An Efficient and Clean Michael Addition of Indoles to Electron-Deficient Olefins Under Solvent- and Catalyst-Free Condition

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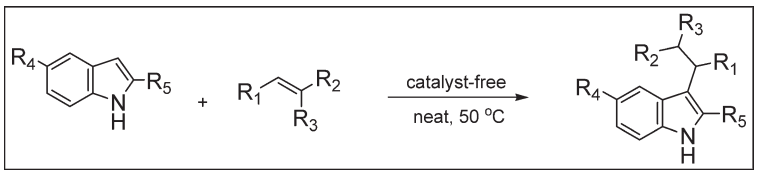

An efficient Michael addition of indoles to electron-deficient olefins under solvent- and catalyst-free condition afforded biologically important 3-substituted indole derivatives in good to excellent yields was reported. The acidic N—H proton of indole plays a key role in Michael addition of indoles to electron-deficient olefins. This very simple procedure provides an efficient and clean process for the synthesis of indole derivatives.

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INTRODUCTION

The development of new environmentally friendly reaction is a challenging goal for organic chemist [1–3]. Due to its low cost, reduced pollution, simplicity in process, and handling, the reaction under the solvent-free conditions has been extensively explored recently [4,5]. Indole and many of its derivatives are present in many compounds with pharmacological and biological activities [6,7]. Therefore, the development of green strategies to synthesize indole derivatives has attracted much attention in recent years. Michael addition is one of the most important tools for the synthesis of 3-substituted indole derivatives [8–10]. Electron-deficient olefins are strong Michael acceptors, and Michael adducts of electron-deficient olefins can be readily transformed into different functionalities [8–10].

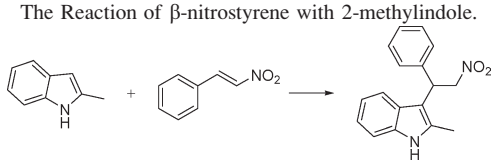
Owing to the importance of this transformation, several procedures have been reported in literature. A wide variety of acid catalysts [11,12], Lewis acids [13–19], or other catalysts [20–30] were used for this reaction. However, these catalysts still appeared to have several shortcomings, for example, toxicity of metal salts. Recently, catalyst-free Michael addition of nitrostyrene with indole was developed [31,32]. However, the reaction required higher temperature and use benzene or water as the solvent [31,32]. The development of more efficient and environmentally accessible method is still required. Here, we would like to report for the first time a clean Michael addition of indoles to electron-deficient olefins under solvent- and catalyst-free condition. The reaction avoids both an organic solvent and the need for a catalyst. Considering that the indole has an acidic N—H proton and hydrogen bonding can play a key role in organcatalysts, we supposed indole itself as catalyst in Michael addition of indoles to electron-deficient olefins. This very simple procedure provides an efficient and clean process for the synthesis of indole derivatives.

RESULTS AND DISCUSSION

In our initial study, we observed the reaction of β-nitrostyrene with 2-methylindole at 50°C without any catalyst in different solvents. Conducting the reaction in CH_2ClCH_2Cl or toluene did not get the desired product after 12 h. Only 6% of adduct was obtained after 12 h when CH_3CN was used as solvent (Table 1, entry 3). During the period, an interesting phenomenon attract our attention, after mixing the two starting materials together, a thick yellow oil was formed quickly without the addition of solvent. Considering that indole has an acidic N—H proton, we hypothesize indole itself can act as catalyst in Michael addition of indoles to electron-deficient olefins. When the oil was heated at 50°C without any solvent, the desired product was obtained in excellent yield within 1.5 h (Table 1, entry 4). When the reaction was carried out under argon with identical experimental conditions, the desired Michael addition product was obtained with the excellent yield (95%) (Table 1, entry 5), which showed the procedure did not require any inert atmospheric condition. The addition also occurs at room temperature but extensive reaction time (4 h) is required and isolated yield of product is lower (81%; Table 1, entry 6).

Table 1

The Reaction of β-nitrostyrene with 2-methylindole.



