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Synthesis and Diels–Alder reactions of α , β -unsaturated- γ -sultams[†]

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Abstract—An efficient synthesis of prop-1-ene 1,3-sultam 4 and its Diels–Alder reactions is reported. Sultams are also prepared as chiral auxiliaries for asymmetric transformations. © 2001 Elsevier Science Ltd. All rights reserved.

In the past decade, our team have explored the uses of different sulfur-based functional groups such as sulfoxide, sulfinate and sulfonate as activators of either acetylenic or vinyl units.¹ Several versatile two- or three-carbon synthons, including chiral acetylenic sulfoxides and prop-1-ene 1,3-sultone 1,² have been prepared and have found application in Diels–Alder reactions and asymmetric synthesis.³ Sulfonamides are a very common organic functional group.⁴ Compounds containing sulfonamides are well known for their widerange of biological activities such as antibacterial⁵ and peptiomimetic.⁶ Recently, α , β -unsaturated sulfonamides were also identified as potent, irreversible inhibitors of cysteine proteases,⁷ which are essential to the life cycles of many pathogenic protozoa. However, the ability of the sulfonamide group to activate an unsaturated carbon–carbon unit as a dieneophile in Diels–Alder reactions has not been studied in detail. The only recent example found in the literature is the intramolecular Diels–Alder reactions of vinyl sulfonamides reported by Metz and co-workers.⁸ They reported that the electron withdrawing ability of the sulfonamide group toward the vinylic unit in intramolecular Diels–Alder reaction is comparable to that of a sulfonate. Based on our studies of the chemistry of α , β -unsaturated- γ -sultones, we report in this paper the synthesis and the Diels–Alder reactions of the α , β -unsaturated- γ -sultam, prop-1-ene 1,3-sultam 4.



Scheme 1. Reagents: i. reflux THF; ii. POCl₃; iii. (a) HCO₂H, 70°C, (b) KOH/EtOH; iv. BuLi; R³COCl.

Keywords: unsaturated sultam; Diels-Alder reaction; chiral auxiliaries.

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[†] This paper is dedicated to Professor Barry Sharpless on the occasion of his 60th birthday.

Our approach to 4 started from the unsaturated sultone **1**. For the unsaturated γ -sultone **1**, there are two possible carbon sites for nucleophilic attack, conjugate addition at the β -carbon or nucleophilic ring opening at the γ -carbon. It was reported that aziridinium betaine 3 was formed when butylamine was reacted with the unsaturated γ -sultone 1 (Scheme 1) presumably via the conjugate addition intermediate 2. However, we found that when a slightly more bulky primary amine, such as benzylamine 5 or α -methylbenzylamine (±)-6, was used as the nucleophile in THF, only the ring-opened products resulting from nucleophilic attack at the γ -carbon were observed. Without isolation of the ring opened products, in situ cyclization with POCl₃ afforded the N-alkylated unsaturated γ -sultams 7 and 8 in good overall yield directly from sultone 1 (60% for 5 and 75% for 6). Debenzylation with formic acid followed by deformy lation in ethanolic KOH afforded a convenient synthesis of the parent unsaturated γ -sultam, prop-1ene 1,3-sultam 4.⁹

To investigate the activating ability of the sulfonamide group, we studied the Diels–Alder reactions of **4** and the results are summarized in Table 1. Good yields of the cycloadducts were obtained but the reactivity of **4** is much lower than that of the unsaturated sultone **1**. It required days at 110°C to complete the reactions. Several Lewis acids were screened to enhance the reactivity of **4** and we found that $Ti(OEt)_4$ gave the best results. Although the reaction temperature can be lowered to $60^{\circ}C$ in CHCl₃, the rate of the reaction is still not very fast. In the case of cyclopentadiene, the *endo/exo* ratio of the cycloadducts were much improved under Lewis acid conditions (entries 1 and 2). In comparison with

