ORGANIC LETTERS

2007
Vol. 9, No. 5
833−836

Asymmetric Synthesis of *anti*- and *syn*-2,3-Diamino Esters Using Sulfinimines. Water and Concentration Effects

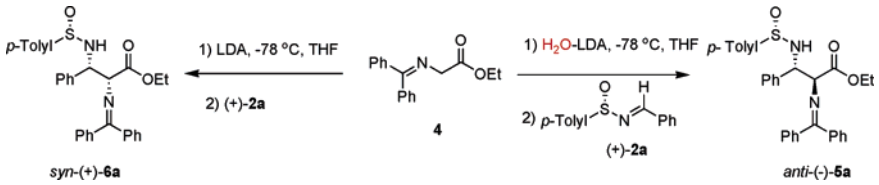
Franklin A. Davis,* Yanfeng Zhang, and Hui Qiu

Department of Chemistry, Temple University, Philadelphia, Pennsylvania 19122

fdavis@temple.edu

Received December 18, 2006

ABSTRACT



In the absence of water, an excess of the lithium enolate of *N*-(diphenylmethylene)glycine ethyl ester (4) adds to sulfinimines to give *syn*-2,3-diamino esters 6, and in the presence of water, this enolate gives the *anti*-2,3-diamino esters 5. These unusual results are interpreted in terms of those factors that inhibit the retro-Mannich fragmentation in the diamino esters.

The beneficial effects of stoichiometric and substoichiometric amounts of water on organic and organometallic reactions have occasionally appeared in the literature and were often the result of serendipitous observations by the investigators. In their excellent review on the subject, Ribe and Wipf grouped these effects into three categories: (1) water as a hydrolyzing agent leading to secondary products that serve as catalysts or promoters; (2) water as an internal quenching agent to drive chemical equilibria; and (3) water as a Lewis acid activator or co-activator.[1] We describe here an unusual example of how water influences the diamino ester anti/syn selectivity resulting from the addition of glycine enolates to sulfinimines (*N*-sulfinyl imines).

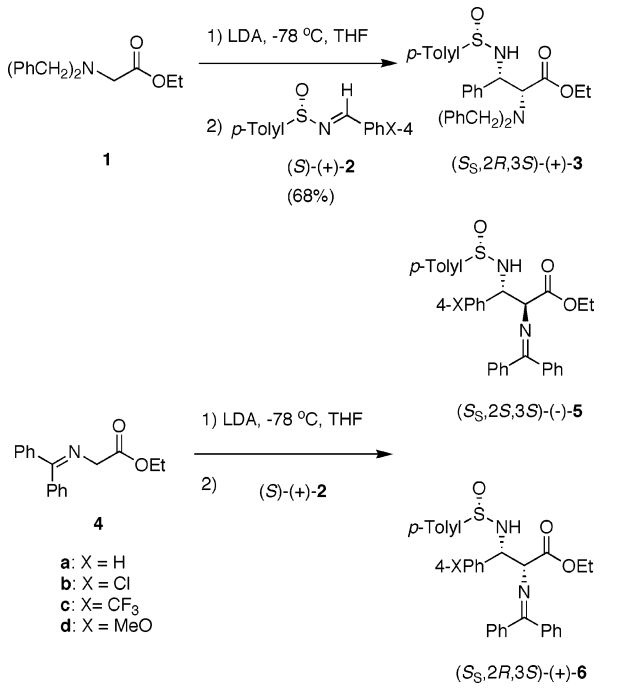
2,3-Diamino acids are key structural units of biologically active compounds and valuable synthetic intermediates.[2] In 2004, we disclosed a new one-pot method for the asymmetric synthesis of *syn*- and *anti*-2,3-diamino esters (+)-**3** and (−)-**5a**, involving addition of the prochiral lithium enolates of ethyl (dibenzylamino)acetate (**1**) and *N*-(diphenylmethylene)-glycine ethyl ester (**4**) to (*S*)-(+)-*N*-(benzylidene)-*p*-toluene-sulfinamide (**2a**) (Scheme 1).[3] The mechanistic rationale for the high syn/anti selectivity was the formation of the (*E*)- and (*Z*)-enolates by **1** and **4**, respectively. However, in subsequent studies aimed at exploring and expanding the scope of the methodology for the formation of the *anti*-2,3-diamino ester **5**, the reaction became unreliable with the anti/syn selectivity varying from 1:1 to better than 33:1. It soon became evident that the water content in the THF was an important factor determining the selectivity (Table 1).

