Ferric hydrogensulfate as a recyclable catalyst for the synthesis of some new bis(indolyl)methane derivatives

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New bis(indolyl)methanes were synthesised in excellent yields by the reaction of indole derivatives with aromatic and aliphatic aldehydes in the presence of ferric hydrogensulfate as an efficient, inexpensive, heterogeneous, reusable and non-toxic catalyst.

Keywords: aldehydes, bis(indolyl)methanes, catalysis, indoles, ferric hydrogensulfate

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Indoles and their derivatives are an important class of heterocyclic compounds in medicinal chemistry. Bis(indolyl)methanes (BIMs) have been found to have anticancer,[1] antihyperglycemic, antiviral, antimicrobial, and tranquiliser activity.[2] The development of a high throughput-method for the synthesis of bis(indolyl)methanes is a topic of current interest. Numerous methods have been reported for the synthesis of bis (indolyl)methanes based on the reaction of indoles and carbonyl compounds using different catalysts such as protic acids,[3] Lewis acids,[4,5] heterogeneous acidic catalysts,[6,7] and reagents such as iodine,[8] NBS,[9] CAN,[10] and the hexamethylenetetramine bromine adduct.[11] However, there are still some drawbacks to these catalytic systems including the requirement for large amounts of catalyst,[5,12-14] long reaction times,[12,15] low yields of product,[16] drastic reaction conditions for catalyst preparation,[17] and tedious workup leading to the generation of large amount of toxic waste. Recently, metal triflate in ionic liquid,[18] Fe(III) salts in ionic liquid[19] and other ionic liquids,[8] have been reported to be efficient systems for this transformation, but they are highly expensive. For these reasons, a superior catalyst which is cheap, less toxic, easily available and air stable is desirable.

To the best of our knowledge there are no reports on the use of $Fe(HSO_4)_3$ as a catalyst for this conversion. We now report ferric hydrogensulfate as an efficient, mild, inexpensive and recyclable catalyst for the electrophilic condensation of indoles with aldehydes.

Results and discussion

Ferric hydrogensulfate was prepared by the reaction of anhydrous ferric chloride and concentrated sulfuric acid. The IR spectrum of the solid showed similar absorption to that of $NaHSO_4$ and differed from that of Na_2SO_4 and $Fe_2(SO_4)_3$ thus supporting the formulation of ferric hydrogensulfate as $Fe(HSO_4)_3$ rather than as a double salt of $Fe_2(SO_4)_3$ and H_2SO_4.

In order to determine the best molar ratio of catalyst, we studied the reaction of 2-methylindole with naphthaldehyde in dichloromethane in the presence of different amount of $Fe(HSO_4)_3$ at room temperature (rt).

The best result was obtained with 5 mole% of $Fe(HSO_4)_3$ in which after 10 minutes, the product started to precipitate out and the reaction was completed in 30 minutes. The work-up procedure which was very simple, was performed by filtration of the precipitated product and washing with n-hexane-dichloromethane (50 : 50) and water, respectively.

To prove the generality of the protocol, the reaction was then extended with a variety of aldehydes and different indoles (Scheme 1). The results are summarised in Table 1.

This method is effective for aldehydes bearing both electron-withdrawing and electron-donating substituents on the aromatic ring. Aliphatic aldehydes also react satisfactorily under these conditions. The products **3p–t** are new derivatives of bis(indolyl)methanes and are synthesised from the reaction of 2-methyl-5-nitroindole with different aldehydes.

The re-use of $Fe(HSO_4)_3$ was investigated in the reaction between 4-chlorobenzaldehyde and 2-methylindole. After completion of the reaction, the products together with the catalyst precipitate out. The catalyst was separated from the precipitate by adding acetone which dissolved the organic compound. The catalyst was found to be reusable four times without significant loss of activity.

Comparing of catalytic efficiency of $Fe(HSO_4)_3$ with Lewis acid like $FeCl_3$ and Bronsted acid like HCl showed that ferric hydrogensulfate was acting as a bifunctional catalyst.

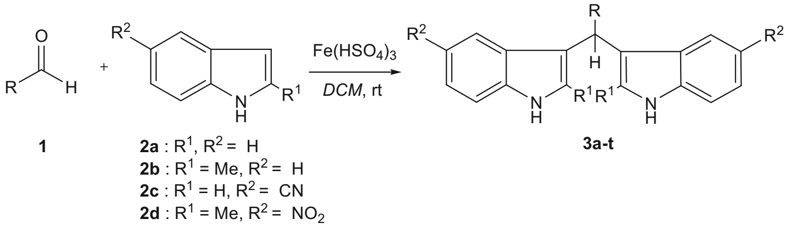
In summary, we have developed a new method for the synthesis of bis(indolyl)methanes from aldehydes and indoles using $Fe(HSO_4)_3$ as an efficient, mild, practical and recyclable catalyst.

