ORGANIC LETTERS
2007
Vol. 9, No. 10
2007−2010

Catalytic Asymmetric Formation of β-Sultams

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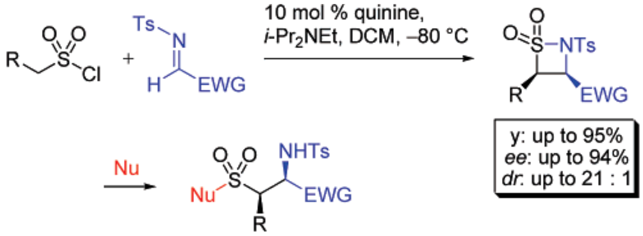
Received March 16, 2007

ABSTRACT



β-Sultams, highly strained sulfonyl analogues of β-lactams, were prepared enantio- and diastereoselectively by tertiary amine catalyzed [2 + 2] cycloaddition reactions. The title compounds are practical precursors of highly enantioenriched biologically interesting β-aminosulfonyl derivatives.

Recently, we have started to address an unsolved problem in organic synthesis, namely the application of sulfenes **1**, the sulfonyl equivalents of ketenes,[1] in asymmetric catalysis.[2] In contrast to sulfenes, ketenes are widely used substrates in asymmetric catalysis allowing the highly stereoselective formation of numerous important compound classes such as β-lactones or β-lactams.[3] Although sulfenes are far less stable than ketenes, we succeeded in the catalytic asymmetric formation of β-sultones via reactive sulfene intermediates.[2] Since chiral sulfonyl analogues of carbonyl derivatives are gaining an increasingly important role in medicinal chemistry,[4] partly because their structural and electronic properties mimic the transition states leading to tetrahedral intermediates, the development of catalytic asymmetric methods toward enantiomerically pure sulfonyl derivatives is of high importance.

In addition to our previous work, we planned the catalytic asymmetric formation of β-sultams **2**, the highly reactive sulfonyl analogues of β-lactams. β-Sultams are of significant biological and medicinal interest, since they can act as irreversible active-site-directed inhibitors of elastases with the active site serine being sulfonylated via an S−N bond fission.[5] Moreover, β-sultams serve as both β-lactamase[6] and DD-peptidase inhibitors[4c] and are consequently appealing for the development of new antibiotics. Title molecules of type **2** can also be regarded as cyclic sulfonamide derivatives of the ubiquitous β-aminosulfonic acid taurine which plays numerous important physiological roles in the tissues of

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(1) Zwanenburg, B. *Sci. Synth.* **2004**, *27*, 123.

(2) Koch, F. M.; Peters, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 2685.

(3) (a) Tidwell, T. T. *Eur. J. Org. Chem.* **2006**, 563. (b) Tidwell, T. T. *Ketenes*, 2nd ed.; John Wiley & Sons: Hoboken, New Jersey, 2006. (c) Tidwell, T. T. *Angew. Chem., Int. Ed.* **2005**, *44*, 5778. (d) Orr, R. K.; Calter, M. A. *Tetrahedron* **2003**, *59*, 3545.

(4) Selected examples: (a) Tsang, W. Y.; Ahmed, N.; Harding, L. P.; Hemming, K.; Laws, A. P.; Page, M. I. *J. Am. Chem. Soc.* **2005**, *127*, 8946. (b) Ghosh, A. K.; Kumaragurubaran, N.; Hong, L.; Lei, H.; Azhar Hussain, K.; Liu, C.-F.; Devasamudram, T.; Weerasena, V.; Turner, R.; Koelsch, G.; Bilcer, G.; Tang, J. *J. Am. Chem. Soc.* **2006**, *128*, 5310. (c) Llinás, A.; Ahmed, N.; Cordaro, M.; Laws, A. P.; Frère, J.-M.; Delmarcelle, M.; Silvaggi, N. R.; Kelly, J. A.; Page, M. I. *Biochemistry* **2005**, *44*, 7738. (d) McIntyre, J. A.; Castaner, J. *Drugs Future* **2004**, *29*, 985. (e) Wada, C. K.; Holms, J. H.; Curtin, M. L.; Dai, Y.; Florjancic, A. S.; Garland, R. B.; Guo, Y.; Heyman, H. R.; Stacey, J. R.; Steinman, D. H.; Albert, D. H.; Bouska, J. J.; Elmore, I. N.; Goodfellow, C. L.; Marcotte, P. A.; Tapang, P.; Morgan, D. W.; Michaelides, M. R.; Davidsen, S. K. *J. Med. Chem.* **2002**, *45*, 219. (f) Becker, D. P.; Barta, T. E.; Bedell, L.; DeCrescenzo, G.; Freskos, J.; Getman, D. P.; Hockerman, S. L.; Li, M.; Mehta, P.; Mischke, B.; Munie, G. E.; Swearingen, C.; Villamil, C. I. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2719.

