ORGANIC LETTERS

2005
Vol. 7, No. 1
35−38

Stereoselective Synthesis of α,α′-Biprolines

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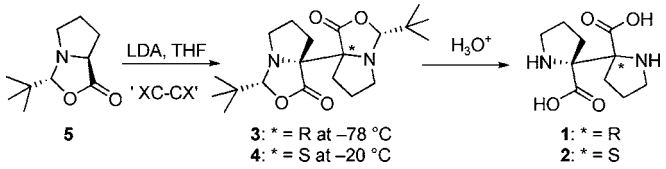
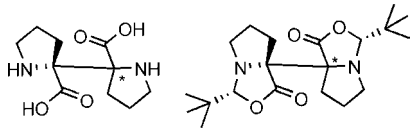
Received October 5, 2004

ABSTRACT



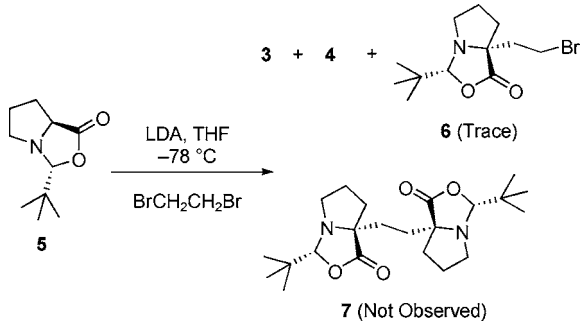
A means to induce dehydrodimerization of Seebach's oxazolidinone (5), the stereochemical outcome of which is entirely temperature dependent, is described. The resultant dimers 3 and 4 are precursors to (*R,R*)-α,α′-biproline (1) and *meso*-α,α′-biproline (2), respectively. An organohypobromite and an iminium halide are proposed to serve as electrophiles in the reaction with the enolate of 5 to give 3 and 4, respectively.

Oxidative dimerization of amino acids at their α-positions can yield several useful derivatives of diamino succinic acid. The C_2-symmetric diamino functionality of the *threo* isomers is especially interesting from the viewpoint of organocatalysis.[1] To our knowledge, the enantioselective synthesis of amino acid dimers other than glycine has not been achieved. Herein, we wish to report the first synthesis of (*R,R*)-α,α′-biproline (**1**) and *meso*-α,α′-biproline (**2**) via the biprolyl oxazolidinones **3** and **4**, respectively, that in turn were obtained from the diastereoselective dimerization of the pivaloyl oxazolidin-5-one derivative of proline (**5,** Seebach's oxazolidinone,[2] Scheme 1).



Derivatization of amino acids as their oxazolidin-5-ones with bulky, nonenolizable aldehydes such as pivalaldehyde greatly influences the stereochemical outcome of reactions that they undergo at their α-carbons. The pivaloyl oxazolidinones of several amino acids undergo stereoselective alkylation at their α-carbons, either directly or indirectly, due to the steric bulk of the *tert*-butyl group.[3] Consequently, **5** has been used extensively for the preparation of optically pure α-substituted proline derivatives.[4]

Scheme 1. Dehydrodimerization Reaction of **5**



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10.1021/ol047958+ CCC: $30.25
Published on Web 12/09/2004

In one of our uses of **5**, our initial aim was the synthesis of the C2-linked bioxazolidinone **7** by alkylating the lithium enolate of **5** with dibromoethane (Scheme 1). However, instead of obtaining **7**, we observed the formation of dehydrodimers **3** and **4**, plus a trace of the monoalkylated product **6**. Runs of the reaction at −20 °C resulted primarily in the formation of **4** while subsequent runs at −78 °C yielded **3** as the major diastereomer (Table 1). Although some

Table 1. Effects of Temperature, Counterion, and Halogen Equivalent on the Ratio of **3** and **4**

entry	*T* (°C)	HMPA (3 equiv)	E[a]	**3**/**4**	yield (%)
1	−78	yes	a	13:1	63
2	−78	yes	b	10:1	83
3	−78	no	b	15:1	43
4	−55	no	b	8:1	74
5	−55	yes	b	8:1	85
6	−40	no	b	4:1	65
7	−40	yes	b	3:2	75
8	−30	no	b	1:12	25
9	−30	yes	b	<1:20	70
10	−20	yes	b	<1:20	56
11	−20	no	b	1:9	46
12	−78	no	c	6:1	45
13	−78	no	d	<1:20	40

[a] Halogen equivalents: a, dibromoethane; b, 1,2-dibromo-1-phenylethane; c, iodine; d, 1,2-dibromo-1-phenylethane + silver triflate (1 equiv).

facial bias is to be expected during the reaction due to the asymmetric nature of **5**, this neither explains the formation of **3** and **4** nor does it explain the highly intriguing temperature-dependent "flip" in diastereoselectivity.

