A facile method for the synthesis of various 3-substituted indoles via Michael addition reaction using NbCl$_5$ §

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A mild and efficient method for the synthesis of various 3-substituted indoles is described via a Michael addition reaction using NbCl$_5$ as a Lewis acid catalyst. Simple reaction conditions, short reaction times, less amount of catalyst loading, high yields and substrate diversity are the advantages of this methodology.

Keywords: 3-Substituted indoles, heterocyclic compounds, NbCl$_5$, chalcones, Michael addition, natural products

Indole moiety is one of the most important constituent of several biologically potent natural and synthetic compounds; hence chemists consider indole skeleton as a privileged structure$. Among the indole constituted compounds, 3-substituted indoles are of great interest owing to their significant biological and pharmacological properties$^1,2$. For example, they are known for promoting estrogen metabolism in humans$^3$, hence they are effective in the cancer prevention, G-protein coupled receptors$^1b$, and they also serve as very good building blocks for the synthesis of several biologically potent compounds$. In view of their importance from the chemical and medicinal perspective, several synthetic methodologies were developed for the synthesis of 3-substituted indoles mainly via a Friedel-Crafts or a Michael addition strategy involving nucleophilic indole and electrophilic carbon compounds like aldehydes and chalcones using a base, protic or Lewis acids as catalysts (Scheme I) (Ref 4). Some of these methods suffer from the drawbacks like polymerization, side reactions, requirement of high temperature, long reaction times, tedious workup procedures and poor yields. Hence there is need for the development of facile methods which would overcome certain drawbacks as mentioned above.

Results and Discussion

In recent years, NbCl$_3$ has proven to be very mild and efficient Lewis acid catalyst for several organic transformations such as Diels–Alder reaction$^5d$, Sakurai reaction$^5$, Mannich type reaction$^5i$, dealkylation of alkyl aryl ethers$^5g$, homologation$^5n$, ring opening of epoxides$^5i$, Mukaiyama aldol reactions$^5j$ and alkylation of aldehydes, imines$^5k$ and nucleophilic additions to N-acyliminium ions$^5l$, and many others$. As part of the research aimed towards the development of Lewis acid catalysed synthetic methodologies for the C–C bond forming organic transformations$, attention was focused towards developing a mild and efficient methodology for the synthesis of various 3-substituted indoles using niobium pentachloride.

The initial study began with the Michael addition reaction between chalcone $1a$ and indole $2a$ in acetonitrile as a solvent using 5 mol% of NbCl$_3$ at RT. After 8 hr the completion of the reaction could be monitored by TLC and 3-substituted indole product $3a$ was isolate in 92% yield. Then we thought of changing the reaction temperature from RT to reflux conditions to decrease the reaction time and as expected we were able to complete the reaction within 2 hr. The next reaction between indole $2a$ and chalcone $1b$ also behaved in similar manner under reflux condition and gave the product $3b$ in 90% yield after 2 hr. To check the versatility of this methodology with respect to various chalcones, the chalcones $1c$, $1d$, $1e$ and $1f$ were treated with indole $2a$ under similar reaction conditions and the obtained the corresponding 3-substituted indoles were obtained in around 2-3 hrs as shown in Table I. The electronic effects of the substituted chalcones played very important role in terms of the yield of the products.

§Dedicated to (late) Prof. A. Srikrishna for his contributions to synthetic organic chemistry.
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Scheme I — NbCl$_5$ catalyzed Michael addition of indoles to chalcones to yield 3-substituted indoles

Table I — NbCl$_5$ catalyzed facile synthesis of 3-substituted indoles from chalcones

<table>
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<tr>
<th>Entry</th>
<th>Chalcone</th>
<th>Indole</th>
<th>3-substituted indole</th>
<th>Yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>2a</td>
<td>3a</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
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<td>90</td>
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<td>1e</td>
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<td>90</td>
</tr>
<tr>
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<td>1f</td>
<td>2a</td>
<td>3f</td>
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</tr>
<tr>
<td>7</td>
<td>1a</td>
<td>2b</td>
<td>3g</td>
<td>85</td>
</tr>
</tbody>
</table>

Contd —
Table I — NbCl₅ catalyzed facile synthesis of 3-substituted indoles from chalcones — Contd

<table>
<thead>
<tr>
<th>Entry</th>
<th>Chalcone</th>
<th>Indole</th>
<th>3-substituted indole</th>
<th>Yield (%)ᵃ</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>1b</td>
<td>2b</td>
<td>[Chemical Structure Image]</td>
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<td>10</td>
<td>1f</td>
<td>2b</td>
<td>[Chemical Structure Image]</td>
<td>68</td>
</tr>
</tbody>
</table>

ᵃIsolated yields after column chromatography

Scheme II — Solvent optimization for the NbCl₅ catalyzed synthesis of 3-substituted indoles

