A Novel Fragmentation of the β-Lactam Ring: Stereoselective Entry to Vinyl Ethers by Reaction of N-(Arylidene(or alkylidene)amino)-2-azetidinones with Ozone

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Received September 22, 1992 (Revised Manuscript Received November 17, 1992)

Summary: The title compounds undergo a novel 2-azetidinone ring fragmentation by reaction with ozone followed by $NaBH_4$ workup to stereoselectively yield vinyl ethers via intermediate *N*-nitroso-β-lactams.

The strained β-lactam ring renders these fascinating molecules powerful synthetic building blocks[1] and useful intermediates in the synthesis of a variety of β-lactam antibiotics.[2] Opening of the 2-azetidinone ring can occur through cleavage of any of the single bonds of the four-membered ring (Figure 1). Cleavage of the amide bond (*a* in Figure 1) by nucleophiles is a well-known process and has been the subject of many investigations.[3] *N*-Carboxy anhydrides have been obtained by cleavage of the C2–C3 bond (*b* in Figure 1), either by peracid oxidation[4a,b] of azetidine-2,3-diones or ozonation[4c] of α-ethylidene-2-azetidinones. This type of cleavage has also been reported to occur in *N*-halo-2-azetidinones to form haloalkyl isocyanates.[5] 3,3-Diphenyl-4-amino β-lactams undergo C3–C4 bond cleavage (*c* in Figure 1) in the presence of moisture to give substituted amides.[6] C4–N1 bond breakage (*d* in Figure 1)[7] is known to occur when 4-aryl β-lactams are subjected to palladium-catalyzed hydrogenation or metal–ammonia reduction.[8] Additionally, cleavage of monocyclic β-lactams under electron-impact mass spectrometry is known to occur to produce

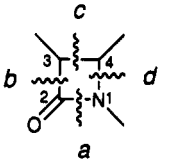


Figure 1.

two different fragmentation patterns, leading to ketene and/or imine ions (A-type cleavage) or to olefin and/or isocyanate ions (B-type cleavage).[9] A-type ring cleavage also occurs under photolysis[10] while pyrolysis promotes B-type fragmentation.[11]

Here, we report the novel fragmentation process of *N*-arylidene- or *N*-(alkylideneamino)-β-lactams 1[12] to yield vinyl ethers stereoselectively. Thus, reaction of compounds 1 with ozone at −78 °C followed by standard sodium borohydride reductive workup affords vinyl ethers 2 in fairly good yields (Table I), and with good stereoselectivity, together with the expected primary alcohols.[13] It is noteworthy that this reaction is the reverse of the well-known vinyl ether–isocyanate route to the 2-azetidinone system but *with the opposite regiochemistry*,[14] and, to the best of our knowledge, this is the first time that a B-type cleavage of the 2-azetidinone ring is reported under smooth chemical conditions. Furthermore, although several routes to vinyl ethers are known,[15] none of them involve a stereoselective process starting from β-lactams.

Formation of vinyl ethers 2 may occur through the electrophilic attack of ozone on the C–N double bond, assisted by the lone electron pair of the endocyclic nitrogen, to form an intermediate *N*-nitroso-β-lactam 3.[16] Inter-

(1) For reviews, see: (a) Manhas, M. S.; Wagle, D. R.; Chiang, J.; Bose, A. K. *Heterocycles* **1988**, *27*, 1755. (b) Kano, S. J. *J. Synth. Org. Chem., Jpn.* **1978**, *36*, 581. (c) Ojima, I.; Hatanaka, N. *J. Synth. Org. Chem., Jpn.* **1982**, *40*, 209. (d) Ojima, I. In *Asymmetric Reactions and Processes in Chemistry*; Eliel, E. L., Otsuka, S., Eds.; ACS Symposium Series; American Chemical Society: Washington, DC, 1982; Vol. 185, p 109. For leading references, see also: (e) Wasserman, H. H.; Leadbetter, M. R.; Kopka, I. E. *Tetrahedron Lett.* **1984**, *25*, 2391. (f) Wasserman, H. H.; Matsuyama, H. *J. Am. Chem. Soc.* **1981**, *103*, 461. (g) Combie, L.; Jones, R. C.; Osborne, S.; Mat-Zin, Ab. R. *J. Chem. Soc., Chem. Commun.* **1983**, 959. (h) Ojima, I.; Pei, Y. *Tetrahedron Lett.* **1992**, *33*, 887.