Experimental

Melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrometer and only noteworthy absorptions are listed. The ^{1}H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. Chemical shifts are reported in ppm downfield from TMS as internal standard; coupling constants (*J*) are given in Hz. The mass spectra were obtained on a Varian. Mat CH-7 at 70 eV. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyser. 2-Methyl-5-nitro-indole[22] was prepared according to the published method. Other reagents which were commercially available, were obtained from the Merck and Aldrich companies.

Preparation of ferric hydrogensulfate

A 500 mL suction flask was equipped with a constant-pressure dropping funnel. A gas outlet was connected to a vacuum system



Scheme1

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Table 1 Synthesis of bis indolylmethanes by the reaction of indoles and aldehydes in the presence of $Fe(HSO_4)_3$ in dichloromethane at room temperature

Entry	Aldehyde/R	Indole	Product	Time/min	Yield/%	M.p °C/Lit.[a]
1	C_6H_5	**2a**	**3a**	40	90	124–127 (124–126)[20]
2	4-OMeC_6H_4	**2a**	**3b**	35	90	192–194 (195)[20]
3	4-ClC_6H_4	**2a**	**3c**	30	80	79–81 (76–78)[21]
4	4-MeC_6H_4	**2a**	**3d**	40	85	95–97 (96–98)[20]
5	$4\text{-NO}_2C_6H_4$	**2a**	**3e**	25	97	241–243 (245–246)[20]
6	4-OHC_6H_4	**2a**	**3f**	25	91	120–123 (119–121)[20]
7	2-OMeC_6H_4	**2a**	**3g**	35	93	129–132 (131–133)[20]
8	$3\text{-NO}_2C_6H_4$	**2a**	**3h**	25	91	267–269 (261–263)[20]
9	C_6H_5	**2b**	**3i**	45	93	247–248 (244–246)[21]
10	$CH_3(CH_2)_6$	**2b**	**3j**	35	70	Oily liquid
11	4-MeC_6H_4	**2b**	**3k**	30	85	175–177 (175–177)[21]
12	$4\text{-NO}_2C_6H_4$	**2b**	**3l**	30	95	239–241 (241–243)[21]
13	C_6H_5	**2c**	**3m**	45	94	241–243 (240–242)[20]
14	4-OMeC_6H_4	**2c**	**3n**	40	87	245–248 (245)[20]
15	$4\text{-NO}_2C_6H_4$	**2c**	**3o**	45	82	157–159 (158–159)[20]
16	$4\text{-NO}_2C_6H_4$	**2d**	**3p**	40	85	170–172
17	$1\text{-C}_{10}H_7$	**2d**	**3q**	50	83	156–159
18	3-OHC_6H_4	**2d**	**3r**	60	80	138–140
19	4-ClC_6H_4	**2d**	**3s**	60	75	145–147
20	2-OHC_6H_4	**2d**	**3t**	60	79	135–137

[a]The products were characterised by comparison of their spectroscopic and physical data with authentic samples synthesised by the procedure given in the references.

through an absorbing solution (water) and an alkali trap. Anhydrous $FeCl_3$ (250 mmol) was charged into the flask and concentrated sulfuric acid (98%, 73.5 g, 750 mmol) was added dropwise over a period of 30 min at r.t. HCl gas was evolved immediately. After completion of the addition of the H_2SO_4, the mixture was shaken for 30 min; meanwhile, the residual HCl was exhausted by suction. A pale brown solid material was thus obtained.[23,24] In order to eliminate of any H_2SO_4 contamination, this solid washed with absolute ethanol to give an almost white solid. The atomic absorption analysis shows the expected percentage of Fe and the titration of an aqueous solution of $Fe(HSO_4)_3$ with NaOH solution did not show any contamination of the catalyst with H_2SO_4. The structure of the catalyst was further confirmed by comparison of its IR spectrum (KBr disk) with the IR spectra of the $NaHSO_4$, Na_2SO_4 and $Fe_2(SO_4)_3$.

General procedure for BIMs **3a–t**

A mixture of benzaldehyde (0.11 g 1 mmol) and indole (0.26 g, 2 mmol) in dichloromethane (5 mL) was stirred at rt in the presence of a catalytic amount of $Fe(HSO_4)_3$ (0.2 mmol) for an appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the precipitated was filtered and washed with n-hexane-dichloromethane (4 mL) (50:50) and then water (10 mL). After drying the product in the air, practically pure product was obtained. More purification was achieved by crystallisation from suitable solvent such as n-hexane-ethyl-acetate or EtOH–water.

