

AlCl₃-Catalyzed Synthesis of 3-Alkylated/3-Alkenylated Indoles from 1,3-Dicarbonyl Compounds

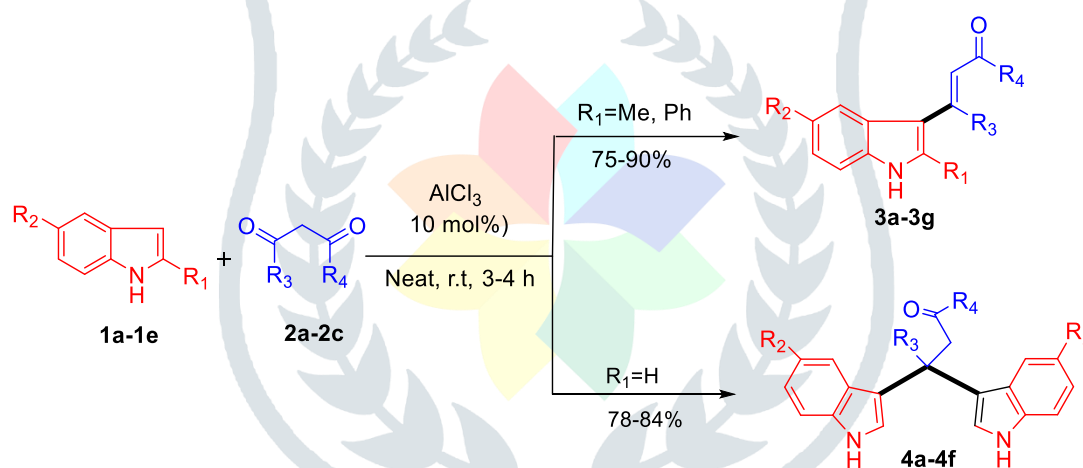
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Abstract: The absolute remarkability of AlCl₃ has been found to be an efficient and inexpensive catalyst for the synthesis of 3-alkylated/3-alkenylated indoles in substantial yields by using different indoles and 1, 3-dicarbonyl compounds at room temperature.

Key words: Aluminium Chloride, 3-alkenylated indoles, 1,3-dicarbonyl compounds, bis(indolyl)carbonyl compounds.

