A facile clay-mediated synthesis of 3,3-diindolyl-2-indolinones from isatins

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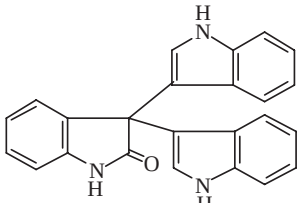
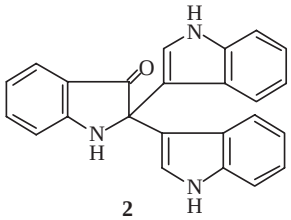
Dry reaction of isatins (**3a, 3b**) with indoles (**4a–e**) on montmorillonite K10 clay at room temperature furnished within minutes 3,3-bis(3′-indolyl)-2-indolinones (**1a–f**) in high yields. 5-Nitroisatin (**3c**) furnished, in addition to the expected indolinone **1h**, 3-hydroxy-3-(3′-indolyl)-5-nitro-2-indolinone (**6**), a likely intermediate to **1h**.

Keywords: isatins, indoles, 3,3-bis(indol-3'-yl)-2-indolinones, montmorillonite clay

2-Indolinones (oxindoles)[1] in general, and 3,3-diaryl-2-indolinones in particular, display a broad spectrum of biological activities, *e.g.* antibacterial, antiprotozoal, antiinflammatory and antiproliferative activities[2] as well as laxative properties.[3] Of the 3,3-diaryl compounds, the 3,3-diindolyl-2-indolinones† appeared interesting to us for two reasons. Firstly, only one member of this class, *viz*. 3,3-bis(3'-indolyl)-2-indolinone (**1a**), named trisindoline,[4] and one of its structural isomers, 2,2-bis(3'-indolyl)-3-indolinone (**2**)[5] (Fig. 1) have been reported from a marine bacterium, *Vibrio* sp. Secondly and more importantly, both these indolinones, along with two racemic chiral-centre-bearing bis- and tris(indolyl)alkanes and a high yield of indole, have been reported from a marine bacterium closely related to *V. parahaemolyticus*,[6] which led the workers to suggest that some of these metabolites might be of abiotic origin and formed non-naturally from indole and the corresponding carbonyl compounds in reactions catalysed by traces of acetic acid generated *in situ* from moist ethyl acetate used during extraction. Although these workers failed to isolate isatin, necessary for the formation of **1a** and **2**, from the *Vibrio* sp., isatin had earlier been reported from a marine *Altermonas* sp.[7]



1a



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We became interested in exploiting this suggested acid-catalysed abiotic formation of diindolylindolinones. Both 3,3-diaryl- and 3,3-bis-(3'-indolyl)-2-indolinones have earlier been prepared by acid-catalysed reactions. Thus, a superacid-induced condensation of isatins with arenes[8] and also the addition of aryl Grignard reagents to isatins, followed by Friedel–Crafts-type condensation of the resulting hydroxy-arylindolinones with appropriate arenes,[2e] are reported to generate the diaryl-2-indolinones. Furthermore, a number of diindolylindolinones have been reported to be formed by the reaction of isatin or *N*-methylisatin with indoles in acetic acid,[9] by the conversion of 2-indolinone into its 3,3-dibromo derivative followed by treatment with indoles in the presence of silver carbonate,[4] and by the alum-catalysed reaction of indole and 2-methylindole with isatins at room temperature as well as under microwave irradiation.[10]

As part of our ongoing interest in the use of the environmentally benign montmorillonite K10 clay, possessing both Brønsted and Lewis acidities and a large specific area,[11] in a study of the solvent-free reactions of indoles,[12] we have developed a general clay-mediated synthesis of 3,3-diindolyl-2-indolinones from isatins and indoles. The successful outcome of our experiments is presented in this paper.

