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# Study of Friedel-Crafts Acylation of 5-Substituted Indoles to Access 3-Acylindole Derivatives

**Siti Zafirah Zulkifli[1,2], Ayisy Amirul Afti Bakhtiar Afendy[1,2], Aimi Suhaily Saaidin[1] and Noor Hidayah Pungot[1,2]***
[1]Organic Synthesis Laboratory, Institute of Science, Universiti Teknologi MARA, Puncak Alam Campus, 42300 Bandar Puncak Alam, Selangor, Malaysia
[2]Faculty of Applied Sciences, Universiti Teknologi MARA, 40450, Shah Alam, Selangor, Malaysia
*Corresponding author (e-mail: noorhidayah977@uitm.edu.my)

Indole has long stood as a pivotal structural backbone in numerous biologically potent natural compounds and pharmaceuticals. While several synthetic strategies have been developed to construct this framework with reasonable yields, certain obstacles have been encountered. Building upon previous investigations, this study unveils a robust and efficient method to synthesize the 3-acylindole core, utilizing various Lewis acids depending on the nature of the substituent at the C5 position of the indole ring.

**Keywords**: 3-Acylindole; diethyl aluminum chloride; Friedel-Crafts acylation; 5-substituted indole; tin (IV) chloride

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Indole is an aromatic heterocyclic organic compound, consisting of a benzene ring fused with a pyrrole ring. It is plentiful in nature and a key component of many biological compounds, including the amino acid tryptophan, neurotransmitters such as serotonin, and various alkaloids [1]. This compound can be abundantly found and derived from natural resources or through microbial fermentation [2]. Indole is commonly synthesized using a variety of techniques, including the classical method of Fischer indole synthesis, the Bischler–Napieralski reaction, Madelung synthesis, and others [3]. The synthesis of indole and its derivatives is crucial since they have diverse applications in organic synthesis, pharmaceuticals, perfumery, and agriculture.

Although indole is well-known for its fascinating bioactivity, its synthesis is quite challenging. This is due to its multiple reactive sites and inability to control the chemical reaction at specific positions [4]. This regioselectivity contributes to the versatility in organic synthesis and may involve various chemical reactions such as electrophilic and nucleophilic substitutions, oxidation, reduction, and cyclization. The C2 position of indole can act as a nucleophile in various reactions, such as electrophilic aromatic substitution and nucleophilic addition reactions due to the lone pair of its neighbouring nitrogen [5]. Meanwhile the C3 position is also susceptible to nucleophilic attack and functionalization [6].

Indole at C3 position is the most reactive site for electrophilic attack, however, low yields are usually reported because of the ambident reactivity of indoles which can lead to the competitive formation of different products [7]. Particularly, when indole reacts with acylating agents such as acyl chlorides or acid anhydrides, the electrophilic attack can occur at both the C2 and C3 positions resulting in the formations of 1-acylated and 1,3-diacylated products, respectively. Several strategies for controlling the regioselectivity and improving the yields of the products have been highlighted, including the use of protecting groups to selectively block certain reactive sites on the indole ring [8]. Consequently, an additional step is required. Other side reactions can also occur in acidic conditions, including self-polymerization and the less common formation of di-indolylmethanes [8].

In this article, we report a Friedel-Crafts type acylation of 5-substituted indole using a very simple process to provide 3-acylindoles in moderate to higher yields with regioselectivity and without time-consuming workups. Following the investigation by Ottoni et al., we came across an update from a prior study with different groups of substituted indoles under Friedel-Crafts condition using suitable Lewis’s acids and acetyl chloride as acyl chlorides.

## EXPERIMENTAL

### 1. Procedure to Synthesize 5-substituted-3-acetylindole

A 50 mL round bottom equipped with a magnetic stirring bar was added with 5-substituted indole (0.5 g,

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†Paper presented at the International Conference in Organic Synthesis 2024 (ICOS 2024)

2.1 mmol) in dichloromethane ($CH_2Cl_2$) (10 mL) under an argon gas at 0 °C. Tin (IV) chloride ($SnCl_4$) (0.3 mL, 2.52 mmol) was then added in a single portion via syringe and chilled for 10 minutes. After the ice bath was removed, the mixture was stirred at room temperature for 30 minutes, and then acetyl chloride (0.18 mL, 2.52 mmol) was added in small portions followed by nitromethane (7 mL) to increase the solubility of the solid indole-Lewis acid complexes. The mixture was stirred for certain hours at room temperature and monitored via Thin Layer Chromatography (TLC). After the reaction was completed, the mixture was quenched with ice water (20 mL) and filtered to remove inorganic precipitates, and the organic material was extracted with ethyl acetate. The organic phase was dried over sodium sulphate ($Na_2SO_4$) and concentrated to yield a solid product.

