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# $FeCl_3$-catalyzed alkylation of indoles with 1,3-dicarbonyl compounds: an expedient synthesis of 3-substituted indoles

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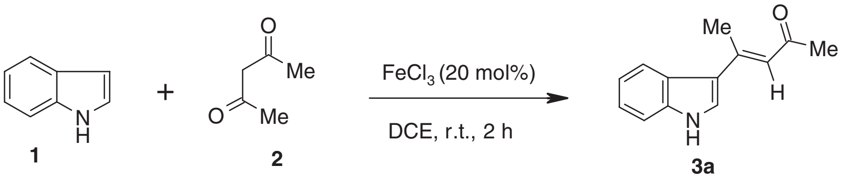
**Abstract**—Indoles undergo smooth alkylation at the 3-position with 1,3-dicarbonyl compounds in the presence of 20 mol % of $FeCl_3$ under mild reaction conditions to produce a wide range of 3-substituted indoles in excellent yields and with high *E*-selectivity.

The indole nucleus is frequently found in natural products, pharmaceuticals, functional materials, and agrochemicals.[1] Substituted indoles are capable of binding to many receptors with high affinity. Therefore, the synthesis and selective functionalization of indoles have been the focus of active research over the years.[2–4] 3-Substituted indoles are important building blocks for the synthesis of various biologically active molecules. Consequently, there is a continuing interest in the development of improved methods for the synthesis of 3-substituted indoles.[5] One such reaction is the transition metal mediated intermolecular C–C bond formation between these heterocycles and other organic substrates.[6] Typically, organometallic couplings require that one or both entities are prefunctionalized as halides or with another disposable functionality.[7] Particular focus is devoted to developing new methods to couple indoles and pyrroles with carbonyl compounds directly, without modification of either coupling partner. In this context, the reaction of indoles at C-3 and of pyrroles at C-2 with the α-carbon of carbonyl compounds has been reported using transition metal-catalysis.[8] Recently, the reaction of indoles and pyrroles with 1,3-dicarbonyl compounds has also been reported using gold(III) catalysis.[9] However, this method involves long reaction times, high temperatures, expensive reagents, and low conversions and selectivity, which limit its practical utility in organic synthesis. In recent years, iron(III) chloride has emerged as a powerful Lewis acid catalyst and performs many useful organic transformations under mild reaction conditions.[10] Moreover, iron-salts are inexpensive, easy to handle and are environmentally friendly. There have been no previous reports on the direct coupling of indoles with 1,3-dicarbonyl compounds using $FeCl_3$ as a catalyst.

In this Letter, we report a direct $FeCl_3$-catalyzed selective 3-alkenylation of indoles with 1,3-dicarbonyl compounds under mild conditions. We first attempted the coupling of indole (**1**) with acetylacetone (**2**). The



**Scheme 1.**

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*Keywords*: Indoles; Iron(III) reagents; 1,3-diketones; C-3 alkylation.

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**Table 1.** $FeCl_3$-catalyzed alkenylation of indoles with 1,3-dicarbonyl compounds

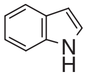
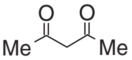
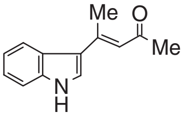
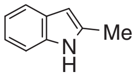
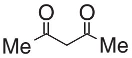
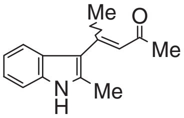
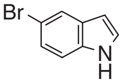
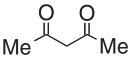
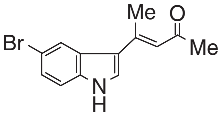
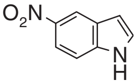
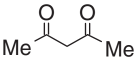
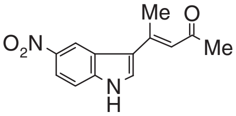
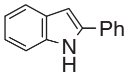
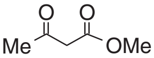
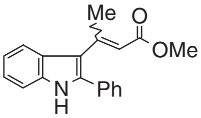
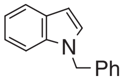
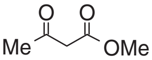
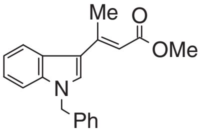
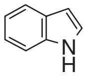
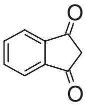
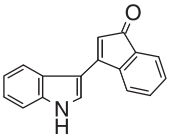
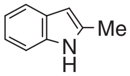
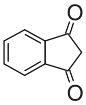
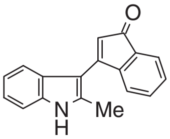
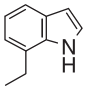
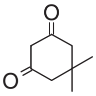
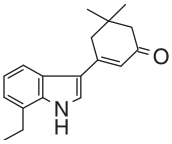
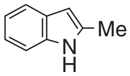
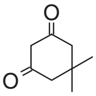
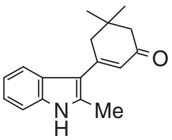
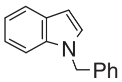
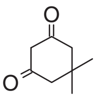
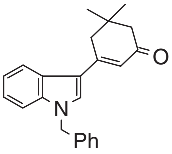
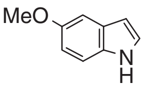
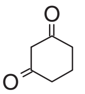
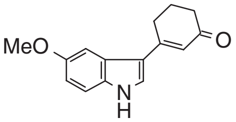
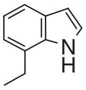
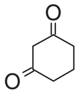
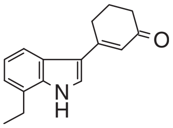
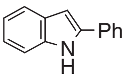
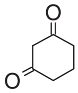
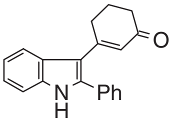
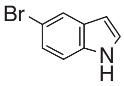
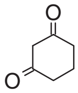
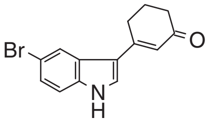
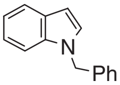
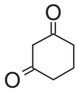
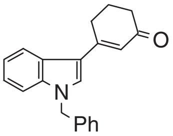
| Entry | Indole | 1,3-Dicarbonyl compound | Product[a] | Time (h) | Yield[b] (%) |
|---|---|---|---|---|---|
| a |  |  |  | 2.0 | 88 |
| b |  |  |  | 2.0 | 90[c] |
| c |  |  |  | 2.0 | 84 |
| d |  |  |  | 2.5 | 85 |
| e |  |  |  | 2.5 | 82[c] |
| f |  |  |  | 2.0 | 85 |
| g |  |  |  | 5.0 | 80 |
| h |  |  |  | 4.5 | 83 |
| i |  |  |  | 6.0 | 80 |
| j |  |  |  | 5.5 | 90 |
| k |  |  |  | 5.0 | 91 |
| l |  |  |  | 6.0 | 86 |

