Pergamon

Tetrahedron Letters 43 (2002) 5109–5111

TETRAHEDRON LETTERS

Efficient asymmetric synthesis of 3-substituted β-sultams

Dieter Enders* and Stefan Wallert

Institut für Organische Chemie, Rheinisch-Westfälische Technische Hochschule, Professor-Pirlet-Str. 1, 52074 Aachen, Germany

Received 8 May 2002; accepted 23 May 2002

Abstract—The asymmetric synthesis of 3-substituted 1,2-thiazetidine 1,1-dioxides by cyclization of β-amino-sulfonyl chlorides is reported. The synthesis is based on the aza-Michael addition of (*R*,*R*,*R*)-2-amino-3-methoxymethyl-2-azabicyclo[3.3.0]octane (RAMBO) to alkenyl–sulfonates.

1,2-Thiazetidine 1,1-dioxides (β-sultams) are the sulfonyl analogues of β-lactams. They contain three different heteroatom bonds: N–S, S–C and N–C. Cleavage of these bonds leads to a wide range of interesting building blocks for the synthesis of other heterocyclic systems or β-amino-sulfonic acids.[1]

Due to their higher reactivity compared to β-lactams (approx. 10^3-fold more reactive),[2] β-sultams are important compounds from a chemical and pharmacological point of view.

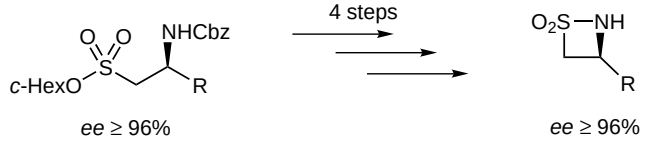
Especially, the synthesis of highly substituted β-sultams has been investigated thoroughly.[3] In addition, a major effort has been placed upon the search of new antibiotics among these β-sultams, corresponding to the β-lactam antibiotics. But so far none of the synthesized compounds have shown remarkable antibacterial activities.

Less attention was paid to the synthesis of lower substituted β-sultams, even though at least one of them has shown biological activities: *N*-benzoyl β-sultam is an irreversible inhibitor of the human neutrophil elastase (HNE). HNE has been implicated in the development of diseases such as emphysema, cystic fibrosis and rheumatoid arthritis.[4]

Enantiopure 3-substituted β-sultams have also found application in enantioselective catalysis.[5]

To the best of our knowledge only one stereoselective synthesis of β-sultams exists. Baldoli et al. used chiral tricarbonyl(η^6-arene)chromium(0) complexes in the synthesis of *N*-*tert*-butyl-3-(2-phenyl substituted)-1,2-thiazetidine 1,1-dioxide derivatives.[6] The products are enantiomerically pure, but restricted in the C-3 position (*o*-substituted phenyls).

We now wish to report an efficient four step asymmetric synthesis of 3-substituted β-sultams according to Scheme 1. In an earlier publication we presented the synthesis of β-amino-cyclohexyl sulfonates **2**.[7] The key step of this synthesis, as shown in Scheme 2, is the Lewis acid catalyzed aza-Michael addition of (*R*,*R*,*R*)-2-amino-3-methoxymethyl-2-azabicyclo[3.3.0]octane (RAMBO) to alkenylsulfonic esters **1**.



R = Et, *n*-Pr, *i*-Pr, *n*-Bu, $(CH_2)_2Ph$

Scheme 1.

1 (*S*)-**2**, *ee* ≥ 96%

R = Et, *n*-Pr, *i*-Pr, *n*-Bu, $(CH_2)_2Ph$

Scheme 2.

Keywords: asymmetric synthesis; β-sultams; 1,2-thiazetidine 1,1-dioxides; alkenyl sulfonates; Michael addition.

