Simple and Efficient *Friedel–Crafts* Alkylation of 1*H*-Indole with Electron-Deficient Alkenes Promoted by Zinc Acetate

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An efficient method for the *Friedel–Crafts* alkylation of 1*H*-indole with nitro alkenes in the presence of zinc acetate is described. The procedure is applicable to a variety of nitro alkenes and substituted indoles, and the yields are very high.

Introduction. – A traditional method for *C*-alkylation at C(3) of 1*H*-indole is based on a *Michael* type addition reaction [1]. There are numerous methods for the functionalization of 1*H*-indole at C(3) based on the addition reaction approach. Triflates are known to promote conjugate addition of alkenes to 1*H*-indole (1.5 to 5 h) [2]. *C*-Alkylation of 1*H*-indole at C(3) has been reported in aqueous media using $InBr_3$ [3] as a catalyst with longer reaction time (16 h). Basic alumina [4] has been used as a catalyst for conjugate addition of nitro alkenes to 1*H*-indole. Recently, bis[acyl arenes] have been employed [5] for the addition to indole in toluene with extended reaction time (72 h). Sulfamic acid [6] has been reported as a catalyst for the *Michael* addition of nitro alkenes to 1*H*-indole in dry media. However, most of the methods suffer from certain drawbacks like the use of dry organic solvents, longer reaction times, or expensive reagents. In addition, some of the methods lack the generality towards substituted indoles [4]. $Zn(OAc)_2$ has become an attractive catalyst in organic synthesis because of efficiency and inexpensiveness. Recently, it has been successfully employed for many organic transformations [7].

Results and Discussion. – The reaction of 1*H*-indole with nitro alkenes was performed in different solvents like CH_2Cl_2, DMF, MeCN, and EtOH in the presence of $Zn(OAc)_2$ at room temperature (*Scheme*). EtOH was found to be the solvent of choice. We found that 5 mol-% of $Zn(OAc)_2$ was required for an optimum yield. When the amount of catalyst was reduced to 2 mol-%, a longer reaction time was required for the completion of the reaction.

Next, we examined the reaction of substituted indoles under optimized conditions. 2-Methyl-1*H*-indole (*Table*, *Entries 7–12*) and 7-methoxy-1*H*-indole (*Table*, *Entries 25–30*) reacted smoothly with nitro alkenes in the presence of $Zn(OAc)_2$ and resulted in the formation of the corresponding products in high yields. It is worth mentioning that with indoles bearing an electron-donating substituent such as Me or MeO, the reaction proceeds efficiently to give the expected products in good yields. However, substrates with electron-withdrawing groups like CN require longer reaction times for

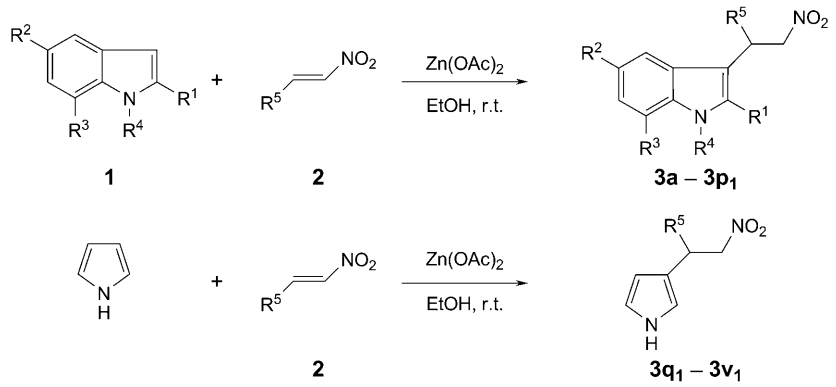
an optimum conversion. The reaction of the nitro alkenes with pyrrole (*Scheme*; *Table*, *Entries 43–48*) took place favorably under the optimized conditions to form the expected adducts in high yields.

In the literature, nitro alkenes containing a napth-1-yl substituent are not reported for *Michael* additions because of their low reactivity. However, the present reaction conditions are suitable for the reaction of indoles and pyrrole with 1-(2-nitroethenyl)naphthalene (*Table*, *Entries 5*, *11*, *17*, *23*, *29*, *35*, *41*, and *47*), which gave good yields.

