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Enantioselective Synthesis of 3,4-Disubstituted *cis*- and *trans*-1,2,5-Thiadiazolidine-1,1-dioxides as Precursors for Chiral 1,2-Diamines

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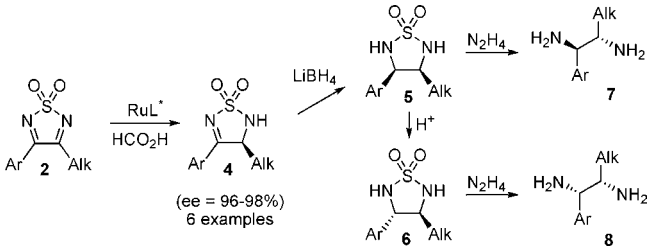
ABSTRACT



Both, *cis*- and *trans*-3,4-disubstituted thiadiazolidines 5 and 6 can enantioselectively be obtained from thiadiazoles 2 which, in turn, are efficiently prepared from the respective 1,2-diketone by an improved protocol. An asymmetric ruthenium-catalyzed transfer hydrogenation followed by a diastereoselective hydride addition furnishes exclusively the *cis*-isomers 5 which, under acidic conditions, undergo a novel isomerization into the *trans*-isomers 6. These cyclic sulfamides can be transformed into 1,2-diamines as well as 2,3-diamino acids.

The sulfamide moiety belongs to the most important pharmacophores in medicinal chemistry and is found in many pharmaceutical agents.[1] Cyclic sulfamides are especially interesting due to their conformational rigidity, and the 5-ring derivatives, i.e. 1,2,5-thiadiazolidine-1,1-dioxides, can be modified to selectively interact with various biological receptors. Among others this comprises inhibitors of α-mannosidase,[2a] the TNF-α converting enzyme,[2c] γ-secretase involved in Alzheimer's disease,[2d] serine proteases,[2e] and HIV protease,[2f] as well as antibiotics[2b] and agonists at serotonin receptors.[2g] Moreover, 1,2,5-thiadiazolidines are used as chiral auxiliaries,[3] building blocks in supramolecular chemistry,[4] and intermediates for the preparation of chiral 1,2-diamines.[5]

Their synthesis typically starts from acyclic 1,2-difunctionalized precursors such as 1,2-diamines, 1,2-aminoalcohols, or 2-chloroalkylamines, and enantioselective preparations thus critically depend on the availability of the respective

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(1) Review: Winum, J.-Y.; Scozzafava, A.; Montero, J.-L.; Supuran, C. T. *Med. Res. Rev.* **2006**, *26*, 767–792.

(2) (a) Benltifa, M.; García Moreno, M. I.; Ortiz Mellet, C.; García Fernández, J. M.; Wadouachi, A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2805–2808. (b) Kim, S. J.; Park, H. B.; Lee, J. S.; Jo, N. H.; Yoo, K. H.; Baek, D.; Kang, B.-w.; Cho, J.-H.; Oh, C.-H. *Eur. J. Med. Chem.* **2007**, *42*, 1176–1183. (c) Cherney, R. L.; King, B. W.; Gilmore, J. L.; Liu, R.-Q.; Covington, M. B.; Duan, J. J.-W.; Decicco, C. P. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1028–1031. (d) Sparey, T.; Beher, D.; Best, J.; Biba, M.; Castro, J. L.; Clarke, E.; Hannam, J.; Harrison, T.; Lewis, H.; Madin, A.; Shearman, M.; Sohal, B.; Tsou, N.; Welch, C.; Wrigley, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4212–4216. (e) Zhong, J.; Gan, X.; Alliston, K. R.; Groutas, W. C. *Bioorg. Med. Chem.* **2004**, *12*, 589–593. (f) Spaltenstein, A.; Almond, M. R.; Bock, W. J.; Cleary, D. G.; Furfine, E. S.; Hazen, R. J.; Kazmiersky, W. M.; Salituro, F. G.; Tung, R. D.; Wright, L. L. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1159–1162. (g) Castro, J. L.; Baker, R.; Guiblin, A. R.; Hobbs, S. C.; Jenkins, M. R.; Russell, M. G. N.; Beer, M. S.; Stanton, J. A.; Scholey, K.; Hargreaves, R. J.; Graham, M. I.; Matassa, V. G. *J. Med. Chem.* **1994**, *37*, 3023–3032.

