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Oxidative Coupling of Indoles with Ethyl 2-(Disubstituted Amino)Acetates: An Approach to Achieve Indolylglycine Derivatives

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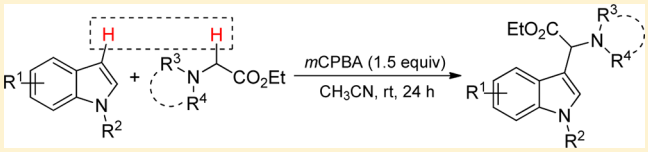
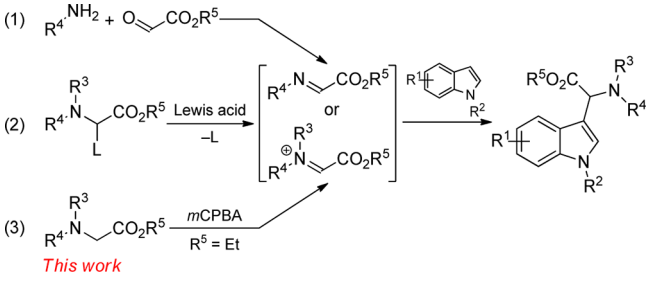
Supporting Information

ABSTRACT: An efficient method for the synthesis of indolylglycine derivatives is described. The oxidative coupling reactions of ethyl 2-(disubstituted amino)acetates with indoles proceeded smoothly in the presence of *meta*-chloroperoxybenzoic acid (*m*CPBA) under ambient conditions to produce indolylglycine derivatives in satisfactory to excellent yields.



The development of convenient and efficient methods for the synthesis of indolylglycine derivatives has attracted considerable attention. Indolylglycine derivatives are important synthetic intermediates or building blocks for drug development[1] and natural product synthesis.[2] Over the past three decades, many methods have been developed for the preparation of indolylglycine derivatives.[3] Among them, the direct coupling of indoles with imines[4] or iminium ions[5] generated in situ through Mannich-type Friedel–Crafts reaction appears more useful in the indolylglycine derivative synthesis (Scheme 1, eqs 1 and 2). However, these reactions need to use unstable alkyl glyoxylate as a starting material or require suitable leaving groups and Lewis acid catalysts.

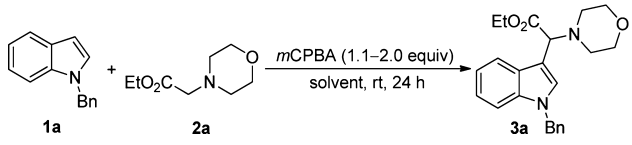
Scheme 1. Indolylglycine Derivative Synthesis via Mannich-type Friedel–Crafts Reaction



In the course of the continuous research of our group on new strategies for the direct functionalization of sp^3 C–H bonds adjacent to a nitrogen atom via tertiary amine *N*-oxide intermediates,[6] the oxidative coupling of ethyl 2-(disubstituted amino)acetates with indoles has been found to proceed in the presence of *meta*-chloroperoxybenzoic acid (*m*CPBA) under metal-free conditions to provide indolylglycine derivatives in satisfactory to excellent yields (Scheme 1, eq 3). The results are reported in the current work.

In our initial studies, the reaction of *N*-benzylindole (**1a**) with ethyl 2-morpholinoacetate (**2a**) was chosen as a model reaction for optimizing the reaction conditions. The optimization included selecting the most suitable solvents and proportions of substrates as well as oxidant *m*CPBA under ambient conditions for 24 h (Table 1). Different solvents

Table 1. Reaction Condition Screening[a]



1a 2a 3a

entry	**2a** (equiv)	*m*CPBA (equiv)	solvent	yield (%)[b]
1	1.2	1.1	CH_2Cl_2	66
2	1.2	1.1	THF	23
3	1.2	1.1	toluene	trace
4	1.2	1.1	DMF	27
5	1.2	1.1	EtOH	22
6	1.2	1.1	CH_3CN	77
7	1.1	1.1	CH_3CN	74
8	1.1	1.2	CH_3CN	70
9	1.5	1.2	CH_3CN	84
10	1.6	1.5	CH_3CN	89
11	2.2	2.0	CH_3CN	90

[a]Reaction conditions: *N*-benzylindole (**1a**, 0.25 mmol, 51.8 mg), ethyl 2-morpholinoacetate (**2a**, 1.1–2.2 equiv), and *m*CPBA (1.1–2.0 equiv) in CH_3CN (2.0 mL) under ambient conditions for 24 h. [b]Isolated yield.

including CH_2Cl_2, THF, toluene, DMF, EtOH, and CH_3CN were initially tested using 1.2 equiv of **2a** and 1.1 equiv of *m*CPBA (entries 1–6). CH_3CN proved to be the best solvent (entry 6). The proportions of substrates and oxidant *m*CPBA were then screened using CH_3CN as the solvent (entries 6–11). To facilitate the complete transformation of the indole substrate **1a** to product, slight excesses of **2a** and *m*CPBA were used. The results indicated that the yield of product **3a** was increased by **2a** to a slightly greater extent than *m*CPBA.

