Pergamon

Tetrahedron Letters 43 (2002) 4075–4078

TETRAHEDRON
LETTERS

Dry reaction of indoles with carbonyl compounds on montmorillonite K10 clay: a mild, expedient synthesis of diindolylalkanes and vibrindole A

Manas Chakrabarty,[a,]* Nandita Ghosh,[a] Ramkrishna Basak[a] and Yoshihiro Harigaya[b]

[a] *Department of Chemistry, Bose Institute, 93/1, APC Road, Kolkata 700009, India*
[b] *School of Pharmaceutical Sciences, Kitasato University, Minato-ku, Tokyo 108, Japan*

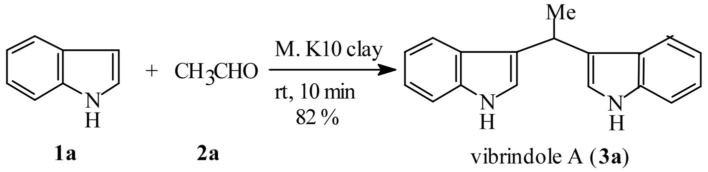
Received 12 February 2002; revised 27 March 2002; accepted 5 April 2002

Abstract—Dry reaction of indoles **1a**–**c** with aldehydes **2a**–**i**, ketones **2j**–**o** and an acetal **2p** on M. K10 clay at room temperature furnished 3,3′-diindolylalkanes (DIAs: **3a**–**h**, **j**–**r**). The novel formation of tris(3-indolyl)methane **4** from **2i** through tandem reactions and of the DIAs **6** and **8** from **1d** through Plancher rearrangements were also observed. © 2002 Elsevier Science Ltd. All rights reserved.

The diindolylalkanes (DIAs) constitute an old[1a,b] but important class of compounds, reviewed recently by us.[2] The syntheses of the DIAs reported up to the sixties are well reviewed.[3a,b] The first isolation of a hallucinogenic DIA from a fungus in 1977[4] and the subsequent isolation of other DIAs, including some bioactive members, from natural sources[5a–d] have made this field a rapidly growing area. The principal synthetic avenues to the DIAs comprise the protic or Lewis acid-catalysed reaction of indoles or indolyl Grignard reagents with aldehydes (or their acetals), ketones, α-ketoacids, imines, iminium salts or nitrones.[2] Most of these methods suffer from various disadvantages such as long reaction periods (e.g. 10 days[6]), use of expensive Lewis acids (e.g. dysprosium triflate[7]) or preformed reagents (e.g. oxazolidines/tetrahydrooxazines,[8a,b] nitrones[9a,b]), etc., yet furnishing the DIAs in extremely low (e.g. 2%[5a]) or unspecified[8b] yields in some cases. Moreover, none of these methods is environmentally friendly, since always an excess of solvent and often toxic or hazardous chemicals are employed.

In continuation of our ongoing interest[10a,b] in green chemistry, we have developed a mild and expedient synthesis of symmetrical DIAs using montmorillonite K10 clay as the catalyst. The method is highly efficient and free from the aforesaid drawbacks. A brief account of our work and its main findings as well as the advantages of this method over the extant synthetic routes are discussed in this communication.

Montmorillonite K10 clay is known to behave as both a protic and a Bronsted acid (Hammett acidity function, H_0: −5.5 to 5.9) and has a large specific surface area (500–760 m^2/g), compared to other solid acidic catalysts like silica gel (400–600 m^2/g).[11] We, therefore, used this clay in a solvent-free reaction of indoles with mainly aldehydes and ketones. Initially, indole **1a** was treated with 0.5 equiv. of acetaldehyde **2a**, both adsorbed on M. K10 clay (2 g/1 mM of **1a**). A simple work-up furnished vibrindole A **3a**, a bacterial metabolite,[5c] as the sole product in 10 min and in very good yield (Scheme 1).



Scheme 1.

Keywords: diindolylalkanes; vibrindole A; green synthesis; clay.

