Brønsted Acid-Catalyzed Straightforward Synthesis of Benzo[b]carbazoles from 2,3-Unsubstituted Indoles

Anisley Suárez, a Patricia García-García, a Manuel A. Fernández-Rodríguez, a and Roberto Sanz a,*

a Área de Química Orgánica, Departamento de Química, Facultad de Ciencias, Universidad de Burgos, Pza. Misael Bañuelos s/n, 09001-Burgos (Spain)
Fax: (+34)-947-258831; E-mail: rsd@ubu.es

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.

Abstract. Described is a general and efficient synthesis of valuable benzo[b]carbazoles by Brønsted acid-catalyzed reaction between simple C2,C3-unsubstituted indoles and o-(α-(hydroxy)benzyl)benzaldehyde acetals. Highly selective migration processes are involved as key steps in the overall cascade sequence that implies the one-pot formation of two new bonds and a cycle in a regioselective fashion.

Keywords: Brønsted acid catalysis; heterocycles; benzo[b]carbazoles; 1,2-alkyl shift; synthetic methods

Aryl- and heteroaryl-condensed carbazoles have attracted considerable interest because of their broad spectrum of useful biological activities. Among the benzocarbazole frameworks, annulated[b]carbazoles, such as ellipticine and its derivatives, are relevant due to their interesting pharmacological activities as well as their utility in the field of material chemistry. Different approaches for accessing this type of heterocyclic compounds have been described, although most of them imply multi-step sequences and restricted substitution patterns. In this regard, benzo[b]carbazoles are commonly constructed from either properly functionalized indoles or carbazoles, substituted naphthalenes, or more particularly from ketenimines and imidoyl selenides by radical cyclizations, or from ynamides by dehydro Diels–Alder reactions. Herein we wish to report our results on the Brønsted acid-catalyzed reaction between indoles and aromatic aldehyde acetals possessing an α-(hydroxy)benzyl group at the ortho-position, which enables a facile entry into the synthesis of

On the other hand, the reaction of indoles with carbonyl derivatives, including acetals, in the presence of Lewis or protic acids is the most general method for the synthesis of symmetric 3,3’-bisindolylmethanes (3,3’-BIMs) (II). Their formation is proposed to proceed through the intermediacy of an azafulvenium species such as I (with Nu = H) that undergoes further addition of a second indole molecule (Scheme 1). When intermediates I are functionalized with an additional nucleophilic group such as an electron-rich aromatic (Nu = Ar), a second Friedel–Crafts alkylation process can take place affording products like III (Scheme 1). Alternatively, it’s well known that neutral alkylideneindolenine intermediates related with I (Nu = H), commonly formed from precursors having a suitable leaving group at the benzylic position of 3-substituted indoles, are able to add external nucleophiles in a conjugate fashion. Herein we wish to report our results on the Brønsted acid-catalyzed reaction between indoles and aromatic aldehyde acetals possessing an α-(hydroxy)benzyl group at the ortho-position, which enables a facile entry into the synthesis of
regioselectively functionalized benzo[b]carbazoles through an unprecedented cascade sequence.

![Scheme 1](image)

**Scheme 1.** Reported reactions of indoles and benzaldehyde derivatives: synthesis of 3,3'-BIMs (II) and C3-carbocyclic-functionalized indoles (III).

In the last years, we have been interested in the development of new methodologies for the direct C3-alkylation of indoles with alcohols.\(^{14}\) As part of this research, we study the reaction between \(N\)-methylindole \(1\) and \((2\text{-}(\text{diethoxymethyl})\text{phenyl})(\text{phenyl})\text{methanol} 2\) using various acid catalysts (Scheme 2). The use of selected \(\sigma\)-Lewis acids, previously employed for the reaction of indoles with carbonyl derivatives, afforded isobenzofuran derivative \(3\), obtained as a mixture of diastereoisomers, as the only product without formation of the corresponding 3,3'-BIM. Surprisingly, the same reaction under Brønsted acid catalysis (20 mol% of PTSA) selectively afforded a \(\sigma\)-Lewis acids (5 mol%) catalyst. Selective formation of 3aa and 4aa.

