Synthesis of Bis(3-indolyl)methanes Mediated by Potassium tert-Butoxide

A. Sofia Santos,[a, b] Rita D. Ferro,[a] Nuno Viduedo,[a] Luisa B. Maia,[a] Artur M. S. Silva,[b] and M. Manuel B. Marques*[a]

The indole moiety is an important N-heterocycle found in natural products, and a key structural component of many value-added chemicals including pharmaceuticals. In particular, bis(3-indolyl)methanes (BIMs) are an important subgroup of indoles, composed of two indole units. Herein, we report the development of a simple method to access BIMs derivatives in yields of up to 77% by exploiting a tBuOK-mediated coupling reaction of indoles and benzyl alcohols.

Introduction

Nitrogen heterocycles are one of the most frequently occurring structures in pharmaceuticals.[11] Access to a wide variety of functionalized N-heterocyclic compounds is of critical importance to drive more efficient drug discovery programs. The indole scaffold is a privileged structure with potential applications in the medicinal chemistry field. It is found in natural products, and a key structural component of many value-added chemicals including pharmaceuticals. When properly functionalized, indole can exhibit a wide range of pharmacological properties including anticancer,[10] antioxidant[3] and anti-inflammatory activities.[14] In particular, bis(3-indolyl)methanes (BIMs) are an important subgroup of indoles, composed of two indole units, that is present in several natural products like arundine, streptindole, arsindoline A, barakacin and vibrindole A (Figure 1).

Preparation of these compounds is usually done by addition of aldehydes or ketones to two molecules of indole via acid[7] or base catalysis.[15] Furthermore, alternative and more sustainable methods have emerged, based on metal-catalysed[8] and metal-free reactions.[9] This includes metal-catalysed carbon–carbon coupling and alkylation reactions,[11–13] and organocatalysed reactions.[14] Other examples also include the use of metal-free oxidative reactions.[15,16] Recently, several examples have been reported using aryl amines (1),[17] aldehydes (2),[18–20] ketones (3),[21,24] benzyl amines (4)[19,25] and benzyl alcohols (5)[26–28] as starting materials (Scheme 1).

Despite of the efficiency of metal-catalysed methods employing abundant metals, which constitute a key advance in this field, some catalysts are sensitive to air and not so easy to handle or prepare. Furthermore, removal of metal impurities and secondary products originating from metal-catalysed methods can lead to complex work-up procedures and purifications. Thus, the development of a method that allows simple access to BIMs derivatives is of great interest.

In the last few years, the use of potassium tert-butoxide has been reported for many chemical reactions,[30] including acceptorless dehydrogenative transformations,[31] oxidations,[32] and radical pathways.[33]

Recently, Yu and co-workers reported the acceptorless dehydrogenation of N-heterocycles using potassium tert-butoxide.[31] Furthermore, tBuOK has been reported as the sole additive in a novel radical condensation reaction[34] for the transamination of primary and tertiary amines at room temperatures, giving access to secondary amines.[35] In continuation of our interest in developing synthetic methodologies to access N-heterocycles, such as azaindoles and indoles,[36–40] we envisaged to investigate the synthesis of BIMs.

Figure 1. Examples of bis(3-indolyl)methanes (BIMs) present in different natural products.

Supporting information for this article is available on the WWW under https://doi.org/10.1002/open.202200265

© 2023 The Authors. Published by Wiley-VCH GmbH
Results and Discussion

Herein, we developed a novel approach based on a tBuOK-mediated synthesis of several BIMs derivatives with a wide range of substrates and functional group compatibility.

A model reaction was chosen, where indole 1, benzyl alcohol 2 and tBuOK were mixed in toluene to afford the corresponding BIM compound 3a (Table 1).