* Corresponding author. Tel.: 91 33 350 2402/2403/6619; fax: 91 33 350 6790; e-mail: manas@boseinst.ac.in

0040-4039/02/$ - see front matter © 2002 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(02)00682-2

The potential of this method became apparent when the conditions and the yield of **3a** were compared with those of its five previous syntheses, all from indole (Table 1).

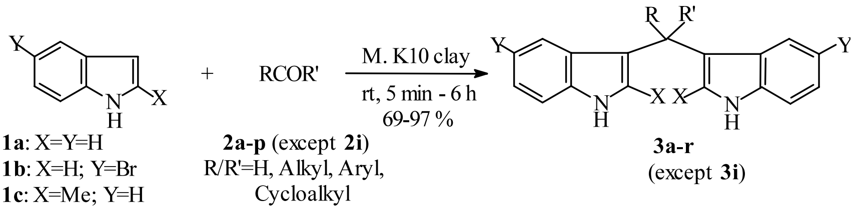
Prompted by this success, we extended this reaction of indole with a range of other aldehydes **2a**–**i**, ketones **2j**–**o** and an acetal **2p** under similar conditions, furnishing (except for **2i**) the respective symmetrical DIAs **3a**–**p** (except **3i**) in good to excellent yields. 5-Bromoindole **1b** and 2-methylindole **1c** behaved similarly with the aldehydes **2b** and **2c**, respectively forming the respective DIAs **3q** and **3r** in excellent yields (Scheme 2).

Our findings (Table 2) reflect the wide applicability and usefulness of our method. For most aldehydes **2a**–**e**, the reactions were exceedingly fast (5–10 min), whereas for salicylaldehyde **2f**, the reaction required 2 h perhaps because of its hydrogen bonding. The yields were also excellent, viz. 92–97%, except for acetaldehyde **2a** where the somewhat lower yield (82%) can be

Table 1. Comparative evaluation of the syntheses of vibrindole A (**3a**) from indole (**1a**)

Sl. no.	Reagent	Temp.	Time	Yield[a] (%)	Lit. ref.
1	MeCHO, AcOH	Rt	10 days	58	6
2	(i) Propiolic acid, MeOH; (ii) -CO_2	Reflux	5 h	45	12
3	An oxazolidine,[b] MeCN, CF_3CO_2H	Rt	15 min	25	8a,b
4	EtOH, DMCD,[c] aq. $NaClO_4$, Pt-electrode	Rt	Not stated	86	13
5	$MeCH{=}N^+(Bn)O^-$, Me_3SiCl, CH_2Cl_2	Rt	17 h	83	9a,b
6	Present method: MeCHO, M. K10 clay	Rt	10 min	82	

[a] Refer to isolated yields.
[b] 2-Methyl-3-phenyloxazolidine.
[c] 2,6-Di-*O*-methyl-β-cyclodextrin.



Scheme 2.

Table 2. Dry reaction of indoles (1 mM) with aldehydes and ketones[a] (0.5 mM) using M. K10 clay (2 g)

Sl. no.	1a + Aldehydes/ketones	Time	Prod.	Yield[b] (%)
1	**1a** + MeCHO (**2a**)	10 min	**3a**	82
2	**1a** + PhCHO (**2b**)	5 min	**3b**	97
3	**1a** + *o*-$O_2NC_6H_4CHO$ (**2c**)	5 min	**3c**[c]	96
4	**1a** + *m*-$O_2NC_6H_4CHO$ (**2d**)	5 min	**3d**	95
5	**1a** + *p*-$MeOC_6H_4CHO$ (**2e**)	10 min	**3e**	92
6	**1a** + *o*-OHC_6H_4CHO (**2f**)	2 h	**3f**	95
7	**1a** + 2-CHO-thiophene (**2g**)	10 min	**3g**[c]	80
8	**1a** + 2-CHO-furan (**2h**)	1 h	**3h**	81
9	**1a** + 2-CHO-pyrrole (**2i**)	4 h	**4** (not **3i**)	88
10	**1a** + MeCOMe (**2j**)	4.5[d] (8) h	**3j**	83
11	**1a** + MeCOEt (**2k**)	4 h	**3k**[c]	69
12	**1a** + MeCOPh (**2l**)	6[d] (16) h	**3l**	71
13	**1a** + Cyclopentanone (**2m**)	6 h	**3m**	76
14	**1a** + Cyclohexanone (**2n**)	2 h	**3n**	77
15	**1a** + 4-Me-cyclohexanone (**2o**)	2 h	**3o**[c]	73
16	**1a** + Phthalimido-$CH_2CH(OEt)_2$ (**2p**)	4[d] (8) h	**3p**[c]	97
17	**1b** + **2b**	5 min	**3q**[c]	96
18	**1c** + **2c**	5 min	**3r**[c]	93
19	**1d** + **2c**	2 h	**5**[c]; **6**[c]	63; 27
20	**1d** + **2d**	2 h	**7**[c]; **8**[c]	52; 37

