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A combination of water and microwave irradiation promotes the catalyst-free addition of pyrroles and indoles to nitroalkenes

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ABSTRACT

A combination of water and microwave irradiation was used for the first time to perform a catalyst-free nitro-Michael addition of pyrroles and indoles. Under superheated conditions, the water trends to ionize by changing its chemical and physical properties. Therefore, we performed a new green-protocol using the water either as environmentally no harm solvent or as catalyst. The reaction success is independent from the kind of pyrrole, indole or nitroalkenes rapidly affording the corresponding adducts and giving excellent yields.

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1. Introduction

In recent years, green chemistry has become an important research area,[1] and in particular the combination of 'microwave irradiation' with alternative reaction media, such as solvent-free conditions, ionic liquid, the use of environment-friendly solvents and the use of supported reagents.[2] Green chemistry leads to the development of clean, economical, and environmentally harmless 'green processes'. Water is, obviously, the cleanest and safest available solvent but it is not commonly used as most organic compounds are poorly water soluble.[3] This issue can be overcome by using 'superheated water' (>100 °C) under microwave irradiation.[4] It has actually been demonstrated that, from room temperature to 'superheated conditions', water's chemical, and physical properties change by behaving both as a pseudo-organic solvent and acid.[4d,5] As a consequence, under these conditions without any catalyst, a lot of the acid-catalyzed transformations very efficiently and rapidly occur.[4d,5,6]

Pyrroles and indoles are widely distributed in nature. Their framework is found in many natural substances and they are the component of more complex macrocycles including porphyrins of heme, alkaloids, pigments.[7] Furthermore, 3-alkylindoles and 2-alkylpyrroles are versatile medicinal compounds synthesis synthons.[8]

The Michael addition is the most widely used and extensively studied tool for the synthesis of 3-substituted indoles and 2-substituted pyrroles[7a] and, in particular the use of nitroalkenes, strong Michael acceptors, has attracted much attention because of the activating effect of the nitro group and of the easy transformation of the adducts to a number of functional groups.[9]

The most recently synthetic approaches involve different catalysts,[10] and different media.[11]

Examples of the functionalization of indoles and pyrroles via microwave heating are available in literature.[12] The microwave-assisted methods are efficient but they all require catalysts in order to obtain high product yields.

Some aqueous organic procedures are also reported.[13] These procedures are assisted by the addition of suitable water-tolerant catalysts in order to promote the reaction and the addition of surfactants in order to increase the substrates solubility. An example[14] of uncatalysed addition of indoles to nitrostyrenes at 100 °C in water has recently been reported, however, the reaction times and the adduct yields are affected by the electronic density of the indole ring and by the nature of the substituent on the β-nitrostyrene.

In this context, our attention was focused on the fact that a combination of microwave irradiation and 'superheated water' could be a successful way to synthesize pyrrole and indole derivatives. This method is benefits from the rate enhancement effects found when using microwave heating and when the water is heated in sealed vessels above its boiling point.

Herein, we present the results from our investigations on nitro-Michael addition of *N*-methyl pyrrole, 2-methyl indole, substituted derivatives of indole, and pyrrole to nitroalkenes in water under microwave irradiation.

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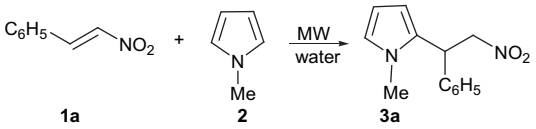
2. Results and discussion

We first examined the catalyst-free conjugate addition of β-nitrostyrene **1a** to 1-methyl pyrrole **2** in water under microwave irradiation (Scheme 1) at various times and temperatures (Table 1) using CEM Discover single-mode reactor.



Scheme 1.

Table 1
Catalyst-free nitro-Michael addition of **1a** to **2** under microwave irradiation[a]

Entry	Time/min	Temp (°C)	Yield[a,b] (%)
1	4	120	27
2	4	130	32
3	4	150	50
4[c]	4	150	10
5	6	150	80
6	8	150	80

[a] Isolated yield after column chromatography.
[b] NMR spectra of the product **3a** is in accordance with the literature[10b].
[c] The reaction was performed under solvent-free conditions.

The best yield of adduct **3a** (80%) was obtained at 150 °C in 6 min (entry 5) in water (1 mL) showing that the presence of water and the temperature rise from 120 °C to 150 °C were essential for a successful reaction. It is obvious that the reaction benefits from happening in the 'subcritical region' of water (150–300 °C).

Moreover, under microwave irradiation the reaction was clean and proceeded with high regioselectivity: 2,5-dialkylpyrrole as the side product was not obtained and no other by-products (dimers or trimers) were observed.

When the reaction was carried out under conventional heating using the same sealed microwave tube into pre-heated oil bath at 150 °C for 12 min, the yield of the adduct was only 20% and a considerable amount of starting material was recovered.

Therefore, having established the optimal reaction conditions (entry 5, Table 1), we extended the scope of the reaction to wide varieties of nitroalkenes (Table 2).

Although is reported in literature[13] that the nature of the substituent on the β-nitrostyrene affects the reaction times and the efficiency of the reaction, we observed that, under our reaction conditions, the electronic properties of the nitroalkene aromatic ring did not have any effect. In fact, the β-nitrostyrenes possessing strong electron-withdrawing groups (entries 2–4) gave Michael adducts with excellent yields and in very short time as the β-nitrostyrenes possessing strong electron-donating groups (entries 5–8), for which long reaction time were reported.[13,14] At last, the nitroolefin **1i** (entry 9) added to **2** in high yield (80%) without any interference of the sensitive heterocyclic nucleus.