Initially, as dictated by the stoichiometry of the reactants in the targeted reactions, a solution of isatin (**3a**) and two equivalents of indole (**4a**) in the minimum volume of methanol / ethyl acetate (1 : 1) was adsorbed on montmorillonite K10 clay and the solvent was allowed to evaporate off at room temperature. Although the reaction started progressing (TLC), the isatin was not consumed after 2 h. Therefore the reaction was repeated using three equivalents of indole, when the reaction was complete in just 5 min. Leaching of the clay with ethyl acetate and removal of the solvent afforded a solid mass. Removal of excess of indole by triturating this mass with hot petroleum ether (b.p. 60–80 °C), followed by crystallisation of the remaining crude product, furnished pure product **1a** in 87% yield.

This success prompted us to extend this reaction of isatin to other indoles, *viz*. the 2-methyl (**4b**), 5-bromo (**4c**), 1-methyl (**4d**), 1-ethyl (**4e**) and 3-methyl (**4f**) derivatives. For **4b–e**, the reactions were complete in 5 min at room temperature, to furnish, following similar work-ups, the respective 3,3-bis (3'-indolyl)-2-indolinones (**1b–e**) in 75–92% yields. But for skatole (**4f**), the reaction with isatin was extremely sluggish, requiring 24 h for completion, and furnished two products, separated by preparative TLC. The major product was the expected indolinone **1g** (55%) and the minor product (10%), identified as 3-methyl-3-(3'-methyl-2'-indolyl)-2-indolinone (**5**), had earlier been demonstrated by us to be generated by the slow autoxidation of skatole (**4f**) itself on montmorillonite K10 clay.[12c] 1-Methylisatin (**3b**) also reacted similarly with **4d**, furnishing 3,3-bis(1'-methyl-3'-indolyl)-1-methyl-2-indolinone (**1f**) in 89% yield. The reactions are depicted in Scheme 1 and the results in Table 1. The 5-bromo derivative **1c** had been prepared earlier in a two-step method *via* 3, 3-dibromo-2-indolinone, but the yield was not mentioned therein.[4]

All the products were thoroughly characterised by spectroscopic analyses (*vide* Experimental). The IR spectra of **1a–g** showed a characteristic band at 1705–1734 cm^{-1} (C=O) apart from other bands for NH. Their ^1H and ^{13}C NMR spectra revealed the presence of two indolyl moieties (having similar chemical shifts except for **1b**) and one 3,3-disubstituted 2-indolinone moiety in each of them. The carbonyl carbon of the 3,3-disubstituted indolinone moiety appeared at around δ 179 and the C-3, a non-protonated carbon, around δ 53.

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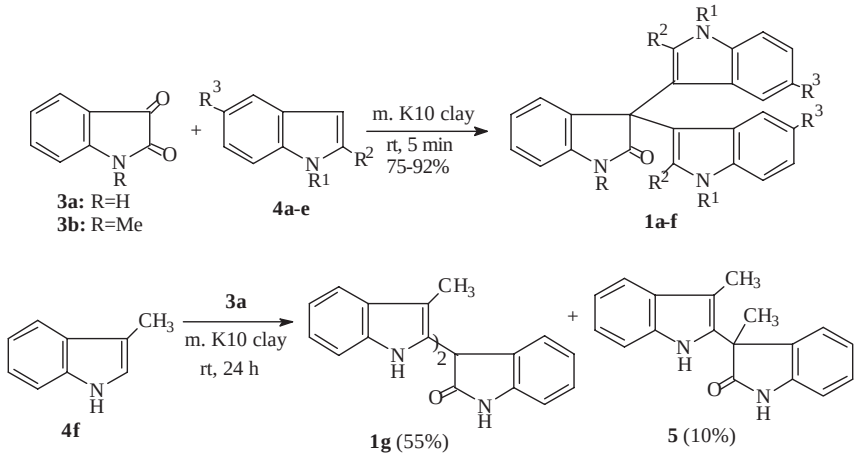
† Chemical Abstracts names the parent (**1a**) of the series as [3,3'(2'H):3',3''-ter-1H-indol]-2'-one (CAS no. 75833-70-4). The Beilstein system names it as 3,3-bis(3-indolyl)oxindole. For clarity and simplicity, because the two outer indole rings are identical, we prefer to describe the compounds in this paper as diindolyl 2-indolinones.



