A novel method for the synthesis of 1-aryltetrahydroisoquinolines.

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Abstract- Carbenium ions generated from substituted benzhydryls using acid catalysis undergo smooth intramolecular trapping by pendant sulfonamide groups to provide excellent yields of 1-aryltetrahydroisoquinolines.

Keywords: 1-Aryltetrahydroisoquinolines; carbenium ions; trapping; intramolecular; acid-catalyzed.

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The 1-aryltetrahydroisoquinoline nucleus 1 occupies an important position, both in natural product chemistry and in the design of many, highly active and vital pharmaceuticals. As well as being found in many, usually oxygenated alkaloids of varying complexity,¹ both natural and synthetic examples containing this residue have been found to possess a remarkable spectrum of bioactivities, ranging from antidiabetic activity, multidrug resistance reversal and serotonin reuptake inhibition to CNS activities offering prophylaxis against Huntington’s, Alzheimer’s and Parkinson’s diseases, as well as acting as ligands in a class of novel anti-cancer compounds.² Therefore it is not surprising that many synthetic approaches to these compounds have been developed, the most prevalent of which are the closely related Pictet-Spengler³ and Bischler-Napieralski cyclisation, along with introduction of the 1-substituent onto a suitably functionalised parent heterocycles.⁴ Inevitably, asymmetric versions of such reactions have more recently been developed.²⁴⁵

![Figure 1](image)

**Figure 1.** The 1-aryltetrahydroisoquinoline nucleus and its synthesis by a Pictet-Spengler reaction.

In the classical Pictet-Spengler method (Fig. 1), the key bond formation features electrophilic attack by an aryl group onto a pendant iminium species 2 derived *in situ* from a β-arylamine 3 and an aldehyde 4. Despite being an intramolecular process, it is usually necessary for the nucleophilic aryl function to be activated by at least one methoxy group or a similar substituent. We have recently reported that, in general, tetrahydro-isoquinolines 6 can be efficiently prepared by acid-catalysed cyclisations of the corresponding β-(2-alkenylaryl)amines 5, given the incorporation of a suitable N-protecting group, R³ (Scheme 1).⁶ This alternative procedure does not suffer from the limitation of requiring an electron rich aryl group and generally leads to a predominance of the 1,3-*cis*-stereoisomers but does require the use of strong acid catalyst such as trifluoromethanesulfonic (triflic) or concentrated sulfuric acid. Suitable protecting groups, R³, include tosyl, nosyl (nitrophenylsulfonyl) and
methoxycarbonyl. In favourable cases, even benzyloxy carbonyl (Z) groups can survive these relatively vigorous conditions.6,7

\[
\begin{align*}
\text{R}^1 & \quad \text{NHR}^3 \\
\text{R}^2 & \quad \text{H}^+ \\
\end{align*}
\]

Scheme 1. Acid-catalysed tetrahydroisoquinoline synthesis.

Clearly, such a disconnection featuring an alkene could not be used to form 1-aryl derivatives 1. Instead, the necessary carbenium ions 7 should be available from the corresponding benzhydryls 8, given smooth, acid-catalysed water loss and subsequent trapping by the pendent amine function before rearrangement or some other undesired reaction (Fig. 2). The role of an equivalent of water, which is not generated during the related cyclisations onto alkenes (Scheme 1), was also an unknown factor.

\[
\begin{align*}
\text{R}^1 & \quad \text{NHR}^3 \\
\text{R}^2 & \quad \text{Ar} \\
\end{align*}
\]

Figure 2. The retrosynthetic analysis for acid-catalysed 1-aryl tetrahydroisoquinoline formation.

