Metal catalyzed reactions: Synthesis of bioactive compounds and C-C bond forming reactions

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INTRODUCTION

The indole nucleus is found in many structurally diverse natural products, pharmaceutical agents, functional materials, and agrochemicals[1]. Therefore; significant efforts have been directed towards the synthesis of these molecules. Syntheticly, these compounds are obtained from the condensation of indoles with aldehydes and ketones in the presence of protic or Lewis acids[2,3]. Generally, traditional Lewis acid catalysts are moisture sensitive and are easily decomposed or deactivated in the presence of even a small amount of water. Consequently, there is a continuing interest in the development of improved methods for the synthesis of indole derivatives[4]. One such reaction is the transition metal mediated intermolecular C–C bond formation between these heterocycles and other organic substrates[5].

Recently, we have been using copper salts as versatile catalyst in many organic reactions[6]. In continuation of our studies towards the synthesis of bioactive heterocycles using copper salts as convenient catalyst, we report the synthesis of bis(indoly) ketones in good to excellent yields by the double indolylation of various aldehydes using 5% CuCl2 as the catalyst.

RESULTS AND DISCUSSION

In a typical experiment a mixture of indole 1 (1.18g,10.0 mmol), benzaldehyde 2a (1.06g,5.0 mmol) and catalytic amount of CuCl2-H2O (10 mol%) was stirred at room temperature. Cupric Chloride and indole dissolves rapidly as the reaction proceeds and after 10 minutes the mixture turns to be a clear oil. After 20 minutes of stirring the reaction ceased as the oil starts solidifying, as indicated by TLC. The resulting reaction mixture was quenched with water (25 ml) and extracted with ethylacetate (15 ml). The combined organic layer was separated and dried (Na2SO4). The resulting organic layer was then concentrated and the crude product was purified by a silica gel column chromatography and using EtOAc-Hexane as the eluent. The structure of the isolated compound was found to be bis(indoly) methane (3a) which was fully confirmed by spectral and analytical data. The same process was successfully extended to a wide range of structurally varied aldehydes (2b-j), and the corresponding bis (indoly) methanes 3b-j were obtained in good to excellent yields with less time of reaction (TABLE 1). All the known compounds were checked further by comparison with the m.p. of the literature reports.
EXPERIMENTAL

Materials and methods

All chemicals were obtained from commercially available sources and used without further purification. All other reagents were used as obtained unless otherwise noted. Melting points were uncorrected. All NMR spectra were recorded on 300 and 400 MHz spectrometers with TMS as an internal standard. $^1$H chemical shifts are reported in delta (δ) units, in parts per million (ppm) downfield from tetramethylsilane and also with reference to residual protic solvent (CDCl$_3$, δ H = 7.26 ppm). $^{13}$C chemical shifts are referenced to the solvent signal (CDCl$_3$). Infrared (IR) data were recorded as films on potassium bromide (KBr) pellets on a FT-IR spectrometer. Absorbance frequencies are reported in reciprocal centimeters (cm$^{-1}$).

3,3'-Bis-indolyl phenylmethane (3a)

mp, 125-126°C (lit.$^a$ 124-125°C); $^1$H NMR (300 MHz, CDCl$_3$): δ 7.58 (brs, 2H), 7.45-7.18 (m, 13H), 6.51 (s, 2H), 5.91 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 137.1, 134.3, 133.7, 130.2, 130.1, 127.1, 125.1, 123.0, 119.4, 118.9, 114.3, 21.5; IR (KBr): 3416, 1634, 1378, 737 cm$^{-1}$; MS m/z 322 (M$^+$); Anal. Calcd for C$_{23}$H$_{18}$N$_2$: C, 85.68; H, 5.63; N, 8.69; Found: C, 85.59; H, 5.68; N, 8.54.

3.3'-Bis-indolyl-(3-nitrophenyl)methane (3e)

mp, 216-217°C; $^1$H NMR (300 MHz, CDCl$_3$): δ 8.18 (brs, 2H), 6.75 (d, 2H, J=2.3 Hz), 6.85 (d, 2H, J=8.0 Hz), 7.25 (t, 2H, J=8.0 Hz), 7.35 (s, 1H), 7.75 (br s, 2H, NH). EIMS: m/z (%) = 390 (100, M$^+$), 265 (10), 245 (50), 69 (20). IR (KBr): ν = 3480, 3060, 2980, 1620, 1490, 1230, 1070, 760 cm$^{-1}$; Anal. Calcd for C$_{25}$H$_{16}$N$_2$O$_2$: C, 78.67; H, 4.95; N, 7.18; Found: C, 78.69; H, 5.02; N, 7.68.