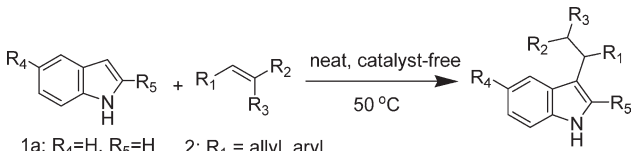
Entry[a]	*T* (°C)	Solvent	Time (h)	Yield[b] (%)
1	50	CH_2ClCH_2Cl	12	Trace
2	50	Toluene	12	Trace
3	50	CH_3CN	12	6
4	50	Neat	1.5	95
5[c]	50	Neat	1.5	95
6	r.t.	Neat	4	81

[a] Unless noted, reactions were carried out with 0.5 mmol of 2-methylindoles, 0.4 mmol of β-nitrostyrene.
[b] Isolated yield after flash chromatography.
[c] The reaction was carried out in Ar.

With the best reaction conditions in hand, we next turned our interest to the reaction scope, and the results are summarized in Table 2. It clearly indicates that β-nitrostyrenes, vinyl ethyl cyanoacetates, and vinyl malononitriles (Scheme 1) could react with indoles under the best reaction conditions to give the corresponding 3-substituted indole derivatives in good to excellent yields. First, indole **1a** was used as a standard substrate to study the reactivity of different nitroalkenes in this reaction. A wide range of nitroalkenes bearing electron-donating (**3d**–**3g**), electron- withdrawing (**3b**, **3c**) group substituted at aromatic ring, and heteroaromatic (**3h**) groups could react with indole **1a** and the Michael addition products **3** were obtained with excellent yields (Table 2, entries 1–8). The results suggest that nitroalkenes with an electron-withdrawing group substituted at aromatic ring react much faster than nitroalkenes with an electron-donating substituent (Table 2, entries 1–7). The generality of the reaction was further demonstrated by using substituted indoles such as 5-methylindole, 5-methoxyindole, and 2-methylindole; good to excellent yields were obtained. As seen in Table 2, the indole bearing Br group resulted in a lower yield and required a longer reaction time (Table 2, entry 9). When we introduced a 5-methoxy group or methyl group to

Table 2

The Michael addition of indoles to electron-deficient olefins under solvent-free and catalyst-free condition.



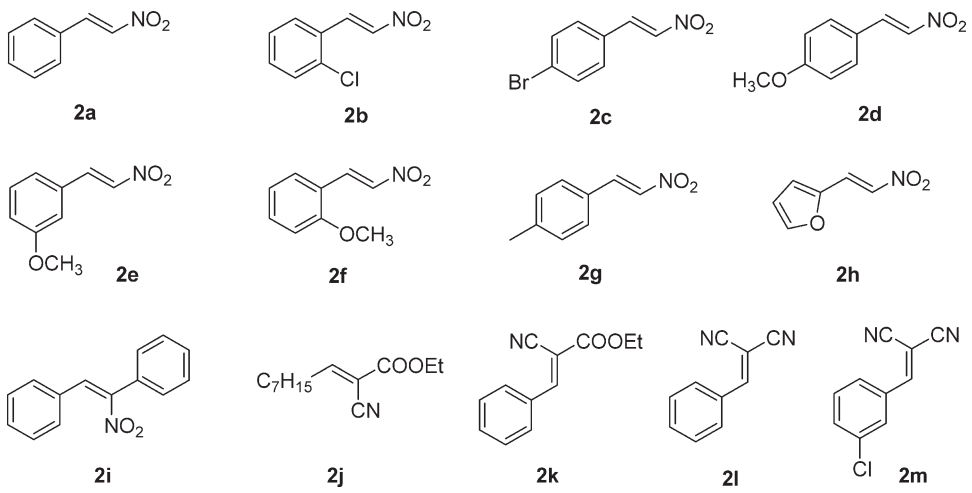
1a: R_4=H, R_5=H
1b: R_4=H, R_5=Me
1c: R_4=Br, R_5=H
1d: R_4=MeO, R_5=H