Initial experiments involved the use of 0.1 equiv. of tBuOK at 50 °C (entry 1). Since the reaction did not seem to progress, as no starting material consumption was observed, the temperature was increased to 80 °C (entry 1). Even after 24 h, these conditions only allowed formation of the desired product 3a in 3% yield. Wondering whether the increase in temperature could be a crucial factor, the reaction was performed at 110 °C for 24 h (entry 2). Indeed, a great increase in yield was observed and the product 3a was obtained in 53% yield. Next, the amount of base was studied, and experiments were carried out with 0.1, 0.5, 0.75, 1, 1.5 and 2 equiv. of tBuOK at 110 °C (entries 3–8). After 6 h, using either 0.1 equiv. or 0.5 equiv., the product 3a was obtained in low yields (22% and 24% yield, respectively, entries 3 and 4). A significant increase in yield was observed when 0.75 equiv. were used (54%, entry 5). Finally, experiments using 1 equiv. (entry 6), 1.5 equiv. (entry 7) and 2 equiv. of tBuOK (entry 8) were performed. Increasing the amount of base to 1 equiv. improved the yield to 77%; above these values, the yield decreased (entries 6–8). This shows that the amount of base is crucial for product formation, as higher conversion was obtained with an equimolar amount of base. Still, the use of an increasing excess (entries 7 and 8) seems to compromise the reaction outcome, probably due to a rapid formation of side products, as the reaction mixture revealed to be more complex.

Furthermore, experiments with 2 equiv. of tBuOK at 130 °C were carried out and the reaction seemed to progress smoother with a total yield of 67% (entry 9). Since these conditions were harsher and involved an excess of base, we decided to focus our efforts on using milder conditions. Subsequently, different bases were tested such as KOH, tBuONa and NaH, with corresponding yield of 63%, 31% and 53% (entries 10–12). These results suggest that the use of potassium tert-butoxide as base seems to be essential for the reaction mechanism (entry 7).

Table 1. Optimization of the synthesis of BIMs.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base [equiv.]</th>
<th>Time [h]</th>
<th>T [°C]</th>
<th>3a [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>tBuOK (0.1)</td>
<td>24</td>
<td>50–80</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>tBuOK (0.1)</td>
<td>24</td>
<td>110</td>
<td>53</td>
</tr>
<tr>
<td>3</td>
<td>tBuOK (0.1)</td>
<td>6</td>
<td>110</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td>tBuOK (0.5)</td>
<td>6</td>
<td>110</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>tBuOK (0.75)</td>
<td>6</td>
<td>110</td>
<td>34</td>
</tr>
<tr>
<td>6</td>
<td>tBuOK (1)</td>
<td>6</td>
<td>110</td>
<td>77</td>
</tr>
<tr>
<td>7</td>
<td>tBuOK (1.5)</td>
<td>6</td>
<td>110</td>
<td>59</td>
</tr>
<tr>
<td>8</td>
<td>tBuOK (2)</td>
<td>6</td>
<td>110</td>
<td>40</td>
</tr>
<tr>
<td>9</td>
<td>tBuOK (2)</td>
<td>6</td>
<td>130</td>
<td>67</td>
</tr>
<tr>
<td>10</td>
<td>KOH (1)</td>
<td>6</td>
<td>110</td>
<td>63</td>
</tr>
<tr>
<td>11</td>
<td>tBuONa (1)</td>
<td>6</td>
<td>110</td>
<td>31</td>
</tr>
<tr>
<td>12</td>
<td>NaH (1)</td>
<td>6</td>
<td>110</td>
<td>53</td>
</tr>
<tr>
<td>13[a]</td>
<td>tBuOK (1)</td>
<td>6</td>
<td>110</td>
<td>64</td>
</tr>
<tr>
<td>14[a]</td>
<td>tBuOK (1)</td>
<td>6</td>
<td>110</td>
<td>55</td>
</tr>
<tr>
<td>15</td>
<td>tBuOK (1)</td>
<td>18</td>
<td>110</td>
<td>62</td>
</tr>
</tbody>
</table>

[a] Schlenk tube, under N₂; [b] Schlenk tube, under air; [c] 1 equiv. of benzyl alcohol; [d] yield quantified by quantitative NMR (qNMR) using 1,3,5-trimethoxybenzene as the standard.
The reaction was also carried out in open air to access the influence of the presence of oxygen. Under these conditions, a slightly lower yield was obtained (64%, entry 13) when compared with the same reaction carried out in nitrogen atmosphere (77%, entry 6). Next, 1 equiv. of benzyl alcohol was used and a decrease in yield was observed, suggesting that an excess of alcohol is needed to promote the formation of the imine intermediate (entry 14; see intermediate 1c in mechanistic proposal below Scheme 4). Additionally, leaving the reaction for 18 h did not significantly influence the product formation (entry 15). The best conditions found involved 1 equiv. of tBuOK for 6 h at 110 °C (entry 7).