* Corresponding author. Tel.: +49(241)8094676; fax: +49(241) 8092127; e-mail: enders@rwth-aachen.de

0040-4039/02/$ - see front matter
PII: S0040-4039(02)00980-2

Subsequent N–N bond cleavage of the generated hydrazines utilizing BH_3·THF, and protection of the amines with CbzCl, *N*-Cbz-protected β-amino-sulfonic esters (*S*)-**2** were obtained in good yields and excellent enantiomeric excesses (ee ≥ 96%).

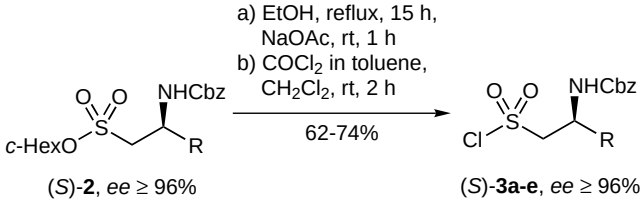
These products have now been used in the synthesis of highly enantioenriched 3-substituted β-sultams. As shown in Scheme 3, cleavage of the sulfonates (*S*)-**2** to achieve the free sulfonic acids succeeded by refluxing in ethanol. Without further purification, the crude acids were transferred to their sodium salts, followed by chlorination utilizing a $COCl_2$ solution in toluene. Chlorination by means of $SOCl_2$ or PCl_5 resulted in low yields.

After work-up, the Cbz-protected β-amino-sulfonyl chlorides (*S*)-**3a**–**e** were obtained in good yields (62–74% over two steps) and high enantiomeric excesses (ee ≥ 96%, Table 1). The enantiomeric excesses are based on those determined for the β-sultams (*S*)-**4a**–**e**.

The Cbz-protected β-amino-sulfonyl chlorides were deprotected utilizing HBr·HOAc, resulting in β-amino-sulfonyl chlorides, which were cyclized in situ using an excess of NEt_3 (Scheme 4).

Other deprotecting reagents (e.g. BCl_3) were also tested, but for the given system the best results were obtained with HBr·HOAc.

3-Substituted β-sultams (*S*)-**4a**–**e** were obtained in moderate to good yields (29–78% over two steps) and high enantiomeric excesses (ee ≥ 96%, Table 2). The enantiomeric excesses were determined by GC on chiral stationary phase (Daicel AD) by comparison with racemic samples.

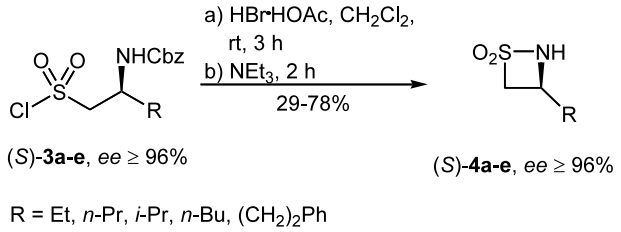


Scheme 3.

Table 1. Synthesis of Cbz-protected β-amino-sulfonyl chlorides (*S*)-**3a**–**e**

(*S*)-**3**	R	Yield (%)[a]	ee (%)[b]
(*S*)-**3a**	Et	64	≥96
(*S*)-**3b**	*n*-Pr	74	≥96
(*S*)-**3c**	*i*-Pr	67	≥96
(*S*)-**3d**	*n*-Bu	64	≥96
(*S*)-**3e**	$(CH_2)_2Ph$	62	≥96

[a] Over two steps.
[b] Based on the ee values of **4**.



Scheme 4.

Table 2. Synthesis of 3-substituted β-sultams (*S*)-**4a**–**e**

(*S*)-**4**	R	Yield (%)[a]	ee (%)[b]
(*S*)-**4a**	Et	29	≥96
(*S*)-**4b**	*n*-Pr	68	≥96
(*S*)-**4c**	*i*-Pr	47	≥96
(*S*)-**4d**	*n*-Bu	78	≥96
(*S*)-**4e**	$(CH_2)_2Ph$	55	≥96

[a] Over two steps.
[b] Determined by GC on chiral stationary phase (Daicel AD) by comparison with racemic samples.