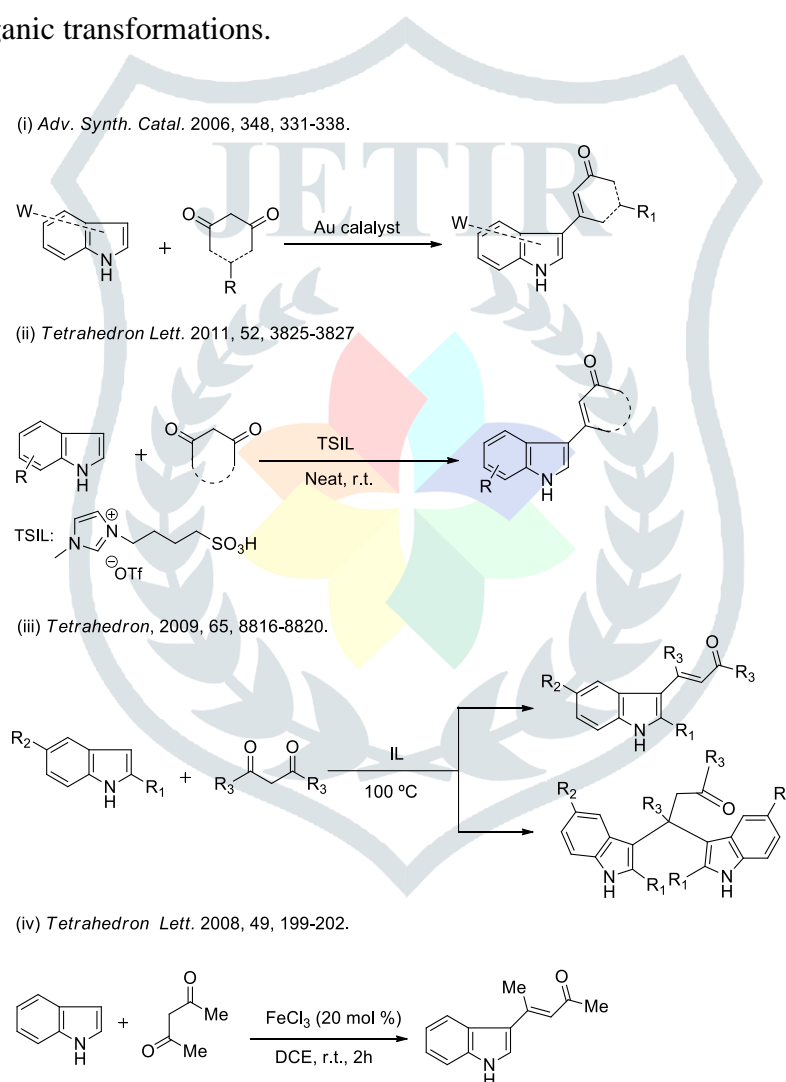


1a: R₁=CH₃, R₂=H, **1b:** R₁=C₆H₅, R₂=H, **1c:** R₁=H, R₂=H, **1d:** R₁=H, R₂=Br, **1e:** R₁=H, R₂=OCH₃

2a: R₃=CH₃, R₄=CH₃, **2b:** R₃=CH₃, R₄=OCH₂CH₃, **2c:** R₃,R₄= -(CH₂)₃-

Introduction: The indole nucleus is one of the most ubiquitous heterocycles in nature and represents a “privileged” structural motif with broad spectrum of pharmaceutical and biological activities.¹⁻⁴ Among different substitution patterns, 3-substituted indoles are of special interest as vital building blocks of therapeutic agents, and display activities such as anticancer, antimigraine, antidepressant, anti-inflammatory, antiestrogen, antagonist, etc.⁵⁻¹⁰ Therefore, the synthesis and selective functionalization of indoles at C-3 position represents an important theme of heterocycle research.¹¹⁻¹² 3-Alkylated indoles are vital compounds in pharmaceutical chemistry, and their direct synthesis involves the conjugate addition of indoles to α , β -unsaturated compounds in the presence of protic or Lewis acids.¹³⁻²¹ While these methods for preparing 3-

alkylated indoles are well established, there exist only a few reports for the preparation of 3-alkenylated indoles such as, gold(III) chloride-catalyzed direct coupling of indoles and pyrroles with 1,3-dicarbonyl compounds,²² a task-specific ionic liquid (TSIL)-catalyzed coupling of indoles with 1,3-dicarbonyl compounds,²³ guanidinium based ionic liquids catalyzed 3-alkylation/vinylation of indoles,²⁴ and iron(III) chloride-catalyzed alkylation of indoles with 1,3-dicarbonyl compounds,²⁵ (Scheme 1). These methods are valuable; however, suffer from one or other drawback such as use of strongly acidic conditions and expensive reagents. Therefore, there remains enough room for the development of more mild and efficient methods for the preparation of 3-alkenylated indoles. The use of AlCl₃ has received considerable attention as Lewis acid catalyst for various organic transformations.



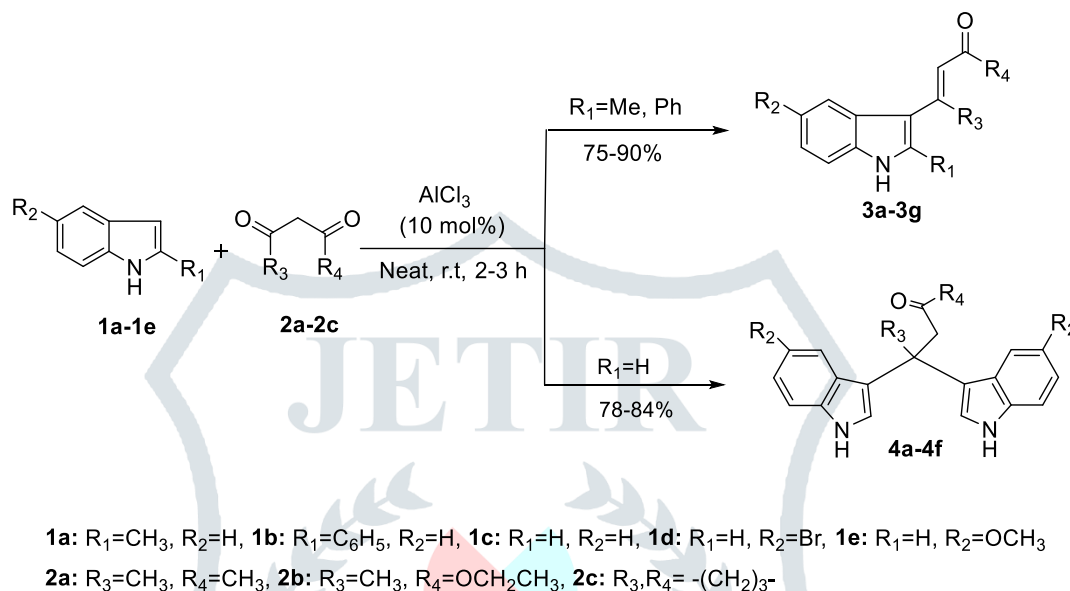
Scheme 1. Some approaches to alkenylated indoles