We chose to synthesise representative examples of the necessary benzhydryls 8 starting from the readily available racemic amino alcohol 9, which was first converted into the N-tosyl aziridine 10 as previously reported (Scheme 2).8 Subsequent copper-catalysed addition9 of the Grignard reagent derived from 2-bromobenzaldehyde diethyl acetal then gave the β-arylamine derivative 11, which was protected on nitrogen by the addition of a Boc (t-butyloxy carbonyl) group in order to avoid a requirement for two equivalents of the next Grignard reagent. Selective hydrolysis of the acetal function in the resulting doubly-protected amine using iron(II) chloride10 then gave the aldehyde 12 in good overall yield.
The final step was the addition of representative examples of aromatic Grignard reagents or lithiated heteroaromatics to give the precursors to the anticipated acid-catalysed cyclisation (Fig. 2). As expected, the resulting products were a mixture of diastereoisomers, in ratios of between 2-3:1, which were neither separated nor structurally assigned. What was not expected however was an N → O migration of the Boc group such that these products were not the benzhydryls 13 but rather the carbonates 14.11 On reflection, this was not surprising when considering the relative stability of the two anions involved: clearly, all other aspects being approximately equal, the initially formed alkoxides 15 are essentially not stabilized whereas the sulfonamide anions 16 formed after Boc migration benefit from charge delocalisation onto the sulfonyl group. (Fig 3). Whether this process is an intramolecular or an intermolecular reaction is unclear.
Figure 3. The two anions.

At this stage, we did not think that this would present a problem but, to keep to our original aims, the new carbonate function was removed by selective base-induced hydrolysis to give the corresponding free alcohol 17a, in the case of the phenyl derivative 14a (Scheme 3).

Scheme 3. Reagents and conditions: i) K$_2$CO$_3$, MeOH, reflux, 24 h (95%).

We were delighted to find that brief exposure of the benzhydryl alcohol 17a to 0.4 equivalents of triflic acid in dichloromethane at 0 °C gave an essentially quantitative return of the desired 1-phenyltetrahydroisoquinoline 18a (Scheme 4). Evidently, formation of an equivalent amount of water did not have a deleterious effect.

Scheme 4. The first successful cyclisation.
The product 18a was isolated in a very clean state after a simple work-up consisting of neutralisation of the triflic acid using aqueous potassium carbonate and separation of the organic layer, which was then washed once with water, dried (MgSO₄) and filtered through a short silica gel plug. Additional chromatographic purification was unnecessary. However, the product was obtained as a 3:1 mixture of cis- and trans- isomers; fortunately, the stereochemistry of this and many structurally related tetrahydroisoquinolines has been determined by a combination of NMR and X-ray analyses. It turns out that there were usually insufficient differences between the two sets of ¹³C NMR data to allow for reliable assignments to be made in the case of such 1-aryl derivatives. In contrast, ¹H NMR data could be used to secure such assignments using clear differences in chemical shifts, δH in CDCl₃, between the following protons: the benzylic methine singlets (cis, ~ 6.2; trans, ~ 6.1), the benzylic methylene double doublets [cis, ~ 2.95 (J = 16.2 and 4.7 Hz) and ~ 2.75 (16.2 and 6.9 Hz); trans, ~ 2.81 (15.9 and 4.5 Hz) and 2.30 (15.9 and 6.8 Hz)] and the non-benzylic (3-) protons α- to nitrogen (cis, m, ~ 4.0; trans, m, ~ 3.7).

Given the relative facility of this conversion, we wondered if separate removal of the Boc group was actually necessary. Mechanistically, protonation of this group should lead either to rapid formation of the corresponding alcohol 17a or to direct formation of the required carbenium ion derived from it. In the event, the presence of the Boc group had very little effect on the progress of the cyclisation (Table 1, first entry), producing essentially the same result to that obtained using the free alcohol (Scheme 3). We then examined the reactivity of the OBoc derivative 14a with a variety of weaker acids; the results are collected in Table 1. Trifluoroacetic (TFA) and concentrated sulfuric acid were equally effective in producing the desired product 18a, with similar isomeric ratios, although the required reaction times were longer while p-toluenesulfonic acid was only successful when the reaction was carried out in toluene at reflux. Silica gel was ineffective even after prolonged exposure at ambient temperature, in contrast to the corresponding p-methoxy derivative (vide infra). Of particular interest was the increased stereoselectivity in favour of the cis-isomer of product 18a when the reaction time using triflic acid was increased (second entry), suggesting that a ring opening and re-closure equilibration was in operation and that, as expected, the 1,3-cis isomer was the thermodynamic product. This idea is also consistent with the observation that the much weaker acid, p-TSA, led to formation of predominantly the trans-isomer, evidently the
kinetic isomer, despite the reaction requiring a much higher temperature when using this reagent. This led us to carry out similar tests with the alternative substrates described below.