Having found mild conditions to efficiently and directly access 4aa from readily available \(N\)-methylindole we decided to check if this methodology could be general for the synthesis of a variety of benzo[b]carbazoles. First, \(N\)-methylindole \(1\) was treated with selected benzylic alcohols \(2\)-i, prepared from 2-lithiobenzaldehyde diethyl acetal and selected (hetero)aryl carboxaldehydes. As proved in Table 1, both EDG and EWG substituents on the \(Ar\) group, as well as heteroaromatics, were adequately tolerated in the process and 11-aryl-5H-benzo[b]carbazoles \(4\) were obtained typically in high yields. Reactions with highly activated benzylic alcohols bearing EDG groups proceed faster and with a lower amount of the Brønsted acid catalyst (entries 5–9 vs 1–4). Interestingly, no influence in the process or yield was observed by varying the acetal moiety as we determined in the synthesis of benzo[b]carbazole \(4\) from 2 and 2e (entry 5). In addition, NH-indole \(1\) also reacted with selected hydroxyacetals to furnish benzocarbazole derivatives \(4\) in good yields (entries 10–14). Moreover, even less nucleophilic 5-functionalized indoles \(1\)-f are able to participate in this reaction allowing the regioselective preparation of benzo[b]carbazoles \(4\) and \(4\) in moderate to high yields (entries 15–18). However, the presence of an aromatic group (Ar) as substituent in the starting alcohol \(2\) seems to be mandatory for the success of the reaction as substrates bearing alkyl (\(n\)-Bu), cyclopropyl, \((E)-\beta\)-styrenyl (CH=CPh), or phenylethynyl (C=Ph) gave only rise to decomposition products under the standard reaction conditions.

**Table 1.** Synthesis of benzo[b]carbazoles 4.

![Scheme 2](image)
Remarkably, all these reactions selectively occurred to form 11-aryl-5H-benzo[b]carbazoles 4 while the corresponding regioisomeric 6-aryl-substituted benzo[b]carbazoles 5 were only observed in trace to minor amounts in some cases (entries 9 and 14). Intrigued by these particular results, we decided to further explore this process by using hydroxyacetals 2j-n functionalized with a methoxy group at the aryl ring that contains the acetal group and with different aryl groups at the benzylic position. Their reactions with N-methylindole 1a under the standard conditions, PTSA (20 mol%) in MeCN at RT, mainly gave rise to the expected 11-aryl-5H-benzo[b]carbazoles 4 that could be isolated in synthetically useful yields (Table 2). With hydroxyacetals 2j-l bearing neutral, moderately electron-rich, or electron-poor aryl substituents (entries 1–3), the corresponding benzo[b]carbazoles 4 were almost exclusively obtained. However, in the case of highly activated hydroxyacetals 2m,n with a 2-thiophenyl or a trimethoxyphenyl group as Ar substituent, variable amounts of regioisomeric benzo[b]carbazoles 4’, differing on the final position of the methoxy group initially located at a defined position in the starting hydroxacetel 2, were obtained (entries 4,5).

Table 2. Brønsted acid-catalyzed reaction of N-methylindole 1a with functionalized acetals 2j-n. Competitive formation of benzo[b]carbazoles 4 vs 4’ and 5.

