

One-Pot Synthesis of 5-Hydroxypyrrolin-2-one Derivatives from Modified Morita-Baylis-Hillman Adducts *via* a Consecutive CuI-Mediated Aerobic Oxidation, Allylic Iodination, Hydration of Nitrile, and Lactamization

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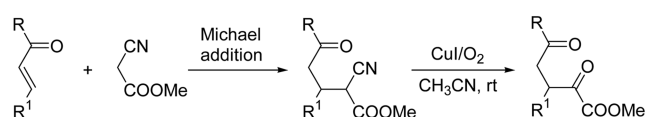
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The Morita-Baylis-Hillman (MBH) adducts have been used as useful intermediates for the synthesis of various cyclic and acyclic compounds.^{1,2} Among them the synthesis of various lactam derivatives has received a special attention.² Very recently, we reported the synthesis of 5-hydroxypyrrolin-2-ones from MBH adducts.^{2a} 5-Hydroxypyrrolin-2-one moiety was found in many biologically active compounds, thus numerous approaches have been reported for the syntheses of these compounds.^{2a,3} In this paper, we described the serendipitous synthesis of 5-hydroxypyrrolin-3-iodomethyl-2-one derivatives from the modified MBH adducts *via* a consecutive CuI-mediated aerobic oxidation, allylic iodination, hydration of nitrile, and lactamization.

Recently, we reported an efficient synthesis of 2,5-diketo esters *via* a conjugate addition of methyl cyanoacetate to α,β -unsaturated ketone and a following CuI-mediated aerobic oxidation, as shown in Scheme 1.⁴ 2,5-Diketo esters thus prepared have been used for the synthesis of furans, pyrroles,

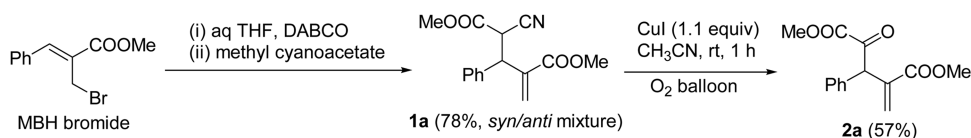


Scheme 1

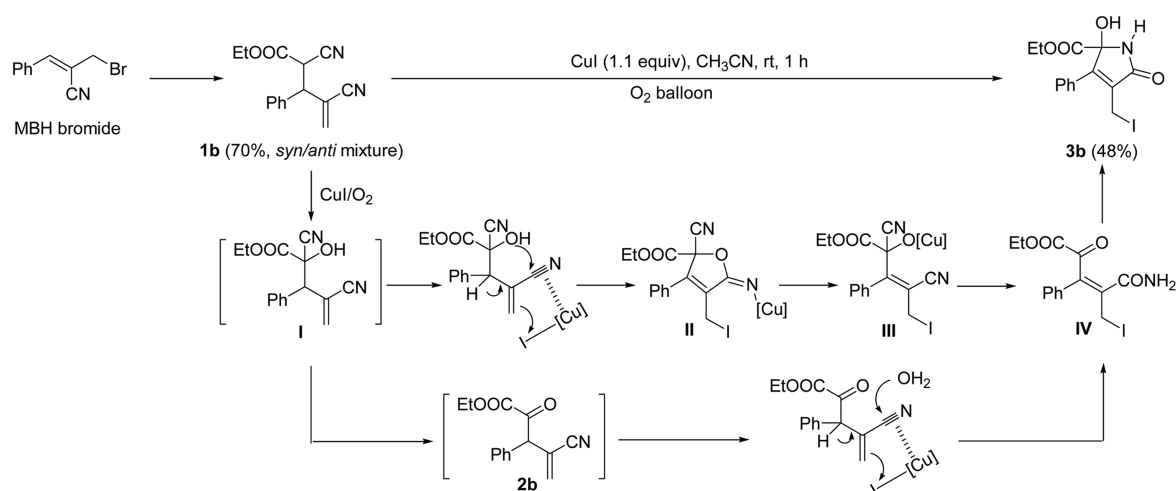
and thiophenes.⁵

In order to shed more lights on the CuI-mediated aerobic oxidation process, we examined the synthesis of 2,5-diketo ester **2a** bearing a methylene moiety at the 4-position, as shown in Scheme 2. The introduction of methyl cyanoacetate at the secondary position of MBH adduct to form **1a** was carried out as reported,⁶ from the MBH bromide *via* the corresponding DABCO salt. As reported in a similar case,⁴ CuI-mediated aerobic oxidation of **1a** furnished the desired product **2a** in a moderate yield (57%).

