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Fine-Tuned Aminal Cleavage: A Concise Route to Differentially Protected Enantiopure *syn*-α,β-Diamino Esters

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A survey of routes for aminal cleavage of *N*-sulfinylimidazolidines has been carried out, and selective conditions to cleave the aminal moiety while preserving the sulfinamide group unaltered have been found. Thus, the treatment of enantiopure *N*-sulfinylimidazolidines with aqueous H_3PO_4 in THF affords enantiopure *N*-sulfinyldiamino esters in excellent yields, while the presence of MeOH as cosolvent allows for the simultaneous removal of the sulfinamide group and aminal cleavage. The behavior of these substrates in a variety of chemical transformations has been explored.

Introduction

Optically active α,β-diamino acids are components of natural products with varied biological activities (antifungal, antibiotic, etc.).[1] This has attracted the attention of many groups, and there are several routes of varying length and complexity reported in the literature to prepare these compounds,[2] particularly the *anti* isomers. In contrast, a short, simple, and general route to the *syn* diastereomers remains elusive,[3] particularly when the molecule is disconnected retrosynthetically between C_α and C_β.[4] In this paper we describe a general, concise, and high-yielding route to *syn*-*N*-sulfinyl-α,β-diamino esters from readily available *N*-sulfinyl-1,3-imidazolidines.

During the past few years we have been engaged in the development of efficient routes to enantiopure *N*-sulfinylimidazolidines **D** from readily available precursors, such as sulfinimines **A** and lithiated imino esters **B** (Scheme 1).[5] Our initial efforts to carry out the

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(1) (a) For a comprehensive summary of literature related to the isolation and biological activity of α,β-diamino acids, see: Luo, Y.; Blaskovich, M. A.; Lajoie, G. A. *J. Org. Chem.* **1999**, *64*, 6106−6111. (b) Lucet, D.; Gall, T. L.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580−2627. (c) Westermann, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 151−153.

(2) For a summary of existing methodology, see ref 1. For recent references, see: (a) Han, H.; Yoon, J.; Janda, K. D. *J. Org. Chem.* **1998**, *63*, 2045−2048. (b) Kuwano, R.; Okuda, S.; Ito, Y. *Tetrahedron: Asymmetry* **1998**, *9*, 2773−2775. (c) Merino, P.; Lanaspa, A.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1998**, *9*, 629−646. (d) Knudsen, K. R.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 5843−5844. (e) Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2992−2995. (f) Zhou, X.-T.; Lin, Y.-R.; Dai, L.-X. *Tetrahedron: Asymmetry* **1999**, *10*, 855−862. (g) Hennings, D. D.; Williams, R. M. *Synthesis* **2000**, 1310−1314. (h) Chuang, T.-H.; Sharpless, K. B. *Org. Lett.* **2000**, *2*, 3555−3557. See also previous papers by this group. (i) Lee, S. H.; Yoon, J.; Chung, S.-H.; Lee, Y.-S. *Tetrahedron* **2001**, *57*, 2139−2145. (j) Robinson, A. J.; Stanislawski, P.; Mulholland, D.; He, L.; Li, H.-Y. *J. Org. Chem.* **2001**, *66*, 4148−4152. (k) Pei, W.; Timmons, C.; Xu, X.; Wei, H.-X.; Li, G. *Org. Biomol. Chem.* **2003**, *1*, 2919−2921. (l) Ambroise, L.; Dumez, E.; Szeki, A.; Jackson, R. F. W. *Synthesis* **2002**, 2296−2308. (m) Brown, D.; Brown, G. A.; Andrews, M.; Large, J. M.; Urban, D.; Butts, C. P.; Hales, N. J.; Gallagher, T. *J. Chem Soc., Perkin Trans. 1* **2002**, 2014−2021. (n) Chhabra, S. R.; Mahajan, A.; Chan, W. C. *J. Org. Chem.* **2002**, *67*, 4017−4029.

(3) Enantiopure *syn*-α,β-diamino acid derivatives have been prepared by a number of routes: (a) From an L-allothreonine derivative by Mitsunobu inversion with HN_3: Schmidt, U.; Mundinger, K.; Riedl, B.; Haas, G.; Lau, R. *Synthesis* **1992**, 1201−1202. For a related approach, see: Nakamura, Y.; Hirai, M.; Tamotsu, K.; Yonezawa, Y.; Shin, C. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1369−1377. (b) Cleavage of *N*-carboxyanhydrides derived from β-lactams: Palomo, C.; Aizpurua, J. M.; Cabré, F.; Cuevas, C.; Munt, S.; Odriozola, J. M. *Tetrahedron Lett.* **1994**, *35*, 2725−2728. See also: Palomo, C.; Aizpurua, J. M.; Gamboa, I.; Carreaux, F.; Cuevas, C.; Maneiro, E.; Ontoria, J. M. *J. Org. Chem.* **1994**, *59*, 3123−3130 See also: Palomo, C.; Aizpurua, J. M.; Galarza, R.; Mielgo, A. *Chem. Commun.* **1996**, 633−634. (c) From a hydroxyoxazolidinone obtained via Sharpless asymmetric epoxidation: Rossi, E. T.; Yoon, R.; Rosenberg, L.; Meinwald, J. *Tetrahedron* **1996**, *52*, 10279−10286. (d) From enantiopure β-amino esters by α-hydroxylation and inversion via mesylate: Bunnage, M. E.; Burke, A. J.; Davies, S. G.; Millican, N. L.; Nicholson, R. L.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2003**, *1*, 3708−3715. (e) From regioselective ring opening of an aziridine obtained via Sharpless asymmetric aminohydroxylation: see ref 2a. (f) From (*E*)- α,β-bis(*N*-acylamino)acrylates by enantioselective hydrogenation: see ref 2b. (g) From a protected L-serine-derived nitrone by addition of Grignard reagents: see ref 2c. (h) From a β-amino-α-hydroxy ester, obtained by aminohydroxylation, by hydroxyl inversion followed by Mitsunobu with HN_3: see ref 2i. (i) From enamides by enantioselective hydrogenation: see ref 2j. (j) From 1,3-dihydro-2-imidazolone by a rather elaborate sequence including resolution: Seo, R.; Ishizuka, T.; Abdel-Aziz, A. A.-M.; Kunieda, T. *Tetrahedron Lett.* **2001**, *42*, 6353−6355. (k) Direct diamination of olefins: Muñiz, K.; Nieger, M. *Synlett* **2003**, 211−214.

