Stevens Rearrangement of a Cyclic Hemiacetal System: Diastereoselective Approach to Chiral α-Amino Ketone

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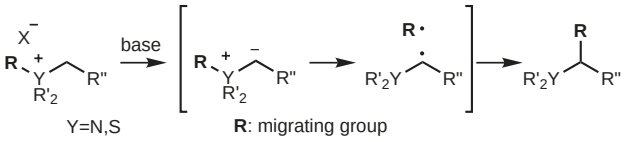
Abstract: The base-promoted reaction of ammonium ylide **1a**, which forms a cyclic hemiacetal structure, is shown to afford the *anti*-hemiacetal **3a** in high diastereopurity, via the Stevens rearrangement followed by efficient thermodynamic epimerization.

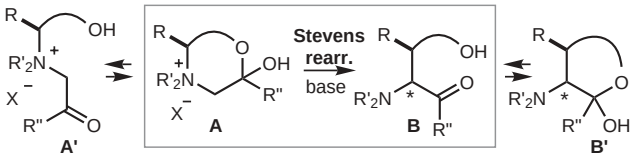
Key words: acetal, amino alcohols, stereoselective synthesis, ketones, rearrangements

The Stevens rearrangement is a general class of the 1,2-alkyl shift from nitrogen or sulfur to carbon on a quaternary ylide system.[1] This type of rearrangement is now well recognized to proceed via a radical dissociation–recombination mechanism (Scheme 1).[1,2]



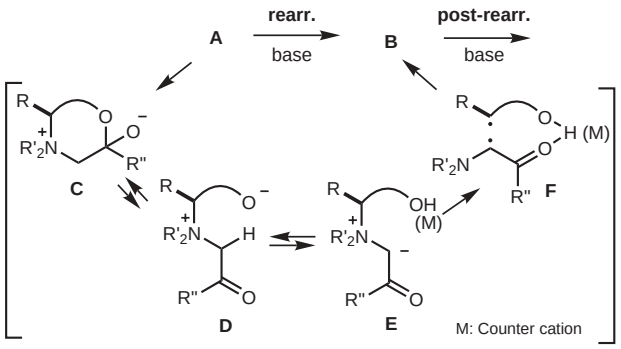
Scheme 1

Despite the long history of the Stevens rearrangement, its synthetic application as a diastereoselective approach to chiral amines is limited due to the difficulty of stereocontrol at the α-amino position.[3] Herein we wish to report a novel Stevens rearrangement system using the hemiacetal **A** (a tautomer of a hydroxy ketone **A′**) as a substrate which provides the α-amino ketone **B** and its tautomer, acetal **B′**, in good yield with excellent diastereoselectivity (Scheme 2).



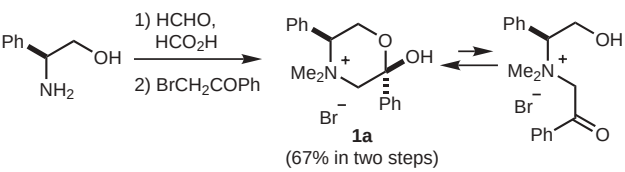
Scheme 2

During the course of our study on acetal and hemiaminal chemistry,[4] we were interested in studying the rearrangement of a hemiacetal **A** that has an ammonium ylide moiety at the β-position. An alkoxide **C** derived from hemiacetal **A** will isomerize to acyclic form **D**, which has an alkoxide on the migrating group (Scheme 3). This alkoxide moiety could act as the intramolecular base and/or chelation counterpart in the rearrangement step and/or the post-rearrangement step. Thus, it was expected that the stereochemistry at the α-amino position of rearrangement product **B** could be controlled by these intramolecular alkoxide effects.



