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Reversal of regioselection in the rearrangement of cinnamate diol cyclic iminocarbonates

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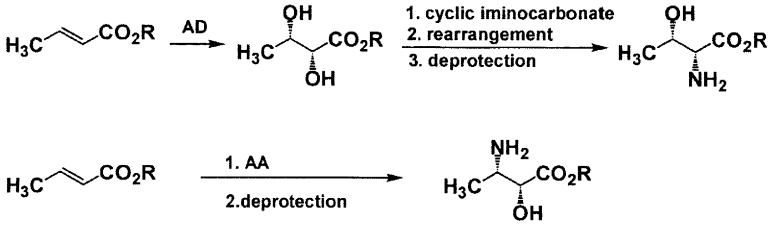
Abstract

The rearrangement of cinnamate diol cyclic iminocarbonates can be regioselectively controlled by using, as the nucleophile, Bu_4NBr (for β[benzylic]-nitrogen regioselection) or LiI (for the α-nitrogen isomers). This discovery will expand the synthetic utilities of the cyclic iminocarbonate rearrangement and the asymmetric dihydroxylation processes.

Keywords: regioselection; cyclic iminocarbonate rearrangement; asymmetric dihydroxylation.

Rearrangement of vicinal diol cyclic iminocarbonates provides an easy access to aminoalcohol functionality.[1] Coupled with Sharpless's asymmetric dihydroxylation (AD),[2] this process affords *syn*-aminoalcohols in high enantiomeric purity. In addition to the unique stereochemical course of the reaction in which the configurations at both carbinol carbons are retained, the regiochemistry is such that in a crotonate-type substrate, α-amino-β-hydroxy derivatives are obtained, complementing, in effect, Sharpless's asymmetric aminohydroxylation (AA) process (Scheme 1).[3]



Scheme 1.

With cinnamate diols, the rearrangement usually yields mixtures of regioisomers, the exact levels of the selectivity depending on the nature of substituents on the aryl ring. Thus, from unsubstituted cinnamate diol, a 2.7:1 mixture of regioisomers has been obtained, of which the major product has a nitrogen function at α to the carbonyl and an oxygen at the β(benzylic) site (see entry 1, Table 1), while

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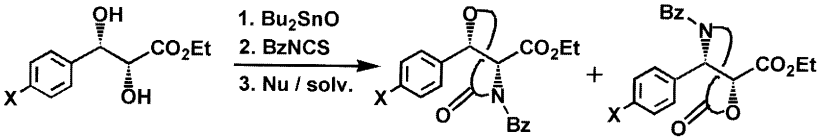
an electron-donating methoxy group at the *para*-position slightly favors a nitrogen at the β(benzylic) site (1:1.4 selectivity,[4] entry 7). In order to widen the synthetic utility of the rearrangement of vicinal diol cyclic iminocarbonates, we sought to improve the regioselectivity of the process with cinnamate diol substrates. Initially, we concentrated our efforts on directing the nitrogen function at the β(benzylic) site as we required such a regioselection in our synthetic endeavors for some natural products.[5] Disclosed herein are the results.

Table 1
Optimization of reaction conditions for regioselective rearrangement of cinnamate diol cyclic iminocarbonate



entry	X	Nu[a]	solvent	yield[b]	regioselectivity[c] (α-*N* : β-*N*)
1	H	Bu_4NBr	dichloroethane	77%	2.7 : 1
2		LiI	dichloroethane	10%	1 : 5
3		Bu_4NI	dichloroethane	50%	2.4 : 1
4		LiBr	dichloroethane	26%	1 : 1.7
5		LiI	acetonitrile	43%	1 : 4.6
6		LiI	$C_2H_4Cl_2$-CH_3CN	60~83%	1 : 3~3.5
7	OMe	BuN_4Br	dichloroethane	83%	1 : 1.4
8		LiI	$C_2H_4Cl_2$-CH_3CN	68%	only β
9		LiBr	$C_2H_4Cl_2$-CH_3CN	66%	only β
10		LiI (0.2eq)	$C_2H_4Cl_2$-CH_3CN	70%	only β
11	NO_2	Bu_4NBr	dichloroethane	47%	6 : 1
12		LiI	$C_2H_4Cl_2$-CH_3CN	43%	1 : 3

a. Except for entry 10, the amount of the nucleophile used in all the other reactions was 1~2 molar equivalent.

b. Combined yields of the two regioisomers.

c. Determined by NMR.

In the course of our discovery of the vicinal diol cyclic iminocarbonate rearrangement process, we noted that aryl-substituted diols (e.g., stilbene diol and anethole diol) had initially given poor results with Bu_4NBr or Bu_4NI as nucleophile, but changing it to lithium halide (LiI) produced satisfactory results.[1] On the other hand, the lithium salts (LiI or LiBr) were observed to be less effective than the tetraalkylammonium halides with non-aromatic diols (e.g., tartrate ester).[6] We therefore postulated that in the cyclic iminocarbonate rearrangement of cinnamate diols, a lithium halide nucleophile might direct the reaction preferentially at the benzylic site, eventually to yield β-amino-α-hydroxy compounds. The idea was tested with ethyl cinnamate diol as substrate (see Table 1).

