A Practical Indium Tribromide Catalysed Addition of Indoles to Nitroalkenes in Aqueous Media

Marco Bandini,* Paolo Melchiorre, Alfonso Melloni, Achille Umani-Ronchi*

Dipartimento di Chimica 'G. Ciamician', Università di Bologna, Via Selmi 2, 40126 Bologna, Italy
Fax +39(51)2099456; E-mail: bandini@ciam.unibo.it, umani@ciam.unibo.it

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Abstract: The 1,4-conjugate addition of indoles to nitroalkenes was efficiently carried out in aqueous media using a catalytic amount of indium tribromide (5 mol%). The reusability of the indium tribromide was tested by performing consecutive cycles with the same catalyst.

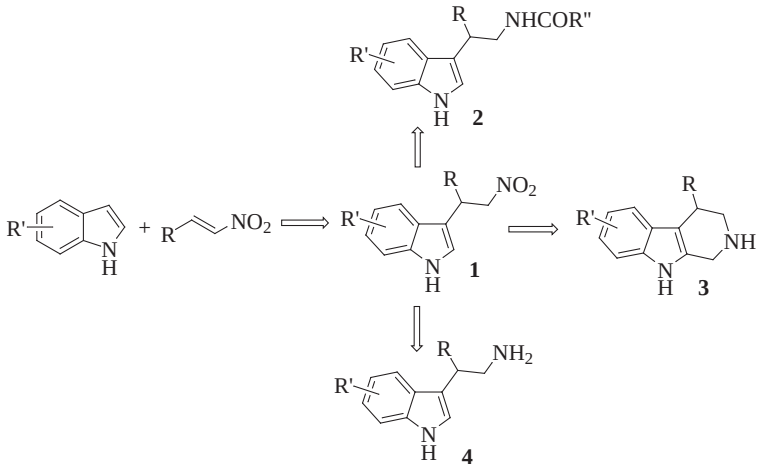
Key words: alkaloids, catalysis, indium, indoles, Michael additions

In recent years, catalytic Michael-type additions of nucleophiles to nitroalkenes have emerged as a powerful method for the formation of new carbon–carbon bonds in organic synthesis.[1] In particular, the use of electron-rich hetero-aromatic compounds such as indoles, acting as nucleophiles, allows the synthesis of 2-indolyl-1-nitroalkanes **1**, highly versatile intermediates for the preparation of several classes of biological active compounds such as melatonin analogs **2**,[2] 1,2,3,4-tetrahydro-β-carbolines (THBCs) **3**[3] and 'triptans' **4**[4] (Scheme).

Since pioneering papers published by Noland et al. on the addition of indolylmagnesium iodide to nitro-olefins,[5] many efforts have been devoted to the development of Friedel–Crafts type addition of indoles to nitroalkenes.[6] However, the tendency of electron-rich hetero-aromatic rings to polymerize under acid-catalysed conditions makes these processes still challenging.

During our ongoing studies on the conjugate addition of indoles to α,β–unsaturated ketones catalysed by indium tribromide,[7] we found that $InBr_3$ (1 mol%) smoothly promoted the addition of 2-methylindole (**5a**) to *trans*-β-nitrostyrene (**6a**) in CH_2Cl_2 affording the desired 2-phenyl-2-[3′-(2-methylindolyl)]nitroethane (**7aa**) in 93% isolated yield after 16 h.[8] However, due to the well known tolerance of indium salts towards aqueous conditions and considering the higher reactivity of nitroalkenes in comparison to other Michael acceptors, we tested the effectiveness of the catalytic protocol in aqueous media. Thus, we started an investigation of Michael additions between nitro-olefin **6a** and variously substituted indoles catalysed by $InBr_3$ in H_2O–THF (9:1) as the solvent leading to a library of β-nitroindoles **7** (Table 1).