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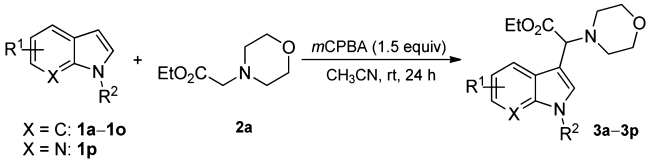
Finally, the yield of product **3a** was improved to 89% when 1.6 equiv of **2a** and 1.5 equiv of *m*CPBA were employed (entry 10). However, the yield of **3a** could not be further considerably improved with increased amounts of **2a** and *m*CPBA to 2.2 and 2.0 equiv, respectively (90%, entry 11). Therefore, the subsequent reactions of indoles with ethyl 2-(disunstituted amino)acetates were performed in the presence of *m*CPBA (1.5 equiv) as an oxidant in CH_3CN under ambient conditions for 24 h.

The tertiary amine substrate **2a** was used as a starting material to determine the scope of indole substrates under the optimized reaction conditions. The results are shown in Table 2. The reactions of indoles **1a**−**1e** with various *N*-protecting groups such as benzyl (Bn), allyl, *n*-butyl (^{n}Bu), *n*-heptyl (^{n}Hep), and methyl (Me) proceeded smoothly to provide corresponding products **3a**−**3e** in good to excellent yields (entries 1−5, 86−93%). This result indicated that the size of the *N*-protecting group did not influence the reactivity of the indole substrate. The *N*-Me indoles **1f**−**1h** bearing the electron-donating groups OMe and Me on benzene rings can also undergo the desired oxidative coupling reaction smoothly to give products **3f**−**3h** in good yields (entries 6−8, 85−87%). However, the *N*-Me indole **1i** bearing a bromine atom, an electron-withdrawing group, on a benzene ring exhibited relatively low reactivity in this type of oxidative coupling reaction. Product **3i** was obtained in 76% yield when the reaction of **1i** with **2a** was performed for a long time (entry 9, 36 h). These results indicated that the reaction yield was remarkably influenced by the electronic property of the substituent linked to the benzene ring of indole. Subsequent studies revealed that the free (NH)-indole substrates **1j**−**1o** can also be involved in this type of oxidative coupling reaction. Products **3j**−**3o** were obtained in good to excellent yields (entries 10−15, 85−93%). Similar to the reaction of bromine-substituted *N*-Me indole **1i** described above, the reaction of bromine-substituted free (NH)-indole **1n** required a long reaction time (36 h) to complete. Finally, the reactions of 1-methyl-1*H*-pyrrolo[2,3-b]pyridine (**1p**) was examined to expand further the substrate scope. The reaction of **1p** with **2a** was completed within 36 h to afford coupling product **3p** in 78% yield (entry 16).

The reactions of the indole substrates **1a**, **1e**, and **1j** with the ethyl 2-(disubstituted amino)acetates **2b**−**2d** were then examined to explore the scope of amine substrates, and the results are shown in Table 3. As expected, the reactions of the indole substrates **1a**, **1e**, and **1j** with ethyl 2-(piperidin-1-yl)acetate (**2b**) proceeded smoothly to give corresponding coupling products **3q**−**3s** in good to excellent yields (entries 1−3, 76−90%). When the indole substrates **1a** and **1e** were treated with ethyl 2-(benzyl(methyl)amino)acetate (**2c**), a noncyclic amine derivative, coupling products **3t** and **3u** were obtained in moderate yields (entries 4 and 5, 51 and 65%, respectively). Coupling product **3v** was isolated in 87% yield from the reaction of **1j** with ethyl 2-(4-tosylpiperazin-1-yl)acetate (**2d**). These results indicated that the reactivities of cyclic amine substrates were higher than those of noncyclic ones. The relatively low reactivity of noncyclic amine derivatives is perhaps due to their steric effect.

To explore the mechanism of this type of oxidative coupling reaction, ethyl 2-morpholinoacetate *N*-oxide (**4**) was isolated from the reaction of **2a** with *m*CPBA in good yield and short reaction time (Scheme 2, 83% yield, 5 min). Valuable information for understanding the present reaction mechanism was obtained by treating a mixture of indole (**1j**) and **4**

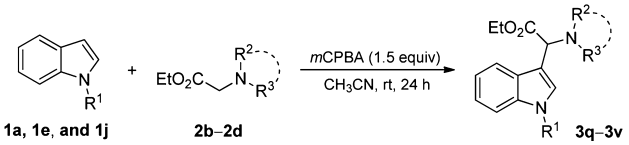
Table 2. Oxidative Coupling of various Indole Derivatives with Ethyl 2-Morpholinoacetate[a]