(5) Hinchliffe, P. S.; Wood, J. M.; Davis, A. M.; Austin, R. P.; Beckett, P. R.; Page, M. I. *Org. Biomol. Chem.* **2003**, *1*, 67.

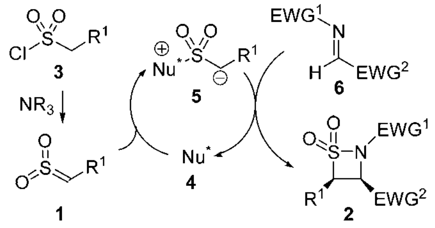
(6) See ref 4a and Page, M. I.; Hinchliffe, P. S.; Wood, J. M.; Harding, L. P.; Laws, A. P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4489.

10.1021/ol070644c CCC: $37.00 © 2007 American Chemical Society
Published on Web 04/21/2007

mammals.[7] As β-sultams are at least 2 orders of magnitude more reactive than β-lactams toward nucleophilic ring-opening reactions,[8] they also have the potential to act as versatile synthetic building blocks.[9]

In analogy to our catalytic asymmetric synthesis of β-sultones,[2] we hypothesized that a zwitterionic nucleophilic intermediate **5** generated by the addition of an enantiomerically pure nucleophile **4** to the sulfene S-atom might be capable of initiating an asymmetric [2 + 2] cycloaddition with electron-poor imines **6** to provide the title compounds **2** enantioselectively (Scheme 1).[10] The imines **6** would have to be non-nucleophilic to avoid a non-enantioselective competitive reaction as a result of direct nucleophilic addition of the imine to sulfene **1** without involvement of the enantiopure nucleophile **4**.[11] In contrast, all previously reported [2 + 2] cycloadditions of sulfenes and imines relied on the use of nucleophilic imines.[9,10]

Scheme 1. Initial Proposal for the Title Reaction



To determine whether the formation of β-sultams catalyzed by a nucleophile would at all be feasible, a catalytic amount of quinuclidine was employed as a simple achiral model system for cinchona alkaloid derivatives (Scheme 2, Table 1, entry 1). Propanesulfonylchloride (**3a**) and the chloral-derived imine **6a** reacted in dichloromethane (DCM)[12] at −80 °C in the presence of $i\mathrm{Pr_2NEt}$ (Hünig's base) as a non-nucleophilic stoichiometric auxiliary base, giving the product **2a** in high yield and with high cis-diastereoselectivity.

Scheme 2. Catalytic Formation of β-Sultams Using $n\mathrm{PrSO_2Cl}$ **3a**

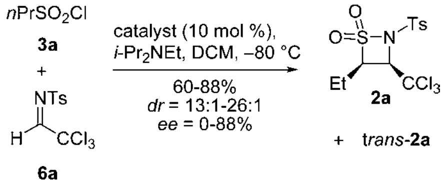
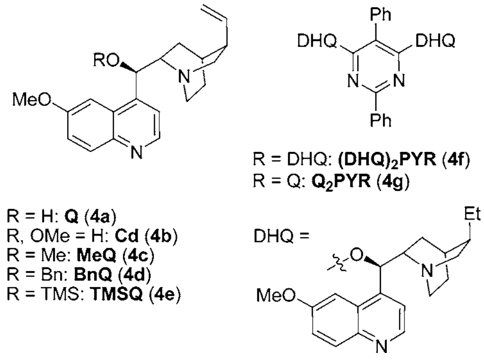


