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Preparation of enantiopure sultams by intramolecular Diels–Alder reaction of furan-containing vinylsulfonamides†

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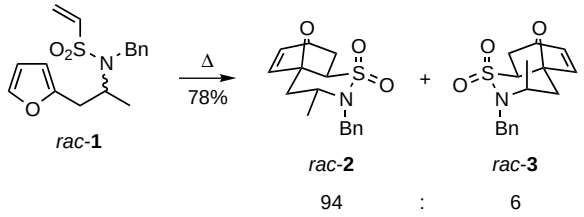
Abstract—Enantiomerically pure δ- and γ-sultams have been prepared by intramolecular [4+2] cycloaddition of *N*-1-phenylethyl substituted vinylsulfonamides with purely thermal activation and under high pressure. An optimized procedure for reductive debenzylation of the resultant δ-sultams is also reported.

We recently reported a highly diastereoselective access to δ- and γ-sultams by intramolecular Diels–Alder reaction of vinylsulfonamides[1,2] bearing furan,[1a] carbocyclic[1c] or acyclic[1c] 1,3-diene moieties (Scheme 1).

Since sultams[3] have proven to be useful heterocycles for medicinal chemistry[2a] and asymmetric synthesis,[4] we investigated the enantioselective preparation of six- and five-membered cyclic sulfonamides via thermal and high pressure[5,6] intramolecular [4+2] cycloadditions. Here we communicate our studies with furan-containing substrates featuring an external chiral auxiliary attached to the nitrogen atom.



Scheme 1.

Vinylsulfonamide **7** carrying a nitrogen-bound (*S*)-(−)-1-phenylethyl unit was easily available by nucleophilic substitution from mesylate **5**[7] derived from alcohol **4**,[8] followed by treatment of the resultant amine **6** with vinylsulfonyl chloride[9] (Scheme 2). After refluxing a solution of **7** in toluene or subjecting a solution of **7** in dichloromethane to a pressure of 13 kbar at room temperature,[10] sultams **8** and **9** were isolated in high yield. The diastereomeric ratio[11] **8**:**9** was only 1:1 for the high pressure reaction, while the (*S*)-(−)-1-phenylethyl substituent caused a significant, albeit rather low asymmetric induction under purely thermal activation.[12] Nevertheless, sultams **8** and **9** could be readily separated by flash chromatography, and their configuration was unambiguously established by X-ray diffraction analysis.[13]

Vinylsulfonamide **12** incorporating a three atom tether connecting diene and dienophile was prepared from aldehyde **10** via the known amine **11**[14] (Scheme 3). In this case, the 13 kbar cycloaddition was associated with a higher asymmetric induction than the reflux/ambient pressure process.[10,11] Again, the two sultam diastereomers produced were readily separated by flash chromatography, and their configuration was unequivocally determined by X-ray diffraction analysis of **13**.[13] Interestingly, *exo* sultam **13** was favored by (*S*)-(−)-1-phenylethyl substitution in vinylsulfonamide **12**, whereas the corresponding maleic monoamide derivative of **11** preferentially (65:35) led to the opposite configuration of the newly generated stereogenic centers at ambient temperature and pressure.[14] This is probably due to the higher steric demand of a tetrahedral sulfon-

Keywords: Diels–Alder reactions; pressure; reactions under; sultams; debenzylation.

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† Dedicated to Professor Lutz F. Tietze on the occasion of his 60th birthday.

‡ X-Ray diffraction analysis.