2: R_1 = allyl, aryl
R_2, R_3 = CN, NO_2, COOEt, aryl

Entry[a]	Indoles	Olefins	Product	Time (h)	Yield[b] (%)
1	**1a**	**2a**	**3a**	20	95 (85)[f]
2	**1a**	**2b**	**3b**	10	99
3	**1a**	**2c**	**3c**	10	98
4	**1a**	**2d**	**3d**	24	94 (76)[f]
5	**1a**	**2e**	**3e**	24	95
6	**1a**	**2f**	**3f**	24	96
7	**1a**	**2g**	**3g**	20	95 (81)[f]
8	**1a**	**2h**	**3h**	20	90 (68)[f]
9	**1c**	**2a**	**3i**	50	76 (73)[f]
10	**1d**	**2a**	**3j**	5	93 (83)[f]
11	**1b**	**2a**	**3k**	1.5	94 (80)[f]
12	**1b**	**2d**	**3l**	3	96
13	**1b**	**2g**	**3m**	2	98
14	**1b**	**2i**	**3n**	24	90[c]
15	**1b**	**2j**	**3o**	24	61[d]
16	**1b**	**2k**	**3p**	20	85[e]
17	**1b**	**2l**	**3q**	28	70
18	**1b**	**2m**	**3r**	20	96

[a] Unless noted, reactions were carried out with 0.4 mmol of electron-deficient olefins, 0.5 mmol of indoles.
[b] Isolated yield after flash chromatography.
[c] dr = 3.8:1.
[d] dr = 1.3:1.
[e] dr = 1.1:1.
[f] Data of H_2O as catalyst in parentheses refers to the results in literature [32].

Scheme 1. The structure of olefins.



5-position of indole or 2-position of indole, to our delight, the reaction proceeded very well, giving the corresponding products in excellent yield even with shorter reaction time (Table 2, entries 10–13). A possible explanation may be due to the presence of 5-methoxy group in 5-position of indole or the methyl group in 2-position of indole, which increased the electron density of the aromatic ring to accelerate the reaction. Moreover, with α,β-disubstituted nitroalkene, we observed low diastereoselectivity, the ^{1}H-NMR spectra of **3n** revealed the presence of diastereomer in the ratio of 3.8:1 for **3n** (Table 2, entry 14). Furthermore, to the best of our knowledge, few reports about conjugate addition of indoles with vinyl ethyl cyanoacetates and vinyl malononitriles have been reported in the literature. The results (Table 2, entries 15–18) showed that our present synthetic methodology can get these conjugate addition products with high yields. The ^{1}H-NMR spectra of **3o**, **3p** revealed the presence of diastereomers in the ratio of 1.3:1 for **3o** and 1.1:1 for **3p**.

To demonstrate the synthetic utility of the present system, we carried out the reaction in large scale. The mixture of 40 mmol of (*E*)-1-(2-nitrovinyl)benzene and 60 mmol of 2-methylindole was stirred at 50°C without solvent and catalyst for 1.5 h. The corresponding adduct **3k** was obtained in 96% yield (Scheme 2).

To gain insight into the reaction mechanism, we examined *N*-methylindole as a substrate under solvent- and catalyst-free condition at 50°C (Scheme 3). As expected, it was found that the target Michael adducts was obtained only in a trace amount even with prolonged reaction time (10 h). In any event, the presence of the acidic N—H proton seems mandatory as every attempt to use *N*-methylindole for these reactions failed to get the product. Therefore, we assume that an acidic N—H proton of indole activates the nitro moiety, a drastic enhancement of the rates and the yields of the products are observed (Scheme 4). Further application of the catalytic activity of acidic N—H proton of indole and a detailed study of the catalytic mechanism are in progress.

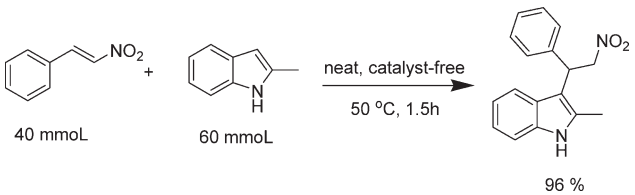
CONCLUSIONS

In summary, we have developed a rare example of an efficient Michael addition of indoles to electron-deficient olefins that avoids both an organic solvent and the need for a catalyst. The reaction is a green method for the synthesis of important 3-substituted indole derivatives with the advantages such as mild condition and high yields. Furthermore, this reaction is the first example of electron-deficient olefins activation catalyzed by an acidic N—H proton of indoles and its application to other addition reactions are underway.

