Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 133–136
Tetrahedron Letters

Desulfurization of sultams with simultaneous methylenation

Victor O. Rogachev,[a,b] Sandra Merten,[a] Tobias Seiser,[a] Olga Kataeva[a,†] and Peter Metz[a,*]

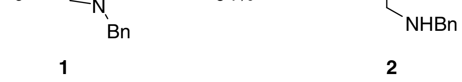
[a] *Department of Chemistry, Technische Universität Dresden, Bergstraße 66, D-01069 Dresden, Germany*
[b] *Department of Organic Chemistry, Tomsk Polytechnic University, pr. Lenina 30, 634050 Tomsk, Russia*

Received 3 October 2007; revised 29 October 2007; accepted 31 October 2007
Available online 4 November 2007

Abstract—Alkylation of γ- and δ-sultams with (iodomethyl)trimethylsilane followed by treatment of the resultant silanes with tetrabutylammonium fluoride gave rise to sulfur-free unsaturated amines. In particular, *N*-THP substituted sultams were found to be useful substrates for the alkylation event. A corresponding one-pot transformation involving sultam α-alkylation with (iodomethyl)magnesium chloride is also reported.

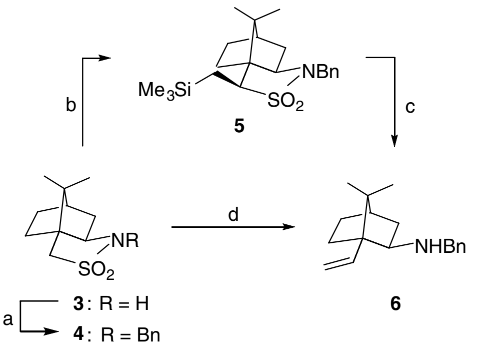
We recently reported the efficient preparation of five- and six-membered sultams by thermal and high pressure intramolecular Diels–Alder reaction (IMDA) of vinylsulfonamides possessing an acyclic, furan, or carbocyclic 1,3-diene moiety,[1] which can be used as novel chiral auxiliaries.[2] Here we communicate a study on the desulfurization of these and other sultams with simultaneous methylenation to give sulfur-free unsaturated amines. Such a transformation is known for sultones,[3] but has not been applied to sultams yet.

Our investigations commenced with a fluoride-induced desulfurization of the racemic trimethylsilyl substituted sultam **1**,[1a–c] which is readily available by IMDA of the corresponding vinylsulfonamide (Scheme 1). Resembling the cleavage of the *N*-β-(trimethylsilyl)ethylsulfonyl (*N*-SES) protecting group,[4] treatment of **1** with a commercial solution of tetrabutylammonium fluoride (5 equiv) in THF afforded amine **2** in 73% yield. Addition of freshly powdered molecular sieves (MS) 3 Å to the reaction mixture improved the yield to 94% after 2 h of reflux. This is probably due to scavenging of residual water within the commercial reagent.



Scheme 1.

While sultam **1** already contained a TMS group β to sulfur due to its method of preparation, introduction of a β-(trimethylsilyl)methyl substituent via alkylation of sultams was investigated first starting from Oppolzer sultam **3** (Scheme 2). N-Benzylation of **3** under conditions reported for the attachment of another *N*-alkyl unit to **3**[5] afforded the test substrate **4** efficiently. Similar to the corresponding elaboration of sultones,[3] desulfurization of sultam **4** with simultaneous methylenation to



Scheme 2. Reagents and conditions: (a) 1.1 equiv NaH, THF, 0 °C to reflux, then 1.1 equiv BnBr, cat. Bu_4NI, 0 °C to reflux, 98%; (b) 1.1 equiv MeLi, THF, 0 °C, then 3 equiv ICH_2SiMe_3, −78 °C to rt, 63%; (c) 6 equiv Bu_4NF, powdered MS 3 Å, THF, rt to reflux, 100%; (d) 1.2 equiv MeLi, THF, 0 °C, then 6 equiv ICH_2MgCl, −90 °C to rt, 63%.

Keywords: Alkenylation; Alkylation; Desulfurization; Sultams.

[*] Corresponding author. Tel.: +49 351 463 37006; fax: +49 351 463 33162; e-mail: peter.metz@chemie.tu-dresden.de

[†] X-ray diffraction analysis.