In the absence of water, all four 2,3-diamino ester isomers were detected by ^{1}H NMR (Table 1, entry 1). However, as the ratio of water to LDA increased, there was dramatic improvement in the formation of the anti product reaching a maximum anti/syn ratio of 33:1 and an isolated yield of (−)-**5a** of 86% when the H_2O/LDA ratio was approximately 1:1 (Table 1, entry 5). As the H_2O/LDA ratio increased to 2:1, the ratio of **5a**/**6a** was maintained along with the yield (Table 1, entry 7). Even when the H_2O/LDA ratio was 4:1, the anti/syn ratio was still 33:1, but the yield had diminished (Table 1, entry 9). This is a general phenomenon also being observed for sulfinimines derived from aromatic aldehydes

(1) Ribe, S.; Wipf, P. *Chem. Commun.* **2001**, 299.
(2) Viso, A.; Fernandez de la Pradilla, R.; Garcia, A.; Flores, A. *Chem. Rev.* **2005**, *105*, 3167.
(3) Davis, F. A.; Deng, J. *Org. Lett.* **2004**, *6*, 2789.

10.1021/ol063058c CCC: $37.00
Published on Web 01/30/2007

Scheme 1



having electron-withdrawing groups **2b** (X = Cl) and **2c** (CF_3) (Table 1, entries 16 and 17) and an electron-donating group **2d** (MeO) (Table 1, entry 19). Replacement of water with methanol resulted in a 10:1 anti/syn ratio of **5a**/**6a**, but the anti/syn ratio for *tert*-butanol was 1:1.3 with the other amino ester isomers being detected (Table 1, entries 12 and 13).

Experimentally, the reaction was conducted by first cooling the THF−H_2O solution to −78 °C followed by addition of the appropriate amount of LDA. *N*-(Diphenylmethylene)-glycine ethyl ester (**4**), 1 equiv in water-free THF, cooled to −78 °C was then added via cannula to the LDA solution. After stirring at −78 °C for 1 h, 0.63 equiv of the sulfinimine (*S*)-(+)-**2** in water-free THF was introduced at −78 °C to the yellow enolate solution. The reaction mixture was quenched after 1.5 h at −78 °C by addition of aqueous NH_4-Cl solution. Diamino esters (−)-**5a**−**d** were isolated by chromatography.

The syn products (+)-**6a** and (+)-**6c** were prepared by reacting 5 equiv of the water-free preformed enolate solution of **4** with (+)-**2a** or (+)-**2c** at a concentration of 0.14 M. The syn products were isolated in 86% and 85% yields, respectively, following chromatography (Table 1, entries 15 and 18).[4] At a lower molar concentration of the enolate, the syn/anti ratio was much poorer (Table 1, entry 14).

The reaction of water with LDA is expected to result in LiOH and diisopropylamine. However, when the addition reaction was carried out with 1.6 equiv of LiOH instead of LDA, there was no reaction (Table, entry 10). Furthermore, if the −78 °C THF−LDA−H_2O solution is warmed to room temperature for 10 min and cooled back to −78 °C prior to addition of **4**, there is also no reaction (Table, entry 11). As the water content increases, the enolate was quenched, albeit slowly, resulting in reduced yields (Table 1, entries 7−9). Although these results imply that water and LDA could coexist at −78 °C, another possibility is that some LDA−hydroxide−diisopropylamine aggregate is the active base species.

