Electrophilic substitution reactions of indole: Part XX —
Use of montmorillonite clay K-10

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It is observed that using Montmorillonite Clay K-10 electrophilic substitution of indole with ketones generally stop at
the diindolyl methane stage unlike mineral and Lewis acids where the predominant electrophiles are obtained from aldol
condensation products. Using four different electrophiles, acetone, an α,β-unsaturated ketone (mesityl oxide), a diketone
system (acetyl acetone) and cyclohexanone, indole in the presence of montmorillonite Clay K-10 affords compounds 1-4.

The study of the reactivity of the indole nucleus towards electrophiles constitutes a fascinating area
for investigation. It has been observed that acid induced reactions of indoles usually proceed beyond the initial stage because of the instability of
indolyl carbinols which are generated in situ in the reaction medium. However, a survey of the
literature on indole chemistry has revealed that not much work has been reported with clay minerals
which are known to act as solid Lewis or Bronsted acids1-3. Montmorillonite clay was chosen as it is
inexpensive and it offers several advantages i.e. strong acidity, non-corrosivity and mild reaction
conditions.

The present paper deals with the investigation of four different electrophiles, acetone, an α,β-
unsaturated ketone (mesityl oxide), a diketone system (acetyl acetone) and cyclohexanone with indole (Chart 1).
The aldol condensation of the electrophiles in situ is prevalent with mineral acids4,5 and Lewis
acids6-7. The simple electrophile acetone is fascinating due to its capability of generating C3-, C6- and C9-
units in situ as has been observed earlier4-7 from the reaction products. Hence it is not surprising that
reactions with this electrophile have proved to be complex in nature and have been continuing as a
subject of interest over a period of 88 years4-11. 

Compound 1 was found to be a symmetrical dimer. This was apparent from its molecular ion (M+) peak at
m/z 274 coupled with its 1H NMR spectral data. The 300 MHz 1H NMR spectrum of 1 in CDCl3 revealed
the presence of two >NH protons as a broad singlet at δ 7.73, two methyl groups as six-proton singlet at
δ 1.99. Ten aromatic protons resonated in the region δ 7.52-6.96 [δ 7.52 (2H, d, J = 8.1 Hz), 7.34 (2H, d, J =
8.1 Hz), 7.17 (2H, t, J = 7.6 Hz), 7.01-6.96 (4H, m)]. The structure was further confirmed from the 75.5
MHz 13C NMR spectrum including DEPT experiment in CDCl3. Six aromatic sp3-quaternary carbon atoms
C-3/C-3', C-3a/C-3'a, C-7a/C-7'a resonated at 125.7, 126.7, 137.2 ppm respectively. Ten aromatic sp3-
tertiary carbon atoms C-2/C-2', C-4/C-4', C-5/C-5', C-6/C-6', C-7/C-7' appeared at 121.3, 120.6, 121.4,
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carbon atom C-8 appeared at 36.0 ppm. Two methyl carbon atoms C-9 and C-10 appeared at 30.0 ppm respectively. From the above spectral analysis the structure of 1 could definitely be established as the diindolyl system.

The molecular ion peak (M⁺) at 215 and 300 MHz ¹H NMR spectrum of compound 2 in CDCl₃ revealed the monomeric nature of the compound. A one-proton singlet at δ 8.46 was assigned to >NH proton of the indole nucleus while five aromatic protons were discernible in the region at δ 7.91-6.89 [7.91 (1H, d, J = 7.7 Hz), 7.39 (1H, d, J = 7.7 Hz), 7.29-7.18 (2H, m), 6.89 (1H, d, J = 2.5 Hz)]. Two methyl groups appeared as six-proton singlet at δ 1.62 whereas the third methyl group appeared as a three-proton singlet at δ 1.60. The presence of the carbonyl group was evident in the IR spectrum at 1710 cm⁻¹.

