Control of Diastereoselectivity in C=O/C=N Reductive Cyclizations Using an Intramolecularly Tethered Hydrazone

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Abstract: Cyclic hydrazones are efficient ketyl radical acceptors in reductive coupling cyclizations mediated by samarium diiodide, affording cyclic amino alcohols with controlled stereochemistry at the new aminated stereocenter. This approach has been successfully applied to the stereoselective synthesis of a fully functionalized trehazolin cyclitol starting from D-glucose, where the required cyclic hydrazone was directly obtained by partial hydrazonolysis of a 1,2-cyclic carbonate.

Key words: carbohydrates, electron transfer, hydrazones, ketones, samarium.

The ubiquitous presence of the vicinal amino alcohol subunit among natural products and synthetic chiral ligands has stimulated the development of a variety of methods for its stereoselective preparation. Since the seminal report of the first example of a pinacol-type radical cyclization of an oxime ether by Corey and Pyne, the ketyl radical addition to an imino group has emerged as a valuable tool for the preparation of vicinal amino alcohols with concurrent formation of a carbon-carbon bond. This reductive coupling reaction usually proceeds under very mild conditions, with high stereoselectivity and is compatible with a wide range of functional groups, offering many advantages over alternative ionic chemistry. Zinc, electroreduction, SmI₂, and n-BuSnH/AIBN have been shown to be efficient at promoting the reductive coupling of aldehydes or ketones with oxime ethers, hydrazones, imines or nitrones in an inter- or intramolecular fashion. The stereochemical features of the reaction have been well delineated for the intramolecular case (Scheme 1). Cyclic trans amino alcohols are preferentially obtained in conformationally unrestricted systems under all conditions, with the only exception of nitrones, which give exclusively the cis isomer. The preference for the trans isomer is probably a consequence of electrostatic repulsions between the ketyl radical anion and the reacting imino group in a presumably highly polarized transition state. In the case of nitrones, the reaction is proposed to involve single electron transfer reduction of the C=N group followed by radical addition to the carbonyl group in a chelated transition state, thus leading to all the different stereochemical outcome observed. When the C=N group is α-substituted, the cyclic product shows exclusively a trans relative stereochemistry between the amino function and the α-substituent in all cases studied. The reasons underlying this stereocontrol can be understood in terms of the lower activation energy associated with the cyclization reaction of the imine conformation with a minimal allylic 1,3-strain, as shown in Scheme 1.

In 1995, we described a simple entry to complex amino- cycloalkanols via a highly efficient tandem carbonyl-oxime ether reductive cyclization and subsequent N-O reductive cleavage promoted by SmI₂. This methodology and related heteropinacol coupling approaches have been successfully applied to the preparation of several natural products, including the trehalase inhibitor trehazolin and a series of analogs. Depending on the protection pattern and the nature of the imino group, any of the two diastereoisomic trehazolin aminocyclopentitols or 3a-c can be selectively obtained from glucose-derived keto-oximes (Scheme 2).

However, direct preparation of the fully functionalized trehazolin cyclitol by a C=O/C=N reductive carbocyclization has not been described yet since it would require of a strategy to overcome the 1,3A strain diastereocонтrolling factor mentioned above. We envisioned that intramolecularly tethering the C=N group to the vicinal hydroxyl (A, Scheme 2) could offer a possible solution to this problem opening an entry to diastereoisomeric aminocyclopentitols not directly accessible from substrates with the usual acyclic imino groups. After initial unsuccessful attempts to implement this strategy using an oxime as imino group and an isopropylidene acetal as tether, we arrived to the solution shown in Scheme 3. Treatment of diol 4, readily available from D-glucose, with Imid₃CO gave the 1,2-cyclic carbonate. Reaction of 5 with hydrazine hydrochloride and i-Pr₂NEt in EtOH at reflux produced the target cyclic hydrazone 6.
via partial, regioselective hydrazinolysis of the cyclic carbonate followed by intramolecular condensation of the resultant hydrazide with the unmasked hemiacetal group. Optimization of this transformation required much experimentation. The reaction conditions assayed and the corresponding yields obtained are collected in part in Table 1. Different combinations of hydrazine sources, solvents and additives were tested. In most cases, highly polar unidentified products were formed that did not progress to the expected cyclic hydrazide product, EtOH being the best solvent for this transformation.