(3) (a) Fécourt, F.; Lopez, G.; Van Der Lee, A.; Martinez, J.; Dewynter, G. *Tetrahedron: Asymmetry* **2010**, *21*, 2361–2366. (b) Ahn, K. H.; Yoo, D. J.; Kim, J. S. *Tetrahedron Lett.* **1992**, *33*, 6661–6664. (c) Sartor, D.; Saffrich, J.; Helmchen, G.; Richards, C. J.; Lambert, H. *Tetrahedron Lett.* **1991**, *32*, 639–642.

(4) (a) Hof, F.; Nuckolls, C.; Craig, S. L.; Martin, T.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2000**, *122*, 10991–10996. (b) Martin, T.; Obst, U.; Rebek, J., Jr. *Science* **1998**, *281*, 1842–1845.

(5) Pansare, S. V.; Malusare, M. G. *Tetrahedron Lett.* **1996**, *37*, 2859–2862.

(6) For examples, see refs 2, 3a, 3b, and: (a) Hannam, J.; Harrison, T.; Heath, F.; Madin, A.; Merchant, K. *Synlett* **2006**, 833–836. (b) Kim, I.-W.; Jung, S.-H. *Arch. Pharm. Res.* **2002**, *25*, 421–427. (c) Nicolaou, K. C.; Longbottom, D. A.; Snyder, S. A.; Nalbanadian, A. Z.; Huang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 3866–3870. (d) Regainia, Z.; Abdaoui, M.; Aouf, N.-E.; Dewynter, G.; Montero, J.-L. *Tetrahedron* **2000**, *56*, 381–387.

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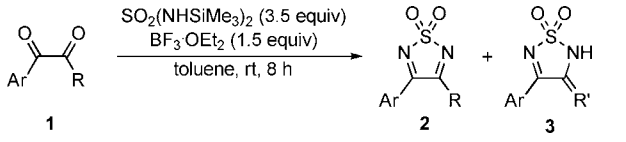
enantiopure starting material.[6] These traditional approaches have been supplemented in recent years by inter- and intramolecular 1,2-diaminations of alkenes[7] and oxidative cyclizations of allylic sulfamides.[8] Being very promising due to their atom efficiency, these methods, however, still suffer from a limited substrate scope and only furnished racemic 1,2,5-thiadiazolidines so far.[9]

In contrast, the utilization of cyclic starting materials has rarely been reported,[10] including racemic syntheses from thiadiazole-1,1-dioxides.[10b,c] These unsaturated analogs containing two C,N-double bonds also have interesting biological properties as histamine H_2-receptor antagonists[11a,b] as well as antihypertensive and vasodilating agents[11c] and are often described in patent literature.[12] Thiadiazole-1,1-dioxides with organic substituents at the C-atoms are obtained from 1,2-diketones by condensation with sulfamide, $SO_2(NH_2)_2$, and 3,4-diaryl substituted compounds can be prepared under mild conditions using Et_3N.[10c] However, alkyl-substituted derivatives are so far only obtainable under harsh conditions, i.e. refluxing with HCl in alcoholic medium, which results in a limited functional group tolerance.[10c,13] Herein, we report on an improved protocol for the preparation of 4-alkyl-3-aryl-1,2,5-thiadiazole-1,1-dioxides and on their transformation into enantiopure *cis*- and *trans*-thiadiazolidine-1,1-dioxides.

The inherent problem of the previous syntheses of thiadiazole-1,1-dioxides is the poor solubility of $SO_2(NH_2)_2$ in aprotic solvents, thus requiring the use of alcoholic media and strong Brønsted acids. To overcome this limitation we devised the use of *N*,*N*′-bis(trimethylsilyl)sulfamide as a less polar reagent which is readily prepared from SO_2Cl_2 and $NH(SiMe_3)_2$.[14] Stirring of 1,2-diketones **1** with an excess of this reagent and stoichiometric amounts of $BF_3 \cdot OEt_2$[15] resulted in smooth formation of the desired condensation products in considerably increased yields of 70−90% (Table 1). Thus, major improvements can be achieved especially in the case of more sensitive compounds (entries 2, 7). In the case of longer *n*-alkyl chains at C^4, the thiadiazoles **2** were formed as mixtures with the respective 4-alkylidenethiadiazolines **3** in varying percentages. Similar observations have been made before[16] and might stem from reduced ecliptic interactions when going from thiadiazoles **2** with a planar ring to the tautomers **3**.[17]