It is noteworthy that while in the absence of $InBr_3$ the reaction afforded the desired product only in 28% yield after 48 h (Table 1, entry 1), the use of 5 mol% of anhyd $InBr_3$ furnished a complete conversion (Table 1, entry 2) after 2 h.[9] The protocol was significantly effective for the addition of several substituted electron-rich indoles such as *N*-methyl-2-methylindole (**5c)** and 5-methoxyindole (**5e**) that furnished the products in excellent yields: 92 and 88%, respectively (Table 1, entries 4 and 6). Under the reported conditions, even indolyl rings bearing electron-withdrawing groups such as the 5-bromoindole (**5d)** are



Scheme Synthetic versatility of indolylnitroalkane derivatives.

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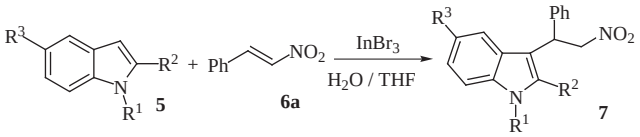
Table 1 $InBr_3$ Catalysed Addition of Indoles to *trans*-β-Nitrostyrene (**6a**)[a]



5a: R^1=H, R^2=Me, R^3=H; **5e**: R^1=H, R^2=H, R^3=OMe;
5b: R^1=H, R^2=H, R^3=H; **5f**: R^1=Me, R^2=H, R^3=H;
5c: R^1=Me, R^2=Me, R^3=H; **5g**: R^1=H, R^2=Ph, R^3=H
5d: R^1=H, R^2=H, R^3=Br;

Entry	Indole	Time (h)	Product	Yield (%)[b]
1	**5a**	24	**7aa**	28[c]
2	**5a**	2	**7aa**	93
3	**5b**	16	**7ba**	60
4	**5c**	2	**7ca**	92
5	**5d**	3	**7da**	65
6	**5e**	2	**7ea**	88
7	**5f**	16	**7fa**	98
8	**5g**	16	**7ga**	75

[a] All the reactions were carried out with 5 mol% of catalyst at r.t. unless otherwise indicated.
[b] Isolated products after flash chromatography.
[c] Without $InBr_3$. A significant amount of byproduct derived from indole polymerization was observed.

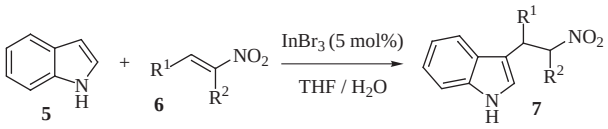
suitable nucleophiles for the Michael addition affording the 1,4-adduct **7da** in satisfactory yield (65%, entry 5).

Having optimized a convenient protocol for the conjugate addition of indoles to **6a**, we became interested in exploring this process with several nitroalkenes (**6a**,**d**). The results are collected in Table 2.

The Michael additions proceeded cleanly and, in particular, commercially available *trans*-2-(2-nitrovinyl)thiophene (**6c**) and 2-(2-nitrovinyl)furan (**6d**) afforded a clear reaction mixture and the products were isolated in excellent yields (up to 99%). However, when 1-nitro-1-cyclohexene (**6b**) was reacted with **5a**, the desired **7ab** was obtained only in moderate yield and diastereoselectivity (44%, 66:34, entry 1, Table 2). This result proves the higher reactivity of β-aryl-α-nitroalkenes with respect to simple α,β-unsaturated nitro derivatives in our catalytic protocol.

A typical request for the design of environmentally friendly catalytic processes is the recovery and reusability of the catalyst. Thus, we tested this possibility simply by carrying out consecutive Michael addition reactions between **5a** and **6a** ($InBr_3$ 10 mol%) with the same catalyst loading (Table 3). The experiment was easily performed by a careful separation of the organic compounds (extraction with CH_2Cl_2) from the aqueous phase after each run. The reusability of the catalyst was remarkable, in fact after five

Table 2 $InBr_3$ Catalysed Addition of Indoles to Nitroalkenes[a]



6a: R^1=Ph, R^2=H; **6c**: R^1=2-thiophenyl, R^2=H;
6b: R^1=R^2=-$(CH_2)_4$-; **6d**: R^1=2-furanyl, R^2=H;

Entry	Indole	Nitroalkene	Product	Yield (%)[b]
1	**5a**	**6b**	**7ab**	44 (66:34)[c]
2	**5a**	**6c**	**7ac**	95
3	**5a**	**6d**	**7ad**	99
4	**5b**	**6d**	**7bd**	92
5	**5c**	**6c**	**7cc**	99
6	**5c**	**6d**	**7cd**	91
7	**5e**	**6d**	**7ed**	65

[a] All the reactions were carried out with 5 mol% of catalyst at r.t. and quenched after 2 h reaction time.
[b] Isolated yield after flash chromatography.
[c] The diastereoisomeric ratio was determined by ^{1}H NMR on the crude product.

