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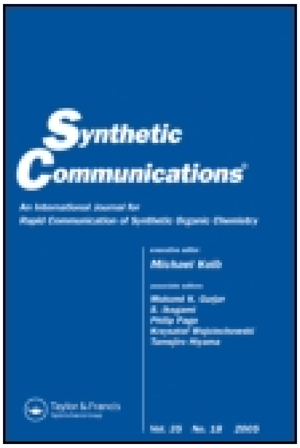

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Thermal and Microwave-Assisted Conjugate Additions of Indole on Electron-Deficient Nitro-olefins

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Thermal and Microwave-Assisted Conjugate Additions of Indole on Electron-Deficient Nitro-olefins

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Abstract: Conjugate addition of indole on nitro-olefins was carried out by three different methods: (i) thermal heating in a sealed tube, (ii) reaction with indolyl magnesium iodide, and (iii) microwave irradiation. Comparison of the results indicated that the microwave technique is most efficient.

Keywords: Conjugate additions, indole, microwave, nitro-olefins

Indole is an important system present in many biologically active and naturally occurring compounds.[1] The increased nucleophilic reactivity of the 3-position of the indole ring is used[2–4] for building up the subsequent rings of indole alkaloids. One of the earlier methods to get the addition at only the 3-position of the indole ring was the use of indolyl, Grignard reagent.[5] Presence of protic solvents[6,7] or Lewis acids[8–11] was required for the other methods such as nucleophilic Friedel–Crafts–type conjugate addition of indole to alkylate indole at the 3-position. The earlier methods required longer time and gave low yields of the products, which were due to polymerization. Recently these reactions are reported using catalysts such as bismuth triflate,[12] indium halides,[13,14] or ytterbium triflate[15] [$Yb(OTf)_3 \cdot 3H_2O$] as Lewis acids. In a recent report,[16] the $CeCl_3 \cdot 7H_2O \cdot NaI\text{-}SiO_2$ system was used for the conjugate addition. As a part of our interest in alkylation of indole at C-3, we studied direct alkylation of indole with nitro-olefins under microwave irradiation. In addition, we have

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also carried out comparative studies involving thermal heating, Grignard reagent–mediated reaction, and microwave irradiation.

Initially indole was treated with methyl magnesium iodide to get indolyl magnesium iodide, which on treatment with nitrostyrene **1** at room temperature gave the expected product **12** in 71% yield in 5 min (Scheme 1). Furthermore, indole and nitrostyrene **1** in dry benzene were heated at 120 °C in a sealed tube for 2 days. Compound **12** was isolated in 80% yield. Finally indole and nitrostyrene **1** were loaded on silica gel (60–120 mesh) and then irradiated in a microwave oven for 2 min to get **12** in almost quantitative yield.

The structure of **12** was supported by IR, ^{1}H NMR, ^{13}C NMR, DEPT spectra, and elemental analysis. From this result, it was apparent that the microwave-irradiation reaction was most efficient with respect to time and yield. Various nitro-olefins (**2**–**8**) and indole provide products (**13**–**19**) in good yields (see Tables 1 and 2).

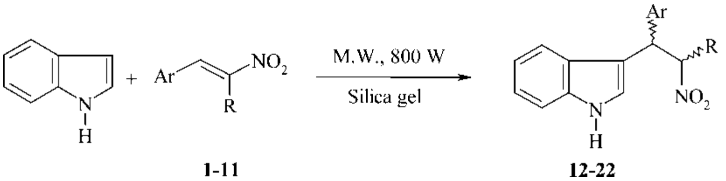
Alkylation of indole with α-methyl nitro-alkenes (**9**–**11**) using microwave irradiation furnished the corresponding Michael addition products (**20**–**22**) (Scheme 1) in good yields (see Table 2). The ^{1}H NMR of **20**–**22** revealed the presence of diastereomers in the ratio of 7:3 for **20**, 1.1:1 for **21** and 1:1 for **22**.

In summary, microwave irradiation is the method of choice for the conjugate addition of indole to nitro-alkenes.

EXPERIMENTAL

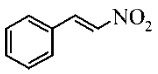
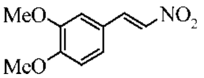
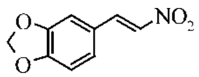
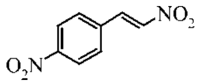
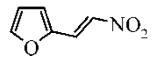
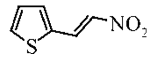
General Remarks

Thin-layer chromatographic analysis was performed using silica gel on glass plates and was detected under UV. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian 300 S instrument. FT-IR spectra were recorded on a Perkin-Elmer 1600. Mass spectra were recorded on a Shimadzu QP 5050.