Table 1. Improved Synthesis of Thiadiazole-1,1-dioxides



entry	product	Ar	R	yield (%)[a]
1	**2a**	Ph	Ph	87 [58][c]
2	**2b**	Ph	Me	78 [29][c]
3	**2c**[b]	Ph	Et	85 [56][c]
4	**2d**[b]	*p*-$MeOC_6H_4$	Et	90 [58][c]
5	**2e**	*p*-$MeOC_6H_4$	*i*Pr	81 [65][c]
6	**2f**[b]	*p*-ClC_6H_4	Et	72 [58][c]
7	**2g**[b]	furan-2-yl	Et	70 [30][c]
8	**2h**[b]	thiophen-3-yl	Et	75

[a] Isolated yield. [b] Obtained as mixture with tautomer **3** in varying percentages. [c] Numbers in brackets indicate isolated yield from preparation according to Wright and Ziegler et al. (refs 10c and 13) with sulfamide and HCl.

The C,N-double bonds in thiadiazole-1,1-dioxides are quite reactive toward nucleophilic additions,[18] yet, asymmetric reductions are unprecedented.[19] A screening of various protocols for such reactions[20] including Ru(II)/binap-

(7) (a) Chávez, P.; Kirsch, J.; Hövelmann, C. H.; Streuff, J.; Martínez-Belmonte, M.; Escudero-Adán, E. C.; Martin, E.; Muniz, K. *Chem. Sci.* **2012**, *3*, 2375–2382. (b) Chavez, P.; Kirsch, J.; Streuff, J.; Muniz, K. *J. Org. Chem.* **2012**, *77*, 1922–1930. (c) Cornwall, R. G.; Zhao, B.; Shi, Y. *Org. Lett.* **2011**, *13*, 434–437. (d) Wang, B.; Du, H.; Shi, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 8224–8227. (e) Zhao, B.; Yuan, W.; Du, H.; Shi, Y. *Org. Lett.* **2007**, *9*, 4943–4945. (f) Muniz, K.; Streuff, J.; Hövelmann, C. H.; Nunez, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7125–7127. (g) Zabawa, T. P.; Chemler, S. R. *Org. Lett.* **2007**, *9*, 2035–2038.

(8) McDonald, R. I.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 5529–5532.

(9) For asymmetric diaminations in general, see: (a) Souto, J. A.; González, Y.; Iglesias, A.; Zian, D.; Lishchynskyi, A.; Muniz, K. *Chem.—Asian J.* **2012**, *7*, 1103–1111. (b) Röben, C.; Souto, J. A.; González, Y.; Lishchynskyi, A.; Muniz, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 9478–9482. (c) Sequeira, F. C.; Turnpenny, B. W.; Chemler, S. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 6365–6368. (d) Cardona, F.; Goti, A. *Nat. Chem.* **2009**, *1*, 269–275. (e) Du, H.; Zhao, B.; Yuan, W.; Shi, Y. *Org. Lett.* **2008**, *10*, 4231–4234. (f) Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 11688–11689.

(10) (a) Lee, S. A.; Kwak, S. H.; Lee, K.-I. *Chem. Commun.* **2011**, *47*, 2372–2374. (b) Pansare, S. V.; Rai, A. N.; Kate, S. N. *Synlett* **1998**, 623–624. (c) Wright, J. B. *J. Org. Chem.* **1964**, *29*, 1905–1909.

(11) (a) Lumma, W. C.; Anderson, P. S.; Baldwin, J. J.; Bolhofer, W. A.; Habecker, C. N.; Hirshfield, J. M.; Pietruszkiewicz, A. M.; Randall, W. C.; Torchiana, M. L.; Britcher, S. F.; Clineschmidt, B. V.; Denny, G. H.; Hirschmann, R.; Hoffman, J. M.; Phillips, B. T.; Streeter, K. B. *J. Med. Chem.* **1982**, *25*, 207–210. (b) Algieri, A. A.; Luke, G. M.; Standridge, R. T.; Brown, M.; Partyka, R. A.; Crenshaw, R. R. *J. Med. Chem.* **1982**, *25*, 210–212. (c) Stegelmeier, H.; Niemers, E.; Rosentreter, U.; Knorr, A.; Garthoff, B. (Bayer AG) D.O.S. 3309655, **1984**; *Chem. Abstr.* 1985, *102*, 24633.