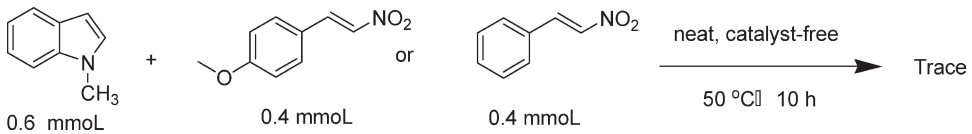
EXPERIMENTAL

Indoles were purchased from Alfa Aesar Company. Electron-deficient olefins were prepared according to the literature procedures and spectral data were consistent with the literature report. All solvent were purchased from commercial sources and used without further purification. Reactions were monitored by thin layer chromatography (TLC) using silica gel GF_{254} plates. Column chromatography was performed on silica

Scheme 2. Large-scale reaction of (*E*)-1-(2-nitrovinyl) benzene with 2-methylindole.



Scheme 3. The reaction of β-nitrostyrenes with *N*-methylindole.



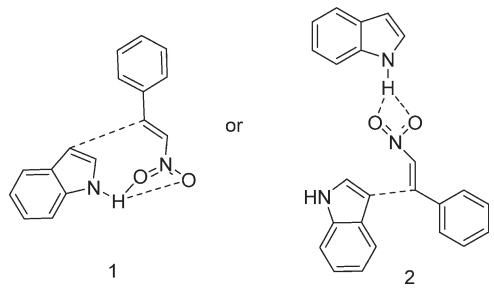
gel (300–400 mesh). NMR spectra were recorded on a 300-MHz instrument. ^{1}H-NMR chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) with the solvent resonance used as the internal standard ($CDCl_3$, δ 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constants (Hz), and integration. ^{13}C-NMR chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard ($CDCl_3$, δ 77.0 ppm). IR data were obtained from FT spectrometer and recorded as cm^{-1}.

The optimization of reaction conditions of β-nitrostyrene with 2-methylindole. In a tube equipped with a magnetic stirring bar, 0.5 mmol of 2-methylindoles, 0.4 mmol of β-nitrostyrene was added. Thick yellow oil was formed quickly, and then the mixture was stirred with the time and temperature shown in Table 1. After the completion of the reaction, the raw product was purified by silica gel column chromatography (EtOAc/petroleum ether) to give light yellow oil with the yield shown in Table 1.

General experimental procedure for the synthesis of 3a–3u. In a tube equipped with a magnetic stirring bar, electron-deficient olefin (0.4 mmol) and indole (0.6 mmol) was added. Then the tube was closed with a rubber stopper, the reaction mixture was stirred for the appropriate time at 50°C. After completion of the reaction, as indicated by TLC, the reaction mixture was directly purified by flash chromatography to yield the desired product. The compounds **3a–3l** and **3r** are known compounds; their identities were proven by means of melting points, ^{1}H-NMR, ^{13}C-NMR, and IR. All the analytical data were in accord with the spectra reported in the literature. The compounds **3m–3q** are new compounds; their identities were proven by means of HRMS, ^{1}H-NMR, ^{13}C–NMR, and IR.

3-(2-Nitro-1-phenylethyl)-1H-indole [33] (3a). Pale yellow viscous oil. yield: 95%. IR (KBr), ν (cm^{-1}): 3411, 2898, 1547, 1453, 1420, 1374, 1336, 742, 700. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 4.89 (dd, J = 8.7, 8.4, 12.5 Hz, 1H), 5.01 (dd, J = 7.5, 7.5, 12.3 Hz, 1H), 5.15 (t, J = 7.8 Hz, 1H), 6.93 (s, 1H), 7.05 (t, J = 7.5 Hz, 1H), 7.14–7.30 (m, 7H), 7.42 (d, J = 7.8 Hz, 1H), 7.99 (br, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 138.8, 136.0, 128.4, 127.3, 127.2, 127.1, 125.6, 122.2, 121.1, 119.4, 118.4, 113.9, 110.9, 79.09, 41.1.