Table 1 Different reaction conditions tested for the synthesis of 6 by hydrazinolysis of cyclic carbonate 5.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Hydrazine source</th>
<th>Additive</th>
<th>Solvent</th>
<th>Yield of 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NH₂NH₂HCl</td>
<td>MeCN</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>NH₂NH₂HCl</td>
<td>EtOH</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>NH₂NH₂HCl</td>
<td>i-Pr₂NEt</td>
<td>Toluene</td>
<td>8%</td>
</tr>
<tr>
<td>4</td>
<td>NH₂NH₂HCl</td>
<td>i-Pr₂NEt</td>
<td>DMF</td>
<td>28%</td>
</tr>
<tr>
<td>5</td>
<td>NH₂NH₂HCl</td>
<td>i-Pr₂NEt</td>
<td>MeCN</td>
<td>30%</td>
</tr>
<tr>
<td>6</td>
<td>NH₂NH₂HCl</td>
<td>DBU</td>
<td>MeCN</td>
<td>17%</td>
</tr>
<tr>
<td>7</td>
<td>NH₂NH₂HCl</td>
<td>pyridine</td>
<td>MeCN</td>
<td>19%</td>
</tr>
<tr>
<td>8</td>
<td>NH₂NH₂HCl</td>
<td>i-Pr₂NEt</td>
<td>EtOH</td>
<td>40-68%</td>
</tr>
<tr>
<td>9</td>
<td>NH₂NH₂HCl</td>
<td>NaOAc</td>
<td>EtOH</td>
<td>14%</td>
</tr>
<tr>
<td>10</td>
<td>NH₂NH₂H₂O</td>
<td>EtOH</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>NH₂NH₂HOAc</td>
<td>DMF</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>NH₂NH₂HOAc</td>
<td>pyridine</td>
<td>EtOH</td>
<td>12%</td>
</tr>
</tbody>
</table>

*At 80 °C for 2-4 days.
*No reaction.
*Only unidentified, highly polar products were formed.

Oxidation of the carbonyl group in 6 to the ketone was smoothly performed with the Dess-Martin periodinane to give the target cyclization substrate 7 in moderate yield. Treatment of 7 with a solution of SmI₂ (3 equiv) in THF at -30 ºC gave the expected cyclopentitol in 65% yield as a 7:1 mixture of isomers that could not be separated by chromatography. A complete assignment of the H and 13C NMR signals of both isomers was performed by a combination of DQ-COSY, HSQC, and HMBC spectra. The stereochemistry at the two new stereocenters was deduced from the corresponding NOESY spectrum of the mixture, which showed that the products were epimers at the new quaternary carbinol stereocenter. Thus, strong NOESY cross-peaks between H-1 and H-2 are observed for both isomers indicating a cis relative disposition between the amino function and the vicinal acyloxy substituent, thus confirming the validity of our approach. The presence of cross-correlations between the hydroxyl proton and H-1 and H-4 in the major isomer, which are absent in the minor isomer, allowed us to assign the stereochemistry at the quaternary center of both compounds as shown in Scheme 4. The major trans relative disposition between the newly formed stereocenters is in line with the general diastereoselectivity trends observed for similar CO/CN reductive cyclizations, as explained above. Since a variety of methods are available for the cleavage of the N–N bond to give the corresponding amine, this approach could be considered a formal synthesis of trehazolamine, the aglycon of trehazolin (see Scheme 2).

In conclusion, cyclic hydrazones are efficient ketyl radical acceptors in reductive coupling cyclizations mediated by samarium diiodide, affording cyclic amino alcohols with controlled stereochemistry at the new aminated stereocenter. This approach complements existing reductive coupling methodologies allowing the preparation of diastereoisomeric cyclic amino alcohols that are not directly accessible via reductive cyclization of substrates with the usual acyclic imino groups. We have successfully applied this approach to the stereoselective synthesis of a fully functionalized trehazolin cyclitol, using a substrate readily prepared from D-glucose.

Scheme 2
Acknowledgment

Financial support by the Ministry of Science and Technology of Spain (project BQU2000-1501-C02-01) and Fundación Ramón Areces (predoctoral fellowship to A. G.) are gratefully acknowledged.