To check the versatility of this process, we tested the additions of nitroolefins **1a**–**i** with 2-methyl indole **4**.The reactions were performed using 2-methyl indole (0.6 mmol) and nitroalkenes (0.5 mmol) in water (1 mL); the mixtures were irradiated at *P* 200 W, *T* 150 °C for 6 min. The experimental results are reported in Table 3.

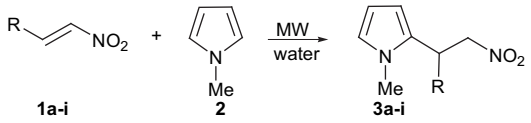
The experiments clearly demonstrate that the procedure is highly efficient: the reaction is in most cases quantitative and the same reaction time (6 min.) is used irrespective of the nature of the substituent on the nitroalkenes.

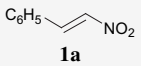
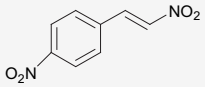
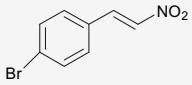
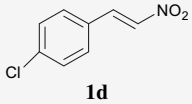
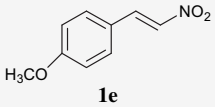
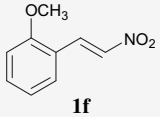
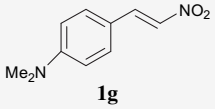
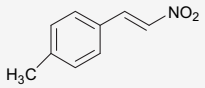
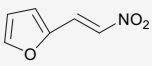
Finally, we examined the Michael addition of pyrrole and a variety of substituted indoles to β-nitrosytrene via our procedure (Table 4).

The pyrrole (entry 1) readily underwent Michael addition at the α-position affording the adduct in quantitative yield and 2,5-disubstituted pyrrole or *N*-alkylpyrrole were not observed. By using substituted indoles (entries 2–7) it was evident that the reactions rapidly proceeded (6 min) and gave high yield irrespective of the electronic density of the indole ring.

As reported in literature,[17] a mechanism for the reaction is the nucleophilic addition of the electron-rich indoles to nitro-derivatives where the superheated water may activate the nitro groups through hydrogen bonding generating an electron-deficient in the nitro-derivative (Fig. 1). The electrophilic substitution on the indole gives the intermediate **I**, which loses a proton forming intermediate **II**. The intermediate **II** abstracts proton either from water or from indole affording **III**, which tautomerizes to give the product.

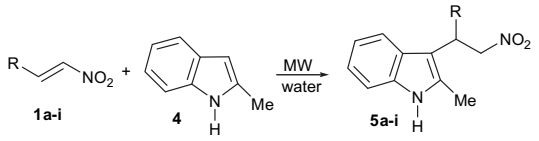
Table 2
Catalyst-free aqueous nitro-Michael addition of various nitroalkenes to **2** under MW irradiation

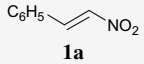
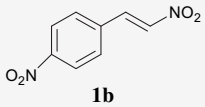
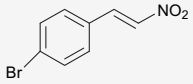
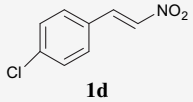
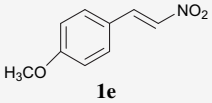
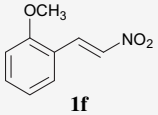
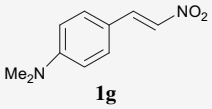
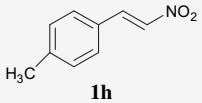
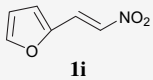


Entry[a]	Michael acceptor	Product	Yield[b,c] (%)
1	 **1a**	**3a**	80[c]
2	 **1b**	**3b**	99[d]
3	 **1c**	**3c**	99
4	 **1d**	**3d**	99[e]
5	 **1e**	**3e**	83c
6	 **1f**	**3f**	97[e]
7	 **1g**	**3g**	96[e]
8	 **1h**	**3h**	99[c]
9	 **1i**	**3i**	80

[a] *P*=200 W, *T*=150 °C, reaction time=6 min.
[b] Isolated yield after column chromatography.
[c] All products were characterized by ^{1}H NMR, ^{13}C NMR and mass spectroscopy (see experimental section).
[d] Run using *P*=200 W, *T*=125 °C, reaction time=6 min.
[e] 1 ml of an aqueous solution of sodium chloride (0.02 M) was used.