### 2. Procedure to Synthesis 5-methoxy-3-acetylindole

The starting material of 5-methoxyindole (0.1 g, 0.679 mmol) was stirred in $CH_2Cl_2$ (5 mL) and 1.13 mL of diethyl aluminum chloride ($Et_2AlCl$) (0.9 mol/L in toluene) was added at 0 °C. The mixture was stirred at 0 °C for 30 minutes and a dropwise of acetyl chloride (0.07 mL, 1.019 mmol) in $CH_2Cl_2$ solution (2 mL) was added. The resulting solution was stirred and monitored via TLC, and pH 7 aqueous buffer was added to quench the reaction and filtered to obtain the product.

**3-acetylindole (1).** Yield 87%, yellow solid. $^1H$ NMR ($C_2D_6OS$, 400 MHz): δ 8.26 (s, 1H), 8.14 (d, 1H), 7.43 (d, 1H), 7.15 (m, 2H), 2.41 (s, 1H). $^{13}C$ NMR ($C_2D_6OS$, 100 MHz): δ 193.3, 137.2, 134.9, 125.8, 123.3, 122.2, 121.8, 117.3, 112.6, 27.8. IR $V_{max}$ cm$^{-1}$: 3410, 3146, 2923, 1595. MS *m/z*: calculated for $C_{10}H_9N_O$, ($M^+$ 159.03) found ($M^+$ 159.08).

**5-trifluoromethyl-3-acetylindole (2).** Yield 70%, green solid. $^1H$ NMR ($CD_3OD$, 400 MHz): δ 8.27 (s, 1H), 8.00 (s, 1H), 7.71 (d, 1H), 7.64 (d, 1H), 2.52 (s, 3H). $^{13}C$ NMR ($CD_3OD$, 100 MHz): δ 195.3, 139.9, 133.4, 126.4, 124.7, 123.3, 117.5, 116.1, 113.9, 110.8, 25.7. IR $V_{max}$ cm$^{-1}$: 3460, 3130, 2945, 1623, 1055. MS *m/z*: calculated for $C_{11}H_8F_3NO$, ($M^+$ 227.04) found ($M^+$ 227.07).

**5-cyano-3-acetylindole (3).** Yield 72%, White solid. $^1H$ NMR ($CD_3OD$, 400 MHz): δ 8.59 (s, 1H), 8.31 (s, 1H), 7.58 (s, 1H), 7.50 (d, 1H), 2.52 (s, 3H). $^{13}C$ NMR ($CD_3OD$, 100 MHz): δ 195.8, 140.8, 133.7, 127.1, 126.6, 124.0, 118.4, 116.3, 112.1, 26.0. IR $V_{max}$ cm$^{-1}$: 3423, 3133, 2932, 2269, 1611.MS *m/z*: calculated for $C_{11}H_8N_2O$, ($M^+$ 184.05) found ($M^+$ 184.07).

**5-fluoro-3-acetylindole (4).** Yield 62%, light brown solid. $^1H$ NMR ($CD_3OD$, 400 MHz): δ 8.17 (s, 1H), 7.84 (s, 1H), 7.34 (d, 1H), 6.97 (d, 1H), 2.477 (s, 3H). $^{13}C$ NMR ($CD_3OD$, 100 MHz): δ 195.1, 160.7, 135.7, 133.6, 126.1, 117.2, 112.6, 112.6, 111.2, 106.6, 25.7. IR $V_{max}$ cm$^{-1}$: 3451, 3127, 2921, 1620, 1219. MS *m/z*: calculated for $C_{11}H_8FNO$, ($M^+$ 177.04) found ($M^+$ 177.07).

**5-chloro-3-acetylindole (5).** Yield 60%, light orange solid. $^1H$ NMR ($CD_3OD$, 400 MHz): δ 8.20 (s, 1H), 8.10 (s, 1H), 7.40 (d, 1H), 7.18 (d, 1H), 2.48 (s, 3H). $^{13}C$ NMR ($CD_3OD$, 100 MHz): δ 194.9, 135.5, 135.3, 127.7, 126.6, 123.2, 120.9, 116.7, 112.8, 25.8. IR $V_{max}$ cm$^{-1}$: 3441, 3117, 2938, 1618, 1222. MS *m/z*: calculated for $C_{11}H_8ClNO$, ($M^+$ 193.02) found ($M^+$ 193.04).

