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OXIDATIVE COUPLING OF INDOLES WITH 3-OXINDOLES

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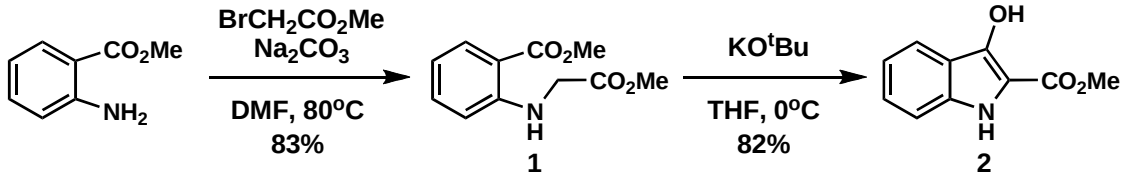
Abstract – A mild procedure for the union of 3-oxindoles with indoles is reported using oxidative coupling.

In 2004, we reported the direct oxidative coupling of enolates with indoles[1] and later expanded these findings to pyrroles,[2] and the heterocoupling of different carbonyl enolate species.[3] As a simple extension to this methodology, a mild and versatile oxidative coupling procedure for union of 3-oxindoles with indoles and pyrroles is presented in this short Note. The procedure is simple, the scope is broad for 3-oxindoles bearing a carboxy group at C-2, and the reaction can be conducted on a gram scale using CAN as the stoichiometric oxidant.

Reports have recently appeared in the literature regarding the construction of 3-oxindoles substituted with indoles at the 2-position.[4,5] The chemistry used for the key C-C bond formation was that of Wasserman[6] and Ke-Qing[7] where a 2-hydroxy-3-oxindole is generated as the key intermediate. In this two-step procedure, a hemiaminal is in equilibrium with an iminium ion which is subsequently attacked by a nucleophile (indole[7] or pyrrole[6]). Previously, one-step oxidative couplings with indoles that occur at C–2 have been reported using manganese triacetate.[8] C-3 substitution was only observed when C-2 was already substituted.[9] Other oxidative couplings for C-3 substitution require prefunctionalization.[10] By analogy to the oxidative couplings that we previously had developed,[1-3] a one step oxidative coupling of indoles to 3-oxindoles that could be conducted under mild conditions was pursued. For this oxidative coupling, 2-carboxymethyl-3-oxindole (**2**) was chosen, as this ester group could, in principle, be transformed to an aromatic group[4] or a tetrahydrofuran ring[5] as seen in the total syntheses of Hinckdentine A[4] and Isatisine A[5] respectively.

Dedicated to Professor Dr. Albert Eschenmoser on the occasion of his 85th birthday

3-Oxindole **2** can be synthesized easily in large scale similar to the procedure developed by Dropinski,[12] where an initial N-alkylation is followed by a Dieckmann condensation[13] to produce 2-carboxymethyl-3-oxindole **2** (Scheme 1).



Scheme 1. Synthesis of the 2-carboxymethyl-3-oxindole used in the mild oxidative couplings.

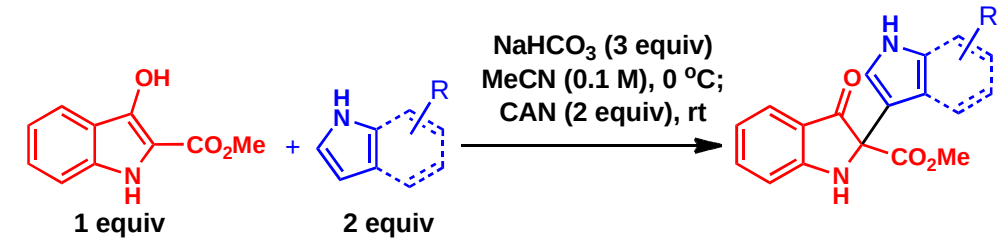
The coupling of **2** to indoles proved to be both simple and general (Table 1). The procedure for this mild oxidative coupling of indole is as follows: to a solution of the indole (2 eq), $NaHCO_3$ (3 eq) and 3-oxindole in MeCN, at zero degrees, is added CAN (2 eq), the reaction is allowed to stir at ambient temperature overnight followed by aqueous work-up.