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>R¹</th>
<th>R²</th>
<th>2 Ar</th>
<th>t [h]</th>
<th>Product</th>
<th>Yield [%][a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>Me</td>
<td>H</td>
<td>2a Ph</td>
<td>16</td>
<td>4aa</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>Me</td>
<td>H</td>
<td>2b 4-ClC₆H₄</td>
<td>24</td>
<td>4ab</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>Me</td>
<td>H</td>
<td>2c 4-BrC₆H₄</td>
<td>16</td>
<td>4ac</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td>Me</td>
<td>H</td>
<td>2d 2-Naphthyl</td>
<td>3.5</td>
<td>4ad</td>
<td>58</td>
</tr>
<tr>
<td>5</td>
<td>1a</td>
<td>Me</td>
<td>H</td>
<td>2e 4-MeOC₆H₄</td>
<td>16</td>
<td>4ae</td>
<td>85[1]</td>
</tr>
<tr>
<td>6</td>
<td>1a</td>
<td>Me</td>
<td>H</td>
<td>2f 2,3,4-(MeO)₃C₆H₂</td>
<td>0.5</td>
<td>4af</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>1a</td>
<td>Me</td>
<td>H</td>
<td>2g 2-Thienyl</td>
<td>2</td>
<td>4ag</td>
<td>73</td>
</tr>
<tr>
<td>8</td>
<td>1a</td>
<td>Me</td>
<td>H</td>
<td>2h 3-Methyl-2-thienyl</td>
<td>1.5</td>
<td>4ah</td>
<td>71</td>
</tr>
<tr>
<td>9</td>
<td>1a</td>
<td>Me</td>
<td>H</td>
<td>2i 5-Methyl-2-furyl</td>
<td>2</td>
<td>4ai</td>
<td>51[4]</td>
</tr>
<tr>
<td>10</td>
<td>1b</td>
<td>H</td>
<td>H</td>
<td>2a Ph</td>
<td>5</td>
<td>4ba</td>
<td>65</td>
</tr>
<tr>
<td>11</td>
<td>1b</td>
<td>H</td>
<td>H</td>
<td>2d 2-Naphthyl</td>
<td>4</td>
<td>4bd</td>
<td>50</td>
</tr>
<tr>
<td>12</td>
<td>1b</td>
<td>H</td>
<td>H</td>
<td>2e 4-MeOC₆H₄</td>
<td>16</td>
<td>4be</td>
<td>92</td>
</tr>
<tr>
<td>13</td>
<td>1b</td>
<td>H</td>
<td>H</td>
<td>2f 2,3,4-(MeO)₃C₆H₂</td>
<td>0.5</td>
<td>4bf</td>
<td>98</td>
</tr>
<tr>
<td>14</td>
<td>1b</td>
<td>H</td>
<td>H</td>
<td>2i 5-Methyl-2-furyl</td>
<td>3.5</td>
<td>4bi</td>
<td>68[4]</td>
</tr>
<tr>
<td>15</td>
<td>1c</td>
<td>H</td>
<td>Br</td>
<td>2e 4-MeOC₆H₄</td>
<td>4</td>
<td>4ce</td>
<td>48</td>
</tr>
<tr>
<td>16</td>
<td>1d</td>
<td>H</td>
<td>NO₂</td>
<td>2f 2,3,4-(MeO)₃C₆H₂</td>
<td>1</td>
<td>4df</td>
<td>85</td>
</tr>
<tr>
<td>17</td>
<td>1e</td>
<td>H</td>
<td>Cl</td>
<td>2f 2,3,4-(MeO)₃C₆H₂</td>
<td>1</td>
<td>4ef</td>
<td>94</td>
</tr>
<tr>
<td>18</td>
<td>1f</td>
<td>H</td>
<td>CO₂Me</td>
<td>2f 2,3,4-(MeO)₃C₆H₂</td>
<td>1</td>
<td>4ff</td>
<td>80</td>
</tr>
</tbody>
</table>

[a] Yield of isolated products 4 based on the starting indole 1. [b] Carried out with 50 mol% of PTSA. [c] Same yield was obtained in a related reaction starting from alcohol 2e bearing an ethylene acetal moiety instead of a diethyl acetal one. [d] 7–10% of the corresponding 6-arylbenzo[b]carbazole 5 was also isolated and characterized.

Entry 2 Ar Product(s)[a] Yield [%][b]
<table>
<thead>
<tr>
<th>Entry</th>
<th>2 Ar</th>
<th>Product(s)</th>
<th>Yield [%][b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2j Ph</td>
<td>4aj</td>
<td>60[2]</td>
</tr>
<tr>
<td>2</td>
<td>2k 4-ClC₆H₄</td>
<td>4ak</td>
<td>68[2]</td>
</tr>
<tr>
<td>3</td>
<td>2l 4-MeOC₆H₄</td>
<td>4al</td>
<td>73[2]</td>
</tr>
<tr>
<td>4</td>
<td>2m 2,3,4-(MeO)₃C₆H₂</td>
<td>4am+4’an</td>
<td>(1/1.7)</td>
</tr>
<tr>
<td>5</td>
<td>2n 2-Thienyl</td>
<td>4an+4’an (2/1)</td>
<td>75[2]</td>
</tr>
</tbody>
</table>