(4) (a) For a recent report on the asymmetric Mannich reaction of glycine imino esters, see: Bernardi, L.; Gothelf, A. S.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 2583−2591. (b) For a noteworthy exception, see: Alker, D.; Harwood: L. M.; Williams, C. E. *Tetrahedron Lett.* **1998**, *39*, 475−478. (c) See also a report describing the oxidative dimerization of lithiated glycinates: Álvarez-Ibarra, C.; Csákÿ, A. G.; Colmenero, B.; Quiroga, M. L. *J. Org. Chem.* **1997**, *62*, 2478−2482. (d) Hayashi, T.; Kishi, E.; Soloshonok, V. A.; Vozumi, Y. *Tetrahedron Lett.* **1996**, *37*, 4969−4972. (e) Soloshonok, V. A.; Avilov, D. V.; Kukhar, V. P.; Van Meervelt, L.; Mischenko, N. *Tetrahedron Lett.* **1997**, *38*, 4671−4674. (f) DeMong, D. E.; Williams, R. H. *Tetrahedron Lett.* **2001**, *42*, 3529−3532.

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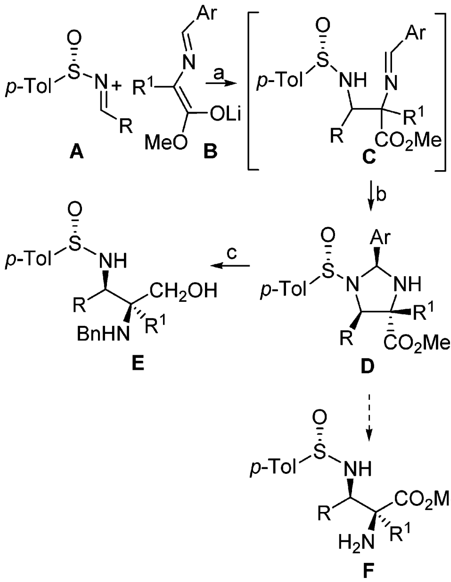
SCHEME 1. Synthesis of α,β-Diamino Esters from Enantiopure Sulfinimines[a]



[a] Reagents and conditions: (a) $BF_3{\cdot}Et_2O$, −78 °C, THF. (b) $CHCl_3$, 2−4 days, rt (60−93%). (c) $LiAlH_4$, Et_2O, 0 °C to rt, 2−7 h (65−85%).

seemingly straightforward hydrolysis to produce *N*-sulfinyldiamino esters of general structure **F** were fruitless, and a retro-Mannich fragmentation of the molecule was observed instead (R = Ph, R^1 = Bn) to give methyl sulfinate and phenylalanine methyl ester.[5b] Carboxylate reduction in **D** allowed for a smooth solvolysis, and totally unprotected diamino alcohols were obtained in good yields. Conditions to access partially protected *N*-sulfinyl-*N′*-benzyldiamino alcohols **E** were later developed,[5c] and the transformation of these intermediates to a variety of piperazines was also described.[5e] While the transformation of these *N*-sulfinyl-*N′*-benzyldiamino alcohols **E** to differentially protected *syn*-diamino esters (e.g., **F**) seemed feasible by standard oxidation procedures, we sought a more direct route to these targets from imidazolidines **D**.

Results and Discussion

At the inception of this work we planned different strategies for the synthesis of diamino esters avoiding the direct acidic cleavage of imidazolidines. The first approach considered consisted of two consecutive steps, oxidation at sulfur followed by hydrolysis, and it was based on the smooth solvolysis of *N*-tosylimidazolidines **1a** and **1b**[5b] to afford racemic *N*-tosyldiamino esters **2a** and **2b** (Table 1, entries 1 and 2). This behavior indicated that the oxidation state at sulfur was a crucial requirement to prevent the undesired fragmentation found before. However, when **1c** was submitted to oxidative conditions, the expected *N*-tosylimidazolidines were not formed.[6] The different reactivity observed for this *N*-sulfinylimidazolidine derived from glycine (**1c**, R^1 = H) could be attributed to the less crowded arrangement at N-3 compared with that of the *N*-sulfinylimidazolidine precursor of **1a** and **1b** (R^1 = Bn).[7] The above results prompted us to explore a different strategy based on the oxidative cleavage of the aminal moiety of **D** when the phenyl group (Ar) was replaced with a PMP group at the imidazolidine (**1d**, R = Ph, R^1 = H) by reaction of the sulfinimine **A** (R = Ph) with the glycine imino ester **B** (Ar = PMP). Unfortunately, under treatment with CAN, low yield of mixtures of *N*-sulfonyl- and *N*-sulfinyldiamino esters **3a** were obtained. Continuing with the search for an efficient method for breaking the aminal fragment, we also examined the hydrogenolysis[8] on substrates where R is not an aromatic group, although a low conversion along with complex mixtures of products was obtained with these methods.[9,10]

After all this fruitless experimentation, we decided to reexamine the procedure that originally led to fragmentation in some cases, namely, TFA in MeOH, under controlled conditions, for glycine-derived imidazolidines **1** (R^1 = H), obtained by our Lewis-acid-assisted protocol[5b] (Table 1). In this manner, unprotected diamino esters **4b** and **4c** were obtained in fair yields along with 11% of *N*-sulfinyldiamino ester **3b** in the first case (entries 3 and 9). Comparable yields of **4b**−**d** were obtained using ethereal 2 N HCl although under these conditions products of partial hydrolysis were not found (entries 4, 10, and 12). These results were encouraging since it appeared that the undesired fragmentation observed before was not a general outcome of the process, but instead it was limited to a specific substitution pattern derived from the uncatalyzed cycloaddition between aromatic sulfinimines and azomethine ylides.