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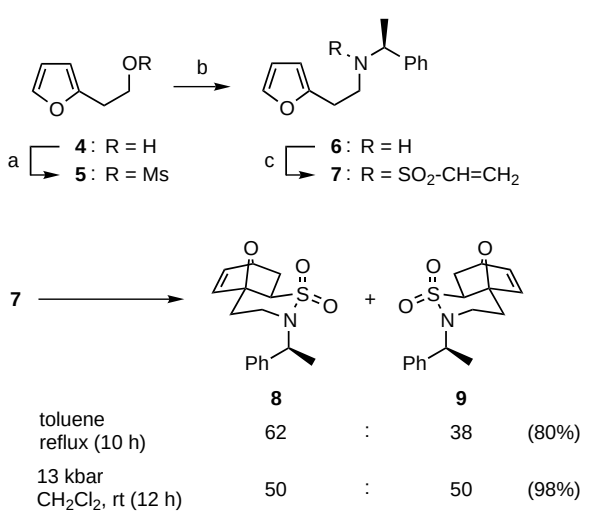
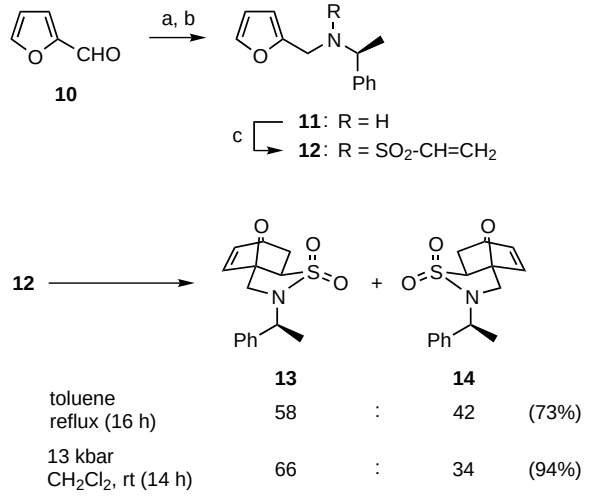


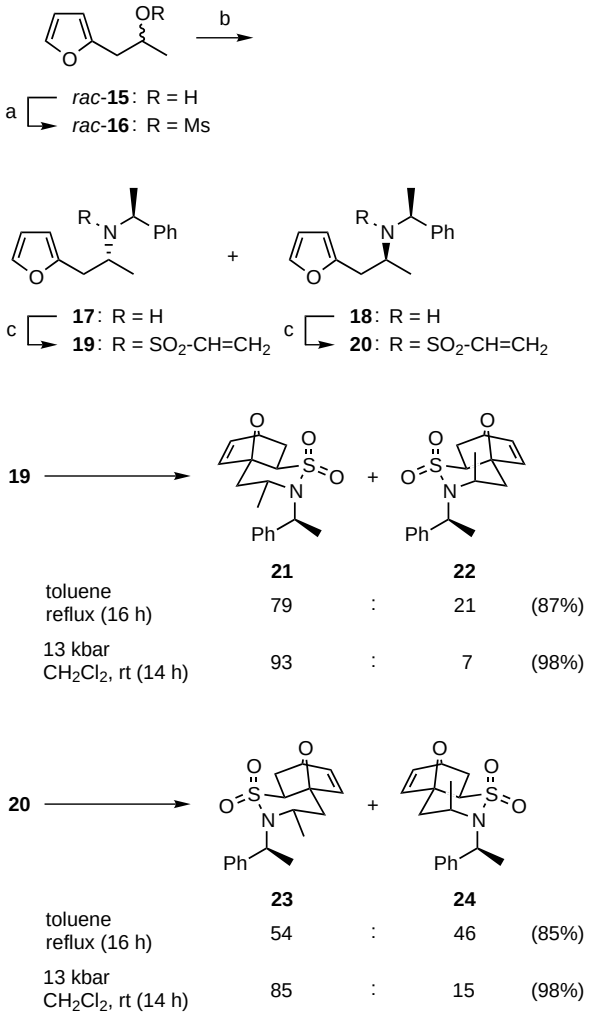
Scheme 2. *Reagents and conditions*: (a) MsCl, Et_3N, CH_2Cl_2, 0°C, 45 min, 98%; (b) 3 equiv. (*S*)-(−)-1-phenylethylamine, 80°C, 12 h, 79%; (c) CH_2=$CHSO_2Cl$, Et_3N, CH_2Cl_2, 0°C, 1 h, 96%.