However, when the nitrile derivative **1b** was subjected under the same reaction conditions, 5-hydroxypyrrolin-3-



Scheme 2



Scheme 3

iodomethyl-2-one derivative **3b** was obtained in moderate yield (48%) serendipitously, as shown in Scheme 3. The plausible reaction mechanism for the formation of **3b** is suggested in Scheme 3. CuI-mediated aerobic oxidation of **1b** could generate the cyanohydrin intermediate **I**.⁴ A subsequent CuI-mediated cyclization-iodination of the intermediate **I** would produce **II**.⁷ The intermediate **II** could be converted to γ -ketoamide **IV** via a copper-assisted hydration,^{8,9} and the final lactamization of **IV** furnished **3b**.^{2c,10} Another plausible route involved the conversion of **I** to **2b** and the following copper-assisted concomitant hydration of nitrile and allylic iodination to form the intermediate **IV**. Although the reaction mechanism is not clear we were much interested in the results, and we decided to examine the

synthesis of 5-hydroxypyrrolin-3-iodomethyl-2-one derivatives.

However, the moderate yield (48%) of **3b** was not improved to our every effort. As some examples, the reactions in the presence of excess amounts of CuI (3.0 equiv), in aqueous CH₃CN, or at elevated temperature (40–50 °C) did not improve the yield of **3b**. Thus, we carried out the reactions with other substrates **1c–g** under the typical conditions (1.1 equiv of CuI/O₂ balloon atmosphere in CH₃CN at room temperature), and the results are summarized in Table 1.

The reactions with other substrates **1c–g**¹¹ afforded the corresponding 5-hydroxypyrrolin-3-iodomethyl-2-one derivatives **3c–g** in moderate yields (35–57%). The reaction of **1b** using CuBr instead of CuI gave the corresponding bromo derivative **3h** (entry 7) in moderate yield (47%). The use of CuCl was ineffective in the reaction.

In summary, 5-hydroxypyrrolin-2-one derivatives were synthesized in moderate yields from the modified MBH adducts under the CuI-mediated aerobic oxidation conditions. Further studies on the reaction mechanism and the synthetic applications of the products are currently underway.

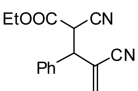
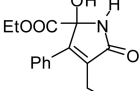
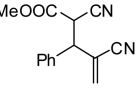
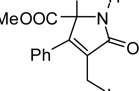
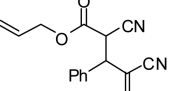
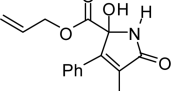
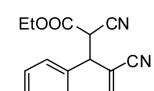
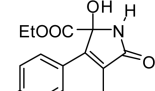
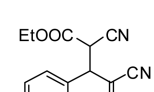
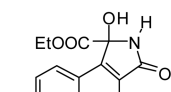
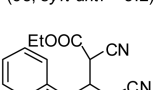
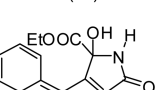
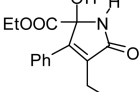
Experimental Section

Typical Procedure for the Synthesis of 1b.⁶ A mixture of MBH bromide (222 mg, 1.0 mmol) and DABCO (124 mg, 1.1 mmol) in aqueous THF (2 mL) was stirred for 30 min at room temperature. To the reaction mixture ethyl cyanoacetate (125 mg, 1.1 mmol) was added and stirred for 12 h at room temperature. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/Et₂O, 5:1), compound **1b** was obtained as colorless oil, 178 mg (70%). Other starting materials **1a** and **1c–g** were prepared similarly, and the spectroscopic data are as follows.

