Uncatalysed Domino Reaction in Hexafluoroisopropanol: A Simple Protocol for the Synthesis of Tetrahydroquinoline Derivatives

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This article is dedicated to Dr Jean-Pierre Bégué for his 65th birthday.

Abstract: A range of tetrahydroquinolines were synthesised in excellent yields through a domino reaction performed in hexafluoroisopropanol, starting from anilines and enol ethers and in the absence of Lewis acid catalysis. This solvent was shown to promote the nucleophilic addition of anilines to enol ethers as well as the aza-Diels–Alder reaction.

Key words: Diels–Alder reactions, domino reactions, cycloaddition, nucleophilic additions, 1,1,1,3,3,3-hexafluoro-2-propanol

The synthesis of tetrahydroquinoline derivatives is the object of continuous interest because of the pharmaceutical importance of this class of compounds.1 A powerful and frequently exploited route for the synthesis of these compounds is the aza-Diels–Alder reaction of N-arylimines.2 According to the literature this reaction requires the presence of a catalyst, such as a classical Lewis acid (BF₃·Et₂O, TiCl₄, AlCl₃, InCl₃, etc.) or a lanthanide triflate [Yb(OTf)₃, Sc(OTf)₃].3 Due to the presence of the relatively basic nitrogen in both the reagent and the product, it is often necessary to use one equivalent of the Lewis acid.

In 1964, Povarov and Michailov published a modification of the procedure in which the imine was formed in situ from a substituted aniline and an enol ether and subsequently underwent an aza-Diels–Alder cycloaddition with a second molecule of the enol ether, to afford the corresponding tetrahydroquinoline (Scheme 1).4 The reaction was performed in benzene and was promoted by BF₃·Et₂O. More recently other investigations about the scope of this reaction showed that it can be performed either with InCl₃ in water or CH₄CN,5,6 with Sc(OTf)₃ in the ionic liquid bmimPF₆,7 or also with Dy(OTf)₃ in CH₄CN.8 This one-pot procedure is the sole published method for the preparation of this class of 4-alkoxy tetrahydroquinolines. In fact, there are to date no reports of cycloadditions between the corresponding imines and enol ethers, probably due to the instability of the intermediate aldimine that can not be isolated.

Recently we have described a simple and efficient procedure for the aza-Diels–Alder reaction of N-benzylidene aniline and alkyl enol ethers in fluorinated alcohols.9 The properties of these solvents, notably their high hydrogen bond donor abilities [for hexafluoroisopropanol (HFIP) α = 1.96, for trifluoroethanol (TFE) α = 1.51]10 were exploited to carry out the reaction in the absence of catalysis. Thus, hexafluoroisopropanol (HFIP) was tested as solvent for the one-pot formation of tetrahydroquinolines from aromatic amines and alkyl enol ethers, hoping that this relatively acidic alcohol (pKa = 9.3) could promote the formation of imines from enol ethers, which probably occurs through the generation of an oxonium salt (Scheme 2). This article reports the results of this study.

In a preliminary experiment the reaction between 1 mmol of aniline (1a) and three equivalents of the ethyl vinyl ether (2) was conducted in 1 mL of HFIP at room temperature (Scheme 3). The reaction (monitored by GC) was complete within 20 minutes, and the tetrahydroquinoline 4a was retrieved in an excellent 96% overall yield after distillation of the solvent and column chromatography on silica gel (Table 1, entry 1). In a similar experiment conducted in trifluoroethanol at reflux temperature the conversion was only 20% after one day. The scope of the reaction in HFIP was then investigated. Table 1 lists the outcome of the reactions between aniline (1a) and a range of enol ethers.
In both cases, with the acyclic ethers 2 and 3 and with the cyclic ethers 8 and 9, the cycloadducts were obtained in good yields in reasonable reaction times. As expected, the acyclic ethoxyethylene (2) proved to be the most reactive ether, affording the best yield in the shortest reaction time, whereas the reaction with 3,4-dihydro-2H-pyran (9) required one day and afforded a lower yield. With all the ethers used, except 2, the reaction yielded a mixture of the stereoisomers 4 and 5, which were not separated. The isomers were identified by comparison with literature data if available. Otherwise, for tetrahydroquinolines 4a,b,d–f, 5b,d–f, 6d, and 7a NMR studies (COSY, HSQC, HMBC, NOESY) were carried out to assign the stereochemistry. The cis-isomer is the prevalent in all of the cases studied. In the cycloaddition step of the reaction the cis products are the outcome of the favourite endo transition states, assuming that the imine is in the favoured E configuration (Scheme 4). The amount of trans-isomer is higher when bulkier enol ethers are employed. So enol ether 3 affords more trans product than 2, and 9 more than 8.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enol ether</th>
<th>Products</th>
<th>Reaction time (°C)</th>
<th>Yield (%) cis/ trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>4a + 5a</td>
<td>20 min r.t.</td>
<td>96/100</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>6a + 7a</td>
<td>5 h r.t.</td>
<td>68/86</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>10a + 11a</td>
<td>2 h r.t.</td>
<td>94/72</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>12a + 13a</td>
<td>1 d r.t.</td>
<td>84/67</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>14</td>
<td>1 h r.t.</td>
<td>94/0</td>
</tr>
</tbody>
</table>