Table 3
Catalyst-free aqueous nitro-Michael addition of **4** to various β-nitrostyrenes under MW irradiation



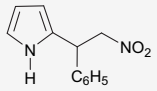
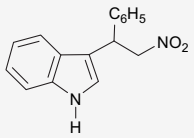
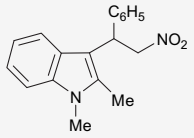
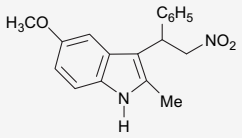
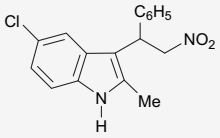
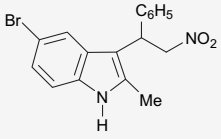
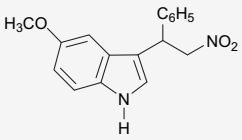
Entry	Michael acceptor	Product	Yield[a,b] (%)
1	 **1a**	**5a**	80[c]
2	 **1b**	**5b**	99
3	 **1c**	**5c**	99
4	 **1d**	**5d**	99
5	 **1e**	**5e**	83[c]
6	 **1f**	**5f**	97
7	 **1g**	**5g**	96
8	 **1h**	**5h**	99[c]
9	 **1i**	**5i**	99[c]

[a] Isolated yield after column chromatography.
[b] All products were characterized by ^{1}H NMR, ^{13}C NMR and mass spectroscopy (see experimental section).
[c] NMR spectra of the products **5a**,[10b] **5e**, [11c] **5h**, and **5i**,[10a] are in accordance with the literature.

3. Conclusion

In conclusion, we have demonstrated a novel, highly efficient, fast and green procedure for nitro-Michael addition of indoles and pyrroles using a combination of water and microwave irradiation without any catalyst. The ability of water to carry out the reaction is due to a change of its chemical and physical properties under

Table 4
Michael addition of pyrrole and various indoles to β-nitrostyrene in water under microwave irradiation[a]

Entry	Product		Yield[b] (%)
1		**7a**	99[c]
2		**9a**	90[c]
3		**11a**	99[c]
4		**13a**	90[d]
5		**15a**	80[d]
6		**17a**	94[c]
7		**19a**	90[c]

[a] P=200 W, T=150 °C, reaction time=6 min.
[b] Isolated yield after column chromatography.
[c] NMR spectra of the adducts **7a**,[10b] **9a**,[10b] **11a**, [13e] **17a**,[11c] **19a**,[15] are accordance with the literature.
[d] The products were characterized by ^{1}H NMR, ^{13}C NMR and mass spectroscopy (see experimental section).

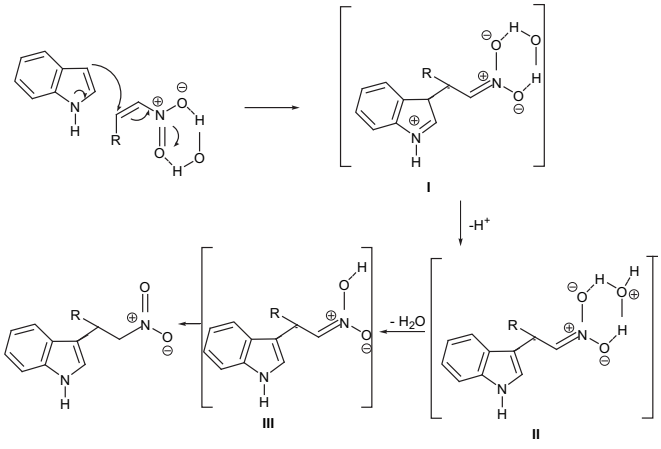


Figure 1.

microwave mediated 'superheated conditions'. As opposed to conventional heating, the our procedure is a better efficient method with time respect (6 min.) and yields (up to 80%) unaffected by the electronic density of the indole ring and by the nature of the substituent on the β-nitrostyrene.

The reaction is applicable to different kinds of pyrroles and indoles, which makes it a useful and attractive strategy for the synthesis of natural products with indole and pyrrole moiety.

4. Experimental

4.1. General remarks

Microwave reactions were conducted using a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC). The machine consists of a continuous focused microwave power delivery system with operator-selectable power output from 0 to 300 W. Reactions were performed in glass vessels (capacity 10 mL) equipped with a magnetic stirring bar and sealed with a septum. The target temperature was set and fixed during the irradiation. Settings and readings for power (W) and pressure were taken from the instrument. Melting points were determined in open capillary tubes using a Electro Thermal 9100 series apparatus. Elemental analyses were performed on the FlashEA 1112 Series with Thermal Conductivity Detector (Thermo Electron Corporation). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 250 (250.13 MHz for ^{1}H; 62.89 MHz for ^{13}C), Bruker DRX 300 (300 MHz for ^{1}H; 75 MHz for ^{13}C) and Bruker DRX 400 (400 MHz for ^{1}H; 100 MHz for ^{13}C). *J* values are given in hertz. The ^{1}H chemical shifts were referenced to the solvent peak: $CDCl_3$ (7.26 ppm), and the ^{13}C chemical shifts were referenced to the solvent peak: $CDCl_3$ (77.0 ppm). Mass spectra were recorded on a Micromass Quattro micro API mass spectrometer (EI, 70 eV).

Thin-layer chromatography was performed on Merck Kiesegel 60 (0.25 mm) in appropriate solvent. Column chromatography was carried out using silica gel 60 (70–230 mesh ASTM, Merck).

4.2. General procedure for the nitro-Michael addition

A sealed 10 mL glass tube containing a solution of the nitroalkenes[16a,b] (0.5 mmol) and pyrrole (2.5 mmol) or indole derivative (0.6 mmol) in distilled water (1 mL) was introduced in the cavity of a microwave reactor (CEM Co., Discover System, single-mode reactor) and irradiated for an appropriate time and temperature under magnetic stirring. After cooling to room temperature by an air-flow, the tube was removed from the rotor, the reaction mixture was diluted with ethyl acetate and poured into a separating funnel. Water was added and the organic material was extracted. The combined ethyl acetate extracts were then dried over $MgSO_4$ and after removal of the solvent the mixture was purified by short column chromatography (hexane/AcOEt as eluent) to give pure products.