Compound 1a: 78% (1:1, *syn/anti* mixture); colorless oil; IR (film) 2251, 1750, 1723, 1252, 1149 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 3.69 (s, 3H*0.5), 3.70 (s, 3H*0.5), 3.71 (s, 3H*0.5), 3.75 (s, 3H*0.5), 4.24 (d, *J* = 8.7 Hz, 1H*0.5), 4.45 (d, *J* = 7.2 Hz, 1H*0.5), 4.64 (d, *J* = 1H*0.5 + 1H*0.5), 5.76 (s, 1H*0.5), 5.99 (s, 1H*0.5), 6.50 (s, 1H*0.5), 6.53 (s, 1H*0.5), 7.26–7.37 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 41.67, 42.08, 46.45, 47.16, 52.27, 52.35, 53.54, 53.56, 115.37, 115.44, 127.46, 127.92, 128.11, 128.19, 128.40, 128.56, 128.87, 128.89, 136.26, 136.94, 138.33, 138.76, 165.20, 165.26, 165.96, 166.09; ESIMS *m/z* 296 [M+Na]⁺. Anal. Calcd for C₁₅H₁₅NO₄: C, 65.92; H, 5.53; N, 5.13. Found: C, 66.05; H, 5.78; N, 5.02.

Compound 1b: 70% (4:1, *syn/anti* mixture); colorless oil; IR (film) 2251, 2226, 1746, 1247 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.12 (t, *J* = 7.2 Hz, 3H*0.2), 1.22 (t, *J* = 7.2 Hz, 3H*0.8), 4.07–4.28 (m, 4H), 5.92 (s, 1H*0.8), 6.11 (s, 1H*0.8), 6.12 (s, 1H*0.2), 6.15 (s, 1H*0.2), 7.30–7.46 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 13.63, 13.79, 41.43, 41.51, 49.40, 50.19, 63.38, 63.46, 114.22, 114.47, 116.52, 116.57, 121.76, 122.25, 127.65, 128.21, 129.10, 129.25, 129.35, 129.38, 133.36, 133.54, 133.90, 134.49, 163.60, 163.87; ESIMS *m/z* 277 [M+Na]⁺. Anal. Calcd for C₁₅H₁₄N₂O₂: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.59;

Table 1. Synthesis of 5-hydroxypyrrolin-2-one derivatives

Entry	Substrate (%) ^a	Product (%) ^b
1	 1b (70, <i>syn/anti</i> = 4:1)	 3b (48)
2	 1c (64, <i>syn/anti</i> = 3:2)	 3c (36)
3	 1d (71, <i>syn/anti</i> = single)	 3d (35)
4	 1e (75, <i>syn/anti</i> = 1:1)	 3e (41)
5	 1f (68, <i>syn/anti</i> = 3:2)	 3f (43) ^c
6	 1g (71, <i>syn/anti</i> = 1:1)	 3g (57)
7	1b	 3h (47) ^d

^aConditions: (i) MBH bromide (1.0 mmol), aq THF, DABCO (1.1 equiv), rt, 30 min; (ii) active methylene compound (1.1 equiv), rt, 12 h. Assignment of *syn/anti* is arbitrary. ^bConditions: Substrate **1** (0.5 mmol), CuI (1.1 equiv), CH₃CN, O₂ balloon, rt, 1 h. ^cReaction time was 18 h. ^dCuBr was used and reaction time was 4 h.

H, 5.76; N, 10.93.

Compound 1c: 64% (3:2, *syn/anti* mixture); colorless oil; IR (film) 2252, 2225, 1752, 1261 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 3.70 (s, 3H*0.4), 3.78 (s, 3H*0.6), 4.09–4.28 (m, 2H), 5.93 (s, 1H*0.6), 6.11 (s, 1H*0.6+1H*0.4), 6.16 (s, 1H*0.4), 7.28–7.46 (m, 5H); ^{13}C NMR (75 MHz, CDCl_3) δ 41.26, 41.36, 49.32, 49.91, 53.89, 53.92, 114.07, 114.32, 116.53 (2C), 121.63, 122.17, 127.56, 128.13, 129.11, 129.26, 129.39 (2C), 133.35, 133.64, 133.86, 134.47, 164.12, 164.37; ESIMS m/z 263 $[\text{M}+\text{Na}]^+$. Anal. Calcd for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.11; H, 5.08; N, 11.45.