**Table 1** (*continued*)

| Entry | Indole | 1,3-Dicarbonyl compound | Product[a] | Time (h) | Yield[b] (%) |
|---|---|---|---|---|---|
| m |  |  |  | 5.5 | 83 |
| n |  |  |  | 5.0 | 85 |
| o |  |  |  | 5.0 | 88 |
| p |  |  |  | 4.5 | 89 |

[a] All products were characterized by $^1$H NMR, IR, and mass spectroscopy.

[b] Yield refers to pure products after chromatography.

[c] *E*/*Z* ratio 9:1.

reaction was carried out using 20 mol % anhydrous $FeCl_3$ in dichloroethane, and went to completion in 2 h at room temperature giving product **3a** in 88% yield with complete *E*-selectivity (Scheme 1).

Similarly, acetylacetone reacted smoothly with various other indoles such as 2-methyl-, 5-bromo-, and 5-nitro derivatives to produce the corresponding C-alkenyl indoles (Table 1, entries b–d). Like acetylacetone, methyl acetoacetate also participated well in this reaction (Table 1, entries e and f). In the case of 2-substituted indoles such as 2-methyl-, and 2-phenylindoles, the products were obtained as a mixture of *E*/*Z* isomers in a 9:1 ratio, favoring the *E*-isomer (Table 1, entries b and e). Encouraged by these results, we turned our attention to various cyclic 1,3-diones and found that indane-1,3-dione, dimedone, and 1,3-cyclohexadione reacted efficiently with various indoles to produce 3-substituted indole derivatives in high yields (Table 1, entries g–p, Scheme 2).

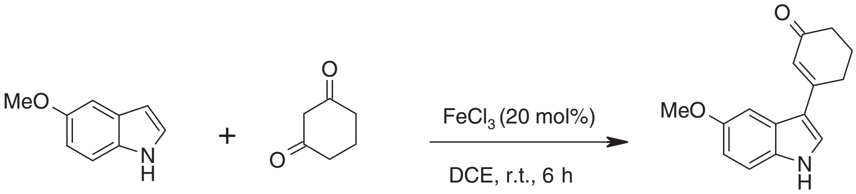
Both electron-rich as well as electron-deficient indoles reacted effectively with 1,3-dicarbonyl compounds under these reaction conditions. In addition, *N*-benzylindole also participated well at room temperature (Table 1, entries f, k, and p). In the absence of catalyst, the reaction failed to give the desired product. The products were characterized by $^1$H NMR, IR, and mass spectrometry and also by comparison with authentic samples.[9] The advantages of this procedure include mild conditions as well as short reaction times, easy work-up, and good yields. This method is effective even with unprotected indoles. There was no considerable difference in yields when comparing protected and unprotected indoles. No bis-indoles were formed in this reaction. As solvent, dichloroethane gave the best

**Table 2.** The effects of various Lewis acids on the preparation of **3a** at room temperature

| Entry | Catalyst | Time (h) | Conversion[a] (%) |
|---|---|---|---|
| 1 | $InBr_3$ | 8.0 | 20 |
| 2 | $InCl_3$ | 8.0 | 15 |
| 3 | $ZrCl_4$ | 8.0 | 12 |
| 4 | $CeCl_3$ | 8.0 | 10 |
| 5 | $YbCl_3$ | 10 | <10 |
| 6 | $YCl_3$ | 10 | <10 |
| **7** | **$FeCl_3$** | **2.0** | **88**[b] |

[a] Conversion by GCMS.