[a] Benzophenone failed to react with **1a**.
[b] Refers to isolated yields.
[c] New compounds.
[d] Using 6 g clay; time periods within parentheses were needed using 2 g clay.

accounted for by our observation that **2a** decomposes rapidly on clay. For ketones **2j–o**, the reactions were slower (2–6 h) and the yields were also lower (69–83%), presumably because of steric crowding in the resulting DIAs. That acetone and acetophenone required increasingly more time, whereas benzophenone did not react at all with **1a**, lends support to our view. For **2p**, the reaction was also slow (4 h), but the yield of **3p** was excellent (97%).

Of the 2-formylheteroarenes **2g–i**, the reaction was inexplicably very fast (10 min) only with **2g**. More surprisingly, whereas **2g** and **2h** furnished the expected DIAs **3g** and **3h**, respectively, **2i** provided tris(3-indolyl)methane **4**,[10b,14a,b] instead of the expected DIA **3i** (X = Y = H; R,R′ = 2-pyrrolyl). In light of our recently reported clay-mediated, general synthesis of triindolylmethanes,[10b] the formation of **4** may be considered to proceed through the successive formations of the expected DIA **3i** and the indoleninium species **3′i** (Scheme 3). Pyrrole was found to decompose rapidly on M. K10 clay, which accounts for the fact that, contrary to expectation, no pyrrole could be isolated from the reaction mixture. However, it remains obscure as to why **2i** behaved differently from **2g** and **2h**.

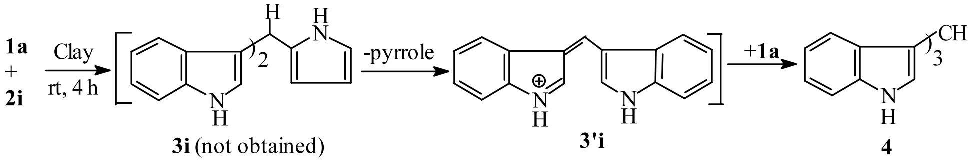
The time required to complete the reactions of **1a** with **2i**, **2l** and **2p** could be considerably reduced from 8, 16 and 8 h to 4.5, 6 and 4 h, respectively using thrice the amount of clay (6 g/1 mM). These results suggested that the greater the surface area of clay available, the faster is the rate of the reactions.

When skatole **1d** was separately treated with **2c** and **2d** in a similar manner, both the reactions were considerably slower and furnished, besides the expected respective 2,2′-DIAs **5**[15] and **7**, the unexpected 2,3′-DIAs **6**[16] and **8**, respectively. The structures of **5–8** and the distinction of **5**/**7** from **6**/**8** were proved by analysing their spectra and by comparing the same with those of **3r**. Thus, both **5** and **6** possessed the same molecular formulae (HRMS) and similar structural units (IR, ^{1}H, ^{13}C). But, for **6**, two different signals appeared for the two NH's (IR, ^{1}H) as well as for the two methyls (^{1}H, ^{13}C), which disclosed its unsymmetrical nature. Further, the ^{13}C chemical shifts of the 2-methyl-3-substituted indole nucleus of **3r** (a 3,3′-DIA) and those of the 3-methyl-2-substituted indole ring of **5** (a 2,2′-DIA) were more or less reproduced in the ^{13}C NMR spectrum of **6**, which demonstrated it to be a 2,3′-DIA. The situation was analogous for **7** and **8**.

