An Efficient Method for the Synthesis of 3-Arylpyrroles

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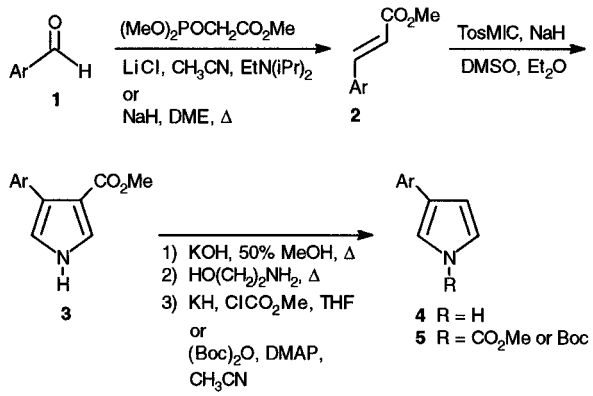
The introduction of substituents in the 3β-position of pyrroles is of great importance as intermediates in the synthesis of natural products and conducting polymers.[1,2] It is well-known that pyrroles have a propensity to undergo kinetic electrophilic substitution reactions predominantly at the 2-position.[3] However, the 3-substituted pyrroles are less accessible. The 3-substituted pyrroles have been previously prepared by (a) ring closure reactions,[4,5] (b) metal-catalyzed reactions,[6,7] (c) utilization of a removable deactivating substituent at the 2-position (usually acyl) to direct entry of an electrophile to the 4β-position,[8] (d) acid-mediated isomerization of 2-substituted isomers,[9] (e) Lewis acid-catalyzed reactions of acylating agents with 1-(benzenesulfonyl)pyrrole,[10] and (f) use of a sterically bulky *N*-substituent to obstruct electrophilic attack at the 2-position.[11] However, some of these methods are somewhat limited to the electrophilic substitution of an acyl group. Herein we report an expeditious method for the synthesis of a series of 3-aryl-substituted pyrroles in good overall yields.

As illustrated in Scheme 1, the 3-arylpyrroles were prepared in a short reaction sequence from the readily available aryl aldehydes **1**. The aldehydes **1** were converted into the corresponding methyl 3-arylacrylate esters **2** using a Masamune−Rousch or a Wadsworth−Emmons (**2f** and **2h**) olefination procedure.[12,13] Under both of these reaction conditions, 3-indolecarboxaldehyde was unreactive. However, the *N*-benzyl derivative **1h** reacted smoothly under Wadsworth−Emmons reaction conditions to afford **2h** in 80% yield.

The pyrrole ring system was generated by the procedure developed by van Leusen *et al.*[14] Treatment of **2**

Scheme 1



with TosMIC afforded the 4-aryl-3-(methoxycarbonyl)-pyrroles **3** in good yields (Scheme 1, Table 1). Electron neutral or electron-deactivated aryl vinyl esters could be successfully employed in the cyclization reaction. However, the TosMIC addition reaction with **2** which possessed electron-rich substituents on the aryl ring (i.e., Ar = *p*-$CH_3OC_6H_5$) did not yield the desired pyrroles, but rather gave intractable mixtures. The disubstituted pyrrole derivatives **3** were found to be air-stable easily handled solids.

Initially, attempts were made to remove the 3-methoxycarbonyl ester moiety in a single step. However, treatment of the 3,4-disubstituted pyrroles under strong acidic conditions (H_2SO_4, PTSA, CF_3CO_2H) at elevated temperatures resulted in the decomposition of many of the heteroaromatic substituents and incomplete conversion.[15] Therefore as an alternative approach the ester moieties were hydrolyzed to the carboxylic acids with excess KOH in 50% MeOH. The acid derivatives were then decarboxylated by heating in 2-ethanolamine to give the 3-substituted pyrroles **4** in good yield (Table 1).[16]

Several of the pyrrole derivatives (**4c**−**e**, **g**) were found to decompose slowly in the presence of air. As a result, these analogs were protected immediately upon isolation as the corresponding methyl carbamates **5c**,**d**,**g**. The chloropyridyl derivative **4e** was protected as the *tert*-butyl carbamate **5e**. This afforded air-stable solid compounds which were easily characterized and could be stored over extended periods.