Scheme 3. *Reagents and conditions*: (a) 3 equiv. (*S*)-(−)-1-phenylethylamine, $MgSO_4$, ether, 0°C to rt, 15 h, 98%; (b) $LiAlH_4$, ether, rt, 6 h, 95%; (c) CH_2=$CHSO_2Cl$, Et_3N, CH_2Cl_2, 0°C, 2 h, 98%.

amide as compared to a trigonal carboxylic amide.[15] In contrast to the crystal structures of the *N*-1-phenylethyl δ-sultams obtained in this study, all of which feature an sp^2 hybridized nitrogen atom, an sp^3 hybridization on nitrogen was unveiled by the crystal structure of γ-sultam **13**.[13]

In a third series of experiments, the double stereodifferentiation brought about by the simultaneous presence of a stereogenic center within the tether (see Scheme 1) and a chiral auxiliary on nitrogen (see Scheme 2) was investigated (Scheme 4). To this end, hydroxyalkylfuran *rac*-**15**[16] was converted by mesylation and nucleophilic substitution to give a 1:1 mixture of the diastereomeric amines **17** and **18**, which were separated by flash chromatography. Subsequent treatment of **17** and **18** with



Scheme 4. *Reagents and conditions*: (a) MsCl, Et_3N, CH_2Cl_2, 0°C, 45 min, 97%; (b) 3 equiv. (*S*)-(−)-1-phenylethylamine, 80°C, 12 h, 67%; (c) CH_2=$CHSO_2Cl$, Et_3N, CH_2Cl_2, 0°C, 2–3 h, 84% **19**, 82% **20**.

vinylsulfonyl chloride delivered the vinylsulfonamides **19** and **20**,[13] respectively, as pure stereoisomers. As depicted in Scheme 4, the diastereoselectivities noted for the high pressure cycloadditions[10,11] of **19** and **20** was hardly affected by the (*S*)-(−)-1-phenylethyl unit (compare Scheme 2), and equatorial disposition of the methyl substituent on the δ-sultam—and in the corresponding transition state—clearly dominated the stereochemical outcome of these reactions. On the other

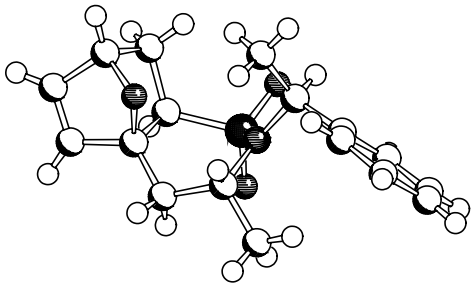
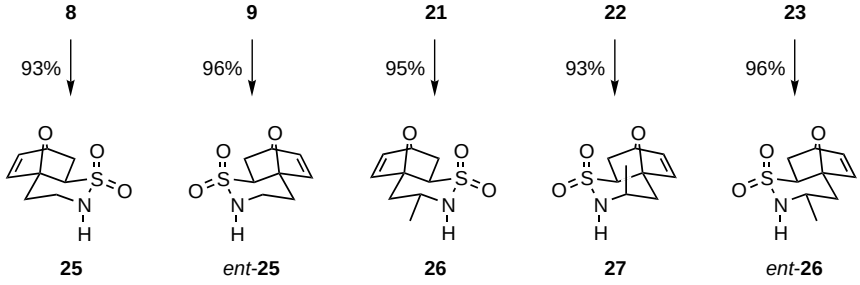


Figure 1. Crystal structure of sultam **21**.[13,17]



Scheme 5. Reductive debenzylation of *N*-1-phenylethyl δ-sultams (see text for conditions).

hand, the diastereoselectivities observed for the thermal process at ambient pressure[10,11] were critically dependent on the relative configuration of **19** and **20**.