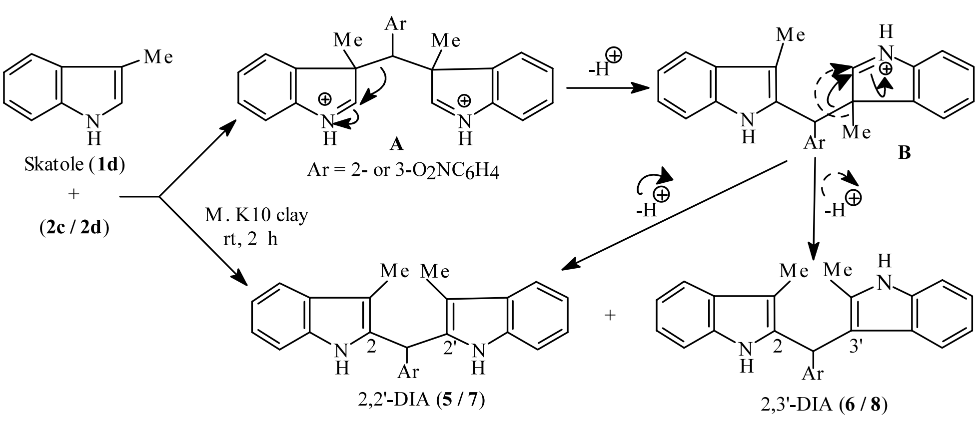
The reactions no doubt proceeded through the two successive intermediates **A** and **B**, followed by separate Plancher rearrangements.[17a–c] One involved the usual migration of an arylalkyl group and led to the 2,2′-DIAs **5** and **7**. The other involved the hitherto unreported migration of a methyl group, in preference to an arylalkyl group, and led to the 2,3′-DIAs **6** and **8** (Scheme 4). Pertinently, this is the first record of the formation of 2,3′-DIAs from 3-alkylindoles, since only 2,2′-DIAs were reported to have been formed in all previous cases.[2]

The clay, recovered from the reaction of **1a** with **2j** was washed and dried at 110–120°C for 12 h and used in a second reaction between **1a** and **2b.** The product **3b** was obtained in similar yield (96%) and time (5 min) as in the experiment using fresh clay. The recyclability of M. K10 clay in these reactions was thus demonstrated.

In conclusion, we have developed an expedient, clay-mediated green synthesis of symmetrical DIAs.[18] It is superior to the extant synthetic routes for a number of



Scheme 3.



Scheme 4.

reasons, viz. (i) it is fast and efficient, employs a cheap, non-toxic and reusable clay as the catalyst and involves a simple work-up; (ii) it furnishes DIAs **3c–d** from nitrobenzaldehydes **2c–d** exceedingly fast (5 min) and in excellent yields (≥95%) in contrast to a recent slow (10 h) synthesis (using lithium perchlorate as catalyst) with moderate yield (67%);[19] (iii) on hydrazinolysis, the phthalimido-DIA **3p** produced the corresponding diindolylethylamine (**3**: $X=Y=H$; $R,R'=H$, CH_2NH_2) much faster (6.5 h) and in a better yield (92%) than its earlier three-step synthesis from indole and glyoxylic acid (>80 h; 32%).[20] Our method has enormous potential in the synthesis of naturally occurring DIAs, upon which we have recently embarked.

Acknowledgements

The authors express their sincere thanks to the Director, Bose Institute for providing laboratory facilities, Mr. B. Majumdar (NMR Laboratory, B.I.), Professor D. E. Games and Mrs. B. K. Stein (University of Swansea Wales, UK) for recording the Mass spectra and the CSIR, Govt. of India for financial support (a project to M.C., N.G. and an ad hoc fellowship to R.B.).