References

(9) Storch de Gracia, I. Ph. D. Thesis, Universidad Autónoma de Madrid, 2002. See also: ref. 4b (X = NOMe), 4c and 6h.
(11) Preparation of compound 5. To a solution of 4 (1.0 g, 2.22 mmol) in anhydrous CHCl₃ (30 mL) under argon was added carboxyldimidazole (0.767 g, 4.73 mmol) and Et₃N (0.9 mmol, 2.8 mmol) and the mixture was stirred at rt for 5 h. The reaction was concentrated under reduced pressure, diluted with CH₂Cl₂ (10 mL) and washed with aq. HCI 2% (3 x 10 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography (silicagel, hexane/EtOAc 5:1) to give 5 (799 mg, 86%) as a white solid. M.p. = 60-61°C; [α]D 28 +4.9 (c 4.8, CHCl₃); IR (KBr) νmax 3435, 2862, 1813, 1453, 1367, 1355, 1156, 1050, 746, 696 cm⁻¹; 1H NMR (300 MHz, CDCl₃) δ 7.39-7.28 (m, 13 H), 7.26-7.17 (m, 2 H), 6.06 (d, 1 H, J = 6.3 Hz, H-1), 7.40-4.42 (m, 7 H, H-2, 3 OCH₂Ph), 3.93 (t, 1 H, J = 4.2 Hz), 3.84-3.81 (m, 2 H, 2 H), 3.69-3.65 (m, 2 H); 13C NMR (75 MHz, CDCl₃) δ 152.4, 137.5, 137.3, 136.7, 128.5, 128.4, 128.2, 128.0, 127.9, 127.8, 127.8, 97.3, 77.2, 75.8, 73.4, 72.3, 71.1, 72.6, 71.6, 68.3; MS (ES+): m/z = 477.1 [M+H+]O; 499.1 [M+Na]+. Anal. Calc. for C₂₈H₂₈O₇C: 70.57; H: 5.92; found: C 69.79; H: 6.12.
(12) **Preparation of compound 6.** To a solution of 5 (200 mg, 0.42 mmol) in EtOH (2 mL) was added i-Pr,N,Ni (161 µL, 0.92 mmol) and hydrazine hydrochloride (32 mmol, 0.46 mmol) and the mixture was heated at 80 °C for 4 days. The reaction was terminated at reduced pressure and the crude was purified by flash chromatography (silicagel, hexane/EtOAc 3:1) to give 6 (140 mg, 68 %) as a yellowish oil.  \([\alpha]_D^{20} -0.9 \text{ (c } 1.7, \text{ CHCl}_3\); IR (KBr) \nu_{max} 3306, 292, 1748, 1722, 1545, 1360, 1260, 1212, 1072, 1026, 751, 698 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 7.91 \text{ (bs, 1 H, NH), 7.49-7.27 (m, 13 H), 7.26-7.17 (m, 2 H), 7.02 (d, 1 H, } J = 2.4 \text{ Hz, H-1), 4.91 (dd, 1 H, } J = 1.8, 5.4 \text{ Hz, H-2), 4.75 (d, 1 H, c 11.7 \text{ Hz, OCH}_2\text{Ph}), 4.64 (d, 1 H, } J = 11.4 \text{ Hz, OCH}_2\text{Ph}), 4.54-4.48 (m, 4 H, 2 OCH_2\text{Ph}), 4.11 (dd, 1 H, } J = 4.2, 5.1 \text{ Hz), 4.01 (q, 1 H, H-5), 3.80 (dd, 1 H, } J = 3.9, 7.5 \text{ Hz), 3.71-3.62 (m, 2 H), 2.56 (d, 1 H, } J = 6.6 \text{ Hz, OH), 13C NMR (75 MHz, CDCl}_3\) \(\delta 128.9, 128.8, 128.4, 128.4, 80.5, 76.9, 74.7, 74.3, 73.8, 73.5, 70.4, 70.1\); MS (ES\(^+\)): m/z = 491.1 \([\text{M}+H]^+\), 508.3 \([\text{M}+\text{Na}]^+\).

(13) **Preparation of compound 7.** To a solution of 6 (50 mg, 0.101 mmol) in CH\(_2\)Cl\(_2\) (1 mL) under argon was added a suspension of Dess-Martin periodinane (86.5 mg, 0.203 mmol) in CH\(_2\)Cl\(_2\) (0.5 mL). After stirring at rt for 1 h, the mixture was diluted with CH\(_2\)Cl\(_2\) (5 mL) and washed with aq. sat. NaHCO\(_3\) (2 x 3 mL). The organic phase was washed with aq. 10 % Na\(_2\)SO\(_4\) (2 x 3 mL), dried over Na\(_2\)SO\(_4\), filtered and concentrated at reduced pressure. The crude was purified by flash chromatography (silicagel, hexanes/EtOAc 2:1) to give 7 (25 mg, 51%) as a colorless oil. \([\alpha]_D^{20} -6.6 \text{ (c 0.8, CHCl}_3\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 7.89 \text{ (s, 1 H, NH), 7.36-7.20 (m, 15 H), 7.00-7.00 (d, 1 H, } J = 2.1 \text{ Hz, H-1), 4.86 (dd, 1 H, } J = 2.1, 5.4 \text{ Hz, H-2), 4.50 (s, 2 H OCH}_2\text{Ph), 4.57 (d, 1 H, } J = 11.4 \text{ Hz, H-6), 4.48 (s, 1 H), 4.39 (d, 1 H, } J = 11.4 \text{ Hz, H-6'), 4.31 (d, 1 H, } J = 3.9 \text{ Hz), 4.19 (m, 3 H), 13C NMR (75 MHz, CDCl}_3\) \(\delta 206.8, 148.2, 140.0, 136.9, 136.3, 135.9, 129.0, 129.0, 128.9, 128.8, 128.4, 128.4, 80.5, 76.9, 74.7, 74.3, 74.3, 73.5, 73.4, 73.4, 73.5, 73.4.