In the solid state, X-ray crystal structures of lithium enolates show dimers, tetramers, and hexamers.[5] However, as pointed out by Collum and co-workers, the assignment of such structures in solution is difficult.[6] For these reasons, it is not possible to provide a structure for the H_2O−LDA or the enolate species at this time. However, Willard and MacEwan in a study of the cocrystallization of lithium or potassium *tert*-butoxide with a Li^+ or K^+ preformed enolate of 3,3-dimethyl-2-butanone in THF identified a unique aggregated species by X-ray diffraction analysis. This species contained an encapsulated hydroxide at the center of the aggregate.[7]

Table 1. Influence of Water on the Formation of *anti*-2,3-Diamino Ester (−)-**5**[a]

entry	**2**, (X)	H_2O[b]/LDA[c] ratio	anti/syn **5/6** ratio[d]	% yield[e]
1	**2a** (H)	0:1	1:1	[f]
2		0.5:1	1:1	[f]
3		0.7:1	16:1	80
4		0.98:1	25:1	86
5		1.09:1	33:1	86
6		1.35:1	33:1	86
7		2.0:1	33:1	85
8		3.1:1	33:1	78
9		3.9:1	33:1	60
10		LiOH[g]	no reaction	[h]
11		2.0:1[i]	no reaction	[h]
12		1.5:1 MeOH[j]	10:1	[f]
13		1.5:1 *t*-BuOH[j]	1:1.3	[f]
14		0:1[k]	1:5	[f]
15		0:1[k,l]	1:33	86
16	**2b** (Cl)	1.9:1	25:1	80
17	**2c** (CF_3)	2.0:1	25:1	87
18	**2c** (CF_3)	0:1[k,l]	1:25	85
19	**2d** (MeO)	1.9:1	25:1	85

[a] These results are the average of at least two experiments. [b]The water content was determined by Karl Fisher titration. [c]Enolate concentration was 0.02 M unless otherwise noted. [d]Determined by ^{1}H NMR on the crude reaction mixture. [e]Isolated yield of the major diastereoisomer. [f]In addition to **5** and **6**, the other two diamino ester isomers, (S_S,2*S*,3*R*) and (S_S,2*S*,3*R*) were detected in the ^{1}H NMR of the crude reaction mixture. These isomers could not be separated. [g]The equivalent of added LiOH was 1.6 compared to (+)-**2a**. [h]Starting materials were recovered. [i]The −78 °C water−THF−LDA solution was warmed to rt for 10 min and cooled back to −78 °C prior to addition of **4**. [j]Alcohol was used in the place of water. [k]5 equiv of the enolate compared to (+)-**2a** and a 2.0 M LDA solution was used. [l]Enolate concentration was 0.14 M.

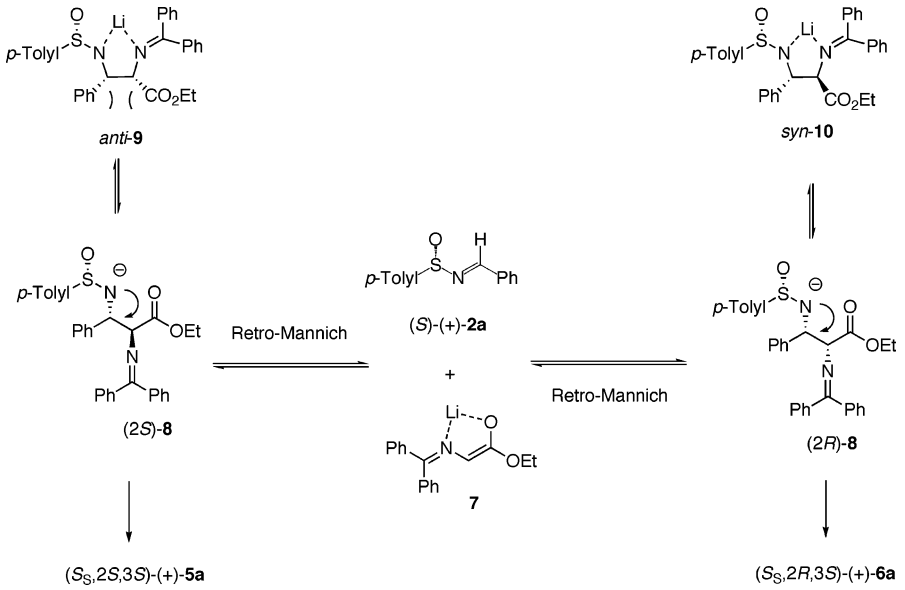
(4) The syn stereochemistry of (+)-**6a** was determined as previously described in ref 3.