(12) A SciFinder search revealed more than 45 patent documents describing thiadiazole-1,1-dioxides since 2000. For a review, see: Arán, V. J.; Goya, P.; Ochoa, C. *Adv. Heterocycl. Chem.* **1988**, *44*, 81–197.

(13) Vorreither, H. K.; Ziegler, E. *Monatsh. Chem.* **1965**, *96*, 216–219.

(14) Becke-Goehring, M.; Wunsch, G. *Liebigs Ann. Chem.* **1958**, *618*, 43–52.

(15) Catalytic amounts of $BF_3 \cdot OEt_2$ led to incomplete conversion.

(16) Aimone, S. L.; Caram, J. A.; Mirifico, M. V.; Vasini, E. J. *J. Phys. Org. Chem.* **2001**, *14*, 217–223.

(17) (a) Castellano, E. E.; Piro, O. E.; Caram, J. A.; Mirífico, M. V.; Aimone, S. L.; Vasini, E. J.; Márquez-Lucero, M.; Glossman-Mitnik, D. *J. Mol. Struct.* **2001**, *597*, 163–175. (b) Aimone, S. L.; Caram, J. A.; Mirifico, M. V.; Vasini, E. J. *J. Phys. Org. Chem.* **2000**, *13*, 272–282. (c) Castellano, E. E.; Piro, O. E.; Caram, J. A.; Mirifico, M. V.; Aimone, S. L.; Vasini, E. J.; Glossman, M. D. *J. Phys. Org. Chem.* **1998**, *11*, 91–100.

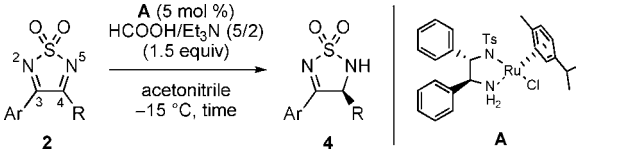
(18) For examples, see refs 10b and 17b as well as: (a) Luo, Y.; Hepburn, H. B.; Chotsaeng, N.; Lam, H. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 8309–8313. (b) Mirífico, M. V.; Caram, J. A.; Piro, O. E.; Vasini, E. J. *J. Phys. Org. Chem.* **2007**, *20*, 1081–1087.

(19) For Rh(TsDPEN)-catalyzed hydrogenations of 3-aryl-1,2,5-thiadiazoline-1,1-dioxides, see ref 10a. For Ru(TsDPEN)-catalyzed hydrogenations of 1-arylpropan-1,2-diones, see: (a) Koike, T.; Murata, K.; Ikariya, T. *Org. Lett.* **2000**, *2*, 3833–3836. For asymmetric hydrogenations of other related compounds, see: (b) Lee, H.-K.; Kang, S.; Choi, E. B. *J. Org. Chem.* **2012**, *77*, 5454–5460. (c) Yu, C.-B.; Wang, D.-W.; Zhou, Y.-G. *J. Org. Chem.* **2009**, *74*, 5633–5635. (d) Yang, Q.; Shang, G.; Gao, W.; Deng, J.; Zhang, X. *Angew. Chem., Int. Ed.* **2006**, *45*, 3832–3835. (e) Mao, J.; Baker, D. C. *Org. Lett.* **1999**, *1*, 841–843. (f) Ahn, K. H.; Ham, C.; Kim, S.-K.; Cho, C.-W. *J. Org. Chem.* **1997**, *62*, 7047–7048. (g) Oppolzer, W.; Wills, M.; Starkemann, C.; Bernardinelli, G. *Tetrahedron. Lett.* **1990**, *31*, 4117–4120.