The isolation of a small amount of *N*-sulfinyldiamino ester **3b** under TFA/MeOH conditions (entry 3) prompted us to devote considerable effort to fine-tuning these solvolytic conditions with mixed results. Selective aminal cleavage of **1f** was produced at low temperature (−78 to −20 °C) but with a low conversion (entry 5). Subsequently, acids weaker than TFA[11] were used in an effort to achieve selective solvolysis. Thus, the reaction of **1f** with Cl_2CHCO_2H afforded a mixture of **3b** and **4b** along

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(5) (a) Viso, A.; Fernández de la Pradilla, R.; Guerrero-Strachan, C.; Alonso, M.; Martínez-Ripoll, M.; André, I. *J. Org. Chem.* **1997**, *62*, 2316−2317. (b) Viso, A.; Fernández de la Pradilla, R.; García, A.; Guerrero-Strachan, C.; Alonso, M.; Tortosa, M.; Flores, A.; Martínez-Ripoll, M.; Fonseca, I.; André, I.; Rodríguez, A. *Chem.—Eur. J.* **2003**, *9*, 2867−2876. (c) Viso, A.; Fernández de la Pradilla, R.; García, A.; Alonso, M.; Guerrero-Strachan, C.; Fonseca, I. *Synlett* **1999**, 1543−1545. (d) Viso, A.; Fernández de la Pradilla, R. *Recent Res. Dev. Org. Chem.* **2000**, *4*, 327−334. (e) Viso, A.; Fernández de la Pradilla, R.; López-Rodríguez, M. L.; García, A.; Tortosa, M. *Synlett* **2002**, 755−758.

(6) A detailed account of these experiments is included in the Supporting Information.

(7) On the other hand, addition of imino ester **B** (R^1 = H, Ar = Ph) to *p*-toluensulfonimine did not render *N*-tosylimidazolidines related to **1a** and **1b** but a mixture of racemic *N*-sulfonyldiamino esters with poor selectivity (*syn*:*anti* = 70:30); see ref 5b.

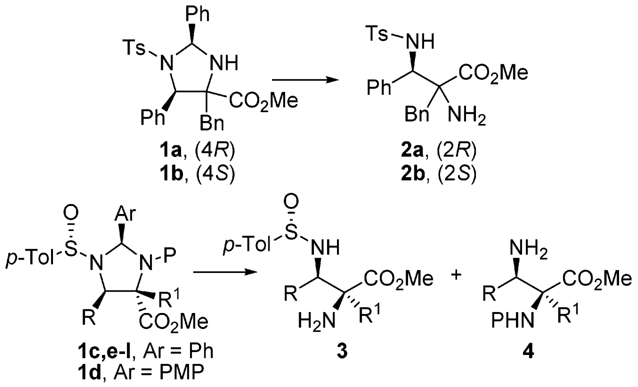
(8) Several hydrogenolysis conditions were examined [$Pd(OH)_2$–H_2, Pd(C)−H_2]; see: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999; Chapter 7, pp 579−580.

(9) We also reconsidered the use of acidic conditions to hydrolyze imine **C**; however, addition of different acids to the reaction mixture gave erratic mixtures of imidazolidines and diamino esters probably due to uncontrolled cyclization of the latter with benzaldehyde during the workup process.

(10) For full details of all these experiments, see the Supporting Information.

(11) For comparative purposes the standard values of pK_a (25 °C, H_2O) have been considered: TFA, 0.23; Cl_2CHCO_2H, 1.48; H_3PO_4, 2.12; HOAc, 4.75. For the use of H_3PO_4 in a related context see: Moreno-Vargas, A. J.; Vogel, P. *Tetrahedron: Asymmetry* **2003**, *14*, 3173−3176.

TABLE 1. Synthesis of Enantiopure Diamino Esters and *N*-sulfinyldiamino Esters under Acidic Conditions



entry	compd	R	R^1	P	method^a	**2** (yield, %)^b	**3** (yield, %)^b	**4** (yield, %)^b
1	**1a**				TFA/MeOH	**2a** (70)		
2	**1b**				TFA/MeOH	**2b** (86)		
3	**1f**	Ph(CH$_2$)$_2$	H	H	TFA/MeOH		**3b** (11)	**4b** (61)
4	**1f**	Ph(CH$_2$)$_2$	H	H	HCl/Et$_2$O			**4b** (59)
5^c	**1f**	Ph(CH$_2$)$_2$	H	H	TFA/MeOH		**3b** (50)	
6^d	**1f**	Ph(CH$_2$)$_2$	H	H	Cl$_2$CHCO$_2$H/MeOH		**3b** (20)	**4b** (30)
7	**1f**	Ph(CH$_2$)$_2$	H	H	HOAc/MeOH		see the text	see the text
8	**1f**	Ph(CH$_2$)$_2$	H	H	H$_3$PO$_4$/THF		**3b** (81)	
9	**1g**	*p*-FC$_6$H$_4$	H	H	TFA/MeOH			**4c** (61)
10	**1g**	*p*-FC$_6$H$_4$	H	H	HCl/Et$_2$O			**4c** (60)
11	**1g**	*p*-FC$_6$H$_4$	H	H	H$_3$PO$_4$/THF		**3c** (76)	
12	**1e**	*i*-Pr	H	H	HCl/Et$_2$O			**4d** (60)
13	**1e**	*i*-Pr	H	H	H$_3$PO$_4$/THF		**3d** (88)	
14	**1c**	Ph	H	H	H$_3$PO$_4$/THF		**3a** (73)	**4a** (20)
15	**1c**	Ph	H	H	H$_3$PO$_4$/MeOH			**4a** (59)
16	**1h**	Ph(CH$_2$)$_2$	H	Cbz	H$_3$PO$_4$/MeOH			**4e** (65)
17	**1i**	1-Naph	H	H	H$_3$PO$_4$/THF		**3e** (75)	
18	**1j**	Me	H	H	H$_3$PO$_4$/THF		**3f** (81)	
19	**1k**	(CH$_2$)$_4$OTs	H	H	H$_3$PO$_4$/THF		**3g** (68)	
20^e	**1l**	*i*-Pr	Me	H	H$_3$PO$_4$/THF		**3h** (84)	

