 (br s, 1H); ESIMS *m/z* 300 $[M+Na]^+$.

Compound 4e: 83%; white solid, mp 170-172 °C; IR (KBr) 3447, 3163, 1623, 1606, 1490, 1356 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.39 (br s, 2H), 6.45 (s, 1H), 7.07-7.63 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 111.03, 124.70, 127.18, 127.31, 127.82, 127.99, 128.30, 128.49, 128.59, 128.65, 128.81, 129.07, 131.87, 135.22, 138.12, 139.02, 163.22; ESIMS *m/z* 339 $[M+H]^+$. Anal. Calcd for $C_{23}H_{18}N_2O$: C, 81.63; H, 5.36; N, 8.28. Found: C, 81.68; H, 5.62; N, 8.02.

Compound 4f: 52%; pale yellow solid, mp 88-90 °C; IR (KBr) 1696, 1501, 1459, 1363 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.04 (s, 3H), 3.43 (s, 3H), 6.12 (s, 1H), 7.24-7.50 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.89, 50.57, 110.75, 119.55, 126.67, 127.59, 127.70, 128.04, 128.76, 129.39, 133.60, 136.17, 136.28, 139.71, 161.50; ESIMS *m/z* 292 $[M+H]^+$. Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.45; H, 5.76; N, 4.67.

Compound 6a:[9a] 100%; white solid, mp 147-148 °C (lit.[9a] 150-155 °C); IR (KBr) 1691, 1595, 1493, 1231 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.75 (d, *J* = 2.1 Hz, 1H), 7.15-7.40 (m, 14H), 7.58-7.62 (m, 2H); ESIMS *m/z* 296 $[M+H]^+$.

Compound 6b: 98%; colorless oil; IR (film) 1704, 1598, 1499, 1396 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.24 (d, *J* = 0.9 Hz, 3H), 6.37 (dq, *J* = 2.1 and 0.9 Hz, 1H), 7.07 (d, *J* = 2.1 Hz, 1H), 7.13-7.19 (m, 1H), 7.30-7.54 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.99, 106.57, 117.95, 124.50, 124.97, 125.44, 125.67, 127.02, 128.59, 129.13, 130.19, 135.58, 140.17; ESIMS *m/z* 234 $[M+H]^+$. Anal. Calcd for $C_{17}H_{15}N$: C, 87.52; H, 6.48; N, 6.00. Found: C, 87.34; H, 6.44; N, 5.76.

Typical Procedure for the Synthesis of Thiophene 5a: A mixture of **1b** (148 mg, 0.5 mmol) and Lawesson's reagent (243 mg, 0.6 mmol) in benzene (2.0 mL) was heated to 50-60 °C for 3 h. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/Et_2O, 45:1) compound **5a** was obtained as a white solid, 119 mg (81%). Other thiophene derivatives **5b** and **5c** were synthesized similarly, and the spectroscopic data are as follows.

Compound 5a:[12c] 81%; white solid, mp 71-73 °C; IR (KBr) 1709, 1439, 1254 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.77 (s, 3H), 7.28 (s, 1H), 7.32-7.52 (m, 8H), 7.62-7.66 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.86, 125.34, 126.09, 127.40, 127.81, 128.01, 128.85, 129.08, 129.10, 133.11, 135.70, 148.41, 149.55, 162.36; ESIMS *m/z* 295 $[M+H]^+$.

Compound 5b: 41%; pale yellow solid, mp 165-167 °C; IR (KBr) 3346, 3269, 3138, 1622, 1423 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.72 (br s, 1H), 7.17 (br s, 1H), 7.21 (s, 1H), 7.25-7.52 (m, 8H), 7.62-7.68 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 125.94, 127.68, 128.76, 128.97, 129.04, 129.09, 129.42, 133.01, 135.38, 138.64, 140.82, 151.39, 191.82; ESIMS *m/z* 296 $[M+H]^+$. Anal. Calcd for $C_{17}H_{13}NS_2$: C, 69.11; H, 4.44; N, 4.74. Found: C, 69.31; H, 4.56; N, 4.58.

Compound 5c:[12d] 79%; white solid, mp 97-99 °C (lit.[12d] 95-97 °C); IR (KBr) 1713, 1454, 1262, 1223 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.50 (d, *J* = 0.9 Hz, 3H), 3.73 (s, 3H), 6.77 (q, *J* = 0.9 Hz, 1H), 7.31-7.45 (m, 5H); ESIMS *m/z* 255 $[M+Na]^+$.

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