*Reaction conditions: aniline (1 mmol), enol ether (3 equiv), HFIP (1 mL).*  
*Isolated yields.*  
*Yielded 1-(isopropylidene)phenylamine (15) quantitatively.*

It must be remarked that, following the reaction, the formation of the intermediate imine could not be detected by GC analysis. Moreover, even when enol ether 2 was reacted with an excess of aniline the only product recovered was cycloadduct 4a. This indicates that the rate limiting...
step is the formation of the imine through an oxonium cation or an intermediate with a cationic character (Scheme 2). The formation of this cationic species and the subsequent elimination of a molecule of alcohol is promoted by the acidity of HFIP. Once formed the imine reacts in a fast step with the enol ether, confirming the efficiency of HFIP in promoting Diels–Alder cycloadditions.

In one case though, with enol ether 14, the reaction did not afford any cycloaddition products, and after only 1 hour 1-(isopropylidene)phenylamine (15) was obtained in quantitative yield (Scheme 5). Even after prolonged reaction time and refluxing overnight the imine remained unchanged. Moreover, when three equivalents of the more reactive ether 2 were added to imine 15, formed in situ, it was not possible to detect the formation of the corresponding tetrahydroquinoline. The failure to afford the desired product in this case can therefore be attributed to the steric hindrance and hence the low reactivity of imine 15 in the aza-Diels–Alder reaction.

This first set of reactions proved the ability of HFIP to promote the formation of imines from enol ethers and anilines and, in agreement with previously reported results, [4+2] cycloadditions, and showed that efficient reactions can be performed in this solvent without catalysis. A comparison with literature data for reactions with pyran 9 shows that in terms of endo/exo selectivity in the cycloaddition step the behaviour of HFIP is very similar to that of water but the reaction is faster. On the other hand, the procedures in the ionic liquid bmimPF₆ or in CH₃CN are more selective towards the cis-product and have shorter reaction times (Table 2).

In the next step of the study different substituted anilines were reacted with an acyclic and a cyclic enol ether (2 and 8, respectively) in order to investigate the effect of the substitution in the aromatic ring on the reaction. In this case the reactions were conducted at a lower concentration (0.33 M in aniline) in order to slow down the reaction rate and make the comparison easier. The results are reported in Table 3. The efficiency of the reaction is easily related to the electronic properties of the substituted anilines and, as expected, electron-donating substituents like methoxy or methyl groups give the best results whereas the electron-withdrawing nitro group is inefficient and even after one day at reflux the conversion was not complete and only traces of the product could be recovered from a complex crude mixture. The outcome of the reaction with 4-chloroaniline (1e) confirms that deactivating substituents on the aniline decrease the efficiency, even though in this case an excellent yield could be obtained increasing the concentration of the reagents. The effect of the electronic nature of the substituent on the reaction rate had already been noted when the reaction was carried out in water with InCl₃ by Li and coworkers. Even in the reactions with deactivated aniline 1e it was not possible to detect the formation of the intermediate imine by GC.

### Table 2: Comparison Between Published Methods for the One-pot Synthesis of Tetrahydroquinolines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aniline</th>
<th>Enol ether</th>
<th>Products</th>
<th>Method</th>
<th>Yield (%)</th>
<th>cis/trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>9</td>
<td>12a + 13a</td>
<td>HFIP</td>
<td>84</td>
<td>67/33</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>9</td>
<td>12a + 13a</td>
<td>H₂O, InCl₃</td>
<td>90</td>
<td>68/32</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>9</td>
<td>12a + 13a</td>
<td>CH₃CN, InCl₃</td>
<td>90</td>
<td>95/5</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>9</td>
<td>12a + 13a</td>
<td>bmimPF₆, Sc(OTf)₃</td>
<td>87</td>
<td>95/5</td>
</tr>
</tbody>
</table>

*Ref. 7.

*Ref. 6.

*Ref. 5.

### Table 3: Reactions of Substituted Anilines with Enol Ethers

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aniline</th>
<th>Enol ether</th>
<th>Products</th>
<th>Reaction time (°C)</th>
<th>Yield (%)</th>
<th>cis/trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>2</td>
<td>4a + 5a</td>
<td>7 h r.t.</td>
<td>79</td>
<td>100/0</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>2</td>
<td>4b + 5b</td>
<td>1.5 h r.t.</td>
<td>97</td>
<td>83/17</td>
</tr>
</tbody>
</table>
confirming the ability of HFIP to promote the aza-Diels–Alder cycloaddition, we show that enol ethers can undergo nucleophilic addition of anilines in this medium.

The scope of the reaction was investigated and it was shown that this method can be used to synthesise a range of tetracydroquinolines in excellent yields starting from cyclic and acyclic enol ethers and a range of anilines. The evidence shows that the electronic properties of the aniline influence the efficiency of the nucleophilic addition step whereas the use of a hindered enol ether hampers the cycloaddition step of the procedure.

This new procedure permits to avoid the use of a catalyst, to work without taking any particular precautions to remove moisture, and to recover the products without work-up.