Table 1. Catalyst Screening for the Model Reaction (Scheme 2)



entry	catalyst[a]	yield[b] (%)	dr[c]	ee[d] (%)
1	quinuclidine	88	18:1	
2	quinine (Q, **4a**)	82	20:1	79
3	cinchonidine (**4b**)	78	19:1	81
4	MeQ **4c**	78	24:1	48
5	BnQ **4d**	88	26:1	60
6	TMSQ **4e**	62	14:1	39
8	$\mathrm{(DHQ)_2PYR}$ **4f**	73	13:1	1
9	$\mathrm{Q_2PYR}$ **4g**	60	13:1	21

[a] MeQ = methylquinine, BnQ = benzylquinine, TMSQ = trimethylsilylquinine. [b] Yield determined by ^{1}H NMR using nitromethane as internal standard. [c] Determined by ^{1}H NMR. [d] ee of the cis-diastereomer determined by chiral column HPLC (Daicel OD-H).

After proof of concept, various cinchona alkaloid derivatives were investigated as chiral enantiopure catalysts (catalyst loading: 10 mol %, Table 1).

The highest stereoselectivities were obtained with the alkaloids quinine (**4a**) and cinchonidine (**4b**) with free hydroxyl moieties (entries 2−3). The conditions used were found to be optimal regarding yields and ee values for all investigated sulfonylchlorides **3** having R ≥ Et (Table 2, ee = 79−94%, dr = 11:1−21:1), while the best result for ethanesulfonylchloride (**3f**) was realized with $\mathrm{Q_2PYR}$ (**4g**, entry 6).

The (R,R)-configuration of **2b** was established by X-ray crystal structure analysis (Figure 1). The ring system of the cis-configured species is only slightly puckered (dihedral angle: 6.5°), and the C−S−N angle of 79.5° explains the high reactivity as a result of ring strain.[13,14]

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(7) Selected articles: (a) Huxtable, R. J. *Physiol. Rev.* **1992**, *72*, 101. (b) Lin, C.-T.; Song, G.-X.; Wu, J.-Y. *Brain Res.* **1985**, *337*, 293. (c) Liebowitz, S. M.; Lombardini, J. B.; Salva, P. S. *Biochem. Pharmacol.* **1988**, *37*, 1303.

(8) Baxter, N. J.; Rigoreau, L. J. M.; Laws, A. P.; Page, M. I. *J. Am. Chem. Soc.* **2000**, *122*, 3375.

(9) (a) Review: Iwama, T.; Kataoka, T. *Rev. Heteroatom Chem.* **1996**, *15*, 25. (b) Hiraoka, T.; Kobayashi, T. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 480. (c) Szymonifka, M. J.; Heck, J. V. Tetrahedron Lett. **1989**, *30*, 2869.

(10) Diastereoselective [2 + 2] cycloadditions have been performed with unsubstituted sulfene and nucleophilic enantiomerically pure benzaldehyde imines: Kataoka, T. *Phosphorus, Sulfur Silicon Relat. Elem.* **1999**, *153−154*, 193.

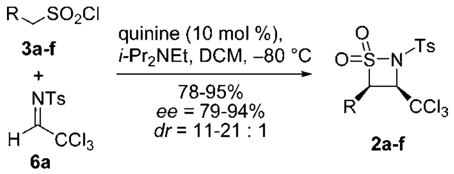
(11) Catalytic stereoselective syntheses of β-lactams using imines and ketenes have recently been reported: (a) France, S.; Shah, M. H.; Weatherwax, A.; Wack, H.; Roth, J. P.; Lectka, T. *J. Am. Chem. Soc.* **2005**, *127*, 1206. (b) Lee, E. C.; Hodous, B. L.; Bergin, E.; Shih, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 11586.

(12) The model reaction proceeded in significantly lower yields in THF, $\mathrm{Et_2O}$, or toluene.

(13) Supplemantary crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as deposition 635193. This material is available free of charge via the Internet at http://pubs.acs.org and http://www.ccdc.cam.ac.uk/products/csd/request/.