Next, the reaction scope was investigated while applying the optimal reaction conditions (Table 1, entry 5), using different N-heterocycles and benzyl alcohol derivatives (Scheme 2). The use of different indole derivatives bearing halogen atoms at the aromatic ring seemed to, in general, decrease the reaction yield (see compounds 3b, 3c and 3f), but still the reaction proceeded smoothly with the best yield obtained for 5-bromo-indole (3f, 56%). The use of 7-azaindole was also effective under the described conditions, with the corresponding bis-azaindole 3g obtained in 62% yield. Comparing the reactivity of 7-azaindole with indole (3a vs. 3g), the slight decrease in yield of product 3g can be justified by the electron-deficient nature of the pyridine ring which can decrease the reactivity of the conjugated system in the pyrrole ring. Next, different benzyl alcohols were tested, one bearing an electron-donating group on the aromatic ring (–OCH3) and the other bearing a pyridine ring, which possesses electron-withdrawing properties. The best yield was observed when the pyridine ring was present in the alcohol moiety (3i, 57%), most likely due to the electron-withdrawing nature of the pyridine that allows an easier attack of the second unit of indole, since a more reactive imine-like intermediate is formed (see mechanistic considerations below). The use of furfuryl alcohol also led to the desired product 3j in 31% yield, which shows the versatility of the proposed methodology.

Additionally, experiments with p-trifluoromethyl and p-nitro benzyl alcohol were also carried out, but only trace amounts of both products were observed by TLC. Finally, competition experiments were performed using benzyl alcohol and two different indoles. Indeed, the synthesis of unsymmetrical BIMs is interesting and requires dedicated strategies.41 When indole and 5-bromo indole were used as coupling partners, both products 3a and 3h were isolated from the reaction mixture in a 1:2.3 ratio, respectively. This distribution can be attributed to the formation of both indole and 5-bromo indole imine-like intermediates. When the imine-like product is formed from indole, two possible nucleophilic attacks (from indole and 5-bromo indole) can occur, leading to the formation of 3a and 3h, respectively. On the other hand, formation of the 5-bromo indole-derived imine-like product is only attacked by indole 3h, since no formation of product 3f was observed. This reinforces the higher reactivity of indole as a nucleophile in this reaction.

Furthermore, the use of indole and 7-azaindole with benzyl alcohol as coupling partners led to the formation of products 3g and 3d in a 1:1.5 ratio, respectively. These results suggest that the imine-like intermediate from azaindole might be more electrophilic, undergoing a subsequent nucleophilic attack by both indole and 7-azaindole. No formation of 3a was observed.

Additional competitive experiments were also attempted with different benzyl alcohols. Experiments were performed with p-methoxybenzyl alcohol using indole and 6-bromoindole, and a mixture of 3 products was formed in a 1:1.8:0.9 ratio (identified by 1H NMR spectroscopy). The major product contains both indole units (see Supporting Information).

Furthermore, the same reaction was performed using pyridyl benzyl alcohol, indole and 6-bromoindole, and a similar result was observed, three compounds with a 1:1.7:0.6 ratio (see Supporting Information).

The results from these competition experiments suggest that functionalization of the benzylo moiety of the alcohol influences the reactivity of the intermediates generated. Indeed, simple benzyl alcohol leads to the formation of two products, while, when electron-withdrawing or electron-donating groups are present in the alcohol moiety, three compounds are formed. Interestingly, the major product contains both indole units, independently of the alcohol used.

This observation reinforces that the most electrophilic imine-like intermediate (generated from the most electrophilic indole) preferentially reacts with the most nucleophilic indole.