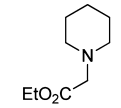
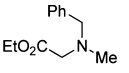
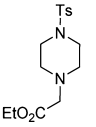


entry	indole **1**	product **3**	yield (%)[b]
1	**1a**, R^1 = H, R^2 = Bn	**3a**	89
2	**1b**, R^1 = H, R^2 = allyl	**3b**	86
3	**1c**, R^1 = H, R^2 = ^{n}Bu	**3c**	87
4	**1d**, R^1 = H, R^2 = ^{n}Hep	**3d**	93
5	**1e**, R^1 = H, R^2 = Me	**3e**	91
6	**1f**, R^1 = 5-OMe, R^2 = Me	**3f**	85
7	**1g**, R^1 = 7-Me, R^2 = Me	**3g**	87
8	**1h**, R^1 = 5-Me, R^2 = Me	**3h**	87
9	**1i**, R^1 = 5-Br, R^2 = Me	**3i**	76[c]
10	**1j**, R^1 = H, R^2 = H	**3j**	89
11	**1k**, R^1 = 5-OMe, R^2 = H	**3k**	91
12	**1l**, R^1 = 7-Me, R^2 = H	**3l**	93
13	**1m**, R^1 = 5-Me, R^2 = H	**3m**	87
14	**1n**, R^1 = 5-Br, R^2 = H	**3n**	85[c]
15	**1o**, R^1 = 2-Me, R^2 = H	**3o**	86
16	**1p**, R^1 = H, R^2 = Me	**3p**	78[c]

[a]Reaction conditions: indole (0.25 mmol), ethyl 2-morpholinoacetat (0.4 mmol, 69.3 mg), and *m*CPBA (0.38 mmol, 76.0 mg, 85% purity) in CH_3CN (2.0 mL) under ambient conditions for 24 h. [b]Isolated yield. [c]The reaction was performed for 36 h.

Table 3. Oxidative Coupling of Indole Derivatives with Ethyl 2-(Disubstituted amino)acetates[a]



entry	indole **1**	amine **2**	product **3**	yield (%)[b]
1	**1a**, R^1 = Bn	 **2b**	**3q**	76
2	**1e**, R^1 = Me		**3r**	90
3	**1j**, R^1 = H		**3s**	83
4	**1a**, R^1 = Bn	 **2c**	**3t**	51
5	**1e**, R^1 = Me		**3u**	65
6	**1j**, R^1 = H	 **2d**	**3v**	87

[a]Reaction conditions: indole (0.25 mmol), ethyl 2-(disubstituted amino)acetate (0.4 mmol), and *m*CPBA (0.38 mmol, 76.0 mg, 85% purity) in CH_3CN (2.0 mL) under ambient conditions for 24 h. [b]Isolated yield.

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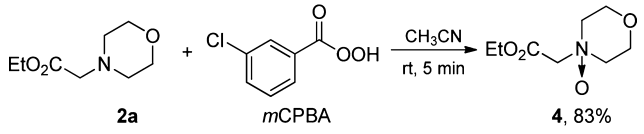
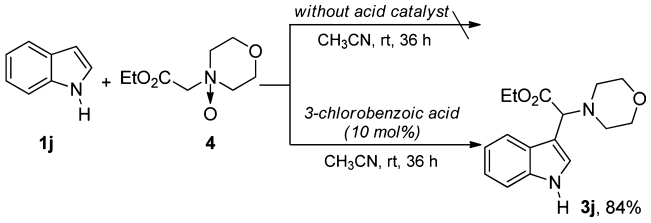
Scheme 2. Preparation of Ethyl 2-Morpholinoacetate *N*-Oxide



(Scheme 3). The reaction of **1j** with **4** did not proceed in the absence of an acid catalyst but proceeded smoothly when 3-

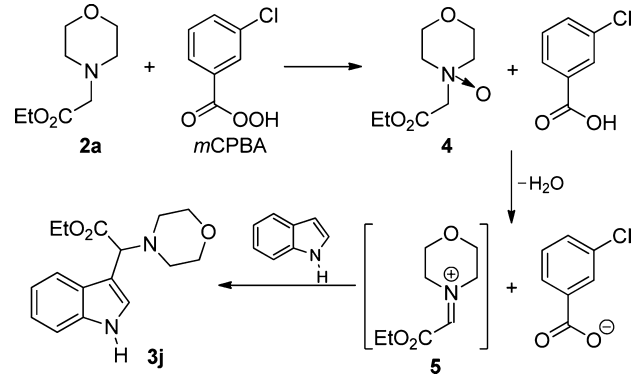
Scheme 3. Acid-Catalyzed Coupling Reaction of Indole with Ethyl 2-Morpholinoacetate *N*-Oxide



chlorobenzoic acid was used as a catalyst. Product **3j** was obtained in 84% yield. These results indicated that the present oxidative coupling proceeds via 3-chlorobenzoic acid-catalyzed reaction between indoles and amine *N*-oxide intermediates. Both 3-chlorobenzoic acid and amine *N*-oxide intermediate were generated in situ.

The plausible mechanism for the oxidative coupling reaction of indoles with ethyl 2-aminoacetate derivatives is shown in Scheme 4. *m*CPBA oxidized **2a** to *N*-oxide **4** before being

Scheme 4. Proposed Mechanism for Oxidative Coupling of Indoles with Ethyl 2-Aminoacetate Derivatives

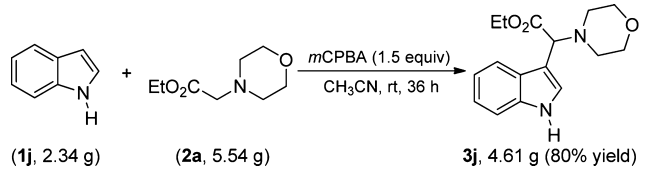


transformed into 3-chlorobenzoic acid. The interaction of **4** with 3-chlorobenzoic acid led to the generation of the iminium ion **5** and 3-chlorobenzoate anion.[7] The Mannich-type Friedel–Crafts reaction of **5** with indole may have occurred to generate the coupling product **3j**. The generated 3-chlorobenzoate anion acted as a proton acceptor.

