SHORT PAPER

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Electrophilic substitution reactions of indoles with carbonyl compounds using ceric ammonium nitrate: A novel and efficient method for the synthesis of di- and tri-indolylmethanes[1,†]

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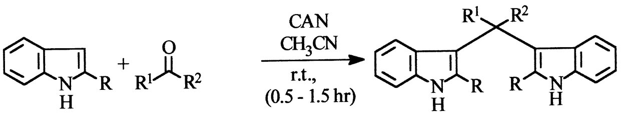
Ceric ammonium nitrate (CAN) is used to catalyse the electrophilic substitution reactions of indoles with carbonyl compounds at room temperature to produce di- and tri-indolylmethanes in high yields.

Keywords: indoles, carbonyl compounds, ceric ammonium nitrate, di- and tri-indolylmethanes

Indoles are familiar for their manifold biological activity. They possess cytotoxic, antibacterial, antioxidative and insecticidal properties.[2] Some indole compounds are used as antibiotics.[2b] Different derivatives of indole have been synthesised to study their bioactivity. Di- and tri-indolylmethanes are well known amongst these compounds, and the electrophilic substitution reaction of indoles with carbonyl compounds is an important method for their preparation. Both protic[2a,3] and Lewis[4] acids are known to catalyse these reactions. However, low yields, long reaction times and complex reaction mixtures are the drawbacks of using of some of the reported acids. Protic acids (*e.g.* HCl, H_2SO_4) and Lewis acids (*e.g.* BBr_3, BF_3) which are generally used are hazardous and difficult to handle. The Lewis acids are also deactivated by nitrogen-containing reagents. Some of the acids may even decompose the starting indoles. Lanthanide triflates[5] and lithium perchlorate[6] have also been used, but these compounds are not common bench reagents and not easily available.

The electrophilic substitution of indoles with carbonyl compounds in presence of protic and Lewis acids follows a general mechanism. The catalyst activates the carbonyl group by attracting the lone pair of electrons of oxygen so that the bond formation at C-3 of indoles with the carbonyl group is favoured. We have recently discovered that ceric ammonium nitrate (CAN) is a novel and efficient catalyst for the preparation of di- and tri-indolylmethanes by electrophilic reactions of indoles with aldehydes and ketones (Scheme 1 and Table 1). CAN is a mild oxidising agent.[7] It is readily available and easy to handle. Indoles when reacted with 3-formylindole in presence of CAN produced tri-indolylmethanes while other carbonyl compounds yielded di-indolylmethanes. The reactions proceed at room temperature to afford the products in high yields in short reaction times. The time required for the preparation of the tris-indolylmethanes is longer than that required for the di-indolylmethanes. The assigned structures of all the prepared compounds were consistent with their spectral data.[6]



Scheme 1

In conclusion: we have developed a simple, novel and highly efficient method for electrophilic substitution reactions of indoles with carbonyl compounds to produce di- and tri-indolylmethanes by use of CAN as catalyst. The short reaction time, high yields, ready availability of the catalyst and mild experimental conditions are the main advantages of the present procedure. CAN has been used as a versatile reagent in modern chemical synthesis[8]. However, to our knowledge, this is the first report of its application to electrophilic substitution reactions of indoles with carbonyl compounds.

Experimental

Melting points were measured in a Buchi-510 apparatus. 1H-NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer using TMS as internal standard, IR spectra on a Nicolet 740 FTIR spectrophotometer, and mass spectra (EIMS) on a VG Micromass 7070H (70 eV).

Reaction of indoles with carbonyl compounds in presence of CAN

To a stirred solution of the carbonyl compound (1 mmol) and indole (2 mmol) in acetonitrile (5 ml) under N_2 atmosphere CAN (0.3 mmol) was added. Stirring was continued at room temperature and the reaction was monitored by TLC. On completion, the solvent was removed and the mixture was extracted with EtOAc (3 × 10 ml). The concentrated extract was subjected to column chromatography over silica gel and the product di/tri–indolylmethane was eluted with hexane - EtOAc (4 : 1).

Spectroscopic and analytical data of the novel di- and tri-indolylmethanes:

Compound **4**: m.p.122–124 °C. ^1H NMR ($CDCl_3$ + DMSO-d_6): $\delta = 5.68$ (s, 1H, >CH-) 6.62 (d, 4H, $J = 8.2$ Hz), 6.83 (t, 2H, $J = 8.1$ Hz), 7.02 (t, 2H, $J = 8.1$ Hz), 7.08 (d, 2H, $J = 2.4$ Hz), 7.28 (d, 4H, $J = 8.2$Hz), 8.71 (brs, OH), 10.24 (brs, 2H, NH). EIMS: *m/z* (%): 338 (100 $M^{+\cdot}$), 337 (40), 245 (50), 222 (35), 116 (20), 93 (10). IR (KBr): ν_{max} 3430, 3150, 2970, 1610, 1560, 1070, 1015, 760 cm^{-1}. Anal. Calcd for $C_{23}H_{18}N_2O$ (338.41): C, 81.63; H, 5.36; N, 8.28. Found: C, 81.53; H, 5.21; N, 8.29.

