APPLICATION OF HEXAMETHYLENETETRAMINE IN A PICTET-SPENGLER TYPE REACTION FOR SYNTHESIS OF ISOQUINOLINE DERIVATIVES

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Abstract - Hexamethylenetetramine was used successfully as amino- and amidoalkylation cyclization reagent for the synthesis of 3,4-dihydroisoquinolines, tetrahydroisoquinolines and 1,4-dihydro-3(2H)-isoquinolinones. The reagent provides a simple and convenient pathway for the preparation of a range of these compounds.

It was found that the reaction of 2-phenylethylamines (1) with HMTA (2) led surprisingly but readily only to 6,7-dimethoxy-3,4-dihydroisoquinolines (5) (Scheme 1, Table 1, 5a, b). The reaction was carried out in a mixture of glacial acetic and trifluoroacetic acids (ratio 4:1) at a reflux for 15 min or in PPA for 30 min at 80°C. The reactions were successful only in the presence of activating groups in the aromatic ring of 2-phenylethylamines (1) (R=MeO) as are the requirements for Bischler-Napieralski cyclization to 3,4-dihydroisoquinolines from their amides. Two feasible routes are possible to 5: formylation of the activated aromatic ring of 1 (Duff reaction) and then spontaneous cyclization to 5 or Pictet-Spengler’s cyclization to 4 of an iminium intermediate (3) and then its oxidation to 5 from HMTA. Several experiments were carried out for clarification of the reaction route. We found that 6,7-dimethoxytetrahydroisoquinoline (4a) (as base or hydrochloric salt), 1-phenyl- or 1-methyl-6,7-dimethoxytetrahydroisoquinoline as well as tetrahydroisoquinoline can be converted to their 3,4-dihydro derivatives in good yields with HMTA in a mixture of glacial acetic and trifluoroacetic acids (ratio 4:1) at a reflux of the reaction mixtures for 10 min. Similar oxidation with HMTA of 1,4-benzodiazepines to the corresponding imines is known from the literature. It was found also that the reaction of N-methyl-3,4-dimethoxy-2-phenylethylamine (6) (Scheme 1, R=OMe, R1=H) with HMTA at the same reaction conditions afforded N-methyl-6,7-dimethoxytetrahydroisoquinoline (Procedure A, Table 1, 7e, 94%
yield) as a result of an intramolecular aminooalkylation. Our efforts for formylation of 1,2-dimethoxybenzene with HMTA at the same reaction conditions (Duff reaction) were unsuccessful. The above results and the fact that the reaction of 1 without activating groups in the aromatic ring (R=H) with HMTA to 5 was not successful leads to the assumption that the reaction proceeds through 3 and 4 as intermediates. The procedure can be regarded as a variation of Bischler-Napieralski method for synthesis of 3,4-dihydroisoquinolines and an advantage of this approach is the successful synthesis of 3-substituted 3,4-dihydroisoquinolines as 5b. Similar yields of 3,4-dihydroisoquinolines were obtained when the above reactions were carried with N-ethylmethanimine (1,3,5-triethylhexahydrotriazine) instead of HMTA.

The reaction of HMTA with 2-phenylethylamines using formic acid as a solvent at reflux of the reaction mixture for 1 h afforded N-methyltetrahydroisoquinolines (7a,b) (Scheme 1, Procedure B) and traces of the corresponding 5 (Table 1). Thus, the reaction of 1a (R=MeO, R1=R2=H) with HMTA in HCOOH at a reflux afforded 78% of 7a and 10% of 5a while the reaction of N-methyl-3,4-dimethoxy-2-phenylethylamine (1c) with HMTA led only to N-methyl-6,7-dimethoxytetrahydroisoquinoline (7c) (Procedure B, Table 1, yield 93%). Our attempts to carry out a reductive methylation of 6,7-dimethoxy-3,4-dihydroisoquinoline to 7a with HMTA at the same reaction conditions (1 h reflux in HCOOH) were

![Scheme 1](image)

