With compliments of the Author
Synthesis of Dii ndolyl- and Heterocyclic(indol yl)methanes
Mohit L. Deb, Pulak J. Bhuyan*
Medicinal Chemistry Division, North East Institute of Science & Technology (Formerly RRL), Jorhat 785006, Assam, India
Fax +91(376)2370011; E-mail: pulak_jyoti@yahoo.com
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Abstract: 3-Alkylated indoles, obtained from a three-component reaction of indole, aldehyde, and N,N-dimethylbarbituric acid, undergo an elimination–addition reaction with another indole molecule or heterocyclic nucleophile giving unsymmetrical diindolylmethanes or heterocyclic(indolyl)alkanes in the absence of a catalyst.

Key words: unsymmetrical diindolylmethanes, indole, 3-alkylated indole, anticancer

3,3′-Diindolylmethane (DIM) is a major digestive product of indole-3-methanol, a potential anticancer component of cruciferous vegetables.1 3,3′-Diindolylmethane is a potent activator of the immune response system in vivo.2 It activates and potentiates interferon-gamma signaling in human cells3 and its use as supplement in human increases the 2-hydroxylation of estrogen metabolites.4 It reduces the growth of breast cancer cells by 95%.5 3,3′-Diindolylmethane exhibits potent anti-proliferative and anti-angiogenic properties in androgen-dependent human prostate cancer cells.6 Its various potent anticancer properties have lead to the National Cancer Institute of the United States beginning clinical trials of 3,3′-diindolylmethane as a therapeutic for numerous forms of cancer. Recently it was found that 3,3′-diindolylmethane A (Figure 1) worked as HIV-1 integrase inhibitor.7 Vibrindole A, a metabolite of the marine bacterium Vibrio parahaemolyticus (isolated from the toxic mucus of the boxfish Ostracion cubicus), has been demonstrated to exhibit antibacterial activity.8 Compound C has growth inhibitory activity on prostate cancer cell lines.9 Compound D was reported to act as a nonsteroidal aromatase inhibitor against breast cancer.10

Symmetrical diindolylalkanes can readily be synthesized by Lewis or protic acid catalyzed indole–aldehyde condensation reactions,11 but the synthesis of unsymmetrical 3,3′-diindolylmethanes have a number of drawbacks and limitations.12 Vallee and co-workers12a reported the first synthesis of unsymmetrical 3,3′-diindolylmethanes, but the procedure was complex. Chakrabarty et al.,12b reported another method for the preparation of such 3,3′-diindolylmethanes through the Michael reaction of 3-(2-nitrovinyl)indole with indoles. However, the method was limited to 2,2-bis(indol-3-yl)-1-nitroethane derivatives. Ji and co-workers13 reported the synthesis of unsymmetrical 3,3′-diindolylmethanes from the reaction of indoles with (1H-indol-3-yl)(alkyl)ethanols catalyzed by ammonium cerium(IV) nitrate and ultrasound. Although the yields of the products were good, the reaction took a long time to go to completion. Recently Csaky and co-workers14 have synthesized unsymmetrical 3,3′-diindolylmethanes from gramine using an expensive catalyst, moreover, the procedure was operationally difficult.

Recently we reported15 the synthesis of some novel 3-alkylated indoles utilizing equimolar amounts of indole, aldehyde, and N,N-dimethylbarbituric acid in one pot under thermal and solvent-free conditions. In the reaction we also observed the formation of small amounts of diindolylmethanes for which a mechanism was proposed. That interesting observation encouraged us to explore the utility of the reaction for the preparation of unsymmetrical diindolylmethanes 3 from the reaction of 3-alkylated indoles 1 and indoles 2 (Scheme 1).

The 3-alkylated indoles 1 were prepared from the reaction of indoles, aldehydes, and N,N-dimethylbarbituric acid.15 Then equimolar amounts of 3-alkylated indole 1a and indole 2a were refluxed in ethanol–water for 30 minutes to afford, after workup, diindolylmethane 3a in excellent
yield. The \(N, N\)-dimethylbarbituric acid (4) eliminated during the reaction was isolated and identified. With suitable conditions established for the reaction, compounds 3b–o were synthesized by utilizing 3-alkylated indoles 1a–i with indoles 2a–f and characterized (Table 1).

The reactions were then studied in various other solvents (e.g., MeOH, MeCN, toluene, CHCl₃, etc.) and also in the absence of solvent, however, the reactions proceeded smoothly only in methanol. A few drops of water to the reaction mixture accelerated the reaction considerably with improved yields of the products.