The “green chemistry” concept has evolved as a central theme to meet the scientific challenges of protecting human health and the environment. Green chemistry is defined as “the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture, and application of chemical products” and focuses on minimum hazard as the criteria while designing new chemical processes.²⁶ Greener aspects in organic synthesis now invariably include the use of benign reaction media or solvent-free reactions. Solvent-free organic reactions, where neat reagents (solid-solid or solid-

liquid) react together in the absence of a solvent, have come up as a fast-developing technology.^{27,28} Scott et al. have postulated a model for such solvent-free reactions for better understanding of the mechanism.²⁹

Results and Discussion:

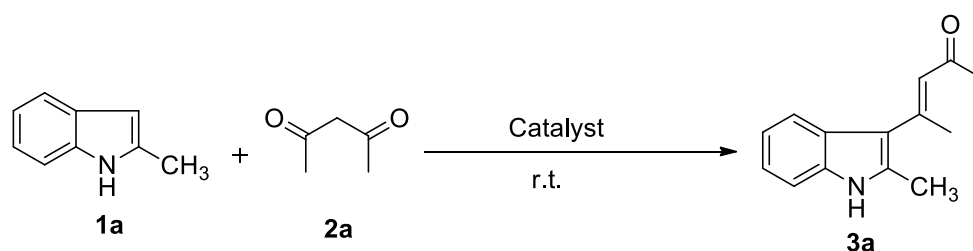
In view of the above we describe herein an AlCl_3 (10 mol %) catalyzed, mild, simple and efficient procedure for the construction of 3-alkenylated/alkylated indoles (**3/4**) at room temperature using different indoles **1** and 1,3-dicarbonyl compounds **2** (Scheme 2).



Scheme 2. C-3 Alkylation/alkenylation of indoles

In order to optimize the reaction conditions, the effect of different catalysts and solvents was investigated in detail for a typical reaction of 2-methylindole (**1a**), and acetylacetone (**2a**). As the solvent-free synthesis has gained much current interest, it was imperative to investigate the reaction under solvent-free conditions as well. The outcome is given in Table 1.

Table 1. Optimization of reaction conditions^a



| Entry | Catalyst (mol %) | Solvent | Time (h) | Yield % |
|-------|----------------------------|---------|----------|-----------------|
| 1 | - | - | 10 | nr ^b |
| 2 | [bmim]BF ₄ (10) | - | 10 | nr ^b |
| 3 | [bmim]PF ₆ (10) | - | 10 | nr ^b |
| 4 | ZnCl ₂ (10) | - | 3 | 75 |

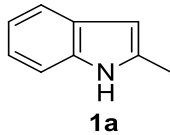
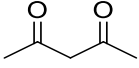
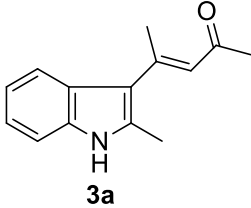
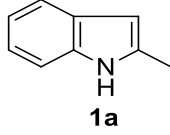
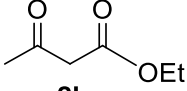
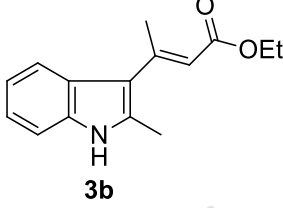
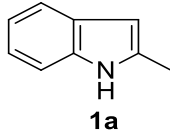

