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Novel clay-mediated, tandem addition–elimination-(Michael) addition reactions of indoles with 3-formylindole: an eco-friendly route to symmetrical and unsymmetrical triindolylmethanes

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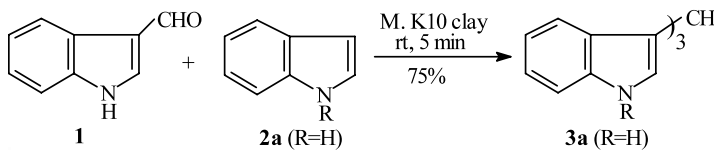
Abstract—Dry reaction of 3-formylindole (**1**) with indole (**2a**) on Montmorillonite K10 clay at room temperature furnished within minutes tris(indol-3-yl)methane (**3a**) in high yield. The reaction of **1** with other mono- and dialkylindoles (**2b–c**, skatole, **8a–c**) under similar conditions yielded either or both of symmetrical (**3b–c**, **9**) and unsymmetrical (**4b–c**, **5b–c**, **10**, **11a–c**) triindolylmethanes.

In organic syntheses and reactions, increasing attention is being focused on green chemistry using environmentally benign reagents and conditions and particularly, solvent-free procedures, i.e. dry reactions[1] which often lead to clean, eco-friendly and highly efficient procedures involving simplified work-ups. A large number of reactions have been carried out on the surface of silica gel,[2] alumina,[2,3] zeolites,[4] clays[5] and polymers,[1,2a,6] frequently in conjunction with microwave irradiation[7] which lead to accelerated reaction rates and enhanced yields resulting from microwave dielectric heating. Of the various solid supports used, Montmorillonite K10 (M. K10) clay is being more and more used with success because of its large specific surface area (500–760 m^2/gm)[8] and high Brønsted acidity (Hammett acidity function H_0: −6 to −8).[9]

In continuation of our interest in clay-mediated reactions of indoles,[10] we have successfully carried out a novel, dry reaction of indole and alkylindoles with 3-formylindole on M. K10 clay, leading to either or both of symmetrical and unsymmetrical triindolylmethanes (TIMs). The experiments, their outcome and the significance of our findings have been briefly presented in this communication.

When a solution of 3-formylindole (**1**) and three molar equivalents[11] of indole (**2a**) was adsorbed on M. clay and the solvent allowed to evaporate off at room temperature, **1** was consumed (TLC) within 5 min to furnish tris(indol-3-yl)methane (**3a**) as the only product (Scheme 1). This method is better than the previous synthesis of **3a** by a protic acid-catalysed condensation of **1** and **2** in solution,[12] since the yields are comparable but the present one is faster and requires milder conditions (75%, room temperature, 5 min as against 80%, reflux, 0.6 h in the previous case).

With *N*-methylindole (**2b**) under similar conditions, **1** was again consumed within 5 min and furnished the TIMs, tris(*N*-methylindol-3-yl)methane (**3b**), (indol-3-yl)-bis(*N*-methylindol-3′-yl)methane (**4b**), bis(indol-3-yl)-(*N*-methylindol-3′-yl)methane (**5b**) and indole in an



1 **2a** (R=H) **3a** (R=H)

Scheme 1.

Keywords: condensation; 3-formylindole; (alkyl)indoles; clay; triindolylmethanes.

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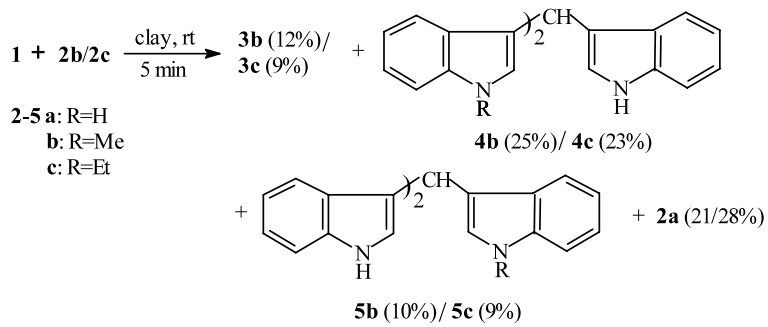
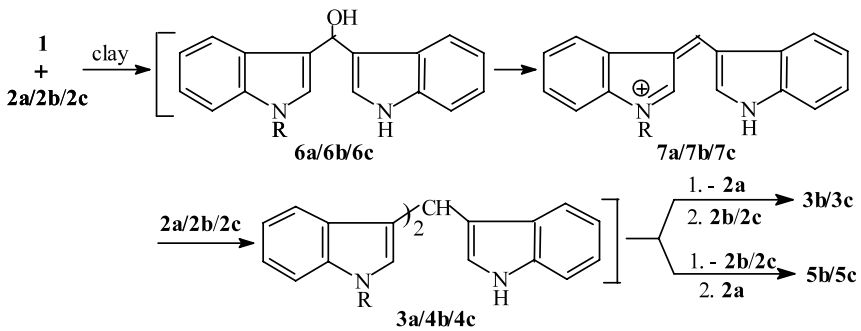
overall yield of 68%. *N*-Ethylindole (**2c**) behaved[13] similarly with **1**, furnishing the symmetrical TIM **3c**[14] and the unsymmetrical TIMs **4c**[15] and **5c**[16] in addition to indole (Scheme 2).