The method described above extends the methodology developed by van Leusen *et al.*[14] and is believed to be a very facile approach for the preparation of 3-arylpyrrole derivatives not readily available by other synthetic methods. In addition, this methodology has the advantage that it employs readily available precursors and is tolerant of a wide variety of aryl and heteroaryl systems. The yields obtained by this method are superior to those reported by previous methods.[5] For example, a recent report describes the synthesis of **4a** from benzaldehyde in five steps and 37% overall yield, while the new method described above afforded **4a** in four steps and 52% overall yield. In summary, this new synthetic method allows for the efficient preapartion of 3-arylpyrroles in good overal yield and represents a dramatic improvement over existing methodology.

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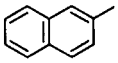
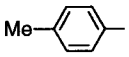
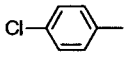
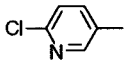
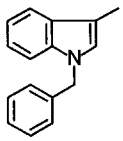
Table 1. Synthesis of 3-Arylpyrrole Derivatives

entry	Ar	**3** (%)[a]	**4** (%)[a]	**5** (%)[a]
a		70	82	
b		60	67	
c		64	63	88[b]
d		60	81	84[b]
e		68	70	86[c]
f		64	65	
g		60	60	80[b]
h		48	70	

Experimental Section

All chemicals were purchased from Aldrich Chemical Co., Milwaukee, WI, unless otherwise noted. Ether (E. M. Science) and THF were dried by distillation from Na/benzophenone. Dimethyl sulfoxide was dried by vacuum distillation over CaH_2. Acetonitrile was dried by distillation over P_2O_5. Chromatography refers to flash chromatography on silica gel (silica gel 60, 230−400 mesh, E. M. Science) and petroleum ether refers to pentanes with a boiling point range of 30−60 °C. Reported melting points are uncorrected. Elemental analyses were obtained from Atlantic Microlab, Inc., Norcross, GA.

Method A. Preparation of 3,4-Disubstituted Pyrroles 3a−h. A solution of TosMIC (5.1 mmol) and α,β-unsaturated ester (5.0 mmol) in a dry ether/DMSO (2:1) solution was added dropwise under an N_2 atmosphere to a stirred solution of NaH (6.4 mmol) in ether. The mixture started to reflux due to the exothermic reaction. After 1 h, water was carefully added to the mixture and the aqueous phase was extracted with ether (1 × 50 mL) and CH_2Cl_2 (2 × 75 mL). The combined organic extracts were dried (Na_2SO_4) and then concentrated under reduced pressure. The residue was purified by column chromatography.

Method B. Preparation of 4a−h. The 3,4-disubstituted pyrroles **3a−h** (2.5 mmol) were refluxed for 2−3 h in a solution of 50% MeOH containing an excess of KOH (25 mmol). Water was added, and the mixture was acidified with 12 N HCl. The precipitate was filtered. The filtrate was extracted with CH_2Cl_2 (2 × 25 mL) or Et_2O (2 × 25 mL). The solvents were removed under reduced pressure. The residue was then refluxed in 2-ethanolamine (freshly distilled) for 2 h. The reaction mixture was cooled and poured into ice. The aqueous phase was extracted with Et_2O (3 × 50 mL) or CH_2Cl_2 (3 × 50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2).

Method C. Preparation of Alkyl Carbamates 5c,d,g. To a stirred solution of KH (2 mmol) in THF under N_2 at 0 °C was added the pyrrole (1 mmol). The solution was stirred for 45 min, and then the methyl chloroformate (1 mmol) was added. The mixture was stirred overnight, diluted with water, and extracted with ether (3 × 50 mL) or CH_2Cl_2 (3 × 50 mL). The solvent was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography.

3-(Methoxycarbonyl)-4-phenylpyrrole (3a). Method A with **2a** afforded pale yellow crystals (0.71 g, 70%): mp 181−182 °C (MeOH) [lit.[14] mp 182−183 °C]; ^{1}H NMR ($CDCl_3$) δ 8.45 (br s, 1H), 7.50−7.26 (m, 6H), 6.79 (s, 1H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 164.1, 134.7, 129.2, 129.0, 127.3, 126.9, 125.8, 119.3, 117.5, 51.6.