Scheme 3

Based on this hypothesis, we designed the ammonium salt **1a** (*racemic*) for the rearrangement substrate, and it was readily prepared from phenylglycinol in two steps: N-methylation followed by treatment with bromoacetophenone (Scheme 4).[5] According to the ^{1}H NMR, ^{13}C NMR, H-H COSY NMR and HMQC NMR analyses and NOE experiment, it was confirmed that the resulting salt **1a** exists predominantly as a cyclic hemiacetal form.[6]



Scheme 4

A rearrangement of hemiacetal **1a** was performed by treatment with potassium *tert*-butoxide (2 equiv) in ethanol at 0 °C to r.t.[7,8] The reaction gave the expected hydroxy ketone **2a**[5] in 35% yield as a single diastereomer (>95% dr, *anti*) along with a hemiacetal **3a**[5] in 40% yield also as a single diastereomer (>95% dr, *anti*,*syn*).[9]

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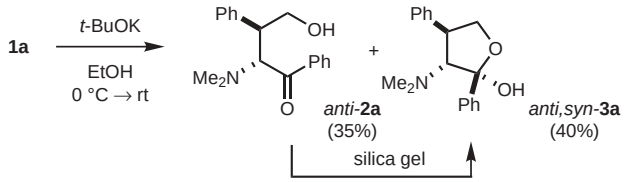
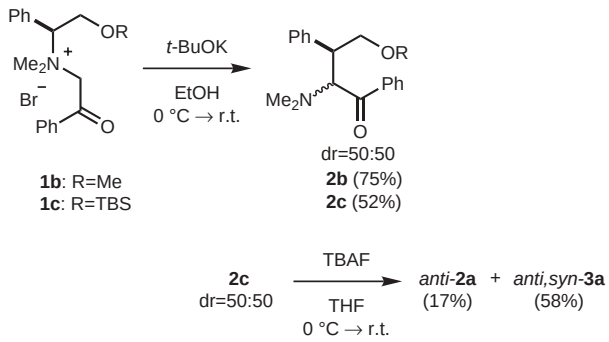
Furthermore, it was observed that the thus-obtained hydroxy ketone **2a** easily tautomerized to a hemiacetal **3a** on silica gel (Scheme 5). These results reveal that the present hemiacetal rearrangement provides the single diastereomer of the product as expected.



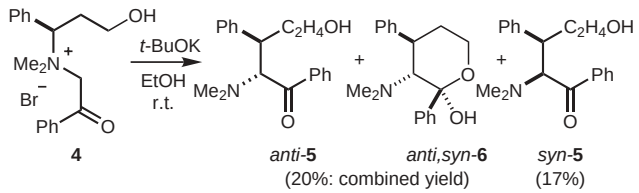
Scheme 5

To clarify the intramolecular alkoxide effect in the stereocontrol of the rearrangement, next we examined a similar rearrangement of hydroxyl-protected derivative of **1a**. In sharp contrast to the above-mentioned result, the reactions of methyl ether **1b** and silyl ether **1c** provide only a 1:1 diastereomer mixture of products **2b** and **2c**, respectively (Scheme 6). However, interestingly enough, desilylation of a diastereomer mixture of **2c** with TBAF (2 equiv) gave a mixture of *anti*-**2a** (17%) and its tautomer *anti*,*syn*-**3a** (58%), did not give the *syn*-isomer.



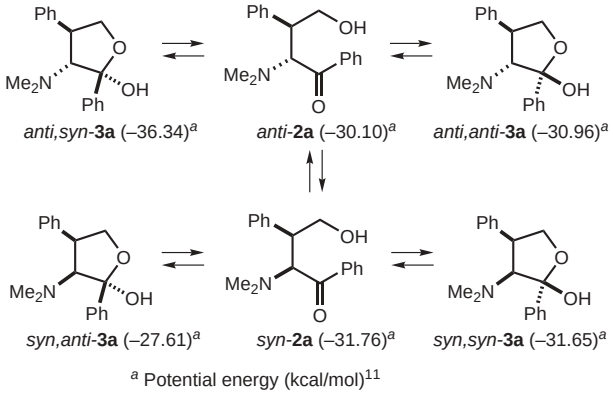
Scheme 6

Furthermore, we found that a similar reaction of γ-hydroxy homologue **4** gave poor diastereoselectivity. Namely, the Stevens rearrangement of ammonium salt **4**, which exists as an acyclic hydroxy ketone, provides a diastereomer mixture of δ-hydroxy ketone **5** and a hemiacetal *anti*,*syn*-**6**,[10] tautomer of *anti*-**5** (Scheme 7).