(14) **Reductive cyclization of compound 7.** A solution of 7 (90 mg, 0.184 mmol) in THF (5 mL) was added dropwise under argon to a 0.1 M THF solution of SmI\(_2\) (0.1M, 5.5 mL, 0.552 mmol) and r-BuOH (88 µL, 0.92 mmol) at ~30 °C. After stirring at ~30 °C for 2 h, the flask was opened to air to oxidize excess SmI\(_2\) and the crude reaction mixture was filtered through Florisil\(^8\), rinsing with CH\(_2\)Cl\(_2\)/MeOH 10:1. The filtrate was evaporated at reduced pressure and the residue was purified by flash chromatography (silicagel, hexane/EtOAc 1:2) to give 8 as a 7:1 mixture of isomers (58 mg, 65%). IR (KBr) \(\nu_{max} 3272, 2868, 1709, 1453, 1093, 1061, 924, 737, 697 \text{ cm}^{-1}; \(^1\)H RMN (400 MHz, CDCl\(_3\)) \(8a\): \(\delta 7.37-7.12 \text{ (m, 15 H), 6.92 (s, 1 H, NH), 5.04 (dd, 1 H, } J = 3.5, 5.4 \text{ Hz, H-2), 4.73 (d, 1 H, } J = 12.0 \text{ Hz, OCH}_2\text{Ph), 4.54 (d, 1 H, } J = 12.0 \text{ Hz, OCH}_2\text{Ph), 4.55 (d, 2 H, } J = 12.0 \text{ Hz, OCH}_2\text{Ph), 4.47 (dd, 1 H, } J = 1.5, 12.6 \text{ Hz, NH), 4.42 (d, 1 H, } J = 11.7 \text{ Hz, OCH}_2\text{Ph), 4.35 (d, 1 H, } J = 11.7 \text{ Hz, OCH}_2\text{Ph), 4.19 (d, 1 H, } J = 3 \text{ Hz, H-3), 3.75 (s, 1 H, H-4), 3.72 (d, 1 H, } J = 9.6 \text{ Hz, H-6), 3.62 (d, 1 H, } J = 9.6 \text{ Hz, H-6'), 3.51 (dd, 1 H, } J = 1.5, 5.4, 12.6 \text{ Hz, H-1), 3.31 (s, OH); 8b (partial spectrum): 6.81 (s, 1 H, NH), 4.58 (dd, 1 H, } J = 3.4, 8.3 \text{ Hz, H-2), 4.36 (m, 1 H, H-3), 3.93 (d, 1 H, } J = 8.1 \text{ Hz), 3.75 (m, 1 H, H-1), 3.40 (d, 1 H, } J = 9.2 \text{ Hz, H-6), 3.26 (d, 1 H, } J = 9.2 \text{ Hz, H-6'), 3.10 (s, OH); 13C NMR (75 MHz, CDCl}_3\) \(8a\): \(\delta 153.5 \text{ (C-O), 137.3, 137.0, 136.5, 128.4, 128.4, 128.3, 128.1, 128.0 127.9, 127.8, 127.7, 88.2 (C-3), 87.9 (C-2), 86.6 (C-4), 80.7 (C-5), 73.7 (OCH}_2\text{Ph), 72.0 (OCH}_2\text{Ph), 71.6 (OCH}_2\text{Ph), 68.3 (C-6), 62.4 (C-1); 8b (partial spectrum): \(\delta 156.0 \text{ (C-O), 137.4, 87.2 (C-3), 83.2 (C-2), 80.1 (C-4), 73.4 (OCH}_2\text{Ph), 73.3 (OCH}_2\text{Ph), 69.4 (C-6), 55.3 (C-1); MS (ES\(^+\)): m/z = 491.1 \([\text{M+H}]^+, 513.3 \([\text{M+Na}]^+\).

(15) For clarity, the numbering of the carbons in the starting glucose derivative 4 has been kept for all the compounds.

Stereoselective CO/CN Reductive Cyclization of Cyclic Hydrazones