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

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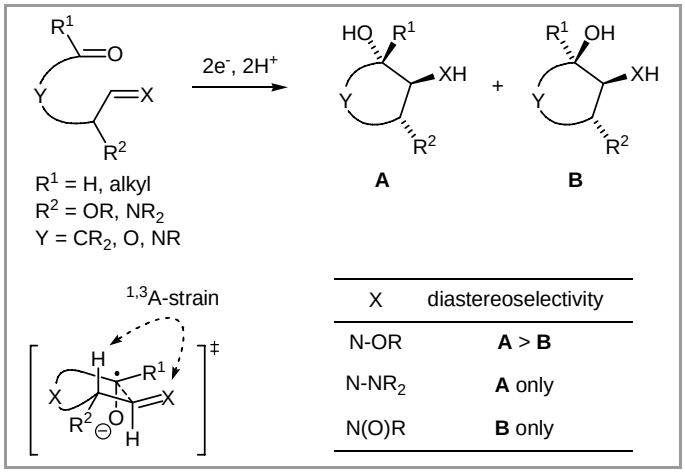
Abstract: Cyclic hydrazones are efficient ketyl radical acceptors in reductive coupling cyclizations mediated by samarium diiodide, affording cyclic amino alcohols with controlled stereochemistry at the new aminated stereocenter. This approach has been successfully applied to the stereoselective synthesis of a fully functionalized trehazolin cyclitol starting from D-glucose, where the required cyclic hydrazone was directly obtained by partial hydrazynolysis 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.[1] Since the seminal report of the first example of a pinacol-type radical cyclization of an oxime ether by Corey and Pyne,[2] 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.[3,4] 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,[2,5] electroreduction,[6] SmI_2,[4,7] and *n*-Bu_3SnH/AIBN[8] have been shown to be efficient at promoting the reductive coupling of aldehydes or ketones with oxime ethers,[4,6,7a,7c-g,7i,7p,8] hydrazones,[4f,7b] imines[5,7h,7j,7k,7m-o] or nitrones[7l,q] 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,[7l,q] 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[7l,q] 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 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 conformer with a minimal allylic 1,3-strain, as shown in Scheme 1.

In 1995, we described a simple entry to complex aminocycloalkanols via a highly efficient tandem carbonyl-oxime ether reductive cyclization and subsequent N–O reductive cleavage promoted by SmI_2.[7c] This methodology and related heteropinacol coupling approaches have been successfully applied to the preparation of several natural products,[4] including the trehalase inhibitor trehazolin[4c,d] and a series of analogs.[7c-f,i,p,q] Depending on the protection pattern and the nature of the imino group, any of the two diasteroisomeric trehazolin aminocyclopentitols **2a-c** or **3a-c** can be selectively obtained from glucose-derived keto-oximes **1a-c** (Scheme 2).