[a] When two regioisomers were generated, the ratio (in brackets) was determined by ¹H NMR analysis of the crude reaction mixture. [b] Yield of isolated product 4 based on the starting N-methylindole 1a. [c] ca. 5% of the corresponding 6-arylbenzo[b]carbazole 5 was also isolated and characterized. [d] Trace amounts of 4’al and 5al were also formed. [e] Yield for the mixture of regioisomers. The major one was isolated and characterized. [f] 56% of 4’an and 19% of 4’an were isolated and characterized.

With all these results in hand, a catalytic cycle that could account for the formation of
benzo[b]carbazoles 4, 4', and 5 is shown in Scheme 3. Initially, an equilibrium between hydroxyacetal 2 and cyclized acetal 6 is established in the acidic medium. Its reaction with the corresponding indole 1 would afford isobenzofuran derivatives 3, as it was observed when using several σ-Lewis acids or lower amounts of PTSA (see Table in Supporting Information).\[21\] Probably favoured by the presence of the Brønsted acid these isobenzofurans 3 are in equilibrium with the corresponding 3,3'-BIMs 8 through the iminium intermediate 7 (path a).\[22\] This hypothesis was supported by previous reports\[12\] and by isolation of bisindole 8ab (Ar = 4-ClC₆H₄; G = H), along with 3ab, when carrying the reaction with 5 mol% of PTSA for 30 minutes. Reactions under conditions reported in Table 1 (entry 2) of both isolated dihydroisobenzofuran 3ab and bisindole 8ab furnished benzo[b]carbazole 4ab. Having proved the intermediacy of 3, as well as its equilibrium with 8 in the reaction media, the formation of benzo[b]carbazole 4 would be explained by an alternative path b which would imply a nucleophilic addition of C3 of the indole that would generate spiro species 9. This key intermediate could undergo two different 1,2-alkyl shifts (Ciamician-Plancher rearrangement) to recover aromaticity after loss of a proton.\[23\] Migration of the hydroxyalkyl group (path i) would lead to alcohol 10 that upon loss of water would afford benzo[b]carbazole 4. On the other hand, a competitive migration of the benzylic group (path ii) would lead to regioisomeric alcohol 11 that would provide the corresponding benzo[b]carbazole 5 after protonation and loss of water, probably through the iminium intermediate 12, and subsequent aromatization by further removal of a proton. However, both pathways do not account for the generation of benzo[b]carbazoles 4, 4', in which the relative position of the G substituent and the Ar group have changed with respect to the starting alcohol 2. So, we propose that the iminium intermediate 12 could also evolve through an alternative pathway involving a [1,4]-aryl migration. Subsequent loss of a proton would explain the formation of benzo[b]carbazoles 4'. This competitive process seems to be partially operative exclusively when the hydroxymethyl group is located at C3 (intermediate 11 vs 10), probably due to the high stabilization of iminium intermediate 12. On the basis of this proposal the two 1,2-alkyl shifts (pathways i and ii) could not be distinguished for non-functionalized hydroxyacetals 2 (G = H) as both of them collapse to the same product (4' = 4 for G = H). From the results of Table 2 it seems that pathway i is the preferred one whereas the benzylic migration (pathway ii) resulted to be competitive only for highly activated substrates (G = OMe and Ar = 2-Th or 2,3,4-(MeO)₃C₆H₂) with an increased carbocation stabilization ability at the benzylic position. Also, the subsequent [1,4]-aryl migration on intermediate species 12 is favoured for electron-rich aromatics as Ar substituents. In other case, only trace amounts of regioisomers 5 are formed.