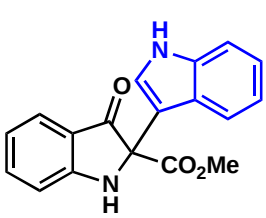
The reaction proved very robust with regards to both electronic factors and substitution patterns. With unsubstituted indole the reaction was performed on gram scale and similar yields were obtained. N-methylated indoles (see **4** in Table 1) reacted in good yield under these conditions, while N-substituted indoles did not give any coupling products for our earlier oxidative couplings.[1b] 2- and 3-substituted indoles produced the expected products, **5** and **6**, respectively, where **6** is the 2-substituted product as the 3-position is already occupied. Using electron withdrawing groups (**7**, **8**) high yields are observed whereas for electron donating groups (**9**) a low yield was observed. A similar trend is seen for the electron rich pyrrole (**11**). For halogen substituents (**10**) a good yield is observed.

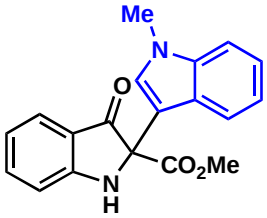
As shown in Scheme 2, when either the nitrogen or the oxygen of the 3-oxindole is acetylated, **13** and **14** respectively, no reaction is observed. On the other hand, alkylation of the nitrogen in the 3-oxindole (**12**) is tolerated and a high yield of the ensuing product is observed, which is similar to the yield observed for the 3-oxindole **2**.

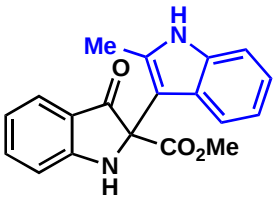
We must therefore assume that the lone pair on nitrogen in the 3-oxindole **2** must play an important role in this mild oxidative coupling, when neither simple malonates nor N-acylated 3-oxindoles participate in this reaction. Other oxidants where tried for this oxidative coupling, including $Mn(OAc)_3$, DDQ and $K_3Fe(CN)_6$ – none of which produced any product. Only from the reaction with Cu(II)-2-ethylhexanoate as the oxidant could product be observed, but only in very low yield (8%).

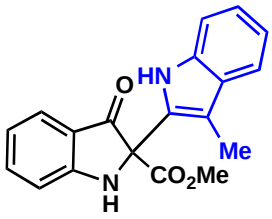
Table 1. Oxidative coupling of substituted indoles and pyrroles with 2-carboxymethyl-3-oxindole.[a]

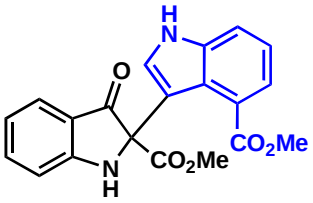


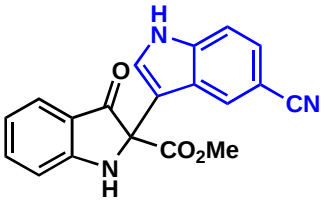

3 (indole)
89% [gram scale]