Both biprolyl oxazolidinones were crystalline solids that were obtained pure from a fast crude crystallization followed by a slow fractional crystallization from MeOH/H_2O. The absolute stereochemistry of the Cα atoms of **3** and **4** was confirmed by X-ray crystallography to be *R*,*R* and *R*,*S*, respectively (Figure 1).[5]

Halogens (I_2, Br_2) and halogen equivalents,[6] lead-based oxidants,[7] and molecular oxygen[8] are known to function as oxidizing agents in the dimerization of enolates and other carbanions. Specifically, dibromoethane is known to oxidatively dimerize dithiane anions.[9] With respect to amino acids, the only known dimerizations are those with glycine Schiff-base enolates using I_2[6] and the photochemical dimerization of pyroglutamic acid.[10] In both cases, radical intermediates have been implicated.

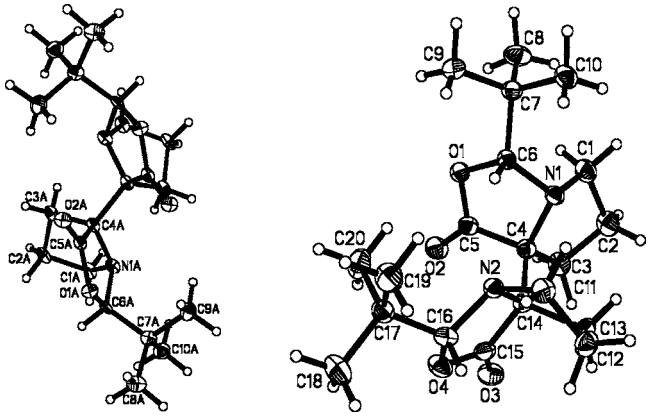

Figure 1. X-ray crystal structures of **3** (left) and **4** (right).

To probe the role of the vicinal dihalide dibromoethane in the dehydrodimerizaton reaction of **5**, we examined the reaction mixture by ^1H NMR and observed the presence of ethylene. For want of more tangible evidence of the apparent dehalogenation in the dimerization reaction, the *vic*-dihalide 1,2-dibromo-1-phenylethane was used in the reaction (Table 1, entry 2). Styrene was isolated as the byproduct in the dehydrodimerization reaction, thereby indicating that the *vic*-dihalides, dibromoethane and 1,2-dibromo-1-phenylethane, essentially function as halogen equivalents in this reaction. We also were able to use iodine, albeit with lower yields (Table 1, entry 12).

An increase in temperature caused a gradual "flip" in the diastereomeric ratio of **3**/**4**. At higher temperatures **4** predominated, while **3** predominated at lower temperatures irrespective of the mode of addition of reactants (normal versus inverse addition). HMPA had a modest effect, wherein it generally resulted in increased formation of **4**. Perhaps the most intriguing effect was that seen with the addition of 1 equiv of silver triflate to the reaction employing 1,2-dibromo-1-phenylethane at −78 °C (Table 1, entry 13). This addition resulted in a complete reversal of the diastereomeric ratio whereby **4** now predominated.

Since the captodative α-carbon of **5** seemed potentially susceptible to free-radical reactions, experiments were conducted to examine such a possible mechanism. In one case, benzophenone, a known inhibitor of I_2-mediated dimerization of enolates,[6] was added to the dimerization reaction of **5** at a level of 5 mol %. Under these conditions, **3** and **4** were still formed. This result was not viewed as conclusive evidence against a radical mechanism, however, since benzophenone also functioned as an electrophile in the reaction where it gave the alcohol adduct with **5**. Stronger evidence against a radical mechanism was provided with the

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(5) The crystal structure of **3** appears to be unique. The molecular symmetry of (*R*,*R*)-biprolyl oxazolidinone is a 2-fold rotation. In the crystalline form four molecules are found in the unit cell, each of which is located on an unique crystallographic 2-fold axis: space group *P*2 has four unique crystallographic 2-fold axes. Thus, the asymmetric unit contains four-half molecules. The Zorky notation for this structure is *P*2, $Z = 8(2^4)$. No molecular structure with similar attributes was found in the Cambridge Structural Database (Allen, F. H. *Acta Crystallogr*. **2002**, *B58*, 380−388).