(14) Typical C−S−N angles in acyclic sulfonamides are ca. 113° (see ref 8).

Table 2. Reaction of Imine **6a** with Sulfonyl Chlorides **3**



entry	R	product	yield[a] (%)	dr[b]	ee[c] (%)
1	Et	**2a**	82	20:1	79
2	*n*Pr	**2b**	81	18:1	91
3	$(CH_2)_2Cl$	**2c**	78	11:1	94
4	CH_2Ph	**2d**	94	21:1	94
5	$(CH_2)_2OC_6H_4OMe$	**2e**	95	13:1	87
6[d]	Me	**2f**	80	17:1	80[e]

[a] Yield determined by ^{1}H NMR using nitromethane as internal standard. [b] Determined by ^{1}H NMR. [c] ee of the cis-diastereomer determined by chiral column HPLC (Daicel OD−H). [d] **4g** was used instead of quinine. [e] The product was formed with (*S*,*S*)-configuration, see Supporting Information.

The assumed base-promoted dehydrohalogenation of sulfonylchlorides **3** was examined by deuteration experiments under the standard cycloaddition conditions, but in the presence of H_3COD instead of **6a**. **3a** was mainly recovered unchanged and only traces of α-deuterated methylester were formed thus demonstrating that a sulfene is not generated in significant amounts. In the case of the catalytic asymmetric formation of *β*-sultones, we have unambiguously demonstrated the generation of sulfenes at −15 °C by deuteration experiments.[2]

According to the fact that almost no sulfene is generated at −80 °C, our mechanistic hypothesis is as follows: we assume that the quinuclidine N atom of the catalytically active species forms a zwitterionic aminal intermediate **7** by nucleophilic addition to imine **6a** and that the negatively charged N atom subsequently attacks the sulfonylchloride without prior sulfene formation (Scheme 3). The sulfonimide **8** thus generated would then be deprotonated at the α-CH_2-position of the SO_2 group to form a zwitterionic carbanion which subsequently undergoes an intramolecular nucleophilic substitution reaction to release the catalyst for the next turnover.

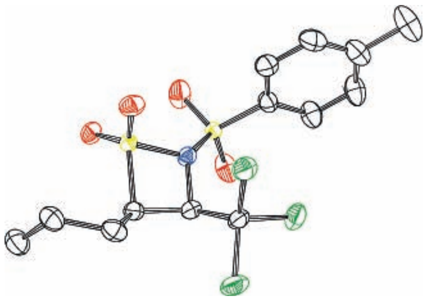
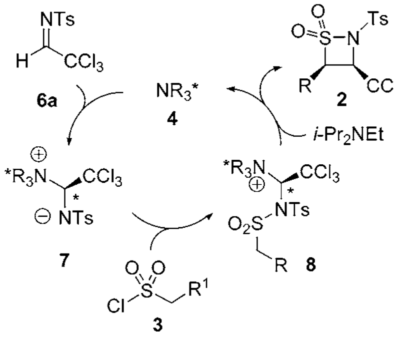


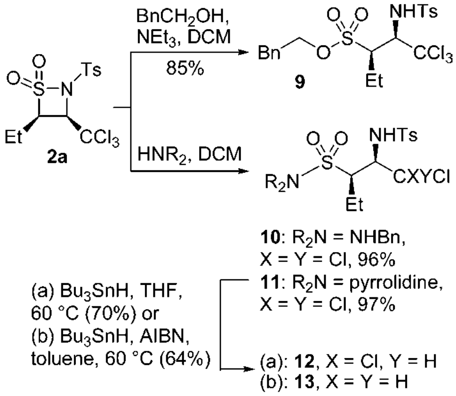
Figure 1. Ortep representation of *β*-sultam **2b** in the crystal structure. The 50% probability ellipsoids have the following color code: C, black; Cl, green; O, red; N, blue; S, yellow. H atoms are omitted for clarity.

Scheme 3. Proposed Mechanism for the *β*-Sultam Formation



The synthetic utility of the strained target compounds **2a** was demonstrated by ring opening reactions (Scheme 4).