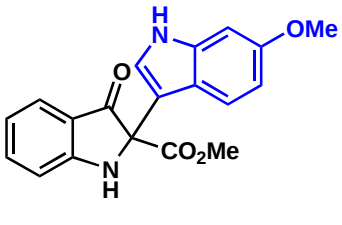

4 (1-methylindole)
79%

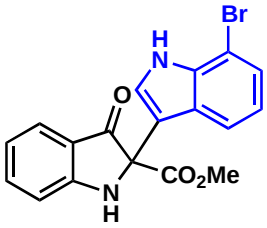

5 (2-methylindole)
61%

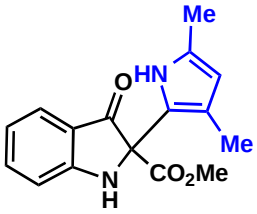

6 (3-methylindole)
48%


7 (4-carboxymethylindole)
98%


8 (5-cyanoindole)
91%

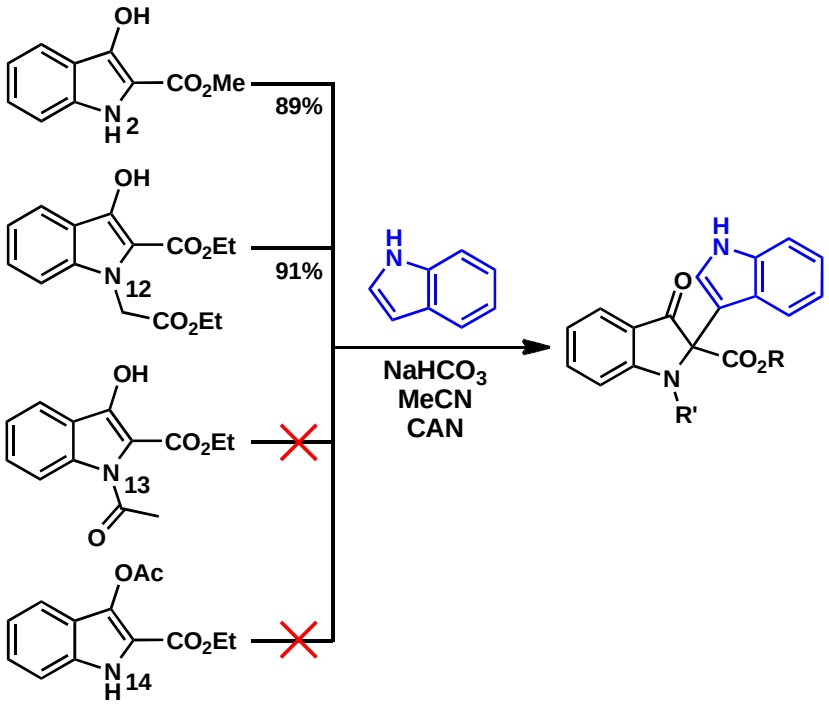

9 (6-methoxyindole)
17%


10 (7-bromoindole)
66%


11 (2,4-dimethylpyrrole)
18%

[a]typical reaction conditions: A solution of 2-carboxymethyl-3-oxindole (15 mg), $NaHCO_3$ (3 eq) and indole (2 eq) in MeCN (0.1 M) was cooled to 0 °C and CAN (2 eq) was added. After 10 min the ice bath was removed and the reaction was stirred overnight. Workup with NH_4Cl and extraction, followed by silica gel chromatography yielded pure products.

We must therefore assume that the lone pair on nitrogen in the 3-oxindole **2** must play an important role in this mild oxidative coupling, when neither simple malonates nor N-acylated 3-oxindoles participate in this reaction. Other oxidants where tried for this oxidative coupling, including $Mn(OAc)_3$, DDQ and $K_3Fe(CN)_6$ – none of which produced any product. Only from the reaction with Cu(II)-2-ethylhexanoate as the oxidant could product be observed, but only in very low yield (8%).



Scheme 2. Scope for 3-oxindoles.

In summary, an extension of our existing oxidative couplings of indoles has been developed. The reaction tolerates a variety of functional groups, proceeds readily at ambient conditions, and no prefunctionalisation is required. The oxidant is readily available and cheap, and the reaction can easily be performed on large scale.

EXPERIMENTAL

Methyl 2-(2-methoxy-2-oxoethylamino)benzoate **1**, colorless oil: Methyl antranilate (5.00 mL, 38.6 mmol) and anhydrous Na_2CO_3 (4.20 g, 39.6 mmol) was dissolved in anhydrous DMF (40 ml). Methyl α-bromoacetate (5.00 mL, 52.6 mmol) was added and the reaction mixture was heated to 80°C for 20 hours. The mixture was then poured into H_2O and extracted with Et_2O. The organic phase was washed with Brine and dried with $MgSO_4$, filtered and concentrated to yield pure diester **1** (7.2 g) in 83% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (s, 1 H), 7.93 (dd, 1 H, J = 1.7Hz, 8.0Hz), 7.36 (m, 1 H), 6.66 (ddd, 1H, J = 1.1Hz, 7.2Hz, 8.2Hz), 6.53 (d, 1 H, J = 8.5Hz), 4.02 (d, 2 H, J = 5.5Hz), 3.87 (s, 3 H), 3.79 (s, 3 H), which corresponds to the litterature.[12]