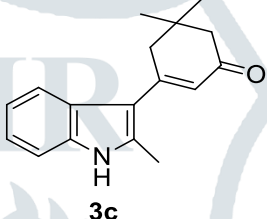
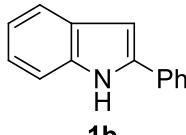
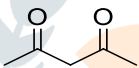
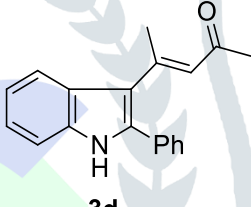
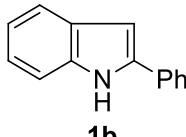
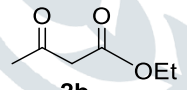
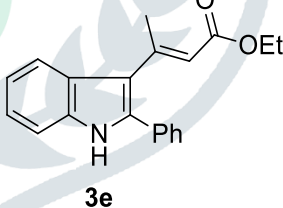
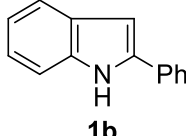
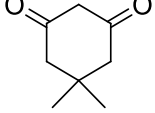
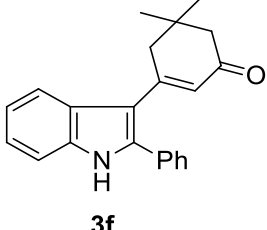
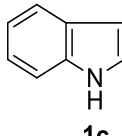
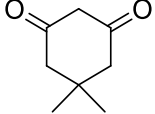
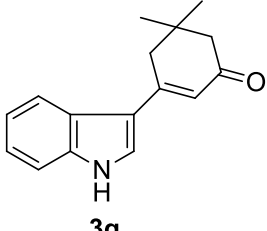
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|-----------|--|---------------------------------|----------|-----------|
| 5 | MnCl ₂ ·6H ₂ O(10) | - | 3 | 60 |
| 6 | NiCl ₂ ·6H ₂ O(10) | - | 3 | 70 |
| 7 | CuCl ₂ (10) | - | 3 | 72 |
| 8 | LiClO ₄ (10) | - | 3 | 50 |
| 9 | NH ₂ ·SO ₃ H(10) | - | 4 | 55 |
| 10 | AlCl₃ (10) | - | 2 | 90 |
| 11 | AlCl ₃ (10) | CH ₂ Cl ₂ | 2 | 90 |
| 12 | AlCl ₃ (10) | CH ₃ CN | 2 | 78 |
| 13 | AlCl ₃ (10) | THF | 2 | 75 |
| 14 | AlCl ₃ (10) | EtOH | 2 | 78 |
| 15 | AlCl ₃ (10) | MeOH | 2 | 75 |
| 16 | AlCl ₃ (5) | - | 5 | 70 |
| 17 | AlCl ₃ (15) | - | 2 | 89 |
| 18 | AlCl ₃ (20) | - | 2 | 90 |