References

1. (a) Fischer, E. *Liebigs Ann. Chem.* **1887**, *242*, 372; (b) Noland, W. E.; Robinson, D. N. *Tetrahedron* **1958**, *14*, 68.
2. Chakrabarty, M.; Basak, R.; Harigaya, Y. *Heterocycles* **2001**, *55*, 2431.
3. (a) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970; p. 39; (b) Remers, W. A. In *The Chemistry of Heterocyclic Compounds*; Houlihan, W. J., Ed.; Wiley-Interscience: New York, 1972; p. 1.
4. Porter, J. K.; Bacon, C. W.; Robbins, J. D.; Himmelsbach, D. S.; Higman, H. C. *J. Agric. Food Chem.* **1977**, *25*, 88.
5. (a) Osawa, T.; Namiki, M. *Tetrahedron Lett.* **1983**, *24*, 4719; (b) Fahy, E.; Potts, B. C. M.; Faulkner, D. J.; Smith, K. *J. Nat. Prod.* **1991**, *54*, 564; (c) Bell, R.; Carmeli, S.; Sar, N. *J. Nat. Prod.* **1994**, *57*, 1587; (d) Bifulco, G.; Bruno, I.; Riccio, R.; Lavayre, J.; Bourdy, G. *J. Nat. Prod.* **2000**, *63*, 596.
6. Kamal, A.; Qureshi, A. A. *Tetrahedron* **1963**, *19*, 512.
7. Chen, D.; Yu, L.; Wang, P. G. *Tetrahedron Lett.* **1996**, *37*, 4467.
8. (a) Singh, H.; Sarin, R.; Singh, K. *Heterocycles* **1986**, *24*, 3039; (b) Singh, H.; Singh, K. *Tetrahedron* **1988**, *44*, 5897.
9. (a) Denis, J.-N.; Mauger, H.; Vallee, Y. *Tetrahedron Lett.* **1997**, *38*, 8515; (b) Chalaye-Mauger, H.; Denis, J.-N.; Averbuch-Pouchot, M.-T.; Vallee, Y. *Tetrahedron* **2000**, *56*, 791.
10. (a) Chakrabarty, M.; Basak, R.; Ghosh, N. *Tetrahedron Lett.* **2001**, *42*, 3913; (b) Chakrabarty, M.; Sarkar, S. *Tetrahedron Lett.* **2002**, *43*, 1351.
11. Laszlo, P. *Science* **1987**, *235*, 1473.
12. Zee, S. H.; Chen, C. S. *J. Chin. Chem. Soc.* **1974**, *21*, 229; *Chem. Abstr.* **1975**, *82*, 125215y.
13. Suda, K.; Takanami, T. *Chem. Lett.* **1994**, 1915.
14. (a) Balmer, C. T.; Kinder, H.; Gutman, L. *J. Med. Chem.* **1965**, *8*, 397; (b) Akgun, E.; Pindur, U.; Muller, J. *J. Heterocycl. Chem.* **1983**, *20*, 1303.
15. **5**: Orange prisms, mp 218–220°C (pet. ether–CH_2Cl_2); yield: 124 mg (63%); IR: 3396, 1520, 1348, 744 cm^{-1}; MS: *m/z* 395 (M^+), 265 (100%), 235, 219–217, 204, 131, 130; ^1H NMR ($CDCl_3$; 500 MHz): δ 2.11 (6H, s, 2×CH_3), 6.75 (1H, s, Ar_3CH), 7.12 and 7.15 (2H, t each, *J* 7.5 Hz), 7.21 (2H, d, *J* 8 Hz), 7.23 (1H, d, *J* 8.5 Hz), 7.45 and 7.51 (1H, t, each *J* 7.5 Hz), 7.54 (2H, d, *J* 7.5 Hz), 7.59 (2H, br s, 2×NH), 7.94 (1H, d, *J* 8 Hz); ^{13}C NMR ($CDCl_3$; 125 MHz): δ 8.8 (2×CH_3), 37.7 (Ar_3CH), 111.3, 119.1, 120.1, 122.5, 125.8, 128.9, 131.1, 133.8 (all Ar-CH), 109.9, 129.9, 131.8, 135.6, 135.8, 149.4 (all Ar-C).
