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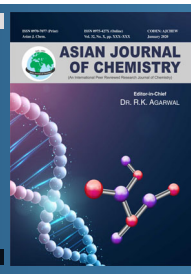

$NbCl_5$ and $AgClO_4$ Promoted Regio-Selective Acylation of Indoles

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In present study, an efficient and simple strategy towards chemo-selective and regio-selective acylation of indole using $NbCl_5$ and $AgClO_4$ catalyst are reported. This method utilizes the catalytic potentiality of $NbCl_5$ and $AgClO_4$ towards acylation of unprotected indoles in a synergistic manner. The combination of these catalytic system results into numerous advantages such as excellent yields of product, short reaction times and easier isolation of products.

Keywords: Regioselective acylation, Silver salt, Indole, Acyl chloride.

INTRODUCTION

Bioactive scaffold 3-acylindoles are important precursors in the synthesis various heterocycles including indole derivatives and alkaloids [1-3]. They exhibit a variety of biological activities such as HIV-1 inhibitor, anticancer, antidiabetic and antinociceptive [4-6], therefore the drugs ramosetron and pravodoline also has 3-acylindoles as structural feature. The most classical approach towards the synthesis of 3-acylindoles is Friedel-Crafts acylation [7-15]. The another methods comprises Vilsmeier-Hack formylation [16-18], Grignard reaction [19-21] and palladium catalyzed coupling of 3-indolyl and acyl chloride [22,23]. The substrate indole is most reactive and non selective in nucleophilic as well as electrophilic substitution reactions are concern and hence in Lewis acid condition in Fridel Crafts reaction it shows multiple acylation products, even in Mannich reaction shows polyacylated compounds. To overcome these undesired products, N-protected or N-deactivated indoles are the most suitable substrates for the acylation reaction. The drawback of these methodologies is that it requires protection-deprotection additional steps and also limits the structural diversity of indole. Lewis acid $AlCl_3$ is conventionally employed in Friedel-Crafts acylation, consequences in polyacylation of indole owing to its strong acidity. To overcome these lacunas many alternative protocols based on mild Lewis acidity has been reported and the Lewis acids used such as imidazolium chloroaluminate, $RAlCl_3$ and $SnCl_4$. Moreover, these methods suffer from many disadvantages which includes non-availability, toxic nature and difficulty in handling of various acylating reactants and requires tedious work-up procedure. In acylation of indoles generates HCl which is mainly responsible for the polymerization. The choice of Lewis acid is most crucial as it favours the Friedel-Crafts acylation and acts as scavenger for HCl by the reaction of acylating reagent to form an acylium ion.

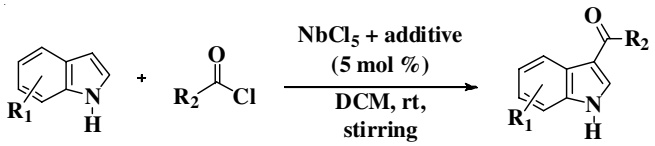
In recent times, strong Lewis acid $NbCl_5$ has been well known and most employed reagent in synthetic organic chemistry owing to its stability, less hygroscopic nature and easy of handling relative to other Lewis acids. Many of the organic transformation catalyzed by $NbCl_5$ have been reported in literature [24]. Furthermore, use of $NbCl_5$ as catalyst in the cleavage of ethers [25] and C-P bond formation [26] has been reported. A strategy for selective dealkylation of alkyl-aryl ethers with a catalytic amount of $NbCl_5$ [27] is also reported. In present method, the potentiality of $NbCl_5$ catalyst towards the Friedel-Crafts acylation as fundamental tool in organic synthesis [28-31] is evaluated.

The present protocol represents simple, mild, and efficient method towards the regio-selective Friedel-Crafts acylation of indole using acyl chlorides with elimination of undesired

products. A wide variety of alkyl/aryl chlorides underwent acylation smoothly with unprotected substituted indoles, which gives 3-acylindoles in moderate to high yields using $NbCl_5$ and $AgClO_4$ as Lewis acid and promoter in DCM at ambient condition.