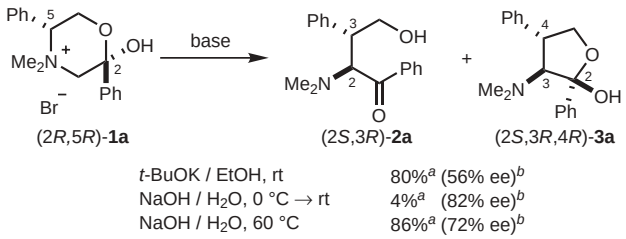
Scheme 7

These results strongly suggest that the high level of diastereoslectivity observed in the reaction of **1a** is a result of the base-catalyzed epimerization of the product, and the properly positioned alkoxide is essential for this stereocontrol. The stereochemical outcome of the rearrangement of **1a** is explicable as a result of the efficient thermodynamic control in the post-rearrangement step that includes the base-catalyzed epimerization at the α-amino position and the hydroxy ketone/hemiacetal tautomerization. To evaluate the thermodynamic stability of possible products, the potential energies were examined by semiempirical calculation.[11] As shown in Scheme 8, the calculation predicted that *anti*,*syn*-**3a** (tautomer of *anti*-**2a**) is favored over other isomers (>4.58 kcal/mol). This result and experimental facts indicate that the formation of a stable cyclic acetal plays the key role in attaining high stereoselectivity.



Scheme 8

Next, we examined an asymmetric variant of the present Stevens rearrangement using an optically active hemiacetal (2*R*,5*R*)-**1a**.[12] The reaction performed in ethanol at room temperature provides a mixture of (2*S*,3*R*)-**2a** and (2*S*,3*R*,4*R*)-**3a** in 56% ee (Scheme 9). In contrast, when water was used as a solvent, the enantiopurity of products was raised to 72–82% ee. These results show that the rearrangement proceeds predominantly with retention of configuration at the migrating carbon[13] and the degree of asymmetric transmission is highly dependent on the solvent used.[14]



Scheme 9

In summary, we have described a highly diastereoselective approach to the chiral hemiacetal, tautomer of β-chiral α-amino ketone, based on a novel Stevens rearrangement of a cyclic hemiacetal system.

Acknowledgment

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(2) Ollis, W. D.; Ray, M.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1009.

(3) Only a few successful examples are reported so far. For these the stereocontrol is based on the chirality transfer from chiral nitrogen atom of the ammonium salt to carbon: (a) Hill, R. K.; Chan, T.-H. *J. Am. Chem. Soc.* **1966**, *88*, 866. (b) Naidu, B. N.; West, F. G. *Tetrahedron* **1997**, *53*, 16565. (c) Glaeske, K. W.; West, F. G. *Org. Lett.* **1999**, *1*, 31.