Compound **7**: m.p. 226–228 °C. ^1H NMR ($CDCl_3$ + DMSO-d_6): $\delta = 5.99$ (s, 1H, >CH-), 6.71 (d, 2H, $J = 2.3$ Hz), 6.92 (t, 2H, $J = 8.1$ Hz), 7.08 (t, 2H, $J = 8.1$ Hz), 7.29 (t, 2H, $J = 8.2$ Hz), 7.41 (t, 2H, $J = 8.1$ Hz), 7.57 (d, 2H, $J = 8.2$ Hz), 8.12 (d, 2H, $J = 8.2$ Hz), 10.18 (br s, 2H, NH). EIMS: *m/z* (%): 367 (100, $M^{+\cdot}$), 366 (20), 245 (60), 251 (25), 204 (12), 160 (8), 122 (15), 116 (10), 97 (20). IR (KBr): ν_{max} 3440, 3120, 2990, 1620, 1490, 1240, 1015, 760 cm^{-1}. Anal. Calcd for $C_{23}H_{17}N_3O_2$ (367.41): C, 75.19; H, 4.66; N, 11.43. Found: C, 75.06; H, 4.42; N, 11.21.

Compound **11**: m.p. 245-247 °C. ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 6.41 (s, 1H, >CH-), 6.69 (d, 3H, $J = 2.4$ Hz), 6.82 (t, 3H, $J = 8.0$ Hz), 6.98 (t, 3H, $J = 8.0$ Hz), 7.24 (d, 3H, $J = 8.0$ Hz), 7.39 (d, 3H, $J = 8.0$ Hz) ,9.89 (brs, 3H, NH). EIMS *m/z* (%): 361 (100, $M^{+\cdot}$), 360 (48), 243 (52), 216 (5), 117 (5). I.R. (KBr): ν_{max} 3430, 3400, 2970, 1620, 1470, 1335, 1030, 740 cm^{-1}. Anal. Calcd for $C_{25}H_{19}N_3$ (361.44): C, 83.11; H, 5.25; N, 11.63. Found: C, 83.03; H, 5.39; N, 11.93.

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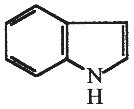
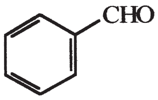
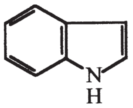
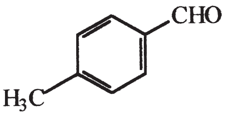
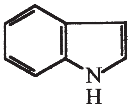
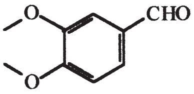
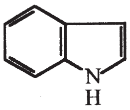
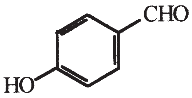
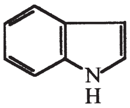
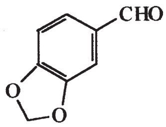
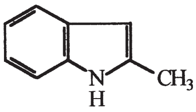
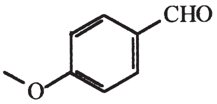
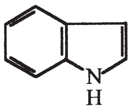
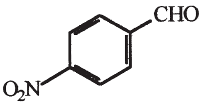
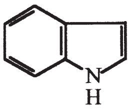
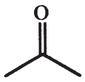
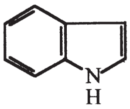
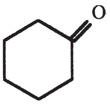
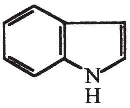
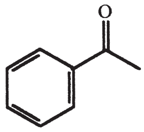
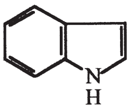
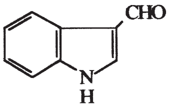
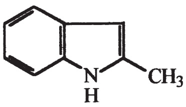
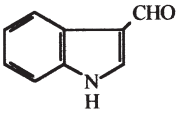
[†] This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 CAN catalysed synthesis of di-and tri-indolylmethanes

Entry	Indole	Carbonyl compound	Time /h	Isolated yields /%	M.p./°C (reported)
1			0.5	89	90–91 (88–90[6])
2			0.5	91	96–97 (95–97[6])
3			0.5	90	197–198 (198–200[6])
4			0.5	92	122–124
5			0.5	91	97–98 (97–99[6])
6			0.5	84	99–101 (98–100[6])
7			0.5	81	222–228
8			0.5	94	167–168 (164–165[9])
9			0.75	81	120–121 (118–120[6])
10			0.5	85	190–192 (191–193[9])
11			1.5	82	245–247
12			1.5	86	273–275

Compound **12**: m.p:273–275 °C. ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 2.12 (s, 6H, 2 × Me), 6.09 (s, 1H, >CH-), 6.68 (t, 3H, J = 8.1 Hz), 6.87 (t, 3H, J = 8.1 Hz), 6.98-7.32 (m, 7H), 9.86 (br s, 2H, -NH-), 9.98 (brs,1H, NH). EIMS: m/z (%): 389 (100 $M^{+\cdot}$), 388 (35), 374 (70), 257 (80), 130 (50), 117 (20), 77 (25), 43(90). I.R. (KBr): ν_{max} 3430, 3400, 3050, 2930, 2850, 1450, 1415, 1330, 760 cm^{-1}. Anal. Calcd for $C_{27}H_{23}N_3$ (389.49): C, 83.26; H, 5.95; N, 10.78. Found: C, 83.01; H, 5.85; N, 10.93.

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1 Part 11 in the series 'Studies on Novel Synthetic Methodologies', for Part 10 see N. Ravindranath, C. Ramesh and B. Das; *Synlett*, 2001 1777. IICT Communication No. 4667.

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