Rearrangement of 3-Aryl-4-methylmorpholinium-4-methylides

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Fluoride-ion induced desilylation reaction of 3-Aryl-4-methyl-4-[(trimethylsilyl)methyl]morpholinium iodies 5a, b gave 4-methyl-6-phenyl-1,4-oxazepane (9a, Stevens rearrangement product) from 5a, and 10-methoxy-2-methyl-1,2,3,4,6,11a-hexahydro-5,2-benzoxazoline (7b) from 5b. In the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene, however, both reactions afforded 10-substituted 2-methyl-1,2,3,4,6,7-hexahydro-5,2-benzoxazones 8a, b (Sommelet–Hauser rearrangement products).

We previously reported that ring-expansion reaction of 1-methyl-2-phenyl-1-[(trimethylsilyl)methyl]piperidinium iodies to 2-methyl-1,3,4,5,6,11a-hexahydro-2H-2-benzazepines (nine-membered cyclic amines) by treatment with cesium fluoride in dimethylformamide or hexamethylphosphoramide at room temperature. Application of this reaction in synthesis of cyclic amines containing more hetero-atoms seems to be promising because the desilylation proceeds under nonbasic and mild reaction conditions. In this paper, we report the ring expansion reaction of 3-phenylmorpholines to 1,2,3,4,6,7-hexahydro-5,2-benzoxazones whose syntheses have not been published yet.

3-Phenyl-4-[(trimethylsilyl)methyl]morpholine (4a) was synthesized by reaction of (chloromethyl)trimethylsilane with 3-phenylmorpholine (3), which was prepared by cyclization of 2-phenyl-3-aza-1,5-pentanediol. 3-(4-Methoxyphenyl)-4-[(trimethylsilyl)methyl]morpholine (4b) was prepared from 2-(4-methoxyphenyl)-3-aza-1,5-pentanediol (1) via (trimethylsilyl)methylation followed by cyclization. Amines 4a, b were quaternized with iodo-methane to 4-methyl-3-phenyl-4-[(trimethylsilyl)methyl]morpholinium iodide (5a) and the 3-(4-methoxyphenyl) analogue 5b. They were used for the next reaction, without further purification, because isolation of the stereoisomers was difficult.

Reaction of 5a, b with cesium fluoride was carried out in dimethylformamide at room temperature (Table 1). 4-Methyl-6-phenyl-1,4-oxazepane (9a) was obtained from 5a as the main product accompanied by small amounts of N-(2-hydroxyethyl)-N-methyl-2-vinylbenzylamine (10a) (entry 1). 10-Methoxy-2-methyl-1,2,3,4,6,11a-hexahydro-5,2-benzoxazoline (7b) was formed as the sole product from 5b (entry 3). Oxazepane 9a is a Stevens rearrangement product of 4-methyl-3-phenylmorpholinium-4-methylide (6a), and benzoxazoles

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ammonium Salt</th>
<th>Additivea</th>
<th>Product Yieldb (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>5a</td>
<td></td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>5a</td>
<td>DBU</td>
<td>61</td>
</tr>
<tr>
<td>3</td>
<td>5b</td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>5b</td>
<td>DBU</td>
<td>35</td>
</tr>
</tbody>
</table>

a Two mole equivalents were added.

b Determined from the proton ratios of 1H-NMR.

Table 1. Reaction of 3-Aryl-4-methyl-4-[(trimethylsilyl)methyl]-morpholinium Iodides 5a, b with Cesium Fluoride

Scheme 1
nine 7b is a [2,3] sigmatropic rearrangement product of 3-(4-methoxyphenyl)-4-methylmorpholinium-4-ylmethylide (6b).

It was earlier thought that Stevens rearrangement products were directly formed by [1,2] radical rearrangement of N-ylides.5-7 We previously revealed that the Stevens rearrangement products produced from benzylammonium-N-alkylides were not the result of the [1,2] radical rearrangement of the N-ylides but were formed by a [2,3] sigmatropic rearrangement followed by a [1,3] radical rearrangement via the conjugated triene compounds.8 When the reaction was carried out in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), the main product changed from the Stevens to a Sommelet–Hauser product as a result of acceleration of a [1,3] proton transfer pathway from the conjugated trienes.9 We also reported that the conjugated triene compounds produced from 4-methoxy-substituted benzylammonium-N-ylmethides were stable at room temperature.10