Table 1. Diels–Alder reactions of α , β -unsaturated- γ -sultams

			Without Lewis acid ^a	With $Ti(OEt)_4^b$	Adducts
Entry	Dienes	Sultams	<i>T</i> /°C ; <i>t</i> /days (% yield ; <i>endo</i> : <i>exo</i>)		$\mathbf{R} = \mathbf{H}; -\mathbf{COC}_{6}\mathbf{H}_{5}; -\mathbf{COC}_{2}\mathbf{H}_{5}$
1		4	110;3 (87%;4:1)	60 ; 4 (68% ; 45 : 1)	SO ₂ NR
2		9	110 ; 4.3 (75% ; 4 : 1)	60 ; 4.8 (60% ; 35 : 1)	NR NR
3		10	110 ; 4 (80% ; 4 : 1)	60 ; 5 (75% ; 40 : 1)	
4		(+)8	110 ; 4 (80% ^c ; 7 : 3)	$\begin{array}{c} 60;5\\ (75\%^c;10:1) \end{array}$	$R = -C + \frac{CH_3}{C_6H_5}$
5	\bigcirc	4	110 ; 5 (80% ; <i>endo</i> only)	60 ; 6 (70% ; <i>endo</i> only)	
6		10	110 ; 5.4 (69% ; <i>endo</i> only)	60 ; 6.4 (65% ; <i>endo</i> only)	
7	Me	4	110 ; 6 (67%)	60;7 (65%)	
8	Me	10	110 ; 8 (60%)	60 ; 9 (57%)	Me ^r V <u>i</u> H
9	Cl ₄	4	110 ; 5 (80% ; <i>endo</i> only)	60 ; 5.7 (75% ; <i>endo</i> only)	
10		10	110 ; 5.5 (55% ; <i>endo</i> only)	60 ; 6.6 (54% ; <i>endo</i> only)	$L_{NR}^{f^{-2}}$
11		(+)8	110 ; 6 (85% ^c ; <i>endo</i> only)	60 ; 7 (80% ^c ; <i>endo</i> only)	$R = -C_{0}H_{3}$

^{*a*} Toluene; seal tube, ^{*b*} 0.9 equivalent, CHCl₃, ^{*c*} mixture of diastereomers.



X-ray structure of 11a

Scheme 2.

the unsaturated sultone, we envisaged that for the unsaturated sultam, electron withdrawing appending groups could be attached to the nitrogen atom to further moderate the reactivity or selectivity of the unsaturated sultam. Extra coordination sites could also be created for Lewis acid catalyzed reactions. Two N-acylated derivatives 9 and 10 were prepared and subjected to Diels–Alder reactions. However, their reactivities were similar to that of the parent sultam in both the uncatalyzed and Lewis acid catalyzed reactions (entries 2, 3, 6, 8 and 10).

Homochiral sultams such as the Oppolzer's camphor sultams are important chiral auxiliaries in asymmetric synthesis.¹⁰ We envisaged that if a chiral group is attached to the sultam's nitrogen, optically pure tricyclic sultams can be synthesized from the Diels-Alder cycloadducts. Homochiral unsaturated γ -sultam (+)-8 was synthesized using optically pure (S)-(-) α -methylbenzylamine (-)-6 in the reaction with the sultone (Scheme 1). When (+)-8 was subjected to the uncatalyzed Diels-Alder reactions with cyclopentadiene, 80% yield of the diastereomeric cycloadducts with endo/exo ratio of 7:3 were formed (entry 4). The diastereomeric ratio of the endo-isomers was 1:1 as determined by NMR. They can be separated into optically pure forms by column chromatography. After debenzylation, optically pure exo- and endo-tricyclic sultams were obtained. With Ti(OEt)₄, the endo-diastereomers were almost the exclusive product. However, the diastereoselectivity was not improved. These tricyclic sultams had also been previously prepared by us from Diels-Alder cycloadducts using unsaturated sultone 1 as the dieneophile.¹¹ The present approach to the synthesis of these chiral tricyclic sultams with unsaturated γ -sultam (+)-8 as the dieneophile is more convergent. In the reaction with 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene, either under uncatalyzed or Lewis acid catalyzed conditions (entry 11), only the endodiastereomers 11a, 11b (1:1) were obtained. The two endo-diastereomers were separated into optically pure forms by column chromatography. The structure of one of the diastereomers 11a was determined by X-ray analysis.¹² After debenzylation, a new pair of enantiomerically pure chlorine substituted tricyclic sultams (**12a**, **12b**) were obtained (Scheme 2). Methods for using these optically pure tricyclic sultams in asymmetric synthesis are in progress.