catalyzed hydrogenations revealed that the best results can be achieved with the transfer hydrogenation catalyst RuCl(TsDPEN) **A**, introduced by Noyori et al. (Table 2).[21] Under these conditions, the C^4,N^5-double bond is substantially more reactive than the C^3,N^2-double bond, enabling a selective formation of thiadiazolines **4**. While the Ph,Ph derivative **2a** only furnished racemic product **4a** even when stopping the reaction at low conversions (entry 1), the aryl,alkyl derivatives underwent regio- and enantioselective reductions of the alkyl-substituted C^4,N^5-double bonds. This behavior should be due to the fact that the aryl rings in thiadiazoles **2** are twisted out of plane to avoid ecliptic interactions.[17c] In thiadiazolines **4**, however, the aryl rings are almost coplanar with the C^3,N^2-double bonds, thus stabilizing them against further reduction.[17a] Only in the case of prolonged reaction times, 2-fold reduction was observed which, however, occurred with lower stereoselectivity. Therefore, the reaction was stopped at the stage of thiadiazolines **4**, which were obtained in high yields and excellent enantiopurities in most cases (Table 2). The yield of the Ph,Me derivative **4b** was moderate due to partial dimerization of the starting material (entry 2),[16] and transformation of substrates **2c**, **2d**, and **2f** revealed an electronic effect: Better results were generally obtained in the case of electron-rich aryl substituents. Thus, the electron-poor *p*-ClC_6H_4-derivative **2f** furnished a mixture of the desired **4f** and its regioisomer formed by reduction of the aryl-substitued C^3,N^2-double bond.[22] Notably, the reaction also tolerates secondary alkyl groups at C^4 (entry 5) as well as heteroaromatic substituents at C^3 (entries 7,8), and complete conversions were detected even when starting from mixtures of tautomers **2** and **3** which points to a fast isomerization under the reaction conditions.

This transfer hydrogenation is not suitable for a selective reduction of the second C,N-double bond, yet literature precedence suggested $NaBH_4$ for this purpose.[10b] The corresponding reaction of thiadiazolines **4** in EtOH led to diastereoselective formation of *cis*-thiadiazolidines **5**,[23] albeit it was accompanied by a serious drop in enantiopurity. This partial racemization is caused by the alkaline, protic reaction medium: stirring compound **4d** in EtOH at 50 °C for 24 h led to a drop from 96% ee to 83% ee, and complete racemization occurred upon stirring **4d** with 1.2 equiv of DBU in EtOH at rt for 24 h. In contrast, stirring of

Table 2. Asymmetric Transfer Hydrogenation

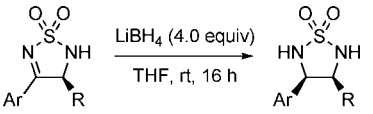


entry	product	Ar	R	time (h)	yield (%)[a]	ee (%)[b]
1	**4a**	Ph	Ph	5	71	0
2	**4b**	Ph	Me	30	55	98
3	**4c**[c]	Ph	Et	30	73	97
4	**4d**[c]	*p*-$MeOC_6H_4$	Et	40	97	96
5	**4e**	*p*-$MeOC_6H_4$	*i*Pr	48	94	96
6	**4f**[c]	*p*-ClC_6H_4	Et	41	70[d]	66
7	**4g**[c]	furan-2-yl	Et	50[e]	85	96
8	**4h**[c]	thiophen-3-yl	Et	55[e]	72	96

[a] Isolated yield. [b] Determined by HPLC on a chiral stationary phase. [c] Prepared from a mixture of compounds **2** and **3**. [d] Yield determined by ^1H NMR from a mixture of **4f** and a regioisomer. [e] Reaction performed at −20 °C.

4d in THF led to no changes, and among various tested boranes and borohydrides, $LiBH_4$ arose as the reagent of choice. Thus, all transformations occurred in almost quantitative yields (Table 3), and only the Ph,Me derivative **5b** still showed a slightly reduced ee (entry 1). All sulfamides **5** are colorless solids, and an X-ray crystallographic analysis of compound **5e** allowed for the determination of its absolute configuration as (3*R*,4*S*).[24]

Table 3. Diastereoselective Reduction with $LiBH_4$



entry	product	Ar	R	yield (%)[a]	ee (%)[b]
1	**5b**	Ph	Me	91	92
2	**5c**	Ph	Et	93	95
3	**5d**	*p*-$MeOC_6H_4$	Et	93	96
4	**5e**	*p*-$MeOC_6H_4$	*i*Pr	95	95
5	**5g**	furan-2-yl	Et	97	95
6	**5h**	thiophen-3-yl	Et	96	94

[a] Isolated yield. [b] Determined by HPLC on a chiral stationary phase.