Next, we investigated the reaction mechanism and conducted several control experiments (Scheme 3).

First, 1.0 equiv. and 2.0 equiv. of 2,2,6,6-tetramethylpiperidinooxy (TEMPO) were added, respectively, to the reaction system under the optimized conditions and the formation of the final product 3a was suppressed by the increasing amount of TEMPO as mirrored in the lowered yields.
The use of a different radical scavenger like galvinoxyl (1.0 equiv.) completely inhibited the reaction. Furthermore, these control experiments suggested that a possible formation of radical intermediates might take place.

To confirm the formation of radical species, we used electron paramagnetic resonance (EPR) spectroscopy. The reaction of indole (1.0 equiv.), benzyl alcohol (2.0 equiv.) and tBuOK (1.0 equiv.), in toluene, at 110 °C, for 2 h, yielded a broad, nearly isotropic EPR spectrum, probably originating from different radical species (Figure 2, red spectrum). To shed light on the components responsible for the formation of these radicals, the spectra of reaction mixtures without one of the three reagents (benzyl alcohol, tBuOK and indole) were also acquired. In the absence of benzyl alcohol or tBuOK, no radical species was detected (Figure S2, Supporting Information), suggesting that it is the reaction between these two components (benzyl alcohol and tBuOK) that generates the initiating radical species. In accordance, in the presence of only benzyl alcohol and tBuOK (absence of indole), a strong EPR spectrum was observed (Figure 2, blue spectrum), clearly supporting that the reaction of benzyl alcohol with tBuOK is able to generate radical species in high concentration.

As the reaction proceeds, the concentration of radicals decreases, which is reflected in the much lower intensity of the red spectrum (note the scaling factor of 0.1 for the blue spectrum in Figure 2). Eventually, all radical species relevant to the reaction are consumed and the reaction stops. A similar role for the tBuOK/benzyl alcohol-derived radicals in the generation of 3-arylp propaneamides was suggested by Azizi and Madsen, who also used EPR spectroscopy to prove the generation of radicals.

Furthermore, 3-methyl indole and N-methyl indole were investigated to prove the crucial role of the free NH position and position C-3 of the indole moiety. Unsurprisingly, no reaction was observed when these substrates were used, since an NH group is needed as a precursor for the reaction mechanism. Besides that, the blockage of position 3 of the indole moiety hinders the reaction success since this is where the functionalization by benzyl alcohol takes place.

Based on the EPR spectra, that clearly showed the ability of the system tBuOK/benzyl alcohol to generate radical species in high concentrations, the following reaction mechanism is proposed (Scheme 4). First, benzyl alcohol is deprotonated by the base to form alkoxide 2a, followed by initiation, generating radical anion 2b. Radical 2b then reacts with indole 1 in position C-3 to give radical anion intermediate 1a. This intermediate 1a then undergoes rapid homolytic cleavage of the C3 C–H bond forming a C–C double bond in 1b. Next, two possible pathways can occur, either by heterolytic cleavage through an elimination reaction or by homolytic cleavage and capture of the previously generated H-atom (shown as 1bb), leading to the formation of an imine-like intermediate 1c. This highly reactive intermediate 1c undergoes a second nucleophilic attack by indole to obtain the desired product 3 (Scheme 4). Our results demonstrate the important role of tBuOK in the generation of radical species.

**Scheme 3.** Control experiments for mechanistic insights.

**Figure 2.** EPR spectra of the following reaction mixtures: blue - benzyl alcohol, tBuOK and toluene reacted at 110 °C, for 2 h; red - benzyl alcohol, tBuOK, toluene and indole reacted at 110 °C, for 2 h. Other reaction details are described in the Supporting Information. Spectra were acquired at room temperature (298 K) as described in the Supporting Information. To facilitate comparison between the two spectra, the blue one was multiplied by 0.1.
Conclusion
A novel base-mediated methodology and simple route to access BIMs derivatives was developed. This emerges as suitable and reliable alternative to the use of complex metal-catalysts that are not always stable and easy to handle. Taking advance of a potassium tert-butoxide-mediated coupling, several BIMs were synthesized with yields up to 77% in refluxing toluene. Furthermore, control experiments and EPR spectroscopic studies allowed conclusions regarding the role of the base in the reaction mechanism. The mechanistic studies revealed that a radical mechanism is involved in the C-3 alkylation of indoles and azaindoles, in which the tBuOK facilitates the reaction to proceed smoothly and to be complete after 6 h. This report constitutes a proof of concept on the relevance of tBuOK and its role in C–C bond-forming reactions involving benzyl moieties.