Scheme 1. **1, 12**: Ar = phenyl, R = H; **2, 13**: Ar = 3,4-dimethoxyphenyl, R = H; **3, 14**: Ar = 3,4-methylenedioxyphenyl, R = H; **4, 15**: Ar = *p*-nitro phenyl, R = H; **5, 16**: Ar = 2-furyl, R = H; **6, 17**: Ar = 2-thienyl, R = H; **7, 18**: Ar = *p*-methoxyphenyl, R = H; **8, 19**: Ar = *m*-methoxyphenyl, R = H; **9, 20**: Ar = 2-furyl, R = CH_3; **10, 21**: Ar = *p*-methoxyphenyl, R = CH_3; **11, 22**: Ar = *p*-nitro phenyl, R = CH_3.

Table 1. Time and yields for the products **12–17** using Grignard reaction, sealed tube reaction, and microwave reaction

			Grignard reaction		Sealed tube reaction		Microwave reaction	
Entry	Electrophile	Product	Time	Yield (%)	Time (h)	Yield (%)	Time (min)	Yield (%)
1		**12**	5 min	71	48^a	80	2	95
2		**13**	20 h	73	72^b	53	10	80
3		**14**	20 h	73	72^b	60	10	89
4		**15**	5 min	35	48^b	65	10	84
5		**16**	5 min	60	48^a	85	2	86
6		**17**	5 min	58	48^a	82	2	93

[a] Heating at 120 °C.
[b] Heating at 140 °C.

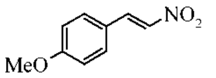
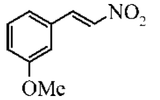
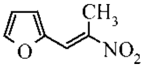
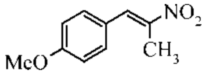
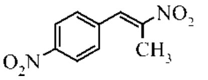
General Procedure for Reaction of Nitro-olefins (1–6) with Indolyl Magnesium Iodide

Nitro-olefins (**1**–**6**) (0.003 mol) in dry toluene (5 ml) were slowly added to freshly prepared indolyl magnesium iodide[17] in ether. After the reaction was completed as judged by TLC, the reaction mixture was quenched by adding water, extracted with dichloromethane, washed with brine, dried over sodium sulphate, and evaporated. The residue was chromatographed on silica gel using hexane–ethyl acetate as an eluent to give **12**–**17**.

General Procedure for Reaction of Nitro-olefins (1–6) with Indole in a Sealed Tube

Nitro-olefins (**1**–**6**) (0.003 mol) and indole (0.0032 mol) in dry benzene (5 ml) were heated for two days at 120 °C. The crude product obtained after removal of the solvent was chromatographed on silica gels using hexane–ethyl acetate to get the pure product (**12**–**17**).

Table 2. Time and yields for the products **18–22** using the microwave reaction

Entry	Electrophile	Product	Time (min)	Yield (%)
1		**18**	10	92
2		**19**	10	94
3		**20**	20	96
4		**21**	1	87
5		**22**	1	82

General Procedure for Reaction of Nitro-olefins (1–12) with Indole using Microwave Irradiation

A mixture of indole (0.0012 mol) and nitro-olefin (0.001 mol) was loaded on silica gel (60–120 mesh) and was irradiated in a microwave oven. The completion of the reaction was confirmed by TLC. The same silica gel was loaded on a silica-gel column, and chromatographic separation using hexane–ethyl acetate furnished the products (**12–22**).

Data

Compound 12: Mp 99 °C. IR (Nujol): 3393 cm^{-1} (NH), 1532 and 1373 cm^{-1} (NO_2). ^{1}H NMR δ 4.95 (dd, 1H, $J = 8.2$, 12.3 Hz), 5.08 (dd, 1H, $J = 7.6$, 12.3 Hz), 5.20 (t, 1H, $J = 8.2$ Hz), 7.04–7.18 (m, 2H), 7.18–7.4 (m, 7H), 7.44 (d, 1H, $J = 7.9$ Hz), 8.1 (bs, 1H). ^{13}C NMR δ 41.47, 76.58, 111.36, 114.22, 118.84, 119.86, 121.56, 122.61, 125.99, 127.51, 127.70, 128.86, 136.37, 139.09. $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.3. Found: C, 72.35; H, 5.45.