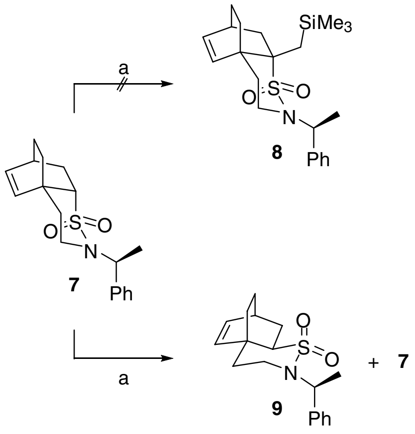
0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.10.153

give the desired amine **6** was accomplished by two alternative procedures. From a screening of different lithium bases for the deprotonation[6] of sultam **4**, methyllithium in THF (1 h 0 °C) emerged as the optimum reagent. Subsequent alkylation of **4** with (iodomethyl)trimethylsilane[7] led to a single diastereomer **5**, the relative configuration of which was elucidated by 2D NMR experiments. Fluoride-induced β-elimination of **5** in the presence of powdered MS 3 Å then gave rise to a quantitative yield of amine **6**. Next to this two-step method, the transformation of **4** to furnish **6** was also achieved with identical overall yield in a one-pot process through the treatment of α-lithiated **4** with the Julia carbenoid (iodomethyl)magnesium chloride.[8]

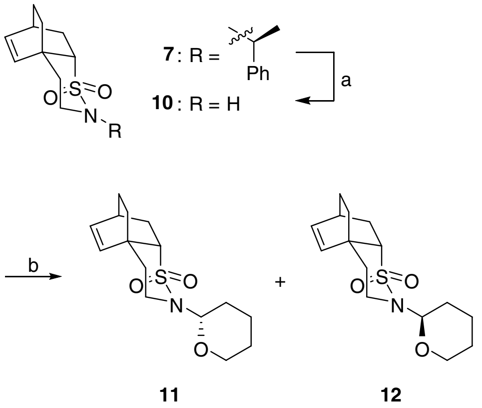
The *N*-benzyl or *N*-phenylethyl substituted δ- or γ-sultams synthesized in our earlier IMDA studies,[1a–c] for example enantiopure **7**, did not undergo alkylation by deprotonation with an alkyllithium reagent followed by treatment with methyl iodide, benzyl bromide, or (iodomethyl)trimethylsilane to give a derivative such as **8** (Scheme 3). Only a partial epimerization α to sulfur was noted under these conditions, and sultam **9**, the relative configuration of which was proven by X-ray analysis,[9] was isolated next to starting material **7**. Since TLC indicated the additional formation of a highly polar material, we suspected that a competing ring opening of the sultam with formation of an unstable sulfene might occur through decomposition of the α-lithiated sultam. Aqueous work-up would then give rise to an ammonium sulfonate.

With the aim of disfavoring such an undesired pathway, we removed the *N*-phenylethyl moiety[1a–c] from **7** and attached a potentially chelating tetrahydropyran (THP) substituent to the NH group of the resultant sultam **10** (Scheme 4).[10] Diastereomers **11** and **12** were obtained in quantitative total yield with a ratio of 4:1.[11] Unambiguous configurational assignment was achieved by X-ray diffraction analyses of sultams **11** and *ent*-**12** prepared analogously from *ent*-**10**.[9]

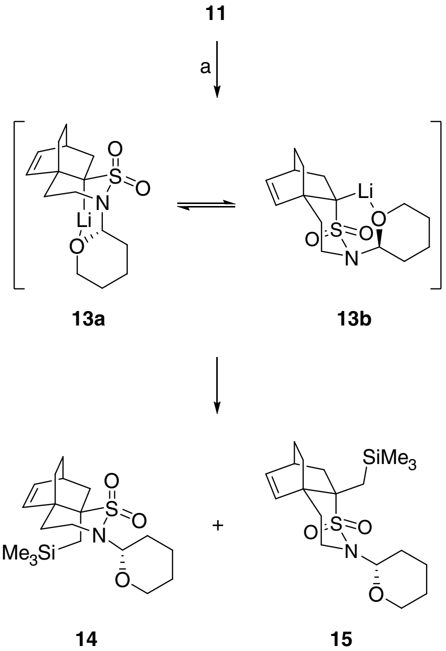
To facilitate analysis, only the pure major *N*-THP derivative **11** was subjected to desulfurization with simultaneous methylenation by the two-step procedure (Scheme 5).[12] Alkylation of **11** with (iodomethyl)trimethylsilane afforded the silyl compounds **14** and **15**[11]