[a] Reagents and conditions: (a) TFA, MeOH, rt, 4−14 h. (b) 2 N HCl, Et$_2$O, rt, 2 h. (c) 2 equiv of Cl$_2$CHCO$_2$H, MeOH, 0 °C to rt, 20 h. (d) 8 equiv of HOAc, MeOH, rt to reflux, 24 h. (e) H$_3$PO$_4$, THF/H$_2$O (7:3), 0 °C to rt, 1−5 h. (f) H$_3$PO$_4$, THF/MeOH/H$_2$O (6:3:1), 0 °C, 90 min. [b] Yields of isolated pure compounds. [c] Reaction performed from −78 to −20 °C; 30% of the starting material was also recovered. [d] 50% of the starting material was recovered. [e] Starting material also contained a 35% yield of **1l′** (epimer at C-2).

with a high amount of recovered starting material (50%), and HOAc led to recovered starting material or to its decomposition under reflux (entries 6 and 7). After considerable experimentation focused on the search for optimal conditions for the selective hydrolysis process, we found that treatment of imidazolidine **1c** with aqueous 0.5 M H$_3$PO$_4$ in THF provided a good isolated yield of *N*-sulfinyldiamino ester **3a** (entry 14) as a single isomer that was fully characterized. The generality of this protocol was then examined, and to our delight, good to excellent yields of enantiopure *N*-sulfinyldiamino esters were obtained for R = aryl (entries 11, 14, and 17) and R = alkyl (entries 8, 13, 18, and 19). The straightforward, high-yielding, and expedient preparation of enantiopure **3h** (entry 20), bearing an additional substituent at C$_\alpha$ (R^1 = Me), is particularly noteworthy since it illustrates that the undesired fragmentation observed before is not always related to additional substitution at C$_\alpha$, and also, to our knowledge, it is the first known example of a stereoselective preparation of an α,β-diamino ester bearing additional substituents at both C$_\alpha$ and C$_\beta$.[12]

Additionally, reaction of **1c** with H$_3$PO$_4$ in MeOH smoothly provided the simultaneous removal of the aminal and sulfinyl moieties to give a fair yield of **4a**, and similarly, when *N*-benzyloxycarbonylimidazolidine **1h** was submmited to the above conditions, *N*-benzyloxycarbonyldiamino ester **4e** was produced selectively (entries 15 and 16). Finally, as expected, removal of the sulfinyl group of *N*-sulfinyldiamino esters **3b** and **3d** was achieved by using either TFA/MeOH or H$_3$PO$_4$/MeOH.

These results point to phosphoric acid as the reagent of choice for these transformations probably due to a combination of a suitable acidity and a low nucleophilicity of the phosphate counterion. Indeed, H$_3$PO$_4$ (in THF/H$_2$O) protonates *N*-sulfinylimidazolidines **1**, but attack at the sulfinamide group does not take place, and this produces the selective cleavage of the aminal moiety. However, the presence of a nucleophilic solvent (methanol) or counterion (HCl) in the reaction mixture leads to the simultaneous removal of the sulfinyl group, even for aminals such as **1h** with low basicity at N-3 due to the presence of a carbamate functionality (Figure 1). Additionally, the role of methanol is supported by the formation of substantial amounts of methyl *p*-toluenesulfinate in these processes.

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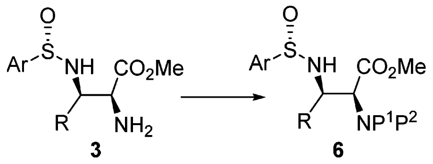
(12) For an isolated example of α-substituted β-unsubstituted derivatives, see: Hartwig, W.; Mittendorf, J. *Synthesis* **1991**, 939−941.

TABLE 2. Reactivity of *N*-Sulfinyldiamino Esters



entry	substrate	conditions	6	yield, %
1	**3c**	BnBr/K_2CO_3/rt	**6a** (R = *p*-FPh, P^1 = H, P^2 = Bn)	93
2	**3d**	BnBr/K_2CO_3/rt	**6b** (R = *i*-Pr, P^1 = H, P^2 = Bn)	79
3	**3c**	BnBr/K_2CO_3/rt to Δ	**6c** (R = *p*-FPh, P^1 = P^2 = Bn)	66[a]
4	**3c**	$Br(CH_2)_4Br$/$NaHCO_3$/Δ	**6d** [R = *p*-FPh, P^1 = P^2 = $(CH_2)_4$]	65[b]
5	**3c**	HN=C(Ph)$_2$/rt	**6e** (R = *p*-FPh, P^1 = P^2 = CPh_2)	78
6	**3d**	$ClCH_2COCl$/$NaHCO_3$/EtOAc/0 °C to rt	**6f** (R = *i*-Pr, P^1 = H, P^2 = $COCH_2Cl$)	90
7	**3d**	(*S*)-(+)-MPA/DCC/DMAP/rt	**6g** [R = *i*-Pr, P^1 = H, P^2 = (*S*)COCH(OMe)Ph]	65

[a] CH_3CN was used as solvent. A 9% yield of **6a** was also isolated. [b] Toluene was used as solvent.

