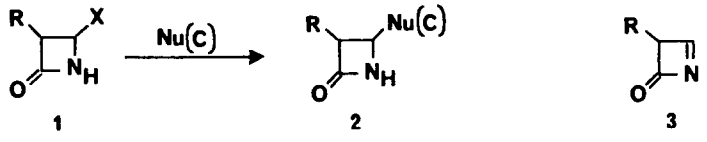
Tetrahedron Letters,Vol.26,No.51,pp 6309-6312,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

CYCLOCONDENSATION ADDUCTS FROM THE LEWIS ACID MEDIATED REACTION OF 4-ACETOXY-2-AZETIDINONE WITH SILOXYDIENES

Yasutsugu Ueda [a*,b] and Susan C. Maynard[a]
Pharmaceutical Research and Development Division, Bristol-Myers Co.,
a: PO Box 4755, Syracuse, NY, 13221-4755, USA
b: Candiac, Quebec, J5R 1J1, Canada

Abstract: A successful trapping of 1-azetin-4-one with siloxydienes as cyclocondensation adducts is described.

Recent advances in the displacement reactions of 2-azetidinone 1 at the 4-position with carbon nucleophiles[1] have made a significant contribution to the development of new synthetic approaches to carbapenem antibiotics such as thienamycin[2]. Among these methods, the Lewis acid mediated displacement reaction of 4-acetoxy-2-azetidinone 1 (X=OAc) with silylenolethers as carbon nucleophiles[1c,1d] was of particular interest to us[3]. In this type of reaction, the azetinone 3 has been postulated as a reactive intermediate based on the stereochemical outcome of the reaction. The involvement of the azetinone 3 as an intermediate had previously been proposed in similar substitution reactions[4]. However, no report of a succsssful experiment to trap this reactive intermediate 3 as a cycloadduct has so far appeared[1b,5].



1 2 3

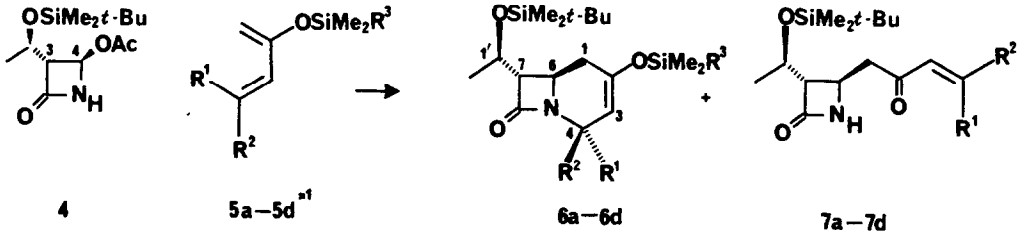
X = OAc, Cl, etc.

[2+4] Cycloaddition of dienes to activated imines have been well documentated[6]. Recently, Danishefsky and Kerwin reported [7] the Lewis acid catalyzed cyclocondensation of non-activated imines with a siloxydiene to give hetero Diels-Alder adducts under mild conditions[8]. In view of their results it is reasonable to assume that azetinone 3, generated from 4-acetoxyazetidinone 1 (X=OAc), might be trapped as a cyclocondensation adduct using a proper siloxydiene in the presence of a Lewis acid.

Here we wish to report the isolation of the cyclocondensation adducts from the zinc chloride mediated reaction of 4-acetoxy-2-azetidinone with siloxydienes. The siloxydiene 5a,

derived from methyl vinyl ketone, was subjected to $ZnCl_2$ mediated reaction [1c,1d,3] with 4-acetoxy-2-azetidinone 4[9] (Scheme 1). In CH_2Cl_2 at room temperature or in refluxing CH_3CN, the reaction, as anticipated, gave a cyclocondensation adduct 6a[10] as well as an expected displacement product 7a. Trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf) as a catalyst[1b] in place of $ZnCl_2$ failed to give any cyclocondensation adduct 6a, producing only a 4-substituted azetidinone 7a in low yield. Three other silyoxydienes, 5b-5d, were also subjected to the $ZnCl_2$ mediated reaction with 4-acetoxy-2-azetidinone 4. The siloxydiene 5b, derived from trans-pent-3-en-2-one[11], also successfully trapped the azetinone 3 as a cycloadduct to give 4β-methyl-carbaceph-2-em 6b[10] as a major stereoisomer. The stereoselectivity, observed here, may be explained by the endo addition of the imine to the siloxydiene[6] or a stepwise mechanism through a chair-like transition state.[12] The other two siloxydienes 5c and 5d did not give any cyclocondensation adducts. These results are summarized in the Scheme 1.