EXPERIMENTAL

Synthesis: In a round-bottom flask, an indole (153 mg, 1.3 mmol) was dissolved in a dry DCM (1.5 mL) at 0 ºC then the solution of acyl chloride (140 mg, 1 mmol) in DCM (1.5 mL) with syringe and 1 mol % of $NbCl_5$ and 3 mol % of $AgClO_4$ was added. The reaction temperature was then slowly increased to 30 ºC and the reaction was carried out at this constant temperature constantly. After 4 h the reaction was completed and monitored by TLC, then reaction mass was quenched by adding 5 mL water and extracted with ethyl acetate (2 × 15 mL). This subsequent extract was washed with water 10 mL, dried over anhydrous $MgSO_4$ and evaported under vacuum. The purification of crude mass was done column chromatography on silica gel (100-200 mesh) by eluting with ethyl acetate and petroleum ether (10:90), which offered 3-benzoylindole (177 mg, 75 % yield) (**Scheme-I**). The yield of other indoles and acyl chlorides are given in Table-1.

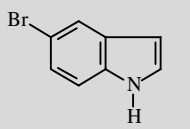
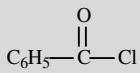
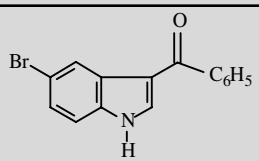
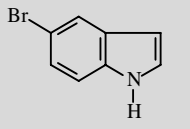
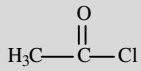
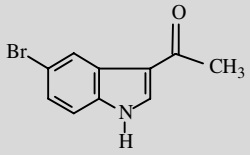
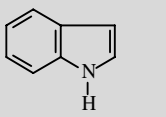
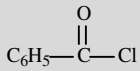
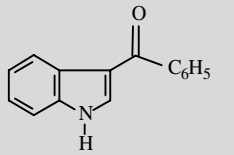
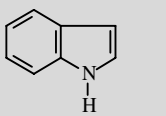
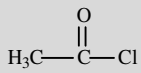
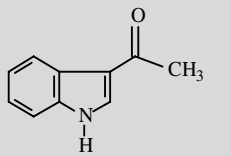
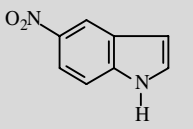
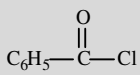
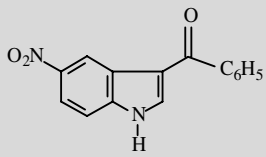
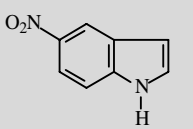
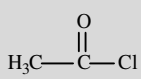
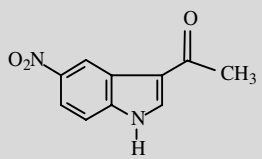
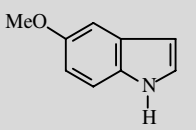
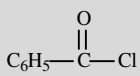
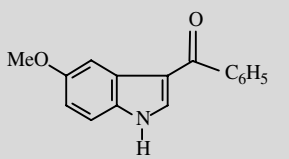


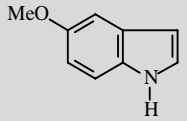
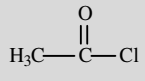
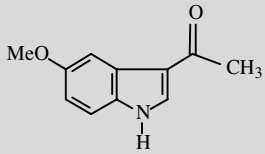
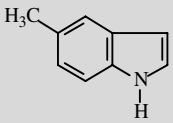
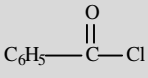
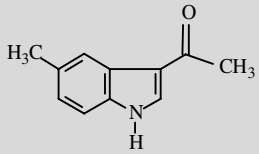
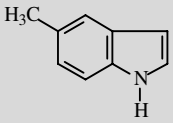
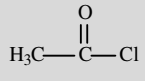
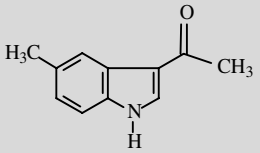
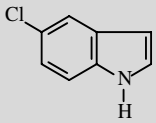
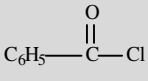
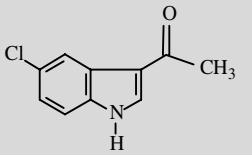
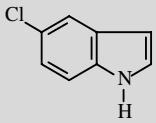
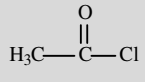
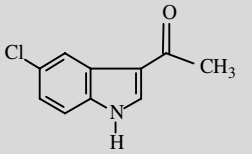
Scheme-I