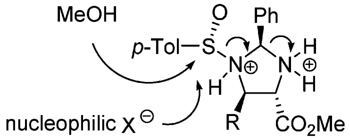
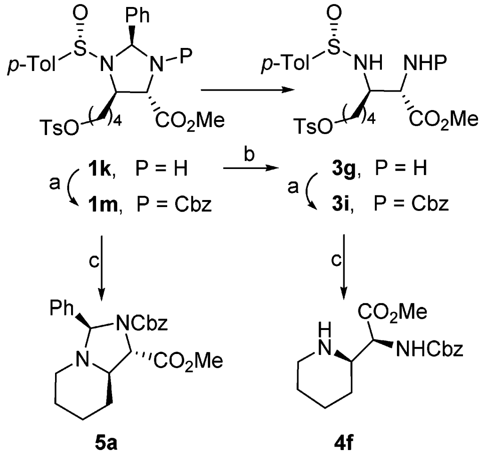


FIGURE 1. Aminal cleavage of *N*-sulfinylimidazolidines under acidic conditions.

SCHEME 2. Synthesis of Methyl 2-Piperidinyl Glycinate from *N*-Sulfinylimidazolidines[a]



[a] Reagents and conditions: (a) CbzCl, 1 N NaOH, CH_2Cl_2, 0 °C to rt. (b) H_3PO_4, THF, 0 °C to rt. (c) H_3PO_4, MeOH, rt.

On the other hand, the application of this novel reactivity of H_3PO_4 to *N*-sulfinylimidazolidine **1k** provides a new route for the synthesis of enantiopure 2-piperidinyl glycinates (Scheme 2).[13] The first attempts to remove the sulfinamide and aminal moieties of **1k** using H_3PO_4/MeOH led to complex reaction mixtures; however, treatment of *N*-benzyloxycarbonylimidazolidine **1m** with H_3PO_4 in MeOH gave the bicyclic imidazolidine **5a** as the major product in good yield, and although small amounts of the piperidinyl glycinate **4f** were occasionally obtained upon standard handling of the samples, we did not succeed in finding conditions to carry out complete removal of this unusually stable bicyclic aminal.[14] However, an efficient synthesis of **4f** was finally carried out from *N*-benzyloxycarbonyl-*N′*-sulfinyldiamino ester **3i** by desulfinylation (H_3PO_4/MeOH) followed by cyclization upon basic aqueous workup.[15]

To broaden the scope of the methodology, we chose to explore the behavior of our *N*-sulfinyldiamino esters in a variety of procedures commonly used in α-amino acid chemistry. Table 2 shows selected examples of these transformations.[16] All cases examined allowed for smooth monobenzylation under standard conditions[17] to produce *N*-sulfinyl-*N′*-benzyldiamino esters **6a**,**b** (entries 1 and 2). In fact, surprisingly, dibenzylation was achieved only upon using an excess of reagents and refluxing the reaction mixtures to produce *N*-sulfinyl-*N′*-dibenzyldiamino ester **6c** in fair yields (entry 3), often accompanied by small amounts of the corresponding monobenzylated derivatives.[18] Finally, **6c** was desulfinylated under standard conditions to produce the corresponding di-*N*-benzyldiamino ester **7** in fair yield. On the other hand, intramolecular dialkylation of **3c** with 1,4-dibromobutane efficiently afforded pyrrolidine diamino ester **6d** (entry 4).

To gain insight into the reactivity of these substrates, we carried out the reaction of diamino ester **3d** with benzophenone imine, giving rise to imine **6e** in good yield. Subsequently, amide formation was also explored with excellent results, either under biphasic conditions with $ClCH_2COCl$ to produce **6f**, a potential precursor to monoketopiperazines, or with DCC/DMAP using (*S*)-(+)-methoxyphenylacetic acid to produce **6g**[19] (entries 6 and 7).

In conclusion, different routes to transform readily available *N*-sulfinylimidazolidines **1** into differentially *N*-protected diamino esters have been explored. Selective

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(13) (a) Herdeis, C.; Nagel, U. *Heterocycles* **1983**, *20*, 2163–62167. (b) Chung, H.; Kim. H.; Chung, K. *Heterocycles* **1999**, *51*, 2983–2989.

(14) Under typical solvolytic conditions we have mainly recovered starting material **5a**: 2 N HCl, Et_2O, rt to reflux or TFA, MeOH, rt to reflux.

(15) For a related procedure for the synthesis of piperidines from *p*-tolylsulfinimines, see: Davis, F. A.; Prasad, K. R.; Nolt, M. B.; Wu, Y. *Org. Lett.* **2003**, *5*, 925–927.

(16) For more examples of mono- and dibenzylation (**6h**, R = Me, P^1 = H, P^2 = Bn; **6i**, R = *i*-Pr, P^1 = P^2 = Bn; **6j**, R = Me, P^1 = P^2 = Bn), see the Supporting Information.

(17) For a recent reference, see: Hulme, A. N.; Montgomery, C. H.; Henderson, D. K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1837–1841. See also: Reetz, M. T.; Drewes, M. W.; Schwickardi, R. *Org. Synth.* **1998**, *76*, 110–122.

(18) A small amount (<10%) of a tribenzylated derivative, **6c′**, was obtained upon dibenzylation of **3c**. For full details see the Supporting Information.

acidic cleavage of the aminal moiety using H_3PO_4 allowed for a very concise route to these products (three linear steps, four total steps). The methodology appears to be compatible with additional substitution at C_α, and complete removal of the aminal and the sulfinyl groups was also produced using methanol as cosolvent even when a Cbz moiety is attached to N-3. In addition, the *N*-sulfinyldiamino esters are amenable to a number of subsequent selective transformations at the free amino functionality. Applications of this methodology are being pursued in our laboratories.

Experimental Section

General Procedure for Preparation of *N*-Sulfinyldiamino Esters by Selective Solvolytic Cleavage of the Aminal Moiety of *N*-Sulfinylimidazolidines. To a solution of *N*-sulfinylimidazolidine **1**[5b] in a mixture of THF and H_2O (7:3, 7 mL/mmol of H_3PO_4) was added 3−6 equiv of H_3PO_4 (85% aqueous solution). The mixture was stirred from 0 °C to rt until disappearance of **1** (TLC of aliquots neutralized with solid $NaHCO_3$). The mixture was diluted with Et_2O (5 mL/mmol), and the aqueous layer was basified with solid K_2CO_3 to pH 10−11 and extracted with $CHCl_3$ (3 × 8 mL/mmol). The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum to afford fairly pure diamino esters **3** that were further purified by column chromatography on silica gel.