The compounds **3a**,[10b] **5a**,[10b] **5e**,[11c] **5h**,[10a] **5i**,[10a] **7a**,[10b] **9a**,[10b] **11a**,[13e] **17a**,[11c] **19a**,[15] were previously described.

*4.2.1. 1-Methyl-2-[2-nitro-1-(4-nitrophenyl)ethyl]-1H-pyrrole (**3b**).* Yield (136 mg, 99%) as a brown oil; (found: C, 56.74; H, 4.80; N, 15.30. $C_{13}H_{13}N_3O_4$ requires C, 56.72; H, 4.76; N, 15.27%); R_f (hexane/AcOEt 8/2) 0.30; ν_{max}(neat)=3410, 2950, 1597, 1550, 1514, 1497; δ_H (300 MHz; $CDCl_3$) 3.36 (s, 3H), 4.75–4.84 (m, 1H), 4.95–5.03 (m, 2H), 6.13–6.14 (m, 2H), 6.60–6.63 (m, 1H), 7.36–7.39 (d, *J*=8.7 Hz, 2H), 8.16–8.19 (d, *J*=8.7 Hz, 2H). δ_C (75 MHz; $CDCl_3$) 33.8, 41.2, 78.7, 106.5, 107.3, 123.6, 124.3, 127.7, 129.0, 145.4, 147.5; *m*/*z* 275 (M^+).

*4.2.2. 2-[1-(4-Bromophenyl)-2-nitroethyl]-1-methyl-1H-pyrrole (**3c**).* Yield (151 mg, 99%) as dark brown oil; (found: C, 50.46; H, 4.22; N, 9.05. $C_{13}H_{13}BrN_2O_2$ requires C, 50.50; H, 4.24; N, 9.06%); R_f (hexane/AcOEt 8/2) 0.42; ν_{max}(liquid film)=3434, 2920, 1550, 1473, 1428, 1380, 1196, 1121, 1098, 1075, 1030, 996, 885, 791, 726; δ_H (400 MHz; $CDCl_3$) 3.35 (s, 3H), 4.72 (dd, *J*=11.7, 7.5 Hz, 1H), 4.84 (t, *J*=7.5 Hz, 1H), 4.94 (dd, *J*=11.7, 7.5 Hz, 1H), 6.11–6.12 (m, 2H), 6.58–6.60 (m, 1H), 7.05 (d, *J*=8.3 Hz, 2H), 7.44 (d, *J*=8.3 Hz, 2H). δ_C (75 MHz; $CDCl_3$) 33.8, 41.1, 79.1, 106.0, 107.0, 121.9, 123.2, 128.6, 129.6, 132.2, 137.1; *m*/*z* 308(M^+).

*4.2.3. 2-[1-(4-Chlorophenyl)-2-nitroethyl]-1-methyl-1H-pyrrole (**3d**).* Yield (129 mg, 99%) as dark brown oil; (found: C, 58.96; H, 4.93; N, 10.56. $C_{13}H_{13}ClN_2O_2$ requires C, 58.99; H, 4.95; N, 10.58%); R_f (hexane/AcOEt 8/2) 0.40; ν_{max}(liquid film)=3430, 2940, 1551, 1475, 1430, 1383, 1199, 1124, 1096, 1070, 1027, 994, 881, 787, 724; δ_H (400 MHz; $CDCl_3$) 3.35 (s, 3H), 4.73 (dd, *J*=12.1, 7.7 Hz, 1H), 4.87 (t, *J*=7.7 Hz, 1H), 4.93 (dd, *J*=12.1, 7.7 Hz, 1H), 6.11–6.12 (m, 2H), 6.59–6.60 (m, 1H), 7.11 (d, *J*=8.4 Hz, 2H), 7.29 (d, *J*=8.4 Hz, 2H). δ_C (62.89 MHz; $CDCl_3$) 33.7, 41.0, 79.1, 106.0, 106.9, 123.1, 128.6, 129.0, 129.2, 133.7, 136.5; *m*/*z* 264 (M^+).

*4.2.4. 2-[1-(4-Methoxyphenyl)-2-nitroethyl]-1-methyl-1H-pyrrole (**3e**).* Yield (108 mg, 83%) as brown oil; (found: C, 64.57; H, 6.18; N, 10.73. $C_{14}H_{16}N_2O_3$ requires C, 64.60; H, 6.20; N, 10.76%); R_f (Hexane/AcOEt 8/2) 0.32; ν_{max}(liquid film)=3420, 3005, 2910, 2056, 1894, 1721, 1610, 1555, 1379, 1250, 1177, 1030, 914, 843, 798, 727; δ_H (300 MHz; $CDCl_3$) 3.34 (s, 3H), 3.77 (s, 3H), 4.71 (dd, *J*=11.5, 7.4 Hz, 1H), 4.82 (t, *J*=7.4 Hz, 1H), 4.93 (dd, *J*=11.5, 7.4 Hz, 1H), 6.09–6.11 (m, 2H), 6.57–6.58 (m, 1H), 6.83 (d, *J*=8.8 Hz, 2H),7.07 (d, *J*=8.8 Hz, 2H). δ_C (75 MHz; $CDCl_3$) 33.7, 40.9, 55.1, 79.5, 105.5, 106.7, 114.3, 122.8, 128.8, 129.8, 131.1, 159.0; *m*/*z* 260 (M^+).