5-Bromo-1*H*-indol-3-ylphenylmethanone (a): Colorless solid; m.p.: 265-267 ºC; IR (KBr, ν_{max}, cm^{-1}): 3150, 2932,1585; ^1H NMR (400 MHz, DMSO-d_6): δ 8.42 (d, J = 2 Hz, 1H), 8.04 (s, 1H), 7.82-7.78 (m, 2H), 7.64-7.62 (m, 1H), 7.58-7.51 (m, 3H), 7.42 (dd, J = 8.6, J = 2 Hz, 1H). Anal. calcd. (found) % for $C_{15}H_{10}NOBr$: C, 60.02 (59.31); H, 3.37 (3.07); Br, 26.63 (25.23); N, 4.66 (4.18); O, 5.32 (5.00).

5-Bromo-(1*H*-indol-3-yl)ethanone (b): White solid; m.p.: 222-227 ºC; IR (KBr, ν_{max}, cm^{-1}): 3100, 2923,1580; ^1H

TABLE-1
LIBRARY SYNTHESIS OF 3-ACYLINDOLES USING $NbCl_5$ AND $AgClO_4$ CATALYSTS

Entry	Indole (R_1 and R_2)	Acyl chloride (R_3)	Product	Time (h)	Yield (%)
a				7.00	72
b				3.50	60
c				4.50	72
d				5.20	75
e				6.00	60
f				7.00	65
g				5.30	70

h				5.00	70
i				6.00	77
j				5.30	70
k				4.00	82
l				4.30	75

NMR (400 MHz, DMSO-d_6): δ 8.21 (d, J = 7.2 Hz, 1H), 8.23 (s, 1H), 7.31-7.39 (m, 2H), 2.48 (s, 3H). Anal. calcd. (found) % for $C_{15}H_8NOBr$: C, 50.45 (49.32); H, 3.39 (3.06); Br, 33.56 (32.47); N, 5.88 (5.17); O, 6.72 (6.01).

1*H*-Indol-3-yl-phenylmethanone (c): White solid; m.p.: 243-245 ºC; IR (KBr, ν_{max}, cm^{-1}): 3144, 2935, 1598; ^1H NMR (400 MHz, DMSO-d_6): δ 8.26 (d, J = 7.2 Hz, 1H), 7.93 (s, 1H), 7.79 (d, J = 7.4 Hz, 2H), 7.60 (d, J = 6.8 Hz, 1H), 7.55 (t, J = 7.6 Hz, 3H), 7.29-7.24 (m, 2H). Anal. calcd. (found) % for $C_{15}H_{11}NO$: C, 81.43 (80.32); H, 5.01 (5.00); N, 6.33 (5.17); O, 7.23 (6.91).

1-(1*H*-Indol-3-yl)ethanone (d): White solid; m.p.: 189-190 ºC; IR (KBr, ν_{max}, cm^{-1}): 3155, 2920, 1612; ^1H NMR (400 MHz, DMSO-d_6): δ 8.22 (d, J = 7.2 Hz, 1H), 8.13 (s, 1H), 7.45 (d, J = 7.2 Hz, 1H), 7.23-7.20 (m, 2H), 2.52 (s, 3H). Anal. calcd. (found) % for $C_{10}H_9NO$: C, 75.45 (74.32); H, 5.70 (4.90); N, 8.88 (7.92); O, 10.05 (9.91).