SCHEME 1



	conditions*2	yield of (%)*3	
		6	7
a:R^1=R^2=H, R^3=Me	$ZnCl_2/CH_2Cl_2$,rt	16	37
	$ZnCl_2/CH_3CN$, reflux	18	75
	Me_3SiOTf/CH_2Cl_2, rt	0	18
b: R^1=H, R^2=R^3=Me	$ZnCl_2/CH_3CN$, reflux	20	47
c: R^1=H, R^2=Ph, R^3=tBu	$ZnCl_2/CH_2Cl_2$,rt	0	72
d: R^1=R^2=R^3=Me	$ZnCl_2/CH_3CN$, reflux	0	48

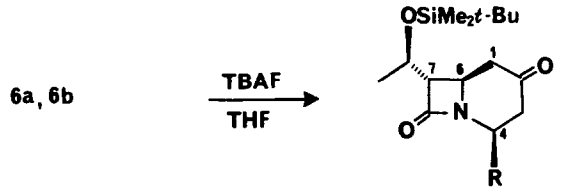
*1 Siloxydienes 5a, 5b and 5d were prepared from the corresponding ketones by the method of Jung [14] and siloxydiene 5c was prepared by the method described in ref. 3.

*2 Typically, 4 (1 mmol) and 5 (1.5-2.0 mmol) in CH_2Cl_2 (10 mL) were treated with $ZnCl_2$ (0.5 mmol, fused) or Me_3SiOTf (0.2 mmol).

*3 Isolated yield after column chromatography on silica gel.

The structural and stereochemical assignments of the cycloadducts, 6a and 6b, were made based on the analysis of their ir spectra and 350-MHz ^{1}H nmr spectra[10] which included homonuclei decoupling experiments. The trans-stereochemistry of the β-lactam in adducts, 6a and 6b, was readily established from the H_6-H_7 coupling constant of 1.3 Hz[13]. The presence of the trimethylsilylenolether moiety in 6a and 6b was evident based on their ^{1}H nmr spectra which exhibited the trimethyl group at 0.18-0.19 ppm as a siglet and vinyl proton (H=3) at 4.76-4.82 ppm as a multiplet.

The assignment of the structure and stereochemistry of cycloadducts, 6a and 6b, was further supported by their transformation to bicyclic ketones, 8a[10] and 8b[10], respectively and by the complete analysis of their 360-MHz ^{1}H nmr spectra[10] including decoupling studies.



8a; R=H
8b; R=Me

Similar cycloadducts were also obtained from the $ZnCl_2$ mediated reaction of the parent 4-acetoxy-2-azetidinone 1 (X=OAc, R=H) with siloxydienes, 5a and 5b.
To our knowledge this is the first demonstration that the much postulated reactive intermediate, 1-azetin-4-one 3, has been trapped as a cyclocondensation adduct with siloxydienes.
Notwithstanding the low yield, this reaction, the formation of a cyclocondensation adduct, provides a unique one-step process to a carbacephem/carbacepham ring system from 4-acetoxy-2-azetidinones.

Acknowledgements: We would like to thank Dr. A. Martel for helpful discussions and Drs. M. Menard, B. Belleau and R. A. Partyka for their interest in this work. We would also like to acknowledge the Analytical Research Department (Syracuse) for the 360-MHz ^{1}H nmr spectra and decoupling experiments.

References and Notes

1. a) For a review, see: T. Kametani, Heterocycles 17, 463 (1982)
b) R. P. Attrill, A. G. M. Barrett, P. Quayle, J. van der Westhuizen, and M. J. Betts, J. Org. Chem., 49 1679 (1984) and references therein
c) P. J. Reider, R. Rayford, and E. J. J. Grabowski, Tetrahedron Lett., 23, 379 (1982)
d) P. J. Reider and E. J. J. Grabowski, Tetrahedron Lett., 23, 2293 (1982).