For example, p-nitro-substituted chalcone 1a gave better yield (92%) with indole 2a, when compared to simple chalcone 1b (90%), this could be due to the –I effect of nitro group, the electrophilicity has been increased and thus it facilitates the nucleophilic attack by indole 2a. A similar observation has been made in case of p-methoxychalcone, due to +M effect of methoxy group the yield of 3c is lower (85%) than 3a and 3b. The reaction between 5-bromoindole 2b and chalcone 1a also gave the product 3g in 85% yield in 2.5 hr. Similarly, 5-bromoindole 2b reacted with other chalcones 1b, 1c, 1f and gave the corresponding 3-substituted indoles in good yield. All these results are summarized in the Table I. Thereafter, we screened solvents for Michael addition reaction between indole 2a and chalcone 1a (Scheme II).

Experimental Section

General experimental procedure for the Michael addition reaction of indole with chalcones

All the experiments were performed under nitrogen atmosphere; niobium pentachloride was purchased from Aldrich chemicals, aldehydes were commercially available. Solvents were dried using standard procedures, NMR spectra were recorded on 400 MHz machine using CDCl₃ as a solvent and TMS as the
internal standard. IR was recorded on Perkin Elmer Labtronics digital melting point apparatus; chalcones were prepared using known procedures.

To a stirred solution of chalcones (1.0 equiv) and indole (1.1 equiv) in acetonitrile (10 mL) was added 5 mol% of NbCl₃ at RT under nitrogen atmosphere. The progress of reaction was monitored by TLC (mostly the time taken for all these reactions was 2-3 hr). After completion of the reaction, water (10 mL) was added and the reaction mass extracted with ethylacetate (3 x 10 mL). Combined organic layers were washed with brine (15 mL), dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The crude reaction mixture was purified by silica gel column chromatography using hexanes and ethylacetate as eluents. (Note: after completion of the reaction, we also tried without work up procedure that is, solvent was directly evaporated and reaction mixture was absorbed on silica gel and purified by column chromatography as mentioned above. Surprisingly we did not observe any difference in the isolated yields of the products). All these products were characterized by melting point, IR, ¹H and ¹³C NMR, and mass spectral data, which are in accordance with the reported data. Spectral data for some of the selected compounds is presented:

3-(4-Chlorophenyl)-3-(1H-indol-3-yl)-1-phenylpropan-1-one, 3e: White solid, m.p. 92-94°C; IR (KBr): 3400, 3084, 3026, 1682, 1596, 1579, 1489, 1387, 1203, 820, 746 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.00 (s, 1H, NH), 7.92 (d, J = 7.6 Hz, 2H, ArH), 7.54 (t, J = 7.0 Hz, 1H, ArH), 7.42 (t, J = 6.8 Hz, 2H, ArH), 7.38 (d, J = 8.4 Hz, 1H, ArH), 7.32 (d, J = 8.0 Hz, 1H, ArH), 7.24-7.18 (m, 4H, ArH), 3.78 (dd, J = 6.8, 6.8 Hz, 1H, CH₂); ¹³C NMR (100 MHz, CDCl₃): δ 198.2, 142.6, 136.9, 136.5, 133.2, 131.9, 129.2, 128.6, 128.5, 128.0, 126.4, 122.3, 121.2, 119.5, 119.4, 118.8, 111.2, 44.9, 37.5; MS (EI): m/z 359.

3-(5-Bromo-1H-indol-3-yl)-1, 3-diphenylpropan-1-one, 3h: IR (KBr): 3422, 2920, 1665, 1597, 1458, 1285, 1049, 799 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.00 (S, 1H, NH), 7.90 (d, J = 7.2 Hz, 2H, ArH), 7.55-7.52 (m, 2H, ArH), 7.42 (t, J = 7.6 Hz, 2H, ArH), 7.43-7.16 (m, 7H, ArH), 6.88 (s, 1H, NCH), 4.89 (t, J = 7.2 Hz, 1H, CH), 3.68 (dd, J = 6.8, 6.8 Hz, 1H, CH₂), 3.6 (dd, J = 6.8, 7.2 Hz, 1H, CH₂); ¹³C NMR (100 MHz, CDCl₃): δ 198.3, 143.8, 137.1, 135.2, 133.1, 128.6, 128.4, 128.1, 127.7, 126.5, 125.1, 122.5, 122.0, 119.1, 112.8, 112.5, 45.2, 38.0; MS (EI): m/z 404.

**Conclusion**

In summary, a methodology has been successfully described for the synthesis of diverse 3-substituted indoles using indoles and various electrophilic partners such as chalcones in presence of catalytic amount of NbCl₃ via Michael addition reaction. This method involves simple reaction conditions, shorter reaction times, substrate diversity and provides access to the biologically potent 3-substituted indoles in good yields.

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**References**