3-(Methoxycarbonyl)-4-(2-naphthyl)pyrrole (3b). Method A with **2b** after column chromatography (SiO_2, Et_2O/hexane, 1:1) afforded a white solid (0.76 g, 60%): mp 199−202 °C; ^{1}H NMR (acetone-d_6) δ 10.75 (br s, 1H), 8.01 (s, 1H), 7.88−7.81 (m, 3H), 7.69 (d, J = 3.0 Hz, 1H), 7.59 (s, 1H), 7.47−7.44 (m, 2H), 7.08 (s, 1H), 3.68 (s, 3H); ^{13}C NMR (acetone-d_6) δ 165.4, 134.3, 134.0, 133.1, 129.3, 128.6, 128.2, 127.6, 127.4, 126.8, 126.7, 126.5, 126.0, 120.1, 113.6, 50.8. Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.41; H, 5.21; N, 5.57. Found: C, 76.08; H, 5.35; N, 5.63.

3-(Methoxycarbonyl)-4-(4-methylphenyl)pyrrole (3c). Method A with **2c** after column chromatography (SiO_2, Et_2O/hexane, 2:1) afforded white crystals (0.69 g, 64%): mp 156−159 °C; ^{1}H NMR (acetone-d_6) δ 10.67 (br s, 1H), 7.50 (s, 1H), 7.39 (d, J = 7.5 Hz, 2H), 7.11 (d, J = 7.8 Hz, 2H), 6.89 (s, 1H), 3.64 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (acetone-d_6) δ 165.2, 135.8, 133.2, 129.6, 128.8, 126.7, 126.4, 119.3, 113.2, 50.7, 20.9. Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.53; H, 6.08; N, 6.52. Found: C, 72.53; H, 6.07; N, 6.49.

4-(4-Chlorophenyl)-3-(methoxycarbonyl)pyrrole (3d). Method A with **2d** after column chromatography (SiO_2, EtOAc/hexane, 1:3) afforded white crystals (0.7 g, 60%): mp 171−173 °C. ^{1}H NMR (acetone-d_6) δ 10.81 (br s, 1H), 7.57−7.54 (m, 3H), 7.35 (d, J = 6.0 Hz, 2H), 7.03 (s, 1H), 3.71 (s, 3H); ^{13}C NMR (acetone-d_6) δ 165.3, 135.1, 132.0, 131.5, 128.3, 126.9, 125.5, 120.0, 113.3, 50.9. Anal. Calcd for $C_{12}H_{10}ClNO_2$: C, 61.14; H, 4.27; N, 5.95. Found: C, 61.29; H, 4.33; N, 5.89.

4-[5-(2-Chloropyridyl)]-3-(methoxycarbonyl)pyrrole (3e). Method A with **2e** after column chromatography (SiO_2, Et_2O/hexane, 6:1) afforded a white solid (0.81 g, 68%): mp 179−181 °C; ^{1}H NMR (acetone-d_6) δ 10.91 (br s, 1H), 8.53 (s, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.64 (s, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.16 (s, 1H), 3.73 (s, 3H); ^{13}C NMR (acetone-d_6) δ 165.8, 150.7, 149.8, 141.1, 132.0, 127.9, 124.3, 122.3, 121.2, 114.1, 51.5. Anal. Calcd for $C_{11}H_9ClN_2O_2$: C, 55.83; H, 3.83; N, 11.84. Found: C, 55.79; H, 3.85; N, 11.77.

3-(Methoxycarbonyl)-4-(3-pyridyl)pyrrole (3f). Method A with **2f** after column chromatography (SiO_2, EtOAc/hexane, 5:1) afforded a white solid (0.64 g, 64%): mp 154−157 °C; ^{1}H NMR (acetone-d_6) δ 10.89 (br s, 1H), 8.69 (s, 1H), 8.43 (d, J = 4.7 Hz, 1H), 7.89 (d, J = 7.5 Hz, 1H), 7.60 (s, 1H), 7.33−7.30 (m, 1H), 7.07 (s, 1H), 3.68 (s, 3H); ^{13}C NMR (acetone-d_6) 165.6, 149.6, 149.1, 141.4, 131.9, 127.2, 125.1, 121.9, 121.1, 113.8, 51.2. Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.30; H, 5.03; N, 13.75.