3.3'-Bis-indolyl-(3-nitrophenyl)methane (3e)

mp, 198-200°C; $^1$H NMR (200 MHz, CDCl$_3$): δ 3.80 (s, 3H), 3.75 (s, 1H), 6.70 (d, 2H, J=2.2 Hz), 6.85 (d, 2H, J=8.0 Hz), 6.90 (d, 2H, J=8.0 Hz), 7.05 (t, 2H, J=8.0 Hz), 7.30 (t, 4H, J=8.0 Hz), 7.60 (br s, 2H, NH). EIMS: m/z (%) = 382 (100, M$^+$), 265 (10), 245 (50), 69 (20). IR (KBr): ν = 3450, 3060, 2980, 1620, 1490, 1230, 1005, 760 cm$^{-1}$; Anal. Calcd for C$_{25}$H$_{22}$N$_2$O$_2$: C, 78.51; H, 5.80;
### TABLE 1: CuCl$_2$.2H$_2$O-catalyzed synthesis of bis (indolyl) methanes under solvent free condition

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>$^\circ$C found</th>
<th>mp ($^\circ$C reported)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(3a)</td>
<td>C$_6$H$_5$</td>
<td>25</td>
<td>92</td>
<td>125-126</td>
<td>125-127$^{\text{a}}$</td>
</tr>
<tr>
<td>(3b)</td>
<td>O</td>
<td>26</td>
<td>92</td>
<td>103-106</td>
<td>104-105$^{\text{a}}$</td>
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<tr>
<td>(3c)</td>
<td>4-MeOC$_6$H$_4$</td>
<td>20</td>
<td>95</td>
<td>98-100$^{\text{a}}$</td>
<td>98-100$^{\text{a}}$</td>
</tr>
<tr>
<td>(3d)</td>
<td>4-MeC$_6$H$_4$</td>
<td>25</td>
<td>93</td>
<td>95-97$^{\text{a}}$</td>
<td>95-97$^{\text{a}}$</td>
</tr>
<tr>
<td>(3e)</td>
<td>3-NO$_2$C$_6$H$_4$</td>
<td>30</td>
<td>90</td>
<td>153-156$^{\text{a}}$</td>
<td>154-156$^{\text{a}}$</td>
</tr>
<tr>
<td>(3f)</td>
<td>3,4-(Cl)$_2$C$_6$H$_3$</td>
<td>25</td>
<td>93</td>
<td>198-200$^{\text{a}}$</td>
<td>198-200$^{\text{a}}$</td>
</tr>
<tr>
<td>(3g)</td>
<td>3,4-(OMe)$_2$C$_6$H$_3$</td>
<td>35</td>
<td>90</td>
<td>188-190</td>
<td>186-188$^{\text{a}}$</td>
</tr>
<tr>
<td>(3i)</td>
<td>MeO</td>
<td>25</td>
<td>85</td>
<td>oil</td>
<td>-</td>
</tr>
<tr>
<td>(3j)</td>
<td></td>
<td>40</td>
<td>80</td>
<td>238-240</td>
<td>240$^{\text{a}}$</td>
</tr>
</tbody>
</table>

$^\text{a}$Reaction condition: Aldehyde (5 mmol), Indole (10 mmol), CuCl$_2$.2H$_2$O (10 mol%), room temperature.

δ = 1.35 (t, 3H, J=6.9 Hz), 1.45 (t, 3H, J=6.9 Hz), 3.95 (q, 2H, J=6.9 Hz), 4.05 (q, 2H, J=6.9 Hz), 5.75 (s, 1H), 6.65 (d, 2H, J=2.3 Hz), 6.75 (m, 2H) 6.85 (m, 1H), 6.95 (t, 2H, J=8.1 Hz), 7.05 (t, 2H, J=8.1 Hz), 7.30 (m, 4H), 7.85 (br s, 2H, NH). EIMS: m/z (%) = 410 (70, M$^+$), 266 (15), 248 (20), 215 (5), 160 (60), 135 (100), 121 (30), 91 (40). IR (KBr): ν= 3470, 3050, 2960, 1590, 1470, 1270, 1005, 760 cm$^{-1}$. Anal. Calcd for C$_{28}$H$_{26}$N$_2$: C, 81.8; H, 5.79; N, 8.04. Found: C, 81.85; H, 5.72; N, 8.07.

### CONCLUSION

In conclusion, we have successfully demonstrated the synthetic applications of cupric chloride as a transition metal catalyst in multicomponent reactions to synthesize bioactive dihydropyrimidines and also in the synthesis of bisindolylmethanes in good to excellent yields. Both the reaction approach avoid the use of solvent and the ready availability of a wide range of substrates from cheap starting materials, make this new strategy highly attractive in diversity oriented synthesis.

### ACKNOWLEDGMENTS

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