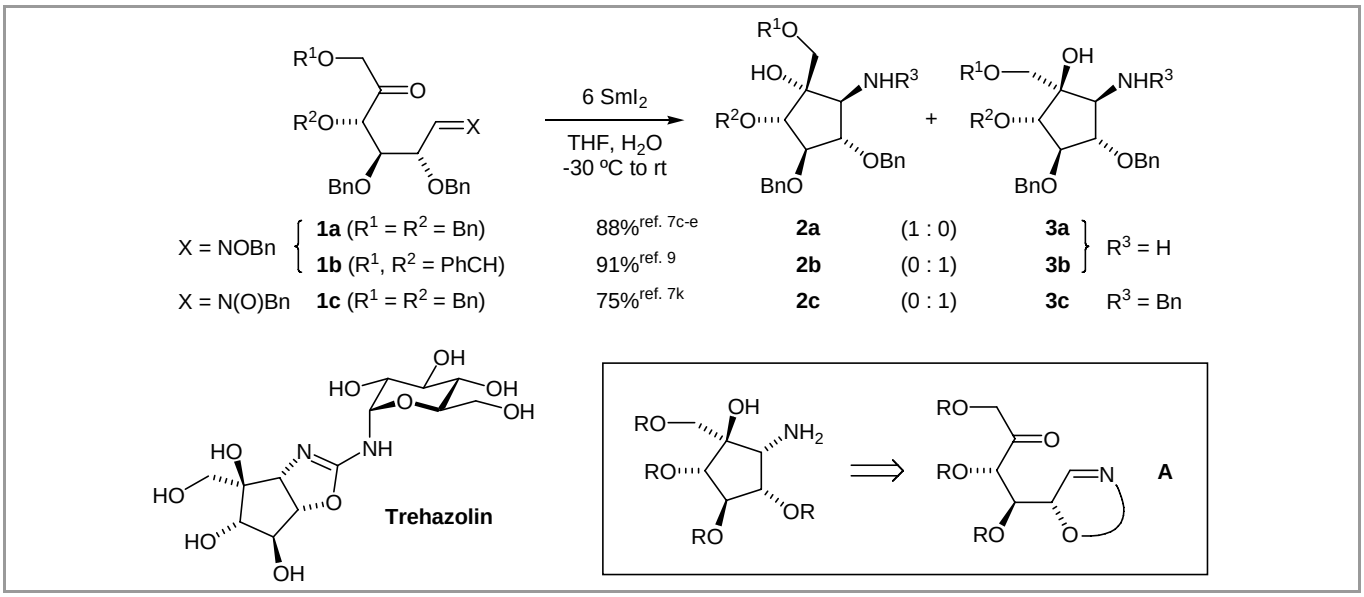


X	diastereoselectivity
N-OR	**A** > **B**
$N-NR_2$	**A** only
N(O)R	**B** only

Scheme 1

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 ^{1,3}A strain diastereocontrolling 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 aminocyclitols 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,[10] with $Imid_2CO$ gave the 1,2-cyclic carbonate **5**.[11] Reaction of **5** with hydrazine hydrochloride and *i*-Pr_2NEt in EtOH at reflux produced the target cyclic hydrazone **6**[12]

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 of 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 **6** upon prolonged heating. Only the combination of an acidic hydrazine derivative (hydrazine hydrochloride) in the presence of a base afforded the expected cyclic hydrazide product **6**, EtOH being the best solvent for this transformation.



Scheme 2

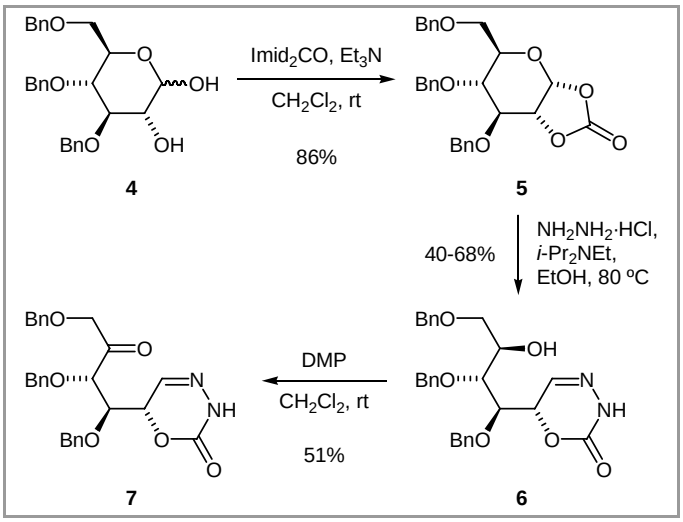
Table 1 Different reaction conditions tested for the synthesis of **6** by hydrazinolysis of cyclic carbonate **5**.[a]

Entry	Hydrazine source	Additive	Solvent	Yield of **6**
1	$NH_2NH_2{\cdot}HCl$		MeCN	[b]
2	$NH_2NH_2{\cdot}HCl$		EtOH	[c]
3	$NH_2NH_2{\cdot}HCl$	*i*-Pr_2NEt	Toluene	8%
4	$NH_2NH_2{\cdot}HCl$	*i*-Pr_2NEt	DMF	28%
5	$NH_2NH_2{\cdot}HCl$	*i*-Pr_2NEt	MeCN	30%
6	$NH_2NH_2{\cdot}HCl$	DBU	MeCN	17%
7	$NH_2NH_2{\cdot}HCl$	pyridine	MeCN	19%
8	$NH_2NH_2{\cdot}HCl$	*i*-Pr_2NEt	EtOH	40-68%
9	$NH_2NH_2{\cdot}HCl$	NaOAc	EtOH	14%
10	$NH_2NH_2{\cdot}H_2O$		EtOH	[c]
11	$NH_2NH_2{\cdot}HOAc$		DMF	[b]
12	$NH_2NH_2{\cdot}HOAc$	pyridine	EtOH	12%