To prove the practicality of the present method in the synthesis of indolylglycine derivatives, a gram-scale synthesis of the indolylglycine derivative **3j** was performed, and the result is shown in Scheme 5. When 2.34 g of the indole **1j** and 5.54 g of **2a** were utilized, 4.61 g of product **3j** was obtained in 80% yield.

In conclusion, a new strategy for the functionalization of sp^3 C–H bonds adjacent to a nitrogen atom via tertiary amine *N*-oxide intermediates was successfully applied to the coupling

Scheme 5. Gram-Scale Synthesis of the Indolylglycine Derivative 3j



reaction of ethyl 2-(disubstituted amino)acetates with indoles. The proposed oxidative coupling reaction proceeded smoothly under ambient conditions to provide indolylglycine derivatives in satisfactory to excellent yields. *m*CPBA and its derivative, 3-chlorobenzoic acid, acted as an oxidant and an acid catalyst in this type of oxidative coupling reaction, respectively.

EXPERIMENTAL SECTION

General Procedure for Oxidative Coupling Reaction. To a solution of ethyl 2-(disubstituted amino)acetate (**2**, 0.4 mmol) in CH_3CN (2.0 mL), *m*CPBA (0.38 mmol, 76.0 mg, 85% purity) and indole (**1**, 0.25 mmol) were added. After the resulting mixture was stirred under ambient conditions for 24 h, the solvent was then removed under reduced pressure. The residue obtained was purified via silica gel chromatography (eluent: petroleum ether/ethyl acetate = 3:1) to afford indolylglycine derivatives **3**.

*Ethyl 2-(1-benzyl-1H-indol-3-yl)-2-morpholinoacetate (**3a**).* Yield 89%, 84.2 mg, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.19 (t, J = 7.1 Hz, 3H), 2.53–2.62 (m, 4H), 3.70–3.72 (m, 4H), 4.10–4.21 (m, 2H), 4.40 (s, 1H), 5.27 (s, 2H), 7.08–7.30 (m, 9H), 7.86 (d, J = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 50.3, 51.4, 60.9, 66.4, 67.1, 109.2, 110.0, 120.0, 122.3, 126.9, 127.8, 128.0, 128.4, 128.9, 136.7, 137.2, 171.6; IR (neat) 742, 1030, 1116, 1153, 1182, 1496, 1736, 2814, 2854, 2958, 3031 cm^{-1}. HRMS (EI) calcd for $C_{23}H_{26}N_2O_3$: 378.1943 $[M]^+$. Found: 378.1952.

*Ethyl 2-(1-allyl-1H-indol-3-yl)-2-morpholinoacetate (**3b**).* Yield 86%, 70.6 mg, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21 (t, J = 7.1 Hz, 3H), 2.51–2.61 (m, 4H), 3.70–3.72 (m, 4H), 4.10–4.23 (m, 2H), 4.37 (s, 1H), 4.68 (d, J = 4.5 Hz, 2H), 5.07 (d, J = 17.1 Hz, 1H), 5.19 (d, J = 10.2 Hz, 1H), 5.92–6.02 (m, 1H), 7.14 (dd, J = 7.8, 7.1 Hz, 1H), 7.19–7.24 (m, 2H), 7.29 (d, J = 7.9 Hz, 1H), 7.84 (d, J = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 49.0, 51.4, 60.9, 66.4, 67.1, 108.9, 109.8, 117.7, 119.8, 120.1, 122.1, 127.86, 127.92, 133.2, 136.5, 171.7; IR (neat) 743, 923, 1032, 1117, 1266, 1336, 1370, 1466, 1550, 1614, 1644, 1732, 2814, 2854, 2958, 3051 cm^{-1}. HRMS (EI) calcd for $C_{19}H_{24}N_2O_3$: 328.1787 $[M]^+$. Found: 328.1796.

*Ethyl 2-(1-butyl-1H-indol-3-yl)-2-morpholinoacetate (**3c**).* Yield 87%, 74.0 mg, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.92 (t, J = 7.4 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H), 1.27–1.37 (m, 2H), 1.77–1.84 (m, 2H), 2.51–2.61 (m, 4H), 3.70–3.72 (m, 4H), 4.06–4.22 (m, 4H), 4.36 (s, 1H), 7.13 (dd, J = 7.9, 7.0 Hz, 1H), 7.20–7.25 (m, 2H), 7.32 (d, J = 8.2 Hz, 1H), 7.82 (d, J = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 14.4, 20.3, 32.3, 46.4, 51.6, 60.9, 66.5, 67.2, 108.4, 109.7, 119.6, 120.1, 122.0, 127.9, 128.0, 136.4, 171.9; IR (neat) 742, 1033, 1117, 1153, 1182, 1467, 1548, 1732, 2855, 2958, 3049 cm^{-1}. HRMS (EI) calcd for $C_{20}H_{28}N_2O_3$: 344.2100 $[M]^+$. Found: 344.2097.