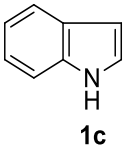
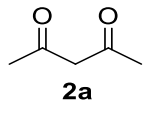
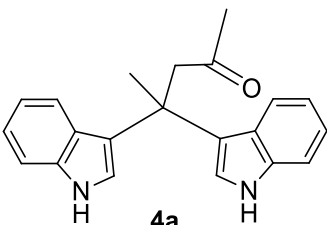
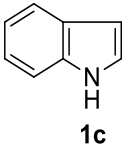
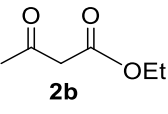
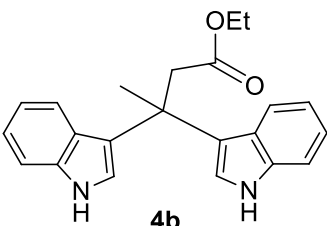
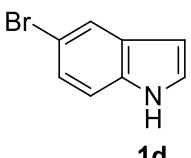
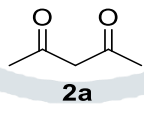
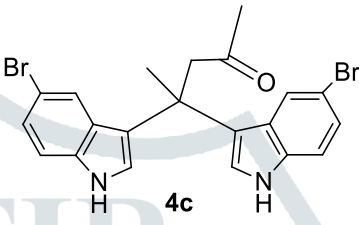
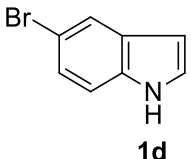
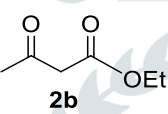
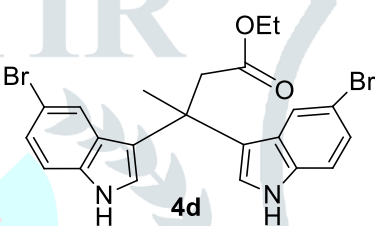
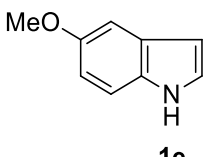
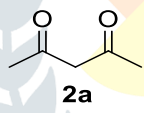
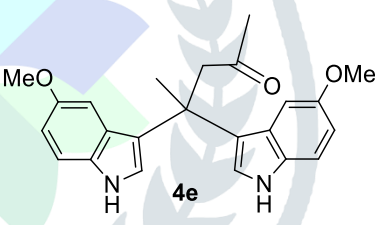
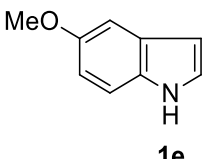
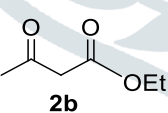
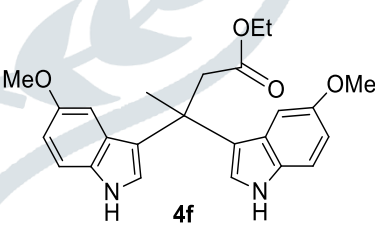
^a Using equimolar ratio of **1a** and **2a**.

^b nr = no reaction.

It is evident that no conversion to the product was obtained in the absence of a catalyst and solvent even after a prolonged reaction time of 10 h (Table 1, entry 1). A number of catalysts were then screened to make the process possible. Due to their intrinsic advantages as green catalysts, attempts were initially made to study the model reaction employing common ionic liquids such as [bmim]BF₄ and [bmim]PF₆, which could not succeed (entries 2 & 3). Many other catalysts viz. ZnCl₂, MnCl₂·6H₂O, AlCl₃, NiCl₂·6H₂O, and CuCl₂, however, promoted the reaction to a considerable extent (entries 4-8), but the catalysts like lithium perchlorate and sulfamic acid provided rather low product yields (entries 8 & 9). When AlCl₃ was tried as catalyst, it gave rise to the best result to afford the product **3a** in 90% yield at room temperature under solvent-free conditions (entry 10). In terms of catalyst concentration, 10 mol % of AlCl₃ was necessary and sufficient for the effective completion of the reaction (entry 10), as the reaction remained unfinished when 5 mol % of the catalyst was used (entry 16). No further improvement was observed with 15 or 20 mol % of AlCl₃ (entries 17 & 18). In order to screen the effect of solvent, the reaction was undertaken at room temperature using 10 mol % of AlCl₃ in different solvents (entries 11-15). The best conversion was finally achieved either under solvent-free conditions or in dichloromethane at room temperature (entries 10 & 11). To refrain from the use of dichloromethane, AlCl₃ (10 mol %) under solvent-free conditions at room temperature was chosen as the best fit and was subsequently applied to the reaction of 2-methylindole (**1a**), and 2-phenylindole (**1b**) with 1,3-dicarbonyl compounds such as acetylacetone (**2a**), ethyl acetoacetate (**2b**) and dimedone (**2c**) to afford a variety of 3-alkenylated indole derivatives (**3a-3g**) in excellent yields with complete *E*-selectivity (Table 2).