The structure of compound 2 was further confirmed from the ¹³C NMR data including DEPT experiment. Three aromatic sp²-quaternary carbon atoms C-3, C-3a, C-7a resonated at 123.2, 125.4, 137.2 ppm respectively and five aromatic sp³-tertiary carbon atoms C-2, C-4, C-5, C-6, C-7 appeared at 120.6, 120.5, 121.3, 118.8 and 111.6 ppm respectively. The carbonyl carbon atom C-10 and one sp³-quaternary carbon atom C-8 appeared at 209.2 and 34.3 ppm respectively. Three methyl carbon atoms C-11, C-12/C-13 resonated at 31.4 and 28.7 ppm respectively.

Compound 3, C₁₂H₁₄N₂O, M⁺ 316 revealed the presence of two >NH protons in its 300 MHz ¹H NMR spectrum in d⁶-acetone as singlet at δ 10.09. Two methyl groups appeared as three proton singlets each at δ 1.94, 1.47 and two methylene protons as a singlet at δ 3.49. The remaining ten aromatic protons resonated in the region δ 7.33-6.67 [δ 7.33 (2H, d, J = 8.0 Hz), 7.29 (2H, d, J = 7.4 Hz), 7.26 (2H, d, J = 8.0 Hz), 6.95-6.90 (2H, m), 6.72-6.67 (2H, m)]. The presence of the carbonyl group was evident in IR spectrum at 1690 cm⁻¹. Based on these observations the structure of the compound could be established as 3 which was further supported by ¹³C NMR data including DEPT experiment. Six aromatic sp²-quaternary carbon atoms C-3/C-3', C-3a/C-3'a, C-7a/C-7'a resonated at 124.3, 128.0, 139.3 ppm respectively. Ten aromatic sp³-tertiary carbon atoms C-2/C-2', C-4/C-4', C-5/C-5', C-6/C-6', C-7/C-7' appeared at 123.1, 122.5, 123.1, 119.8 and 113.0 ppm respectively. The carbonyl carbon atom, C-10, and one sp³-quaternary carbon atom, C-8 appeared at 209.0 and 39.2 ppm. Two methyl carbon C-11, C-12 and one methylene carbon atom, C-9 resonated at 32.7, 28.6 and 54.8 ppm respectively.

Compound 4 showed a molecular ion (M⁺) peak at m/z 314. The symmetrical dimeric structure of the compound was apparent from its 300 MHz ¹H NMR spectrum in CDCl₃. The two >NH protons resonated at δ 7.86 as a singlet. Ten aromatic protons appeared at δ 7.60-6.90 [7.60 (2H, d, J = 8.0 Hz), 7.30 (2H, d, J = 8.0 Hz), 7.11-7.05 (4H, m), 6.95-6.90 (2H, m)]. Four proton multiplet at δ 2.58-2.55 and six proton
multiplet at $\delta$ 1.68-1.62 were assigned to five pairs of methylene protons.

Based on these observations the structure of the compound could be established as 4. This received further support from its 75.5 MHz $^{13}$C NMR spectral analysis including DEPT experiment. Ten aromatic $sp^2$-tertiary carbon atoms C-2/C-2', C-4/C-4', C-5/C-5', C-6/C-6', C-7/C-7' resonated at 121.2, 121.4, 122.0, 118.5 and 111.0 ppm respectively. Six aromatic $sp^3$-quaternary carbon atoms C-3/C-3', C-3a/C-3'a, C-7a/C-7'a appeared at 123.6, 126.4, 137.1 ppm respectively. One $sp^3$-quaternary carbon atom, C-8, appeared at $\delta$ 39.6 ppm. Five $sp^3$-secondary methylene carbon atoms C-9/C-13, C-10/C-12 and C-11 resonated at 36.9, 23.0 and 26.6 ppm respectively.

Unlike earlier reports with mineral and Lewis acids reactions of the same electrophiles using montmorillonite Clay K-10 stopped at the diindoly methane stage except for mesityl oxide.

Experimental Section

General. Melting points were determined in an electrically heated chamber and are uncorrected. UV spectra (in MeOH) were recorded on a Hitachi U-2000 spectrophotometer; IR spectra in KBr on a Perkin-Elmer 782 spectrophotometer; $^1$H and $^{13}$C NMR spectra using a Bruker AM-300L spectrometer, IH and 13C NMR spectra on a Hitachi U-3000 spectrophotometer; IR spectra in KBr on a Perkin-Elmer 782 spectrophotometer. Column chromatographic analysis was carried out using neutral grade alumina standardized according to Brockmann (BDH, column, product No. 21285). TLC analysis was carried out using silica gel G (Spectrochem. India).