*4.2.5. 2-[1-(2-Methoxyphenyl)-2-nitroethyl]-1-methyl-1H-pyrrole (**3f**).* Yield (126 mg, 97%) as brown oil; (found: C, 64.57; H, 6.17; N, 10.75. $C_{14}H_{16}N_2O_3$ requires C, 64.60; H, 6.20; N, 10.76%); R_f (hexane/AcOEt 8/2) 0.30; ν_{max}(liquid film)=3431, 2940, 2358, 1603, 1554, 1490, 1380, 1243, 1120, 1030, 913, 802, 726; δ_H (400 MHz; $CDCl_3$) 3.34 (s, 3H), 3.92 (s, 3H), 4.80 (d, *J*=7.8 Hz, 2H), 5.36 (t, *J*=7.8 Hz, 1H), 6.10–6.12 (m, 1H), 6.17–6.18 (m, 1H), 6.58–6.59 (m, 1H), 6.79–6.92 (m, 3H), 7.23–7.27 (m, 1H). δ_C (62.9 MHz; $CDCl_3$) 33.4, 34.7, 55.4, 77.3, 106.4, 106.8, 110.4, 121.0, 122.5, 125.9, 128.8, 129.0, 129.3, 156.3; *m*/*z* 260 (M^+).

*4.2.6. N,N-Dimethyl-4-[1-(1-methyl-1H-pyrrol-2-yl)-2-nitroethyl]-benzeneamine (**3g**).* Yield (131 mg, 96%) as red oil; (found: C, 65.88; H, 6.99; N, 15.34. $C_{15}H_{19}N_3O_2$ requires C, 65.91; H, 7.01; N, 15.37%); R_f (hexane/AcOEt 8/2) 0.31; ν_{max}(liquid film)=3400, 2930, 1550, 1384, 1293; δ_H (400 MHz; $CDCl_3$) 2.93 (s, 6H), 3.35 (s, 3H), 4.70 (dd, *J*=11.9, 7.6 Hz, 1H), 4.78 (t, *J*=7.6 Hz, 1H), 4.91 (dd, *J*=11.9, 7.6 Hz, 1H), 6.08–6.11 (m, 2H), 6.56–6.57 (m, 1H), 6.65 (d, *J*=8.6 Hz, 2H), 7.01 (d, *J*=8.6 Hz, 2H). δ_C (75 MHz; $CDCl_3$) 33.7, 40.4, 40.9, 79.7, 105.4, 106.6, 112.8, 122.6, 128.5, 130.0, 131.4, 149.8; *m*/*z* 273 (M^+).

*4.2.7. 1-Methyl-2-(2-nitro-1-p-tolyl-ethyl)-1H-pyrrole (**3h**).* Yield (119.5 mg, 99%) as dark yellow oil, (found: C, 68.79; H, 6.57; N, 11.45. $C_{14}H_{16}N_2O_2$ requires C, 68.83; H, 6.60; N, 11.47%); R_f (hexane/AcOEt 8/2) 0.60; ν_{max}(liquid film)=3390, 2920, 1544, 1515, 1440, 1380, 1193, 1124, 1032; δ_H (400 MHz; $CDCl_3$) 2.31 (s, 3H), 3.35 (s, 3H), 4.72 (dd, *J*=12.1, 7.6 Hz, 1H), 4.83 (t, *J*=7.6 Hz, 1H), 4.93 (dd, *J*=12.0, 8.0 Hz, 1H), 6.09–6.11 (m, 2H), 6.57–6.58 (m, 1H), 7.05 (d, *J*=8.0 Hz, 2H), 7.12 (d, *J*=8.0 Hz, 2H). δ_C (100 MHz; $CDCl_3$) 21.0, 33.7, 41.3, 79.5, 105.7, 106.7, 122.8, 127.7, 129.1, 129.7, 135.0, 137.5; *m*/*z* 244 (M^+).

*4.2.8. 2-[1-(Furan-2-yl)-2-nitroethyl]-1-methyl-1H-pyrrole (**3i**).* Yield (88.4 mg, 80%) as brown oil; (found: C, 59.95; H, 5.46; N, 12.70. $C_{11}H_{12}N_2O_3$ requires C, 59.99; H, 5.49; N, 12.72%); R_f

(hexane/AcOEt 8/2) 0.51; ν_{max}(liquid film)=3430, 3125, 2920, 2360, 1554, 1503, 1433, 1375, 1337, 1184, 1147, 1095, 1012, 918, 797, 730; δ_H (400 MHz; $CDCl_3$) 3.54 (s, 3H), 4.85 (dd, *J*=12.8, 8.0 Hz, 1H), 4.92–5.04 (m, 2H), 6.04–6.05 (m, 1H), 6.09–6.12 (m, 2H), 6.29–6.31 (m, 1H), 6.60–6.61 (m, 1H), 7.36–7.37 (m, 1H). δ_C (100 MHz; $CDCl_3$) 33.6, 35.2, 79.0, 106.5, 107.1, 107.6, 110.4, 122.9, 127.0, 142.5, 151.1; *m*/*z* 221 (M^+).