Experimental Section
Materials and methods
All reagents and solvents were acquired commercially and usually used without further purification. The solvents used during the reactions were dried and distilled using typical methods. Analytical TLC was performed on Merck Kieselgel GF 254, 0.2 mm plates with benzyl alcohol as solvent. compounds were prepared in 5 or 3 mm NMR tubes using CDCl$_3$ or DMSO-$d_6$, and the corresponding trace as reference

General procedure for synthesis of BIMs derivatives
A Schlenk tube was equipped with a stirring bar was subjected to vacuum while heating to remove all possible moisture. After the tube reached room temperature indole (30 mg, 1 equiv.) and tBuOK (1 equiv.) were added under nitrogen stream and then the solids remained under vacuum. After that, 3 cycles of vacuum/nitrogen were done to ensure the nitrogen atmosphere. Dry toluene (1 mL) was added to the solids, followed by benzyl alcohol (2 equiv.). The mixture was allowed to reach 110°C and stirred for 6 h. The reaction was followed by TLC until consumption of starting material. After the reaction completion, the mixture was filtered over a celite pad and the solvent removed. The desired product was isolated after purification by chromatography.

An alternative work-up procedure was also tested that consisted on addition of ethyl acetate to the crude residue and washing two times with HCl (1 M). The combined aqueous layers were extracted with ethyl acetate to remove all the remaining product. The combined organic layers were dried with anhydrous sodium sulphate, filtered and concentrated. Both work-up protocols afforded the product with same yields.

3,3′-(Phenylmethylene)bis(1H-indole) (3a)$^{[42]}$

Purification: silica gel, Hexane/AcOEt (6:1) with gradient; PTLC, Hexane/AcOEt (6:1) with gradient; Yield: 77% (31.7 mg); red oil; 1H NMR (400 MHz, CDCl$_3$): δ = 7.85 (s, 2H), 7.42 (s, 1H), 7.40–7.36 (m, 5H), 7.33–7.28 (m, 2H), 7.24 (d, J = 7.2 Hz, 1H), 7.18 (t, J = 7.5 Hz, 2H), 7.02 (t, J = 7.5 Hz, 2H), 6.67 (s, 2H), 5.91 (s, 1H). 13C NMR (101 MHz, CDCl$_3$): δ = 144.14, 136.79, 128.85, 128.34, 127.19, 126.23, 123.75, 122.03, 120.05, 119.79, 119.34, 111.16, 104.31.

3,3′-(Phenylmethylene)bis(5-fluoro-1H-indole) (3 b)$^{[42]}$

Purification: silica gel, Hexane/AcOEt (6:1) with gradient; PTLC, Hexane/AcOEt (6:1) with gradient; Yield: 52% (20.5 mg); red oil; 1H NMR (400 MHz, CDCl$_3$): δ = 7.98 (s, 2H), 7.37–7.23 (m, 7H), 7.01 (d, J = 9.7 Hz, 2H), 6.93 (t, J = 9.0 Hz, 2H), 6.74 (s, 2H), 5.76 (s, 1H); 13C NMR (101 MHz, CDCl$_3$): δ = 157.68 (d, J = 234.5 Hz), 143.41, 133.35, 128.62 (d, J = 20.8 Hz), 127.51 (d, J = 9.8 Hz), 126.56, 125.39, 119.62 (d, J = 4.7 Hz), 111.79 (d, J = 9.6 Hz), 110.54 (d, J = 26.4 Hz), 105.04, 104.80.