(+)-Methyl [(2*S*,3*R*,S_S)-2-Amino-3-phenyl-3-(*p*-tolylsulfinylamino)]propanoate, 3a. From **1c** (105 mg, 0.250 mmol), 4 equiv of H_3PO_4, and 2 additional equiv after 1 h and 15 min, according to the general procedure (3 h and 30 min), was obtained an 80:20 mixture of diamino esters **3a** and **4a**. Purification by chromatography (0−5% MeOH−CH_2Cl_2) gave **3a** (61 mg, 0.183 mmol, 73%) as a white solid and **4a** (10 mg, 20%) as a colorless oil. The following are the data for **3a**. R_f = 0.24 (4% MeOH−CH_2Cl_2). Mp: 104−107 °C. $[\alpha]^{20}_D = +25.1$ (c = 0.47). ^1H NMR (300 MHz): δ 1.54 (br s, 2 H), 2.29 (s, 3 H), 3.73 (s, 3 H), 3.81 (d, 1 H, J = 4.0 Hz), 4.71 (dd, 1 H, J = 7.6, 4.0 Hz), 5.48 (d, 1 H, J = 7.6 Hz), 7.07−7.24 (m, 7 H), 7.40 (d, 2 H, J = 8.3 Hz). ^{13}C NMR (50 MHz): δ 21.1, 52.3, 58.1, 59.7, 125.8 (2 C), 126.8 (2 C), 127.2, 128.1 (2 C), 129.0 (2 C), 139.7, 140.8, 140.9, 173.0. IR (KBr): 3420, 3351, 3280, 3059, 1750, 1586, 1452, 1264, 1224, 1201, 1094, 1062, 999, 889, 806, 780, 704 cm^{-1}. MS (ES): m/z 687 $[2M + Na]^+$, 355 $[M + Na]^+$, 333 $[M + 1]^+$ (100). Anal. Calcd for $C_{17}H_{20}N_2O_3S$: C, 61.42; H, 6.06; N, 8.43; S, 9.65. Found: C, 61.19; H, 6.40; N, 8.74; S, 9.21.

(+)-Methyl [(2*S*,3*R*,S_S)-2-Amino-5-phenyl-3-(*p*-tolylsulfinylamino)]pentanoate, 3b. From **1f** (63 mg, 0.140 mmol) and 4 equiv of H_3PO_4, according to the general procedure (1 h and 30 min), was obtained after purification by chromatography (0−3% MeOH−CH_2Cl_2) **3b** (41 mg, 0.114 mmol, 81%) as a colorless oil. R_f = 0.20 (5% MeOH−CH_2Cl_2). $[\alpha]^{20}_D = +95.2$ (c = 1.20). ^1H NMR (300 MHz): δ 1.61 (br s, 2 H), 1.86 (m, 2 H), 2.39 (s, 3 H), 2.52 (m, 1 H), 2.67 (m, 1 H), 3.67 (m, 2 H), 3.77 (s, 3 H), 4.49 (d, 1 H, J = 8.4 Hz), 7.09−7.28 (m, 7 H), 7.54 (d, 2 H, J = 8.2 Hz). ^{13}C NMR (50 MHz): δ 21.3, 32.2, 35.1, 52.3, 57.1, 57.5, 125.7 (2 C), 125.9 (2 C), 128.3 (2 C), 128.4 (2 C), 129.5, 141.2, 141.3, 141.9, 174.3. IR (film): 3302, 3026, 2949, 1737, 1602, 1429, 1454, 1227, 1089, 1059, 813, 750, 700 cm^{-1}. MS (ES): m/z 743 $[2M + Na]^+$, 383 $[M + Na]^+$, 361 $[M + 1]^+$ (100). Anal. Calcd for $C_{19}H_{24}N_2O_3S$: C, 63.31; H, 6.71; N, 7.77; S, 8.90. Found: C, 63.72; H, 6.22; N, 7.34; S, 8.79.

General Procedure for Preparation of 2,3-Diamino Esters 4. The preparation of these compounds was carried out by different methods.

From *N*-Sulfinylimidazolidines. Method A. To a solution of the *N*-sulfinylimidazolidine **1** in MeOH (10 mL/mmol) at room temperature and under an argon atmosphere was added dropwise 4 equiv of TFA, and the reaction was monitored by TLC of aliquots neutralized with solid $NaHCO_3$. The reaction mixture was heated under reflux to reach completion when necessary. The crude mixture was evaporated under vacuum, redissolved in CH_2Cl_2 (8 mL/mmol), and neutralized with aqueous saturated $NaHCO_3$ solution (5 mL/mmol). The layers were separated, and the aqueous phase was further basified to pH 10−11 with solid K_2CO_3 and extracted with CH_2Cl_2 or CH_2Cl_2−MeOH (20:1, 3 × 10 mL/mmol). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a product that was purified by column chromatography on silica gel (ca. 1 g/mmol).

Method B. To a suspension of the *N*-sulfinylimidazolidine **1** in Et_2O/H_2O (1:1, 15 mL/mmol) at room temperature and under an argon atmosphere was added dropwise an aqueous 2 N solution of HCl (5 mL/mmol), and the reaction was monitored by TLC of aliquots neutralized with solid $NaHCO_3$. Upon completion, the layers were separated and the products isolated as indicated in method A.

Method C. Alternatively, the TFA used in method A can be replaced by 3−4 equiv of H_3PO_4 (85% aqueous solution) in THF/MeOH/H_2O (6:3:1, 10 mL/mmol), following the same procedure for isolation as indicated before.

From *N*-Sulfinyldiamino Esters. Method D. Desulfinylation of *N*-sulfinyldiamino esters **3** was performed using 4 equiv of TFA or 4 equiv of a 0.5 M aqueous solution of H_3PO_4 in MeOH (10 mL/mmol) following the same procedure indicated in method A for isolation of the final products.