1H NMR and 13C NMR spectra were recorded on either a 200 MHz or a 400 MHz multinuclear Bruker spectrometer. COSY, NOESY, HSQC and HMBC experiments were performed on a 400 MHz multinuclear Bruker spectrometer. Chemical shifts (δ) are given in ppm relative to TMS. Coupling constants are given in Hz. Elemental analyses were performed by the Service de Microanalyses of the Centre d’Etudes Pharmaceutiques, Châtenay-Malabry. GC analyses were performed using a SE 30 capillary column (12 m). All starting materials are commercially available. HFIP was provided by Central Glass Co. Ltd.

cis-4-Ethoxy-2-methyl-1,2,3,4-tetrahydroquinoline (4a); Typical Procedure
Aniline (1a, 0.09 mL, 1 mmol) and ethoxyethylene (2, 0.3 ml, 3 mmol) were stirred in HFIP (1 mL) at r.t. The reaction was monitored by GC. After 20 min the solvent was distilled and the residue was purified by column chromatography on silica gel (EtOAc–Et 2 O, 1:9) to afford 0.183 g (96% yield) of 4a as a pale yellow oil.

IR (neat): 3367, 2926, 1501 cm–1.

Pale yellow oil.

cis–4-Ethoxy-2-methyl-1,2,3,4-tetrahydroquinolines (4b and 5b)
Pale yellow oil.

IR (neat): 3367, 2926, 1501 cm–1.

1H NMR and 13C NMR spectra were recorded on either a 200 MHz or a 400 MHz multinuclear Bruker spectrometer. COSY, NOESY, HSQC and HMBC experiments were performed on a 400 MHz multinuclear Bruker spectrometer. Chemical shifts (δ) are given in ppm relative to TMS. Coupling constants are given in Hz. Elemental analyses were performed by the Service de Microanalyses of the Centre d’Etudes Pharmaceutiques, Châtenay-Malabry. GC analyses were performed using a SE 30 capillary column (12 m). All starting materials are commercially available. HFIP was provided by Central Glass Co. Ltd.

The cis/trans ratio does not show a strong dependence on the electronic properties of the substituents in the aniline ring.

In conclusion we describe a simple protocol for the formation of tetracydroquinolines in HFIP from anilines and enol ethers in the absence of Lewis acid catalysis. Besides

### Table 3 Reactions of Substituted Anilines with Enol

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aniline</th>
<th>Enol ether</th>
<th>Products</th>
<th>Reaction time</th>
<th>T (°C)</th>
<th>Yield (%)</th>
<th>cis/trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td></td>
<td>2</td>
<td>4f + 5f</td>
<td>2 h</td>
<td>r.t.</td>
<td>93</td>
<td>92/8</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>2</td>
<td>4d + 5d</td>
<td>3 h</td>
<td>r.t.</td>
<td>80</td>
<td>65/35</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>2</td>
<td>4e + 5e</td>
<td>7 d</td>
<td>r.t. + reflux</td>
<td>traces</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>2</td>
<td>4e + 5e</td>
<td>1 d</td>
<td>r.t.</td>
<td>65</td>
<td>77/23</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>8</td>
<td>10a + 11a</td>
<td>1 h</td>
<td>r.t.</td>
<td>60</td>
<td>74/26</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>8</td>
<td>10b + 11b</td>
<td>1 h</td>
<td>r.t.</td>
<td>81</td>
<td>80/20</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>8</td>
<td>10c + 11c</td>
<td>2 d</td>
<td>reflux</td>
<td>traces</td>
<td></td>
</tr>
</tbody>
</table>

* Reaction conditions: aniline (1 mmol), enol ether (3 equiv), HFIP (3 mL).
* Isolated yields.
* 6 d at r.t. + 1 d at reflux.
* The same reaction in 1 mL of HFIP afforded 98% yield with the same cis/trans ratio.

The cis/trans ratio does not show a strong dependence on the electronic properties of the substituents in the aniline ring.

In conclusion we describe a simple protocol for the formation of tetracydroquinolines in HFIP from anilines and enol ethers in the absence of Lewis acid catalysis. Besides

Anal. Calcd for C$_7$H$_{15}$NO: C, 70.56; H, 8.65; N, 6.53. Found: C, 70.44; H, 8.79; N, 6.32.

4-Ethoxy-2-methyl-1,2,3,4-tetrahydroquinolines (4d and 5d)

Pale yellow oil.

IR (neat): 3405, 3058, 1246, 1112, 1079, 1064 cm$^{-1}$.

Yellow oil.

Anal. Calcd for C$_{13}$H$_{19}$NO: C, 76.06; H, 9.33; N, 6.82. Found: C, 75.75; H, 9.67; N, 6.57.

6-Chloro-4-ethoxy-2-methyl-1,2,3,4-tetrahydroquinolines (4e and 5e)

Pale yellow oil.

IR (neat): 3383, 2971, 2868, 1489, 1101 cm$^{-1}$.

Pale yellow oil.

Anal. Calcd for C$_{13}$H$_{19}$NO: C, 70.43; H, 8.79; N, 6.32.

References