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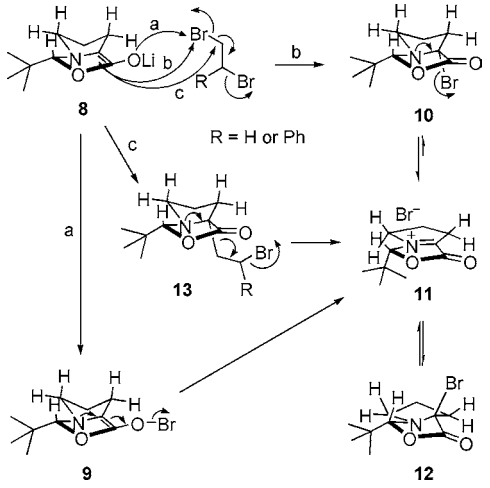
free radical inhibitor *m*-dinitrobenzene, which has been used previously in examining the potential involvement of free radicals in the dimerization of dithianes.[9] Furthermore, we found that *m*-dinitrobenzene inhibits the I_2-mediated dimerization of Schiff-base enolates of glycine, a process that has been shown to involve free radicals.[6] *m*-Dinitrobenzene concentrations of 5, 10, and 150 mol % with respect to **5** failed to inhibit the dimerization reaction of **5**. Thus, the dimerization of **5** appears to involve a mechanism other than one that involves radical intermediates.

In the reaction of the enolate of **5**, intermediate **8**, with a *vic*-dihalide, one can envision the possible formation of either an *O*-brominated product,[11] organohypobromite **9** (Scheme 2, pathway a), or a *C*-brominated product, *gem*-haloamine

Scheme 2. Formation of the Organohypobromite, Iminium, and *gem*-Haloamine Intermediates



10 (Scheme 2, pathway b). The latter is the result of attack from the bottom face of the enolate as predicted by Seebach's concept of self-reproduction of chirality that is inherent in **8**.[2] This lithium−bromonium exchange is akin to that proposed in the dimerization of dithiane anions with dibromoethane.[9]

If **10** were formed, the elimination of bromide from this haloamine would give iminium intermediate **11**, which could exist in equilibrium with haloamine **12**[12] as a result of bromide attack on the less sterically hindered side of **11**. One also can envision the organohypobromite **9** breaking down to give **11**. Another possible route to iminium **11** involves pathway c and the formation of α-alkylated oxazolidinone **13**. A subsequent Grob-type fragmentation[13] involving the elimination of alkene and bromide from **13** would yield **11**. However, this pathway seems unlikely given that the reaction of the enolate of **5** with bromoethyl triflate yields cleanly the 2-bromoethyl alkylated oxazolidinone **6** as the sole stable product.

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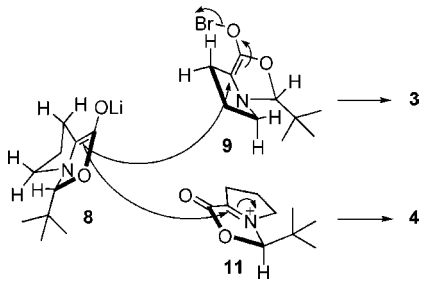
We postulate that of the possible intermediates formed in the reaction of **8** with a *vic*-dihalide (Scheme 2) intermediates **9** and **11** would seem to be the most likely to function as electrophiles in subsequent reactions with enolate **8** (Scheme 3). Alkylations of **8** have been shown to occur on the syn

Scheme 3. Reaction of **8** with **9** or **11**



side of the pseudoequatorial *tert*-butyl group because of the steric hindrance provided by the axial hydrogens.[2] Also, we have found that with **8** the stereoselectivity of alkylation does not change with increasing temperature. The attack of **8** from its preferred bottom face on the analogous preferred *re* face of **9** would give **3**. In the case of **11**, the relatively flat conformation of this species is structurally analogous to the enolates of oxazolidinone derivatives of amino acids where the nitrogen is acylated or carbamoylated.[3c] In such enolates, alkylation occurs *anti* to the *tert*-butyl group because of its pseudoaxial position. The pseudoaxial orientation of the *tert*-butyl group of **11**, in an analogous fashion, makes the *re* face of the iminium species quite hindered, thus favoring the approach of **8** to the *si* face to give **4**.

Electrophilic attack on **10** is viewed as unlikely, since its energy-minimized structure shows its top face to have a concave nature that is heavily shielded by axial hydrogens. An energy calculation (CVFF force field) on **12** showed the *trans*-fusion geometry to be about 0.45 kcal more stable than the *cis*-fused conformation. This may be due to steric interactions between the *tert*-butyl group and the axial hydrogens of the pyrrolidine ring that exist in the latter conformation. The *trans*-form, in a fashion analogous to **8**, positions the *tert*-butyl group in an equatorial position thereby minimizing its steric effect. This could allow enolate **8** to attack from the side opposite that of the bromo group thereby giving **3**. Such an attack would probably be much more sterically demanding than the attack of **8** on **9**, however, and thus much less likely to be the mechanism behind the formation of **3**.

