An efficient one pot conversion of alkynes to bis(indolyl) and bis(pyrrolyl)alkanes in aqueous ethanol

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Mercury (II) chloride efficiently catalyzes the reaction between indoles/pyrrole and substituted phenyl acetylenes to furnish bis(indolyl)alkane and bis(pyrrolyl)alkane in good to excellent yields under room temperature and moderate reaction time. The reaction is carried out in ethanolic water medium.

Keywords: Alkynes, indoles, bis(indolyl)alkanes, bis(pyrrolyl)alkanes, aqueous ethanolic medium, mercuric chloride

Synthesis of bis(indolyl)alkane derivatives had always been an area of active research interest for synthetic organic chemists. The due attention gained by the moiety is due to its diversified pharmacological activity. Bis(indolyl)methanes and their derivatives are found in metabolites of terrestrial and marine origin. Bis(indolyl)methane is also known to promote estrogen metabolism in both women and men and is effective in the prevention of cancer. Vibrindole A was demonstrated for the first time to exhibit antibacterial activity against S. aureus, S. albus and B. subtilis where gentamycin is used as the standard drug. Bis(indolyl)methanes oxidized by DDQ are efficient chromogenic sensing molecules based on proton transfer signaling mode.

Results and Discussion

The root to the motif in question had largely been prepared by the condensation of indoles with aldehydes and ketones in presence of protic acids or Lewis acids. Rare earth metal triflates and green methodologies are particularly important. A highly efficient method for synthesis of bis(indolyl) and tris(indolyl)alkanes using antimony trichloride (SbCl₃) as catalyst has been reported earlier. In continuation of previous work, the scope of direct transformation of alkynes to bis(indolyl)alkanes has been explored. Similar reactions were earlier performed by Yadav et al. using 10 mol% of gallium(III) chloride or bromide in toluene under refluxing condition and then by Echavarren et al. who investigated the scope of the reaction using AuCl₃ and Au(I) complexes with bulky phosphine ligands as catalyst. Recently, J. Barluenga et al. disclosed a reaction between homopropargyl alcohol derivatives and indoles using 5 mol% (Ph₃P)AuCl along with AgSbF₆ as promoter. It is thus seen that highly expensive metal salts were utilized for transformation neglecting the economic demand. In the present study, various catalysts, solvents and catalyst-solvent combinations were tried and tested for the purpose of the reaction between indole and phenylacetylene (Scheme I).

A special emphasis was placed on Hg (II) salts as catalyst because of its ability to polarise carbon-carbon triple bonds making them more susceptible to nucleophilic attack. Moreover, in recent times there has been a trend to explore the catalytic properties of Hg (II) triflate. The results of the current study are summarized in Table I.

From the results, it is evident that HgCl₂ was the best in terms of yield, reaction conditions and time. An added advantage was that it also supported an aqueous medium for the reaction. In fact, to the best of the knowledge it is the first report of a reaction between indoles and alkynes in aqueous-ethanolic medium. A small amount of ethanol was added to overcome the problems relating to phase equilibria as phenylacetylene is only sparingly soluble in water alone.

Though aqueous ethanol and aqueous methanol gave comparative yields, methanol was not used owing to its toxic effects. The solvent system used for this particular reaction was environment friendly.
Encouraged by these results, the reaction of various substituted phenylacetylenes was performed with indoles (Table II) and pyrroles (Scheme II, Table III). In all cases good to excellent yields were obtained. Pyrrole reacted in a similar fashion to indole furnishing dipyrrolylalkanes in excellent yield. Attention was focused on this reaction as dipyrrolylalkanes are potential precursors for tetrapyrrolic macrocycles. Pyrroles usually react with aldehydes or ketones to yield porphyrin rings. Pyrrole reacted faster than indole which might be attributed to the higher reactivity of pyrrole compared to indole. It is also quite apparent that electronic nature of the substituents had a considerable effect on the reaction rate. N-methylindole reacted faster than the N-unsubstituted derivatives. On the other hand 4-methoxyphenylacetylene reacted much slower than phenylacetylene itself, which in turn reacted slower than 3-nitrophenylacetylene. Regarding the mechanism of the reactions described in Table II and Table III, there are two possible mechanistic pathways. One possibility is through mercuric chloride catalyzed hydration of phenylacetylene resulting in the formation of a substituted acetophenone intermediate, which subsequently adds two indole or pyrrole units across carbon-oxygen double bond. The other possibility is addition of one unit of heterocycle to the alkynes complexed with mercury (II) ion leading to a further reactive alkenylindole-Hg (II) or alkenylpyrrole-Hg (II) complex as the case may be, to which another unit of heteroaromatic moiety is added up. It is proposed that...
Table II — Reaction between phenylacetylenes and indoles$^{a,b}$

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<th>Entry</th>
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<th>Time (hr)</th>
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the second mechanism is the major pathway operating, as traces of the acetophenones were detected in the reaction mixture. Moreover, the treatment of phenylacetylene alone with 3 mol% of HgCl$_2$ afforded acetophenone but the reaction was much slower than the reaction with indole or pyrrole. Furthermore the reaction between acetophenone and indole in aqueous ethanol by Hg (II) catalysis was low yielding.