(+)-Methyl [(2*S*,3*R*)-2,3-Diamino-4-methyl]pentanoate, 4d. From **1e** (80 mg, 0.207 mmol) and 1 mL of 2 N HCl, according to general procedure B (1 h and 30 min), was obtained after chromatography (5:1 CH_2Cl_2−MeOH) **4d** (20 mg, 0.124 mmol, 60%) as a colorless oil. **4d** was also obtained by desulfinylation of **3d** (method D, 68%). R_f = 0.20 (15% MeOH−CH_2Cl_2). $[\alpha]^{20}_D = +3.1$ (c = 0.62). ^1H NMR (200 MHz): δ 0.95 (d, 3 H, J = 6.8 Hz), 0.97 (d, 3 H, J = 6.8 Hz), 1.51 (br s, 4 H), 1.65 (m, 1 H), 2.69 (dd, 1 H, J = 7.7, 3.8 Hz), 3.54 (d, 1 H, J = 3.8 Hz), 3.72 (s, 3 H). ^{13}C NMR (50 MHz): δ 18.6, 20.2, 30.8, 52.1, 56.4, 59.6, 175.8. IR (film): 3353, 2961, 2924, 2854, 1738, 1671, 1455, 1413, 1376, 1092, 865, 800 cm^{-1}. MS (ES): m/z 399 $[2M - CO_2 + Na]^+$, 257 $[2(M + 1 - CO_2) + Na]^+$ (100), 161 $[M + 1]^+$. Anal. Calcd for $C_7H_{16}N_2O_2$: C, 52.48; H, 10.07; N, 17.48. Found: C, 52.23; H, 9.97; N, 17.33.

(−)-Methyl [(2*S*,3*R*)-3-Amino-2-benzyloxycarbonylamino-5-phenyl]pentanoate, 4e. From **1h** (40 mg, 0.069 mmol) and 4 equiv of H_3PO_4 (0.275 mmol, 33 mg, 20 μL), according to general procedure C (23 h), was obtained after purification by chromatography (0−1% EtOH−Et_2O) and crystallization with Et_2O **4e** (16 mg, 0.045 mmol, 65%) as a colorless solid. R_f = 0.28 (0.05% EtOH−Et_2O). Mp: 62−63 °C. $[\alpha]^{20}_D = -1.3$ (c = 2.00). ^1H NMR (300 MHz): δ 1.20 (br s, 2 H), 1.59 (m, 1 H), 1.75 (m, 1 H), 2.70 (ap t, 2 H, J = 7.9 Hz), 3.30 (br s, 1 H), 3.73 (s, 3 H), 4.40 (d, 1 H, J = 7.7 Hz), 5.12 (s, 2 H), 5.70 (d, 1 H, J = 8.5 Hz), 7.14−7.20 (m, 4 H), 7.25−7.33 (m, 6 H). ^{13}C NMR (50 MHz): δ 32.5, 36.2, 52.2, 52.4, 57.9, 67.1, 126.0, 128.1 (2 C), 128.4 (2 C), 128.5 (2 C), 128.6 (2 C), 136.3, 141.3, 156.6, 172.3. IR (KBr): 3321, 3062, 3029, 2951, 2857, 1715, 1659, 1603, 1497, 1454, 1437, 1228, 1086, 1051, 1029, 774, 749, 699 cm^{-1}. MS (ES): m/z 357 $[M + 1]^+$ (100). Anal. Calcd for $C_{20}H_{24}N_2O_4$: C, 69.40; H, 6.79; N, 7.86. Found: C, 69.34; H, 6.63; N, 7.95.

Synthesis of (+)-Methyl [(2*S*,3*R*,S_S)-2-(Benzylamino)-4-methyl-3-(*p*-tolylsulfinylamino)]pentanoate, 6b. To a solution of **3d** (78 mg, 0.261 mmol) in anhydrous CH_3CN (15 mL/mmol) were added BnBr (63 μL, 0.522 mmol) and solid K_2CO_3 (144 mg). The mixture was stirred at rt and monitored

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(19) This experiment was also carried out with the racemic acid, giving rise to a diastereomeric mixture with well-resolved signals in the ^1H NMR spectra. This conclusively established the optical purity of **3d**, as a representative example, to be ≥99%, with the other diastereomer not being detected in a carefully recorded 300 MHz ^1H NMR spectrum.

by TLC until completion (24 h). After removal of CH_3CN under vacuum, the residue was partitioned between CH_2Cl_2 (10 mL/mmol) and H_2O (10 mL/mmol). The aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL/mmol). The combined organic layers were washed with brine (5 mL/ mmol), dried over Na_2SO_4, filtered, and concentrated under vacuum. Purification by chromatography (30−100% Et_2O−hexane) afforded **6b** (80 mg, 0.206 mmol, 79%) as a colorless oil along with dibenzylated **6i** (8 mg, 0.011 mmol, 6%). The following are the data for **6b**. R_f = 0.40 (Et_2O). $[\alpha]^{20}_D = +43.0$ (*c* = 1.70). ^1H NMR (400 MHz): δ 0.79 (d, 3 H, *J* = 6.6 Hz), 0.96 (d, 3 H, *J* = 6.8 Hz), 1.81 (m, 1 H), 2.02 (br s, 1 H), 2.37 (s, 3 H), 3.36 (dt, 1 H, *J* = 8.3, 2.6 Hz), 3.40 (d, 1 H, *J* = 2.6 Hz), 3.57 (d, 1 H, *J* = 12.8 Hz), 3.77 (s, 3 H), 3.93 (d, 1 H, *J* = 12.8 Hz), 4.02 (d, 1 H, *J* = 8.3 Hz), 7.21−7.32 (m, 7 H), 7.58 (d, 2 H, *J* = 8.3 Hz). ^{13}C NMR (75 MHz)/HSQC: δ 19.5, 19.8, 21.3, 30.7, 52.0, 52.8, 62.0, 63.4, 125.7 (2 C), 127.1, 128.3 (2 C), 128.5 (2 C), 129.4 (2 C), 139.8, 141.2, 142.4, 174.5. IR (film): 3302, 3201, 3060, 3028, 2956, 2872, 1738, 1597, 1494, 1454, 1434, 1259, 1200, 1151, 1090, 1058, 1018, 994, 923, 812, 747, 701 cm^{-1}. MS (ES): *m*/*z* 799 $[2M + Na]^+$, 389 $[M + 1]^+$ (100). Anal. Calcd for $C_{21}H_{28}N_2O_3S$: C, 64.92; H, 7.26; N, 7.21; S, 8.25. Found: C, 64.75; H, 7.52; N, 7.17; S, 8.34.