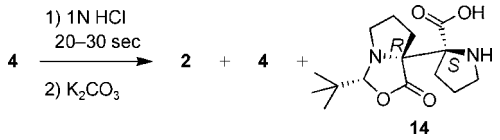
If **9** and **11** are indeed the electrophiles that react with **8** to form **3** and **4**, respectively, then it appears that at low temperatures **9** is initially formed and that it is able to react with **8** to give **3** before decomposing to **11**. As the temperature is increased the decomposition of **9** to **11** increasingly competes with the reaction between **9** and **8**, and thus, increasing levels of **4** are observed as **8** reacts with **11** that is formed. The observed decrease in the ratio of **3**/**4** with the use of I_2 may reflect the greater instability of the

organohypoiodite intermediate versus the organohypobromite intermediate. The dramatic reversal in the diastereomeric ratio with the addition of silver triflate likely comes about because silver triflate facilitates the breakdown of **9** to **11** as a result of the formation of AgBr.

The bioxazolidinones **3** and **4** were found to exhibit different susceptibilities to hydrolysis. Dimer **3** proved to be extremely resistant to hydrolysis. Previously, we showed that alkylated products of Seebach's oxazolidinone can be successfully hydrolyzed with silica gel in a mixture of MeOH and H_2O.[14] This method proved ineffective for **3** both at room temperature and under reflux conditions. Instead, heating at reflux in 6 N HCl overnight was required to give **1**. On the other hand, **4** was found to be very susceptible to hydrolysis. It broke down to **2** in plain water, albeit at a slow rate, while it was quickly converted to **2** with silica gel in methanol and water.

We observed a difference in hydrolytic susceptibility between the two oxazolidinone rings of **4** when **4** was subjected to hydrolysis with 1 N HCl. Exposure of **4** to 1 N HCl for 20−30 s followed by neutralization with K_2CO_3 yielded a mixture of **2**, **4**, and **14**[15] in a ratio of 6:1:9 (Scheme 4). Exposure of the above mixture to 1 N HCl for an additional 1−2 min resulted in the complete hydrolysis of **14** to **2**. Mono-oxazolidinone **14** also was found to breakdown to **2** in D_2O within 10−15 min.

Scheme 4. Hydrolysis of **4** in 1 N HCl



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Acid stability of Cα(*R*)-alkyl/aryl derivatives of **5** is well documented, and it is attributed to steric hindrance from diaxial interactions in forming the tetrahedral transition state.[2] Such steric hindrance is not as problematical in the Cα(*S*)-oxazolidinone ring. Furthermore, once the Cα(*S*)-oxazolidinone ring is hydrolyzed the hydrolysis of the remaining Cα(*R*)-oxazolidinone ring is enhanced, possibly through intramolecular catalysis involving either the amino or carboxyl functionalities of the newly formed amino acid.

In summary, the synthesis of the novel (*R*,*R*)-α,α′-biproline (**1**) and *meso*-α,α′-biproline (**2**) via a temperature-dependent diastereoselective dimerization of the pivaloyl oxazolidin-5-one derivative of proline has been achieved. Since several other amino acids form oxazolidinones with pivalaldehyde, benzaldehyde, and other bulky nonenolizable aldehydes, this dehydrodimerization reaction with its temperature-dependent "flip" in diastereoselectivity may serve as a means of dimerizing amino acids with a predictable stereochemical outcome.

Acknowledgment. We thank Drs. Richard Hsung and Thomas Hoye of the Department of Chemistry for valuable input on the mechanistic studies. X-ray data collection time was provided by ChemMatCARS Sector 15, which is principally supported by the National Science Foundation/Department of Energy under Grant No. CHE0087817 and by the Illinois Board of Higher Education. The Advanced Photon Source is supported by the U.S. Department of Energy, Basic Energy Sciences, Office of Science, under Contract No. W-31-109-Eng-38. This work was supported by NIH Grant No. NS20036.

Supporting Information Available: Experimental procedures and spectral data for **1**−**4** and **6**; X-ray crystallographic data for **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) ESI-HRMS *m*/*z* 297.1805 $(M + H)^+$ $C_{15}H_{24}N_2O_4$ requires 297.1808. The presence of only one N−CH−O resonance in the ^1H NMR of **14** at 4.37 ppm indicated that it was the oxazolidinone ring with the Cα(*S*) configuration of **4** that had been hydrolyzed.