Table 3 Consecutive Michael Additions Promoted by the Same Amount (10 mol%) of $InBr_3$

Run	1	2	3	4	5
Time (h)	0.5	3	12	16	24
Yield (%)	93	93	92	91	91

runs the compound **7aa** was isolated in almost quantitative yields.

At the end of the reactions, the pH of the aqueous phase was measured to be about 3.5, probably due to a partial acidic hydrolysis of the indium salt in water. However, the possibility that the Brønsted acid formed in situ could be the real promoter of the Michael reaction was denied by a comparative experiment carried out between **6a** and **5a** in an acidic solution (pH 3, by HBr 10^{-3} M). Under these conditions, the reaction, monitored by TLC, was significantly slower (10 h for a complete conversion) and a tentative experiment of reusability failed.

In summary, with the present study we described a general and mild $InBr_3$ catalysed protocol for the conjugate addition of indoles to nitroalkenes. The reactions are easily performed and remarkably tolerant of substituents at different positions of the indolyl rings. The simple process performed in aqueous media provides the access to highly functionalised compounds in excellent yields and allows

the reusability of the catalyst for several times without loss of effectiveness.

^{1}H NMR spectra were recorded by means of Varian Gemini-200 (200 MHz) or Varian INOVA-300 (300 MHz) spectrometers. Chemical shifts are given in δ with respect to TMS and coupling constants *J* are measured in Hz. Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet). ^{13}C NMR spectra were recorded on a Varian Gemini-200 (50 MHz) or Varian INOVA-300 (75 MHz) spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (deuterochloroform: δ = 77.0). Column flash chromatographies were run over 270–400 mesh silica gel. Commercially available anhyd $InBr_3$, indoles and nitroalkenes were purchased from the Aldrich and Co. and used as received. Elemental analyses were carried out by using a EACE 1110 CHNOS analyzer. IR analysis were performed with a FT-IR NICOLET 205 spectrophotometer. IR spectra of neat compounds are expressed by wavenumber (cm^{-1}). The melting points were uncorrected. The compound **7ba** has been previously described.[8]

Catalytic Michael addition; Typical Procedure

To a round-bottomed flask were added solvent (H_2O–THF, 9:1; 2 mL), anhyd $InBr_3$ (5 mg, 0.015 mmol) and nitrostyrene (0.3 mmol). After 10 min stirring, to the resulting pale-yellow solution, indole (0.45 mmol) was added. The reaction was stirred at r.t. until complete consumption of the nitro compound (checked by TLC) and then extracted with Et_2O (3 × 5 mL). The organic phases were collected, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was finally purified by flash chromatography.

7aa

Yield: 93%; pale pink solid; mp 98–101 °C; flash chromatography (cyclohexane–Et_2O, 85:15), R_f 0.30.

IR (Nujol): 3393, 3031, 2923, 2853, 1551, 1460, 1378 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.40 (s, 3 H), 5.08–5.13 (m, 1 H), 5.17–5.29 (m, 2 H), 6.98–7.18 (m, 3 H), 7.25–7.42 (m, 6 H), 7.89 (br, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.97, 40.44, 78.56, 108.68, 110.62, 118.47, 119.60, 121.20, 126.71, 126.96, 127.18, 128.65, 132.77, 135.26, 139.37.

Anal. Calcd for ($C_{17}H_{16}N_2O_2$): C, 72.84; H, 5.75, N, 9.99. Found: C, 72.78; H, 5.70; N, 9.97.

7ca

Yield: 92%; orange solid; mp 135–139 °C; flash chromatography (cyclohexane–Et_2O, 85:15), R_f =0.27.