Compound 13: Mp 145 °C. IR (Nujol): 3343 cm^{-1} (NH), 1551 and 1371 cm^{-1} (NO_2). ^{1}H NMR δ 3.80 (s, 3H), 3.84 (s, 3H), 4.89 (dd, 1H, $J = 8.2$, 12.1 Hz), 5.03 (t, 1H, $J = 7.1$ Hz), 5.1 (dd, 1H, $J = 7.7$, 15.6 Hz), 6.77–6.88 (m, 3H), 7.0 (d, 1H, $J = 2.5$ Hz), 7.06 (t, 1H, $J = 7.7$ Hz), 7.18 (t, 1H, $J = 7.1$ Hz), 7.35 (d, 1H, $J = 8.2$ Hz), 7.44 (d, 1H, $J = 7.7$ Hz), 8.1 (bs, 1H). ^{13}C NMR δ 41.31, 55.89, 55.92, 79.73, 111.20, 111.35, 111.49, 114.55, 118.96, 119.73, 119.95, 121.65, 122.70, 126.1, 131.72, 136.56, 148.36, 149.18. $C_{18}H_{18}N_2O_4$: C, 66.24; H, 5.56. Found: C, 66.44; H, 5.60.

Compound 14: Mp 145 °C. IR (Nujol): 3400 cm^{-1} (NH), 1542 and 1376 cm^{-1} (NO_2). ^{1}H NMR δ 4.87 (dd, 1H, $J = 8.2$, 12.1 Hz), 5.02 (t, 1H, $J = 7$ Hz), 5.12 (dd, 1H, $J = 7.9$, 13.7 Hz), 5.9 (AB quartet, 2H, $J = 1.3$, 4.9 Hz), 6.7–6.8 (m, 3H), 7.07–7.1 (m, 2H), 7.18 (t, 1H, $J = 7.9$ Hz), 7.35 (d, 1H, $J = 7.9$ Hz), 7.42 (d, 1H, $J = 7.9$ Hz), 8.0 (bs, 1H). ^{13}C NMR δ 41.19, 55.78, 79.61, 111.06, 111.22, 111.36, 114.45, 118.85, 119.6, 119.84, 121.53, 122.59, 125.99, 131.58, 136.43, 148.24, 149.06. $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.55. Found: C, 65.83; H, 4.78.

Compound 15: Mp 142 °C. IR (Nujol): 3401 cm^{-1} (NH), 1598, 1545, 1345, and 1375 cm^{-1} (NO_2). ^{1}H NMR δ 4.98 (dd, 1H, $J = 8.8$, 12.6 Hz), 5.08 (dd, 1H, $J = 7.1$, 12.6 Hz), 5.26 (t, 1H, $J = 8.2$ Hz), 7.02 (m, 2H), 7.21 (t, 1H, $J = 8.5$ Hz), 7.3–7.4 (m, 2H), 7.47 (d, 2H, $J = 8.8$ Hz), 8.13 (d, 2H, $J = 8.5$ Hz), 8.22 (bs, 1H). ^{13}C NMR δ 41.17, 78.66, 111.62, 112.83, 118.45, 120.28, 121.58, 123.06, 124.14, 125.57, 128.73, 136.41, 146.67, 147.23. $C_{16}H_{13}N_3O_4$: C, 61.73; H, 4.21. Found: C, 61.57; H, 4.73.

Compound 16: Mp 69 °C. IR (Nujol): 3399 cm^{-1} (NH), 1548 and 1376 cm^{-1} (NO_2). ^{1}H NMR δ 4.91 (dd, 1H, $J = 7.3$, 12.6 Hz), 5.06 (dd, 1H, $J = 7.9$, 12.6 Hz), 5.26 (t, 1H, $J = 7.6$ Hz), 6.16 (d, 1H, $J = 3.2$ Hz), 6.31 (t, 1H, $J = 2.9$ Hz), 7.13 (m, 2H), 7.23 (t, 1H, $J = 8.79$ Hz), 7.38 (m, 2H), 7.56 (d, 1H, $J = 7.9$ Hz), 8.14 (bs, 1H). ^{13}C NMR δ 35.65, 77.81, 107.34, 110.43, 111.51, 118.65, 120.01, 122.59, 122.69, 125.6, 136.22, 142.2, 152.1. $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72. Found: C, 65.65; H, 5.01.

Compound 17: Mp 94 °C. IR (Nujol): 3412 cm^{-1} (NH), 1548 and 1378 cm^{-1} (NO_2). ^{1}H NMR δ 4.96–5.10 (m, 2H), 5.47 (t, 1H, $J = 7.6$ Hz), 6.93–7.0 (m, 2H), 7.2–7.26 (m, 4H), 7.38 (d, 1H, $J = 8.2$ Hz), 7.52 (d, 1H, $J = 8.2$ Hz), 8.14 (bs, 1H). ^{13}C NMR δ 35.65, 76.57, 107.35, 110.43, 111.51, 118.65, 120.02, 122.6, 122.69, 125.61, 136.23, 142.22, 152.1. $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44. Found: C, 61.65; H, 4.63.