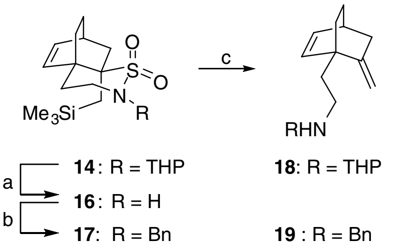
Scheme 3. Reagents and conditions: (a) 1.2 equiv MeLi, THF, −78 °C to rt, then 3 equiv ICH_2SiMe_3, −78 °C to rt, 25% **9**, 22% **7**.



Scheme 4. Reagents and conditions: (a) HCO_2H, rt, 98%; (b) 3,4-dihydro-2*H*-pyrane, PPTS, CH_2Cl_2, rt, 80% **11**, 20% **12**.



Scheme 5. Reagents and conditions: (a) 1.2 equiv MeLi, THF, −78 °C to rt, then 3 equiv ICH_2SiMe_3, −78 °C to rt; 36% **14**, 11% **15**.

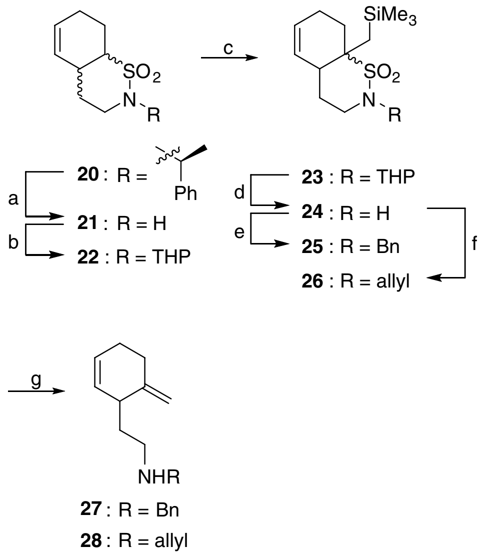


Scheme 6. Reagents and conditions: (a) EtOH, PPTS, 60 °C, 98%; (b) 1.2 equiv NaH, THF, 0 °C to reflux, then 1.5 equiv BnBr, 0 °C to reflux, 98%; (c) 5 equiv Bu_4NF, powdered MS 3 Å, THF, 0 °C to reflux, 97% **18** from **14**, 93% **19** from **17**.

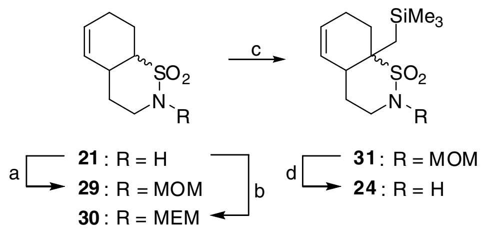
via the α-metalated intermediates **13a** and **13b**,[13] which are probably stabilized by chelate formation. The *exo* sultam **14** was obtained as the major product. Unequivocal configurational assignment was possible by X-ray diffraction analyses of sultams **14**, *ent*-**14** prepared analogously from *ent*-**11** and **15**.[9]

Exchange of the THP substituent in sultam **14** against a benzyl group additionally provided the *N*-benzyl sultam **17** as an alternative substrate for the key process (Scheme 6). Subsequent treatment of sultams **14** and **17** with tetrabutylammonium fluoride in THF furnished the desired sulfur-free amino methylenecyclohexenes **18**[11] and **19**, respectively, in high yield. Compound **18** was also produced nearly quantitatively from a mixture of **14** and **15**, which implies that the minor *endo* sultam **15** undergoes a smooth desulfurization with simultaneous methylenation as well. This methodology was also successfully applied to give *ent*-**18**[11] and *ent*-**19** commencing with sultam *ent*-**10**.[1] For sultam **17**, another X-ray diffraction analysis was achieved.[9]