Methyl 3-hydroxy-1*H*-indole-2-carboxylate **2**, off-white solid: Diester **1** (5.6 g, 25.1 mmol) was dissolved in anhydrous THF (79 mL) and cooled to 0 °C. Potasium *tert*-butoxide (3.0 g, 26.7 mmol, 1.1 eq) was dissolved in anhydrous THF (25 mL) and added dropwise to the cold solution via canula, the reaction mixture turned dark red. The reaction was monitored by TLC and after 3 hours the mixture was concentrated to remove most of the THF. H_2O/AcOH (4:1) (50 mL) was added and the product was

extracted with CH_2Cl_2. The organic phase was washed with Brine and dried over $MgSO_4$, before being filtered and concentrated. Flash column chromatography Et_2O /hexanes (1:1) yielded pure 3-oxindole **2** (4.0 g) in 82% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (bs, 1 H), 7.75 (dd, 1H, *J* = 1.1Hz, 8.1Hz), 7.35 (m, 1 H), 7.27 (m, 1 H), 7.10 (m, 1 H), 3.97 (s, 3 H), which corresponds to the litterature.[12]

Methyl 3-oxo-2,3'-biindoline-2-carboxylate **3**, yellow solid: ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.22 (s, 1 H), 7.70 (dd, 1 H, *J* = 0.8Hz, 7.5Hz), 7.59 (d, 1 H, *J* = 8.0Hz), 7.53 (ddd, 1 H, *J* = 1.3Hz, 7.2Hz, 8.3Hz), 7.40 (d, 1 H, *J* = 2.6Hz), 7.37 (d, 1 H, *J* = 8.2Hz), 7.21 (t, 1 H, *J* = 7.6Hz), 7.11 (t, 1 H, *J* = 7.6Hz), 7.01 (d, 1 H, *J* = 8.2Hz), 6.94 (t, 1 H, *J* = 7.4Hz), 5.73 (s, 1 H), 3.81 (s, 3 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 194.8, 169.1, 161.2, 138.1, 136.6, 125.6, 123.6, 122.8, 120.0, 119.6, 113.7, 111.8, 111.7, 72.5, 53.9 ppm; IR (neat) 3367, 1698, 1614, 1467, 1235 cm^{-1}; mp 108 ^{o}C; HRMS (EI), calcd for $C_{18}H_{14}N_2O_3$ +H^+ 307.1079, found: 307.1077.

Methyl 1'-methyl-3-oxo-2,3'-biindoline-2-carboxylate **4**, yellow solid: ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.70 (d, 1 H, *J* = 7.8Hz), 7.57 (d, 1 H, *J* = 8.0Hz), 7.52 (t, 1 H, *J* = 7.7Hz), 7.31 (d, 1 H, *J* = 8.2Hz), 7.27 (d, 1 H, *J* = 6.2Hz), 7.24 (t, 1 H, *J* = 7.6Hz), 7.11 (t, 1 H, *J* = 7.5Hz), 6.99 (d, 1 H, *J* = 8.3Hz), 6.93 (t, 1 H, *J* = 7.4Hz), 5.76 (s, 1 H), 3.81 (s, 3 H), 3.74 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 194.9, 169.1, 161.1, 138.0, 137.4, 128.1, 126.0, 125.5, 122.3, 120.4, 120.1, 199.9, 119.5, 113.7, 109.9, 109.9, 72.5, 53.9, 33.0 ppm; IR (neat) 3363, 2951, 1739, 1698, 1614, 1485, 1467, 1325, 1238 cm^{-1}; mp 82 ^{o}C; HRMS (EI), calcd for $C_{19}H_{16}N_2O_3$ +H^+ 321.1234, found: 321.1230.