*4.2.9. 2-Methyl-3-[2-nitro-1-(4-nitro-phenyl)-ethyl]-1H-indole (**5b**).* Yield (161 mg, 99%) as brown solid, mp 165–166 °C; (found: C, 62.73; H, 4.67; N, 12.95. $C_{17}H_{15}N_3O_4$ requires C, 62.76; H, 4.65; N, 12.92%); R_f (hexane/AcOEt 8/2) 0.49; ν_{max}(neat)=3750, 2920, 2850, 1549, 1515, 1347; δ_H (400 MHz; $CDCl_3$) 2.41 (s, 3H), 5.07–5.13 (m, 1H), 5.25–5.31 (m, 2H), 7.03–7.07 (m, 1H), 7.02–7.16 (m, 1H), 7.27–7.30 (m, 2H), 7.47 (d, *J*=8.8, 2H), 8.11 (br s, 1H), 8.13 (d, *J*=8.8 Hz, 2H). δ_C (100 MHz; $CDCl_3$) 11.9, 40.2, 80.9, 102.5, 110.9, 117.9, 120.0, 121.6, 123.9, 126.2, 128.2, 133.1, 135.4, 146.8, 147.0; *m*/*z* 325 (M^+).

*4.2.10. 3-[1-(4-Bromo-phenyl)-2-nitro-ethyl]-2-methyl-1H-indole (**5c**).* Yield (177.2 mg, 99%) as pale yellow oil; (found: C, 56.81; H, 4.18; N, 7.82. $C_{17}H_{15}BrN_2O_2$ requires C, 56.84; H, 4.21; N, 7.80%); R_f (hexane/AcOEt 8/2) 0.47; ν_{max}(liquid film)=3420, 2920, 1549, 1487, 1375; δ_H (300 MHz; $CDCl_3$) 2.33 (s, 3H), 5.04–5.20 (m, 3H), 7.06–7.25 (m, 5H), 7.35 (d, *J*=7.8 Hz, 1H), 7.41 (d, *J*=8.4 Hz, 2H), 8.03 (br s, 1H). δ_C (75 MHz; $CDCl_3$) 11.9, 39.9, 78.2, 108.2, 110.8, 118.3, 119.8, 121.0, 121.4, 126.5, 129.0, 131.8, 132.9, 135.3, 138.5; *m*/*z* 358 (M^+).

*4.2.11. 3-[1-(4-Chloro-phenyl)-2-nitro-ethyl]-2-methyl-1H-indole (**5d**).* Yield (155.4 mg, 99%) as pale yellow solid, mp 155–156 °C; (found: C, 64.90; H, 4.78; N, 8.91. $C_{17}H_{15}ClN_2O_2$ requires C, 64.87; H, 4.80; N, 8.90%); R_f (hexane/AcOEt 8/2) 0.48; ν_{max}(KBr)=3413, 3056, 2918, 1546, 1463, 1375; δ_H (400 MHz; $CDCl_3$) 2.36 (s, 3H), 5.06 (dd, *J*=10.8, 7.4 Hz, 1H), 5.13–5.23 (m, 2H), 7.02–7.06 (m, 1H), 7.10–7.14 (m, 1H), 7.24–7.27 (m, 5H), 7.32 (d, *J*=8 Hz, 1H), 8.02 (br s, 1H). δ_C (100 MHz; $CDCl_3$) 12.0, 39.8, 78.3, 108.3, 110.8, 118.3, 119.8, 121.4, 126.5, 128.6, 128.8, 132.9, 135.4, 137.4, 138.0; *m*/*z* 314 (M^+).

*4.2.12. 3-[1-(2-Methoxy-phenyl)-2-nitro-ethyl]-2-methyl-1H-indole (**5f**).* Yield (150.3 mg, 97%) as brown solid, mp 128–129 °C; (found: C, 69.68; H, 5.90; N, 9.07. $C_{18}H_{18}N_2O_3$ requires C, 69.66; H, 5.85; N, 9.03%); R_f (hexane/AcOEt 8/2) 0.30; ν_{max} (KBr)=3407, 2925, 1612, 1549, 1509, 1463, 1375, 1249, 1114, 1025, 743; δ_H (250 MHz; $CDCl_3$) 2.36 (s, 3H), 3.88 (s, 3H), 5.15 (dd, *J*=12.4, 9.9 Hz, 1H), 5.26 (dd, *J*=12.4, 5.8 Hz, 1H), 5.48 (dd, *J*=9.9, 5.8 Hz, 1H), 6.86–7.37 (m, 8H), 7.81 (br s, 1H). δ_C (62.9 MHz; $CDCl_3$) 11.8, 35.6, 55.2, 77.5, 107.7, 110.4, 110.6, 118.7, 119.4, 119.5, 120.4, 120.8, 127.2, 128.2, 128.3, 133.2, 135.2, 156.7; *m*/*z* 310 (M^+).