In a further series of experiments, desulfurization of sultam **20** was investigated using the mixture of four diastereomers formed upon IMDA of the corresponding vinylsulfonamide[1b] (Scheme 7). To this end, the phenylethyl substituent was exchanged against a THP group. After alkylation of the resultant product **22** with (iodomethyl)trimethylsilane, the THP unit was removed from **23** to give sultam **24**. Subjecting N-metalated **24** in THF to benzyl bromide or allyl iodide delivered *N*-benzyl sultam **25** or *N*-allyl sultam **26**, respectively, in good yields. Finally, sultams **25** and **26** were converted to the sulfur-free dienyl amines **27** and **28**, respectively, by treatment with tetrabutylammonium fluoride. The low yield of **28** is due to its low boiling point, which caused a significant product loss during isolation.



Scheme 7. Reagents and conditions: (a) HCO_2H, rt, 95%; (b) 3,4-dihydro-2*H*-pyrane, PPTS, CH_2Cl_2, rt, 92%; (c) 1.2 equiv MeLi, THF, −78 °C to rt, then 3 equiv ICH_2SiMe_3, −78 °C to rt, 48%; (d) EtOH, PPTS, 60 °C, 93%; (e) 1.2 equiv NaH, THF, 0 °C to reflux, then 1.5 equiv BnBr, 0 °C to reflux, 92%; (f) 1.2 equiv NaH, THF, 0 °C to 55 °C, then 1.5 equiv allyl iodide, 0 °C to 55 °C, 91%; (g) 5 equiv Bu_4NF, powdered MS 3 Å, THF, 0 °C to reflux, 94% **27** from **25**, 34% **28** from **26**.



Scheme 8. Reagents and conditions: (a) 1.2 equiv NaH, THF, 0 °C to reflux, then 1.5 equiv MOMCl, 0 °C to reflux, 42%; (b) 1.9 equiv NaH, THF, rt, then 1.1 equiv MEMCl, 0 °C to rt, 80%; (c) 1.2 equiv MeLi, THF, 0 °C to rt, then 3 equiv ICH_2SiMe_3, −78 °C to rt, 26% **31** from **29**; (d) EtOH, PPTS, 60 °C, 43%.

With sultam **21**, the performance of two other potentially stabilizing groups on nitrogen during the alkylation step was examined (Scheme 8). Thus, **21** was converted to the *N*-MOM sultam **29** and the *N*-MEM sultam **30**. Whereas alkylation of **29** with (iodomethyl)trimethylsilane was achieved to give sultam **31**, albeit in lower yield compared to the preparation of **23** from **22**, the corresponding *N*-MEM substituted sultam **30** did not undergo alkylation upon treatment with methyl iodide as a test electrophile at all. While deblocking of *N*-MOM sultam **31** to give **24** succeeded, the yield was inferior to the corresponding deprotection of **23**. Hence, the *N*-THP unit gives the best results in terms of sultam α-alkylation as well as subsequent removal among the three *N*,*O*-acetals investigated.

In conclusion, the desulfurization of a range of γ- and δ-sultams with simultaneous methylenation was accomplished. Using the stabilizing effect of an *N*-THP unit at the stage of the α-lithio sultam, α-(trimethylsilyl)methyl substituted δ-sultams were readily obtained by alkylation. Fluoride-induced desulfurization of these silanes provided the sulfur-free unsaturated amines in good yields.

Acknowledgments

Financial support of this work by the Deutsche Forschungsgemeinschaft, the Ministry of Science and Education of Russia, the DAAD and the Bundesministerium für Bildung und Forschung is gratefully acknowledged.

References and notes

1. (a) Rogachev, V. O.; Metz, P. *Arkivoc* **2007**, 167–190; (b) Rogachev, V. O.; Metz, P. *Nat. Protoc.* **2006**, *1*, 3076–3087; (c) Rogachev, V. O.; Filimonov, V. D.; Fröhlich, R.; Kataeva, O.; Metz, P. *Heterocycles* **2006**, *67*, 589–595; (d) Rogatchov, V. O.; Bernsmann, H.; Schwab, P.; Fröhlich, R.; Wibbeling, B.; Metz, P. *Tetrahedron Lett.* **2002**, *43*, 4753–4756; (e) Plietker, B.; Seng, D.; Fröhlich, R.; Metz, P. *Tetrahedron* **2000**, *56*, 873–879; (f) Metz, P.; Seng, D.; Fröhlich, R.; Wibbeling, B. *Synlett* **1996**, 741–742.