The reaction of **1** with **2a–c** clearly proceeded through the successive intermediacies of the related bis(indol-3-yl)carbinols **6a–c** and the indoleninium species **7a–c** (both of which were obviously formed through the mediation of clay) to form the symmetrical TIMs **3a** and **4b–c**. The subsequent loss of a molecule of indole (or *N*-alkylindole), followed by Michael addition of *N*-alkylindole (or indole), resulted in the unsymmetrical TIMs **3b–c** (or **5b–c**) (Scheme 3). The isolation of indole and *N*-alkylindoles from the respective experiments lends support to the suggested mechanism.

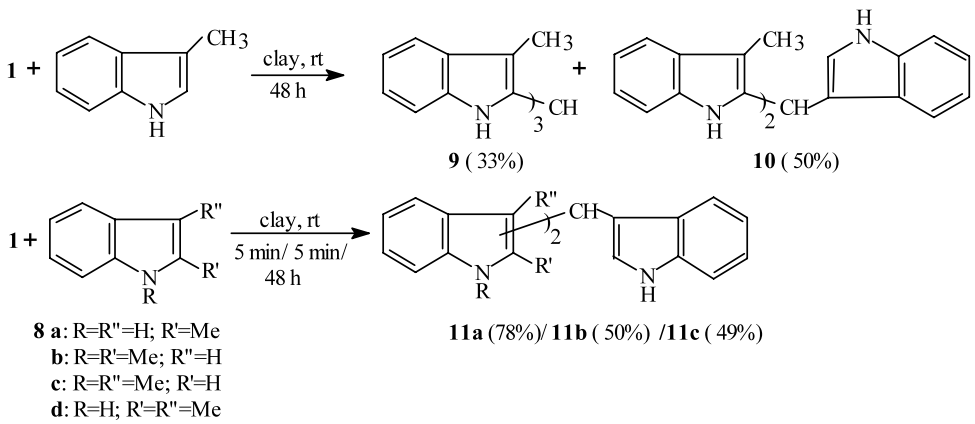
In order to ascertain the influence of alkyl substitution at the fused pyrrole ring, the reaction of **1** was next carried out with skatole, 2-methylindole (**8a**), 1,2-dimethylindole (**8b**), 1,3-dimethylindole (**8c**) and 2,3-dimethylindole (**8d**) separately. No reaction took place with **8d**. With skatole, both a symmetrical TIM (**9**) and an unsymmetrical TIM (**10**) were formed. With each of **8a–c**, however, only one type of unsymmetrical TIM, viz. **11a**/**b**/**c** was formed (Scheme 4). In all likelihood, steric crowding in **8a–c** is responsible for the lack of formation of the respective symmetrical TIMs and for the formation of only one type of unsymmetrical TIM. Pertinently, the reactions with skatole and **8c** were sluggish, requiring 48 h for the completion of the reactions using twice the amount of clay, thereby pointing to the roles of both 3-alkylation and the surface area of clay in influencing the rate of the reactions.



Scheme 2.



Scheme 3.



Scheme 4.

To our knowledge, this is the first report of the formation of both symmetrical and unsymmetrical triindolylalkanes by tandem addition–elimination-(Michael) addition reaction of indoles, and that too on a clay surface. This reaction should be typical of the indole ring, provided the nucleophilicity of the latter is not destroyed by, for example, *N*-acylation/aroylation. Our findings are significant in view of the recent identification of a bacterial metabolite as a triindolylalkane,[17] the conversion of derivatised triarylalkanes into important cage compounds[18] and the physicochemical studies of several triarylalkyl cations.[19] Additionally, the present work opens up the possibility of the development of a new, general synthesis of symmetrical TIMs without the use of any protic or Lewis acid. This lead is at present being explored by us.