*4.2.13. Dimethyl-{4-[1-(2-methyl-1H-indol-3-yl)-2-nitro-ethyl]-phenyl}-amine (**5g**).* Yield (155.0 mg, 96%) as orange solid, mp 161–162 °C; (found: C, 70.59; H, 6.58; N, 13.01. $C_{19}H_{21}N_3O_2$ requires C, 70.57; H, 6.55; N, 12.99%); R_f (hexane/AcOEt 8/2) 0.31; ν_{max}(KBr)=3425, 2980, 1547, 1380, 1290; δ_H (400 MHz; $CDCl_3$) 2.38 (s, 3H), 2.90 (s, 3H), 5.07–5.19 (m, 3H), 6.67 (d, *J*=8.8 Hz, 2H), 7.0–7.48 (m, 7H), 7.90 (br s, 1H). δ_C (62.9 MHz; $CDCl_3$) 12.0, 39.7, 40.8, 79.0, 109.2, 110.6, 111.8, 113.1, 118.8, 119.6, 121.1, 126.9, 128.1, 131.5, 132.6, 135.4, 149.4; *m*/*z* 323 (M^+).

*4.2.14. 5-Methoxy-2-methyl-3-(2-nitro-1-phenyl-ethyl)-1H-indole (**13a**).* Yield (139.5 mg, 96%) as pale yellow oil; (found: C, 69.72; H, 5.88; N, 9.01. $C_{18}H_{18}N_2O_3$ requires C, 69.66; H, 5.85; N, 9.03%); R_f (hexane/AcOEt 8/2) 0.47; ν_{max}(liquid film)=3398, 3065, 1560, 1480, 1372; δ_H (400 MHz; $CDCl_3$) 2.31 (s, 3H), 3.78 (s, 3H), 5.05–5.13 (m, 1H), 5.17–5.24 (m, 2H), 6.77–6.83(m, 1H), 7.11 (d, *J*=8.0 Hz, 1H), 7.35–7.23 (m, 6H), 7.86 (br s, 1H). δ_C (100 MHz; $CDCl_3$) 11.9, 40.2, 55.8, 78.3, 101.4, 108.4, 110.3, 111.2, 127.0, 127.2, 128.7, 130.0, 133.7, 139.3, 153.8; *m*/*z* 310 (M^+).

*4.2.15. 5-Chloro-2-methyl-3-(2-nitro-1-phenyl-ethyl)-1H-indole (**15a**).* Yield (125.6 mg, 80%) as colorless oil; (found: C, 64.83; H, 4.77; N, 8.88. $C_{17}H_{15}ClN_2O_2$ requires C, 64.87; H, 4.80; N, 8.90%); R_f (hexane/AcOEt 8/2) 0.31; ν_{max}(liquid film)=3410, 2920, 1548, 1510, 1432; δ_H (300 MHz; $CDCl_3$) 2.29 (s, 3H), 5.06–5.21 (m, 3H), 7.02–7.11 (m, 2H), 7.22–7.34 (m, 6H), 7.93 (br s, 1H). δ_C (75.5 MHz; $CDCl_3$) 11.9, 40.2, 78.4, 108.4, 111.7, 117.8, 121.5, 125.2, 127.1, 127.3, 127.8, 128.9, 133.7, 134.7, 138.9; *m*/*z* 314 (M^+).