Based on our proposed mechanism we envisioned that acetal derivatives 13 bearing a tertiary benzylic hydroxy group could be potential precursors of 6,11-disubstituted benzo[b]carbazoles thus expanding the scope of the reported benzoacarbazole synthesis. Gratifyingly, treatment of indole 1a with hydroxyacetals 13a-c under the standard Brønsted acid catalysis selectively afforded the aimed 6,11-disubstituted benzo[b]carbazole derivatives 14 (that correspond with 4' in the general mechanism depicted in Scheme 3) in good yields (Scheme 4).\[24\] It is interesting to note that for these acetals 13 the scope of the substitution at the benzylic carbon bearing the hydroxy group is not limited to aromatic substituents, like in secondary alcohols 2, as shown for 13ac having an alkynyl group that affords the corresponding benzo[b]carbazole 14ac. As we anticipated, by increasing the migratory aptitude of the benzylic carbon in intermediate 15 (tertiary in 15 vs secondary in 9) an initial selective migration of the t-alkyl group (pathway ii in Scheme 3) occurred to form iminium species 16. These intermediates, in contrast with related ones 12 in Scheme 3, only could evolve by a formal [1,4]-migration to recover the
aromaticity after loss of a proton (Scheme 4). Interestingly, the observed [1,4]-aryl or alkynyl shift has not precedent and opens the door to future developments in this field. Specially significant results the migration of an alkynyl group in the formation of 14ac as it is known the low migratory aptitude of these groups in carbocation rearrangements.\[^{25}\]

![Scheme 4. Reactions of 1a with tertiary alcohols 13a-c. Synthesis of 6,11-disubstituted-5H-benzo[b]carbazoles 14.](image)

Moreover, the reported methodology resulted to be also useful for the synthesis of heteroaryl-fused carbazoles. So, 10-aryl-5H-thieno[3,2-b]carbazoles 18 were selectively prepared under the standard Brønsted acid-catalysis from thiophene-based hydroxyacetals 17a,b (Scheme 5). Interestingly, starting from regioisomeric hydroxyacetal 19, the corresponding thieno[2,3-b]carazole derivative 20 was exclusively formed (Scheme 5). In addition, benzo[4,5]thieno[2,3-b]carazole 22 as well as benzofuro[2,3-b]carbazole 24 could also be prepared with this methodology from a properly functionalized benzo[b]thiophene 21 and benzo[b]furan 23 respectively (Scheme 5). The formation of all of these carbazole derivatives could be understood in the same way as benzo[b]carbazoles 4, thus involving initial hydroxyalkyl shift (pathway i in Scheme 3) followed by loss of water. Furthermore, the synthesis of these adducts was completely selective with the exception of carbazole derivative 24 which formation was accompanied with regioisomeric benzofuro[2,3-b]carbazole 25 in a ca. 1.6:1 ratio (Scheme 5).\[^{26}\] On the contrary, hydroxyacetals bearing N-heterocycles such as pyridines or indoles led to no reaction or decomposition under the established conditions (Figure 2).\[^{27}\]

![Scheme 5. Synthesis of heteroaryl[b]carbazoles 18, 20, 22, 24 and 25.](image)

Figure 2. Not successful N-heterocycles-functionalized hydroxyacetals.

In conclusion, we have described a straightforward and regioselective synthesis of aryl-functionalized (hetero)aryl-annulated[b]carbazoles from easily available starting materials such as indoles and o-(α-(hydroxy)benzyl)benzaldehyde acetals under simple Brønsted acid-catalysis through a new cascade sequence. This efficient and metal-free methodology affects the current synthetic scenario for the preparation of benzo[b]carbazoles by adding a new strategy that allows the direct use of C2,C3-unsubstituted indoles. Further studies to prove the proposed mechanism of this new transformation and to extend its synthetic scope are currently in progress in our laboratory.
Experimental Section

General Remarks

All reactions involving air sensitive compounds were carried out under a N2 atmosphere (99.99%). All glassware was oven-dried (120 °C), evacuated and purged with nitrogen. All common reagents and solvents were obtained from commercial suppliers (VWR, Alfa and Aldrich) and used without any further purification. Solvents were dried by standard methods. Hexane and ethyl acetate were purchased as extra pure grade reagents and used as received. For the preparation of starting alcohols see the Supporting Information. TLC was performed on aluminum-backed plates coated with silica gel 60 with 250-240 mesh. Solvents were dried using mixtures of anhydrous Na2SO4 (200 g) and anhydrous CaCl2 (15 mL). The combined organic layers were dried over 

