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

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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*-toluenesulfinamide (**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 ¹H 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 H₂O:LDA ratio was approximately 1:1 (Table 1, entry 5). As the H₂O:LDA ratio increased to 2:1, the ratio of **5a:6a** was maintained along with the yield (Table 1, entry 7). Even when the H₂O: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 having electron withdrawing groups **2b** (X = Cl) and **2c** (CF₃) (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-H₂O solution to -78 °C followed by addition of the appropriate amount of LDA. *N*-(Diphenylmethylene)glycine ethyl ester (**4**), one equivalent 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 equivalents 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 NH₄Cl solution. Diamino esters (-)-**5a-d** were isolated by chromatography.

The *syn* products (+)-**6a** and (+)-**6c** were prepared by reacting 5 equivalents of the water free preformed enolate solution of **4** with (+)-**2a** or (+)-**2c** at a concentration of 0.14 molar. The *syn* products were isolated in 86% and 85% yields, respectively, following chromatography (Table 1, entries 15 and 18).⁴ At 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-H₂O 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, 8, and 9). While these results imply that water and LDA could coexist at -78 °C, another possibility is that some LDA-hydroxide-isopropylamine 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 coworkers, the assignment of such structures in solution is difficult.⁶ For these reasons it is not possible to provide a structure for the H₂O-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

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 H₂O: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 H₂O-LDA the *syn* isomer was recovered in 80% 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).

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 sulfonamide 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 H₂O-LDA species is used to generate enolate **7** it apparently stabilizes the anion at nitrogen in (2*S*)-**8** preventing the retro-Mannich reaction and on work up 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 work-up (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-H₂O conditions because the retro-Mannich fragmentation is 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

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. [PubMed: 16092828]
3. Davis FA, Deng J. Org Lett 2004;6:2789. [PubMed: 15281770]
4. The *syn* stereochemistry of (+)-**6a** was determined as previously described in reference ³.
5. Seebach D. Angew Chem Int Ed 1988;27:1624.
6. McNeil AJ, Toombes GES, Gruner SM, Lobkovsky E, Collum DB, Chandramouli SV, Vanasse BJ, Ayers TA. J Am Chem Soc 2004;126:16559. [PubMed: 15600361]
7. Williard PG, MacEwan GJ. J Am Chem Soc 1989;111:7671.
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 sp² nitrogen atom. Numerous experimental results have been rationalized in terms of this chelated enolate structure. See (a) McIntosh JM, Leavitt RK, Mishra P, Cassidy KC, Drake JE, Chadha R. J Org Chem 1988;53:1947 and references cited there in (b) Alvarez-Ibara C, Csaky AG, Colmenero B, Ouirouga ML. J Org Chem 1997;62:2478. [PubMed: 11671585] (c) Ezquerra J, Pedregal C, Merino I, Florez J, Barluenga J, Garcia-Granda S, Llorca MA. J Org Chem 1999;64:6554. [PubMed: 11674657] (d) Ref. 2.
9. (a) O'Donnell MJ. Acc Chem Res 2004;37:506. [PubMed: 15311949] (b) O'Donnell MJ. Aldrichimica Acta 2001;34:3.
10. For leading references see (a) Zhou P, Chen BC, Davis FA. Tetrahedron 2004;60:8003. (b) Davis FA. J Org Chem 2006;71:8993. [PubMed: 17109522]

11. For recent reviews on the chemistry of sulfinimines see: (a) Morton D, Stockman RA. *Tetrahedron* 2006;62:8869. (b) Senanayake CH, Krishnamurthy D, Lu ZH, Han Z, Gallou I. *Aldrichimica Acta* 2005;38:93.. (c) Ref. 9. (d) Ellman JA, Owens TD, Tang TP. *Acc Chem Res* 2002;35:984. [PubMed: 12437323]

Scheme 1.

Scheme 2.

Table 1The influence of water on the formation of *anti*-2,3-diamino ester (–)-**5**.^a

entry	2, (X) H ₂ O ^b LDAC ratio	anti/syn ratio ^d	5:6 % yield ^e	
1	2a (H)	0:1	1:1	<i>f</i>
2		0.5:1	1:1	<i>f</i>
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	<i>h</i>
11	2.0:1 ⁱ	no reaction	<i>h</i>	
12	1.5:1 MeOH ^j	10:1	<i>f</i>	
13	1.5:1 <i>t</i> -BuOH ^j	1:1.3	<i>f</i>	
14	0:1 ^k	1:5	<i>f</i>	
15	0:1, ^{kl}	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, ^{kl}	1:25	85
19	2d (MeO)	1.9:1	25:1	85

^aThese results are the average of at least two experiments.^bThe water content was determined by Karl Fisher titration.^cEnolate concentration was 0.02 molar unless otherwise noted.^dDetermined by ¹H NMR on the crude reaction mixture.^eIsolated yield of the major diastereoisomer.^fIn 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 ¹H NMR of the crude reaction mixture. These isomers could not be separated.^gEquiv of added LiOH was 1.6 compared to (+)-**2a**.^hStarting materials were recovered.ⁱThe –78 °C water-THF-LDA solution was warmed to rt for 10 min and cooled back to –78 °C prior to addition of **4**.^jAlcohol was used in the place of water.^kFive equiv of the enolate compared to (+)-**2a** and a 2.0 molar LDA solution was used.^lEnolate concentration was 0.14 molar.

Table 2Reaction of *anti*-**5a** and *syn*-**6a** with bases at -78°C for 1.5 h.^a

entry	diaminoester	conditions(equiv of LDA to 5a or 6a)	products [% yield] ^{bc}
1	<i>anti</i> - 5a	LDA (1.1:1)	5a:6a :other isomers(10:9:6:8) ^d [80], 2a [9], 4 [9]
2		H ₂ O-LDA ^e (1.1:1)	5a [77], 2a [10], 4 [10]
3		LDA- 4f (1.1:1)	5a:6a :other isomers (5:1:1:1) ^d [82]
4	<i>syn</i> - 6a	LDA- 4f (5:1)	6a [84]
5		LDA (1.1:1)	5a:6a :other isomers (10:10:5:8) ^d [86] 2a [6], 4 [6]
6		H ₂ O-LDA ^e (1.1:1)	6a [80], 2a [10], 4 [10]
7		LDA- 4f (1.1:1),	6a [84]
8		LDA- 4f (5:1)	6a [90]

^aWater free THF used unless otherwise noted.^bDetermined integration the *p*-tolyl methyl on the crude reaction mixtures.^cIsolated yield.^dIsomers could not be separated.^eRatio of water to LDA (2.5:1).^fPreformed enolate of **4** used.