The spots were detected with iodine vapour. Analytical samples were routinely dried in vacuo over P$_2$O$_5$ for 24 hr. Anhydrous sodium sulphate was used for drying solvents.

Reaction of indole with acetone. A solution of indole (1 g) and acetone (15 mL) in methylene chloride (20 mL) was added to activated montmorillonite clay-K10 (0.5 g). The reaction was carried out under nitrogen atmosphere and the mixture was stirred for 3 hr at 27°C. It was filtered off from the clay and concentrated. The concentrate was chromatographed over neutral grade alumina using solvents of increasing polarity as eluates.

Compound 1: It was obtained from the earlier fractions of benzene eluates (R$_f$ 0.64 in benzene ethyl acetate 9:1), yield 22%, m.p. 166°C (brown needles from petrol-methylene chloride). Anal. Calc'd for C$_{19}$H$_{19}$N$_2$: C, 83.21; H, 6.57; N, 10.22. Found: C, 82.97; H, 6.24; N, 10.1%; UV (MeOH): 282, 223 nm (log $\varepsilon$ 4.09, 4.82 respectively); UV (MeOH + 50% HClO$_4$): 351, 261 and 233 nm (log $\varepsilon$ 4.14, 4.46 and 4.26 respectively); IR (KBr): 3400, 1460, 1340, 760 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$, $\delta$): 7.73 (2H, s), 7.52 (2H, d, $J$ = 8.1 Hz), 7.34 (2H, d, $J$ = 8.1 Hz), 7.17 (2H, t, $J$ = 7.6 Hz), 7.01-6.96 (4H, m), 1.99 (6H, s); $^{13}$C NMR (75.5 MHz, CDCl$_3$, ppm): 137.2 (C-7a,C-7'a), 126.7 (C-3a-C-3'a), 125.7 (C-3/C-3'), 121.4 (C-5/C-5'), 121.3 (C-2/C-2'), 120.6 (C-4/C-4'), 118.7 (C-6/C-6'), 111.2 (C-7/C-7'), 36.0 (C-8), 30.0 (C-9/C-10); MS: m/z 274 (M, base peak).

Reaction of indole with mesityl oxide. A solution of indole (1 g) and mesityloxide (5 mL) in methylene chloride (30 mL) was added to activated montmorillonite clay-K10 (0.5 g). The reaction mixture was stirred for 4½ hr at 27°C under nitrogen atmosphere. The reaction mixture was filtered off, dried, concentrated and chromatographed.

Compound 2: It was obtained from the later fractions of hexane-benzene (1:1) eluates (R$_f$ 0.55 in benzene), yield 18%, m.p. 97°C (pink crystals from mixture of hexane and methylene chloride). Anal. Calc'd for C$_{21}$H$_{27}$NO: C, 78.14; H, 7.9; N, 6.51. Found: C, 77.70; H, 7.6; N, 6.28%; UV (MeOH): 281, 221 nm (log $\varepsilon$ 3.84, 4.60 respectively); UV (MeOH + 50% HClO$_4$): 356, 259 and 203 nm (log $\varepsilon$ 4.25, 3.83 and 4.02 respectively); IR (KBr): 3320, 1710, 1450, 1370, 760 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$, $\delta$): 8.46 (1H, s), 7.91 (1H, d, $J$ = 7.7 Hz), 7.39 (1H, d, $J$ = 7.7 Hz), 7.29-7.18 (2H, m), 6.89 (1H, d, $J$ = 2.5 Hz), 3.04 (2H, s), 1.62 (6H, s), 1.60 (3H, s); $^{13}$C NMR (75.5 MHz, CDCl$_3$, ppm): 209.2 (C-10), 173.2 (C-7a), 125.4 (C-3a), 123.26 (C-3), 121.3 (C-5), 120.6 (C-2), 120.5 (C-4), 118.8 (C-6), 111.6 (C-7), 55.0 (C-9), 34.3 (C-8), 31.4 (C-11), 28.7 (C-12/C-13); MS: m/z 274 (M, base peak).