(5) Seebach, D. *Angew. Chem., Int. Ed.* **1988**, *27*, 1624.

(6) McNeil, A. J.; Toombes, G. E. S.; Gruner, S. M.; Lobkovsky, E.; Collum, D. B.; Chandramouli, S. V.; Vanasse, B. J.; Ayers, T. A. *J. Am. Chem. Soc.* **2004**, *126*, 16559.

(7) Williard, P. G.; MacEwan, G. J. *J. Am. Chem. Soc.* **1989**, *111*, 7671.

Scheme 2



To determine whether the anti and syn products are formed under kinetic or thermodynamic control, they were subjected to treatment with LDA. Reaction of *anti*-**5a** at −78 °C with 1.1 equiv of LDA in water-free THF for 1.5 h resulted in isomerization and detection of all four amino ester isomers (Table 2, entry 1). There was no effect on the stereochemistry of *anti*-**5a** on reaction with H_2O/LDA (2.5:1), and it was recovered in 77% yield (Table 2, entry 2). Retro-Mannich products **2a** and **4** were also isolated in ca. 10% yield. Similar results were noted for *syn*-**6a** with these base combinations. With LDA, all four isomers were detected, but with H_2O−LDA, the syn isomer was recovered in 80% yield in addition to small amounts of the retro-Mannich products (Table 2, entries 5 and 6). Significantly, when *anti*-**5a** was treated with 5 equiv of the glycine enolate, *syn*-**6a** was isolated in 84% yield (Table 2, entry 4). However, similar reaction of this enolate with *syn*-**6a** had no effect (Table 2, entries 7 and 8).

Table 2. Reaction of *anti*-**5a** and *syn*-**6a** with Bases at −78 °C for 1.5 h[a]

entry	diamino ester	conditions (equiv of LDA to **5a** or **6a**)	products[b] [% yield][c]
1	*anti*-**5a**	LDA (1.1:1)	**5a/6a**/other isomers (10:9:6:8)[d] [80], **2a** [9], **4** [9]
2		H_2O−LDA[e] (1.1:1)	**5a** [77], **2a** [10], **4** [10]
3		LDA−**4**[f] (1.1:1)	**5a/6a**/other isomers (5:1:1:1)[d] [82]
4		LDA−**4**[f] (5:1)	**6a** [84]
5	*syn*-**6a**	LDA (1.1:1)	**5a/6a**/other isomers (10:10:5:8)[d] [86], **2a** [6], **4** [6]
6		H_2O−LDA[e] (1.1:1)	**6a** [80], **2a** [10], **4** [10]
7		LDA−**4**[f] (1.1:1)	**6a** [84]
8		LDA−**4**[f] (5:1)	**6a** [90]

[a] Water-free THF used unless otherwise noted. [b]Determined integration of the *p*-tolyl methyl on the crude reaction mixtures. [c]Isolated yield. [d]Isomers could not be separated. [e]Ratio of water to LDA (2.5:1). [f]Preformed enolate of **4** used.