Scheme 1

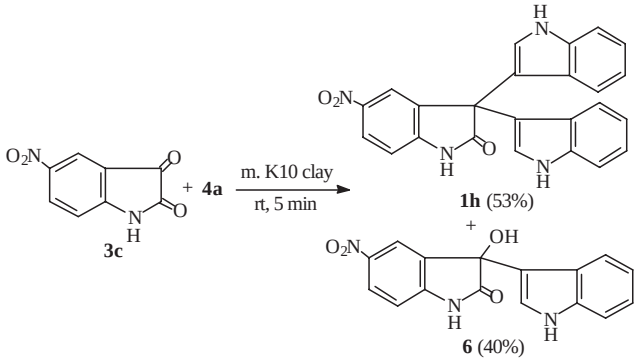
Table 1 Synthesis of bis(indolyl)indolinones (**1a–g**) from isatins (**3a,b**) and indoles (**4a–f**) on montmorillonite K10 clay

Isatin (**3a/3b**)	Indole[a]	R^1	R^2	R^3	Rxn. time	Product[ref.]	Yield/%[b]
3a	**4a:**	H	H	H	5 min	**1a**[4,9]	87
3a	**4b:**	H	Me	H	,,	**1b**[10]	92
3a	**4c:**	H	H	Br	,,	**1c**[4,10]	85
3a	**4d:**	Me	H	H	,,	**1d**[9]	90
3a	**4e:**	Et	H	H	,,	**1e**	75
3b	**4d:**	Me	H	H	,,	**1f**[9]	89
3a	**4f**	24	h			**1g**	55
						5[12c]	10

[a]3 Mmol of **4a–f** for 1 mmol of isatins **3a,b**. [b]Refer to isolated, pure products.

In the case of **1b**, signals for all the protons (except two) and carbons appeared at different chemical shifts. The reason for this exception is perhaps the steric crowding resulting from the proximity of the two 2-methylindol-3-yl moieties in this compound, thereby making the proton and carbon chemical shifts of the two indolyl moieties non-equivalent, as was independently observed by Azizian *et al.*[10]. Notably, in its ^{13}C NMR spectrum, 24 signals appeared instead of the expected 26, which suggested that two of the observed signals must represent four carbons.

In order to study the effect of the presence of an electron-withdrawing group in the phenyl ring of isatin, 5-nitroisatin (**3c**) was allowed to react with indole on montmorillonite K10 clay in a similar manner. As a result, two products were formed. The major product (53%) was identified spectroscopically as the expected 3,3-bis(3'-indolyl)-5-nitro-2-indolinone (**1h**), prepared recently by alum-catalysed reaction from the same starting materials.[10] The second product (40%), a high melting solid with molecular formula $C_{16}H_{11}N_3O_4$ (HR FAB-MS), showed the presence of an indolyl moiety (^1H and ^{13}C NMR), a hydroxyl group (IR: 3530-3120 cm^{-1}; δ_H 6.734, 1H, s), an oxygenated carbon (δ_c 80.0) and the 2-indolinone carbonyl carbon (δ_c 184.0) of the expected 5-nitro-2-indolinone moiety. It was thus identified as the hitherto elusive indolylcarbinol, viz. 3-hydroxy-3-(3'-indolyl)-5-nitro-2-indolinone (**6**). Pertinently, the desnitro derivative of **6** is reported to have been previously prepared by diethylamine-catalysed condensation of indole with isatin.[13] To our knowledge, this is the first report of the formation of such a product on clay surface. Besides, the isolation of **6** suggests that 3-hydroxy-3-indolyl-2-indolinones are likely to be the intermediates to the 3,3-bis(indolyl)-2-indolinones. This view received additional support from the fact that a series diindolylalkanes along with the corresponding indolylcarbinols, the intermediates to the



Scheme 2

former class, have been isolated by the clay-mediated reaction of indoles with diethyl mesoxalate.[14]

Since the reactions are very fast (except for **1f**), involving simple isolation procedures and furnishing the products in high yields, the present method may be considered as a facile and efficient method for the one-step synthesis of 3,3-diindolyl-2-indolinones with biological potential. The latter, however, remains to be explored.