As shown in Table 2, the β-sultams with longer alkyl chains were obtained in higher yields. This behaviour might be explained with their increasing stability towards hydrolysis. All of the synthesized β-sultams were stable under argon-atmosphere at –20°C for several weeks.

Conclusion

In summary, we have developed an efficient asymmetric synthesis of 3-substituted β-sultams. The reaction sequence starts with the cleavage of *N*-Cbz-protected β-amino-sulfonic esters to the corresponding sulfonic acids, followed by chlorination to yield β-amino-sulfonyl chlorides. After deprotection of the amino group and cyclization, the β-sultams are obtained in excellent enantiomeric purity.[8–10]

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft (SFB 380) and the Fonds der Chemischen Industrie. We thank Degussa AG, BASF AG, Bayer AG and Aventis Pharma for the donation of chemicals.

References

1. (a) Grunder, E.; Leclerc, G. *Synthesis* **1989**, 135–136; (b) Iwama, T.; Kataoka, T.; Muraoka, O.; Tanabe, G. *Tetrahedron* **1998**, *54*, 5507–5522; (c) Kataoka, T.; Iwama, T.; Takagi, A. *Tetrahedron Lett*. **1996**, *37*, 2257–2260; (d) Iwama, T.; Ogawa, M.; Kataoka, T.; Muraoka, O.; Tanabe, G. *Tetrahedron* **1998**, *54*, 8941–8974.
2. Baxter, N. J.; Rigoreau, L. J. M.; Laws, A. P.; Page, M. I. *J. Am. Chem. Soc*. **2000**, *122*, 3375–3385.