**5-bromo-3-acetylindole (6).** Yield 60%, light green solid. $^1H$ NMR ($CD_3OD$, 400 MHz): δ 8.34 (s, 1H), 8.13 (s, 1H), 7.33 (m, 2H), 2.48 (s, 3H). $^{13}C$ NMR ($CD_3OD$, 100 MHz): δ 195.0, 135.8, 135.2, 127.1, 125.8, 124.0, 116.6, 116.6, 115.2, 113.2, 25.8. IR $V_{max}$ cm$^{-1}$: 3414, 3112, 2901, 1626, 1226. MS *m/z*: calculated for $C_{11}H_8BrNO$, ($M^+$ 236.06) found ($M^+$ 236.09).

**1H-indol-5-yl 2-chlorobenzoate (7).** Yield 78%, white solid. $^1H$ NMR ($CD_3OD$, 400 MHz): δ 7.88 (s, 1H), 7.32 (s, 1H), 7.10 (d, 1H), 6.48 (d, 1H), 3.92 (s, 3H), 2.67 (s, 3H) . $^{13}C$ NMR ($CD_3OD$, 100 MHz): δ 194.0, 163.9, 145.5, 135.3, 133.8, 133.7, 130.6, 130.5, 129.8, 126.5, 126.3, 119.0, 116.1, 112.0, 25.1. IR $V_{max}$ cm$^{-1}$: 3411, 3131, 2948, 1727, 1603. MS *m/z*: calculated for $C_{15}H_{10}ClNO_2$, ($M^+$ 271.04) found ($M^+$ 271.07).

**1H-indol-5-yl 3-(trifluoromethyl) benzoate (8).** Yield 76%, white solid. $^1H$ NMR ($CD_3OD$, 400 MHz): δ 8.41 (d, 2H), 8.17 (s, 1H), 8.04 (s, 1H), 7.96 (d, 1H), 7.75 (t, 1H), 7.47 (d, 1H), 7.10 (d, 1H) 2.48 (s, 3H). $^{13}C$ NMR ($CD_3OD$, 100 MHz): δ 195.1, 164.4, 146.4, 135.4, 135.1, 133.2, 130.8, 129.9, 129.7, 126.1, 125.9, 117.3, 117.2, 113.9, 112.2, 25.8. IR $V_{max}$ cm$^{-1}$: 3416, 3127, 2952, 1730, 1616. MS *m/z*: calculated for $C_{16}H_{10}F_3NO_2$, ($M^+$ 305.08) found ($M^+$ 305.11).

**5-methoxy-3-acetylindole (9).** Yield 77%, brown solid. $^1H$ NMR ($C_2D_6OS$, 400 MHz): δ 8.22 (s, 1H), 7.67 (s, 1H), 7.34 (d, 1H), 6.84 (d, 1H), 3.77 (s, 3H), 2.42 (s, 3H). $^{13}C$ NMR ($C_2D_6OS$, 100 MHz): δ 194.0, 153.1, 131.3, 129.9, 127.2, 116.5, 112.2, 111.1, 103.8, 60.1, 26.5. IR $V_{max}$ cm$^{-1}$: 3472, 3154, 2998, 1614, 1213. MS *m/z*: calculated for $C_{11}H_{11}NO_2$, ($M^+$ 189.05) found ($M^+$ 189.09).

**5-nitro-3-acetylindole (10).** Yield 69%, yellow solid. $^1H$ NMR ($C_2D_6OS$, 400 MHz): δ 8.98 (d, 1H), 8.52 (d, 1H), 8.07 (d, 1H), 8.05 (2, 3H), 7.62 (dd, 1H), 2.46 (s, 3H). $^{13}C$ NMR ($C_2D_6OS$, 100 MHz): δ 193.5, 143.2, 138.2, 130.6, 125.2, 118.3, 118.1, 113.3, 27.8. IR $V_{max}$ cm$^{-1}$: 3436, 3049, 1718, 1340, 1211. MS *m/z*: calculated for $C_{10}H_8N_2O_3$, ($M^+$ 204.05) found ($M^+$ 204.06).