*Ethyl 2-(1-heptyl-1H-indol-3-yl)-2-morpholinoacetate (**3d**).* Yield 93%, 89.8 mg, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (t, J = 7.1 Hz, 3H), 1.20–1.29 (m, 11H), 1.80–1.83 (m, 2H), 2.54–2.60 (m, 4H), 3.71 (t, J = 4.6 Hz, 4H), 4.05–4.13 (m, 4H), 4.36 (s, 1H), 7.13–7.32 (m, 4H), 7.82 (d, J = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 14.3, 22.6, 27.0, 28.9, 30.1, 31.7, 46.5, 51.5, 60.8, 66.3, 67.1, 108.3, 109.6, 119.5, 120.0, 121.8, 127.8, 127.9, 136.3, 171.8; IR (neat) 741, 1033, 1117, 1152, 1181, 1468, 1548, 1732, 2855, 2929, 3049 cm^{-1}. HRMS (EI) calcd for $C_{23}H_{34}N_2O_3$: 386.2569 $[M]^+$. Found: 386.2576.

*Ethyl 2-(1-methyl-1H-indol-3-yl)-2-morpholinoacetate (**3e**).*[4b] Yield 91%, 68.7 mg, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ

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1.23 (t, J = 7.1 Hz, 3H), 2.54−2.60 (m, 4H), 3.70−3.72 (m, 4H), 3.77 (s, 3H), 4.10−4.22 (m, 2H), 4.36 (s, 1H), 7.13−7.31 (m, 4H), 7.83 (d, J = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4, 33.0, 51.5, 61.0, 66.5, 108.7, 109.5, 119.7, 120.2, 122.1, 127.8, 129.0, 137.2, 171.9.

*Ethyl 2-(5-methoxy-1-methyl-1H-indol-3-yl)-2-morpholinoacetate (**3f**).* Yield 85%, 70.6 mg, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (t, J = 7.1 Hz, 3H), 2.50−2.61 (m, 4H), 3.70−3.71 (m, 7H), 3.86 (s, 3H), 4.08−4.21 (m, 2H), 4.30 (s, 1H), 6.89 (dd, J = 2.2, 8.8 Hz, 1H), 7.12 (s, 1H), 7.17 (d, J = 8.8 Hz, 1H), 7.3 (d, J = 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 33.1, 51.4, 56.0, 60.8, 66.5, 67.1, 101.8, 107.9, 110.1, 112.3, 128.0, 129.3, 132.4, 154.2, 171.8; IR (neat) 731, 898, 1034, 1116, 1179, 1223, 1264, 1454, 1492, 1578, 1623, 1732, 2247, 2852, 2956, 3112 cm^{-1}. HRMS (EI) calcd for $C_{18}H_{24}N_2O_4$: 332.1736 [M]$^+$. Found: 332.1742.

*Ethyl 2-(1,7-dimethyl-1H-indol-3-yl)-2-morpholinoacetate (**3g**).* Yield 87%, 68.8 mg, white solid: mp 76−78 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (t, J = 7.1 Hz, 3H), 2.51−2.61 (m, 4H), 2.75 (s, 3H), 3.70 (t, J = 4.6 Hz, 4H), 4.02 (s, 3H), 4.07−4.25 (m, 2H), 4.34 (s, 1H), 6.92 (d, J = 7.0 Hz, 1H), 6.99 (dd, J = 7.1, 7.8 Hz, 1H), 7.06 (s, 1H), 7.64 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4, 19.8, 37.0, 51.5, 60.9, 66.2, 67.2, 108.2, 118.0, 119.9, 121.5, 124.8, 128.9, 130.6, 135.8, 171.8; IR (KBr) 746, 1032, 1117, 1185, 1260, 1326, 1459, 1732, 2853, 2928, 2957 cm^{-1}. HRMS (EI) calcd for $C_{18}H_{24}N_2O_3$: 316.1787 [M]$^+$. Found: 316.1781.

*Ethyl 2-(1,5-dimethyl-1H-indol-3-yl)-2-morpholinoacetate (**3h**).* Yield 87%, 68.6 mg, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22 (t, J = 7.1 Hz, 3H), 2.47 (s, 3H), 2.51−2.61 (m, 4H), 3.70−3.71 (m, 7H), 4.06−4.24 (m, 2H), 4.34 (s, 1H), 7.05 (d, J = 8.3 Hz, 1H), 7.11 (s, 1H), 7.17 (d, J = 8.3 Hz, 1H), 7.58 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 21.6, 32.9, 51.4, 60.8, 66.3, 67.0, 107.7, 109.1, 119.4, 123.7, 127.9, 128.9, 129.0, 135.5, 171.8; IR (neat) 790, 861, 1033, 1117, 1149, 1264, 1378, 1451, 1491, 1736, 2243, 2854, 2919, 2956 cm^{-1}. HRMS (EI) calcd for $C_{18}H_{24}N_2O_3$: 316.1787 [M]$^+$. Found: 316.1795.