It is reported that indoles bearing Br, CN, or Ph substituents failed to react with nitro alkenes. However, we have noticed that substituted 1*H*-indoles also react with electron-deficient alkenes under the present reaction conditions to afford alkylated products in high yields.

Further, we have extended this protocol to 1*H*-pyrrole which reacted with electron-deficient alkenes under the standard conditions in high yields to give the expected products (*Table*, *Entries 43–48*).

Scheme. Friedel–Crafts *Alkylation of 1*H-*Indoles with Electron-Deficient Alkenes Catalyzed by* $Zn(OAc)_2$



Conclusions. – We have demonstrated a general and efficient method for the *Michael* addition of electron-deficient alkenes to indoles. The method is applicable for a variety of alkenes. The products are isolated in high yields. In addition, easy workup and an inexpensive catalyst are the advantages of the present procedure.

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Experimental Part

General. All reactions were carried out without any special precautions in an atmosphere of air. Chemicals were purchased from *Fluka* and *S. D. Fine Chemicals*. TLC: precoated silica gel plates (SiO_2; *60* F_{254}, 0.2-mm layer; *E. Merck*). ^{1}H-NMR Spectra: *Varian 200* or *Bruker 300* spectrometer; in $CDCl_3$; δ in ppm, *J* in Hz. MS: *VG Autospec*; in *m*/*z*.

General Procedure. A mixture of 1*H*-indole **1** or 1*H*-pyrrole (1 mmol), nitro alkene **2** (1 mmol) and $Zn(OAc)_2$ (5 mol-%) in EtOH (4 ml) was vigorously stirred at r.t. for the appropriate time (see *Table*).

Table. Michael *Addition of 1*H-*Indole and 1*H-*Pyrrole to Nitro Alkenes Catalyzed by Zn(OAc)$_2$*