As is apparent from the result listed in Scheme 2 and can be extrapolated from the reaction of *N*-benzyl vinylsulfonamide *rac*-**1** shown in Scheme 1, formation of sultam **21** should be favored by virtue of both stereogenic elements present in **19**. However, for substrate **20** a mismatched combination results that causes a decrease in stereocontrol. While this argument provides a consistent rationale in a qualitative sense, explanation of the very low ratio **23**:**24** = 54:46 has to take into account that the two inducing elements are not acting independently of each other. Specifically during formation of **21** and **23**, a non-bonded interaction between the methyl group on the sultam and the branched *N*-1-phenylethyl substituent can hardly be avoided. Sultams **21** and **22** were readily separated by flash chromatography, while this was not possible for the mixture of sultams **23** and **24**. Gratifyingly, pure isomer **23** could be obtained by recrystallization (ethanol) of the product mixture from the high pressure reaction instead. Unambiguous configurational assignment was achieved by X-ray diffraction analysis of sultams **21**, **22** and **23**.[13]

A consequence of the non-bonded interaction mentioned above is obvious from the crystal structure of sultam **21** (Fig. 1). In contrast to other δ-sultams investigated by X-ray crystallography in this study, all of which have a chair conformation of the sultam ring, a twist boat conformation avoiding close contacts of the sultam methyl and the exocyclic substituent on nitrogen was revealed for the six-membered heterocycle in **21**.[13]

Finally, conditions reported for reductive debenzylation of *N*-1-phenylethyl γ-sultams[2b,4d] were optimized to eventually allow a smooth and efficient cleavage of the chiral auxiliary from the δ-sultams prepared in this study (Scheme 5). First attempts using formic acid at 70°C followed by hydrolysis with 10% KOH at room temperature met with failure. However, simply stirring a 0.03 M solution of the δ-sultam in concentrated formic acid for 4 h at room temperature under argon, removal of the solvent in vacuo at maximum 40°C and flash chromatography of the residue (ethyl acetate) provided the desired debenzylated δ-sultam in high yield.[18,19] Interestingly, X-ray diffraction analysis of sultam **26** (and *ent*-**26**) unveiled an sp^3 hybridized nitrogen with axial orientation of N–H on a chair δ-sultam.[13]

In conclusion, a range of enantiopure δ- and γ-sultams was readily prepared by intramolecular Diels–Alder reaction of *N*-1-phenylethyl substituted vinylsulfonamides. Further synthetic elaboration of these heterocycles as well as extension of these studies to non-furan dienes will be reported in due course.

Acknowledgements

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10. Substrate concentration 0.025 M for all thermal cycloadditions and 0.05 M for all high pressure cycloadditions reported in this study.
11. Diastereomeric ratios were determined by ^{1}H NMR integration of the crude product mixture. Only *exo* sultams were formed.
12. For intermolecular Diels–Alder reactions of an α,β-unsaturated *N*-1-phenylethyl γ-sultam with cyclopentadienes (no asymmetric induction by the chiral *N*-substituent observed), see Ref. 2b.
13. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 183950 (**8**), CCDC 183128 (**9**), CCDC 183129 (**13**), CCDC 183130 (**20**), CCDC 183131 (**21**), CCDC 183132 (**22**), CCDC 183133 (**23**), CCDC 183134 (**26**), CCDC 183135 (*ent*-**26**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: 144-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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18. **25**: $[\alpha]_D^{20}=-10.7$ (*c* 1.0, CH_2Cl_2); *ent*-**25**: $[\alpha]_D^{20}=+10.7$ (*c* 1.0, CH_2Cl_2); **26**: $[\alpha]_D^{20}=+3.2$ (*c* 1.0, CH_2Cl_2); *ent*-**26**: $[\alpha]_D^{20}=-3.2$ (*c* 1.0, CH_2Cl_2); **27**: $[\alpha]_D^{20}=+17.8$ (*c* 1.0, CH_2Cl_2).
19. No intact γ-sultam was obtained from *N*-1-phenylethyl γ-sultams **13** and **14** using this procedure.