Synthesis of (−)-Methyl [(2*S*,3*R*,S_S)-3-(*p*-Fluorophenyl)-2-(pyrrolidin-1-yl)-3-(*p*-tolylsulfinylamino)]propanoate, 6d. To a round-bottomed flask fitted with a Dean−Stark trap was added a solution of **3c** (70 mg, 0.199 mmol) in anhydrous toluene (10 mL/mmol), 1,4-dibromobutane (69 μL, 0.259 mmol), and solid $NaHCO_3$ (42 mg, 0.498 mmol). The mixture was heated under reflux for 14 h, then allowed to reach rt, and filtered to remove inorganic salts, and the solid residue was washed with toluene. The filtrate was washed with H_2O, dried over Na_2SO_4, and filtered, and the solvent was evaporated under reduced pressure. **6d** (52 mg, 0.129 mmol, 65%) was obtained after chromatography on silica gel (50−100% Et_2O−hexane) as a white solid that was crystallized from 5% CH_2Cl_2−hexane to give white crystals. R_f = 0.40 (80% Et_2O−hexane). Mp: 138−142 °C. $[\alpha]^{20}_D = -2.9$ (*c* = 0.80). ^1H NMR (300 MHz): δ 1.76 (m, 4 H), 2.19 (s, 3 H), 2.67 (m, 2 H), 2.84 (m, 2 H), 3.38 (s, 3 H), 3.53 (d, 1 H, *J* = 11.0 Hz), 4.75 (d, 1 H, *J* = 11.0 Hz), 5.74 (s, 1 H), 6.58 (t, 2 H, *J* = 8.8 Hz), 6.87 (m, 4 H), 7.22 (d, 2 H, *J* = 8.3 Hz). ^{13}C NMR (75 MHz): δ 21.1, 23.6 (2 C), 48.2 (2 C), 49.7, 50.9, 68.7, 114.3 (d, 2 C, J_o(C−F) = 21.7 Hz), 125.6 (2 C), 128.6 (2 C), 130.1 (d, 2 C, J_m(C−F) = 8.1 Hz), 135.3, 139.4, 140.7, 161.7 (d, J_{ipso}(C−F) = 245.3 Hz), 168.8. IR (KBr): 3424, 3276, 2954, 2841, 2809, 1721, 1601, 1510, 1430, 1316, 1297, 1224, 1170, 1135, 1089, 1065, 1031, 1015, 986, 916, 938, 816, 638 cm^{-1}. MS (ES): *m*/*z* 405 $[M + 1]^+$ (100). Anal. Calcd for $C_{21}H_{25}FN_2O_3S$: C, 62.35; H, 6.23; F, 4.70; N, 6.93; S, 7.93. Found: C, 62.72; H, 6.10; N, 6.88; S, 7.67.

Synthesis of (+)-Methyl [(2*S*,3*R*,S_S)-2-[(*S*)-Phenylmethoxyacetylamino)]-4-methyl-3-(*p*-tolylsulfinylamino)]pentanoate, 6g. To a solution of **3d** (20 mg, 0.067 mmol) in CH_2Cl_2 (10 mL/mmol) were added 1.05 equiv of (*S*)-(+)-MPA (11.63 mg, 0.070 mmol), 1 equiv of DCC (15.00 mg, 0.067 mmol), and a catalytic amount of DMAP (1−2 crystals). The mixture was stirred until completion monitored by TLC (1 h). The solvent was evaporated under reduced pressure. A ^1H NMR sample was prepared from this crude product, and the diastereomeric excess of **6g** and the optical purity of the *N*-sulfinyldiamino ester **3d** were measured by integration at the methoxy signals (de > 99%). **6g** (19 mg, 64%) was finally obtained after purification by chromatography (50−100% Et_2O−hexane) as a white foam. R_f = 0.23 (Et_2O). $[\alpha]^{20}_D = +106.1$ (*c* = 1.85). ^1H NMR (300 MHz): δ 0.76 (d, 3 H, *J* = 6.6 Hz), 0.90 (d, 3 H, *J* = 6.8 Hz), 1.56 (m, 1 H), 2.41 (s, 3 H), 3.47 (s, 3 H, OMe), 3.58 (td, 1 H, *J* = 7.5, 2.9 Hz), 3.75 (s, 3 H), 3.89 (d, 1 H, *J* = 7.1 Hz), 4.69 (s, 1 H), 4.82 (dd, 1 H, *J* = 9.5, 2.9 Hz), 7.25−1.37 (m, 5 H), 7.39 (m, 2 H), 7.57 (d, 2 H, *J* = 8.3 Hz), 7.68 (d, 1 H, *J* = 9.5 Hz). ^{13}C NMR (75 MHz)/HSQC: δ 19.1, 19.5, 21.4, 30.1, 52.6, 53.3 57.6, 61.8, 84.0, 125.7 (2 C), 126.6 (2 C), 128.5 (3 C), 129.6 (2 C), 137.1, 141.5, 141.7, 171.3, 171.2. MS (ES): *m*/*z* 915 $[2M + Na]^+$, 447 $[M + 1]^+$ (100). Anal. Calcd for $C_{23}H_{30}N_2O_5S$: C, 61.86; H, 6.77; N, 6.27; S, 7.18. Found: C, 61.52; H, 6.43; N, 6.09; S, 7.07.

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Supporting Information Available: Experimental procedures and characterization for new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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