5-Nitro-1*H*-indol-3-ylphenylmethanone (e): Yellowish white solid; m.p.: 183-184 ºC; IR (KBr, ν_{max}, cm^{-1}): 3430, 2972, 1637; ^1H NMR (400 MHz, DMSO-d_6): δ 8.41-8.39 (m, 1H), 8.33 (d, J = 8.7 Hz, 2H), 7.93 (d, J = 8.7 Hz, 2H) 7.49 (s, 1H), 7.41-7.36 (m, 3H). Anal. calcd. (found) % for $C_{15}H_{10}N_2O_3$: C, 67.67 (66.30); H, 3.79 (2.90); N, 10.52 (9.92); O, 18.03 (17.91).

5-Nitro-(1*H*-indol-3-yl)ethanone (f): Cream white solid; m.p.: 173-174 ºC; IR (KBr, ν_{max}, cm^{-1}): 3400, 2962, 1617; ^1H NMR (400 MHz, DMSO-d_6): δ 8.33 (d, J = 8.7 Hz, 2H), 7.93 (d, J = 8.7 Hz, 1H) 7.49 (s, 1H),2.52 (s, 3H). Anal. calcd. (found) % for $C_{10}H_8N_2O_3$: C, 58.82 (57.30); H, 3.95 (3.90); N, 13.72 (12.45); O, 23.51 (22.91).

5-Methoxy-(1*H*-indol-3-yl)-phenylmethanone (g): White solid; m.p.: 223-225 ºC; IR (KBr, ν_{max}, cm^{-1}): 3412, 2802, 1717; ^1H NMR (400 MHz, DMSO-d_6): δ 8.47 (d, J = 6.0 Hz, 1H), 7.84 (d, J = 8.0 Hz, 2H), 7.58-7.63 (s, 1H), 7.46-7.51 (m, 2H), 7.28 (t, J = 6.5 Hz, 3H), 3.88 (s, 3H). Anal. calcd. (found) % for $C_{16}H_{13}NO_2$: C, 76.48 (75.30); H, 5.21 (4.90); N, 5.57 (4.45); O, 12.73 (11.91).

5-Methoxy-(1*H*-indol-3-yl)ethanone (h): Yellow solid; m.p.: 203-205 ºC; IR (KBr, ν_{max}, cm^{-1}): 3387, 2872, 1700; ^1H NMR (400 MHz, DMSO-d_6): δ 8.47 (d, J = 6.0 Hz, 1H), 7.84 (d, J = 8.0 Hz, 2H), 3.88 (s, 3H), 2.52 (s, 3H). Anal. calcd. (found) % for $C_{11}H_{11}NO_2$: C, 69.83 (68.30); H, 5.86 (4.90); N, 7.40 (6.45); O, 16.94 (10.91).

5-Methyl-(1*H*-indol-3-yl)-phenylmethanone (i): Brown solid; m.p.: 116-118 ºC; IR (KBr, ν_{max}, cm^{-1}): 3100, 2923, 1580; ^1H NMR (400 MHz, DMSO-d_6): δ 8.40-8.41 (m, 1H), 7.71 (d, J = 7.0 Hz, 2H), 7.50-7.48 (s, 1H), 7.41-7.43 (m, 3H), 7.30-7.27 (m, 3H), 3.82 (s, 3H). Anal. calcd. (found) % for $C_{11}H_{11}NO$: C, 76.28 (75.81); H, 6.40 (5.90); N, 8.09 (7.95); O, 9.24 (9.91).

5-Methyl-(1*H*-indol-3-yl)-ethanone (j): Dark brown solid; m.p.: 111-113 °C; IR (KBr, ν_{max}, cm^{-1}): 3055, 2893, 1495; ^1H NMR (400 MHz, DMSO-d_6) δ: 8.10-8.21 (m, 1H), 7.51 (d, J = 7.0 Hz, 2H), 7.50-7.48 (s, 1H), 3.82 (s, 3H),2.52 (s, 3H), Anal. calcd. (found) % for $C_{11}H_{11}NO$: C, 76.28 (75.81); H, 6.40 (5.90); N, 8.09 (7.95); O, 9.24 (9.91).