Scheme 4. Ring Opening of *β*-Sultam **2a**



Using alcohols or primary or secondary amines as nucleophilic agents, *β*-amino sulfonates like **9** or sulfonamides **10** and **11** were formed.[15] Similar results were obtained if both the cycloaddition step and the nucleophilic ring-opening experiments with alcohols or amines were performed in the same pot without isolation of **2a**. Enantiomerically pure *β*-aminosulfonyl derivatives[16] are valuable synthetic targets, since they have been identified, for example, as MMP-13 inhibitors for the treatment of rheumatoid arthritis,[4f] MMP-2 and -9 (gelatinase A and B) inhibitors for cancer treatment,[4e] or as DNA alkylating anticancer compounds.[4d]

The trichloromethyl group can be used, for example, for a partial reduction by Bu_3SnH (Scheme 4). Depending upon reaction conditions, either the di- or the monochloro derivatives **12** or **13** were selectively obtained thus enhancing the synthetic usefulness of the chloral derived *β*-sultams **2**.

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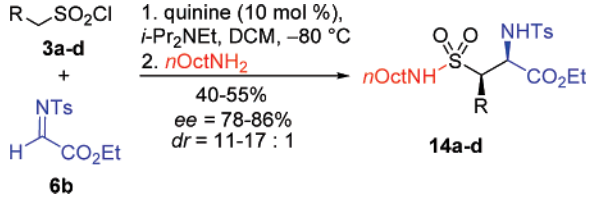
(15) *β*-Sultam **2a** was crystallized prior to use to obtain diastereomerically pure starting material (ee = 85%). The obtained *β*-amino sulfonyl derivatives were diastereomerically pure as well (^{1}H-NMR).

(16) Stoichiometric asymmetric *β*-aminosulfone formation: (a) Velàzquez, F.; Arasappan, A.; Chen, K.; Sannigrahi, M.; Venkatraman, S.; McPhail, A. T.; Chan, T.-M.; Shih, N.-Y.; Njoroge, F. G. *Org. Lett.* **2006**, *8*, 789. (b) Enders, D.; Müller, S. F.; Raabe, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 195. (c) Ma, D.; Zhu, B.; Xu, H. *Tetrahedron Lett.* **2002**, *43*, 8511.

The β-sultam methodology was extended to α-iminoester **6b** carrying a synthetically versatile ester group (Table 3).

Table 3. One-Pot Cycloaddition/Nucleophilic Ring Opening



entry	R	product	yield[a] (%)	dr[b]	ee[c] (%)
1	Et	**14a**	55	11:1	80
2	*n*Pr	**14b**	51	11:1	86
3	CH_2Ph	**14d**	40	17:1	78

[a] Isolated yield after column chromatography. [b] Determined by ^{1}H NMR. [c] ee of the cis-diastereomer determined by chiral column HPLC (Daicel OD-H).

The intermediate cycloaddition products were directly treated in the same pot with *n*-octylamine giving β-aminosulfonamides **14a–d** in moderate yield and with synthetically useful enantioselectivities.

In conclusion, we have developed an organocatalytic method which allows a rapid asymmetric access to highly enantioenriched β-sultams starting from sulfonylchlorides and non-nucleophilic imines. Our studies suggest that a zwitterionic aminal is formed as a reactive intermediate and that no sulfene formation is involved. The β-sultams are valuable precursors for the formation of enantioenriched biologically interesting β-aminosulfonyl derivatives possessing two vicinal stereocenters. Current efforts are being focused on the use of imines bearing alternative electron withdrawing groups on the nitrogen atom.

Acknowledgment. This work was supported by the Roche Research Foundation (Ph.D. fellowship to M.Z.), by the Swiss National Science Foundation, and by F. Hoffmann-La Roche. We thank Paul Seiler (ETHZ) for X-ray crystal structure determination, Prof. Erick M. Carreira and Prof. Peter Chen (both ETHZ) for sharing laboratory equipment, and Prof. Dieter Seebach (ETHZ), Dr. Martin Karpf, and Dr. Paul Spurr (both F. Hoffmann-La Roche) for critically reading this manuscript.

Supporting Information Available: Experimental procedures, full characterization data for all new products, ^{1}H/^{13}C NMR spectra and HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL070644C