TLC (20 x 20 cm), then it was quenched with a 0.5 M solution of PTSA (5 mL) and subsequent heating. Rf values are reported on silica gel. Flash column chromatography was carried out on silica gel 60 with 250-240 mesh. NMR spectra were measured on Varian Mercury-Plus 300 MHz and Varian Inova-400 MHz spectrometers. High resolution mass spectra (HRMS) were recorded on a Micromass Autospec spectrometer using EI at 70eV. Melting points were measured on a Gallenkamp apparatus using open capillary tubes and are uncorrected. GC-MS and low-resolution mass spectra (LRMS) measurements were recorded on an Agilent 6890N/5973 Network GC System, equipped with a HP-5MS column.

General procedure for the PTSA-catalyzed synthesis of benzo[6,9]carbazoles 4, 4', and 5

To a mixture of the corresponding acetal derivative 2 (1 mmol) and the corresponding indole 1, in MeCN (1 mL) was added PTSA (20 mol%, 38 mg). The reaction mixture was stirred at room temperature until complete disappearance of the acetal derivative was observed by TLC (0.5–24 h), then it was quenched with a 0.5 M aqueous solution of NaOH, and extracted with EtOAc (3 15 mL). The combined organic layers were dried over anhydrous Na2SO4 and solvent was removed under reduced pressure. The remaining residue was purified by flash chromatography on silica gel using mixtures of hexane/EtOAc as eluents. The corresponding benzo[6,9]carbazoles 4, 4', and 5 were isolated in the yields reported in the text. Characterization data and NMR spectra are presented in the Supporting Information.

Acknowledgements

We gratefully acknowledge the Ministerio de Economía y Competitividad (MINECO) and FEDER (CTQ2010-15358) for financial support. P.G.-G. and M.A.F.-R. thank MINECO for “Juan de la Cierva” and “Ramón y Cajal” contracts.

References


[11] For a recent review, see: M. Shiri, M. A. Zolfigol, H. Kruger, Z. Tanbakouchian, Chem. Rev. 2010, 110, 2250–2293. Aryl(3-indolyl)carbenium ions I have been recently isolated as stable o-benzenedisulfonamide salts


[15] Prepared from commercially available 2-bromobenzaldehyde diethyl acetal by Br–Li exchange and further reaction with benzaldehyde. See Supporting Information.

[16] For detailed optimization studies, see the Supporting Information.


[20] The structure of all the new compounds 4, 4’, 5, 14 and 18 were determined by NMR techniques including COSY, NOESY and $^1$H–$^1$C 2D experiments. In addition, the substitution at C6 or C11 of the benzo[b]carbazole moiety could be easily established as the substituent at C11 is significantly deshielded by the indole benzene ring. See ref. [5b] and [7b].

[21] The initial formation of isobenzofuran derivatives 3 precludes the possibility of an alternative mechanism involving a prior direct substitution of the hydroxy group by the indole through C3 and further direct cyclization by attack of C2 to the carbonyl.


[24] The structure of 14aa was further confirmed by X-ray analysis. CCDC 959146 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.


[26] Whereas the formation of major regioisomer 24 would involve the expected pathway, i.e. hydroxyalkyl shift followed by loss of water, the minor product 25 seems to arise from a competitive hydroxyalkyl shift followed by [1,4]-ary1 migration, probably due to the effect of the oxygen atom.

[27] Treatment of 1a with pyridine-functionalized hydroxyacetal (Figure 2) led to no reaction under catalytic (20 mol%) or excess (120 mol%) amounts of PTSA.
COMMUNICATION

Brønsted Acid-Catalyzed Straightforward Synthesis of Benzo[b]carbazoles from 2,3-Unsubstituted Indoles


Anisley Suárez, Patricia García-García, Manuel A. Fernández-Rodríguez, Roberto Sanz*