*Ethyl 2-(5-bromo-1-methyl-1H-indol-3-yl)-2-morpholinoacetate (**3i**).* Yield 76%, 72.4 mg, white solid: mp 86−88 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.24 (t, J = 7.1 Hz, 3H), 2.49−2.56 (m, 4H), 3.70−3.74 (m, 7H), 4.08−4.26 (m, 2H), 4.29 (s, 1H), 7.29 (d, J = 7.1 Hz, 1H), 7.98 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4, 33.2, 51.4, 61.0, 66.4, 67.1, 108.4, 111.0, 113.2, 122.8, 125.0, 129.2, 130.1, 135.9, 171.5; IR (KBr) 790, 886, 1031, 1117, 1182, 1268, 1474, 1733, 2852, 2956, 3071 cm^{-1}. HRMS (EI) calcd for $C_{17}H_{21}N_2O_3Br$: 380.0736 [M]$^+$. Found: 380.0741.

*Ethyl 2-(1H-indol-3-yl)-2-morpholinoacetate (**3j**).*[8] Yield 89%, 64.1 mg, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21 (t, J = 7.1 Hz, 3H), 2.53−2.61 (m, 4H), 3.70 (t, J = 4.6 Hz, 4H), 4.08−4.23 (m, 2H), 4.39 (s, 1H), 7.12−7.21 (m, 2H), 7.25 (d, J = 2.2 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 8.63 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 51.5, 61.0, 66.5, 110.0, 111.4, 119.95, 120.02, 122.5, 124.5, 127.1, 136.3, 171.9.

*Ethyl 2-(5-methoxy-1H-indol-3-yl)-2-morpholinoacetate (**3k**).* Yield 91%, 72.4 mg, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22 (t, J = 7.1 Hz, 3H), 2.53−2.62 (m, 4H), 3.70−3.72 (m, 4H), 3.86 (s, 1H), 4.09−4.22 (m, 2H), 4.34 (s, 1H), 6.86 (dd, J = 2.3, 8.8 Hz, 1H), 7.21−7.23 (m, 2H), 7.33 (d, J = 2.1 Hz, 1H), 8.51 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4, 51.5, 56.0, 61.0, 66.7, 67.2, 101.8, 109.8, 112.1, 112.8, 125.1, 127.6, 131.5, 154.4, 171.9; IR (neat) 732, 921, 1029, 1115, 1184, 1213, 1252, 1455, 1488, 1731, 2248, 2830, 2856, 2959, 3329, 3400 cm^{-1}. HRMS (ES) calcd for $C_{17}H_{22}N_2O_4Na$: 341.1477 [M + Na]$^+$. Found: 341.1471.

*Ethyl 2-(7-methyl-1H-indol-3-yl)-2-morpholinoacetate (**3l**).* Yield 93%, 70.3 mg, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21 (t, J = 7.1 Hz, 3H), 2.47 (s, 3H), 2.52−2.61 (m, 4H), 3.70−3.72 (m, 4H), 4.08−4.21 (m, 2H), 4.38 (s, 1H), 7.01 (d, J = 7.0 Hz, 1H), 7.07 (dd, J = 7.2, 7.8 Hz, 1H), 7.29 (d, J = 2.4 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 8.36 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4, 16.7, 51.5, 61.0, 66.6, 67.1, 110.7, 117.7, 120.3, 120.6, 123.1, 124.2, 126.7, 135.9, 171.9; IR (neat) 733, 912, 1031, 1116, 1187, 1262, 1345, 1450, 1729, 2245, 2816, 2857, 2961, 3053, 3321 cm^{-1}. HRMS (ES) calcd for $C_{17}H_{23}N_2O_3$: 303.1709 [M + H]$^+$. Found: 303.1706.

*Ethyl 2-(5-methyl-1H-indol-3-yl)-2-morpholinoacetate (**3m**).* Yield 87%, 65.8 mg, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21 (t, J = 7.1 Hz, 3H), 2.46 (s, 3H), 2.53−2.60 (m, 4H), 3.70−3.72 (m, 4H), 4.07−4.26 (m, 2H), 4.35 (s, 1H), 7.02 (d, J = 8.2 Hz, 1H), 7.22−7.25 (m, 2H), 7.61 (s, 1H), 8.46 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 21.7, 51.6, 61.0, 66.5, 67.1, 109.5, 111.1, 119.4, 124.2, 124.6, 127.4, 129.4, 134.6, 171.9; IR (neat) 732, 796, 918, 1030, 1116, 1179, 1265, 1330, 1450, 1731, 2246, 2858, 2916, 2961, 3322, 3398 cm^{-1}. HRMS (ES) calcd for $C_{17}H_{22}N_2O_3Na$: 325.1528 [M + Na]$^+$. Found: 325.1531.