To explain these novel results, we make the reasonable assumption that **7**, the *Z*-enolate of **4**, adds to sulfinimine (*S*)-(+)-**2a** to give the *anti*-2,3-diamino ester anion (2*S*)-**8**, which is the kinetically favored product (Scheme 2).[3,8,9] The retro-Mannich fragmentation of (2*S*)-**8** regenerates (+)-**2** and enolate **7** and can explain the formation of the various 2,3-diamino ester isomers in water-free THF and on reaction of (−)-**5a** and (+)-**6a** with 1.1 equiv of LDA (Tables 1 and 2). Retro-Mannich fragmentations of sulfinimine-derived sulfinamide products are usually not observed because the *N*-sulfinyl group stabilizes anions at nitrogen.[10,11] However, the combination of steric hindrance and the stability of enolate **7** favor this fragmentation. When the H_2O−LDA species is used to generate enolate **7**, it apparently stabilizes the anion

(8) The lithium enolate of **4** is generally considered to have the (*Z*)-geometry as a consequence of intramolecular chelation of the lithium ion with both the enolate oxygen and the pair of electrons on the sp^2 nitrogen atom. Numerous experimental results have been rationalized in terms of this chelated enolate structure. See: (a) McIntosh, J. M.; Leavitt, R. K.; Mishra, P.; Cassidy, K. C.; Drake, J. E.; Chadha, R. *J. Org. Chem.* **1988**, *53*, 1947 and references cited therein. (b) Alvarez-Ibara, C.; Csaky, A. G.; Colmenero, B.; Ouiroga, M. L. *J. Org. Chem.* **1997**, *62*, 2478. (c) Ezquerra, J.; Pedregal, C.; Merino, I.; Florez, J.; Barluenga, J.; Garcia-Granda, S.; Llorca, M.-A. *J. Org. Chem.* **1999**, *64*, 6554. (d) Ref 2.

(9) (a) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506. (b) O'Donnell, M. J. *Aldrichimica Acta* **2001**, *34*, 3.

(10) For leading references, see: (a) Zhou, P.; Chen, B. C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003. (b) Davis, F. A. *J. Org. Chem.* **2006**, *71*, 8993.

(11) For recent reviews on the chemistry of sulfinimines, see: (a) Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869. (b) Senanayake, C. H.; Krishnamurthy, D.; Lu, Z.-H.; Han, Z.; Gallou, I. *Aldrichimica Acta* **2005**, *38*, 93. (c) Ref 9. (d) Ellman, J. A.; Owens, T. D.; Tang. T. P. *Acc. Chem. Res.* **2002**, *35*, 984.

at nitrogen in (2*S*)-**8** preventing the retro-Mannich reaction and on workup gives *anti*-(−)-**5a**. We suggest that intramolecular chelation in *syn*-**10**, which is in equilibrium with *anti*-(2*S*)-**8**, is sterically favored over similar chelation in *anti*-**9** inhibiting the retro-Mannich fragmentation in the former. In the presence of enolate **7**, *anti*-(−)-**5a** gives the thermodynamically favored syn product (+)-**6a** on workup (Scheme 2).

In summary, manipulation of the water and enolate concentrations makes it possible to prepare either the *anti*- or *syn*-2,3-diamino esters (−)-**5** or (+)-**6**, respectively, from a common enolate precursor *N*-(diphenylmethylene)glycine ethyl ester (**4**) and a chiral sulfinimine. The *anti*-2,3-diamino ester (−)-**5** is favored under the LDA−H_2O conditions because the retro-Mannich fragmentation in inhibited. An excess of the enolate of **4** provides the thermodynamically favored *syn*-2,3-diamino ester (+)-**6** and is explained in terms of intramolecular chelation in *syn*-**10** that inhibits the retro-Mannich fragmentation.

Acknowledgment. We thank David Collum (Cornell University), Martin J. O'Donnell (Indiana Purdue University), David Dalton (Temple University), Scott Sieburth (Temple University), and Paul Williard (Brown University) for helpful discussions. Additionally, we thank J. Deng (Temple University) for preliminary studies and H. Zhang (Temple University) for aid with the Karl Fisher titrations. NIH-NIGMS (GM57870) supported this work.

Supporting Information Available: Experimental details for enolate preparation and addition. This material is available free of charge via the Internet at http://pubs.acs.org.

OL063058C