Scheme 4. The two proposed reaction mechanism.



3-(1-(2-Chlorophenyl)-2-nitroethyl)-1H-indole [33] (3b). White solid. yield: 99%. mp 144.1–145.3°C. IR (KBr), ν (cm^{-1}): 3438, 2958, 2913, 1547, 1436, 1411, 1379, 1334, 1096, 742. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 4.91–5.01 (m, 2H), 5.72 (t, J = 7.8 Hz, 1H), 7.03–7.21 (m, 6H), 7.30 (d, J = 7.8 Hz, 1H), 7.41 (t, J = 5.7 Hz, 2H), 8.05 (br, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 136.5, 133.8, 130.1, 129.0, 128.8, 127.33, 126.2, 122.8, 122.0, 120.0, 118.9, 113.2, 111.4, 77.7, 38.0.

3-(1-(4-Bromophenyl)-2-nitroethyl)-1H-indole [34] (3c). Pale pink solid. yield: 98%. mp 122.7–123.9°C. IR (KBr), ν (cm^{-1}): 3396, 2946, 2915, 1535, 1484, 1427, 1380, 1337, 744. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 4.84 (dd, J = 8.7, 8.4, 12.5 Hz, 1H), 4.98 (dd, J = 7.5, 7.5, 12.3 Hz, 1H), 5.10 (t, J = 7.8 Hz, 1H), 6.92 (s, 1H), 7.06 (t, J = 7.5 Hz, 1H), 7.14–7.21 (m, 3H), 7.30 (d, J = 7.8 Hz, 1H), 7.38 (t, J = 7.5 Hz, 3H), 8.04 (br, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 138.3, 136.5, 132.0, 129.5, 125.9, 122.9, 121.6, 121.5, 120.1, 118.8, 113.8, 111.5, 79.2, 41.0.

3-(1-(4-Methoxyphenyl)-2-nitroethyl)-1H-indole [32] (3d). White solid. yield: 94%. mp 152.5–153.6°C. IR (KBr), ν (cm^{-1}): 3379, 2986, 1547, 1509, 1243, 746. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 3.77 (s, 3H), 4.89 (dd, J = 8.4, 8.4, 12.1 Hz, 1H), 5.04 (dd, J = 7.6, 7.4, 12.0 Hz, 1H), 5.13 (t, J = 7.8 Hz, 1H), 6.84 (d, J = 8.4 Hz, 7.01–7.09 (m, 2H), 7.16–7.25 (m, 3H), 7.35 (d, J = 8.1 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 8.07 (br, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 158.9, 136.5, 131.2, 128.8, 126.1, 122.6, 121.4, 119.9, 119.0, 114.8, 114.3, 111.3, 79.7, 55.2, 40.8.

3-(1-(3-Methoxyphenyl)-2-nitroethyl)-1H-indole [35] (3e). Pale yellow viscous oil. yield: 95%. IR (KBr), ν (cm^{-1}): 3414, 2910, 2834, 1548, 1487, 1456, 1376, 1261, 743. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 3.69 (s, 3H), 4.86 (dd, J = 8.4, 8.4, 12.6 Hz, 1H), 4.97 (dd, J = 7.8, 7.5, 12.5 Hz, 1H), 5.11 (t, J = 15.9 Hz, 1H), 6.76 (d, J = 8.1 Hz, 1H), 6.87 (t, J = 17.4 Hz, 3H), 7.04 (t, J = 14.7 Hz, 1H), 7.12–7.26 (m, 3H), 7.43 (d, J = 7.8 Hz, 1H), 8.01 (br, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 159.9, 141.0, 136.5, 129.9, 126.1, 122.6, 121.7, 120.1, 119.9, 118.9, 114.1, 114.1, 112.5, 111.5, 79.5, 55.2, 41.5.