*Ethyl 2-(5-bromo-1H-indol-3-yl)-2-morpholinoacetate (**3n**).* Yield 85%, 78.0 mg, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.24 (t, J = 7.1 Hz, 3H), 2.51−2.59 (m, 4H), 3.71−3.73 (m, 4H), 4.09−4.24 (m, 2H), 4.33 (s, 1H), 7.22−7.30 (m, 3H), 8.02 (s, 1H), 8.49 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4, 51.4, 61.1, 66.5, 67.1, 110.1, 112.8, 113.5, 122.8, 125.6, 128.8, 135.0, 171.5; IR (neat) 732, 887, 1029, 1114, 1261, 1452, 1729, 2245, 2857, 2961, 3314 cm^{-1}. HRMS (ES) calcd for $C_{16}H_{19}N_2O_3BrNa$: 389.0477 [M + Na]$^+$. Found: 389.0491.

*Ethyl 2-(2-methyl-1H-indol-3-yl)-2-morpholinoacetate (**3o**).* Yield 86%, 65.0 mg, white solid: mp 140−142 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.14 (t, J = 7.1 Hz, 3H), 2.42−2.48 (m, 7H), 3.71−3.73 (m, 4H), 4.00−4.17 (m, 2H), 4.22 (s, 1H), 7.06−7.12 (m, 2H), 7.20−7.22 (m, 1H), 7.93 (d, J = 6.7 Hz, 1H), 8.14 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.3, 14.3, 51.9, 60.8, 66.9, 67.2, 105.9, 110.2, 119.8, 120.2, 121.4, 127.7, 134.4, 135.2, 171.7; IR (KBr) 735, 911, 1033, 1116, 1142, 1187, 1263, 1459, 1727, 2245, 2812, 2857, 2961, 3056, 3396 cm^{-1}. HRMS (ES) calcd for $C_{17}H_{22}N_2O_3Na$: 325.1528 [M + Na]$^+$. Found: 325.1534.

*Ethyl 2-(1-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-2-morpholinoacetate (**3p**).* Yield 78%, 59.2 mg, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (t, J = 7.1 Hz, 3H), 2.49−2.58 (m, 4H), 3.71 (t, J = 4.6 Hz, 4H), 3.87 (s, 3H), 4.11−4.24 (m, 2H), 4.31 (s, 1H), 7.07−7.10 (m, 1H), 7.27 (s, 1H), 8.18−8.20 (m, 1H), 8.34−8.35 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 31.3, 51.4, 61.0, 66.9, 67.1, 107.4, 115.9, 119.8, 128.8, 128.9, 143.5, 148.1, 171.3; IR (neat) 772, 886, 1033, 1117, 1182, 1303, 1459, 1541, 1733, 2814, 2854, 2956, 3056 cm^{-1}. HRMS (EI) calcd for $C_{16}H_{21}N_3O_3$: 303.1583 [M]$^+$. Found: 303.1591.

*Ethyl 2-(1-benzyl-1H-indol-3-yl)-2-(piperidin-1-yl)acetate (**3q**).* Yield 76%, 71.5 mg, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.19 (t, J = 7.1 Hz, 3H), 1.42−1.56 (m, 6H), 2.47−2.55 (m, 4H), 4.09−4.24 (m, 2H), 4.38 (s, 1H), 5.27 (s, 2H), 7.08−7.29 (m, 10H), 7.83 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 24.6, 26.1, 50.3, 52.3, 60.7, 66.7, 110.0, 110.2, 119.7, 120.2, 122.1, 126.9, 127.7, 128.3, 128.4, 128.9, 136.6, 137.4, 172.3; IR (neat) 740, 1029, 1117, 1151, 1466, 1731, 2852, 2933, 3031 cm^{-1}. HRMS (EI) calcd for $C_{24}H_{28}N_2O_2$: 376.2151 [M]$^+$. Found: 376.2158.

*Ethyl 2-(1-methyl-1H-indol-3-yl)-2-(piperidin-1-yl)acetate (**3r**).*[4b] Yield 90%, 67.6 mg, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22 (t, J = 7.1 Hz, 3H), 1.41−1.60 (m, 6H), 2.45−2.55 (m, 4H), 3.74 (s, 3H), 4.07−4.25 (m, 2H), 4.36 (s, 1H), 7.10−7.29 (m, 4H), 7.80 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4, 24.6, 26.1, 32.9, 52.3, 60.7, 66.6, 109.3, 119.4, 120.0, 121.9, 128.1, 128.8, 137.0, 172.5.

*Ethyl 2-(1H-indol-3-yl)-2-(piperidin-1-yl)acetate (**3s**).* Yield 83%, 59.4 mg, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.20 (t, J = 7.1 Hz, 3H), 1.40−1.59 (m, 6H), 2.49−2.56 (m, 4H), 4.07−4.25 (m, 2H), 4.38 (s, 1H), 7.11−7.26 (m, 3H), 7.32 (d, J = 7.3 Hz, 1H), 7.82 (d, J = 7.9 Hz, 1H), 8.62 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4, 24.6, 26.0, 52.4, 60.8, 66.8, 110.9, 111.4, 119.8, 119.9, 122.2, 124.5, 127.6, 136.2, 172.6; IR (neat) 739, 910, 1027, 1113, 1181, 1456, 1732, 2246, 2854, 2935, 3058, 3405 cm^{-1}. HRMS (ES) calcd for $C_{17}H_{23}N_2O_2$: 287.1760 [M + H]$^+$. Found: 287.1764.