**Experimental Section**

$^1$H NMR spectra were recorded with a Bruker 300 (300 MHz) spectrometer as solutions in CDCl$_3$. Chemical shifts are expressed in parts per million (ppm, $\delta$) and with reference to the residual chloroform in CDCl$_3$ ($\delta = 7.27$ ppm) as an internal standard. All coupling constants are absolute values and are expressed in Hz. The description of the signals include: s = singlet, d = doublet, t = triplet, m = multiplet and dd = doublet of doublets. $^{13}$C NMR spectra were recorded with a Bruker 300 (75 MHz) spectrometer as solutions in CDCl$_3$ with complete proton decoupling. High-Resolution Mass Spectra (HRMS) were obtained from a Qtof Micro YA263 spectrometer.

**Table II** — Reaction between phenylacetylenes and indoles$^{a,b}$—Contd

<table>
<thead>
<tr>
<th>Entry</th>
<th>Phenylacetylenes</th>
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$^a$Reaction conditions: Substituted phenyl acetylene (1.5 mmol), indole (2.0 mmol), HgCl$_2$ (0.03 mmol), ethanol (0.5 mL), water (2.5 mL), RT.

$^b$All compounds were characterized by IR, $^1$H and $^{13}$C NMR, and HRMS.

$^c$Yield refers to pure and isolated yield.

**Representative experimental procedure**

To a solution of phenylacetylene (153 mg, 1.5 mmol) in 2.5 mL water and 0.5 mL ethanol, indole (234 mg, 2.0 mmol) was added followed by HgCl$_2$ (8 mg, 0.03 mmol) and stirred at RT. Progress of the reaction was monitored by TLC. On completion, the reaction mixture was quenched with water, extracted with DCM, dried over anhydrous sodium sulphate and volatiles were removed. The aqueous part obtained after workup was disposed as hazardous waste. The crude product was purified by short column chromatography over 60-120 mesh silica gel eluting with 1:9 ethyl acetate-hexane to afford 3,3′-(1-phenylethane-1,1-diyl)bis(1H-indole), 3a (Ref 10): (320 mg, 0.95 mmol, 95%) as a white solid, m.p. 190°C. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.39 (s, 3H), 6.58 (s, 2H), 6.94-7.02 (m, 2H), 7.17 (t, $J = 7.2$ Hz, 2H), 11.4, 118.9, 121.5, 122.1, 123.6, 124.6, 125.9, 126.5, 127.9, 128.2, 137.1, 148.2. $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 28.8, 43.8, 6.58 (s, 3H), 6.94-7.02 (m, 2H), 7.17 (t, $J = 7.2$, 2H), 7.43 (d, $J = 7.8$, 2H), 7.74 (bs, 2H); HRMS. 3,3′-(1-(4-bromophenyl)ethane-1,1-diyl)bis(1H-indole), 3b: $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.34 (s, 3H), 6.58 (s, 2H), 6.94-7.02 (m, 2H), 7.17 (t, $J = 7.2$ Hz, 2H), 7.43 (d, $J = 7.8$, 2H), 7.74 (bs, 2H); HRMS.
Table III — Reaction between phenyl acetylenes and pyrrole\textsuperscript{a,b}

<table>
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<th>Yield (%)\textsuperscript{c}</th>
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<td>1\textsuperscript{c}</td>
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\textsuperscript{a}Reaction conditions: Substituted phenyl acetylene (1.5 mmol), pyrrole (2.0 mmol), HgCl\textsubscript{2} (0.03 mmol), ethanol (0.5 mL), water (2.5 mL), RT, 6 hr.
\textsuperscript{b}All compounds were characterized by \textsuperscript{1}H and \textsuperscript{13}C NMR.
\textsuperscript{c}Yield refers to pure and isolated yield.