## RESULTS AND DISCUSSION

The analysis revealed the withdrawal of both the substituted electrons, and that the unsubstituted indole provided a higher yield (60–87%) with shorter reaction times, and that no polymerization products were observed in any of these circumstances. As indicated in Table 1, the usage of $SnCl_4$ resulted in a good yield for the indole with the electron withdrawing group (EWG), but a poor yield for the electron donating group (EDG). This is supposedly owing to the EWG on the aromatic sides, which improved the reactivity of the indole by increasing the electron deficiency of the ring and making the C3 more susceptible to electrophilic attack. As predicted, indoles with strong EWG, cyano (CN), and trifluoromethyl ($CF_3$) substituents generated higher yield than weak EWG of halogen (**Entry 4-6**) which furnished moderate yield.

It is well known that indole contains a nitrogen atom in its aromatic ring, making it an electron rich compound [9]. Additional electron-donating substituents, on the other hand, can increase the indole's reactivity towards electrophilic substitution reactions by donating their electron density. This was proven when the Friedel-Crafts acylation was attempted on the strong EDG of 5-methoxyindole. The result showed that the reaction utilizing $SnCl_4$ yielded 10% of the desired product. The Lewis acid of titanium (IV) chloride ($TiCl_4$) yielded only 9%. The effects of the Lewis acid were studied further using aluminum chloride ($AlCl_3$), and unfortunately, no product formed. Similarly, the usage of $AlCl_3$ resulted in no product, indole decomposition, and undesired oligomerization [8].

Delving deeper, $AlCl_3$ is a more reactive Lewis's acid compared to $SnCl_4$ and $TiCl_4$, largely due to its greater ability to accept electron pairs, which can lead to the oligomerization of indoles [10]. In contrast, tin and titanium, having larger atomic sizes and more diffused electron clouds than aluminum, are less efficient at accepting electron pairs. This reduced reactivity in $SnCl_4$ and $TiCl_4$ contributes to lower product yields. To mitigate both oligomerization and poor yield, diethyl aluminum chloride ($Et_2AlCl$) was used as an alternative to $AlCl_3$ and $SnCl_4$ in reactions involving indoles substituted with strong electron-donating groups.

Our findings show that replacing $SnCl_4$ with $Et_2AlCl$ increased the percent yields of 5-methoxy-3-acetylindole from 10 % to 77 %. This could be due to the presence of ethyl groups on the aluminum atom, causing $Et_2AlCl$ to have lower Lewis acidity than the unmodified aluminum chloride molecule. The alkyl group itself acts as an EDG, transferring their electron density to the aluminum center while becoming less aggressive in accepting electron pairs. The comparative study was undertaken with 1,4-dimethoxybenzene skeleton, and the reaction was carried out in the same approach as indole. It was noted that the reaction took a longer time, and the starting material was not completely consumed. Thus, it can be inferred that $Et_2AlCl$ is preferable for Friedel-Crafts acylation on strong EDG indole, but not for EDG with a benzene backbone. The proposed mechanism is depicted in Scheme 1.