3-(Methoxycarbonyl)-4-(3-thienyl)pyrrole (3g). Method A with **2g** after column chromatography (SiO_2, EtOAc/hexane, 1:2) afforded a pale yellow solid (0.62 g, 60%): mp 167−168 °C; ^{1}H NMR (acetone-d_6) δ 10.71 (br s, 1H), 7.81 (s, 1H), 7.54 (s, 1H), 7.41−7.36 (m, 2H), 7.13 (s, 1H), 3.72 (s, 3H); ^{13}C NMR (acetone-d_6) δ 165.4, 136.1, 129.4, 126.8, 124.4, 121.6, 121.3, 119.5, 113.0, 50.7. Anal. Calcd for $C_{10}H_9NO_2S$: C, 57.96; H, 4.38; N, 6.76. Found: C, 57.84; H, 4.38; N, 6.66.

4-[3-(1-Benzylindolyl)]-3-(methoxycarbonyl)pyrrole (3h). Method A with **2h** after column chromatography (EtOAc/hexane, 1:2.5) afforded a tan solid (0.77 g, 48%): mp 117−119 °C; ^{1}H NMR (acetone-d_6) δ 10.79 (br s, 1H), 7.89 (s, 1H), 7.77 (d, J = 3.0 Hz, 1H), 7.62 (s, 1H), 7.44−7.01 (m, 9H), 5.51 (s, 2H), 3.70 (s, 3H); ^{13}C NMR (acetone-d_6) δ 165.8, 139.7, 137.4, 130.1, 129.7, 129.2, 128.4, 128.2, 126.6, 122.2, 121.1, 120.2, 119.3, 114.0, 111.0, 110.2, 50.97, 50.68. Anal. Calcd for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48. Found: C, 75.98; H, 5.61; N, 8.38.

3-Phenylpyrrole (4a). Method B with **3a** after column chromatography (SiO_2, Et_2O/hexane, 1:1) afforded a pale yellow oil (0.29 g, 82%) [lit.[4] mp 41−42 °C]: ^{1}H NMR (acetone-d_6) δ 10.21 (br s, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.30−7.08 (m, 5H), 6.83 (s, 1H), 6.49 (s, 1H); ^{13}C NMR (acetone-d_6) δ 137.5, 129.3, 125.7, 125.0, 119.7, 119.5, 115.5, 106.4.

3-(2-Naphthyl)pyrrole (4b). Method B with **3b** after column chromatography (SiO_2, EtOAc/hexane, 1:1) afforded a white solid (0.33 g, 67%): mp 92−94 °C; ^{1}H NMR (acetone-d_6) δ 10.24 (br s, 1H), 8.02 (s, 1H), 7.84−7.78 (m, 4H), 7.43−7.36 (m, 3H), 6.90 (s, 1H), 6.65 (s, 1H); ^{13}C NMR (acetone-d_6) δ 135.1, 135.0, 132.7, 132.6, 128.7, 128.3, 126.7, 125.3, 124.9, 122.5, 120.0, 116.2, 106.5. Anal. Calcd for $C_{14}H_{11}N$: C, 87.01; H, 5.74; N, 7.25. Found: C, 86.77; H, 5.78; N, 7.22.

3-(4-Methylphenyl)pyrrole (4c). Method B with **3c** after column chromatography (SiO_2, Et_2O/hexane, 1:1) afforded a pale yellow solid (0.25 g, 63%): mp 85−87 °C; ^{1}H NMR (acetone-d_6) δ 10.08 (br s, 1H), 7.52 (d, J = 3.0 Hz, 2H), 7.14−7.07 (m, 3H), 6.87 (s, 1H), 6.61 (s, 1H); ^{13}C NMR (acetone-d_6) δ 134.8, 134.7, 129.9, 125.5, 125.0, 119.5, 115.1, 106.3, 21.07. The compound was homogeneous by TLC (SiO_2, Et_2O/hexane, 1:2, R_f = 0.85).

