**SHORT PAPER**

*J. Chem. Research (S),*
2003, 664–665

# Reaction of indole and alkylindoles with ceric ammonium nitrate on silica gel

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Treatment of *N*-methylindole with CAN-on-$SiO_2$ furnished 2,2-bis(*N*-methyl-3'-indolyl)-*N*-methylindoxyl, whereas that of skatole, *N*-methyl and *N*-ethyl skatoles produced the respective 2-nitroskatoles along with 6-nitroskatole and *N*-methyl-5-nitroskatole.

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**Keywords**: indoles, nitration, CAN on silica gel, indoxyl, 2-, 5-, and 6-nitroskatoles

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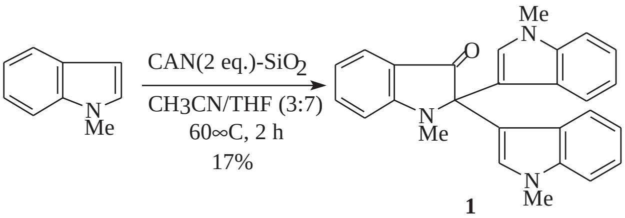
Ceric ammonium nitrate (CAN) is a well-known one-electron oxidant, used in the oxidation of numerous functionalities and in both C–C and C–N (*i.e.* nitration) bond formations.[1] However, the strong oxidising power of CAN often leads to undesired and overoxidised products, thereby limiting its synthetic potential. The increasing applications of reagents adsorbed on inorganic solid supports in organic synthesis[2] has led to the successful application of CAN adsorbed on silica gel (CAN-on-$SiO_2$) in the nitration of aromatics and heteroaromatics,[3a,b] oxidation of phenols,[3c] removal of silyl and trityl groups,[3d] *etc*. In continuation of our ongoing interest in the study of the reaction of indoles on silica gel[4a] and Montmorillonite K10 clay,[4b,c] we studied the reaction of indole and alkylindoles with CAN-on-$SiO_2$, and the resulting novel observations have been presented in this communication.

When each of indole and its 1-, 2- and 3-methyl derivatives was separately treated with CAN (one, two or more equivalents) in acetonitrile from low temperatures up to refluxing, either no reaction took place or the substrates decomposed completely. This failure induced us to try CAN-on-$SiO_2$, which unfortunately led to similar observations for both indole and 2-methylindole even after using up to four equivalents of CAN-on-$SiO_2$ and refluxing temperature. However, when *N*-methylindole was treated with two equivalents of CAN-on-$SiO_2$ at 60°C, it furnished in low yield a fluorescent product which analysed for $C_{27}H_{23}N_3O$, supported by HR MS. It was identified as 2,2-bis(*N*-methyl-3'-indolyl)-*N*-methylindoxyl (**1**) from its IR, $^1H$, $^{13}C$ NMR and mass spectral data (Scheme 1).

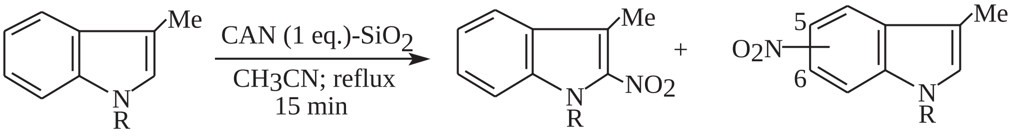


**1**

**Scheme 1** Reaction of *N*-methylindole with CAN-on-$SiO_2$ at 60 °C.

Earlier reports on the formation of the corresponding *N*-desmethyl trimer (**1:** *N*H instead of *N*Me) by the autoxidation of indole[5] suggested that **1** was also similarly formed by autoxidation of *N*-methylindole. This possibility was, however, ruled out by the fact that a similar treatment of *N*-methylindole without using CAN did not produce any product whatsoever. Conceivably, CAN-mediated oxidative radical coupling of the initially formed, unisolated *N*-methylindoxyl with two *N*-methylindole moieties led to the formation of **1**.

Separate treatments of each of skatole (**2a**) and its *N*-methyl (**2b**) and *N*-ethyl (**2c**) derivatives with stoichiometric amounts of CAN-on-$SiO_2$ under reflux furnished very quickly **3a** and **4a** from **2a**, the products **3b** and **4b** from **2b** and only **3c** from **2c**. The compound **3a** was identified from its spectral data as the known 2-nitroskatole, synthesised previously in 4.5%,[6a] 8.5%[6b] and 74%[6c] overall yields. The products **3b** and **3c** were similarly identified as the respective 2-nitroskatoles. The product **4a** appeared to be 5- or 6-nitroskatole from its $^1H$ and $^{13}C$ NMR spectral data. The HMQC and HMBC spectra, specially the HMBC correlation between $\delta$ 7.59 (1H, d, $J$ = 9 Hz, H-4), and the non-protonated carbon at $\delta$ 113.2 (C-3) established that **4a** was 6-nitroskatole. A survey of the literature[7] revealed that 5-nitro(alkyl)indoles do not show any UV absorption maximum beyond 335 nm, whereas 6-nitro(alkyl)indoles show a $\lambda_{max}$ around 360 nm or above.