Table 2. Alkylation/alkenylation of indoles with 1,3-dicarbonyl compounds

| Entry | Indole 1 | 1,3-Dicarbonyl compound 2 | Product 3 | Time (h) | Yield (%) ^a |
|-------|--|--|---|-------------|---------------------------|
| 1. |  1a |  2a |  3a | 2 | 92 |
| 2. |  1a |  2b |  3b | 3 | 78 |
| 3. |  1a |  2c |  3c | 3 | 81 ^b |
| 4. |  1b |  2a |  3d | 2 | 80 |
| 5. |  1b |  2b |  3e | 3 | 75 |
| 6. |  1b |  2c |  3f | 2.5 | 81 ^b |
| 7. |  1c |  2c |  3g | 2 | 77 ^b |

| | | | | | |
|-----|--|--|---|-----|----|
| 8. |  1c |  2a |  4a | 2.5 | 79 |
| 9. |  1c |  2b |  4b | 3 | 84 |
| 10. |  1d |  2a |  4c | 3 | 80 |
| 11. |  1d |  2b |  4d | 2.5 | 79 |
| 12. |  1e |  2a |  4e | 2 | 81 |
| 13. |  1e |  2b |  4f | 3 | 84 |

^a Isolated yield.^b Using DCM as a solvent.

It is meaningful to mention that no side product was obtained under the investigated conditions. Some of the reactions, however, could not proceed smoothly under solvent-free conditions, thereby making the use of DCM necessary to achieve desirable conversion (Table 2, entries 3, 6 & 7). When 2-unsubstituted indoles such as indole (**1c**), 5-bromo indole (**1d**), 5-methoxy indole (**1e**) were made to react with 1,3-dicarbonyl compounds, the formation of bis(indolyl)carbonyl compounds **4a-4f** was interestingly observed as the only isolable products (entries 8-13) rather than the expected alkenylated products.

Experimental

General procedure for 3-alkenylation/3-alkylation of indoles

Indole **1** (1 mmol), 1,3-dicarbonyl compound **2** (1 mmol) and AlCl_3 (10 mol %) were placed in a round-bottom flask fitted with a reflux condenser and the mixture was stirred at room temperature for the stipulated period of time (Table 4.2.2). After completion of the reaction as indicated by TLC, saturated aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$ (5 ml) was added to the mixture, and then extracted with ethylacetate (3×5 ml). The combined organic phase was dried over anhydrous Na_2SO_4 , filtered and evaporated under vacuum to afford crude product, which was finally purified using column chromatography (n-hexane/ethyl acetate).

Spectral data of some products:

(E)-4-(2-Methyl-1H-indol-3-yl)pent-3-en-2-one (3a)

^1H NMR (CDCl_3 , 300 MHz) δ : 8.05 (br s, 1H, NH), 7.66-7.63 (m, 1H, ArH), 7.30-7.10 (m, 3H, ArH), 6.37 (s, 1H, CH), 2.64 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 2.29 (s, 3H, CH_3).

^{13}C NMR (CDCl_3 , 75 MHz) δ : 198.9, 151.3, 135.2, 133.5, 126.9, 124.7, 121.8, 120.4, 120.2, 119.5, 32.1, 21.1, 13.6.

(E)-Ethyl-3-(2-methyl-1H-3-indolyl)-2-butenate (3b)

^1H NMR (CDCl_3 , 300 MHz) δ : 7.99 (br s, 1H, NH), 7.65 (d, $J = 7.5$ Hz, 1H, ArH), 7.29-7.25 (m, 1H, ArH), 7.17-7.09 (m, 2H, ArH), 5.92 (s, 1H, CH), 4.25 (q, $J = 7.2$ Hz, 2H, CH_2), 2.66 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 1.35 (t, $J = 7.2$ Hz, 3H, CH_3).

^{13}C NMR (CDCl_3 , 75 MHz) δ : 167.3, 152.0, 135.0, 132.7, 127.0, 121.7, 120.3, 119.5, 117.1, 116.8, 110.4, 59.5, 20.4, 14.4, 13.4.

5,5-Dimethyl-3-(2-methyl-1H-indol-3-yl)cyclohex-2-enone (3c)

^1H NMR (CDCl_3 , 300 MHz) δ : 8.25 (br s, 1H, NH), 7.68-7.65 (m, 1H, ArH), 7.32-7.30 (m, 1H, ArH), 7.20-7.11 (m, 2H, ArH), 6.20 (s, 1H, CH), 2.78 (s, 2H, CH_2), 2.54 (s, 3H, CH_3), 2.37 (s, 2H, CH_2), 1.17 (s, 6H, 2 × CH_3).