Experimental

Melting points were determined on a Toshniwal apparatus. IR spectra were recorded on a Nicolet FT-IR I-410 spectrophotometer. The LR electron-impact mass spectra were recorded on a JEOL JMS-AX505HA mass spectrometer and the HR FAB-MS (using *m*-nitrobenzyl alcohol as liquid matrix) on a JEOL JMS-700 MStation mass spectrometer. The ^1H (500 MHz) and ^{13}C (125 MHz) NMR and DEPT 135 spectra were recorded on a Bruker DRX 500 NMR spectrometer and the ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra on a Bruker Avance DPX-300 spectrometer. Microanalyses were carried out on a Dr Hans Hoesli Analyser (Type A1; No. 1058). The known compounds were identified by m.p., mixed m.p., TLC and co-TLC with authentic compounds and also by their IR, ^1H and ^{13}C NMR spectral data for some compounds. Montmorillonite K10 clay was commercially procured from Fluka, Switzerland. Petrol refers to petroleum ether boiling at 60–80 °C.

General procedure for the synthesis of 2-indolinones (**1a–h**): A solution of the isatin (3a–c; 1 mmol) and the indole (**4a–f**; 3 mmol) in the minimum volume of methanol / ethyl acetate (1 : 1) was adsorbed on montmorillonite K10 clay (2 g / mmol of **3a–c**) and the solvent was allowed to evaporate off at room temperature, a procedure which took about 5 min, during the course of which the reaction proceeded. After completion of the reaction (TLC), the clay was leached with ethyl acetate (3 × 15 ml); subsequent removal of the solvent afforded a solid mass. Purification of the residue was carried out either by preparative TLC (in the case of **3c**) or by the removal of excess of indole by leaching with hot petroleum ether

(b.p. 60–80 °C), followed by crystallisation of the crude product. The physical and spectroscopic data of the compounds are presented below.

3,3-Bis(3'-indolyl)-2-indolinone (**1a**): Yield 316 mg (87%); colourless needles, m.p. 310 °C (lit.[9] m.p. 312–314 °C).

3,3-Bis(2'-methyl-3'-indolyl)-2-indolinone (**1b**): Yield 360 mg (92%); colourless flakes, m.p. 290 °C (lit.[10] m.p. 300–301 °C). NMR: δ_H (d_6-DMSO, 500 MHz): 10.83, 10.81 and 10.48 (1H, each s, NH), 7.19 (2H, d, *J* = 7.5 Hz), 7.20 (1H, t, *J* = 7 Hz), 7.13 and 6.93 (1H, each d, *J* = 7.5 Hz), 6.88 and 6.86 (1H, each t, *J* = 7 Hz), 6.84 (1H, t, *J* = 7.5 Hz), 6.68 (1H, d, *J* = 8 Hz), 6.62 and 6.59 (1H, each t, *J* = 7.5 Hz), 6.45 (1H, d, *J* = 8 Hz), 2.05 and 1.92 (3H, each s, 2 × Ar–CH_3); δ_C (125 MHz): 180.1 (C), 142.0 (C), 136.4 (C), 135.8 (C), 135.7 (C), 134.7 (C), 132.8 (C), 128.6 (CH), 128.5 (C), 127.9 (C), 126.3 (CH), 122.0 (CH), 120.6 (CH), 120.4 (CH), 120.2 (CH), 120.1 (CH), 118.8 (CH), 118.7 (CH), 111.2 (C), 111.1 (CH), 110.2 (CH), 53.2 (C), 14.0 and 13.8 (2 × Ar–CH_3).