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References

- Lee, A. W. M.; Chan, W. H. In *Top. Curr. Chem.*; Metz, P., Ed.; Springer, 1997; Vol. 190, pp. 103–129.
- Lee, A. W. M.; Chan, W. H.; Jiang, L. S.; Poon, K. W. Chem. Commun. 1997, 611.
- (a) Chan, W. H.; Lee, A. W. M.; Jiang, L. S.; Mak, T. C. M. *Tetrahedron: Asymmetry* 1997, *8*, 2501–2504; (b) Lin, J.; Chan, W. H.; Lee, A. W. M.; Wong, W. Y. *Tetrahedron* 1999, *55*, 13983–13998.
- Tanaka, K. In *The Chemistry of Sulphonic Acid, Esters* and *Their Derivatives*; Patai, S.; Rappoport, Z., Eds.; Wiley: New York, 1991; pp. 401–452.
- 5. Vree, T. B.; Hekstar, Y. A. Antibiol. Chemother. 1987, 37, 1.
- (a) Gennari, C.; Salom, B.; Potenza, D.; Williams, A. Angew. Chem., Int. Ed. Engl. 1994, 33, 2067; (b) Gennari, C.; Nestlei, H. P.; Salom, B.; Still, W. C. Angew. Chem., Int. Ed. Engl. 1995, 34, 1763.
- Roush, W. R.; Gwaltney, II, S. L.; Cheng, J.; Scheidt, K. A.; McKerrow, J. H.; Hansell, E. J. Am. Chem. Soc. 1998, 120, 10994–10995.
- Plietker, B.; Seng, D.; Fröhlich, R.; Metz, P. *Tetrahedron* 2000, 56, 873–879.
- 9. Prop-1-ene 1,3-sultam 4: mp 82–83°C; ¹H NMR (CDCl₃, 270 MHz): δ 4.15 (t, 2H, J=2.43 Hz), 4.88 (s, 1H), 6.73 (dt, 1H, J=6.48, 2.43), 6.87 (dt, 1H, J=6.48, 2.43 Hz).
 ¹³C NMR (CDCl₃, 67.8 MHz): δ 47.6, 127.49, 137.40. IR (KBr) ν (cm⁻¹): 3241, 3100, 1604, 1388, 1276, 1155.

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- Lee, A. W. M.; Chan, W. H.; Yuen, W. H.; Xia, P. F.; Wong, W. Y. *Tetrahedron: Asymmetry* 1999, 10, 1421– 1424.
- 11. Jiang, L. S.; Chan, W. H.; Lee, A. W. M. *Tetrahedron* **1999**, *55*, 2245–2262.
- 12. Crystal data for 11a: $C_{18}H_{19}Cl_4NO_4S$, M = 487.20,

orthorhombic, $P2_12_12_1$ (no. 19), a=9.4717(7), b=14.561(1), c=15.116(1) Å, V=2084.8 (3) Å³, Z=4, T=293 K, μ (Mo-K α)=6.93 cm⁻¹, 12115 reflections measured, 4660 unique, ($R_{\rm int}=0.0241$), final $R_1=0.0284$, $wR_2=0.0757$ (based on F^2) for 4660 [$I>2\sigma(I)$] observed reflections.