We also studied the effect of substituents in the phenyl (R₂), indole (R₁), and barbituric acid moiety. It was found that an electron-donating group on the phenyl ring accelerated the reactions. 5-Bromo-1H-indole and 1-methyl-1H-indole had least reactivity. When 3-alkylated indoles 1 bearing barbituric acid (instead of \(N, N\)-dimethylbarbituric acid) were used, the products were obtained easily with a shorter reaction time. However, it is very difficult to prepare substrates, the 3-alkylated indoles bearing barbituric acid, due to their very low solubility.

A plausible mechanism for the reaction is outlined in Scheme 2. The mechanism is an elimination–addition process. First the barbituric acid moiety eliminates the leaving group by loose coordination with the carbonyl oxygen.

Scheme 2

Thus, the reaction of 1a, e with either heterocyclic nucleophiles 5a–e were also studied and this gave a series of heterocyclic(indolyl)alkane derivatives 6a–e in satisfactory yields (Table 2). The structures of the compounds were determined from spectroscopic data and elemental analysis. Thus, the reaction of 1a and 5a in refluxing ethanol–water gave 6a in 85% yield in 30 minutes. The \(^1\)H NMR spectrum of compound 6a shows the chemical shift for the methyl protons attached to the pyrazoline ring at \(\delta = 2.36\) and for the NH proton of the indole moiety at \(\delta = 9.55\). The mass spectrum (HRMS) shows molecular ion peak at 380.1654 \([M + H]^+\).

Longer reaction times were required for 2-alkylated indole 1h (Table 1, entries 13 and 14) as in this cases the nitrogen in the intermediate could interact only via a nonbenzenoid canonical form whereas in case of 3-alkylated indoles the intermediate retained the aromaticity of the benzene ring. When unsubstituted (indol-3-ylmethyl)barbituric acid derivative 1j was used (Table 1, entry 16), the reaction did not occur, as the barbituric acid moiety could not be eliminated even after an extended period of reflux. This can reasonably be explained by the fact that unlike aromatic aldehydes and aliphatic aldehydes containing an \(\alpha\)-hydrogen, the intermediate is not stabilized by either resonance or hyperconjugation. This fact strongly supports our proposed mechanism. Thus the reactivity is in the order of \(R^2 = \text{aromatic} > \text{aliphatic} > \text{hydrogen}\).

Compounds like 3a and 3b were also synthesized easily by the reverse process that is from the reaction of 1d,e (where the indole moiety contains a methyl group at the 2- or 5-position) with indole (acting as a nucleophile). However, the preparation of compounds 1 of this type is very difficult because the elimination–addition process is so fast that it gives symmetrical diindolylmethanes (in case of 5- or 2-methylindole) as the major compound.

In order to broaden the scope of this reaction, the reactivity of 1a with other heterocyclic nucleophiles 5a–e were also studied and this gave a series of heterocyclic(indolyl)alkane derivatives 6a–e in satisfactory yields (Table 2). The structures of the compounds were determined from spectroscopic data and elemental analysis. Thus, the reaction of 1a and 5a in refluxing ethanol–water gave 6a in 85% yield in 30 minutes. The \(^1\)H NMR spectrum of compound 6a shows the chemical shift for the methyl protons attached to the pyrazoline ring at \(\delta = 2.36\) and for the NH proton of the indole moiety at \(\delta = 9.55\). The mass spectrum (HRMS) shows molecular ion peak at 380.1654 \([M + H]^+\).
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Table 1  Synthesis of Unsymmetrical Diindolylmethanes 3 (continued)

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*a* All reactions were performed on a 1 mmol scale.

*b* Isolated yields.
In conclusion, we have reported a very simple, novel, and efficient method for the synthesis of unsymmetrical diindolylmethanes and some (heterocyclic)(indolyl)alkanes in moderate to excellent yields. It is interesting to note that no catalyst is required in the entire course of the reaction. Moreover, all the reactions proceed smoothly in aqueous solvents were found most suitable for the reaction. The effect of solvents in the reaction was studied and prolonged heating methods, is a valuable addition to the chemistry of indoles.

All chemicals including solvent used for reactions without drying. All reagents and solvents were of reagent grade. All IR spectra were recorded on Perkin Elmer system-2000 FTIR spectrometer. 

NMR and 

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2-[(1H-Indol-3-yl)(phenyl)methyl]-3-methyl-1H-indole (3d)

Pink powder; yield: 242 mg (72%); mp 194–195 °C; Rf = 0.77 (15% EtOAc–PE).