2-Methyl-3-[(2-methyl-5-nitro-1H-3-indolyl)(4-nitrophenyl)methyl]-5-nitro-1H-indole (**3p**): Compound **3p** was obtained as yellow crystals (EtOH), yield (85%), m.p. 170–172 °C; ^1H NMR (100 MHz, CD_3CN) δ = 2.14 (s, 6H), 6.27 (s, 1H), 7.37–7.49 (m, 4H), 7.77 (d, J = 2.1 Hz, 2H), 7.90 (dd, J = 8.8 Hz, J = 2.1 Hz, 2H), 8.15 (d, J = 8.8 Hz, 2H), 9.78 (br s, 2H) ppm; IR (KBr): 3435 cm^{-1} (NH). MS (70 eV): m/z = 485 (M^+). Anal. Calcd for $C_{25}H_{19}N_5O_6$ (485.43): C, 61.85; H, 3.94; N, 14.43. Found: C, 61.77; H, 3.84; N, 14.29%.

2-Methyl-3-[(2-methyl-5-nitro-1H-3-indolyl)(1-naphthyl)methyl]-5-nitro-1H-indole (**3q**): Compound **3q** was obtained as yellow crystals (EtOH), yield (83%), m.p. 156–159 °C; ^1H NMR (100 MHz, CD_3CN) δ = 2.14 (s, 6H), 6.21 (s, 1H), 7.25–7.70 (m, 7H), 7.75 (d, J = 2.1 Hz, 2H), 7.87–8.09 (m, 4H), 9.71 (br s, 2H) ppm; IR (KBr): 3425 cm^{-1} (NH). MS (70 eV): m/z = 540 (M^+). Anal. Calcd for $C_{33}H_{24}N_4O_4$ (540.56): C, 73.32; H, 4.47; N, 10.36. Found: C, 72.98; H, 4.37; N, 10.55%.

3-[(2-Methyl-5-nitro-1H-3-indolyl)(5-nitro-1H-3-indolyl)methyl] phenol (**3r**): Compound **3r** was obtained as yellow crystals (EtOH), yield (80%), m.p. 138–140 °C; ^1H NMR (100 MHz, CD_3CN) δ = 2.13 (s, 6H), 6.17 (s, 1H), 7.24–7.43 (m, 6H), 7.69 (br s, 1H), 7.78 (d, J = 2.0 Hz, 2H), 7.88 (dd, J = 8.6 Hz, J' = 2.0 Hz, 2H), 9.75 (br s, 2H) ppm; IR (KBr): 3435 cm^{-1} (NH), 3480 cm^{-1} (OH). MS (70 eV): m/z = 456 (M^+). Anal. Calcd for $C_{24}H_{18}N_4O_5$ (456.46): C, 65.78; H, 4.42; N, 12.27. Found: C, 65.68; H, 4.38; N, 12.33%.

3-[(4-Chlorophenyl)(2-methyl-5-nitro-1H-3-indolyl)methyl]-2-methyl-5-nitro-1H-indole (**3s**): Compound **3s** was obtained as yellow crystals (EtOH), yield (75%), m.p. 145–147 °C; ^1H NMR (100 MHz, CD_3CN) δ = 2.13 (s, 6H), 6.21 (s, 1H), 6.93 (d, J = 9.0 Hz, 2H), 7.24–7.43 (m, 4H), 7.77 (d, J = 2.1 Hz, 2H), 7.89 (dd, J = 8.6 Hz, J' = 2.1 Hz, 2H), 9.73 (br s, 2H) ppm; IR (KBr): 3425 cm^{-1} (NH). MS (70 eV): m/z = 474 (M^+). Anal. Calcd for $C_{25}H_{19}ClN_4O_4$ (474.90): C, 63.23; H, 4.03; N, 11.80. Found: C, 63.15; H, 4.29; N, 11.73%.

2-[Di(2-methyl-5-nitro-1H-3-indolyl)methyl]phenol (**3t**): Compound **3t** was obtained as yellow crystals (EtOH), yield (79%), m.p. 135–137 °C; ^1H NMR (100 MHz, CD_3CN) δ = 2.12 (s, 6H), 6.20 (s, 1H), 7.33–7.46 (m, 6H), 7.50 (br s, 1H), 7.77 (d, J = 2.0 Hz, 2H), 7.89 (dd, J = 8.6 Hz, J' = 2.0 Hz, 2H), 9.75 (br s, 2H) ppm; IR (KBr): 3435 cm^{-1} (NH), 3480 cm^{-1} (OH). MS (70 eV): m/z = 456 (M^+). Anal. Calcd for $C_{24}H_{18}N_4O_5$ (456.46): C, 65.78; H, 4.42; N, 12.27. Found: C, 65.68; H, 4.38; N, 12.33%.

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