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(5) All new compounds were fully characterized by IR, ^{1}H and ^{13}C NMR analyses. Data for selected compounds are as follows. Compound **1a**: mp 202–204 °C (dec.). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.96 (s, 3 H), 3.25 (s, 3 H), 3.55 (dd, *J* = 12.9, 2.4 Hz, 1 H), 3.93 (d, *J* = 12.9 Hz, 1 H), 4.05 (dd, *J* = 13.4, 2.6 Hz, 1 H), 4.99 (dd, *J* = 13.4, 11.6 Hz, 1 H), 5.13 (dd, *J* = 11.6, 2.6 Hz, 1 H), 7.40–7.70 (m, 11 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 45.9, 54.1, 58.2, 67.2, 71.1, 95.0, 126.1, 128.2, 128.3, 129.2, 130.9, 131.4, 141.3. Anal. Calcd for $C_{18}H_{22}BrNO_2$: C, 59.35; H, 6.09; N, 3.85. Found: C, 58.77; H, 5.96; N, 3.88. Compound *anti*-**2a**: mp 136–139 °C. ^{1}H NMR (300 MHz, CDCl3): δ = 2.42 (s, 6 H), 3.61 (ddd, *J* = 3.9, 9.0, 11.1 Hz, 1 H), 3.88 (dd, *J* = 3.9, 11.4 Hz, 1 H), 4.13 (dd, *J* = 9.0, 11.4 Hz, 1 H), 4.86 (d, *J* = 11.1 Hz, 1 H), 7.04–7.22 (m, 4 H), 7.34–7.51 (m, 4 H), 7.71 (d, *J* = 7.5 Hz, 1 H). ^{13}C NMR (75 MHz, CDCl3): δ = 42.4, 45.0, 68.8, 70.4, 126.1, 127.1, 128.0, 128.4, 128.6, 133.1, 139.0, 139.5, 196.6. Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 75.77; H, 7.37; N, 4.95. Compound *anti*,*syn*-**3a**: ^{1}H NMR (300 MHz, CDCl3): δ = 2.12 (s, 6 H), 3.30 (d, *J* = 8.7 Hz, 1 H), 3.70 (ddd, *J* = 7.2, 8.7, 9.0 Hz, 1 H), 3.98 (dd, *J* = 7.2, 9.0 Hz, 1 H), 4.52 (dd, *J* = 9.0, 9.0 Hz, 1 H), 7.24–7.42 (m, 8 H), 7.71–7.74 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 45.0, 48.7, 74.4, 81.1, 104.2, 126.0, 126.9, 127.7, 128.1, 128.2, 129.0, 142.7, 143.8.

(6) The relative stereochemistry of **1a** was determined by NOE experiment as shown below (Figure 1).

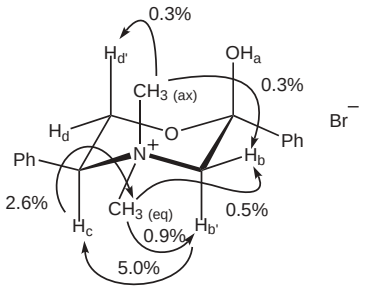

Figure 1

(7) It is considered that potassium ethoxide formed in the reaction mixture acts as a base.

(8) **Typical procedure**: To a solution of the ammonium salt **1a** (50 mg, 0.137 mmol) in EtOH (5 mL) at 0 °C was added potassium *tert*-butoxide (30.8 mg, 0.274 mmol). The reaction mixture was allowed to warm to r.t. and stirred for 12 h. The mixture was quenched by the addition of phosphate buffer (pH 7) and the organic layer was dried and concentrated in vacuo. Purification of the residue by PTLC (SiO_2, hexane/EtOAc = 2/1) gave (2*R**,3*R**)-2-dimethylamino-4-hydroxy-3-phenylbutyrophenone (*anti*-**2a**, 13.4 mg, 35% yield) and (2*S**,3*R**,4*R**)-3-dimethylamino-tetrahydro-2-hydroxy-2,4-diphenylfuran (*anti*,*syn*-**3a**, 15.6 mg, 40% yield).

(9) The relative stereochemistry of *anti*,*syn*-**3a** was determined by NOE experiment as shown below (Figure 2).

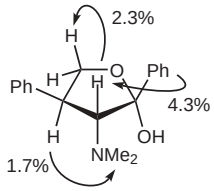

Figure 2

(10) *Anti*-**5** and *anti*,*syn*-**6** were obtained as a chromatographically inseparable mixture.

(11) Conformational analysis of the rearrangement products was carried out with the MacroModel 8.0 package and PC Spartan Pro 1.0.5. Conformational search was performed with Mixed MCMM/LowMode method (1000 structures) using MM2* force field. Further geometry optimization and the potential energy calculation of the most stable conformers were performed by PM3 calculation using Spartan.

(12) The hemiacetal (2*R*,5*R*)-**1a** was prepared from (*R*)-2-phenylglycinol (99% ee) purchased from Aldrich.

(13) This result is consistent with the reported steric course of Stevens rearrangement: see ref. 1.

(14) Similar solvent effect in terms of the asymmetric transmission was reported by Ollis and colleagues, see ref. 2.