IR (CHCl3): 3417 (NH stretch), 3409 (NH stretch), 3055 (w), 2923 (w), 1456 (s), 744 cm⁻¹ (s).

1H NMR (300 MHz, CDCl3): δ = 2.22 (s, 3 H), 5.91 (s, 1 H), 6.64 (s, 1 H), 7.08–7.17 (m, 4 H), 7.21–7.33 (m, 4 H), 7.55–7.58 (d, J = 7.42 Hz, 3 H), 7.85 (s, 2 H), 8.09 (s, 1 H, NH), 8.18 (s, 1 H, NH).

13C NMR (75 MHz, CDCl3): δ = 13.59, 45.37, 112.36, 115.69, 116.22, 123.36, 123.28, 123.99, 124.59, 124.72, 126.01, 126.28, 127.32, 129.03, 131.66, 133.49, 133.55, 133.84, 134.55, 139.96, 140.71, 141.62.

MS: m/z = 337.9 [M + H]+.

5-Bromo-3-[(1H-indol-3-yl)(phenyl)methyl]-3-methyl-1H-indole (3e)

White powder; yield: 248 mg (62%); mp 161–163 °C; Rf = 0.71 (15% EtOAc–PE).

IR (CHCl3): 3410 (NH stretch), 3393 (NH stretch), 3056 (w), 2921 (w), 1456 (s), 744 cm⁻¹ (s).

1H NMR (300 MHz, CDCl3): δ = 5.76 (s, 1 H), 6.49–6.50 (d, J = 3.38 Hz, 2 H), 6.95–6.99 (t, J = 7.62 Hz, 2 H), 7.06–7.13 (m, 3 H), 7.16–7.26 (m, 3 H), 7.44–7.47 (d, J = 8.51 Hz, 2 H), 7.72 (s, 2 H), 8.39 (s, 1 H, NH), 8.57 (s, 1 H, NH).

13C NMR (75 MHz, CDCl3): δ = 40.43, 111.63, 112.98, 113.06, 119.67, 119.74, 120.28, 122.47, 122.70, 124.08, 125.23, 125.33, 126.81, 127.32, 128.81, 129.07, 129.17, 131.65, 137.10, 143.98.


2-Methyl-3-[(3-methyl-1H-indol-2-yl)(phenyl)methyl]-1H-indole (3f)

White solid; yield: 308 mg (88%); mp 217–218 °C; Rf = 0.74 (15% EtOAc–PE).

IR (KBr): 3416 (NH stretch), 3404 (NH stretch), 3058 (w), 2928 (w), 1456 (s), 744 cm⁻¹ (s).

1H NMR (300 MHz, CDCl3): δ = 2.22 (s, 3 H), 2.29 (s, 3 H), 5.89 (s, 1 H), 6.67–6.90 (d, J = 7.18 Hz, 2 H), 7.08–7.18 (m, 5 H), 7.26–7.29 (t, J = 7.44 Hz, 2 H), 7.52–7.55 (d, J = 7.40 Hz, 2 H), 7.96 (s, 2 H), 8.31 (s, 1 H, NH), 8.38 (s, 1 H, NH).

13C NMR (75 MHz, CDCl3): δ = 9.27, 13.05, 41.39, 112.31, 115.60, 116.75, 121.98, 123.11, 123.77, 124.59, 124.71, 126.71, 127.66, 127.09, 128.86, 131.04, 134.44, 134.58, 135.97, 137.11, 139.96, 141.63, 142.54.

MS: m/z = 351.4 [M + H]+.

3-[1H-Indol-3-yl](4-methylphenyl)methyl]-2-methyl-1H-indole (3g)

White shining crystals; yield: 262 mg (75%); mp 198–199 °C; Rf = 0.74 (15% EtOAc–PE).

IR (CHCl3): 3410 (NH stretch), 3402 (NH stretch), 3056 (w), 2927 (w), 1456 (s), 743 cm⁻¹ (s).

1H NMR (300 MHz, CDCl3): δ = 2.28 (s, 3 H), 2.32 (s, 3 H), 5.83 (s, 1 H), 6.62 (s, 1 H), 6.89–7.00 (d, J = 7.17 Hz, 2 H), 7.05–7.08 (d, J = 7.79 Hz, 2 H), 7.11–7.20 (m, 4 H), 7.29–7.40 (m, 4 H), 8.19 (s, 1 H, NH), 8.28 (s, 1 H, NH).