5-Chloro-(1*H*-indol-3-yl)-phenylmethanone (k): Off-white solid; m.p.: 241-242 ºC; IR (KBr, ν_{max}, cm^{-1}): 3297, 3006, 1737, 1591; ^1H NMR (400 MHz, DMSO-d_6): δ 8.24 (d, J = 7.2 Hz, 1H), 7.96 (s, 1H), 7.81 (d, J = 7.6 Hz, 2H), 7.60 (d, J = 7.6 Hz, 2H),7.54 (d, J = 7.2 Hz, 1H), 7.33 7.23 (m, 2H). Anal. calcd. (found) % for $C_{10}H_8NOCl$: C, 62.03 (60.81); H, 4.16 (4.01); N, 7.23 (7.05); Cl, 18.31 (18.00); O, 8.26 (7.99).

5-Chloro-(1*H*-indol-3-yl)-ethanone (l): White solid; m.p.: 230-232 °C; IR (KBr, ν_{max}, cm^{-1}): 3088, 1707, 1555; ^1H NMR (400 MHz, DMSO-d_6) δ: 7.95 (d, J = 7.2Hz, 1H), 7.56

(s, 1H), 7.81 (d, *J* = 7.6 Hz, 2H), 2.12 (s, 3H), Anal. calcd. (found) % for $C_{10}H_8NOCl$: C, 62.03 (60.81); H, 4.16 (4.01); N, 7.23 (7.05); Cl, 18.31 (18.00); O, 8.26 (7.99).

RESULTS AND DISCUSSION

After screening these optimized reaction conditions, we explored the versatility and its scope for acylation of indoles. It is interesting to note that the variety of alkyl/aryl chlorides and indoles undergoes acylation without NH protection and resulted better conversions into 3-acyl indoles selectively using $NbCl_5$ as catalyst and $AgClO_4$ as promoter. This method is highly selective towards acylation of indoles at 3-position eliminating other regiomers. It is appealing to note that there is substantial substituent effect pronounced by various substituent′s in the reaction. For example, an electron donor groups like 5-methoxyindole, is suppose to be highly susceptible for polymerization, was afforded product in moderate yield. This protocol shows more tolerance towards various functionalities, therefore offers acylation methodology for various moieties including therapeutic agents.

Benzoylation of indole was also optimized and used benzoyl chloride under various reaction conditions. It is found 5 mol % of $NbCl_5$ and (1.3 mmol) indole and (1 mmol) benzoyl chloride in DCM at 0 ºC forms 40 % product after longer reaction time. However, with the use of 5 mol % of $AgClO_4$ combined with 5 mol % $NbCl_5$ considerably improved the yield to 55 % (entry 2, Table-2). This observation evident that the essentiality of additive $AgClO_4$ for this transformation. Employing 5 mol % of $AgClO_4$ alone brings about the formation product (entry 3, Table-2). It was interesting to low loadings of catalyst ($NbCl_5$: 1 mol %; $AgClO_4$: 3 mol %) at room temperature in DCM brings 72 % in 4 h and found to be optimized reaction condition for this organic transformtion (entry 4, Table-2).

TABLE-2
OPTIMIZATION $NbCl_5$ AND $AgClO_4$ TOWARDS SYNTHESIS OF 3-ACYL INDOLES

Entry	Catalyst $NbCl_5$ (mol %)	Additive (mol %)	Yield (%)
1	5	None	40
2	5	5	55
3	None	5	60
4	5	4	65
5	3	3	70
6	2	3	72
7	1	3	55
8	5	5	50
9	5	5	50

An important attributes of this process is the easy isolation of products with simple work-up, tolerating wide range functional groups including -OCH_3, -NO_2 and -X (-Cl, -Br) under the ambient condition without protection of indoles undergoes 3-acylation selectively in the presence of $NbCl_5$ and $AgClO_4$ as combined catalyst.

Conclusion

A simple approach wherein $NbCl_5$ and $AgClO_4$ promoted chemo- and regio-selective acylation of indoles was achieved at ambient conditions. This methodology is found to more versatile demonstrating its applicability in which different alkyl and aryl chlorides undergo acylation smoothly without NH protection of indoles. This protocol represents significant advantages such as use of mild Lewis acid, simple workup procedure with better yields of product. The potentiality and feasibility of this method is also tested for the synthesis of bioactive scaffolds which are beneficial in many therapeutic actions.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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