(2) For general reviews in synthesis and biology of β-lactam antibiotics, see: (a) Dürckheimer, W.; Blumbach, J.; Lattrell, R.; Scheunemann, K. H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 180. (b) *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vols. 1–3. (c) *Recent Progress in the Chemical Synthesis of Antibiotics*; Lucas, G., Ohno, M., Eds.; Springer-Verlag: Berlin–Heidelberg, 1990. (d) Hungerbühler, E.; Biollaz, M.; Ernest, I.; Kalvoda, J.; Lang, M.; Schneider, P.; Sedelmeier, G. In *New Aspects of Organic Chemistry I*; Yoshida, Z., Shiba, T., Ohshiro, Y., Eds.; VCH: Tokyo, 1989; p 419.

(3) See, for example: (a) Stoodley, R. J. *Tetrahedron* **1975**, *31*, 2321. (b) Sammes, P. G. *Chem. Rev.* **1976**, *76*, 113. (c) Issacs, N. S. *Chem. Soc. Rev.* **1976**, *5*, 181. (d) Labia, R.; Morin, C. *J. Antibiot.* **1984**, *37*, 1103. (e) *Topics in Antibiotic Chemistry*; Sammes, P. G., Ed.; John Wiley: New York, 1980; Vols. 3 and 4.

(4) (a) Cossio, F. P.; Arrieta, A.; Oiarbide, M.; Aparicio, D.; Rubiales, G.; Palomo, C. *Tetrahedron Lett.* **1988**, *28*, 3133. (b) Palomo, C.; Cossio, F. P.; Rubiales, G.; Aparicio, D. *Tetrahedron Lett.* **1991**, *32*, 3115. (c) Bateson, J. H.; Kaura, A. C.; Southgate, R. *Tetrahedron Lett.* **1991**, *32*, 2065.

(5) Kampe, K. D. *Tetrahedron Lett.* **1969**, 117.

(6) Bose, A. K.; Kugajevsky, I. *Tetrahedron* **1967**, *23*, 957.

(7) 4-Amino-3,3-dimethyl-β-lactams are readily hydrolyzed to amino aldehydes through 1,4-bond cleavage. See: (a) Perelman, H., Mizsak, S. A. *J. Am. Chem. Soc.* **1962**, *84*, 4988. (b) Opitz, G., Koch, J. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 152.

(8) See, for example: (a) Ojima, I.; Chen, H.-J. C.; Nakahashi, K. *J. Am. Chem. Soc.* **1988**, *110*, 278. (b) Ojima, I.; Chen, H.-J. C.; Qiu, X. *Tetrahedron* **1988**, *44*, 5307. (c) Hatanaka, N.; Abe, R.; Ojima, I. *J. Chem. Soc., Chem. Commun.* **1981**, 344.

(9) See, for example: (a) Bourgeois, G.; Picard, J. P.; Cossio, F. P.; Palomo, C. *Adv. Mass Spectrom.* **1989**, *11A*, 876. (b) Georgiev, V. S.; Coomber, D. C.; Mullen, G. B. *Org. Mass. Spectrom.* **1988**, *23*, 283 and references cited therein.

(10) Fischer, M. *Chem. Ber.* **1968**, *101*, 2669.

(11) Thermolysis goes with virtually total retention of the stereochemistry of the starting materials through a concerted [σ2s + σ2a] cycloreversion. See: Paquette, L. A.; Wyvratt, M. J.; Allen, G. R., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 1763. For a related example in 2-azetinones, see: Kappe, C. O., Kollenz, G., Netsch, K.-P., Leung-Toung, R., Wentrup, C. *J. Chem. Soc., Chem. Commun.* **1992**, 488.

(12) Compounds 1 are easily prepared by [2 + 2] cycloaddition of alkoxy ketenes and the appropriate azine. These syntheses will be published elsewhere.