13C NMR (75 MHz, CDCl3): δ = 13.98, 21.22, 44.67, 114.07, 116.04, 123.27, 123.56, 124.06, 124.81, 124.89, 125.02, 126.36, 126.74, 128.61, 128.93, 132.03, 132.41, 133.20, 133.52, 133.89, 136.38, 140.40, 142.35.

MS: m/z = 351.7 [M + H]+.

3-[1H-Indol-3-yl](4-nitrophenyl)methyl]-2-methyl-1H-indole (3h)

Light orange powder; yield: 277 mg (67%); mp 188–191 °C; Rf = 0.65 (15% EtOAc–PE).

IR (CHCl3): 3417 (NH stretch), 3405 (NH stretch), 3056 (w), 2927 (w), 1456 (s), 743 cm⁻¹ (s).

1H NMR (300 MHz, CDCl3): δ = 2.27 (s, 3 H), 5.89 (s, 1 H), 6.66 (s, 1 H), 6.94–6.95 (d, J = 6.13 Hz, 2 H), 7.01–7.09 (m, 3 H), 7.13–7.24 (m, 4 H), 7.35–7.37 (d, J = 7.24 Hz, 3 H), 8.14 (s, 1 H, NH), 8.19 (s, 1 H, NH).

13C NMR (75 MHz, CDCl3): δ = 17.27, 42.56, 109.98, 111.23, 113.36, 116.17, 122.24, 123.28, 124.11, 124.75, 126.34, 126.81, 127.12, 127.43, 128.65, 130.43, 133.31, 134.57, 138.10, 140.03, 141.54, 142.56.

MS: m/z = 415.2 [(M + H)+, 79Br, 100, 417.5 [(M + H)+, 81Br, 98].

3-[5-Bromo-1H-indol-3-yl](3-methylphenyl)methyl]-1-methyl-1H-indole (3k)

Pink powder; yield: 227 mg (55%); mp 211–213 °C; Rf = 0.68 (15% EtOAc–PE).
IR (CHCl₃): 3413 (NH stretch), 3056 (w), 2927 (w), 1456 (s), 1165 (m), 743 cm⁻¹ (s).

1H NMR (300 MHz, CDCl₃): δ = 3.50 (s, 3 H), 5.78 (s, 1 H), 6.66 (s, 1 H), 6.69 (s, 1 H), 6.99–7.02 (d, J = 7.22 Hz, 2 H), 7.05–7.10 (d, J = 7.43 Hz, 3 H), 7.13–7.21 (m, 4 H), 7.35–7.38 (d, J = 7.55 Hz, 3 H), 8.14 (s, 1 H, NH).

13C NMR (75 MHz, CDCl₃): δ = 33.67, 41.86, 109.91, 111.28, 113.36, 115.98, 122.06, 123.29, 124.18, 124.55, 126.37, 126.83, 127.12, 127.47, 128.76, 130.13, 132.88, 134.51, 138.10, 140.21, 141.55, 142.32.

MS: m/z = 415.0 ([M + H]⁺, 79Br, 100), 417.0 ([M + H]⁺, 81Br, 100).


1-Methyl-3-[(2-methyl-1H-indol-3-yl)(phenyl)ethyl]1H-indole (3d)
Pink powder; yield: 168 mg (48%); mp 224–226 °C; Rf = 0.78 (15% EtOAc–PE).

IR (CHCl₃): 3411 (NH stretch), 3056 (w), 2933 (w), 1456 (s), 1013 (m), 744 cm⁻¹ (s).

1H NMR (300 MHz, CDCl₃): δ = 2.15 (s, 3 H), 3.58 (s, 3 H), 5.88 (s, 1 H), 6.50 (s, 1 H), 6.84–7.03 (m, 4 H), 17.15–7.17 (d, J = 6.53 Hz, 2 H), 7.20–7.24 (t, J = 7.38 Hz, 4 H), 7.29–7.31 (d, J = 7.40 Hz, 3 H), 8.18 (s, 1 H, NH).

13C NMR (75 MHz, CDCl₃): δ = 17.13, 37.55, 44.12, 114.0, 114.99, 118.92, 122.29, 123.56, 123.87, 124.35, 124.85, 125.51, 126.32, 128.61, 130.73, 132.74, 132.95, 133.34, 133.68, 136.39, 140.05, 142.22.

MS: m/z = 373.3 [M + Na]⁺.

2-[(1H-Indol-3-yl)(4-methylphenyl)ethyl]-3-methyl-1H-indole (3m)
Straw colored powder; yield: 203 mg (58%); mp 154–156 °C; Rf = 0.62 (15% EtOAc–PE).