Table 1: The reactivity of various acids with the OBoc derivative 14a

<table>
<thead>
<tr>
<th>Acid</th>
<th>Equiv.</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Time</th>
<th>Yield (18a; %)</th>
<th>c/t b ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>TfOH</td>
<td>0.5</td>
<td>CH₂Cl₂</td>
<td>0 °C</td>
<td>10 min.</td>
<td>95</td>
<td>3.5:1</td>
</tr>
<tr>
<td>TfOH</td>
<td>0.5</td>
<td>CH₂Cl₂</td>
<td>0 °C</td>
<td>0.5 h</td>
<td>91</td>
<td>~95:5</td>
</tr>
<tr>
<td>TFA</td>
<td>1.0</td>
<td>CH₂Cl₂</td>
<td>0 °C</td>
<td>1 h</td>
<td>90</td>
<td>3:1</td>
</tr>
<tr>
<td>c.H₂SO₄</td>
<td>0.5</td>
<td>CH₂Cl₂</td>
<td>0 °C</td>
<td>1 h</td>
<td>90</td>
<td>3:1</td>
</tr>
<tr>
<td>p-TSA</td>
<td>1.0</td>
<td>Toluene</td>
<td>110 °C</td>
<td>20 min.</td>
<td>85</td>
<td>1:3</td>
</tr>
<tr>
<td>SiO₂</td>
<td>2.0</td>
<td>CH₂Cl₂</td>
<td>20 °C</td>
<td>24 h</td>
<td>0 c</td>
<td>-</td>
</tr>
</tbody>
</table>

a) TfOH = trifluoromethanesulfonic acid, CF₃SO₃H; TFA = trifluoroacetic acid; p-TSA = 4-toluenesulfonic acid; SiO₂ = Merck Kieselgel 60H silica gel; b) cis to trans ratio determined by ¹H NMR integration; c) cf. cyclisation of p-methoxy derivative 14d during chromatography.

For this brief scope and limitations study, we chose to use triflic acid as the catalyst, in view of both the high yields obtained and the speed of reaction although, no doubt, other acids such as TFA and c.H₂SO₄ might well have been equally effective. The results obtained are collected in Table 2. As already discussed, the phenyl-substituted product 18a underwent isomerisation during prolonged reaction (Entries 1 and 2). Similarly, brief exposure of the 4-chlorophenyl example 14b gave an excellent yield of the tetrahydroisoquinoline 18b in a 2:1 cis-trans ratio (Entry 3). Although not attempted with this derivative, the isomerisation towards the cis-diastereoisomer was again observed with the p-fluoro derivative 14c, where a similar pattern of change was observed (Entries 4-6).
Table 2: The reactivity of various acids with the OBoc derivatives 14

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Time (min.)</th>
<th>Yield (18; %)</th>
<th>c/t ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>10</td>
<td>95</td>
<td>3.5:1</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>30</td>
<td>91</td>
<td>all cis</td>
</tr>
<tr>
<td>3</td>
<td>p-ClC₆H₄</td>
<td>10</td>
<td>93</td>
<td>2:1</td>
</tr>
<tr>
<td>4</td>
<td>p-FC₆H₄</td>
<td>1</td>
<td>90</td>
<td>4:1</td>
</tr>
<tr>
<td>5</td>
<td>p-FC₆H₄</td>
<td>10</td>
<td>97</td>
<td>3:1</td>
</tr>
<tr>
<td>6</td>
<td>p-FC₆H₄</td>
<td>30</td>
<td>93</td>
<td>all cis</td>
</tr>
<tr>
<td>7</td>
<td>p-MeOC₆H₄</td>
<td>5</td>
<td>91</td>
<td>12:1</td>
</tr>
<tr>
<td>8</td>
<td>p-MeOC₆H₄</td>
<td>60</td>
<td>94</td>
<td>all cis</td>
</tr>
<tr>
<td>9</td>
<td>-naphthyl</td>
<td>15</td>
<td>79</td>
<td>3:1</td>
</tr>
<tr>
<td>10</td>
<td>-naphthyl</td>
<td>40</td>
<td>91</td>
<td>10:1</td>
</tr>
<tr>
<td>11</td>
<td>2-thienyl</td>
<td>5</td>
<td>94</td>
<td>10:1</td>
</tr>
<tr>
<td>12</td>
<td>2-thienyl</td>
<td>40</td>
<td>98</td>
<td>all cis</td>
</tr>
</tbody>
</table>

