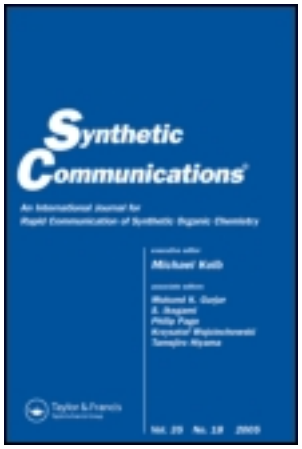

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Boric Acid-Mediated Mild and Efficient Friedel-Crafts Alkylation of Indoles with Nitro Styrenes

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BORIC ACID–MEDIATED MILD AND EFFICIENT FRIEDEL–CRAFTS ALKYLATION OF INDOLES WITH NITRO STYRENES

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An efficient method has been developed for the synthesis of indole 3-derivatives by the Friedel–Crafts alkylation of indole with nitro olefins in presence of boric acid in aqueous medium.

Keywords: Boric acid; indole; N-methyl indole; nitro styrene; water

INTRODUCTION

Indole and its derivatives constitute a core structure of many biologically active natural products some of the indole derivatives are also known to possess important biological[1] and pharmacological[2] activity. For example, hapalindole alkaloids exhibit antibacterial and antimycotic activity, and there is continuous interest in the synthesis of indole derivatives. Commonly indole 3-derivatives are prepared by the Michael addition of indoles with β-nitrostyrenes in the presence of protic[3] or Lewis acid[4] such as SmI_3, $ScCO_2$, $CeCl_3$. $7H_2O$–NaI-SiO_2, $Yb(OTf)_3$, $InCl_3$, $InBr_3$, and I_2 have been reported for this reaction. Sulfamic acid[5] also reported to catalyze the Michael addition of indole in solvent free condition. Recently catalyst-free conjugate addition of indole to β-nitro styrene was reported in aqueous medium[6] at higher temperature with extended reaction time.

Prospectus of water as a media in organic synthesis is an area of great interest because of economical and environmental benefits. Recently boric acid[7] has been employed for various transformations because it is mild and readily available. In addition, boric acid is an environmentally safe reagent. In fact, some pharmaceutical and agricultural products contain boric acid. We envisioned to accelerate the efficiency of the reaction by the addition of boric acid. In our work on the development of green and clean methodologies, we describe the boric acid-promoted efficient and mild Friedel–Crafts alkylation of indole with β-nitro styrene.

Thus the reaction of indole (1 eq.) with β-nitrostyrene (1 eq.) in the presence of boric acid (1 eq.) in water (Scheme 1) leads to high yield of expected product in

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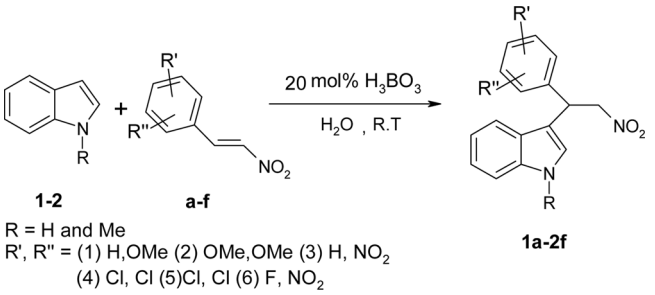


Scheme 1. Friedel–Crafts alkylation of indole with nitro olefins.

10 min. This reaction enhancement may be attributed to the presence boric acid. Next we optimize the ratio of boric acid to catalyze this transformation. It was gratifying to note that 20 mol% of boric acid was found suitable for optimum yield (85%) of product. The same reaction with 10 mol% of boric acid afforded the expected product in 40% in 45 min. We have not observed any substantial increase in the yield of product after addition of more boric acid (30 mol %).

To study the effect of substituent on the reactivity of styrene, we examined the substituted β-nitrostyrene having electron withdrawal and electron donation and observed that nitrostyrene with *m*-nitro substituted (entries 1c and 2c) reacted very rapidly with indole to yield the desired product in high yield. In the electron donating (entry-1a, 1b, 2a and 2b) however, substituent on nitrosryrene suppress the reaction of indole. Further the reaction of N-methyl indole with nitrosyrene gives high yield of product within a short time (entry-2c). This fact suggests that the presence of methyl in nitrogen increases the electron density at third position of indole. Though the reaction is reported only in aqueous medium, the present study showed remarkably great enhancement in the reaction using boric acid which may save the time and energy.