Having achieved an enantioselective synthesis of *cis*-thiadiazolidines **5**, cleavage of the sulfamide moiety was intended to obtain *anti*-1,2-diamines. Accordingly, *cis*-thiadiazolidine **5c** was stirred in H_2SO_4,[25] but instead of ring opening, a smooth isomerization was observed to give the corresponding *trans*-thiadiazolidine **6c** under preservation of the high ee (Table 4, entry 1). Examination of this novel

(20) For reviews about asymmetric reduction of C,N-bonds, see: (a) Fleur-Bregeot, N.; de la Fuente, V.; Castillon, S.; Claver, C. *ChemCatChem* **2010**, *2*, 1346–1371. (b) Spindler, F.; Blaser, H.-U. Enantioselective Hydrogenation of C=N Functions and Enamines. In *The Handbook of Homogeneous Hydrogenation*; de Vries, J. G., Elsevier, C. J., Eds.; Wiley-VCH: Weinheim, 2007; Vol. 3, pp 1193−1214. (c) Samec, J. S. M.; Bäckvall, J.-E.; Andersson, P. G.; Brandt, P. *Chem. Soc. Rev.* **2006**, *35*, 237–248. (d) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226–236.

(21) (a) Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 285–288. (b) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97–102. (c) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916–4917.

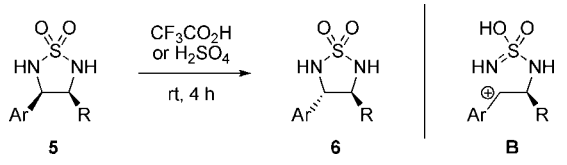
(22) The reduced selectivity obviously stems from the increased reactivity of starting material **2f**. Similarly, the more reactive catalyst Cp*RhCl(TsDPEN) generally leads to unselective reduction. These results are consistent with those obtained by Ikariya et al. in the case of 1-arylpropan-1,2-diones; cf. ref 19a.

(23) This high substrate-controlled diastereoselectivity should be caused by a Cram-chelate type transition state.

(24) See Supporting Information for details.

(25) Newkome, G. R.; Pappalardo, S.; Gupta, V. K.; Fronczek, F. R. *J. Org. Chem.* **1983**, *48*, 4848–4851.

Table 4. *Cis*/*Trans*-Isomerization of 1,2,5-Thiadiazolidines



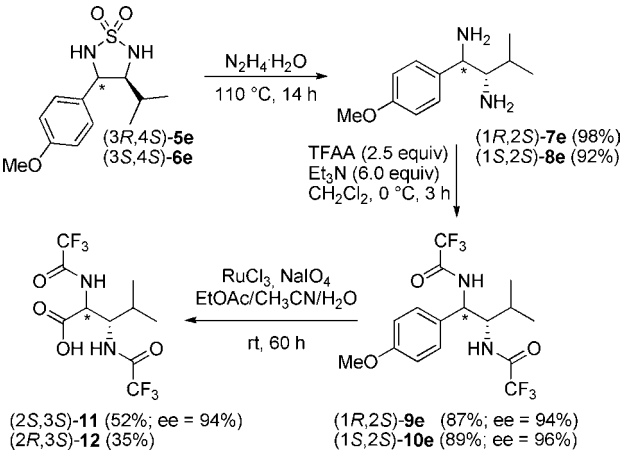
entry	product	Ar	R	acid	yield (%)[a]	ee (%)[b]
1	**6c**	Ph	Et	H_2SO_4	96	96
2	**6d**	*p*-$MeOC_6H_4$	Et	CF_3CO_2H	93	96
3	**6e**	*p*-$MeOC_6H_4$	*i*Pr	CF_3CO_2H	94	95
4	**6h**	thiophen-3-yl	Et	CF_3CO_2H	94	94

[a] Isolated yield. [b] Determined by HPLC on a chiral stationary phase.

reaction mode disclosed that, in the case of electron-rich aryl groups, the isomerization already proceeded in the presence of the milder trifluoroacetic acid (entries 2–4). Thus, the isomerization presumably takes place through protonation at the oxygen of the SO_2 moiety.[26] Subsequent scission of the C^3,N^2-bond leads to a benzyl cation **B** which occurs more readily in the case of the *p*-$MeOC_6H_4$-substituted compounds.[27] Recyclization then furnishes the *trans*-isomers **6** due to reduced torsional strain. Thus, each of the four stereoisomers of 3-aryl-4-alkyl-substituted thiadiazolidine-1,1-dioxides can efficiently be obtained from the respective 1,2-diketone in 3–4 straightforward steps, and in a gram scale process, 3.27 g of **6d** with 96% ee were obtained from **1d** in 75% overall yield.