3H), 6.65 (s, 2H), 6.95 (t, J = 7.6 Hz, 2H), 7.12 (t, J = 7.6 Hz, 2H), 7.28-7.31 (m, 3H), 7.33-7.39 (m, 5H), 7.96 (brs, 2H);
\textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): \( \delta \) 27.8, 43.9, 111.1, 118.5, 121.5, 122.1, 124.7, 125.9, 126.5, 127.8, 128.1, 137.1, 142.9; HRMS: Calcd for [C\textsubscript{24}H\textsubscript{20}BrN\textsubscript{2}]\textsuperscript{+} m/z 415.0804. Found 415.0809.

3,3\textsuperscript{′}-(1-(4-methoxyphenyl)ethane-1,1-diyl)bis(1H-indole), 3c (Ref 11): \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \( \delta \) 2.37 (s, 3H), 3.76 (s, 3H), 6.59 (s, 2 H), 6.93 (t, J = 7.8 Hz, 2H), 7.12 (t, J = 7.8 Hz, 2 H), 7.20–7.38 (m, 8 H), 7.90 (brs, 2H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): \( \delta \) 28.8, 43.0, 55.1, 111.1, 113.0, 118.8, 121.5, 122.1, 123.3, 124.9, 126.4, 129.0, 137.1, 140.3, 157.4.

3,3\textsuperscript{′}-(1-phenylethane-1,1-diyl)bis(1-methyl-1H-indole), 3d (Ref 10): \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \( \delta \) 2.38 (s, 3H), 3.76 (s, 3H), 6.59 (s, 2 H), 6.93 (t, J = 7.8 Hz, 2H), 7.12 (t, J = 7.8 Hz, 2 H), 7.20–7.38 (m, 8 H), 7.90 (brs, 2H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): \( \delta \) 26.1, 37.0, 43.1, 102.3, 111.6, 114.3, 115.5, 116.6, 118.9, 120.1, 121.0, 121.4, 131.1, 141.6.

3,3\textsuperscript{′}-(1-phenylethane-1,1-diyl)bis(1-methyl-1H-indole), 3e: \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \( \delta \) 2.38 (s, 3H), 3.69 (s, 6H), 6.51 (s, 2 H), 6.95 (t, J = 7.5 Hz, 2H), 7.19 (t, J = 7.8 Hz, 2H), 7.22–7.34 (m, 7H), 7.42 (d, J = 7.5 Hz, 2H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): \( \delta \) 26.1, 37.0, 43.1, 102.3, 111.6, 114.3, 115.5, 116.6, 118.9, 120.1, 121.0, 121.4, 131.1, 141.6.

3,3\textsuperscript{′}-(1-(4-methoxyphenyl)ethane-1,1-diyl)bis(1-methyl-1H-indole), 3f: \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \( \delta \) 2.33 (s, 3H), 3.68 (s, 6H), 3.79 (s, 3H), 6.48 (s, 2 H), 6.79 (d, J = 8.7 Hz, 2H), 6.94 (t, J = 7.2 Hz, 2H), 7.17 (t, J = 7.2 Hz, 2H), 7.28–7.37 (m, 6H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): \( \delta \) 26.1, 36.7, 43.8, 56.0, 111.6, 118.9, 121.5, 122.1, 124.7, 125.9, 126.5, 127.8, 128.1, 137.1, 148.1, 156.2; HRMS: Calcd for [C\textsubscript{27}H\textsubscript{27}N\textsubscript{2}O]\textsuperscript{+} m/z 395.2118. Found 395.2123.
3,3'-((1-(3-nitrophenyl)ethane-1,1-diyl)bis(1-methyl-1H-indole), 3g: 1H NMR (300 MHz, CDCl₃): δ 2.38 (s, 3H), 3.70 (s, 6H), 6.52 (s, 2H), 6.95 (s, J = 7.2 Hz, 2H), 7.17-7.50 (m, 7H), 7.74 (d, J = 7.8 Hz, 1H), 8.06 (d, J = 7.8 Hz, 1H), 8.31 (s, 1H), 13C NMR (75 MHz, CDCl₃): δ 25.8, 36.8, 43.9, 102.3, 107.6, 111.8, 112.6, 114.7, 120.2, 121.2, 127.8, 129.1, 130.4, 134.5, 137.8, 147.2, 149.2; HRMS: Calcd for [C₂₆H₂₃N₂O₂]⁺ m/z 410.1863. Found 410.1857.