2. (a) Zhang, S.-J.; Chen, Y.-K.; Li, H.-M.; Huang, W.-Y.; Rogatchov, V.; Metz, P. *Chin. J. Chem.* **2006**, *24*, 681–688; (b) Zhang, S. J.; Chan, W. H.; Lee, A. W. M.; Wong, W. Y.; Rogatchov, V. O.; Metz, P. *J. Chem. Res.* **2005**, 755–756.
3. (a) Merten, J.; Hennig, A.; Schwab, P.; Fröhlich, R.; Tokalov, S. V.; Gutzeit, H. O.; Metz, P. *Eur. J. Org. Chem.* **2006**, 1144–1161; (b) Merten, J.; Fröhlich, R.; Metz, P. *Angew. Chem.* **2004**, *116*, 6117–6120; *Angew. Chem., Int. Ed.* **2004**, *43*, 5991–5994; (c) Plietker, B.; Seng, D.; Fröhlich, R.; Metz, P. *Eur. J. Org. Chem.* **2001**, 3669–3676; (d) Plietker, B.; Metz, P. *Tetrahedron Lett.* **1998**, *39*, 7827–7830; (e) Metz, P. *J. Prakt. Chem.* **1998**, *340*, 1–10; (f) Metz, P.; Seng, D.; Plietker, B. *Tetrahedron Lett.* **1996**, *37*, 3841–3844.
4. (a) Weinreb, S. M.; Demko, D. M.; Lessen, T. A.; Demers, J. P. *Tetrahedron Lett.* **1986**, *27*, 2099–2102; (b) Campbell, J. A.; Hart, D. J. *J. Org. Chem.* **1993**, *58*, 2900–2903.
5. Srirajan, V.; Puranik, V. G.; Deshmukh, A. R. A. S.; Bhawal, B. M. *Tetrahedron* **1996**, *52*, 5579–5584.
6. Kaiser, E. M.; Knutson, P. L. A. *J. Org. Chem.* **1975**, *40*, 1342–1346.
7. Whitmore, F. C.; Sommer, L. H. *J. Am. Chem. Soc.* **1946**, *68*, 481–484.
8. Lima, C. D.; Julia, M.; Verpeaux, J.-N. *Synlett* **1992**, 133–134.
9. Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 656265 (**9**), CCDC 656169 (**11**), CCDC 656266 (*ent*-**12**), CCDC 656170 (**14**), CCDC 656267 (*ent*-**14**), CCDC 656171 (**15**) and CCDC 656172 (**17**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
10. For a single report on an *N*-THP sulfonamide prepared by a different method, see: Torimoto, N.; Shingaki, T.; Nagai, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2780–2784.
11. Compound **11**: $[\alpha]_D^{20}$ −6.0 (*c* 1.0, CH_2Cl_2); **12**: $[\alpha]_D^{20}$ −6.6 (*c* 1.0, CH_2Cl_2); **14**: $[\alpha]_D^{20}$ −80.0 (*c* 1.0, CH_2Cl_2); **15**: $[\alpha]_D^{20}$ +49.4 (*c* 1.0, CH_2Cl_2); **18**: $[\alpha]_D^{20}$ −97.0 (*c* 1.0, CH_2Cl_2); *ent*-**14**: $[\alpha]_D^{20}$ +80.8 (*c* 1.0, CH_2Cl_2); *ent*-**18**: $[\alpha]_D^{20}$ +97.0 (*c* 1.0, CH_2Cl_2).
12. Diastereomer **12** can be equilibrated with 3,4-dihydro-2*H*-pyrane and PPTS in CH_2Cl_2 at room temperature to give a 4:1 mixture of **11** and **12** in 94% yield.
13. For inversion of α-lithiated δ-sultones, see: Durst, T. *Tetrahedron Lett.* **1971**, *44*, 4171–4174.