Compound 1d: 71% (single isomer); white solid, mp 49–51 $^\circ\text{C}$; IR (KBr) 2252, 2227, 1746, 1271, 1245 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 4.26 (s, 2H), 4.62–4.66 (m, 2H), 5.25–5.35 (m, 2H), 5.74–5.87 (m, 1H), 5.92 (s, 1H), 6.11 (s, 1H), 7.35–7.46 (m, 5H); ^{13}C NMR (75 MHz, CDCl_3) δ 41.40, 49.41, 67.71, 114.06, 116.56, 120.21, 122.19, 128.23, 129.30, 129.42, 130.13, 133.45, 133.82, 163.61; ESIMS m/z 289 $[\text{M}+\text{Na}]^+$. Anal. Calcd for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.03; H, 5.52; N, 10.36.

Compound 1e: 75% (1:1, *syn/anti* mixture); colorless oil; IR (film) 2251, 2226, 1747, 1250 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.21 (t, $J = 7.2$ Hz, 3H*0.5), 1.30 (t, $J = 7.2$ Hz, 3H*0.5), 2.41 (s, 3H*0.5), 2.42 (s, 3H*0.5), 4.11–4.33 (m, 4H), 5.97 (s, 1H*0.5), 6.15 (s, 1H*0.5), 6.17 (s, 1H*0.5), 6.20 (s, 1H*0.5), 7.26–7.34 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 13.67, 13.82, 21.09, 21.12, 41.52, 41.56, 49.13, 49.88, 63.35, 63.43, 114.30, 114.56, 116.60, 116.66, 122.01, 122.48, 127.49, 128.04, 130.00, 130.06, 130.87, 131.45, 133.09, 133.22, 139.08, 139.21, 163.65, 163.96; ESIMS m/z 291 $[\text{M}+\text{Na}]^+$. Anal. Calcd for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.76; H, 6.33; N, 10.41.

Compound 1f: 68% (3:2, *syn/anti* mixture); colorless oil; IR (film) 2252, 2226, 1747, 1250 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.09 (s, 3H*0.4), 1.17 (s, 3H*0.6), 3.96–4.25 (m, 4H), 5.85 (s, 1H*0.6), 6.05 (s, 1H*0.6+1H*0.4), 6.09 (s, 1H*0.4), 7.18–7.41 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 13.68, 13.81, 41.27, 41.37, 48.60, 49.45, 63.57, 63.63, 114.00, 114.20, 116.31, 116.38, 121.33, 121.86, 129.04, 129.58, 129.62, 129.65, 132.38, 133.00, 133.50, 133.82, 135.21, 135.38, 163.37, 163.63; ESIMS m/z 311 $[\text{M}+\text{Na}]^+$, 313 $[\text{M}+\text{Na}+2]^+$. Anal. Calcd for $\text{C}_{15}\text{H}_{13}\text{ClN}_2\text{O}_2$: C, 62.40; H, 4.54; N, 9.70. Found: C, 62.31; H, 4.79; N, 9.46.

Compound 1g: 71% (1:1, *syn/anti* mixture); colorless oil; IR (film) 2252, 2226, 1746, 1246 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 0.80–1.42 (m, 3H), 4.15–5.20 (m, 4H), 5.83 (s, 1H*0.5), 6.11 (s, 1H*0.5), 6.24 (s, 1H*0.5+1H*0.5), 7.55–7.91 (m, 7H); ^{13}C NMR (75 MHz, CDCl_3) δ 13.66, 13.72, 41.03, 41.50, 44.01, 44.15, 63.53, 63.59, 114.44, 114.50, 116.60, 116.69, 121.27, 121.45, 121.83, 121.94, 125.08, 125.14, 125.30, 125.36, 126.29, 126.33, 127.19, 127.39, 129.42, 129.54, 129.60, 129.81, 129.87, 130.16, 130.41, 130.87, 133.87, 134.12, 134.13, 134.38, 163.73, 164.03; ESIMS m/z 327 $[\text{M}+\text{Na}]^+$. Anal. Calcd for $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 75.12; H, 5.27; N, 9.03.