Thus, the diol was treated with Bu_2SnO, then with BzNCS as previously described.[1] The resulting cyclic *N*-benzoyliminocarbonate was not isolated, but directly treated with LiI in dichloroethane at reflux. The reaction under these conditions did not seem promising, producing a complex mixture of products, from which the desired rearrangement product (*N*-benzoyloxazolidin-2-ones, ca. 10%) and the cyclic carbonate (ca. 10%) were isolated. Upon closer inspection, however, the product obtained turned out to be a mixture of regioisomers, with the β(benzylic)-nitrogen isomer as major (1:5 selectivity, entry 2). The use of LiI nucleophile was critical for the observed selectivity: substituting Bu_4NI, the rearrangement was reversed to α-nitrogen directing, with comparable regioselectivity to the Bu_4NBr case (2.4:1 with I^-; 2.7:1 with Br^-) and lower yield (50% with I^-; 77% with Br^-, entry 3), while LiBr nucleophile, although resembling LiI in that both lithium halides directed the rearrangement toward β-nitrogen, exhibited a lower level of β-nitrogen selectivity than did LiI (1:5 with I^-; 1:1.7 with Br^-, entry 4).

Having realized the wanted β(benzylic)-nitrogen regioselectivity, albeit in poor yields, on cinnamate diol substrate by using LiI nucleophile, we turned our attention toward improving the yield of the rearrangement. With the idea that polar medium might favor the reaction with LiI, the rearrangement was conducted in polar solvents such as THF, DMF or acetonitrile. In these cases, as the Sn-ketalization still needed to be performed under azeotropic conditions, the reaction sequence up to the cyclic *N*-benzoyliminocarbonate formation was conducted in dichloroethane as before, then the reaction mixture was concentrated, and the residue redissolved in a chosen polar solvent and treated with LiI. Of the polar solvents tried, acetonitrile gave the most promising results: produced from this reaction were the *N*-benzoyloxazolidinones (1:4.6 α-nitrogen:β-nitrogen isomers, combined yield 43%) together with the cyclic carbonate (30%, entry 5). Thus, the reaction with LiI in acetonitrile maintained the more or less same level of regioselection as observed with LiI in dichloroethane, only in higher yields. Assuming that the cyclic carbonate formation was due to the adventitious entry of water during the solvent replacement, the rearrangement reaction was performed in a dichloroethane:acetonitrile co-solvent (1:1–2) by simply diluting the reaction mixture with acetonitrile prior to the addition of LiI. Under these conditions, a somewhat diminished, but still β-nitrogen directing regioselection (1:3–3.5) was observed, with a combined yield of the *N*-benzoyloxazolidinones improving to the synthetically useful range of 60–83% and the cyclic carbonate formation suppressed to less than 8% (entry 6).

A similar pattern of regioselection was observed with substituted cinnamate diols, while the levels of the selectivity depended upon the nature of the substituents. Thus, *p*-methoxycinnamate diol, which had been observed to be already, albeit slightly, β(benzylic)-nitrogen selective with Bu_4NBr due to the presence of the electron-donating methoxy group at the *para*-position (entry 7), now showed a complete regioselection for the β-nitrogen isomer with LiI or LiBr to yield 1-benzoyl-4-ethoxycarbonyl-5-(*p*-methoxyphenyl)-2-oxazolidinone in 66–68% in a dichloroethane–acetonitrile co-solvent system (entries 8 and 9). The rearrangement now became sufficiently fast under these conditions that the reaction could be performed with only a catalytic amount of LiI (entry 10).

While the *p*-NO_2 group rendered the rearrangement α-nitrogen selective with Bu_4NBr nucleophile in dichloroethane (entry 11), the LiI nucleophile was observed to overpower even this powerful electron-

withdrawing group to produce the β-nitrogen isomer selectively (1:3) in the dichloroethane:acetonitrile system (entry 12).

It is not clear at this time why the LiI nucleophile rendered the rearrangement β(benzylic)-nitrogen selective. While a Lewis acidic role of Li-cation (by coordinating to basic site(s) of *N*-benzoyliminocarbonate moiety) may be speculated, no appreciable improvement in regioselectivity was observed when the rearrangement was conducted with added Lewis acids such as Ti^{4+} or Zn^{2+}.

In conclusion, the rearrangement of cinnamate diol cyclic iminocarbonates, a normally α-nitrogen selective process with Bu_4NBr nucleophile in dichloroethane, can be made β-nitrogen selective by using LiI nucleophile in dichloroethane–acetonitrile. Incidentally, with this reversal of regioselection, the cyclic iminocarbonates rearrangement process provides the same type of products in two separate operations (AD+rearrangement) that could be prepared in a single AA step. Thanks to the continuous optimizations, partly to deal with its own regioselectivity as well as the enantioselectivity issues,[7] the AA process now furnishes impressive results particularly with cinnamate-type substrates. Still, compared to the AA, the AD process is a more fully established protocol tested by numerous applications. Accordingly, the AD-based cyclic iminocarbonate rearrangement process of cinnamate diols can be a viable option in the enantioselective synthesis of *syn*-α-hydroxy-β-amino-β-aryl ester derivatives.

Acknowledgements

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4. The regioisomeric ratios given throughout this paper are those of the α:β-nitrogen isomers.
5. Synthetic applications for the reversed regioselective cyclic iminocarbonate rearrangement chemistry will be reported elsewhere.
6. Cho, G. Y.; Ko, S. Y., unpublished results.
7. cf. Tao, B.; Schlingloff, G.; Sharpless, K. B. *Tetrahedron Lett.* **1998**, *39*, 2507.