(13) Vinyl ether nature for compounds 2 was established by independent synthesis of compound 2 ($R^1 = CH_3$; $R^2 = p\text{-}CH_3OC_6H_4$) as 1:1 *Z*/*E* mixture from *p*-methoxybenzaldehyde and methoxymethylenetriphenylphosphonium ylide following the procedure reported by Nicolau. See: Nicolau, K. C., Magolda, R. L., Claremon, D. A. *J. Am. Chem. Soc.* **1980**, *102*, 1404.

(14) See, for example: (a) Effenberger, F.; Kiefer, G. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 951. (b) Effenberger, F.; Prossel, G.; Fischer, P. *Chem. Ber.* **1971**, *104*, 2002.

(15) (a) For a review, see: Chan, T.-H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 2, p 596. (b) Solà, L.; Castro, J.; Moyano, A.; Pericás, M.; Riera, A. *Tetrahedron Lett.* **1992**, *33*, 2863 and references cited therein.

(16) A similar mechanism has been proposed by Erickson et al. for the ozonation of dimethylhydrazones to give carbonyl compounds and *N*-nitrosodimethylamine. See: Erickson, R. E.; Andrulis, P. J.; Collins, J. C.; Lungle, M. L.; Mercer, G. D. *J. Org. Chem.* **1969**, *34*, 2961.

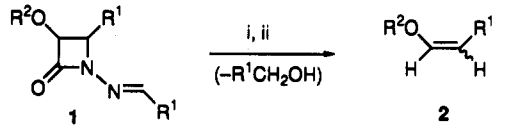
0022-3263/93/1958-0297$04.00/0

Table I. Preparation of Enol Ethers 2 by Ozonation of β-Lactams 1[a]

	compd 1			compd 2[b]	
entry	isomer	R^1	R^2	Z/E ratio[c]	yield[d,e] (%)
a	cis	Ar	CH_3	8:1	60
b	cis	Ar	CH_2Ph	8:1	64
c	trans	Ar	CH_2Ph	1:12	52
d	cis	*i*-Pr	CH_2Ph	3.4:1	44
e	trans	*i*-Pr	CH_2Ph	1:7	52

[a] All β-lactams 1 used in ozonolysis reactions were stereochemically pure compounds. [b] All compounds 2 exhibited physical and spectroscopic properties consistent with their structure. [c] The ratio of Z/E isomers was determined by integration of well-resolved signals in the ^{1}H-NMR spectra of crude reaction mixtures. Assignment of Z/E stereochemistry was made according to the values of the coupling constant between the vinyl protons (for Z isomers J = 6.0–6.9 Hz and for E isomer J = 12.6–13.2 Hz). [d] Isolated yield in pure product. [e] In all cases Ar = *p*-$CH_3OC_6H_4$.