**2a**: R=H
**2b**: R=Me
**2c**: R=Et

**3a**: 14%
**3b**: 17%
**3c**: 15%

**4a**: 9% (6-nitro)
**4b**: 8% (5-nitro)

**Scheme 2** Reaction of 3-methylindoles with CAN-on-$SiO_2$ at reflux in $CH_3CN$.

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Since **4b** showed the highest $\lambda_{max}$ at 334 nm, it was identified as the 5-nitro derivative. The lack of 5- or 6-nitration in the case of *N*-ethylskatole remains unexplained.

Over the years, the nitration of indoles at C-2 has been a problem.[6a] The only high-yielding method, that of Gribble *et al.*,[6c] requires carrying out the reaction at very low temperatures, *viz.* –78°C and –120°C. Our present method thus constitutes a simple alternate route to 2-nitroskatoles, although in low yields. The present study also exemplifies the dual nature of CAN, *viz.* a one-electron oxidant and a nitrating agent, and also underlines the role of silica gel in moderating the effect of CAN. The formation of the 3-indolone **1** assumes importance in view of the recent isolation of the corresponding desmethyl derivative as a bacterial metabolite having antibacterial activity.[8]

## Experimental

The IR spectra were recorded on a Nicolet FT-IR I-410 spectrophotometer, the $^1$H (500 MHz; $CDCl_3$), $^{13}$C (125 MHz), HMBC and HMQC NMR spectra on a Bruker DRX 500 NMR spectrometer, the EI mass spectra on a JEOL JMS-700T Mstation (LR, HR) or AEI MS 30 (LR) mass spectrometers and the UV spectra on a UV-2401 PC spectrophotometer. Microanalyses were carried out on a Dr Hoesli Analyser (Type A1; No.1058). Thin layer (TLC) and column chromatographies (CC) were performed on silica gel G plates (Merck, India) and silica gel (60-120 mesh; Qualigens, India), respectively. All the products were crystallised from $CH_2Cl_2$ – petroleum ether.

*Reaction with N-methylindole*: A solution of CAN (2.4 g, 4.4 mmol) in acetonitrile (3 ml) was adsorbed on silica gel (CC grade; 2 g) and air-dried. It was added to a solution of *N*-methylindole (262 mg; 2 mmol) in $CH_3CN$-THF (3:7; 40 ml) and stirred at 60 °C for 2 h. On completion of the reaction (TLC), the above mixture was adsorbed on fresh silica gel (CC), air-dried and leached with $CH_2Cl_2$ (3 × 25 ml). The solvent was distilled off from the $CH_2Cl_2$ extract and the resulting residue was purified by prep. TLC to furnish 2,2-*bis*(*N-methyl*-3'-*indolyl*)-*N-methylindoxyl* (**1**): Yield: 45 mg (17%); m.p. 180 °C; $\nu_{max}/cm^{-1}$ (KBr): 1701, 1612, 1467, 741; $\delta_H$ 7.65 and 6.82 (1H, d each, $J$ = 7.5/8 Hz), 7.54 and 6.74 (1H, t each, $J$ = 7.5 Hz), 7.35 and 7.28 (2H, d each, $J$ = 8 Hz), 7.18 and 6.96 (2H, t each, $J$ = 7.5 Hz), 6.99 (2H, s), 3.71 and 2.96 (6H and 3H, s each); $\delta_c$ 201.1, 160.1, 138.0, 126.6, 119.0, 111.7 (all Ar-C), 138.1, 130.2, 126.1, 122.1, 119.7, 117.1, 109.1, 108.3 (all Ar-CH), 33.3, 29.9 (both N-$CH_3$). MS: *m/z* 405 ($M^+$; 34%), 377 (31), 376 (100), 362 (60); HR MS: Found: $M^+$ 405.1816. $C_{27}H_{23}N_3O$ requires: 405.1836; Anal. Found: C, 79.88; H, 5.70; N, 10.33. $C_{27}H_{23}N_3O$ requires: C, 80.0; H, 5.67; N, 10.47%.

*Reaction with alkylindoles* **2a**, **2b** and **2c**: Similar reaction conditions, work-ups and isolation procedures were adopted but using one equiv. of CAN and refluxing for 15 min.