IR (CHCl₃): 3410 (NH stretch), 3388 (NH stretch), 3061 (w), 2931 (w), 1456 (s), 744 cm⁻¹ (s).

1H NMR (300 MHz, CDCl₃): δ = 2.20 (s, 3 H), 2.32 (s, 3 H), 5.88 (s, 1 H), 6.55 (s, 1 H), 6.98–7.00 (d, J = 7.37 Hz, 2 H), 7.06–7.17 (m, 4 H), 7.20–7.24 (t, J = 7.34 Hz, 2 H), 7.34–7.37 (d, J = 8.18 Hz, 2 H), 7.54–7.56 (d, J = 6.98 Hz, 2 H), 7.99 (s, 1 H, NH), 8.09 (s, 1 H, NH).

13C NMR (75 MHz, CDCl₃): δ = 9.02, 21.52, 40.40, 111.07, 111.58, 118.14, 118.68, 119.36, 120.16, 121.36, 122.75, 124.35, 127.15, 128.79, 128.88, 129.68, 130.01, 135.37, 136.31, 136.60, 137.09, 139.42.

MS: m/z = 351.5 [M + H]⁺.

2-Methyl-3-[(3-methyl-1H-indol-2-yl)(4-methylphenyl)ethyl]1H-indole (3n)
Brown powder; yield: 240 mg (66%); mp 223–234 °C; Rf = 0.45 (25% EtOAc–PE).

IR (KBr): 3405 (NH stretch), 3056 (w), 2925 (w), 1621 (s), 1561 (w), 1456 (s), 771 cm⁻¹ (s).

1H NMR (300 MHz, DMso-d₆): δ = 2.36 (s, 3 H), 3.63–3.66 (d, J = 8.24 Hz, 1 H), 5.62–5.64 (d, J = 8.19 Hz, 1 H), 6.76 (s, 1 H, NH), 6.96–7.00 (t, J = 7.23 Hz, 2 H), 7.12–7.17 (t, J = 7.41 Hz, 3 H), 7.22–7.29 (m, 3 H), 7.34–7.40 (m, 2 H), 7.62–7.74 (m, 4 H), 9.55 (s, 1 H, NH).

13C NMR (75 MHz, DMSO-d₆): δ = 13.46, 45.77, 54.58, 111.23, 113.65, 116.71, 118.12, 121.43, 121.59, 122.74, 124.38, 125.57, 125.93, 127.89, 131.23, 132.90, 134.27, 139.29, 141.44, 146.45, 161.76.


3-[(Phenyl-1H-pyrrol-2-yl)methyl]-1H-indole (6b)
Brown semisolid; yield: 122 mg (45%); Rf = 0.68 (15% EtOAc–PE).

IR (CHCl₃): 3425 (NH stretch), 3405 (NH stretch), 3060 (w), 1456 (s), 744 cm⁻¹ (s).

1H NMR (300 MHz, CDCl₃): δ = 5.22 (s, 1 H), 6.11–6.15 (m, 2 H), 6.63–6.68 (m, 2 H), 7.09–7.12 (d, J = 7.74 Hz, 3 H), 7.24–7.28 (t, J = 7.19 Hz, 2 H), 7.34–7.47 (m, 4 H), 7.92 (s, 1 H, NH), 8.10 (s, 1 H, NH).

13C NMR (75 MHz, CDCl₃): δ = 44.26, 106.43, 109.0, 113.51, 115.13, 118.35, 121.47, 121.84, 124.42, 125.98, 126.46, 127.81, 128.08, 131.35, 132.91, 137.23, 141.98.

MS: m/z = 295.5 [M + Na]⁺.
6-Amino-5-[(1H-indol-3-yl)(phenyl)methyl]-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (6c)
Colorless crystal; yield: 180 mg (50%); mp 254–256 °C; \( R_f \) 0.60 (40% EtOAc–PE).
IR (KBr): 3442 (br s), 3413 (s), 2955 (w), 1456 (s), 743 cm\(^{-1}\) (s).

**1H NMR (300 MHz, DMSO-\(d_6\)):** \( \delta = 3.22, 3.47, 3.65, 4.58, 6.57, 7.03, 7.17, 8.67 (s, 1 H, NH).\)
**13C NMR (75 MHz, DMSO-\(d_6\)):** \( \delta = 38.15, 50.23, 73.79, 109.74, 113.49, 116.92, 124.78, 128.54, 131.79, 152.38, 153.28, 163.47, \)

3-

References