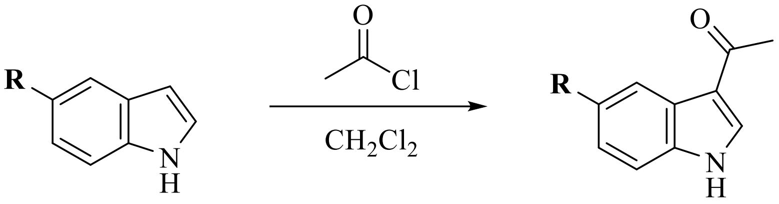
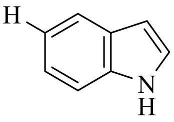
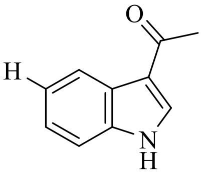
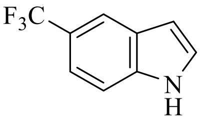
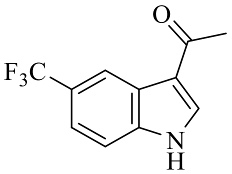
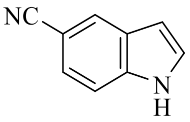
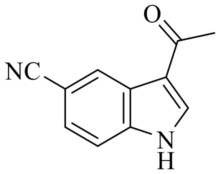
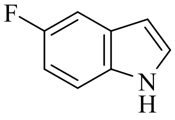
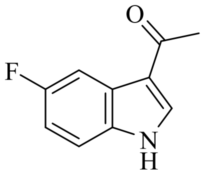
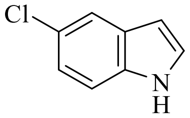
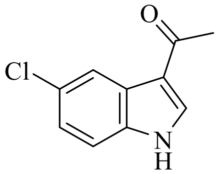
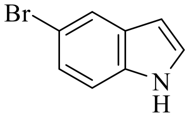
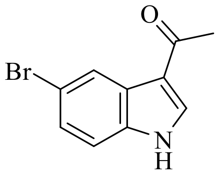
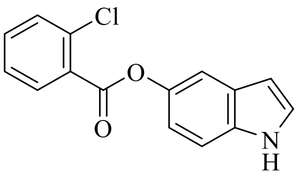
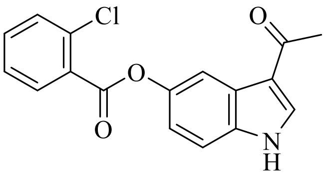
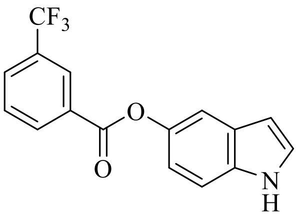
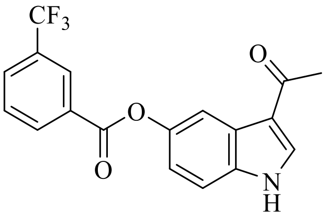
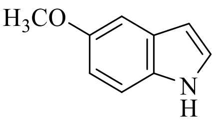
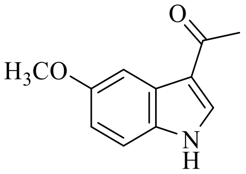
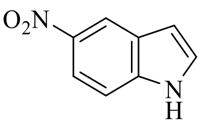
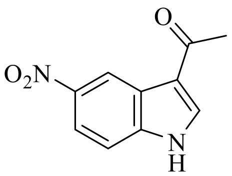
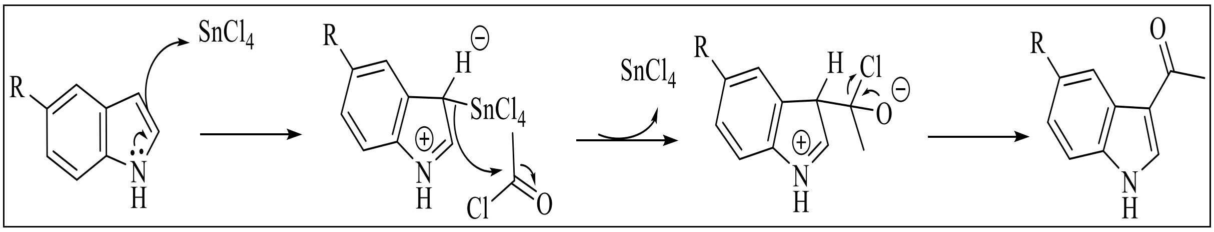


**Table 1.** Effectiveness of acylation on different substituted indole.

| Entry | Starting Material | Lewis's Acids | Reaction Time | Yield (%) | Product |
|---|---|---|---|---|---|
| 1 |  | $SnCl_4$ | 2h | 87 |  |

| | | | | | |
|---|---|---|---|---|---|
| 2 |  | $SnCl_4$ | 5h | 70 |  |
| 3 |  | $SnCl_4$ | 5h | 72 |  |
| 4 |  | $SnCl_4$ | 4h | 62 |  |
| 5 |  | $SnCl_4$ | 4h | 60 |  |
| 6 |  | $SnCl_4$ | 4h | 60 |  |
| 7 |  | $SnCl_4$ | 5h | 78 |  |
| 8 |  | $SnCl_4$ | 4h | 76 |  |
| 9 |  | $AlCl_3$ | 5h | - |  |
| | | $TiCl_4$ | 5h | 9 | |
| | | $SnCl_4$ | 6h | 10 | |
| | | $Et_2AlCl$ | 4h | 77 | |
| 10 |  | $SnCl_4$ | 5h | 69 |  |



**Scheme 1.** Plausible Mechanism of 3-Acylindole Derivatives.

## CONCLUSION

In conclusion, we successfully synthesized 3-acylindoles derivatives through a Friedel-Crafts acylation in the presence of $SnCl_4$, $TiCl_4$ or $Et_2AlCl$, depending on the substituent's located at the C5 position of the indole. Indole with EWG and those that are unsubstituted can be synthesized using $SnCl_4$ in a shorter reaction time, however, the EDG can only be synthesized with $Et_2AlCl$ for a greater yield.

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