3-*Methyl*-2-*nitroindole* (**3a**): Yield: 25 mg (14%); m.p. 140–142 °C; (lit[6a] 140–141.5 °C); $\delta_H$ 9.05 (1H, br s), 7.72 and 7.38 (1H, d each, $J$ = 8 Hz), 7.36 and 7.23 (1H, t, each $J$ = 7.5 Hz), 2.71 (3H, s); MS: *m/z* 176 ($M^+$; 100%), 159 (6), 146 (12), 130 (32).

3-*Methyl*-6-*nitroindole* (**4a**): Yield: 16 mg (9%), m.p. 186 °C; $\nu_{max}/cm^{-1}$ (KBr): 3327, 1620, 1506, 754, 732; UV (EtOH) $\lambda_{max}$ 249, 266, 325, 376 nm; $\delta_H$ 8.62 (1H, br s, NH), 8.32 (1H, d, $J$ = 2 Hz, H-7), 8.0 (1H, dd, $J$ = 9, 2 Hz, H-5), 7.59 (1H, d, $J$ = 9 Hz, H-4), 7.28 (1H, s, H-2), 2.29 (3H, s, Ar-C$H_3$); $\delta_c$ 143.5 (C-6), 135.0 (C-7a), 133.5 (C-3a), 128.2 (C-2), 119.0 (C-4), 115.0 (C-5), 113.2 (C-3), 108.4 (C-7), 9.8 (Ar-C$H_3$); MS: *m/z* 176 ($M^+$; 100%), 146 (88), 130 (89), 118 (47), 103 (50), 77 (75); Anal. Found: C, 61.20; H, 4.50; N, 15.88. $C_9H_8N_2O_2$ requires: C, 61.36; H, 4.54; N, 15.91%.

*1,3-Dimethyl*-5-*nitroindole* (**4b**): yield: 15 mg (8%); m.p. 120–122 °C; $\nu_{max}/cm^{-1}$ (nujol): 1613, 1580, 1527, 744; UV (EtOH) $\lambda_{max}$ 257, 279, 333 nm; $\delta_H$ 8.53 and 6.96 (1H, s each), 8.11 and 7.27 (1H, d each, $J$ = 8.5 Hz), 3.79 and 2.35 (3H, s each); MS: *m/z* 190 ($M^+$; 100%), 174 (4), 160 (22), 144 (60), 143 (65), 132 (22), 115 (34); Anal. Found: C, 63.02; H, 5.23; N, 14.70. $C_{10}H_{10}N_2O_2$ requires: C, 63.16; H, 5.26; N, 14.75%.

*1,3-Dimethyl*-2-*nitroindole* (**3b**): Yield: 32 mg (17%); m.p. 130 °C; $\nu_{max}/cm^{-1}$(nujol): 1613, 1513, 1321, 738; $\delta_H$ 7.72 and 7.36 (1H, d each, $J$ = 8/8.5 Hz), 7.49 and 7.22 (1H, t each, $J$ = 7.5 Hz), 4.04 and 2.67 (3H, s each); MS: *m/z* 190 ($M^+$; 100%), 173 (10), 149 (11), 144 (19), 135 (20), 128 (14), 117 (12), 110 (45); Anal. Found: C, 62.90; H, 5.20; N, 14.65. $C_{10}H_{10}N_2O_2$ requires: C, 63.16; H, 5.26; N, 14.73%.

*1-Ethyl-3-methyl-2-nitroindole* (**3c**): 31 mg (15%), m.p. 155 °C; $\nu_{max}/cm^{-1}$ (nujol): 1619, 1513, 1328, 744; $\delta_H$ 7.72 and 7.37 (1H, d each, $J$ = 8/8.5 Hz), 7.48 and 7.22 (1H, t each, $J$ = 7.5 Hz), 4.55 (2H, q, $J$ = 7 Hz), 2.67 (3H, s), 1.42 (3H, t, $J$ = 7 Hz); MS: *m/z* 204 ($M^+$; 100%), 187 (32), 174 (17), 169 (20), 159 (26), 144 (40), 130 (62); Anal. Found: C, 64.62; H, 5.84; N, 13.65. $C_{11}H_{12}N_2O_2$ requires: C, 64.70; H, 5.88; N, 13.72%.

The authors are thankful to the Director, B.I., for laboratory facilities, Mr B. Majumdar, B.I., Mrs B.K. Stein, University of Wales, Swansea, UK and Dr Jan St.Pyrek, University of Kentucky, Lexington, USA for the spectra, the CSIR, Government of India for providing fellowships (S.S., R.B.) and Mr. S. Chatterjee, a Summer Trainee from IIT, Kharagpur, India for some experimental help.

*Received 1 March 2003; accepted 30 July 2003*
*Paper 03/1834*

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