In conclusion we have demonstrated a very rapid Friedel–Crafts alkylation of indole with nitro styrene in the presence of boric acid. The high yield, shortest reaction time, mild reaction condition and aqueous medium are the important features of the present protocol.

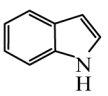
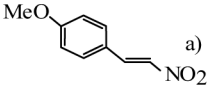
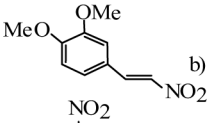
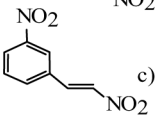
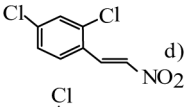
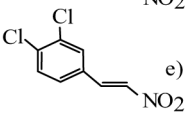
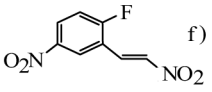
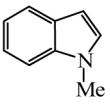
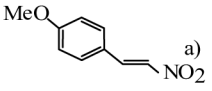
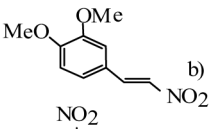
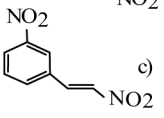
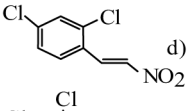
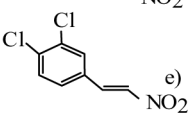
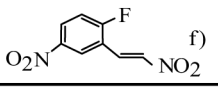
EXPERIMENTAL

General Procedure: Synthesis of 3-(2-Nitro-1-(3-nitrophenyl) ethyl)-1H-Indole

To a mixture of indole (1 eq.) and Nitrostyrene (1 eq.) in water was added boric acid (20 mol %) the mixture was stirred at room temperature for appropriate time (see Table 1). After completion of the reaction as indicated by TLC, the mixture was diluted with water. It was extracted with ethyl acetate, combine organic layer washed with water dried over sodium sulphate and solvent removed under reduced pressure. The crude product was purified by column chromatography using ethyl acetate-hexane (9:1) as an eluent. All the compounds were characterized by spectral data.

Compound 1a: ^{1}HNMR ($CDCl_3$, 300 MHz) δ (ppm) 3.77 (s, 3H), 4.88–5.02 (m, 2H), 5.12 (t, 1H, J = 7.6 Hz), 6.20–6.85 (m, 2H), 7.01–7.10 (m, 2H), 7.17–7.35

Table 1. Friedel–Crafts alkyation of indoles with nitrostyrene

Entry	Indole	Nitrostyrene	Product[a]	Time (min.)	Yield[b] (%)
1		 a)	**1a**	20	80
		 b)	**1b**	25	80
		 c)	**1c**	10	90
		 d)	**1d**	18	83
		 e)	**1e**	15	85
		 f)	**1f**	18	82
2		 a)	**2a**	15	80
		 b)	**2b**	20	84
		 c)	**2c**	9	95
		 d)	**2d**	15	85
		 e)	**2e**	13	88
		 f)	**2f**	14	85

[a] All products were characterized by NMR, IR and mass spectroscopy.
[b] Yield refers to pure products after chromatography.

(m, 4H), 7.45 (d, 1H), 8.06 (s, 1H). IR (KBr) $\nu = 700$, 753, 906, 1120, 1280, 1338, 1378, 1430, 1510, 1550, 1598, 2853, 3010, 3358 cm^{-1}. EIMS: m/z 296 (M^+). **Compound 1b**: ^{1}HNMR ($CDCl_3$, 300 MHz) δ (ppm) 3.78 (s,3H), 3.84 (s, 3H) 4.80–5.04 (m, 2H), 5.10 (t, 1H, J = 7.8 Hz), 6.75–6.86 (m, 3H), 6.96 (d, 1H,