[b] Yield after purification.



**3l**

**Scheme 2.**

results. No chlorination of indole was observed under the reaction conditions. The scope and generality of this process is illustrated in Table 1.[11] The effects of various Lewis acids such as $InCl_3$, $InBr_3$, $ZrCl_4$, $YbCl_3$, $YCl_3$, and $CeCl_3 \cdot 7H_2O$ were studied for this conversion and the results are presented in Table 2. Of these catalysts, anhydrous $FeCl_3$ was found to be the most effective in terms of conversion. Various metal triflates such as $Bi(OTf)_3$, $In(OTf)_3$, $Sm(OTf)_3$, $Yb(OTf)_3$, and $Sc(OTf)_3$ were found to be ineffective for this conversion.

In summary, anhydrous $FeCl_3$ has proved to be a useful and highly efficient catalyst for the C-alkenylation of indoles at the 3-position under mild conditions. In addition to its simplicity and efficiency, this method produces 3-alkenylindoles in excellent yields in short reaction times. This method provides an access to a wide range of potentially valuable 3-substituted indoles.

## Acknowledgment

KP thanks CSIR-UGC for the award of fellowship.

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11. *General procedure*: To a stirred solution of indole (1 mmol) in 1,2-dichloroethane (3 mL) were added the 1,3-dicarbonyl compound (1 mmol) and $FeCl_3$ (0.2 mmol). The resulting mixture was stirred at room temperature for the appropriate time (Table 1). After complete conversion as indicated by TLC, the solvent was removed by evaporation and the residue was diluted with water and extracted with ethyl acetate ($2 \times 10$ mL). The combined organic layers were dried over anhydrous $Na_2SO_4$ and concentrated in vacuo. The resulting product was purified by column chromatography on silica gel (Merck, 100–200 mesh) using ethyl acetate/hexane (3:7) as eluent to afford the pure 3-alkenyl indole derivative.
    Spectroscopic data for selected products:
    *(E)-4-(2-Methyl-1H-3-indolyl)-3-penten-2-one (Table 1, entry b)*: Brown solid, mp 108–110 °C. IR (KBr) $\nu_{(\max)}$: 3245, 2922, 2853, 1654, 1555, 1533, 1456, 1422, 1368, 1257, 741, 700, 530 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ 7.96 (br s, 1H), 7.03–7.59 (m, 4H), 6.32 (s, 1H), 2.63 (s, 3H), 2.53 (s, 3H), 2.26 (s, 3H). $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ 198.9, 151.5, 135.2, 133.9, 130.0, 126.9, 124.3, 121.7, 120.3, 119.4, 110.6, 32.1, 21.0, 13.5. LCMS: *m/z*: 214 $(M+H)^+$. HRMS calcd for $C_{14}H_{16}NO$ $(M+H)^+$: 214.1231. Found: 214.1240.
    *3-(7-Ethyl-1H-3-indolyl)-2-cyclohexen-1-one (Table 1, entry m)*: Brown solid, mp 134–136 °C. IR (KBr) $\nu_{(\max)}$: 3257, 2934, 2866, 1635, 1576, 1439, 1235, 1138, 744 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ 8.60 (br s, 1H), 7.78 (d, $J = 8.3$ Hz, 1H), 7.48 (s, 1H), 7.04–7.16 (m, 2H), 6.62 (s, 1H), 2.80–2.90 (m, 4H), 2.48 (t, $J = 6.7$ Hz, 2H), 2.12–2.21 (m, 2H), 1.37 (t, $J = 7.5$ Hz, 3H). $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ 200.2, 155.7, 127.2, 125.8, 124.5, 124.0, 121.9, 121.9, 121.8, 118.8, 99.9, 37.3, 23.8, 22.7, 13.8. ESI: *m/z*: 254 $(M+H)^+$. HRMS calcd for $C_{17}H_{20}NO$ $(M+H)^+$: 254.1544. Found: 254.1539.
    *3-(1-Benzyl-1H-3-indolyl)-5,5-dimethyl-2-cyclohexen-1-one (Table 1, entry k)*: Pale yellow solid, mp 174–176 °C. IR (KBr) $\nu_{(\max)}$: 3113, 2950, 2869, 1644, 1583, 1516, 1386, 1185, 741 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ 7.96–8.02 (m, 1H), 7.40 (s, 1H), 7.08–7.34 (m,8H), 6.63 (s, 1H), 5.33 (s, 2H), 2.65 (s, 2H), 2.31 (s, 2H), 1.15 (s, 6H). $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ 199.8, 152.7, 136.1, 129.8, 129.9, 128.0, 126.7, 125.7, 123.0, 121.5, 121.3, 120.6, 115.5, 110.4, 99.9, 50.9, 50.4, 42.5, 28.5. ESI: *m/z*: 330 $(M+H)^+$. HRMS calcd for $C_{23}H_{24}NO$ $(M+H)^+$: 330.1857. Found: 330.1863.