IR (Nujol): 3312, 2925, 2853, 1547, 1463, 1376, 743 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.42 (s, 3 H), 3.67 (s, 3 H), 5.10–5.25 (m, 3 H), 6.98–7.10 (m, 1 H), 7.12–7.21 (m, 1 H), 7.26–7.40 (m, 7 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.33, 29.45, 40.63, 78.63, 108.07, 109.00, 118.52, 119.25, 120.76, 125.86, 127.19, 128.63, 134.55, 136.86, 139.75.

Anal. Calcd for ($C_{18}H_{18}N_2O_2$): C, 73.45; H, 6.16; N, 9.52. Found: C, 73.42; H, 6.12; N, 9.50.

7da

Yield: 65%; pale yellow solid; mp 116–120 °C; flash chromatography (cyclohexane–Et_2O, 75:25), R_f 0.30.

IR (Nujol): 3429, 2930, 2853, 1548, 1459, 1376 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.92 (dd, *J* = 7.8, 20.4 Hz, 1 H), 5.00–5.07 (m, 1 H), 5.11–5.16 (m, 1 H), 7.07 (d, *J* = 2.1 Hz, 1 H), 7.20–7.38 (m, 6 H), 7.55 (d, *J* = 1.8 Hz, 1 H), 8.16 (br, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 41.23, 79.35, 100.14, 112.85, 113.15, 113.87, 121.36, 122.72, 125.55, 127.60, 127.71, 128.99, 135.02, 138.65.

Anal. Calcd for ($C_{16}H_{13}BrN_2O_2$): C, 55.67; H, 3.80; N, 8.12. Found: C, 55.62; H, 4.64; N, 8.11.

7ea

Yield: 88%; pale yellow viscous oil; flash chromatography (cyclohexane–Et_2O, 85:15), R_f 0.33.

IR (neat): 3351, 2942, 2850, 1558, 1481, 1370, 1213 $cm^{-1.}$

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.79 (s, 3 H), 4.90–5.04 (m, 2 H), 5.10–5.22 (m, 1 H), 6.85–6.89 (m, 1 H), 6.98 (d, *J* = 2.2 Hz, 1 H), 7.30–7.36 (m, 6 H), 8.19 (br, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 35.64, 55.85, 77.77, 100.41, 107.26, 110.39, 111.05, 112.20, 112.60, 123.25, 126.01, 131.27, 142.11, 152.04, 154.08.

Anal. Calcd for ($C_{17}H_{16}N_2O_3$): C, 68.91; H, 5.44; N, 9.45. Found: C, 68.85; H, 5.40; N, 9.44.

7fa

Yield: 98%; pale yellow viscous oil; flash chromatography (cyclohexane–Et_2O, 9:1), R_f 0.30.

IR (neat): 3058, 3028, 2914, 1549, 1474, 1376, 1333, 741, 701 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.75 (s, 3 H), 4.95 (ddd, *J* = 1.2, 9.6, 12.3 Hz, 1 H), 5.05 (ddd, *J* = 1.2, 7.8, 12.3 Hz, 1 H), 5.19 (t, *J* = 5.7 Hz, 1 H), 7.05–7.10 (m, 1 H), 7.20–7.34 (m, 8 H), 7.45 (dd, *J* = 0.9, 7.8 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.88, 32.69, 41.44, 79.40, 109.38, 112.60, 118.80, 119.27, 122.04, 126.19, 127.32, 127.56, 128.71, 137.11, 139.23.

Anal. Calcd for ($C_{17}H_{16}N_2O_2$): C, 72.84; H, 5.75; N, 9.99. Found: C, 72.80; H, 5.70; N, 9.98.

7ga

Yield: 75%; yellow solid; mp 111–114 °C; flash chromatography (cyclohexane–Et_2O, 9:1), R_f 0.33.

IR (Nujol): 3404, 2923, 2852, 1547, 1458, 1376 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.15–5.21 (m, 2 H), 5.27–5.38 (m, 1 H), 7.09–7.20 (m, 1 H), 7.24–7.56 (m, 13 H), 8.18 (br, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 40.79, 79.01, 109.41, 111.35, 119.83, 120.16, 122.34, 125.04, 127.06, 127.34, 128.48, 128.67, 128.76, 128.81, 132.03, 135.93, 136.84, 139.75. Anal. Calcd for ($C_{22}H_{18}N_2O_2$): C, 77.17; H, 5.30; N, 8.18. Found: C, 77.14; H, 5.26; N, 8.16.

