DOUBLE-CYCLIZATION REACTIONS OF 1-DIBENZYLAMINO-2-PROPANONE AND RELATED COMPOUNDS

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1-Dibenzylamino-2-propanone and its 1-methyl derivative, 2-benzylamino-1-cyclohexanone, 2-benzylamino-1-cyclopentanone, and N,N-dibenzyl-p-X(X=H,Br,NO₂)-phenacylamine, by employing 70%- perchloric acid or triflic acid as cyclization catalyst, afforded 1-aza-5-methyldibenzo[c,f]bicyclo[3.3.1]nona-3,6-diene and its 9-methyl derivative, 1-azadibenzo[h,m]tricyclo-[5.3.3.0²,7]trideca-8,12-diene, 1-azadibenzo[g,l]tricyclo-[4.3.3.0²,6]dodeca-3,6-diene, and 1-aza-5-p-X(X=H,Br,NO₂)-phenyldibenzo[c,f]bicyclo[3.3.1]nona-3,6-diene, in 74-95% isolated yields, respectively.

We reported1) recently that the perchloric acid catalyzed double-cyclization reactions of N,N-dibenzylandinoacetaldehyde diethylacetal gave pharmacologically active 1-azadibenzo[c,f]-bicyclo[3.3.1]nona-3,6-diene in high isolated yields, independent of the nature of the substituents on the aromatic ring.
In the course of our studies on the enlargement of the scope of the strong acid catalyzed double-cyclization reactions, we wish to describe here the first successful example of the double-cyclization reactions of dibenzylylamino ketones(1) with a variety of substituent, by employing 70%-perchloric acid(70-80°C, 3 hrs) or triflic acid(room temperature, overnight) as cyclization catalyst (Scheme 1).

Typically, 1-dibenzylyamino-2-propanone(1a)(1 mmol) was dissolved in perchloric acid(1 ml) at below 0°C, the reaction mixture was allowed to stand overnight at room temperature, then heated, and cooled. The resulting precipitates of perchlorate of 2a were collected, basified with aq. sodium hydroxide, followed by extraction with dichloromethane. The extracted solution was evacuated and the residue was chromatographed on an alumina column affording 1-aza-5-methyl-dibenzo[c,f]bicyclo[3.3.1]nona-3,6-diene(2a)(mp. 124-5°C) in 75% yield. In a similar way, 1-aza-5,9-dimethyl-dibenzo[c,f]bicyclo[3.3.1]nona-3,6-diene(2b)(mp.71-2°C) and 1-aza-dibenzo[h,m]tricyclo[5.3.3.02,7]trideca-8,12-diene(2g)(bp.163-6°C /0.005Torr, HClO₄ salt; mp. =300°C) were isolated from the reactions of the corresponding 1-dibenzylyamino-1-methyl-2-propanone(1b) and
2-dibenzylamino-1-cyclohexanone (2c), in 80% and 92% yield, respectively.

Furthermore, 2-benzylamino-1-cyclopentanone (13), by using triflic acid,\(^3\) was efficiently double-cyclized to 1-azadibenzo[g,1]-tricyclo[4.3.3.0\(^{1,6}\)]dodeca-7,11-diene (2d) (mp. 161-2°C) in 95% yield, whereas the reaction in perchloric acid was not smoothly undergone double-cyclization affording 2d as a minor product (20%)\(^4\) and a single-cyclized product (2d')\(^4\) was isolated in 60% yield.

Finally, the reaction of N,N-dibenzyl-phenacylamine (5) in triflic acid resulted in 95% yield of 1-aza-5-phenyl-dibenzo[c,f]bicyclo[3.3.1]nona-3,6-diene (2e) (mp. 138-9°C), and in the same way, N,N-dibenzyl-p-bromo (1f) and -p-nitro-phenacylamine (1g) gave 1-aza-5-