Reaction of indole with acetyl acetone. A solution of indole (1 g) and acetyl acetone (10 mL) in methylene chloride (30 mL) was added to activated montmorillonite clay-K10 (0.5 g). The reaction was carried out under nitrogen atmosphere and the mixture was stirred for 5 hr at 27°C. The reaction mixture was filtered off, dried, concentrated and chromatographed.

Compound 3: It was obtained from the benzene-ethylacetate (9:1) eluate (R$_f$ 0.58 in methylene...
chloride), yield 11%, m.p. 212°C (d) (colourless needles from benzene ethyl acetate mixture). Anal. Calcd for C₂₁H₂₃N₂O : C, 79.75; H, 6.33; N, 8.86. Found : C, 79.16; H, 6.16; N, 8.78%; UV (MeOH) : 282, 225 nm (log ε 4.05, 4.77 respectively); UV (MeOH + 50% HClO₄) : 354, 261 nm (log ε 3.96, 4.30 respectively); IR (KBr) : 3400, 1690, 1420, 1340, 750 cm⁻¹; ¹H NMR (300 MHz, d₆-acetone, δ) : 10.09 (2H, s), 7.33 (2H, d, J = 8.0 Hz), 7.29 (2H, d, J = 24 Hz), 7.26 (2H, d, J = 8.0 Hz), 6.95-6.90 (2H, m), 6.72-6.67 (2H, m), 3.49 (2H, s), 1.94 (3H, s), 1.47 (3H, s); ¹³C NMR (75.5 MHz, d₆-acetone, ppm) : 209.0 (C-10), 139.3 (C-7a/C-7’a), 128.0 (C-3a/C-3’a), 124.3 (C-3/C-3’), 123.1 (C-5/C-5’), 123.1 (C-2/C-2’), 122.5 (C-4/C-4’), 119.8 (C-6/C-6’), 113.0 (C-7/C-7’), 54.8 (C-9), 39.2 (C-8), 32.7 (C-11), 28.6 (C-12); MS : m/z 314 (M⁺, base peak).

**Reaction of indole with cyclohexanone.** A solution of indole (1 g) and cyclohexanone (5 mL) in methylene chloride (30 mL) was added to activated montmorillonite clay K-10 (0.5 g). The reaction was carried out under nitrogen atmosphere and the mixture was stirred for 2½ hr. at 27°C. The reaction mixture was filtered off, dried, concentrated and chromatographed.

**Compound 4.** Petrol-benzene (1:1) fractions afforded compound 4 in 21% yield (R 0.51 in petrol-benzene 1:4), m.p. 146°C (d) (White glassy crystals from petrol and methanol). Anal. Calcd for C₂₂H₂₂N₂ : C, 84.08; H, 7.00; N, 8.92. Found : C, 83.80; H, 6.89; N, 8.79%; UV (MeOH) : 283, 225 nm (log ε 4.05, 4.80 respectively); UV (MeOH + 50% HClO₄) : 352, 262 and 236 nm (log ε 4.14, 4.39 and 4.23 respectively); IR (KBr) : 3400, 1450, 1340, 740 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, δ) : 7.86 (2H, s), 7.60 (2H, d, J = 8.0 Hz), 7.30 (2H, d, J = 8.0 Hz), 7.11-7.05 (4H, m), 6.95-6.90 (2H, m), 2.58-2.55 (4H, m), 1.68-1.62 (6H, m); ¹³C NMR (75.5 MHz, CDCl₃, ppm) : 137.1 (C-7a/C-7’a), 126.4 (C-3a/C-3’a), 123.6 (C-3/C-3’), 122.0 (C-5/C-5’), 121.4 (C-4/C-4’), 121.2 (C-2/C-2’), 118.5 (C-6/C-6’), 111.0 (C-7/C-7’), 39.6 (C-8), 36.9 (C-9/C-13), 26.6 (C-11), 23.0 (C-10/C-12); MS : m/z 314 (M⁺, base peak).

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**References**

8 Scholtz M, Ber ds chem Ges, 46, 1913, 1082.
9 Majima R & Kotake M, Ber ds chem Ges, 55, 1922, 3865.
11 Banerji J, Unpublished results.