7ab

Yield: 44%; pale yellow solid; dr 66:34; flash chromatography (cyclohexane–Et_2O, 9:1), R_f 0.25.

IR (Nujol): 3398, 2923, 2853, 1539, 1459, 1376 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (major diastereoisomer) = 1.45–1.58 (m, 2 H), 1.63–1.80 (m, 1 H), 1.88–2.10 (m, 4 H), 2.42 (s, 3 H), 2.84–2.94 (m, 1 H), 3.33 (dt, *J* = 4.2, 13.5 Hz, 1 H), 7.04–7.13 (m, 2 H), 7.25 (d, *J* = 7.2 Hz, 1 H), 7.50 (d, *J* = 8.7 Hz, 1 H), 7.77 (br, 1 H); (minor diastereoisomer) 2.36 (s, 3 H), 3.34–3.43 (m, 1 H), 5.09 (dt, *J* = 4.2, 11.1 Hz, 1 H), 7.58 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ (major diastereoisomer) = 13.21, 20.16, 25.32, 26.38, 30.34, 39.42, 85.92, 110.28, 117.82, 119.31,

120.99, 123.39, 126.47, 131.93, 134.71; (minor diastereoisomer) 11.74, 24.61, 25.67, 32.50, 89.16, 119.16, 120.79, 127.92, 129.06.

Anal. Calcd for ($C_{15}H_{18}N_2O_2$): C, 69.74; H, 7.02; N, 10.84. Found: C, 69.72; H, 6.97; N, 10.84.

7ac
Yield: 95%; yellow solid; mp 95–98 °C; flash chromatography (cyclohexane–Et_2O, 9:1), R_f 0.31.

IR (Nujol): 3415, 2923, 2853, 1549, 1458, 1377, 712 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.41 (s, 3 H), 5.12–5.25 (m, 2 H), 5.38–5.43 (m, 1 H), 6.95–6.97 (m, 2 H), 7.06–7.29 (m, 4 H), 7.40 (d, *J* = 7.0 Hz, 1 H), 7.98 (br, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.74, 35.49, 78.85, 108.51, 110.71, 118.57, 119.67, 121.38, 124.42, 124.68, 126.30, 126.77, 132.99, 135.35, 143.31.

Anal. Calcd for ($C_{15}H_{14}N_2O_2S$): C, 62.92; H, 4.93; N, 9.78. Found: C, 62.85; H, 4.89; N, 9.77.

7ad
Yield: 99%; yellow viscous oil; flash chromatography (cyclohexane–Et_2O, 9:1), R_f 0.30.

IR (neat): 3414, 2921, 1706, 1549, 1459, 1428, 1301, 1227, 1015, 734, 646 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.41 (s, 3 H), 4.96 (dd, *J* = 10.6, 3.6 Hz, 1 H), 5.16–5.25 (m, 2 H), 6.09–6.11 (m, 1 H), 6.31 (dd, *J* = 2.0, 3.4 Hz, 1 H), 7.06–7.15 (m, 2 H), 7.27–7.29 (m, 1 H), 7.38–7.42 (m, 2 H), 7.95 (br, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.88, 35.51, 77.18, 106.38, 107.36, 110.60, 110.88, 118.60, 119.77, 121.47, 126.64, 133.39, 135.48, 142.06, 152.35.

Anal. Calcd for ($C_{15}H_{14}N_2O_3$): C, 66.66; H, 5.22; N, 10.36. Found: C, 66.61; H, 5.18; N, 10.34.

7bd
Yield: 92%; brown–yellow oil; flash chromatography (cyclohexane–Et_2O, 95:5), R_f 0.31.