Entry	Substrate	R^1	R^2	R^3	R^4	R^5	Product[a])	Time [min]	Yield [%][b])
1	**1a**	H	H	H	H	Ph	**3a**	20	98
2	**1a**	H	H	H	H	2-Chlorophenyl	**3b**	25	96
3	**1a**	H	H	H	H	2-Nitrophenyl	**3c**	15	97
4	**1a**	H	H	H	H	4-Methoxyphenyl	**3d**	20	91
5	**1a**	H	H	H	H	Naphthalen-1-yl	**3e**	55	89
6	**1a**	H	H	H	H	Furan-2-yl	**3f**	72	88
7	**1b**	Me	H	H	H	Ph	**3g**	15	97
8	**1b**	Me	H	H	H	2-Chlorophenyl	**3h**	20	91
9	**1b**	Me	H	H	H	2-Nitrophenyl	**3i**	11	90
10	**1b**	Me	H	H	H	4-Methoxyphenyl	**3j**	14	87
11	**1b**	Me	H	H	H	Naphthalen-1-yl	**3k**	40	85
12	**1b**	Me	H	H	H	Furan-2-yl	**3l**	63	82
13	**1c**	H	Br	H	H	Ph	**3m**	25	90
14	**1c**	H	Br	H	H	2-Chlorophenyl	**3n**	32	87
15	**1c**	H	Br	H	H	2-Nitrophenyl	**3o**	27	91
16	**1c**	H	Br	H	H	4-Methoxyphenyl	**3p**	36	88
17	**1c**	H	Br	H	H	Naphthalen-1-yl	**3q**	60	82
18	**1c**	H	Br	H	H	Furan-2-yl	**3r**	79	80
19	**1d**	H	CN	H	H	Ph	**3s**	40	81
20	**1d**	H	CN	H	H	2-Chlorophenyl	**3t**	52	79
21	**1d**	H	CN	H	H	2-Nitrophenyl	**3u**	35	82
22	**1d**	H	CN	H	H	4-Methoxyphenyl	**3v**	47	77
23	**1d**	H	CN	H	H	Naphthalen-1-yl	**3w**	75	73
24	**1d**	H	CN	H	H	Furan-2-yl	**3x**	91	70
25	**1e**	H	MeO	H	H	Ph	**3y**	27	89
26	**1e**	H	MeO	H	H	2-Chlorophenyl	**3z**	35	88
27	**1e**	H	MeO	H	H	2-Nitrophenyl	**3a$_1$**	29	85
28	**1e**	H	MeO	H	H	4-Methoxyphenyl	**3b$_1$**	40	82
29	**1e**	H	MeO	H	H	Naphthalen-1-yl	**3c$_1$**	62	79
30	**1e**	H	MeO	H	H	Furan-2-yl	**3d$_1$**	81	77
31	**1f**	H	H	Et	H	Ph	**3e$_1$**	22	94
32	**1f**	H	H	Et	H	2-Chlorophenyl	**3f$_1$**	30	90
33	**1f**	H	H	Et	H	2-Nitrophenyl	**3g$_1$**	25	91
34	**1f**	H	H	Et	H	4-Methoxyphenyl	**3h$_1$**	27	88
35	**1f**	H	H	Et	H	Naphthalen-1-yl	**3i$_1$**	41	87
36	**1f**	H	H	Et	H	Furan-2-yl	**3j$_1$**	60	81
37	**1g**	H	H	H	Me	Ph	**3k$_1$**	35	88
38	**1g**	H	H	H	Me	2-Chlorophenyl	**3l$_1$**	42	84
39	**1g**	H	H	H	Me	2-Nitrophenyl	**3m$_1$**	30	86
40	**1g**	H	H	H	Me	4-Methoxyphenyl	**3n$_1$**	52	81
41	**1g**	H	H	H	Me	Naphthalen-1-yl	**3o$_1$**	75	79
42	**1g**	H	H	H	Me	Furan-2-yl	**3p$_1$**	94	72
43	1*H*-Pyrrole	–	–	–	–	Ph	**3q$_1$**	38	90
44	1*H*-Pyrrole	–	–	–	–	2-Chlorophenyl	**3r$_1$**	42	87
45	1*H*-Pyrrole	–	–	–	–	2-Nitrophenyl	**3s$_1$**	33	88
46	1*H*-Pyrrole	–	–	–	–	4-Methoxyphenyl	**3t$_1$**	49	81
47	1*H*-Pyrrole	–	–	–	–	Naphthalen-1-yl	**3u$_1$**	68	79
48	1*H*-Pyrrole	–	–	–	–	Furan-2-yl	**3v$_1$**	81	71

[a]) All the products exhibited physical and spectral (IR, NMR, MS) properties in accordance with the assigned structure. [b]) Yield after purification.

After completion of the reaction (as indicated by TLC), the solvent was removed under reduced pressure, then the mixture was diluted with H_2O and extracted with AcOEt. The org. layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude mixture was purified by column chromatography (CC) to obtain the pure product. The characteristic data of some representative compounds are given below.

*3-[1-(2-Chlorophenyl)-2-nitroethyl]-1*H-*indole* (**3b**). Brick colour solid. M.p. 142°. IR (KBr): 3438, 3060, 2919, 1546, 1379. ^{1}H-NMR (200 MHz, $CDCl_3$): 4.95 (*d*, *J* = 7.5, 2 H); 5.65 – 5.75 (*m*, 1 H); 7.00 – 7.50 (*m*, 9 H); 8.10 (br. *s*, 1 H). FAB-MS: 324 ($[M+Na]^+$), 302 ($[M+1]^+$), 100.

*3-[2-Nitro-1-(2-nitrophenyl)ethyl]-1*H-*indole* (**3c**). Semisolid. IR (KBr): 3423, 3045, 2933, 2865, 1602, 1547, 1450. ^{1}H-NMR (200 MHz, $CDCl_3$): 4.91 – 5.15 (*m*, 2 H); 5.82 (*t*, *J* = 7.5, 1 H); 6.90 (*t*, *J* = 7.5, 1 H); 7.02 – 7.10 (*m*, 1 H); 7.14 (*t*, *J* = 7.7, 1 H); 7.20 – 7.30 (*m*, 2 H); 7.30 – 7.70 (*m*, 2 H); 7.87 (*d*, *J* = 7.7, 1 H); 8.10 (br. *s*, 1 H). FAB-MS: 312 ($[M+1]^+$), 311 (M^+).