J = 2.0 Hz), 7.03 (t, 1H, J = 7.5 Hz), 7.15 (t, 1H, J = 7.4 Hz), 7.30 (d, 1H, J = 8.1 Hz), 7.40 (d, 1H, J = 7.9 Hz), 8.05 (br, s, 1H). IR (KBr) $\nu = 662$, 694, 753, 862, 904, 1024, 1102, 1143, 1260, 1339, 1377, 1424, 1459, 1514, 1550, 1595, 2853, 2927, 3011, 3367 cm^{-1}. EIMS: m/z 326(M^+). **Compound 1c**: ^{1}HNMR ($CDCl_3$, 300 MHz) δ (ppm) 4.90–5.10 (m, 2H), 5.28 (t, 1H, J = 7.9 Hz), 7.02–7.04 (d, 1H, J = 2.4 Hz), 7.04–7.08 (d, 1H, J = 7.3 Hz), 7.15–7.21 (m, 1H), 7.31–7.36 (d, 2H, J = 8.6 Hz), 7.52 (t, 1H, J = 7.9 Hz), 7.66–7.72 (d, 1H, J = 7.7 Hz), 8.11–8.15 (m, 2H), 8.20 (br, s, 1H). IR (KBr) $\nu = 742$, 807, 1098, 1348, 1461, 1527, 1553, 1616, 1645, 2853, 2923, 3416 cm^{-1}. EIMS: m/z 334 (M^+Na). **Compound 1d**: ^{1}HNMR ($CDCl_3$, 300 MHz) δ (ppm) 4.80–5.00 (m, 2H), 5.62 (t, 1H, J = 7.7 Hz), 7.00–7.08 (m, 3H), 7.12–7.19 (m, 2H), 7.30 (d, 2H, J = 7.9 Hz), 7.46(d, 1H, J = 1.5 Hz), 8.08(br, s, 1H). IR (KBr) $\nu = 752$, 1101, 1375, 1461, 1552, 1636, 2855, 2922, 3419 cm^{-1}. EIMS: m/z 358(M^+Na). **Compound 1e**: ^{1}HNMR (CDCl3, 300 MHz) δ (ppm) 4.80–5.04 (m, 2H), 5.12 (t, 1H), 6.96–6.99 (m, 1H), 7.06 (t, 1H, J = 7.5 Hz), 7.13–7.21 (m, 2H), 7.28–7.37 (m, 3H), 7.40 (br, s, NH). IR (KBr) $\nu = 674$, 746, 1029, 1130, 1195, 1376, 1422, 1464, 1551, 1627, 2854, 2923, 3421 cm^{-1}. EIMS: m/z 358 (M^+ Na). **Compound 1f**: ^{1}HNMR ($CDCl_3$, 300 MHz) δ (ppm) 5.02–5.10 (m, 2H), 5.54 (t, 1H, J = 7.9 Hz), 7.08–7.12 (m, 1H), 7.13–7.16 (t, 1H, J = 2.2 Hz), 7.18–7.24 (m, 1H), 7.26 (s, 1H), 7.28–7.38 (m, 2H), 7.42 (d, 1H, J = 7.9 Hz), 8.14–8.18 (m, 1H), 8.21(br, s, 1H). IR (KBr) $\nu = 703$, 744, 832, 906, 1103, 1248, 1346, 1420, 1461, 1554, 1628, 2853, 2922, 3418 cm^{-1}. EIMS: m/z 329(M^+). **Compound 2a**: ^{1}HNMR ($CDCl_3$, 300 MHz) δ (ppm) 3.78 (s, 3H), 3.82 (s, 3H), 4.81–5.01 (m, 2H), 5.07 (t, 1H, J = 7.7 Hz), 6.21–6.81 (m, 2H), 7.02–7.12 (m, 2H), 7.15–7.38 (m, 2H), 7.42 (m, 2H), 7.54 (m, 1H). IR (KBr) $\nu = 707$, 763, 1112, 1280, 1336, 1410, 