3-(4-Chlorophenyl)pyrrole (4d). Method B with **4c** after column chromatography (SiO_2, Et_2O/hexane, 1:1) afforded a white solid (0.36 g, 81%): mp 116−117 °C; ^{1}H NMR (acetone-d_6) δ 10.28 (br s, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.23 (s, 1H), 6.84 (s, 1H), 6.47 (s, 1H); ^{13}C NMR (acetone-d_6) δ 136.4, 130.5, 129.2, 127.0, 123.8, 120.0, 116.0, 106.4. The compound was homogeneous by TLC (SiO_2, Et_2O/hexane, 1:2, R_f = 0.5).

3-[5-(2-Chloropyridyl)]pyrrole (4e). Method B with **3e** after column chromatography (SiO_2, EtOAc/hexane, 2:1) afforded a white solid (0.31 g, 70%): mp 141−143 °C; ^{1}H NMR (acetone-d_6) δ 10.42 (br s, 1H), 8.60 (s, 1H), 7.92 (d, J = 8.2 Hz, 1H), 7.35 (d, J = 6.6 Hz, 1H), 7.31 (s, 1H), 6.91 (s, 1H), 6.55 (s, 1H); ^{13}C NMR (acetone-d_6) δ 147.6, 146.5, 135.6, 132.5, 124.7, 120.5, 120.1, 116.7, 106.4. The compound was homogeneous by TLC (SiO_2, EtOAc/hexane, 1:1, R_f = 0.41).

3-(3-Pyridyl)pyrrole (4f). Method B with **3f** was used except that the pH was adjusted to neutral with 12 N HCl and concentrated under reduced pressure. The residue was then heated in ethanolamine, followed by the usual workup and after column chromatography (SiO_2, ether) afforded a white solid (0.24 g, 65%): mp 136−137 °C; ^{1}H NMR (acetone-d_6) δ 10.52 (br s, 1H), 8.85 (s, 1H), 8.34 (d, J = 4.5 Hz, 1H), 7.88 (d, J = 7.5 Hz, 1H), 7.35 (s, 1H), 7.27 (d, J = 6.0 Hz, 1H), 6.91 (s, 1H), 6.57 (s, 1H); ^{13}C NMR (acetone-d_6) δ 147.1, 146.8, 133.1, 132.3, 124.3, 121.5, 120.3, 116.3, 106.3. Anal. Calcd for $C_9H_8N_2$: C, 74.98; H, 5.59; N, 19.43. Found: C, 75.01; H, 5.59; N, 19.33.

3-(3-Thienyl)pyrrole (4g). Method B with **3g** after column chromatography (SiO_2, Et_2O/hexane, 1:1) afforded a white solid (0.22 g, 60%): mp 74−76 °C; ^{1}H NMR (acetone-d_6) δ 10.11 (br s, 1H), 7.37−7.13 (m, 3H), 6.81 (s, 1H), 6.43 (s, 1H); ^{13}C NMR (acetone-d_6) δ 138.9, 126.9, 126.0, 120.8, 119.4, 116.4, 115.6, 107.0. The compound was homogeneous by TLC (SiO_2, Et_2O/hexane, 1:1, R_f = 0.5).

3′-(1-Benzylindolyl)pyrrole (4h). Method B with **3h** after column chromatography (SiO_2, Et_2O/hexane, 1.5:1) afforded a pale yellow solid (0.47 g, 70%): mp 173−176 °C; ^{1}H NMR (acetone-d_6) δ 10.12 (br s, 1H), 7.89 (d, J = 3.0 Hz, 1H), 7.50 (s, 1H), 7.43−7.09 (m, 9H), 6.89 (s, 1H), 6.49 (s, 1H), 5.47 (s, 2H); ^{13}C NMR (acetone-d_6) δ 139.4, 137.7, 129.3, 128.1, 127.7, 125.1, 122.1, 120.9, 119.8, 118.7, 118.6, 114.8, 113.2, 110.6, 107.3, 50.2. Anal. Calcd for $C_{19}H_{16}N_2$: C, 83.79; H, 5.92; N, 10.29. Found: C, 83.59; H, 6.08; N, 10.26.