16. **6**: Yellow prisms, mp 222–224°C (pet. ether–CH_2Cl_2); yield: 54 mg (27%); IR: 3449, 3396, 1520, 1354, 738 cm^{-1}; MS: *m/z* 395 (M^+), 265 (100%), 235, 219–217, 204, 131, 130; ^1H NMR ($CDCl_3$; 500 MHz): δ 2.18 and 2.26 (3H s each, 2×CH_3), 6.58 (1H, s, Ar_3CH), 6.41–6.89 (1H, m), 7.09–7.22 (6H, m), 7.44–7.50 (2H, m), 7.51 and 7.82 (1H, br s each, 2×NH), 7.56 (1H, d, *J* 8 Hz), 7.58 (1H, d, *J* 8.5 Hz), 8.01–8.06 (1H, m); ^{13}C NMR ($CDCl_3$; 125 MHz): δ 8.8 and 10.1 (2×CH_3), 53.1 (Ar_3CH), 110.1, 111.4, 119.6, 119.7, 120.1, 120.2, 122.7, 123.2, 124.4, 126.1, 129.3, 129.7 (all Ar-CH), 112.0, 112.2, 129.46, 129.49, 129.8, 134.3, 134.9, 135.9, 136.7, 148.5 (all Ar-C).
17. (a) Ciamician, G.; Plancher, G. *Chem. Ber.* **1896**, *29*, 2475; (b) Jackson, A. H.; Smith, P. *Tetrahedron* **1968**, *24*, 2227; (c) Jackson, A. H.; Naidoo, B.; Smith, P. *Tetrahedron* **1968**, *24*, 6119.
18. *In a typical experiment*, a solution of indole (**1a**; 1 mM) and thiophene-2-carboxaldehyde (**2g**; 0.5 mM) in CH_2Cl_2 (2 ml) was adsorbed on Montmorillonite K10 clay (2 g), and the solvent was allowed to evaporate at rt. After completion of the reaction (TLC), the organic matter was leached with CH_2Cl_2 (3×15 ml), filtered, the solvent removed from the filtrate and the residue crystallised from pet. ether–CH_2Cl_2 to furnish **3g** as red prisms, mp 188–190°C; 132 mg (80%); IR: 3403, 745 cm^{-1}; MS: *m/z* 328 (M^+; 100%), 295, 243, 210, 117; ^1H NMR ($CDCl_3$; 500 MHz): δ 6.15 (1H, s, Ar_3CH), 6.81 (2H, s), 6.88–6.93 (2H, m), 7.02 (2H, t, *J* 7.5 Hz), 7.14 (1H, dd, *J* 5, 1 Hz), 7.16 (2H, t, *J* 7.5 Hz), 7.33 (2H, t, *J* 8 Hz), 7.45 (2H, d, *J* 8 Hz), 7.88 (2H, s, 2×NH); ^{13}C NMR ($CDCl_3$; 125 MHz): δ 35.7 (Ar_3CH), 111.5, 119.7, 120.18, 122.4, 123.5, 124.0, 125.5, 126.8 (all Ar-CH), 120.10, 127.1, 136.9, 149.0 (all Ar-C). All products were identified by IR (nujol), MS (EI/CI), ^1H ($CDCl_3$; 500 MHz) and ^{13}C (125 MHz) NMR, DEPT 135 spectra and, for new compounds, additionally by elemental analysis and/or HR EI/CI-MS.
19. Yadav, J. S.; Reddy, B. V. S.; Murthy, Ch. V. S. R.; Kumar, G. M.; Madan, Ch. *Synthesis* **2001**, 787.
20. Julia, M.; Tilly, G. *Bull. Soc. Chim. Fr.* **1965**, 2175.