These results suggest that 9a was formed from 6a via 2-methyl-1,2,3,4,6,11a-hexahydro-5,2-benzoxazoline (7a). The addition of DBU to the reaction mixtures of 5a, b, indeed, brought about the formation of 2-methyl-1,2,3,4,6,7-hexahydro-5,2-benzoxazoline (8a) instead of 9a, and of 10-methoxy-2-methyl-1,2,3,4,6,7-hexahydro-5,2-benzoxazoline (8b) instead of 7b (entries 2 and 4). There is no direct [1,2] migration pathway from 6 to 9 in this reaction. Small amounts of 10a,b may be formed as a result of a direct migration of a 11a-H to a 5-oxygen via a six-membered intermediate (Scheme 2).

Scheme 2

DMF was dried by distillation from BaO under reduced pressure, and CsF was dried (P2O5) at 180°C under reduced pressure. 1H-NMR spectra were recorded at 100 or 400 MHz. Aluminum oxide (Merck, Aluminomxide 90, 70–230 mesh) was used for column chromatographies. All melting and boiling points are uncorrected.

2-(4-Methoxyphenyl)-3-(trimethylsilyl)methyl-3-aza-1,5-pentanediol (2):

2-(4-Methoxyphenyl)-3-aza-1,5-pentanediol (1): A solution of 2-amino-2-(4-methoxyphenylethanol (39.60 g, 237 mmol) and ethylene oxide (43.36 g, 326 mmol) in EtOH (130 mL) is treated according to the reported method11 to give 1; yield: 44.42 g (89%); mp 93°C.

C17H23O3S+ calc. C 62.54 H 8.11 N 6.63

(211.3) found 62.38 8.18 6.43

IR (Nujol): ν = 3370 cm⁻¹ (OH).

1H-NMR (CDCl3/TMS): δ = 1.80–2.50 (br. 3H, OH, NH), 2.63–2.75 (m, 2H, NCH2), 3.55–3.78 (m, 5H, OCH2, PhCH), 3.80 (s, 3H, OCH3), 6.89, 7.22 (A2B2, 4H, J = 8.6 Hz, H2o).

2-(4-Methoxyphenyl)-3-[ (trimethylsilyl)methyl]-3-aza-pentanediol (2):

A solution of 1 (22.06 g, 104 mmol) and (iodomethyl)trimethylsilane11 (11.18 g, 52 mmol) in MeCN (30 mL) is heated at reflux for 6d and concentrated. The residue is chromatographed on an aluminum oxide column (EtO/MeOH, 100:0 to 0:100) to give 2; yield: 9.29 g (60%); bp 160°C/0.7 Torr.

C17H23NO3Si calc. C 60.57 H 9.15 N 4.71

(297.5) found 60.36 9.26 4.49

IR (film): ν = 800, 1250 (MeSi), 3350 cm⁻¹ (OH).
3-Phenyl-4-[(trimethylsilyl)methyl]morpholine (4a): A mixture of 3-phenylmorpholine (3; 29.56 g, 181 mmol), (chloromethyl)trimethylsilane (11.03 g, 90 mmol), KI (30 g, 180 mmol) in MeCN (50 mL) is heated at reflux for 18 h and then poured into H₂O (100 mL). The Et₂O (4 x 100 mL) extract of this mixture is washed with H₂O (3 x 50 mL), dried (MgSO₄), concentrated, and distilled to give 4a; yield: 11.69 g (52%); bp 105°C/2 Torr.

C₉H₁₇NO₃Si calc. C 67.42 H 9.29 N 5.62
(249.4) found 67.70 9.49 5.59

IR (film): ν = 830, 1250 (SiMe₃), 1110 cm⁻¹ (C=O).

3-H-NMR (CDCl₃/TMS): δ = 0.00 (s, 9H, SiCH₃), 1.40, 2.04 (Abq, 2H, J = 14.5 Hz, SiCH₂), 2.25–2.37, 2.86–2.94 (m, 2H, 5-H), 3.06–3.14 (m, 1H, 3-H), 3.28–3.40 (m, 1H, 2-H), 3.64–3.97 (m, 3H, 2-H, 6-H), 7.29–7.54 (m, 5H, arom.).