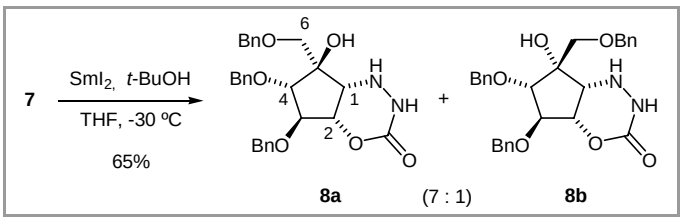
[a] At 80 ºC for 2-4 days.
[b] No reaction.
[c] Only unidentified, highly polar products were formed.

Oxidation of the carbinol group in **6** to the ketone was smoothly performed with the Dess-Martin periodinane to give the target cyclization substrate **7**[13] in moderate yield. Treatment of **7** with a solution of SmI_2 (3 equiv) in THF at –30 ºC gave the expected cyclopentitol **8**[14,15] in 65% yield as a 7:1 mixture of isomers that could not be separated by chromatography. A complete assignment of the ^1H and ^{13}C 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 acyloxi 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,[16] 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 3



Scheme 4

Acknowledgment

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(11) **Preparation of compound 5**. To a solution of **4** (1.0 g, 2.22 mmol) in anhydrous CH_2Cl_2 (30 mL) under argon was added carbonyldiimidazole (0.767 g, 4.73 mmol) and Et_3N (0.9 ml, 2.8 mmol) and the mixture was stirred at rt for 5 h. The reaction was concentrated under reduced pressure, diluted with CH_2Cl_2 (10 mL) and washed with aq. HCl 2% (3 x 10 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated at 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 ºC; $[\alpha]_D^{20}$ +4.9 (*c* 4.8, $CHCl_3$); IR (KBr) ν_{max} 3435, 2862, 1813, 1453, 1367,1355, 1156,1050, 746, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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), 4.70-4.42 (m, 7 H, H-2, 3 OCH_2Ph), 3.93 (t, 1 H, *J* = 4.2 Hz), 3.84-3.81 (m, 2 H), 3.69-3.65 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) 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, 73.2, 73.1, 72.6, 71.6, 68.3; MS (ES+): m/z = 477.1 $[M+H_2O]^+$, 499.1 $[M+Na]^+$. Anal. Calc. for $C_{28}H_{28}O_7$: C, 70.57; H, 5.92; found: C, 69.97; 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_2NEt (161 μL, 0.92 mmol) and hydrazine hydrochloride (32 mg, 0.46 mmol) and the mixture was heated at 80 ºC for 4 days. The reaction was concentrated 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 (*c* 1.7, $CHCl_3$); IR (KBr) ν_{max} 3306, 292, 1748, 1722, 1454, 1360, 1260, 1212, 1072, 1026, 751, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.91 (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 Hz, H-1), 4.91 (dd, 1 H, *J* = 1.8, 5.4 Hz, H-2), 4.75 (d, 1 H, *c* 11.7 Hz, OCH_2Ph), 4.64 (d, 1 H, *J* = 11.4 Hz, OCH_2Ph), 4.54-4.48 (m, 4 H, 2 OCH_2Ph), 4.11 (dd, 1 H, *J* = 4.2, 5.1 Hz), 4.01 (q, 1 H, H-5), 3.80 (dd, 1 H, *J* = 3.9, 7.5 Hz), 3.71-3.62 (m, 2 H), 2.56 (d, 1 H, *J* = 6.6 Hz, OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0, 140.8, 137.4, 137.2, 137.1, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 76.9, 74.8, 74.3, 73.8, 73.5, 70.4, 70.1; MS (ES+): m/z = 491.1 $[M+H]^+$, 508.3 $[M+Na]^+$.