IR (neat): 3559, 3419, 3119, 3058, 2696, 2923, 1552, 1457, 1423, 1378 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.93 (dd, *J* = 4.8, 8.2 Hz, 1 H), 5.07 (dd, *J* = 5.2, 8.2 Hz, 1 H), 5.27 (dd, *J* = 4.8, 5.2 Hz, 1 H), 6.18 (dd, *J* = 0.9, 2.2 Hz, 1 H), 6.33 (dd, *J* = 1.8, *J* = 3.3 Hz, 1 H), 7.12–7.18 (m, 1 H), 7.24–7.27 (m, 3 H), 7.39–7.40 (m, 1 H), 7.59 (dd, *J* = 1.2, 8.1 Hz, 1 H), 8.16 (br, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.68, 77.84, 107.31, 110.42, 111.52, 118.62, 119.98, 122.56, 122.69, 125.65, 136.28, 142.18, 152.20.

Anal. Calcd for ($C_{14}H_{12}N_2O_3$): C, 65.62; H, 4.72; N, 10.93. Found: C, 66.58; H, 4.68, N, 10.92.

7cc
Yield: 99%; pale green solid; mp: 111–113 °C; flash chromatography (cyclohexane–Et_2O, 9:1), R_f 0.25.

IR (Nujol): 3101, 3046, 2922, 2854, 1545, 1471, 1375, 1335 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.42 (s, 3 H), 3.67 (s, 3 H), 5.03–5.28 (m, 2 H), 5.40 (dd, *J* = 6.6, 8.8 Hz, 1 H), 6.91–6.95 (m, 2 H), 7.00–7.13 (m, 1 H), 7.16–7.20 (m, 2 H), 7.28 (d, *J* = 8.0 Hz, 1 H), 7.37 (d, *J* = 7.2 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.26, 29.47, 35.52, 77.00, 105.52, 106.95, 108.89, 110.24, 118.35, 119.01, 120.79, 125.52, 135.63, 136.72, 141.49, 152.31.

Anal. Calcd for ($C_{16}H_{16}N_2O_2S$): C, 63.98; H, 5.37; N, 9.39. Found: C, 63.91; H, 5.33; N, 9.33.

7cd
Yield: 91%; pale yellow solid; mp 115–118 °C; flash chromatography (cyclohexane–Et_2O, 85:15), R_f 0.30.

IR (Nujol): 3121, 2923, 2852, 1559, 1504, 1472, 1411, 1380, 1170, 1012, 911 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.42 (s, 3 H), 3.67 (s, 3 H), 4.90–4.99 (m, 1 H), 5.16–5.27 (m, 2 H) 6.09 (d, *J* = 3.4 Hz, 1 H), 6.29 (dd, *J* = 1.8, 3.2 Hz), 7.08 (dt, *J* = 1.2, 6.6 Hz, 1 H), 7.16 (dt, *J* = 1.2, 6.6 Hz, 1 H), 7.26–7.30 (m, 1 H), 7.37–7.41 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.29, 29.52, 35.50, 77.00, 105.45, 106.98, 108.92, 110.26, 118.36, 119.15, 120.79, 125.49, 134.70, 136.70, 141.70, 152.28.

Anal. Calcd for ($C_{16}H_{16}N_2O_3$): C, 67.59; H, 5.67; N, 9.85. Found: C, 67.55; H, 5.63; N, 9.84.

7ed
Yield: 65%; yellow solid; mp 115–118 °C; flash chromatography (cyclohexane–Et_2O, 85:15), R_f 0.28.

IR (Nujol) 3322, 2923, 2852, 1552, 1489, 1463, 1377, 1213, 742 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.84 (s, 3 H), 4.91–4.95 (m, 1 H), 5.00–5.10 (m, 1 H), 5.18–5.25 (m, 1 H), 6.15–6.18 (m, 1 H), 6.28–6.32 (m, 1 H), 6.86–6.91 (m, 1 H), 6.95–6.98 (m, 1 H), 7.10–7.12 (m, 1 H), 7.26–7.29 (m, 1 H), 7.39 (s, 1 H), 8.05 (br, H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.65, 55.89, 77.82, 100.62, 107.33, 110.46, 111.35, 112.22, 112.77, 123.31, 126.18, 131.42, 142.22, 152.21, 154.34.

Anal. Calcd for ($C_{15}H_{14}N_2O_4$): C, 62.93; H, 4.93; N, 9.79. Found: C, 62.88; H, 4.89; N, 9.78.

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