2. For a review, see: R. W. Ratcliffe, and G. Albers-Schonberg, in "Chemistry and Biology of β-Lactam Antibiotics", Vol. 2, Edited by R. B. Morin and M. Gorman, Academic Press, New York, NY, 1982, pp 227-313.
3. Y. Ueda, G. Roberge, and V. Vinet, Can, J. Chem., 62, 2936 (1984).
4. a) M. D. Bachi, A. Gross, F. Frolow, J. Org. Chem., 47, 765 (1982) and references therein
b) T. Kobayashi, N. Ishida and T. Hiraoka, Chem. Comm., 736 (1980)
c) S. Oida, A. Yoshida, and E. Ohki, Chem. Pharm. Bull. Japan, 28, 3494 (1980).
5. A cycloadduct has been observed from the reaction of 4-chloro-3-bromo-2-azetidinone 1 (X=Cl, R=Br) with 1-ethoxy-1,3-di(trimethylsiloxy)-1,3-butadiene in the absence of catalyst: A. Martel, private communication.
6. S. M. Weinreb and J. I. Levin, Heterocycles, 12, 949 (1979); S. M. Weinreb and R. R. Staib, Tetrahedron, 38, 3087 (1982).
7. S. Danishefsky and J. F. Kerwin, Jr., J. Org. Chem., 47, 3183 (1982); J. F. Kerwin, Jr. and S. Danishefsky, Tetrahedron Lett., 23, 3739 (1982).
8. For recent application, see: J. P. Vacca, Tetrahedron Lett., 26, 1277 (1985).
9. A. Yoshida, T. Hayashi, N. Takeda, S. Oida, and E. Ohki, Chem. Pharm. Bull. Japan, 29, 2899 (1981).
10. Spectral data (^{1}H nmr, 360 MHz, $CDCl_3$, δ ppm): 6a: ^{1}H nmr: 0.05(6H,s), 0.18(9H,s), 0.85(9H,s), 1.22(3H,d,J=6Hz) 2.19(1H,ddq,J=17,9,2.8Hz, allylic and homoallylic couplings $J_{1,3}=J_{1,4}=2.8$Hz were observed, H-1), 2.27(1H,m,H-1), 2.73(1H,dd,J=5.5,1.4Hz,H-7), 3.47(1H,dq,J=17,2.6Hz,H-4), 3.54(1H,ddd,J=9,5.8,1.4Hz,H-6), 4.11(1H,dt,J=17,2.8Hz,H-4) 4.14(1H,m,H-1′), and 4.82(1H,q,J=2.9Hz,H-3); ir(KBr): 1730, 1660cm^{-1}; mp76-8°C. 6b: ^{1}H nmr: 0.05(6H,s), 0.19(9H,s), 0.85(9H,s), 1.21(3H,d,J=6Hz), 1.48(3H,d,J=6.6Hz,4-Me), 2.18-2.25(2H,m,1-H), 2.74(1H,dd,J=5.7,1.7Hz,H-7),3.47(1H,ddd,J=8.3,6.4,1.7Hz,H-6), 3.93(1H,m,H-4; this became q, J=2.3Hz and qt, J=6.6,2.1Hz when irradiated at 1.48 and 4.76 ppm respectively), 4.12(1H,qi,J=6Hz, H-1′), and 4.76 (1H,m,H-3); ir(KBr): 1730,1660cm^{-1}; mp71-3°C.
8a: ^{1}H nmr: 0.04(3H,s), 0.05(3H,s), 0.84(9H,s), 1.21(3H,d,J=6.5Hz), 2.37(1H,dddd,J=14,3.2,2.2,1.2Hz,H-3,eq-like), 2.42(1H,dd,J=13.4,10.5Hz,H-1,ax-like), 2.50(1H,ddd,J=14,10.6,8.2Hz,H-3,ax-like),2.74(1H,ddd,J=14,4.5,1.2Hz,H-1,eq-like), 2.98(1H,dd,J=5.1,1.2Hz,H-7), 3.15(1H,ddd,J=13.4,10.5,3.2Hz,H-4,ax-like), 3.71(1H,ddd,J=10.4,4.5,1.3Hz,H-6,ax-like), 4.20(1H,ddd,J=13.3,8.4,2.2Hz,H-4,eq-like), and 4.20(1H,qi,J=5.5Hz,H-1′); ir (KBr): 1760,1740,1715cm^{-1} mp34-6°C. 8b: ^{1}H nmr: 0.05(3H,s), 0.06(3H,s), 0.85(9H,s), 1.18(3H,d,J=6.4Hz), 1.62(3H,d,J=6.6Hz,4-Me), 2.28(1H,dd,J=13.8,9.8Hz,H-3,ax-like), 2.40(1H,dd,J=13.9,11Hz,H-1,ax-like), 2.43(1H,ddd,J=14,4.4,1.2Hz,H-3,eq-like), 2.68(1H,ddd,J=14,4.4,1.2Hz,H-1,eq-like), 2.87(1H,dd,J=4.4,1.3Hz,H-7), 3.61(1H,m,H-4,ax-like; this became dd, J=10,4.5Hz when irradiated at 1.62 ppm), 3.63(1H,ddd,J=11,4.4,1.3Hz,H-6,ax-like), and 4.17(1H,m,H-1′);ir(film):1760,1735cm^{-1} oil.
11. H. O. House. W. L. Respess, and G. M. Whitesides, J. Org. Chem., 31, 3128 (1966).
12. At this moment, it is not certain whether the mechanism is [4+2] cycloaddition or a stepwise process.
13. P.V. Demarco and R. Nagarajan, in "Cephalosporins and Penicillins: Chemistry and Biology", Edited by E.H. Flynn, Academic Press, New York, NY, 1972, pp.330-340.
14. M. E. Jung and C. A. McCombs, Org. Syn., 58, 163 (1978).

(Received in USA 27 August 1985)