The 4-methoxy analogue 14d was evidently much more reactive, as expected, which is presumably reflected in the isomer ratio of 12:1, obtained even after a brief five minute exposure to the acidic conditions (Entry 7). A longer reaction time gave essentially pure cis-isomer (Entry 8). That this substrate was much more reactive was also indicated by the isolation of a 24% yield of cyclised material, as very largely the cis-isomer, when the precursor 14d was purified by column chromatography (Scheme 5)!
Scheme 5. Unexpected cyclisation of derivative 14d.

Much the same pattern of cyclisation, relative to the phenyl derivative, was found for the naphthyl analogue 14e, which underwent the same type of isomerisation (Entries 9 and 10), while the results obtained from the 2-thienyl derivative 14f (Entries 11 and 12) were consistent with a relatively highly activated system, again as expected.

The 2-furyl analogue showed exceptionally high reactivity, such that we were unable to isolate the intermediate OBoc derivative 14g after a routine work up using aqueous ammonium chloride as a quench; the only product was the cyclised material 18g (Scheme 6). Thus, addition of 2-furyl lithium to the aldehyde 12 at low temperature presumably gave the rearranged OBoc intermediate 19. However, upon quenching the reaction mixture with saturated aqueous ammonium chloride, only the desired cyclised product 18g was isolated in 96% yield, in a 2:1 ratio of stereoisomers (Scheme 6).

Scheme 6. Unexpectedly facile cyclisation of the furyl derivative
Overall, this approach offers an efficient and relatively brief route to 1-aryltetrahydroisoquinolines. The precursor synthesis used in the present work consists of five efficient steps but could be modified using many alternatives, thereby providing additional flexibility. For example, routes to arylacetic acids could be used in combination with Curtius degradations to introduce the amine function, while a combination of a nitroaldol and reduction would achieve the same end. Nitrile chemistry could also be exploited along with a number of directed metatation strategies using $\beta$-arylamine derivatives$^{13}$ or arylacetaldehydes.$^{14}$ Finally, it may also be possible to use the present precursor synthesis to obtain enantiopure products, by starting with an optically pure amino alcohol (Scheme 2), given that the later $trans$-$cis$ isomerizations occur solely by regeneration and trapping of benzylic carbenium ions, as seems likely given that the alternative would require a secondary alkyl-substituted carbenium ion. Future work will address this feature.

Acknowledgements.

We are grateful to the Ministry of Higher Education in Egypt for financial support.

References and notes


11. The key $^1$H NMR characteristics, which allowed these two structures to be distinguished, were resonances due to the methine group adjacent to nitrogen ($\text{CHNHT}_s$ at $\delta_H \sim 3.8$ in contrast to $\text{CHN}(\text{Boc})_T$s at $\delta_H \sim 4.7$), those due to the new $\text{CHOBoc}$ methine which appeared as singlets amongst the aryl resonances between $\delta_H$ 7.0-7.5 and two doublets due to the new NH groups at $\delta_H \sim 4.5$ and 5.0 in the two diastereoisomers.


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1-Aryltetrahydroisoquinolines are formed in excellent yields when suitably substituted benzhydryls are exposed to an acid catalyst.

Keywords: 1-Aryltetrahydroisoquinolines; synthesis; acid-catalysed; cyclisation; carbenium ions.