Methyl 2'-methyl-3-oxo-2,3'-biindoline-2-carboxylate **5**, yellow solid: ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.01 (s, 1 H), 7.72 (d, 1 H, *J* = 7.7Hz), 7.53 (t, 1 H, *J* = 7.3Hz), 7.23 (d, 1 H, *J* = 8.1Hz), 7.15 (d, 1 H, *J* = 8.1Hz), 7.09 (t, 1 H, *J* = 7.6Hz), 6.98 (m, 2 H), 6.94 (t, 1 H, *J* = 7.5Hz), 5.55 (s, 1 H), 3.86 (s, 3 H), 2.25 (s, 3 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 195.5, 169.8, 161.3, 138.1, 135.0, 133.5, 127.2, 125.4, 121.8, 120.4, 120.3, 119.9, 118.2, 113.4, 110.8, 107.2, 73.3, 54.1, 13.6 ppm; IR (neat) 3353, 2923, 1696, 1615, 1487, 1461, 1432, 1325, 1236 cm^{-1}; mp 168 ^{o}C; HRMS (EI), calcd for $C_{19}H_{16}N_2O_3$ +H^+ 321.1234, found: 321.1231.

Methyl 3'-methyl-3-oxo-2,2'-biindoline-2-carboxylate **6**, orange solid: ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.38 (s, 1 H), 7.67 (d, 1 H, *J* = 7.8Hz), 7.55 (m, 2 H), 7.36 (d, 1 H, *J* = 8.1Hz), 7.19 (ddd, 1 H, *J* = 1.1Hz, 7.1Hz, 8.1Hz), 7.10 (m, 2 H), 6.95 (t, 1 H, *J* = 7.4Hz), 5.85 (s, 1 H), 3.79 (s, 3 H), 2.41 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 194.1, 167.4, 161.7, 138.5, 135.01, 129.0, 126.2, 125.7, 122.6, 121.0, 119.4, 119.4, 118.7, 113.9, 111.3, 109.8, 72.1, 54.3, 9.5 ppm; IR (neat) 3385, 2923, 2360, 2342, 1736, 1698, 1614, 1487, 1468, 1329, 1240 cm^{-1}; mp 144 ^{o}C; HRMS (EI), calcd for $C_{19}H_{16}N_2O_3$ +H^+ 321.1234, found: 321.1233.

Dimethyl 3-oxo-2,3'-biindoline-2,4'-dicarboxylate **7**, yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.91 (s, 1 H), 7.76 (dd, 1 H, *J* = 0.7Hz, 7.5Hz), 7.71 (d, 1 H, *J* = 7.8Hz), 7.46 (t, 1 H, *J* = 7.6Hz), 7.29 (dd, 1 H, *J* = 0.7Hz, 8.0Hz), 7.03 (m, 2 H), 6.88 (d, 1 H, *J* = 8.3Hz), 6.83 (m, 2 H), 3.92 (s, 3 H), 3.66 (s, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 196.5, 169.9, 161.3, 138.3, 138.1, 128.1, 125.5, 124.2, 124.2, 122.5, 121.2, 119.1, 118.8, 117.3, 113.0, 112.0, 77.4, 74.1, 53.2, 52.4 ppm; IR (neat) 3376, 2951, 1733, 1696, 1617, 1488, 1437, 1330, 1267 cm^{-1}; mp 235 ^{o}C; HRMS (EI), calcd for $C_{20}H_{16}N_2O_5$ +H^+ 365.1132, found: 365.1133.

Methyl 5'-cyano-3-oxo-2,3'-biindoline-2-carboxylate **8**, yellow solid: ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.65 (s, 1 H), 8.11 (s, 1 H), 7.68 (d, 1 H, *J* = 7.7Hz), 7.59 (t, 1 H, *J* = 7.7Hz), 7.57 (d, 1 H, *J* = 2.6Hz), 7.39 (m, 2 H), 7.09 (d, 1 H, *J* = 8.2Hz), 6.99 (t, 1 H, *J* = 7.4Hz), 5.72 (s, 1 H), 3.84 (s, 3 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 194.3, 168.5, 161.3, 138.4, 138.3, 126.4, 126.0, 125.7, 125.6, 125.3, 121.2, 120.7, 119.8, 114.0, 112.7, 112.6, 103.7, 72.4, 54.2 ppm; IR (neat) 3277, 2221, 1736, 1689, 1615, 1590, 1491, 1467, 1431, 1332, 1293, 1241 cm^{-1}; mp 146 ^{o}C; HRMS (EI), calcd for $C_{19}H_{13}N_3O_3$ +H^+ 332.1035, found: 332.1022.