*Ethyl 2-(benzyl(methyl)amino)-2-(1-benzyl-1H-indol-3-yl)acetate (**3t**).* Yield 51%, 52.6 mg, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.24 (t, J = 7.1 Hz, 3H), 2.28 (s, 3H), 3.64−3.72 (m, 2H), 4.14−4.26 (m, 2H), 4.71 (s, 1H), 5.26 (s, 2H), 7.06−7.32 (m, 14H), 7.83−7.85 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.5, 39.1, 50.2, 58.6, 60.6, 64.6, 109.9, 110.7, 119.8, 120.4, 122.2, 126.7, 127.0, 127.7, 127.9, 128.3, 128.4, 128.9, 129.1, 136.9, 137.4, 139.6, 172.1; IR (neat) 741,

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1028, 1337, 1454, 1466, 1729, 2843, 2980, 3029 cm^{-1}. HRMS (EI) calcd for $C_{27}H_{28}N_2O_2$: 412.2151 $[M]^+$. Found: 412.2163.

*Ethyl 2-(benzyl(methyl)amino)-2-(1-methyl-1H-indol-3-yl)-acetate (**3u**).* Yield 65%, 54.6 mg, colorless oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.26 (t, J = 7.1 Hz, 3H), 2.27 (s, 3H), 3.62−3.72 (m, 5H), 4.13−4.29 (m, 2H), 4.69 (s, 1H), 7.12−7.33 (m, 9H), 7.82 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.5, 32.9, 39.0, 58.5, 60.6, 64.6, 109.4, 109.8, 119.5, 120.3, 122.0, 126.9, 127.7, 128.2, 128.8, 129.1, 137.2, 139.6, 172.3; IR (neat) 741, 1029, 1176, 1454, 1473, 1729, 2842, 2979, 3027 cm^{-1}. HRMS (EI) calcd for $C_{21}H_{24}N_2O_2$: 336.1838 $[M]^+$. Found: 336.1848.

*Ethyl 2-(1H-indol-3-yl)-2-(4-tosylpiperazin-1-yl)acetate (**3v**).* Yield 87%, 96.0 mg, white solid: mp 177−179 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.19 (t, J = 7.1 Hz, 3H), 2.43 (s, 3H), 2.58−2.70 (m, 4H), 3.00−3.03 (m, 4H), 4.07−4.21 (m, 2H), 4.40 (s, 1H), 7.10 (dd, J = 7.6, 7.3 Hz, 1H), 7.18−7.24 (m, 2H), 7.30 (d, J = 7.9 Hz, 2H), 7.36 (d, J = 7.9 Hz, 1H), 7.59 (d, J = 7.9 Hz, 2H), 7.71 (d, J = 8.0 Hz, 1H), 8.23 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4, 21.7, 46.4, 50.0, 61.1, 65.6, 109.9, 111.6, 119.8, 120.1, 122.6, 124.6, 126.9, 128.0, 132.5, 136.4, 143.9, 171.6; IR (KBr) 734, 948, 1166, 1348, 1732, 2255, 2855, 2981, 3059, 3394 cm^{-1}. HRMS (ES) calcd for $C_{23}H_{27}N_3O_4NaS$: 464.1620 $[M + Na]^+$. Found: 464.1638.

*Ethyl 2-morpholinoacetate N-oxide (**4**).* White solid: mp 77−79 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.33 (t, J = 7.1 Hz, 3H), 3.22 (d, J = 10.8 Hz, 3H), 3.78−3.84 (m, 4H), 4.09 (s, 2H), 4.25−4.31 (m, 2H), 4.48−4.54 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 61.6, 62.1, 64.5, 72.0, 164.7; IR (KBr) 861, 1029, 1113, 1211, 1643, 1740, 2985, 3423 cm^{-1}. HRMS (EI) calcd for $C_8H_{15}NO_4$: 189.1001 $[M]^+$. Found: 189.1010.

Treatment of Indole (1j) and Ethyl 2-Morpholinoacetate *N*-Oxide (4) in the Absence of Acid Catalyst. To a solution of ethyl 2-morpholinoacetate *N*-oxide (**4**, 0.4 mmol, 75.7 mg) in CH_3CN (2.0 mL), indole (**1j**, 0.25 mmol, 29.3 mg) was added. The resulting mixture was stirred under ambient conditions for 36 h. The desired reaction did not take place, and the starting materials **1j** and **4** were recovered.

Oxidative Coupling Reaction of Indole (1j) with Ethyl 2-Morpholinoacetate *N*-Oxide (4) Catalyzed by 3-Chlorobenzoic Acid. To a solution of ethyl 2-morpholinoacetate *N*-oxide (**4**, 0.4 mmol, 75.7 mg) in CH_3CN (2.0 mL), indole **1j** (0.25 mmol, 29.3 mg) and 3-chlorobenzoic acid (3.9 mg, 10 mol %) were added. The reaction mixture was stirred under ambient conditions for 36 h, and the solvent was then removed under reduced pressure. The residue obtained was purified via silica gel chromatography (eluent: petroleum ether/ethyl acetate = 3:1) to afford ethyl 2-(1*H*-indol-3-yl)-2-morpholinoacetate (**3j**) as a colorless oil (60.5 mg, 84%).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Characterization for compounds, including copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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