3,3'-((1-polyethylene-1,1-diyl)bis(5-bromo-1H-indole), 3h: 1H NMR (300 MHz, CDCl₃): δ 2.29 (s, 3H), 2.34 (s, 3H), 6.65 (s, 2H), 7.08 (d, J = 7.9 Hz, 2H), 17.8-7.22 (m, 6H), 7.41 (s, 2H), 9.79 (brs, 2H); 13C NMR (75 MHz, CDCl₃): δ 21.3, 26.7, 43.8, 113.7, 116.9, 121.8, 122.1 123.0, 126.4, 127.6, 128.1, 129.4, 134.1, 135.8, 146.5; HRMS: Calcd for [C₂₆H₂₃Br₂N₂]⁺ m/z 507.0066. Found 507.0070.

3,3'-((1-phenylthiethane-1,1-diyl)bis(5-bromo-1H-indole), 3i (Ref 10): 1H NMR (300 MHz, CDCl₃): δ 2.31 (s, 3H), 6.65 (s, 2H), 7.23-7.35 (m, 9H), 7.40 (s, 2H), 7.98 (brs, 2H); 13C NMR (75 MHz, CDCl₃): δ 28.7, 43.5, 112.4, 112.7, 124.1, 124.2, 124.5, 126.2, 127.8, 128.0, 135.7, 147.1.

3,3'-((1-(4-bromophenyl)ethane-1,1-diyl)bis(5-bromo-1H-indole), 3j: 1H NMR (300 MHz, CDCl₃): δ 2.28 (s, 3H), 6.64 (d, J = 2.1 Hz, 2H), 7.18-7.25 (m, 6H), 7.39-7.41 (m, 4H), 8.01 (brs, 2H); 13C NMR (75 MHz, CDCl₃): δ 28.6, 43.3, 112.5, 112.8, 120.2, 123.4, 124.0, 124.5, 127.8, 129.8, 131.1, 135.8, 146.3; HRMS: Calcd for [C₂₄H₂₅Br₂N₂]⁺ m/z 570.9015. Found 570.9018.

3,3'-((1-(3-nitrophenyl)ethane-1,1-diyl)bis(5-bromo-1H-indole), 3k: 1H NMR (300 MHz, CDCl₃): δ 2.36 (s, 3H), 6.66 (d, J = 2.0 Hz, 2H), 7.23-7.29 (m, 2H), 7.35 (s, 2H), 7.45 (t, J = 8.0 Hz, 1H), 7.68 (d, J = 7.5 Hz, 1H), 8.10-8.12 (m, 3H), 8.25 (s, 1H); 13C NMR (75 MHz, CDCl₃): δ 28.6, 43.7, 112.9, 121.6, 122.7, 122.8, 113.0, 123.8, 124.5, 125.1, 127.5, 128.9, 134.1, 135.8, 148.4, 149.5; HRMS: Calcd for [C₂₄H₂₅Br₂N₂O₂]⁺ m/z 537.9760. Found 537.9757.

3,3'-((1-(4-bromophenyl)ethane-1,1-diyl)bis(1-methyl-1H-indole), 3l: 1H NMR (300 MHz, CDCl₃): δ 2.34 (s, 3H), 3.69 (s, 6H), 6.50 (s, 2H), 6.96 (t, J = 7.2 Hz, 2H), 7.19 (t, J = 7.2 Hz, 2H), 7.28-7.39 (m, 8H); 13C NMR (75 MHz, CDCl₃): δ 29.1, 32.6, 43.5, 109.3, 118.5, 119.7, 121.2, 122.0, 122.7, 126.6, 128.1, 130.0, 130.8, 131.9, 137.8, 147.5; HRMS: Calcd for [C₂₆H₂₃N₂O₂]⁺ m/z 443.1117. Found 443.1121.

3,3'-((1-phenylthiethane-1,1-diyl)bis(1H-pyrrole), 5a: 1H NMR (300 MHz, CDCl₃): δ 2.06 (s, 3H), 3.37 (s, 6H), 6.50 (s, 2H), 6.96 (t, J = 7.2 Hz, 2H), 7.19 (t, J = 7.2 Hz, 2H), 7.28-7.39 (m, 8H); 13C NMR (75 MHz, CDCl₃): δ 29.1, 32.6, 43.5, 109.3, 118.5, 119.7, 121.2, 122.0, 122.7, 126.6, 128.1, 130.0, 130.8, 131.9, 137.8, 147.5; HRMS: Calcd for [C₁₉H₁₉N₂O₂]⁺ m/z 237.1386. Found 237.1390.

Conclusion

In conclusion, a new method has been developed for smooth conversion of phenylacetylenes to bis(indoly)alkanes and bis(pyrrolyl)alkanes under mild laboratory reaction conditions with good to excellent yield in aqueous ethanolic medium employing 3 mol% of mercury (II) chloride as catalyst.

Acknowledgements

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References