3-(4-Methoxyphenyl)-4-[(trimethylsilyl)methyl]morpholine (4b): To a solution of 2 (75.5 mg, 19 mmol) and PhP₃ (7.59 g, 29 mmol) in THF (55 mL) is slowly added diethyl azodicarboxylate (DEAD, 41.8 g, 24 mmol) at 0°C. After 10 h of stirring at r.t., the solvent is evaporated under reduced pressure and the residue is chromatographed on an aluminum oxide column (hexane/Et₂O, 100:0 to 0:100) to give 4b; yield: 1.08 g (20%); mp 55–60°C.

CₙH₂₅NO₃Si calc. C 64.47 H 9.02 N 5.01
(279.5) found 64.55 8.76 4.69

3-H-NMR (CDCl₃/TMS): δ = 0.02 (s, 9H, SiCH₃), 1.38, 2.04 (Abq, 2H, J = 14.5 Hz, SiCH₂), 2.30 (ddd, 1H, J = 11.8, 11.6, 3.3 Hz, 5-H), 2.89 (ddd, 1H, J = 11.8, 4.4, 1.7 Hz, 5-H), 3.04 (dd, 1H, J = 10.4, 3.3 Hz, 3-H), 3.32 (dd, 1H, J = 11.4, 10.4 Hz, 2-H), 3.49 (ddd, 1H, J = 11.4, 6.5, 1.1 Hz, 2-H), 3.72 (ddd, 1H, J = 11.6, 11.3, 2.1 Hz, 6-H), 3.80 (s, 3H, OCH₃), 3.86 (ddd, 1H, J = 11.3, 3.3, 1.7 Hz, 6-H), 6.85, 7.23 (A₂B₂, 4H, J = 8.5 Hz, OCH₃), 4.16 (ddd, 1H, J = 12.5, 12.2, 3.4 Hz, 5-H), 4.51 (ddd, 1H, J = 13.0, 12.0, 1.8 Hz, 6-H), 4.71 (dd, 1H, J = 13.9, 10.9 Hz, 2-H), 5.19 (dd, 1H, J = 10.9, 3.3 Hz, 3-H), 6.98, 7.61 (A₂B₂, 4H, J = 8.9 Hz, H₃-OCH₃).

1-H-NMR of cis-5b (CDCl₃/TMS): δ = 0.30 (s, 9H, SiCH₃), 2.29, 3.82–4.10 (Abq, 2H, J = 14.7 Hz, SiCH₂), 3.35 (s, 3H, NCH₃), 3.44–3.50 (m, 1H, 5-H), 3.82–4.10 (m, 3H, 2-H, 4-H, 6-H), 3.82 (s, 3H, OCH₃), 4.35–4.43 (m, 1H, 6-H), 4.96 (dd, 1H, J = 13.9, 10.6 Hz, 2-H), 5.42 (dd, 1H, J = 10.6, 3.0 Hz, 3-H), 6.97, 7.68 (A₂B₂, 4H, J = 8.8 Hz, H₃-OCH₃).

Reaction of 5a,b with Cesium Fluoride; General Procedure: Ammonium salt 5 (3 mmol) is placed in a 30 mL flask equipped with a magnetic stirrer, a septum, and a test tube connected with a short piece of rubber tube. CsF (2.0 g, 13 mmol) is placed in the test tube. The apparatus is stirred under reduced pressure and is flushed with N₂. DMF (10 mL) is added to the flask by syringe, and then CsF is added from the test tube. The mixture is stirred for 24 h at r.t., poured into 1% NaHCO₃ (100 mL), and extracted with Et₂O (4 x 100 mL). The extract is washed with 1% NaHCO₃ (3 x 50 mL), dried (MgSO₄), and concentrated under reduced pressure. The residue from 5a is chromatographed on an aluminum oxide column (hexane/Et₂O, 100:0 to 0:100) to give 9a and 10a.

1-H-NMR and UV (λmax = 310 nm) spectra of the residue from 5b show that the product consists of almost pure 7b, however, further purification is difficult because of the partial isomerization of 7b on an alumina column and decomposition on distillation. The results are shown in Tables 1 and 2.

Reaction of 5a,b with Cesium Fluoride in the Presence of DBU; General Procedure: DBU (2.28 g, 15 mmol) is added by syringe to a solution of 5 (3 mmol) in DMF (10 mL) prepared in a manner similar to that described above. Then, CSF (2.0 g, 13 mmol) is added and treated. The residual oil is purified on an aluminum oxide column (hexane/Et₂O) and distilled. The results are summarized in Tables 1 and 2.

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(4) We temporarily assigned the major product to the trans-isomer and the minor to cis-isomer.