^{13}C NMR (CDCl_3 , 75 MHz) δ : 199.8, 155.8, 135.2, 134.4, 126.8, 124.7, 122.1, 120.7, 119.7, 110.7, 51.1, 44.6, 34.3, 28.3, 14.1.

(E)-4-(2-Phenyl-1H-indol-3-yl)pent-3-en-2-one (3d)

^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ : 11.52 (br s, 1H, NH), 7.64-7.65 (m, 3H, ArH), 7.41-7.58 (m, 3H, ArH), 7.07-7.23 (m, 3H, ArH), 6.53 (s, 1H, CH), 2.36 (s, 3H, CH_3), 2.20 (s, 3H, CH_3).

^{13}C NMR ($\text{DMSO}-d_6$, 75 MHz) δ : 21.5, 32.4, 112.7, 116.9, 119.7, 120.7, 122.5, 126.3, 127.4, 127.2, 128.5, 128.1, 129.8, 133.4, 137.9, 151.3, 198.9.

(E)-Ethyl 3-(2-phenyl-1H-indol-3-yl)but-2-enoate (3e)

^1H NMR (CDCl_3 , 300 MHz) δ : 8.90 (br s, 1H, NH), 7.65 (d, $J = 7.5$ Hz, 1H, ArH), 7.29-7.25 (m, 3H, ArH), 7.19-7.01 (m, 5H, ArH), 5.56 (s, 1H, CH), 4.35 (q, $J = 7.2$ Hz, 2H, CH_2), 2.31 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 1.33 (t, $J = 7.2$ Hz, 3H, CH_3).

^{13}C NMR (CDCl_3 , 75 MHz) δ : 166.9, 155.4, 135.5, 131.9, 129.2, 128.7, 127.5, 126.3, 123.7, 122.3, 121.8, 121.7, 119.8, 111.1, 110.4, 61.5, 14.8, 13.9.

5,5-Dimethyl-3-(2-phenyl-1H-indol-3-yl)cyclohex-2-enone (3f)

^1H NMR (CDCl_3 , 300 MHz) δ : 8.52 (br s, 1H, NH), 7.68-7.65 (m, 1H, ArH), 7.32-7.30 (m, 1H, ArH), 7.20-7.11 (m, 7H, ArH), 6.78 (s, 1H, CH), 2.75 (s, 2H, CH_2), 2.39 (s, 2H, CH_2), 1.13 (s, 6H, $2 \times \text{CH}_3$).

^{13}C NMR (CDCl_3 , 75 MHz) δ : 198.7, 152.9, 135.6, 133.5, 131.6, 129.1, 128.8, 127.4, 126.5, 123.3, 121.7, 121.8, 119.4, 111.1, 110.3, 49.9, 46.2, 33.5, 27.5.

3-(1H-Indol-3-yl)-5,5-dimethylcyclohex-2-enone (3g)

^1H NMR (CDCl_3 , 300 MHz) δ : 8.50 (br s, 1H, NH), 8.01-7.99 (m, 1H, ArH), 7.55-7.54 (m, 2H, ArH), 7.43-7.41 (m, 2H, ArH), 6.70 (s, 1H, CH), 2.70 (s, 2H, CH_2), 2.37 (s, 2H, CH_2), 1.15 (s, 6H, $2 \times \text{CH}_3$).

^{13}C NMR (CDCl_3 , 75 MHz) δ : 199.2, 155.1, 135.5, 134.9, 126.7, 124.4, 122.5, 120.8, 119.7, 111.7, 52.1, 45.6, 34.5, 28.7.

4,4-Di(1H-indol-3-yl)pentan-2-one (4a)

^1H NMR (CDCl_3 , 300 MHz) δ : 7.99 (br s, 2H, NH), 7.37-7.31 (m, 4H, ArH), 7.10-7.06 (m, 4H, ArH), 6.90 (t, $J = 7.5$ Hz, 2H, ArH), 3.51 (s, 2H, CH_2), 1.99 (s, 3H, CH_3), 1.54 (s, 3H, CH_3).

^{13}C NMR (CDCl_3 , 75 MHz) δ : 209.8, 137.4, 126.4, 123.4, 122.1, 121.7, 121.4, 119.5, 111.6, 53.7, 38.3, 32.4, 27.7.