Compound 18: Mp 150–152 °C. IR (Nujol): 3381 cm^{-1} (NH), 1375 and 1548 cm^{-1} (NO_2). ^{1}H NMR δ 3.82 (s, 3H), 4.93 (dd, 1H, $J = 8.5$, 12.36 Hz), 5.08 (dd, 1H, $J = 7.4$, 12 Hz), 5.18 (t, 1H, $J = 7.9$ Hz), 6.88 (d, 2H, $J = 8.8$ Hz), 7.06–7.14 (m, 2H), 7.21–7.3 (m, 3H), 7.4 (d, $J = 8.2$ Hz), 7.4 (d, 1H, $J = 7.9$ Hz), 8.13 (bs, 1H). ^{13}C NMR δ 40.32, 54.62, 79.24, 111.07, 112.92, 113.43, 117.92, 118.54, 121.23, 121.26, 125.35, 128.12, 130.89, 136.03, 157.94. MS: m/z 296 (M$^+$), 249, 236, 44 (100).

Compound 19: Mp Oily liquid. IR (Nujol): 3423 cm^{-1}(NH), 1377 and 1550 cm^{-1} (NO_2). ^{1}H NMR δ 3.66 (s, 3H), 4.81 (dd, 1H, $J = 8.5$, 12.37 Hz), 4.92 (dd, 1H, $J = 7.7$, 12.37 Hz), 5.1 (t, 1H, $J = 7.9$ Hz), 6.72 (dd, 1H, $J = 2.4$, 8.2 Hz), 6.82 (m, 3H), 7.0 (t, 1H, $J = 6.87$ Hz), 7.08–7.2 (m, 3H), 7.4 (d, 1H, $J = 7.9$ Hz), 7.98 (bs, 1H). ^{13}C NMR δ 41.4, 55.08, 79.28, 111.29, 112.25, 113.75, 113.82, 118.60, 119.64, 119.83, 121.44, 122.35, 125.81, 129.71, 136.15, 140.67, 159.57. MS: m/z 296 (M^+), 249 (100), 236.

Compound 20: Mp 153–154 °C. IR (Nujol): 3415 cm^{-1} (NH), 1546 and 1355 cm^{-1} (NO_2). Diasteriomeric ratio 7:3. ^1H NMR δ 1.48 (d, 3H, $J = 6.6$ Hz), 1.57 (d, 3H, $J = 6.6$ Hz), 4.94 (m, 2H), 5.29 (m, 2H), 6.77 (m, 4H), 7.12 (m, 10H), 7.65 (d, 2H, $J = 7.7$ Hz), 8.12 (bs, 2H). MS: m/z 270 (M^+), 224, 223, 196 (100).

Compound 21 (one diastereomer): Mp 170–172 °C. IR (Nujol): 3381 cm^{-1} (NH), 1375 and 1548 cm^{-1} (NO_2). ^1H NMR δ 1.6 (d, 3H, $J = 6.3$ Hz), 3.72 (s, 3H), 4.7 (d, 1H, $J = 11$ Hz), 5.36 (sextet, 1H), 6.76 (d, 2H, $J = 8.2$ Hz), 7.08–7.58 (m, 6H), 7.6 (d, 1H, $J = 7.7$ Hz), 8.10 (bs, 1H). ^{13}C NMR δ 19.32, 47.01, 55.2, 87.83, 111.3, 113.94, 114.76, 118.89, 119.9, 121.42, 122.51, 126.46, 128.5, 132, 135.99, 158.4. MS: m/z 310 (M^+), 263, 249, 236 (100).

Compound 22: Mp 174–176 °C. IR (Nujol): 3406 cm^{-1} (NH), 1548 and 1344 cm^{-1} (NO_2). ^1H NMR δ 1.6 (d, 3H, $J = 6.6$ Hz), 1.8 (d, 3H, $J = 6.6$ Hz), 4.87 (d, 1H, $J = 11$ Hz), 4.96 (d, 1H, $J = 10.17$ Hz), 5.32 (m, 2H), 6.99 (m, 14H), 8.12 (m, 4H), 8.25 (bs, 2H). MS: m/z 325 (M^+), 278, 251 (100), 252.

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