Typical Procedure for the Synthesis of 3b. To a stirred solution of **1b** (127 mg, 0.5 mmol) in CH_3CN (2 mL) was

added CuI (105 mg, 1.1 equiv), and the reaction mixture was stirred at room temperature for 1 h under O_2 balloon atmosphere. After dilution with CH_3CN , the reaction mixture was filtered through a pad of Celite. After removing the solvent and column chromatographic purification process (hexanes/EtOAc, 1:1), compound **3b** was obtained as a white solid, 94 mg (48%). Other compounds **2a** and **3c–h** were prepared similarly, and the spectroscopic data are as follows.

Compound 2a: 57%; colorless oil; IR (film) 1734, 1253, 1143, 1072 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 3.78 (s, 3H), 3.81 (s, 3H), 5.35 (d, $J = 1.5$ Hz, 1H), 5.71 (t, $J = 1.5$ Hz, 1H), 6.46 (d, $J = 1.5$ Hz, 1H), 7.21–7.42 (m, 5H); ^{13}C NMR (75 MHz, CDCl_3) δ 52.44, 53.20, 54.97, 128.30, 129.15, 129.18, 130.01, 132.59, 138.74, 160.63, 166.63, 190.13; ESIMS m/z 285 $[\text{M}+\text{Na}]^+$. Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{O}_5$: C, 64.12; H, 5.38. Found: C, 64.41; H, 5.29.

Compound 3b: 48%; white solid, mp 151–153 $^\circ\text{C}$; IR (KBr) 3314, 3252, 1742, 1709 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.18 (t, $J = 7.2$ Hz, 3H), 4.11 (d, $J = 9.3$ Hz, 1H), 4.18 (d, $J = 9.3$ Hz, 1H), 4.11–4.30 (m, 2H), 4.94 (s, 1H), 7.14 (s, 1H), 7.44–7.61 (m, 5H); ^{13}C NMR (75 MHz, CDCl_3) δ –8.32, 13.89, 63.74, 86.82, 127.86, 128.84, 129.81, 130.42, 132.51, 150.55, 170.15, 170.91; ESIMS m/z 388 $[\text{M}+\text{H}]^+$. Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{INO}_4$: C, 43.43; H, 3.64; N, 3.62. Found: C, 43.28; H, 3.76; N, 3.49.

Compound 3c: 36%; white solid, mp 141–143 $^\circ\text{C}$; IR (KBr) 3312, 1744, 1709, 1263 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 3.77 (s, 3H), 4.06 (d, $J = 9.3$ Hz, 1H), 4.12 (d, $J = 9.3$ Hz, 1H), 4.96 (br s, 1H), 7.17 (br s, 1H), 7.39–7.62 (m, 5H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ –5.66, 52.88, 87.03, 128.10, 128.76, 129.41, 131.00, 131.14, 150.65, 169.48, 169.91; ESIMS m/z 374 $[\text{M}+\text{H}]^+$. Anal. Calcd for $\text{C}_{13}\text{H}_{12}\text{INO}_4$: C, 41.84; H, 3.24; N, 3.75. Found: C, 41.91; H, 3.43; N, 3.55.

Compound 3d: 35%; white solid, mp 147–149 $^\circ\text{C}$; IR (KBr) 3313, 3272, 1744, 1712, 1234, 1152 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 4.05 (d, $J = 9.3$ Hz, 1H), 4.14 (d, $J = 9.3$ Hz, 1H), 4.56–4.71 (m, 2H), 4.78 (s, 1H), 5.19–5.28 (m, 2H), 5.68–5.82 (m, 1H), 6.91 (s, 1H), 7.41–7.60 (m, 5H); ^{13}C NMR (75 MHz, CDCl_3) δ –8.53, 67.89, 86.78, 119.89, 127.89, 128.90, 129.90, 130.12, 130.29, 132.64, 150.42, 170.00, 170.73; ESIMS m/z 422 $[\text{M}+\text{Na}]^+$. Anal. Calcd for $\text{C}_{15}\text{H}_{14}\text{INO}_4$: C, 45.13; H, 3.54; N, 3.51. Found: C, 45.11; H, 3.72; N, 3.36.