Ethyl 3,3-bis(1H-3-indolyl)butanoate (4b)

^1H NMR (CDCl_3 , 300 MHz) δ : 7.95 (br s, 2H, NH), 7.35-7.28 (m, 4H, ArH), 7.10-7.03 (m, 4H, ArH), 6.88 (t, $J = 7.5$ Hz, 2H, ArH), 3.86 (q, $J = 7.2$ Hz, 2H, CH_2), 3.37 (s, 2H, CH_2), 2.08 (s, 3H, CH_3), 0.86 (t, $J = 7.2$ Hz, 3H, CH_3).

^{13}C NMR (CDCl_3 , 75 MHz) δ : 171.3, 135.6, 127.6, 124.5, 123.1, 122.3, 112.6, 112.2, 59.9, 45.5, 37.4, 27.3, 13.7.

4,4-Bis(5-bromo-1H-3-indolyl)pentan-2-one (4c)

^1H NMR (CDCl_3 , 300 MHz) δ : 8.08 (br s, 2H, NH), 7.37 (m, 2H, ArH), 7.20-7.13 (m, 6H, ArH), 3.42 (s, 2H, CH_2), 1.95 (s, 3H, CH_3), 1.60 (s, 3H, CH_3).

^{13}C NMR (CDCl_3 , 75 MHz) δ : 207.0, 135.5, 129.6, 124.7, 123.0, 121.0, 116.4, 113.2, 112.1, 60.3, 37.9, 30.0.

Ethyl 3,3-bis(5-bromo-1H-3-indolyl)butanoate (4d)

^1H NMR (CDCl_3 , 300 MHz) δ : 8.06 (br s, 2H, NH), 7.37 (m, 2H, ArH), 7.20-7.14 (m, 6H, ArH), 3.89 (q, $J = 7.2$ Hz, 2H, CH_2), 3.28 (s, 2H, CH_2), 2.02 (s, 3H, CH_3), 0.91 (t, $J = 7.2$ Hz, 3H, CH_3).

^{13}C NMR (CDCl_3 , 75 MHz) δ : 171.7, 136.9, 126.1, 122.9, 121.4, 121.3, 121.03, 118.8, 111.0, 111.6, 59.7, 45.7, 37.8, 27.4, 13.7.

4,4-Bis(5-methoxy-1H-3-indolyl)pentan-2-one (4e)

^1H NMR (CDCl_3 , 300 MHz) δ : 7.90 (br s, 2H, NH), 7.22-7.07 (m, 4H, ArH), 6.76-6.73 (m, 4H, ArH), 3.61 (s, 6H, $2 \times \text{OCH}_3$), 3.46 (s, 2H, CH_2), 1.95 (s, 3H, CH_3), 1.57 (s, 3H, CH_3).

^{13}C NMR (CDCl_3 , 75 MHz) δ : 209.7, 153.1, 132.3, 126.4, 122.2, 122.0, 112.2, 111.6, 103.4, 55.7, 52.9, 37.6, 31.9, 26.9.

Ethyl 3,3-bis(5-methoxy-1H-3-indolyl)butanoate(4f)

^1H NMR (CDCl_3 , 300 MHz) δ : 7.87 (br s, 2H, NH), 7.19-7.10 (m, 4H, ArH), 6.74-6.71 (m, 4H, ArH), 3.89 (q, $J = 7.2$ Hz, 2H, CH_2), 3.61 (s, 6H, $2 \times \text{OCH}_3$), 3.33 (s, 2H, CH_2), 2.04 (s, 3H, CH_3), 0.90 (t, $J = 7.2$ Hz, 3H, CH_3).

^{13}C NMR (CDCl_3 , 75 MHz) δ : 171.7, 153.0, 132.3, 126.5, 122.3, 122.1, 111.5, 111.0, 103.6, 59.7, 55.7, 45.4, 37.6, 27.1, 13.7.

Conclusion: We have demonstrated the use of AlCl_3 as an inexpensive and efficient catalyst for C-3 alkylation and alkenylation of various indoles with 1,3- dicarbonyl compounds at room temperature, for the most part under solvent-free conditions. Due to the mild nature of reaction, we believe that this process is a useful addition to the available synthetic methodologies.

Acknowledgment: We are grateful to the Council of Scientific and Industrial Research, New Delhi for financial support.

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