Besides being interesting on their own, the prepared thiadiazolidines **5** and **6** are precursors for chiral 1,2-diamines, a substance class of utmost importance.[28] Moreover, the aryl substituent at C^3 can be regarded as a masked carboxy group, thus opening an access to 2,3-diamino acids.[29] For exemplification, both the *cis*- and the *trans*-thiadiazolidines **5e** and **6e** were separately transformed into the *anti*- and *syn*-diamino acids **11** and **12**, respectively; the latter has been reported as a substructure of peptidomimetics (Scheme 1).[30] The cleavage of sulfonamides and sulfamides is rather difficult, and harsh conditions are frequently required. Preliminary experiments for the ring opening of thiadiazolidines **5** by refluxing in pyridine/water (95:5) according to Davis et al.[31] or refluxing in HBr with added phenol according to Pansare et al.[5] led to moderate yields (~50%) of the free diamines, yet especially the latter method is not compatible with sensitive substrates. Better results were obtained when performing a nucleophilic opening of the thiadiazolidine ring by refluxing in hydrazine monohydrate, a rather cheap reagent. Thus, the free diamines **7e** and **8e** were obtained in yields exceeding 90%. To avoid formation of zwitterionic free diamino acids, these compounds were transformed into the bis-trifluoroacetamides **9e** and **10e** prior to oxidative cleavage of the aryl rings which was achieved using a protocol by Boger et al.[32] As can be seen from the ee's of **9e**–**11**, the synthesis of the 1,2-diamines and 2,3-diamino acids occurred without any isomerization.

Scheme 1. Transformation into Chiral 2,3-Diamino Acids



In conclusion, we have developed an improved method for the preparation of thiadiazole-1,1-dioxides from enolizable 1,2-diketones. Moreover, the first enantioselective transformation of these compounds into both *cis*- and *trans*-thiadiazolidines was achieved, featuring an asymmetric transfer hydrogenation, a diastereoselective hydride addition, and an unprecedented *cis*/*trans*-isomerization under acidic conditions. The possibility of using these cyclic sulfamides as precursors for 1,2-diamines and 2,3-diamino acids and to prepare all four stereoisomers of these compounds from a common starting material adds to the synthetic value of this approach. Work is now in progress to further enlarge the utilization of thiadiazoles in organic synthesis especially toward the formation of quaternary stereogenic centers.

Supporting Information Available. Experimental procedures, characterization data, and NMR spectra of all compounds; ORTEP drawing and crystallographic data of compound **5e**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(26) Computational data point to a slightly preferred protonation at oxygen, not nitrogen; see ref 17a.

(27) No isomerization occurred in the case of the methyl,methyl derivative; see Supporting Information for details.

(28) (a) Saibabu Kotti, S. R. S.; Timmons, C.; Li, G. *Chem. Biol. Drug Des.* **2006**, *67*, 101–114. (b) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580–2647.

(29) Viso, A.; Fernández de la Pradilla, R.; Trotosa, M.; García, A.; Flores, A. *Chem. Rev.* **2011**, *111*, PR1–PR42.

(30) (a) von Nussbaum, F.; Beck, H.; Brunner, N.; Endermann, R.; Koebberling, J.; Ragot, J.; Telser, J.; Schuhmacher, J.; Anlauf, S.; Cancho-Grande, Y.; Greschat, S.; Militzer, H.-C.; Schiffer, G. (Aicuris GmbH & Co KG) US2009/203582 A1, 2009. (b) Viso, A.; Fernández de la Pradilla, R.; Flores, A.; García, A.; Tortosa, M.; López-Rodríguez, M. L. *J. Org. Chem.* **2006**, *71*, 1442–1448. (c) Mohan, R.; Chou, Y.-L.; Bihovsky, R.; Lumma, W. C., Jr.; Erhardt, P. W.; Shaw, K. J. *J. Med. Chem.* **1991**, *34*, 2402–2410.

(31) Davis, F. A.; Giangiordano, M. A.; Starner, W. E. *Tetrahedron Lett.* **1986**, *34*, 3957–3960.

(32) Jiang, W.; Wanner, J.; Lee, R. J.; Bounaud, P.-Y.; Boger, D. L. *J. Am. Chem. Soc.* **2003**, *125*, 1877–1887.