(13) **Preparation of compound 7**. To a solution of **6** (50 mg, 0.101 mmol) in CH_2Cl_2 (1 mL) under argon was added a suspension of Dess-Martin periodinane (86.5 mg, 0.203 mmol) in CH_2Cl_2 (0.5 mL). After stirring at rt for 1 h, the mixture was diluted with CH_2Cl_2 (5 mL) and washed with aq. sat. $NaHCO_3$ (2 x 3 mL). The organic phase was washed with aq. 10 % $Na_2S_2O_3$ (2 x 3 mL), dried over Na_2SO_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 (*c* 0.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1 H, NH), 7.36-7.20 (m, 15 H), 7.00-7.00 (d, 1 H, *J* = 2.1 Hz, H-1), 4.86 (dd, 1 H, *J* = 2.1, 5.4 Hz, H-2), 4.50 (s, 2 H OCH_2Ph), 4.57 (d, 1H, *J* = 11.4 Hz, H-6), 4.48 (s, 1H), 4.39 (d, 1H, *J* = 11.4 Hz, H-6'), 4.31 (d, 1 H, *J* = 3.9 Hz), 4.19 (m, 3 H).^{13}C NMR (75 MHz, CDCl3) δ 206.8, 148.2, 140.0, 136.9, 136.3, 135.9, 129.0, 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.

(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 *t*-BuOH (88 μL, 0.92 mmol) at –30 ºC. After stirring at –30 ºC for 2 h, the flask was opened to air to oxidize excess SmI_2 and the crude reaction mixture was filtered through Florisil®, rinsing with CH_2Cl_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) ν_{max} 3272, 2868, 1709, 1453, 1093, 1061, 924, 737, 697 cm^{-1}; ^1H RMN (400 MHz, $CDCl_3$) **8a**: δ 7.37-7.12 (m, 15 H), 6.92 (s, 1 H, NH), 5.04 (dd, 1 H, *J* = 3.5, 5.4 Hz, H-2), 4.73 (d, 1H, *J* = 12.0 Hz, OCH_2Ph), 4.54 (d, 1H, *J* = 12.0 Hz, OCH_2Ph), 4.55 (d, 2 H, *J* = 12.0 Hz, OCH_2Ph), 4.47 (dd, 1H, *J* = 1.5, 12.6 Hz, NH), 4.42 (d, 1H, *J* = 11.7 Hz, OCH_2Ph), 4.35 (d, 1H, *J* = 11.7 Hz, OCH_2Ph), 4.19 (d, 1H, *J* = 3 Hz, H-3), 3.75 (s, 1H, H-4), 3.72 (d, 1 H, *J* = 9.6 Hz, H-6), 3.62 (d, 1 H, *J* = 9.6 Hz, H-6'), 3.51 (ddd, 1 H, *J* = 1.5, 5.4, 12.6 Hz, H-1), 3.31 (s, OH); **8b** (partial spectrum): 6.81 (s, 1 H, NH), 4.58 (dd, 1H, *J* = 3.4, 8.3 Hz, H-2), 4.36 (m, 1H, H-3), 3.93 (d, 1H, *J* = 8.1 Hz), 3.75 (m, 1H, H-1), 3.40 (d, 1 H, *J* = 9.2 Hz, H-6), 3.26 (d, 1 H, *J* = 9.2 Hz, H-6'), 3.10 (s, OH); ^{13}C NMR (75 MHz, $CDCl_3$) **8a**: δ 153.5 (C=O), 137.3, 137.0, 136.5, 128.4, 128.4, 128.3, 128.1, 128.0 127.9, 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_2Ph), 72.0 (O*C*H2Ph), 71.6 (O*C*H2Ph), 68.3 (C-6), 62.4 (C-1); **8b** (partial spectrum): δ 156.0 (C=O), 137.4, 87.2 (C-3), 83.2 (C-2), 80.1 (C-4), 73.4 (O*C*H2Ph), 73.3 (O*C*H2Ph), 72.6 ((O*C*H2Ph), 69.4 (C-6), 55.3 (C-1); MS (ES+): m/z = 491.1 $[M+H]^+$, 513.3 $[M+Na]^+$.

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

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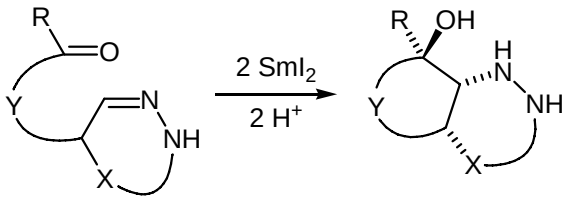

Stereoselective CO/CN Reductive Cyclization of Cyclic Hydrazones