**Table 1. Isoquinoline derivatives (5) and (7 a-g) produced via Scheme 1**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R1</th>
<th>R2</th>
<th>Yields (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>7</td>
<td>7a</td>
<td>b</td>
<td>90a</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>5a</td>
<td></td>
<td>86a</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>7c</td>
<td></td>
<td>94a(93)b</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>7d</td>
<td></td>
<td>92a</td>
<td>7</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>7e</td>
<td></td>
<td>77a</td>
<td>8</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>7f</td>
<td></td>
<td>90a</td>
<td>9</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>7g</td>
<td></td>
<td>85a</td>
<td>10</td>
</tr>
</tbody>
</table>

*aProcedure A; bProcedure B.*
unsuccessful. It can be assumed that the reaction mode is probably as this of Eschweiler-Clark method and included methylation of nitrogen in 1 to 6 and then cyclization to 7.

Next, we investigated of the reaction of HMTA with secondary amides of 2-phenylethylamines. We found that the reaction of N-acyl-2-phenylethylamines (1d,e), N-phenyl-2-phenylethylureas (1f,g) and phenylacetamides (9) with HMTA in AcOH/TFA (4/1) afforded the corresponding N-acyl-tetrahydroisoquinolines (Table 1, 7d,e), N-carbamoyltetrahydroisoquinolines (Table 1, 7f,g) and 1,4-dihydro-3(2H)-isoquinolinones (Scheme 2, Table 2, 11a,b). The cyclization reaction of HMTA with amides (1) was successful also in the cases when there are not activating groups in the aromatic ring (Table 1, 7e,g).

![Scheme 2](image)

The reaction of HMTA with phenylacetamides (9) is also successful when there are no activating groups in the aromatic ring but only in PPA at 80°C for 3 h (Procedure C, Table 2, 11c,d). It can be assumed from the obtained results that the reaction is an intramolecular amidoalkylation with the formation of N-acyliminium ions (10). The successful cyclization and formation of isoquinoline derivatives (11e,g) (Table 1) and (11c,d) (Table 2), without activating groups in the aromatic ring, can be assign to the stronger electrophilicity of the corresponding N-acyliminium ions (10).

The results above demonstrate the application of HMTA as inexpensive and easily available reagent for synthesis of variety of isoquinoline derivatives as a result of an intramolecular amino- and amidoalkylation reactions. The convenient one-pot preparation of 3,4-dihydroisoquinolines from 2-phenylethylamines and HMTA is a Pictet-Spengler reaction combined with an oxidation process.

**EXPERIMENTAL**

All of the obtained isoquinoline derivatives (5, 7, 11) were characterized by their mp, IR and NMR spectra and compared with the data known from the literature.
Preparation of 3,4-Dihydroisoquinolines (5), N-Acyltetrahydroisoquinolines (7) and 1,4-Dihydro-3(2H)-isoquinolinones (11) (Procedure A): To a solution of 2-phenylethylamine or the corresponding amide (3 mmol) in a mixture of AcOH/CF₃COOH (4 mL:1 mL) is added HMTA (841 mg, 6 mmol) and the reaction mixture is refluxed for 30 min (for 5a,b and 7d,g), 3 h at reflux (for 7e), overnight at rt (for 7f) or 1 h at reflux (for 11a,b). The cooled solution is diluted with water (50 mL), basified with Na₂CO₃, and extracted with CH₂Cl₂ (3x20 mL). The combined extracts were dried (Na₂SO₄), the solvent removed and the products were purified by filtration through a column with basic or neutral Al₂O₃ using CH₂Cl₂ as eluent.

Preparation of N-Methyltetrahydroisoquinolines (7a-c) (Procedure B): The reaction is carried with 3 mmol of amine, 6 mmol (841 mg) of HMTA in 100% HCOOH (10 mL) at reflux for 1 h and the reaction mixture is worked up as above.

Preparation of 3,4-Dihydroisoquinolines (5a) and 1,4-Dihydro-3(2H)-isoquinolinones (11c,d) (Procedure C): 2-Phenylethylamines (1) or phenylacetamides (9) (3 mmol) and HMTA (841 mg, 6 mmol) in PPA (10 g) is heated for 30 min at 80°C (for 5a) or 3 h (for 11c,d). The reaction mixture is poured on a crash ice and then worked as above.

REFERENCES