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**Table 1**

<table>
<thead>
<tr>
<th>Comp.*1)</th>
<th>(H_a(d))</th>
<th>(J_{ab}(\text{Hz}))</th>
<th>(H_b(d))</th>
<th>(H_{a'}(d))</th>
<th>(J_{a'b'}(\text{Hz}))</th>
<th>(H_{b'}(d))</th>
<th>(H_C)</th>
<th>Others</th>
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<tbody>
<tr>
<td>2a</td>
<td>4.69</td>
<td>(17.5)</td>
<td>3.95</td>
<td></td>
<td></td>
<td>3.26</td>
<td>s, 2H</td>
<td>1.72</td>
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<tr>
<td>2b</td>
<td>4.67</td>
<td>(17.5)</td>
<td>3.98</td>
<td>4.59</td>
<td>(17.5)</td>
<td>3.83</td>
<td>s, 2H</td>
<td></td>
</tr>
<tr>
<td>2c*2)</td>
<td>4.68</td>
<td>(1.75)</td>
<td>3.95</td>
<td>4.57</td>
<td>(17.5)</td>
<td>3.82</td>
<td>s, 2H</td>
<td></td>
</tr>
<tr>
<td>2d*2)</td>
<td>4.73</td>
<td>(17.5)</td>
<td>4.07</td>
<td>4.60</td>
<td>(17.5)</td>
<td>3.89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2e</td>
<td>4.73</td>
<td>(17.5)</td>
<td>3.97</td>
<td></td>
<td></td>
<td>3.34</td>
<td>s, 2H</td>
<td></td>
</tr>
<tr>
<td>2f</td>
<td>4.72</td>
<td>(17.5)</td>
<td>3.97</td>
<td></td>
<td></td>
<td>3.31</td>
<td>s, 2H</td>
<td></td>
</tr>
<tr>
<td>2g</td>
<td>4.74</td>
<td>(17.5)</td>
<td>3.99</td>
<td></td>
<td></td>
<td>3.34</td>
<td>s, 2H</td>
<td></td>
</tr>
</tbody>
</table>

*1) 2a-2g (2c: HClO\(_4\) salt) gave correct mass spectra and elemental analyses.

*2) \(^{13}\)C-NMR (gated decoupled, ppm downfield from TMS, in CDCl\(_3\)):  
\(2b\): 15.50 (C\(_9\)-CH\(_3\)), 20.46 (C\(_5\)-CH\(_3\)), 36.56 (C\(_5\), s), 57.72 (C\(_2\) or g, t), 58.15 (C\(_9\), d), 60.26 (C\(_2\) or 8, t).

\(2c\): 22.05, 25.89, 27.95, 31.85 (C\(_2\)-CH), 36.89 (C\(_7\), s), 53.64 (C\(_{10}\) or 11, t), 60.07 (C\(_2\), d), 60.26 (C\(_{10}\) or 11, t).
p-bromo (mp. 157-8°C) and -p-nitro-phenyl-dibenzo[c,f]bicyclo[3.3.1]nona-3,6-diene (mp. 236-7°C), in 95% and 74% yield, respectively.

The structures of 2a - 2g depicted in Scheme 1 were identified by their NMR spectra shown in Table 1.

In conclusion, a general synthesis of pharmacologically active 2a and related compounds from the corresponding N,N-dibenzylamino-ketones was achieved.

References and Notes

2) 1a (bp. 110-115°C/0.005Torr), 1b (mp. 81-2°C), 1f (mp. 87-8°C) and 1g (mp. 167-8°C) were prepared by the reactions of dibenzylamine with CH₃COCl₂Br, PhCH₂Br, p-Br and p-NO₂-PhCH₂Br in 75-90% yields, respectively. 1b (bp. 120-2°C/0.003Torr), 1c (mp. 104-5°C) and 1d (mp. 74-4°C) were synthesized by the reactions of dibenzylamine with 3-hydroxy-2-butanone, 2-hydroxy-1-cyclohexanone, and 2-hydroxy-1-cyclopentanone, in 50-75% yields. All of them gave acceptable NMR and Mass spectra.
3) In a typical procedure, 1d (1 mmol) was dissolved in triflic acid (1.5g, 10mmol) at below 0°C and the reaction mixture was allowed to stand overnight. After an usual work up, 2d was isolated.
4) 2d': oil, m/e 261 (M⁺) 170 (M- (C₆H₅-CH₂)), NMR (δ, in CDCl₃).

5) Hot 70%-HClO₄ was not effective, 1e-1g were recovered quantitatively.

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