1520, 1599, 2873, 3011, 3354 cm^{-1}. EIMS: m/z 333 (M^+Na). **Compound 2b**: ^{1}HNMR ($CDCl_3$, 300 MHz) δ (ppm) 3.74 (s, 3H), 3.79 (s, 3H), 3.82 (s, 3H), 4.79–4.98 (m, 2H), 5.05 (t, 1H, J = 7.8 Hz), 6.74 (d, 3H, J = 7.8 Hz), 6.82 (m, 1H), 7.01 (t, 1H, J = 7.8 Hz), 7.16 (t, 1H, J = 7.8 Hz), 7.21 (s, 1H), 7.38 (d, 1H, J = 7.8 Hz). IR (KBr) $\nu = 677$, 734, 761, 803, 840, 861, 905, 1020, 1089, 1133, 1155, 1240, 1264, 1303, 1332, 1374, 1428, 1462, 1511, 1550, 1608, 2925, 3003, 3047, 3119 cm^{-1}. EIMS: m/z 363(M^+Na). **Compound 2c**: ^{1}HNMR ($CDCl_3$, 300 MHz) δ (ppm) 3.80 (s, 3H), 4.91–5.07 (m, 2H), 5.25 (t, 1H, J = 8.2 Hz), 6.88 (s, 1H), 7.04 (t, 1H, J = 7.8z), 7.18–7.22 (t, 1H, J = 6.8 Hz, J = 7.8 Hz), 7.25 (m, 2H), 7.33 (d, 1H, J = 7.8 Hz), 7.51 (t, 1H, J = 7.8 Hz), 7.67 (d, 1H, J = 7.8 Hz), 8.13 (d, 1H, J = 7.8 Hz), 8.19 (br, s, 1H). IR (KBr) $\nu = 690$, 740, 769, 898, 1089, 1218, 1347, 1375, 1432, 1473, 1528, 1617, 2854, 2924, 3040 cm^{-1}. EIMS: m/z 326 ($M^+ + 1$). **Compound 2d**: ^{1}HNMR ($CDCl_3$, 300 MHz) δ (ppm) 3.79 (s, 3H), 4.85–4.93 (m, 2H), 5.61 (t, 1H, J = 7.5 Hz), 6.90 (s, 1H), 7.03 (m, 1H), 7.13–7.28 (m, 2H), 7.30–7.38 (m, 1H), 7.40 (d, 1H, J = 1.5 Hz), 7.45 (s, 1H), 7.62 (d, 1H, J = 8.3 Hz). IR (KBr) $\nu = 700$, 742, 810, 870, 1020, 1230, 1333, 1370, 1420, 1520, 1616, 2923, 3040 cm^{-1}. EIMS: m/z 372(M^+Na). **Compound 2e**: ^{1}HNMR ($CDCl_3$, 300 MHz) δ (ppm) 3.78 (s, 3H), 4.78–5.02 (m, 2H), 5.11 (t, 1H, J = 7.7 Hz), 6.80 (s, 1H), 7.05 (t, 1H, J = 7.9 Hz), 7.14–7.25 (m, 3H), 7.33 (d, 1H, J = 7.9 Hz), 7.35–7.42 (d, 2H, J = 7.9 Hz). IR (KBr) $\nu = 707$, 743, 818, 868, 1030, 1077, 1132, 1245, 1334, 1375, 1403, 1471, 1552, 1616, 2923, 3056 cm^{-1}. EIMS: m/z 349 (M^+). **Compound 2f**: ^{1}HNMR ($CDCl_3$, 300 MHz) δ(ppm) 3.80 (s, 3H), 4.97–5.06 (m, 2H), 5.49 (t, 1H, J = 8.2 Hz), 6.93 (s, 1H), 7.08 (t, 1H, J = 7.8 Hz), 7.19–7.28 (m, 3H), 7.43 (d, 1H, J = 7.8 Hz), 8.14–8.20 (m, 2H). IR (KBr) $\nu = 743$, 833, 905, 1014,