*3-[1-(Naphthalen-1-yl)-2-nitroethyl]-1*H-*indole* (**3e**). Black solid. M.p. 165°. IR (KBr): 3423, 3054, 2922, 2855, 1602, 1548, 1450. ^{1}H-NMR (200 MHz, $CDCl_3$): 5.00 – 5.10 (*m*, 2 H); 5.98 – 6.10 (*m*, 1 H); 7.00 (*t*, *J* = 7.3, 2 H); 7.18 (*t*, *J* = 7.3, 1 H); 7.29 (*d*, *J* = 8.0, 1 H); 7.30 – 7.40 (*m*, 4 H); 7.55 (*quint*, *J* = 7.3, 1 H); 8.00 (br. *s*, 1 H); 8.25 (*d*, *J* = 8.0, 1 H). FAB-MS: 339 ($[M+Na]^+$), 154.

*3-[1-(2-Chlorophenyl)-2-nitroethyl]-2-methyl-1*H-*indole* (**3h**). Brick colour solid. M.p. 121°. IR (KBr): 3414, 3058, 2918, 1547, 1461, 1376. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.40 (*s*, 3 H); 5.10 (*d*, *J* = 8.3, 2 H); 5.40 – 5.50 (*m*, 1 H); 7.00 – 7.50 (*m*, 8 H); 7.82 (br. *s*, 1 H). FAB-MS: 338 ($[M+Na]^+$), 315, 254, 102.

*3-[1-(4-Methoxyphenyl)-2-nitroethyl]-2-methyl-1*H-*indole* (**3j**). White solid. M.p. 120°. IR (KBr): 3431, 3011, 2936, 1602, 1550, 1367. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.45 (*s*, 3 H); 3.7 (*s*, 3 H); 5.00 – 5.20 (*m*, 3 H); 6.80 (*d*, *J* = 8.8, 2 H); 7.00 – 7.40 (*m*, 8 H); 7.81 (br. *s*, 1 H). FAB-MS: 310 (M^+).

*5-Bromo-3-[1-(2-chlorophenyl)-2-nitroethyl]-1*H-*indole* (**3n**). Brick colour solid. M.p. 140°. IR (KBr): 3444, 3130, 2920, 1548, 1458. ^{1}H-NMR (200 MHz, $CDCl_3$): 4.90 (*d*, *J* = 7.5, 2 H); 5.59 – 5.66 (*m*, 1 H); 7.10 – 7.50 (*m*, 8 H); 8.10 (br. *s*, 1 H). FAB-MS: 403 ($[M+Na]^+$), 380, 303, 210.

*5-Bromo-3-[1-(4-methoxyphenyl)-2-nitroethyl]-1*H-*indole* (**3p**). Orange colour solid. M.p. 145°. IR (KBr): 3385, 2921, 1609, 1546, 1510, 1248. ^{1}H-NMR (200 MHz, $CDCl_3$): 3.77 (*s*, 3 H); 4.80 – 5.10 (*m*, 3 H); 6.80 (*d*, *J* = 9.0, 2 H); 7.00 (*d*, *J* = 1.5, 1 H); 7.18 (*d*, *J* = 8.3, 2 H); 7.25 (*d*, *J* = 6.7, 2 H); 7.48 (*s*, 1 H); 8.05 (br. *s*, 1 H). FAB-MS: 377 ($[M+2]^+$), 352, 303, 134, 100.

*3-[1-(2-Chlorophenyl)-2-nitroethyl]-1*H-*indole-5-carbonitrile* (**3t**). Red colour solid. M.p. 136°. IR (KBr): 3382, 2922, 2853, 2220, 1616, 1543, 1429. ^{1}H-NMR (200 MHz, $CDCl_3$): 4.92 (*d*, *J* = 7.5, 2 H); 5.64 – 5.72 (*m*, 1 H); 7.05 (*d*, *J* = 7.5, 1 H); 7.18 (*t*, *J* = 7.5, 1 H); 7.22 – 7.40 (*m*, 4 H); 7.48 (*d*, *J* = 7.5, 1 H); 7.67 (*s*, 1 H); 8.70 (br. *s*, 1 H). FAB-MS: 349 ($[M+Na]^+$), 326 ($[M+1]^+$).