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References and notes

1. (a) Horvàth, I. T. *Green Chem.* **2008**, *10*, 1024; (b) Lancester, M. *Green Chemistry: An Introductory Text*; Royal Society of Chemistry: Cambridge, 2002; (c) Clark, J. H.; Macquarrie, D. *Handbook of Green Chemistry & Technology*; Blackwell: Oxford, 2002; (d) Matlack, A. S. *Introduction to Green Chemistry*; Marcel Dekker: New York, NY, 2001; (e) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University: New York, NY, 1988.
2. Selected examples (a) Caddick, S.; Fitzmaurice, R. *Tetrahedron* **2009**, *65*, 3325; (b) Polshettiwar, V.; Varma, R. S. *Acc. Chem. Res.* **2008**, *41*, 629; (c) Roberts, B. A.; Strauss, C. R. *Acc. Chem. Res.* **2005**, *38*, 653; (d) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250; (e) *Microwaves in Organic Synthesis*, 2nd ed.; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2006; Vol. 1.
3. Narayan, S.; Fokin, D. V.; Sharpless, K. B. In *Organic Reactions in Water: Principle, Strategies and Applications*; Lindstrom, U. M., Ed.; Blackwell: Oxford, 2007; Chapter 11, pp 350–364.
4. (a) Kerton, F. M. In *RSC Green Chemistry Book Series*; Clark, J. H., Kraus, G. A., Eds.; Royal Society of Chemistry: Cambridge, 2009; Chapter 3, pp 44–65; (b) Polshettiwar, V.; Varma, R. S. *Chem. Soc. Rev.* **2008**, *37*, 1546; (c) Polshettiwar, V.; Varma, R. S. *Pure Appl. Chem.* **2008**, *80*, 777; (d) Dallinger, D.; Kappe, C. O. *Chem. Rev.* **2007**, *107*, 2563; (e) Kremsner, J. M.; Kappe, C. O. *Eur. J. Org. Chem.* **2005**, 3672.
5. Liotta, C. L.; Hallet, J. P.; Pollet, P.; Eckert, C. A. In *Organic Reactions in Water: Principle, Strategies and Applications*; Lindstrom, U. M., Ed.; Blackwell Publishing: Oxford, 2007; Chapter 9, pp 256–300.
6. Selected examples (a) Gong, G.-X.; Zhou, J.-F.; An, L.-T.; Duan, X.-L.; Ji, S.-J. *Synth. Commun.* **2009**, *39*, 497; (b) Dolzhenko, A. V.; Pastorin, G.; Dolzhenko, A. V.; Chui, W. K. *Tetrahedron Lett.* **2009**, *50*, 2124; (c) Qu, G.-R.; Wu, J.; Wu, Y.-Y.; Zhang, F.; Guo, H.-M. *Green Chem.* **2009**, *11*, 760; (d) Marzaro, G.; Guiotto, A.; Chilin, A. *Green Chem.* **2009**, *11*, 774; (e) Dandia, A.; Singh, R.; Jain, A. K.; Singh, D. *Synth. Commun.* **2008**, *38*, 3543; (f) Nolen, S. A.; Liotta, C. L.; Eckert, C. A.; Glaser, R. *Green Chem.* **2003**, *5*, 663 and references therein.
7. (a) Saracoglu, N. In *Top. Heterocycl. Chem.*; Gupta, R. R., Ed.; Springer: Berlin/Heidelberg, 2007; Chapter 1, pp 1–61; (b) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 453; (c) Sundberg, R. D. Pyrroles and their Benzo Derivatives: Synthesis and Applications. In *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 4, p 313.
8. (a) Arya, P.; Joseph, R.; Chou, D. T. H. *Chem. Biol.* **2002**, *9*, 145; (b) Zhang, H.-C.; Ye, H.; Moretto, A. F.; Brumfield, K. K.; Maryanoff, B. E. *Org. Lett.* **2000**, *2*, 89; (c) Thomas, L. G.; *Heterocyclic Chemistry*, 3rd ed.; Longman: England, 1997; Vol. 11, Part 1, 2, and 5.
9. Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, NY, 2001.
10. Selected examples (a) Hari, G. S.; Nagaraju, M.; Murthyc, M. *Synth. Commun.* **2008**, *38*, 100; (b) Lin, C.; Hsu, J.; Sastry, M.N.V.; Fang, H.; Tu, Z.; Liu, J.-T.; Ching-Fa, Y. Tetrahedron, 2005, 61, 11751. (c) Dessole, G.; Herrera, R. P.; Ricci, A. *Synlett* **2004**, 2374; (d) Yadav, J. S.; Abraham, S.; Reddy, B. V. S.; Sabitha, G. *Synthesis* **2001**, 2165; (e) Harrington, P. E.; Kerr, M. A. *Synlett* **1966**, 1047.
11. (a) Ballini, R.; Gabrielli, S.; Palmieri, A.; Petrini, M. *Tetrahedron* **2008**, *64*, 5435; (b) Bartoli, G.; Di Antonio, G.; Giuli, S.; Marcantoni, E.; Marcolini, M.; Paletti, M. *Synthesis* **2008**, *2*, 320; (c) An, G. L.-T.; Zou, J.-P.; Zhang, L. L.; Zhang, Y. *Tetrahedron Lett.* **2007**, *48*, 4297; (d) Bartoli, G.; Bosco, M.; Giuli, S.; Giuliani, A.; Lucarelli, L.; Marcantoni, E.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2005**, *70*, 1941; (e) Ballini, R.; Clemente, R. R.; Palmieri, A.; Petrini, M. *Adv. Synth. Catal.* **2006**, *348*, 191; (f) Yadav, J. S.; Abraham, S.; Reddy, B. V. S.; Sabitha, G. *Tetrahedron Lett.* **2001**, *42*, 8063.
12. (a) Kusurkar, R. S.; Alkobati, N. H.; Gokule, A. S.; Puranik, V. *G. Tetrahedron* **2008**, *64*, 1654; (b) Kusurkar, R. S.; Alkobati, N. A.; Gokule, A. S.; Chaudhari, P. M.; Waghchaure, P. B. *Synth. Commun.* **2006**, *36*, 1075; (c) Zhan, Z.-P.; Yang, W.-Z.; Yang, R.-F. *Synlett* **2005**, 2425; (d) Chakrabarty, M.; Basak, R.; Ghosh, N.; Harigaya, Y. *Tetrahedron* **2004**, *60*, 1941.
13. (a) Das, B.; Thirupathi, P.; Kumar, R. A.; Reddy, K. R. *Catal. Commun.* **2008**, *9*, 635; (b) Wu, P.; Wan, Y.; Cai, J. *Synlett* **2008**, 1193; (c) Azizi, N.; Arynasab, F.; Saidi, M. R. *Org. Biomol. Chem.* **2006**, *4*, 4275; (d) Firouzabadi, H.; Iranpoor, N.; Nowrouzi, F.

Chem. Commun. **2005**, 789; (e) Baldini, M.; Melchiorre, P.; Melloni, A.; Umani-Ronchi, A. *Synthesis* **2002**, 1110.
14. Habib, P. M.; Kavala, V.; Kuo, C.-W.; Yao, C.-F. *Tetrahedron Lett.* **2008**, *49*, 7005.
15. Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6576.
16. (a) Richter-Egger, D. L.; Tesfai, A.; Flamm, S. J.; Tucker, S. A. *J. Chem. Educ.* **2001**, *78*, 1375; (b) Trost, B. M.; Muller, C. *J. Am. Chem. Soc.* **2008**, *130*, 2438.
17. Habib, P. M.; Kavala, V.; Raju, B. R.; Kuo, C.-W.; Huang, W.-C.; Yao, C.-F. *Eur. J. Org. Chem.* **2009**, *26*, 4503.