1085, 1122, 1247, 1247, 1345, 1375, 1474, 1527, 1552, 1586, 1623, 2853, 2923, 3044 cm^{-1}. EIMS: m/z 343 (M^+1).

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REFERENCES

1. Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970.
2. (a) Kalir, A.; Szara, S. Synthesis and pharmacological activity of fluorinated tryptamine derivatives. *J. Med. Chem.* **1963**, *6*, 716–719; (b) Moore, R. E.; Cheuk, C.; Yang, X. Q.; Patterson, G. M. L.; Bonjouklian, R.; Smita, T. A.; Myderse, J.; Foster, R. S.; Jones, N. D.; Skiatzendrtuber, J. K.; Deeter, J. B. Hapalindoles, antibacterial and antimycotic alkaloids from the cyanophyte hapalosiphon fontinalis. *J. Org. Chem.* **1987**, *52*, 1036–1043; (c) Noland, W. E.; Christensen, G. M.; Sauer, G. L.; Dutton, G. G. S. The reaction of nitroolefins with indole. *J. Am. Chem. Soc.* **1955**, *77*, 456–457.
3. (a) Bandini, M.; Fagioli, M.; Uma-Ronchi, A. Solid acid–catalysed Michael type conjugate addition of indoles to electron-poor C=C bonds: Towards high atom economical semi-continuous processes. *Adv. Synth. Catal.* **2004**, *346*, 545–548; (b) Szmuskovicz, J. The reaction of substituted indoles with methyl vinyl ketone: New synthesis of 2-methylcarbazole. *J. Am. Chem. Soc.* **1957**, *79*, 2819–2821.
4. (a) Zhang-Ping, Z.; Kai, L. Microwave-accelerated samarium triiodide catalyzed conjugate addition of indoles with electron-deficient olefins. *Synlett* **2005**, *10*, 1551–1554; (b) Komoto, I.; Kobayashi, S. Lewis acid catalysis in supercritical carbon dioxide. Use of poly(ethylene glycol) derivatives and perfluoroalkylbenzenes as surfactant molecules which enable efficient catalysis in $ScCO_2$. *J. Org. Chem.* **2004**, *69*, 680–688; (c) Bartoli, G.; Bosco, M.; Giuli, S.; Giuliani, A.; Lucarelli, L.; Marcantoni, E.; Sambri, L.; Torregiani, E. Efficient preparation of 2-indolyl-1-nitroalkane derivatives employing nitroalkenes as versatile Michael acceptors: New practical linear approach to alkyl 9*H*-β-carboline-4-carboxylate. *J. Org. Chem.* **2005**, *70*, 1941–1944; (d) Harrington, P. E.; Kerr, M. A. Reaction of indoles with electron deficient olefins catalyzed by $Yb(OTf)_3 \cdot 3H_2O$. *Synlett* **1996**, 1047–1048; (e) Yadav, J. S.; Abraham, S.; Reddy, B. V. S.; Sabitha, G. $InCl_3$-catalysed conjugate addition of indoles with electron-deficient olefines. *Synthesis* **2001**, 2165–2169; (f) Bandini, M.; Melchiorre, P.; Melloni, A.; Umani-Ronchi, A. A practical indium tribromide catalysed addition of indoles to nitro alkenes in aqueous media. *Synthesis* **2002**, 1110–1114; (g) Chunch, L.; Jianming, H.; Sastry, M. N. V.; Hulin, F.; Zhijay, T.; Ju-Tsung, L.; Ching-Fa, Y. I_2-catalysed Michael addition of indole and pyrrole to nitroolefins. *Tetrahedron* **2005**, *61*, 11751–11757.
5. Li-Tao, A.; Jian-Ping Z.; Li-Li, Z.; Yong, Z. Sulfamic acid catalysed Michael addition of indoles and pyrrole to electron-deficient nitroolefins under solvent-free condition. *Tetrahedron Lett.* **2007**, *48*, 4297–4300.
6. Pateliya, M. H.; Veerababurao, K.; Chun-Wei, K.; Ching-Fa, Y. Catalyst-free aqueous-mediated conjugative addition of indoles to β-nitrostyrenes. *Tetrahedron Lett.* **2008**, *49*, 7005–7007.
7. (a) Todd, A. H.; Brendan, L. W.; Joanne, T. B. Boric acid catalyzed chemoselective esterfication of α-hydroxycarboxylic acids. *Org. Lett.* **2004**, *6*, 679–681; (b) Pingwah, T. Boric acid catalyzed amide formation from carboxylic acids and amines: N-Benzyl-4-phenylbutyramide. *Org. Synth.* **2005**, *81*, 262–268.