3-(1-(2-Methoxyphenyl)-2-nitroethyl)-1H-indole [33] (3f). Pale yellow viscous oil. yield: 96%. IR (KBr), ν (cm^{-1}): 3415, 2898, 2836, 1548, 1489, 1457, 1373, 1244, 745. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 3.85 (s, 3H), 4.89–5.03 (m, 2H), 5.58 (t, J = 7.8 Hz, 1H), 6.80 (t, J = 7.4 Hz, 1H), 6.88 (d, J = 8.1 Hz, 1H), 7.01–7.27 (m, 6H), 7.45 (d, J = 7.8 Hz, 1H), 7.97 (br, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 156.9, 136.4, 128.9, 128.7, 127.3, 126.5, 122.4, 122.0, 120.8, 119.7, 119.1, 113.9, 111.3, 110.9, 78.2, 55.5, 35.5.

3-(2-Nitro-1-p-tolylethyl)-1H-indole [32] (3g). Pale yellow viscous oil. yield: 95%. IR (KBr), ν (cm^{-1}): 3415, 2916, 1548, 1512, 1455, 1422, 1376, 743. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 2.28 (s, 3H), 4.88 (dd, J = 8.4, 8.7, 12.2 Hz, 1H), 5.01 (dd, J = 7.8, 7.5, 12.2 Hz, 1H), 5.12 (t, J = 7.8 Hz, 1H), 6.94 (s, 1H), 7.02–7.20 (m, 6H), 7.29 (d, J = 8.1 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 8.00 (br, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$),

δ 136.7, 136.0, 135.7, 129.1, 127.1, 125.6, 122.1, 121.1, 119.4, 118.5, 114.1, 110.9, 79.1, 40.7, 20.5.

3-(1-(Furan-2-yl)-2-nitroethyl)-1H-indole [33] (3h). Pale yellow viscous oil. yield: 90%. IR (KBr), ν (cm^{-1}) 3403, 2915, 1543, 1505, 1455, 1421, 1371, 1340, 734. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 4.87 (dd, J = 7.5, 7.5, 12.6 Hz, 1H), 5.01 (dd, J = 8.1, 8.1, 12.3 Hz, 1H), 5.22 (t, J = 7.7 Hz, 1H), 6.13 (d, J = 3 Hz, 1H), 6.28 (s, 1H), 7.02 (s, 1H), 7.08–7.21 (m, 2H), 7.32 (t, J = 18.0 Hz, 2H), 7.53 (d, J = 7.8 Hz, 1H), 8.05 (br, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 152.3, 142.2, 136.3, 125.7, 122.8, 122.6, 120.1, 118.7, 111.6, 110.5, 107.4, 77.9, 35.7.

5-Bromo-3-(2-nitro-1-phenylethyl)-1H-indole [32] (3i). Pale pink solid. yield: 76%. mp 116.6–117.5°C. IR (KBr), ν (cm^{-1}): 3427, 2907, 1548, 1456, 1373, 1104, 799. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 4.89 (dd, J = 8.1, 8.1, 12.3 Hz, 1H), 4.99 (dd, J = 8.4, 8.1, 12.2 Hz, 1H), 5.10 (t, J = 7.8 Hz, 1H), 7.02 (s, 1H), 7.15–7.29 (m, 7H), 7.53 (s, 1H), 8.13 (br, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 138.7, 135.1, 129.0, 127.9, 127.7, 127.6, 125.6, 122.7, 121.4, 114.0, 113.2, 112.8, 79.4, 41.3.

5-Methoxy-3-(2-nitro-1-phenylethyl)-1H-indole [33] (3j). Pale yellow viscous oil. yield: 93%. IR (KBr), ν (cm^{-1}): 3415, 2951, 1549, 1484, 1453, 1375, 798, 701. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 3.74 (s, 3H), 4.89 (dd, J = 8.4, 8.4, 12.3 Hz, 1H), 5.00 (dd, J = 7.5, 7.5, 12.3 Hz, 1H), 5.10 (t, J = 8.0 Hz, 1H), 6.83 (d, J = 5.4 Hz, 2H), 6.92 (s, 1H), 7.15–7.30 (m, 6H), 7.98 (br, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 153.7, 138.7, 131.1, 128.4, 127.2, 127.0, 126.1, 121.8, 113.5, 112.2, 111.6, 100.4, 79.0, 55.4, 41.0.