3,3′-(Phenylmethylene)bis(5-iodo-1H-indole) (3c)$^{[42]}$

Purification: silica gel, Hexane/AcOEt (6:1) with gradient; PTLC, Hexane/AcOEt (6:1) with gradient; Yield: 41% (8.43 mg); red oil; 1H NMR (400 MHz, CDCl$_3$): δ = 8.52 (s, 2H), 8.42 (s, 2H), 7.70 (s, 2H), 7.44 (d, J = 8.5 Hz, 2H), 7.35–7.25 (m, 5H), 7.16 (d, J = 8.5 Hz, 2H), 6.61 (s, 2H), 5.77 (s, 1H); 13C NMR (101 MHz, CDCl$_3$): δ = 143.22, 135.94, 130.60, 129.63, 128.68, 128.67, 128.56, 126.66, 124.52, 118.96, 113.26, 83.07, 39.94.

3-((1H-Indol-3-yl)(phenyl)methyl)-1H-pyrrrolo[2,3-b]pyridine (3 d)

Purification: silica gel, Hexane/AcOEt (6:1) with gradient; PTLC, Hexane/AcOEt (6:1) with gradient; Yield: 41% (8.43 mg); red oil;
Purification: silica gel, Hexane/AcOEt (4 : 1) with gradient; PTLC, -(Pyridin-2-ylmethylene)bis(1H-indole) (3 f)

H NMR (400 MHz, CDCl₃): δ = 8.25 (d, J = 3.8 Hz, 1H), 8.04 (s, 1H), 7.64 (d, J = 7.7 Hz, 1H), 7.41–7.27 (m, 6H), 7.24 (d, J = 7.1 Hz, 1H), 7.18 (t, J = 7.4 Hz, 1H), 7.02 (t, J = 7.5 Hz, 1H), 6.94 (dd, J = 7.8, 4.6 Hz, 1H), 6.84 (s, 1H), 6.66 (s, 1H), 5.87 (s, 1H). ¹³C NMR (101 MHz, CDCl₃): δ = 149.32, 143.65, 142.83, 136.84, 138.80, 128.80, 128.70, 128.46, 128.39, 127.10, 126.49, 124.06, 123.63, 119.94, 119.89, 119.51, 119.39, 118.22, 115.55, 111.23, 40.50. MS (EI) calcd. for C₇₇H₇₈N₆ (M + 1): 324.149. Found: 324.148.

3,3’-((4-Methoxyphenyl)methylene)bis(1H-indole) (3 j)

Purification: silica gel, Hexane/AcOEt (6 : 1) with gradient; Yield: 31% (12.3 mg); red oil; ¹H NMR (400 MHz, CDCl₃): δ = 7.84 (s, 2H), 7.49 (d, J = 7.9 Hz, 2H), 7.34 (d, J = 8.6 Hz, 3H), 7.18 (t, J = 7.5 Hz, 2H), 7.05 (t, J = 7.4 Hz, 2H), 6.85 (d, J = 1.2 Hz, 2H), 6.31 (s, 1H), 6.06 (d, J = 2.9 Hz, 1H), 5.95 (s, 1H). ¹³C NMR (101 MHz, CDCl₃): δ = 157.24, 141.33, 136.66, 126.90, 123.20, 122.05, 119.79, 119.45, 117.26, 117.26, 111.26, 110.26, 106.72, 34.23.

Acknowledgements

The authors thank the Fundação para a Ciência e Tecnologia for the fellowship PO/BD/142876/2018. This work was supported by the Associate Laboratory for Green Chemistry – LAQV which is financed by national funds from FCT/ MCTES UIDB/50006/2020, UIDP/50006/2020 (LAQV). The National NMR Facility is supported by FCT, ROTERO/0031/2013-PINFRA/22161/2016, co-financed by FEDER through COMPETE 2020, POCI, and PORT L and FCT through PIDDAC and CERMAX (022162). LBM also thanks to FCT/MCTES for the CEEC-Individual Program Contract (CEECIND/03810/2017).

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: bis(indolyl)methanes · indole · BuOK · radicals · benzyl alcohols


ChemistryOpen 2023, 12, e202200265 (6 of 7) © 2023 The Authors. Published by Wiley-VCH GmbH