*3-[1-(2-Chlorophenyl)-2-nitroethyl]-5-methoxy-1*H-*indole* (**3z**). Brick colour solid. M.p. 122°. IR (KBr): 3452, 2926, 1550, 1477, 1207, 1034. ^{1}H-NMR (200 MHz, $CDCl_3$): 4.90 – 4.95 (*m*, 2 H); 5.65 (*t*, *J* = 7.5, 1 H); 6.72 – 6.82 (*m*, 2 H); 7.05 (*s*, 1 H); 7.15 – 7.20 (*m*, 4 H); 7.40 (*d*, *J* = 8.3, 1 H); 7.90 (br. *s*, 1 H). FAB-MS: 331 (M^+), 284, 270, 100.

*5-Methoxy-3-[2-nitro-1-(2-nitrophenyl)ethyl]-1*H-*indole* (**3a$_1$**). Semisolid. IR (KBr): 3432, 3054, 2922, 1598, 1549, 1445, 1250. ^{1}H-NMR (200 MHz, $CDCl_3$): 3.71 (*s*, 3 H); 5.00 – 5.10 (*m*, 2 H); 5.75 (*t*, *J* = 7.5, 1 H); 6.60 – 6.65 (*m*, 1 H); 6.79 (*dd*, *J* = 2.2, 9.0, 1 H); 7.08 – 7.10 (*m*, 1 H); 7.18 (*d*, *J* = 9.0, 1 H); 7.39 – 7.52 (*m*, 3 H); 7.90 (*d*, *J* = 7.5, 1 H); 8.00 (br. *s*, 1 H). FAB-MS: 341 (M^+).

*3-[1-(Furan-2-yl)-2-nitroethyl]-1*H-*pyrrole* (**3v$_1$**). Viscous liquid. IR (KBr): 3420, 2923, 2853, 1549. ^{1}H-NMR (200 MHz, $CDCl_3$): 4.70 – 4.91 (*m*, 2 H); 4.98 (*t*, *J* = 7.5, 1 H); 5.98 – 6.20 (*m*, 3 H); 6.27 – 6.36 (*m*, 1 H); 6.56 – 6.73 (*m*, 1 H); 7.35 – 7.41 (*m*, 1 H); 8.14 (br. *s*, 1 H). FAB-MS: 206 (M^+).

REFERENCES

[1] A. Palmieri, M. Petrini, E. Torregiani, *Tetrahedron Lett.* **2007**, *48*, 5653; D. J. Denhart, R. J. Mattson, J. L. Ditta, J. E. Macor, *Tetrahedron Lett.* **2004**, *45*, 3803.

[2] I. Komoto, S. Kobayashi, *Org. Lett.* **2002**, *4*, 1115; P. E. Harrington, M. A. Kerr, *Synlett* **1996**, 1047; M. M. Alam, R. Varala, S. R. Adapa, *Tetrahedron Lett.* **2003**, *44*, 5115.

[3] M. Bandini, P. Melchiorre, A. Melloni, A. Umani-Ronchi, *Synthesis* **2002**, 1110.

[4] R. Ballini, R. R. Clemente, A. Palmieri, M. Petrini, *Adv. Synth. Catal.* **2006**, *348*, 191.
[5] G. Dessole, R. P. Herraera, A. Ricky, *Synlett* **2004**, 2374.
[6] L.-T. An, J.-P. Zou, L.-L. Zhang, Y. Zhang, *Tetrahedron Lett.* **2007**, *48*, 4297.
[7] M. Murakami, N. Hasegawa, M. Hayashi, Y. Ito, *J. Org. Chem.* **1991**, *56*, 7356; E. Ramu, R. Varala, N. Sreelatha, S. R. Adapa, *Tetrahedron Lett.* **2007**, *48*, 7184; T. D. Lash, M. C. Johnson, *Tetrahedron Lett.* **1989**, *30*, 5697; B. A. Morrow, *J. Catal.* **1984**, *86*, 328; C. Ramakrishnan, *Tetrahedron Lett.* **2004**, *45*, 1441.

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