3,3-Bis(5'-bromo-3'-indolyl)-2-indolinone (**1c**): Yield 441 mg (85%); colourless needles, m.p. 318–319 °C (Lit.[10] m.p. 310–311 °C).

3,3-Bis(1'-methyl-3'-indolyl)-2-indolinone (**1d**): Yield 352 mg (90%); colourless needles, m.p. 330 °C (Lit.[9] m.p. 330–332 °C); δ_H (d_6-DMSO, 500 MHz): 10.40 (1H, s, NH), 7.17 (2H, d, *J* = 8 Hz), 6.99–7.06 (4H, m), 6.87 (2H, t, *J* = 7.5 Hz), 6.78 (1H, d, *J* = 7.5 Hz), 6.72 (1H, t, *J* = 7.5 Hz), 6.67 (2H, s), 6.63 (2H, t, *J* = 7.5 Hz), 3.50 (6H, s, 2 × N-CH_3).

3,3-Bis(1'-ethyl-3'-indolyl)-2-indolinone (**1e**): Yield 314 mg (75%); colourless needles from EtOAc-petrol, m.p. 332–334 °C (dec.); IR: ν_{max}/cm^{-1}(nujol): 1705, 1613, 1201, 744; NMR: δ_H (d_6-DMSO, 500 MHz): 10.57 (1H, s), 7.39 (2H, d, *J* = 8 Hz), 7.21 (1H, d, *J* = 7.5 Hz), 7.18 (1H, t, *J* = 7.5 Hz), 7.17 (2H, d, *J* = 8 Hz), 7.03 (2H, t, *J* = 7.5 Hz), 6.95 (1H, d, *J* = 7.5 Hz), 6.90 (1H, t, *J* = 7.5 Hz), 6.88 (2H, s), 6.79 (2H, t, *J* = 7.5 Hz), 4.11 (4H, q, *J* = 7 Hz, 2 × N$CH_2$$CH_3$), 1.24 (6H, t, *J* = 7 Hz, 2 × N$CH_2$$CH_3$); MS: *m/z* 419 ($M^+$; 74%), 391 (41), 390 (100), 389 (22), 361 (30), 275 (18), 247 (18). Anal. Found: C, 79.88; H, 5.99; N, 10.05. $C_{28}H_{25}N_3O$ requires C, 80.19; H, 5.97; N, 10.02 %.

3,3-Bis(1'-methyl-3'-indolyl)-1-methyl-2-indolinone (**1f**): Yield 365 mg (90%); colourless needles, m.p. 230 °C (lit.[9] m.p. 332–334 °C). NMR: δ_H ($CDCl_3$, 500 MHz): 7.43 (1H, d, *J* = 7.5 Hz), 7.30 (1H, t, *J* = 8 Hz), 7.26 (2H, d, *J* = 8 Hz), 7.24 (2H, d, *J* = 7.5 Hz), 7.13 (2H, t, *J* = 7.5 Hz), 6.99 (1H, t, *J* = 8 Hz), 6.96 (1H, d, *J* = 8 Hz), 6.91 (2H, t, *J* = 7.5 Hz), 6.83 (2H, s), 3.66 (6H, s, 2 × N–CH_3), 3.32 (3H, s, N–CH_3).