Scheme I

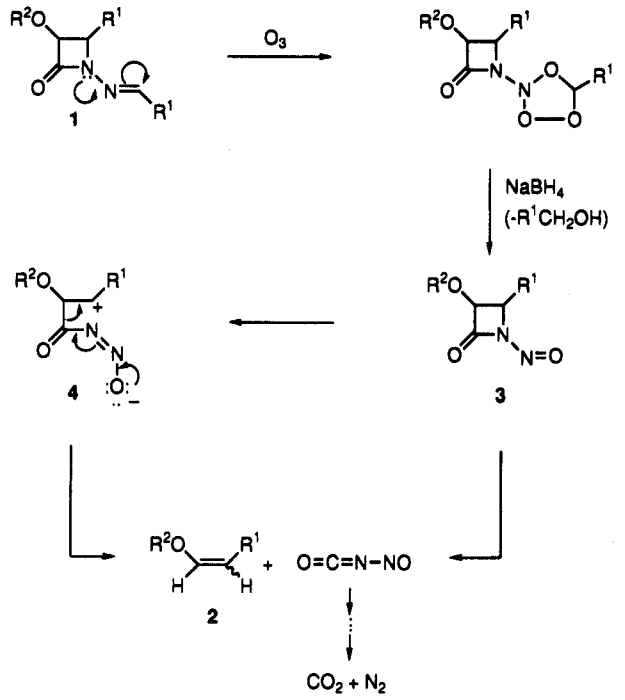


i) O_3/ CH_2Cl_2/ -78°C. ii) $NaBH_4$/ EtOH-H_2O (1 : 1)/ 0 °C→RT

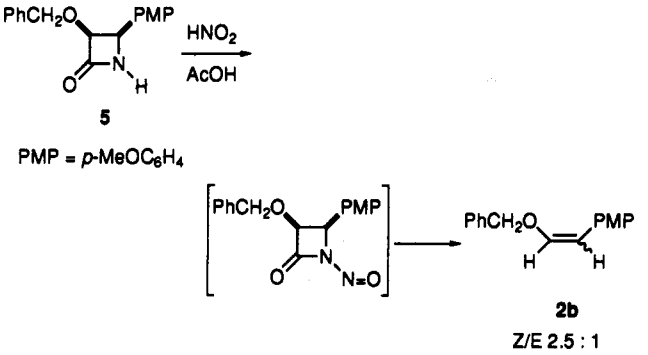
mediate 3 decomposes to final products 2[17] together with unidentified nitrosoisocyanates, either by concerted cycloreversion or through zwitterionic intermediate 4 (formally a resonant form of 3) (Scheme II). Although partial loss of the starting β-lactam stereochemistry[18] in the final vinyl ethers may be better explained by rotation of the intermediate zwitterion 4, stereospecific concerted cycloreversion could be an alternate competitive reaction pathway.[11]

In order to establish the role of *N*-nitroso-β-lactams 3 as intermediates in vinyl ether formation, the synthesis of compound 3 (R^1 = *p*-$MeOC_6H_4$, R^2 = $PhCH_2$) was attempted via N-nitrosation (HNO_2/AcOH) of N-unsubstituted β-lactam 5 following the previously reported methodology.[19] Much to our surprise, vinyl ether **2b** was obtained as a 2.5:1 Z/E mixture in nearly quantitative yield instead of the expected β-lactam (Scheme III). Other reaction conditions, such as N-nitrosation in neutral medium (Cl_2CH_2 or mixtures Cl_2CH_2/EtOH/H_2O) or by using $NOBF_4$, lead to either unreacted starting material or complex reaction mixtures.[20] Therefore, although reaction conditions were different from those used in the

Scheme II



Scheme III



ozonolysis of compounds 1, the results can support *N*-nitroso-β-lactams 3 as probable intermediates in the formation of vinyl ethers 2.

In conclusion, a B-type cleavage of the β-lactam ring under smooth thermal conditions is reported, providing a novel and stereoselective route to vinyl ethers. Studies concerning the scope and generality of this methodology, including the synthesis of optically active vinyl ethers as well as mechanistic implications, are underway in our laboratories.

Acknowledgment. Support for this work under grants PB90-0047 (DGICYT-MEC, Spain) and 290/92 from the CAM (Madrid, Spain) is gratefully acknowledged. One of us (J.P.-C.) thanks U.C.M. for a predoctoral fellowship.

Supplementary Material Available: Full experimental procedure for the preparation of compounds 2, including IR, ^{1}H NMR, ^{13}C NMR, and analytical data (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(17) Ozonide decomposition by Me_2S, Zn/AcOH, or NaOH/H_2O_2 gave complex reaction mixtures confirming that vinyl ethers are not the primary reaction products. Furthermore, it is known that vinyl ethers are reactive toward ozone. See: (a) Crocker, H. P.; Hall, R. H. *J. Chem. Soc.* **1955**, 2052. (b) Schmit, U.; Grafen, P. *Liebigs Ann. Chem.* **1962**, *97*, 656. (c) Griesbaum, K.; Kim, W.-S. *J. Org. Chem.* **1992**, *57*, 5574 and references cited therein.

(18) In situ Z/E isomerization of vinyl ethers was ruled out by stirring an Z/E mixture of compound **2b** for 24 h under identical conditions to those used in $NaBH_4$ workup. Z/E ratio remains unaltered under these conditions.

(19) Pifferi, G.; Consonni, P.; Testa, E. *Gazz. Chim. Ital.* **1967**, *97*, 1719.

(20) Formation of vinyl ethers by N-nitrosation of N-unsubstituted β-lactams and related processes are currently under investigation in our laboratories.