2-Methyl-3-(2-nitro-1-phenylethyl)-1H-indole [33] (3k). Pale pink solid. yield: 94%. mp 94.5–95.7°C. IR (KBr), ν (cm^{-1}): 3413, 2919, 1545, 1457, 1431, 1384, 1299, 741, 704. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 2.31 (s, 3H), 5.08–5.23 (m, 3H), 6.98–7.11 (m, 2H), 7.20–7.36 (m, 7H), 7.82 (br, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 139.1, 134.9, 132.4, 128.3, 126.8, 126.6, 126.4, 120.8, 119.2, 118.1, 110.2, 108.3, 78.1, 40.0, 11.4.

3-(1-(4-Methoxyphenyl)-2-nitroethyl)-2-methyl-1H-indole [12] (3l). Pale pink solid. yield: 96%. mp 155.5–156.4°C. IR (KBr), ν (cm^{-1}): 3425, 2921, 1612, 1546, 1510, 1460, 1381, 1244, 1183, 1031, 745. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 2.28 (s, 3H), 3.71 (s, 3H), 5.01–5.17 (m, 3H), 6.79 (d, J = 8.7 Hz, 2H), 6.98–7.10 (m, 2H), 7.19 (d, J = 8.4 Hz, 3H), 7.35 (d, J = 7.8 Hz, 1H), 7.83 (br, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 158.0, 135.0, 132.3, 131.13, 127.9, 126.4, 120.8, 119.2, 118.1, 113.7, 110.2, 108.5, 78.4, 54.7, 39.4, 11.4.

2-Methyl-3-(2-nitro-1-p-tolylethyl)-1H-indole [36] (3m). Pale pink solid. yield: 98%. mp 152.7–153.9°C. IR (KBr), ν (cm^{-1}): 3413, 2917, 1619, 1544, 1456, 1429, 1384, 1204, 739. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 2.28 (s, 3H), 2.34 (s, 3H), 5.04–5.22 (m, 3H), 6.99–7.09 (m, 4H), 7.17–7.24 (m, 3H), 7.36 (d, J = 7.8 Hz, 1H), 7.82 (br, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 136.2, 135.9, 134.9, 132.2, 128.9, 126.7, 126.6, 126.4, 120.8, 119.2, 118.1, 110.1, 108.5, 78.2, 39.6, 20.4, 11.4.

2-Methyl-3-(2-nitro-1,2-diphenylethyl)-1H-indole (3n). Pale pink solid. yield: 90%. dr = 3.8:1. mp 158.5–161.4°C. IR (KBr), ν (cm^{-1}): 3420, 2921, 1549, 1490, 1454, 1358, 1303, 739. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 2.17 (s, 0.6 H), 2.40 (s, 2.4H), 5.36 (d, J = 12.0 Hz, 1H), 6.68 (d, J = 12.3 Hz, 1H), 6.97–7.39 (m, 11H), 7.49–7.77 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 139.0, 135.4, 133.6, 132.6, 129.8, 129.5, 128.9, 128.8, 128.5, 128.4, 128.3, 127.6, 127.3, 127.1, 126.5, 121.1, 121.0, 119.7, 119.6, 118.7, 110.8, 110.6, 93.7, 93.2, 46.92, 46.5, 12.1. HRMS (ESI-TOF) ($M + H^+$):357.1603, found: 320.1601.

Ethyl 2-cyano-3-(2-methyl-1H-indol-3-yl)decanoate (3o). Pale yellow viscous oil. yield: 61%. dr = 1.3:1. IR (KBr), ν (cm^{-1}): 3394, 2931, 2855, 2360, 2336, 1741, 1459, 1369, 1302, 1245, 1024, 741. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 0.80–0.90 (m, 5H), 1.20 (t, J = 14.7 Hz, 13H), 2.37 (s, 1.7H), 2.43 (s, 1.3H), 3.52–3.60 (m, 1H), 3.93 (t, J = 17.1 Hz, 2H), 4.19 (t, J = 11.1 Hz, 1H), 7.03–7.13 (m, 2H), 7.25 (s, 1H), 7.51 (d, J = 7.2 Hz, 0.5H), 7.59 (d, J = 7.5 Hz, 0.5H), 7.88 (br, 0.5H), 7.95 (br, 0.5H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 166.1, 165.8, 135.5, 135.4, 133.5, 132.9, 126.8, 121.2, 121.1, 119.5, 119.4, 118.7, 118.5, 116.9, 116.6, 110.5, 108.4, 108.3, 62.5, 62.1, 43.7, 43.4, 39.0, 38.9, 31.8, 31.7, 29.2, 29.1, 29.0, 29.0, 27.5, 27.4, 22.55, 14.0, 13.8, 13.4, 12.3, 12.1. HRMS (ESI-TOF) ($M + H^+$):355.2386, found: 355.2388.