3,3-Bis(3'-methyl-2'-indolyl)-2-indolinone (**1g**): Yield 215 mg (55%); colourless needles from EtOAc-petrol, m.p. 302–304 °C (dec.). IR ν_{max}/cm^{-1} (nujol): 3417, 3357, 3332, 1726, 1620, 745; NMR δ_H (d_6-DMSO, 500 MHz): 10.59 (1H, s, NH), 10.23 (2H, s, 2 × NH), 7. (2H, d, *J* = 8 Hz), 7.13 (1H, d, *J* = 7.5 Hz), 7.12 (2H, d, *J* = 8 Hz), 7.08 (1H, t, *J* = 7.5 Hz), 6.83 (1H, d, *J* = 7.5 Hz), 6.81 (1H, t, *J* = 7 Hz), 6.80 (2H, t, *J* = 8 Hz), 6.75 (2H, t, *J* = 7.5 Hz), 1.70 (6H, s, 2 × Ar-CH_3); δ_c (125 MHz): 176.7 (C), 142.3 (C), 136.1 (C), 132.5 (C), 132.0 (C), 129.9 (C), 129.6 (CH), 126.4 (CH), 123.1 (CH), 121.7 (CH), 119.1 (CH), 118.6 (CH), 112.2 (CH), 110.8 (CH), 108.1 (C), 55.4 (C), 9.7 (2 × Ar-CH_3); MS: *m/z* 391 (M^+; 100%), 376 (65), 348 (62), 332 (14), 261 (61), 260 (39), 232 (22), 195 (13), 130 (13); Anal. Found: C, 79.69; H, 5.34; N, 10.70. $C_{26}H_{21}N_3O$ requires: C, 79.79; H, 5.37; N, 10.74 %.

3,3-Bis(3'-indolyl)-5-nitro-2-indolinone (**1h**): Yield 216 mg (53%); yellow needles, m.p. 296 °C (lit.[10] m.p. 298–299 °C); ^{1}H NMR: δ_H (300 MHz, d_6-DMSO) 11.09 (3H, s, 3 × NH), 8.45 (1H, dd, *J* = 8.7, 2 Hz), 7.96 (1H, d, *J* = 2.4 Hz), 7.37 (2H, d, *J* = 8 Hz), 7.20 (2H, d, *J* = 7.8 Hz), 7.19 (1H, d, *J* = 8.7 Hz), 7.03 (2H, t, *J* = 7.2 Hz), 6.95 (2H, d, *J* = 2.4 Hz), 6.82 (2H, t, *J* = 7.5 Hz).

3-Methyl-3-(3'-methyl-2'-indolyl)-2-indolinone (**5**): Yield 62 mg (45%); yellow prisms from CH_2Cl_2, m.p. 200–202 °C (Lit.[12c] m.p. 222–224 °C).

3-Hydroxy-3-(3'-indolyl)-5-nitro-2-indolinone (**6**): Yield 124 mg (40%); m.p. >345 °C (EtOAc–petrol); IR (nujol): ν_{max}/cm^{-1} 3530-3121, 3448, 3383, 1734, 1701, 1620, 1514, 1341, 1303, 1081, 748. NMR: δ_H (d_6-DMSO, 500 MHz) 11.08 and 11.06 (1H, each s, 2 × NH), 8.23 (1H, dd, *J* = 8.5, 2.5 Hz), 8.04 (1H, d, *J* = 2.5 Hz), 7.47 and 7.34 (1H, each d, *J* = 8 Hz), 7.101 (1H, d, *J* = 8.5 Hz), 7.102 (1H, d, *J* = 2.5 Hz), 7.05 and 6.91 (1H, each dt, *J* = 1, 7.5 Hz), 6.73 (1H, s, OH); δ_c (75 MHz): 184.0, 153.6, 147.8, 142.4, 139.8, 132.0, 130.2, 129.4, 126.9, 125.8, 125.5, 124.3, 119.4, 117.2, 115.6, 80.0; MS: *m/z* 309 (M^+; 26%), 292 (100), 291 (57), 264 (86), 246 (19), 245 (19), 234 (12), 218 (63), 190 (18), 164 (17), 144 (19), 117 (23). HR-FAB MS: 309.0760 [M^+] calc. for $C_{16}H_{11}N_3O_4$: 309.0750.

The authors thank the Director, Bose Institute for laboratory facilities, the C.S.I.R., Govt. of India for providing a fellowship (S.S.), Mr B. Majumder, NMR Lab., Mr J. Chatterjee, R.S.I.C. and Mr P. Dey, Microanalytical Lab., all of B.I., for recording the spectra.

Received 5 October 2004; accepted 14 April 2005
Paper 04/2799

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