Compound 3e: 41%; white solid, mp 133–135 $^\circ\text{C}$; IR (KBr) 3369, 3330, 1709, 1254, 1154 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.17 (t, $J = 7.2$ Hz, 3H), 2.38 (s, 3H), 4.06 (d, $J = 9.3$ Hz, 1H), 4.08–4.30 (m, 2H), 4.16 (d, $J = 9.3$ Hz, 1H), 4.93 (s, 1H), 7.15 (s, 1H), 7.27 (d, $J = 8.1$ Hz, 2H), 7.50 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ –7.69, 13.89, 21.45, 63.67, 86.77, 127.46, 127.86, 129.58, 131.67, 140.14, 150.59, 170.25, 170.10; ESIMS m/z 424 $[\text{M}+\text{Na}]^+$. Anal. Calcd for $\text{C}_{15}\text{H}_{16}\text{INO}_4$: C, 44.91; H, 4.02; N, 3.49. Found: C, 45.08; H, 4.24; N, 3.52.

Compound 3f: 43%; white solid, mp 114–116 $^\circ\text{C}$; IR (KBr) 3369, 3315, 1711, 1255, 1154 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.19 (t, $J = 7.2$ Hz, 3H), 4.01 (d, $J = 9.3$ Hz,

1H), 4.08–4.26 (m, 2H), 4.14 (d, $J = 9.3$ Hz, 1H), 4.95 (br s, 1H), 7.27 (br s, 1H), 7.46 (d, $J = 8.4$ Hz, 2H), 7.58 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ –8.70, 13.95, 63.89, 86.73, 128.81, 129.23 (2C), 129.27, 136.08, 149.14, 169.87, 170.50; ESIMS m/z 444 $[\text{M}+\text{Na}]^+$, 446 $[\text{M}+\text{Na}+2]^+$. Anal. Calcd for $\text{C}_{14}\text{H}_{13}\text{ClINO}_4$: C, 39.88; H, 3.11; N, 3.32. Found: C, 39.63; H, 3.39; N, 3.17.

Compound 3g: 57%; yellow solid, mp 165–167 °C; IR (KBr) 3431, 3397, 1730, 1257 cm^{-1} ; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 0.94 (br s, 3H), 3.59 (d, $J = 9.3$ Hz, 1H), 3.67 (d, $J = 9.3$ Hz, 1H), 3.93 (br s, 2H), 7.11 (br s), 7.49–7.76 (m, 5H), 7.97–8.03 (m, 2H), 9.34 (s, 1H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ –8.45, 13.69, 61.76, 88.00, 125.23, 126.29, 126.46, 128.32, 129.13, 130.36, 133.10, 134.54, 151.36, 168.44, 169.63. (Three carbons were overlapped); ESIMS m/z 460 $[\text{M}+\text{Na}]^+$. Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{INO}_4$: C, 49.45; H, 3.69; N, 3.20. Found: C, 49.64; H, 3.67; N, 3.02.

Compound 3h: 47%; white solid, mp 155–157 °C; IR (KBr) 3311, 3239, 1743, 1710 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.16 (t, $J = 7.2$ Hz, 3H), 4.12 (d, $J = 9.9$ Hz, 1H), 4.14–4.31 (m, 2H), 4.23 (d, $J = 9.9$ Hz, 1H), 4.92 (br s, 1H), 7.12 (br s, 1H), 7.43–7.49 (m, 3H), 7.58–7.62 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 13.80, 20.40, 63.88, 86.69, 128.24, 128.89, 130.00, 130.16, 131.14, 153.11, 170.20, 170.76; ESIMS m/z 362 $[\text{M}+\text{Na}]^+$, 364 $[\text{M}+\text{Na}+2]^+$. Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{BrNO}_4$: C, 49.43; H, 4.15; N, 4.12. Found: C, 49.28; H, 4.34; N, 4.01.

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