3. (a) Cavagna, F.; Koller, W.; Linkies, A.; Rehling, H.; Reuschling, D. *Angew. Chem.* **1982**, *94*, 549–550; (b) Szymonifka, M. J.; Heck, J. V. *Tetrahedron Lett.* **1989**, *30*, 2869–2872; (c) Schwenkkraus, P.; Merkle, S.; Otto, H. H. *Liebigs Ann. Rec.* **1997**, 1261–1266; (d) Schwenkkraus, P.; Otto, H. H. *Arch. Pharm.* **1993**, *326*, 437–441; (e) Schwenkkraus, P.; Otto, H. H. *Arch. Pharm.* **1993**, *326*, 519–523; (f) Gordeev, M. F.; Gordon, E. M.; Patel, D. V. *J. Org. Chem.* **1997**, *62*, 8177–8181.
4. Beardsell, M.; Hinchliffe, P. S.; Wood, J. M.; Wilmouth, R. C.; Schofield, C. J.; Page, M. I. *J. Chem. Soc., Chem. Commun.* **2001**, 497–498.
5. Trentmann, W.; Mehler, T.; Martens, J. *Tetrahedron: Asymmetry* **1997**, *8*, 2033–2043.
6. Baldoli, C.; Del Buttero, P.; Perdicchia, D.; Pilati, T. *Tetrahedron* **1999**, *55*, 14089–14096.
7. Wallert, S.; Enders, D. *Synlett* **2002**, 304–306.
8. General procedure for the preparation of compounds (*S*)-**3** and (*S*)-**4**.
   Synthesis of *N*-Cbz-protected β-amino-sulfonyl chlorides (*S*)-**3a**–**e**: *N*-Cbz-protected β-amino-sulfonates (*S*)-**2** were dissolved in EtOH (30 mL/mmol (*S*)-**2**) and refluxed for 15 h. After cooling to room temperature, 1.1 equiv. NaOAc were added and the reaction mixture was stirred for 1 h. The solvent was removed under reduced pressure and the crude sodium salts were dissolved in abs. CH_2Cl_2 (10 mL/mmol (*S*)-**2**) and abs. DMF (0.12 mL/mmol (*S*)-**2**) under argon atmosphere. Then a solution, containing 20% $COCl_2$ in toluene (1 mL/mmol (*S*)-**2**) was added dropwise to the reaction mixture. After stirring for 2 h at room temperature the products were purified by column chromatography (SiO_2, CH_2Cl_2) to afford β-amino-sulfonyl chlorides (*S*)-**3a**–**e**.
   Synthesis of β-sultams (*S*)-**4a**–**e**: β-amino-sulfonyl chlorides (*S*)-**3a**–**e** were dissolved in CH_2Cl_2 (20 mL/mmol (*S*)-**3a**–**e**). A 33% HBr in HOAc-solution was added (1.5 equiv.). After stirring for 3 h at room temperature the reaction mixture was cooled to 0°C and NEt_3 was added (12 mL/mmol (*S*)-**3a**–**e**). The solution was stirred for 2 h while it was allowed to warm up to room temperature. After separation of the organic layer the aqueous phase was extracted with CH_2Cl_2 (3×30 mL/mmol (*S*)-**3a**–**e**). After drying over $MgSO_4$ the solvent was evaporated and the products were purified by column chromatography (SiO_2, *n*-pentane/diethylether) to afford (*S*)-**4a**–**e**.
9. Selected analytical and spectroscopic data of compounds (*S*)-**3** and (*S*)-**4**. Analytic data of compound (*S*)-**3e**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.10$ (m, 2H, CH_2CH_2Ph), 2.67 (m, 2H, CH_2CH_2Ph), 3.83 (dd, $J = 14.0$ Hz, $J = 3.9$ Hz, 1H, SO_2CHH), 4.05 (dd, $J = 14.2$ Hz, $J = 6.7$ Hz, 1H, SO_2CHH), 4.15 (m, 1H, SO_2CH_2CH), 5.09 (s, 2H, OCH_2), 5.42 (d, $J = 8.2$ Hz, 1H, NH), 7.10–7.36 (m, 10H, H_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 32.5$, 35.3, 48.6, 67.5, 68.9, 126.7, 128.4, 128.6, 128.9, 128.9, 136.3, 140.3, 155.8; MS (EI): *m*/*z* 381, 290, 186, 142, 129, 108, 104, 91, 65; IR (KBr): 3676, 3653, 3590, 3331, 3062, 3030, 2927, 2861, 1695, 1541, 1498, 1454, 1383, 1356, 1285, 1255, 1212, 1166, 1083, 1049, 907, 847, 774, 743, 697, 608, 528 cm^{-1}; Anal. calcd for: $C_{18}H_{20}ClNO_4S$: C, 56.61; H, 5.28; N, 3.67. Found: C, 56.69; H, 5.50; N, 3.36%.
   Analytic data of compound (*S*)-**4e**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.08$ (m, 2H, CH_2CH_2Ph), 2.67 (m, 2H, CH_2CH_2Ph), 3.59 (m, 1H, NHCH), 3.81 (dd, $J = 12.6$ Hz, $J = 5.5$ Hz, 1H, SO_2CHH), 4.22 (ddd, $J = 12.6$ Hz, $J = 7.7$ Hz, $J = 3.3$ Hz, 1H, SO_2CHH), 5.50 (s, 1H, NH), 7.13–7.33 (kB, 5H, H_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 32.7, 37.8, 40.8, 65.1, 126.8, 128.6, 129.0, 140.0; MS (EI): $m/z = 211$, 130, 106, 91, 77, 65, 51; IR (KBr): 3676, 3654, 3632, 3273, 3032, 2925, 2856, 1656, 1604, 1497, 1456, 1384, 1331, 1302, 1265, 1231, 1203, 1156, 1098, 1083, 1060, 1031, 972, 934, 805, 753, 701, 629, 572, 519, 479 cm^{-1}; Anal. calcd for: $C_{10}H_{13}NO_2S$: C, 56.85; H, 6.20; N, 6.63. Found: C, 56.58; H, 6.56; N, 6.22%.
10. All new compounds showed suitable spectroscopic data (NMR, MS, IR) and correct elemental analyses.