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11. When two mol equiv. of indole was used, the reaction was very sluggish and did not go to completion. Three mol equiv. of indole or alkylindole was, therefore, used in all the experiments.
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13. In a typical experiment, a solution of **1** (0.6 mmol) in EtOAc:MeOH (1:1; 0.5 ml) was mixed with a solution of **2c** (1.8 mmol) in EtOAc (0.5 ml) and adsorbed on M. K10 clay (5 g), and the solvent was allowed to evaporate off at room temperature. After 5 min of mixing, leaching with CH_2Cl_2 (3×15 ml), removal of the solvent and preparative TLC of the resulting residue in petrol–EtOAc (4:1) furnished **3c**, **2a** (28%), **4c** and **5c** which, along with products from other reactions, were crystallised from petroleum ether (bp 60–80°C)–CH_2Cl_2 and identified by correct elemental analyses, IR (KBr), (LR/HR)EI MS, ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR ($CDCl_3$), DEPT 135, HMQC and HMBC spectra.
14. **3c**: 24 mg (9%); orange needles, mp 216–218°C; IR: 1440, 1360, 740 cm^{-1}; HRMS: m/z 445.2501 ($C_{31}H_{31}N_3$; M^+; 100%); ^{1}H: δ 1.35 (9H, t, J 7.2 Hz, N-CH_2CH_3), 4.05 (6H, q, J 7.2 Hz, N-CH_2CH_3), 6.15 (1H, s, Ar_3CH), 6.70 (3H, s, H-2), 6.96 (3H, t, J 7.2 Hz, H-5), 7.16 (3H, t, J 7.2 Hz, H-6), 7.31 (3H, d, J 8 Hz, H-7), 7.47 (3H, d, J 8 Hz, H-4); ^{13}C: δ 136.8, 128.2, 118.5 (all C), 126.8, 121.3, 120.8, 118.6, 118.5, 109.4, 31.6 (all CH), 41.1 (CH_2), 15.9 (CH_3).
15. **4c**: 58 mg (23%); red prisms, mp 222–224°C; IR: 3406 (*N*H), 1459, 1348, 740 cm^{-1}; MS: m/z 417 (M^+; 100%); ^{1}H: δ 1.35 (6H, t, J 7.2 Hz, N-CH_2CH_3), 4.05 (4H, q, J 7.2 Hz, N-CH_2CH_3), 6.15 (1H, s, Ar_3CH), 6.70 (2H, s, H-2), 6.77 (1H, d, J 1 Hz, H-2), 6.97 (2H, t, J 7.5 Hz, H-5), 7.0 (1H, t, J 7.5 Hz, H-5), 7.16 (1H, t, J 7.5 Hz, H-6), 7.17 (2H, t, J 7.5 Hz, H-6), 7.32 (2H, d, J 8.2 Hz, H-7), 7.35 (1H, d, J 8.2 Hz, H-7), 7.48 (2H, d, J 7.8 Hz, H-4), 7.50 (1H, d, J 7.8 Hz, H-4), 7.85 (1H, br s, *N*H); ^{13}C: δ 137.1, 136.8, 128.1, 127.6, 120.2, 118.3 (all C), 126.8, 123.7, 122.0, 121.4, 120.7, 120.5, 119.3, 118.7, 111.3, 109.5, 31.6 (all CH), 41.1 (CH_2), 15.9 (CH_3).
16. **5c**: 21 mg (9%); orange needles, mp 204–208°C; IR: 3400 (*N*H), 1458, 748 cm^{-1}; MS: m/z 389 (M^+; 100%); ^{1}H: δ 1.34 (3H, t, J 7 Hz, N-CH_2CH_3), 4.04 (2H, q, J 7 Hz, N-CH_2CH_3), 6.15 (1H, s, Ar_3CH), 6.70 (1H, s, H-2), 6.77 (2H, s, H-2), 6.97 (1H, t, J 7 Hz, H-5), 6.99 (2H, t, J 7 Hz, H-5), 7.15 (2H, t, J 7 Hz, H-6), 7.16 (1H, t, J 7 Hz, H-6), 7.31 (1H, d, J 8 Hz, H-7), 7.35 (2H, d, J 8 Hz, H-7), 7.48 (1H, d, J 8 Hz, H-4), 7.49 (2H, d, J 8 Hz, H-4), 7.88 (2H, s, *N*H); ^{13}C: δ 137.1, 127.6, 120.0, 118.7 (all C), 126.7, 123.7, 122.0, 121.4, 120.6, 120.5, 119.4, 111.3, 109.5, 31.6 (all CH), 41.1 (CH_2), 15.9 (CH_3).
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