1-(Methoxycarbonyl)-3-(4-methylphenyl)pyrrole (5c). Method C with **4c** after column chromatography (SiO_2, EtOAc/hexane, 1:3) afforded a white solid (0.19 g, 88%): mp 76−78 °C; ^{1}H NMR (acetone-d_6) δ 7.59 (s, 1H), 7.49 (d, J = 7.8 Hz, 2H), 7.31 (d, J = 2.3 Hz, 1H), 7.15 (d, J = 7.5 Hz, 2H), 6.65 (d, J = 1.5 Hz, 1H), 3.96 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (acetone-d_6) δ 151.5, 137.1, 132.2, 130.3, 129.1, 126.2, 121.9, 116.2, 111.7, 54.7, 21.2. Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.60; H, 6.08; N, 6.40.

3-(4-Chlorophenyl)-1-(methoxycarbonyl)pyrrole (5d). Method C with **4d** after column chromatography (SiO_2, Et_2O/hexane, 1:2) afforded a white solid (0.19 g, 84%): mp 92−94 °C; ^{1}H NMR (acetone-d_6) δ 7.69−7.64 (m, 3H), 7.37 (d, J = 7.8 Hz, 3H), 6.71 (s, 1H), 3.99 (s, 3H); ^{13}C NMR (acetone-d_6) δ 151.5, 134.1, 132.8, 129.8, 128.0, 122.3, 117.2, 111.6, 55.0. Anal. Calcd for $C_{12}H_{10}ClNO_2$: C, 61.16; H, 4.28; N, 5.96. Found: C, 61.19; H, 4.32; N, 5.89.

1-(*tert*-Butoxycarbonyl)-3-[5-(2-chloropyridyl)]pyrrole (5e). 4-(Dimethylamino)pyridine (DMAP, 0.1 mmol) and $(Boc)_2O$ (1.2 mmol) were added to a stirred solution of pyrrole **4e** (1 mmol) in dry CH_3CN under nitrogen. The mixture was stirred overnight, and excess $(Boc)_2O$ was destroyed by addition of [2-(diethylamino)ethyl]amine (DEAEA, 0.3 mmol) with stirring for 10 min. The crude product was obtained by partitioning between Et_2O and $KHSO_4$ (1 M solution). The ether extract was washed with H_2O (25 mL) and $NaHCO_3$ (1 M, 25 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, EtOAc/hexane, 1:3) to afford a white solid (0.24 g, 86%): mp 101−103 °C; ^{1}H NMR (acetone-d_6) δ 8.69 (d, J = 2.4 Hz, 1H), 8.06−8.03 (m, 1H), 7.81 (s, 1H), 7.44 (d, J = 2.5 Hz, 1H), 7.36 (d, J = 2.1 Hz, 1H), 6.75 (s, 1H), 1.64 (s, 9H); ^{13}C NMR (acetone-d_6) δ 149.4, 149.1, 147.3, 136.5, 130.3, 124.9, 123.9, 122.3, 117.8, 110.6, 84.9, 28.0. Anal. Calcd for $C_{14}H_{15}ClN_2O_2$: C, 60.33; H, 5.42; N, 10.05. Found: C, 60.26; H, 5.39; N, 10.04.

1-(Methoxycarbonyl)-3-(3-thienyl)pyrrole (5g). Method C with **4g** after column chromatography (SiO_2, EtOAc/hexane, 1:4) afforded a pale yellow solid (0.16 g, 80%): mp 81−83 °C; ^{1}H NMR (acetone-d_6) δ 7.56 (d, J = 5.7 Hz, 2H), 7.45−7.41 (m, 2H), 7.30 (d, J = 1.8 Hz, 1H), 6.65 (s, 1H), 3.96 (s, 3H); ^{13}C NMR (acetone-d_6) δ 152.4, 137.4, 127.9, 127.8, 125.7, 122.7, 120.8, 117.5, 113.2, 55.6. Anal. Calcd for $C_{10}H_9NO_2S$: C, 57.96; H, 4.38; N, 6.76. Found: C, 58.13; H, 4.44; N, 6.59.

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