Methyl 6'-methoxy-3-oxo-2,3'-biindoline-2-carboxylate **9**, yellow solid: ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.09 (s, 1 H), 7.69 (d, 1 H, *J* = 7.8Hz), 7.53 (ddd, 1 H, *J* = 1.3Hz, 7.2Hz, 8.3Hz), 7.45 (d, 1 H, *J* = 8.8Hz), 7.00 (d, 1 H, *J* = 8.2Hz), 6.93 (t, 1 H, *J* = 7.4Hz), 6.83 (d, 1 H, *J* = 2.2Hz), 6.77 (dd, 1 H, *J* = 2.3Hz, 8.8Hz), 5.69 (s, 1 H), 3.81 (s, 3 H), 3.80 (s, 3 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 194.8, 169.1, 161.1, 156.9, 138.0, 137.5, 125.5, 122.4, 120.5, 120.3, 120.0, 119.8, 113.7, 111.8, 110.6, 95.0, 72.5, 55.8, 53.9 ppm; IR (neat) 3377, 2922, 1737, 1618, 1488, 1466, 1250 cm^{-1}; mp 85 ^{o}C; HRMS (EI), calcd for $C_{19}H_{16}N_2O_4$ +H^+ 337.1183, found: 337.1180.

Methyl 7'-bromo-3-oxo-2,3'-biindoline-2-carboxylate **10**, yellow solid: ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.43 (s, 1 H), 7.69 (d, 1 H, *J* = 7.7Hz), 7.59 (d, 1 H, *J* = 8.1Hz), 7.54 (ddd, 1 H, *J* = 1.3Hz, 7.2Hz, 8.3Hz), 7.48 (d, 1 H, *J* = 2.6Hz), 7.35 (d, 1 H, *J* = 7.6Hz), 7.02 (d, 1 H, *J* = 8.3Hz), 6.99 (t, 1 H, *J* = 7.8Hz), 6.94 (t, 1 H, *J* = 7.4Hz), 5.73 (s, 3 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 194.5, 168.8, 161.2, 138.1, 135.3, 126.7, 125.6, 125.1, 124.2, 121.6, 120.7, 119.9, 119.2, 113.7, 113.0, 105.2, 72.5, 54.0 ppm; IR (neat) 3354, 2974, 1738, 1696, 1614, 1488, 1467, 1433, 1323, 1231 cm^{-1}; mp 101 ^{o}C; HRMS (EI), calcd for $C_{18}H_{13}BrN_2O_3$ +H^+ 385.0182, found: 385.0187.

Methyl 2-(3,5-dimethyl-1*H*-pyrrol-2-yl)-3-oxoindoline-2-carboxylate **11**, yellow solid: ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.92 (s, 1 H), 7.62 (d, 1 H, *J* = 7.7Hz), 7.52 (t, 1 H, *J* = 7.7Hz), 7.02 (d, 1 H, *J* = 8.2Hz), 6.91 (t, 1 H, *J* = 7.4Hz), 5.66 (d, 1 H, *J* = 2.8Hz), 5.64 (s, 1 H), 3.78 (s, 3 H), 2.21 (s, 3 H), 2.09 (s, 3 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 194.8, 168.1, 161.6, 138.3, 127.3, 125.6, 120.6, 119.5, 117.6, 117.6, 113.7, 109.7, 71.9, 54.1, 13.1, 12.2 ppm; IR (neat) 3375, 2921, 1698, 1616, 1487, 1468, 1326, 1231 cm^{-1}; mp 165 ^{o}C; HRMS (EI), calcd for $C_{16}H_{16}N_2O_3$ +H^+ 285.1234, found: 285.1236.

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