Ethyl 2-cyano-3-(2-methyl-1H-indol-3-yl)-3-phenylpropanoate (3p). Pale yellow viscous oil. yield: 85%. dr = 1.1:1. IR (KBr), ν (cm^{-1}): 3401, 2981, 2922, 2245, 1740, 1457, 1305, 1244, 1030, 742, 694. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 0.88 (t, J = 14.4 Hz, 1.5H), 1.06 (t, J = 14.4 Hz, 1.5H), 2.24 (s, 1.5H), 2.34 (s, 1.5H), 3.91–3.99 (m, 1H), 4.05–4.12 (m, 1H), 4.46 (d, J = 9.9 Hz, 0.5H), 4.60 (d, J = 9.9 Hz, 0.5H), 5.01 (t, J = 17.7 Hz, 1H), 7.00–7.08 (m, 2H), 7.17–7.36 (m, 5H), 7.48 (t, J = 18.0 Hz, 2H), 7.91 (br, 0.5H), 7.97 (br, 0.5H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 165.7, 165.4, 139.6, 139.2, 135.4, 135.1, 133.2, 133.0, 128.8, 128.7, 128.6, 127.7, 127.6, 127.4, 127.3, 127.2, 127.0, 121.4, 121.3, 119.8, 119.7, 118.7, 118.4, 116.6, 116.4, 110.7, 110.6, 109.5, 109.4, 62.8, 62.5, 43.4, 43.2, 42.4, 42.0, 13.6, 13.4, 12.4, 12.2. HRMS (ESI-TOF) ($M + H^+$): 333.1603, found: 320.1604.

2-((2-Methyl-1H-indol-3-yl)(phenyl)methyl)malononitrile (3q). White solid. yield: 70%. mp 164.4–166.1°C. IR (KBr), ν (cm^{-1}): 3405, 2895, 2712, 2650, 2252, 1952, 1458, 1419, 1348, 1307, 1245, 1040, 762, 728. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 2.39 (s, 3H), 4.66 (d, J = 9.4 Hz, 1H), 4.94 (d, J = 9.4 Hz, 1H), 7.03–7.15 (m, 2H), 7.25–7.43 (m, 7H), 8.02 (br, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 136.7, 134.9, 133.4, 128.5, 127.5, 126.9, 125.7, 121.3, 119.6, 117.7, 112.2, 112.0, 110.5, 107.4, 43.7, 27.2, 11.8. HRMS (ESI-TOF) ($M + H^+$):286.1344, found: 286.1338.

2-((3-Chlorophenyl)(2-methyl-1H-indol-3-yl)methyl)malononitrile (3r). White solid. yield: 96%. mp 190.4–192.1°C. IR (KBr), ν (cm^{-1}): 3376, 2920, 2255, 1592, 1569, 1456, 1427, 1307, 1244, 1193, 746. ^{1}H-NMR (300 MHz, $CDCl_3$), δ 2.43 (s, 3H), 4.63 (d, J = 9.6 Hz, 1H), 4.90 (d, J = 9.6 Hz, 1H), 7.02–7.17 (m, 2H), 7.25–7.37 (m, 6H), 8.08 (br, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$), δ 139.1, 135.4, 135.0, 134.0, 130.2, 128.3, 127.9, 125.2, 122.0, 120.3, 118.0, 112.4, 112.1, 111.1, 111.0, 107.2, 43.9, 27.6, 12.4. HRMS (ESI-TOF) ($M + H^+$): 320.0955, found: 320.0949.

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