CHEMISTRY LETTERS, pp. 1907-1910, 1985.

REGIOSELECTIVE SULFENYLATION OF OXIME DIANIONS. A NOVEL AND USEFUL METHOD FOR THE REGIOSELECTIVE RING CLEAVAGE

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Treatment of the dianions of cyclic ketoximes with diphenyl disulfide underwent a regioselective sulfenylation at the syn α-carbons. Regioselective alkylation of cyclic ketoxime dianions, followed by sulfenylation with diphenyl disulfide, produced α-alkyl-α'-phenylsulfenyl ketoximes. A Beckmann fragmentation of these sulfenylated ketoximes gave ring cleaved products. This procedure provides a synthetically useful method for the regioselective ring cleavage, remaining valuable functionalities.

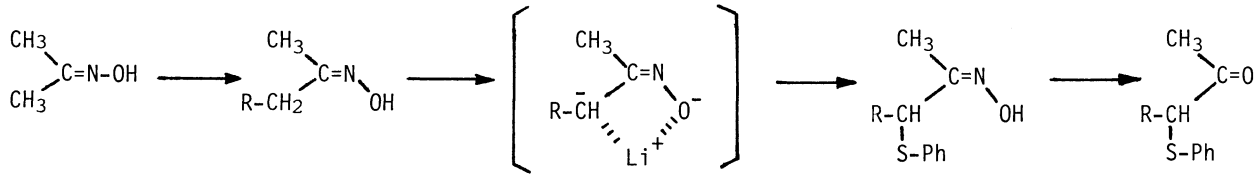
Organosulfur groups have served as synthetically valuable functionalities for elaboration of complex organic molecules and many methods have been developed for the introduction of organosulfur groups, using sulfenyl chlorides,[1a-c] thiosulfates,[1d] sulfenamides,[1e-g] and disulfides[1h-l] as starting sulfenylating reagents. Among them, a disulfide is a practically useful reagent for sulfenylation of various kinds of carbonyl groups,[1h,i] owing to its ready availability and easy handleness.

However, no effort has been made for the regioselective introduction of organosulfur groups, except for the regioselective sulfenylation using the dianions derived from 1,3-dicarbonyl compounds reported by our group.[2]

We wish to communicate herein the first example for the regioselective alkylative sulfenylation of oximes via their dianions and its versatility for the regioselective ring cleavage.

The oxime 1 was alkylated via its dianion regioselectively at the syn α-carbon of the oxime.[3] Treatment of the alkylated oximes 2a-c with lithium diisopropylamide (LDA) (2.4 equiv.) followed by addition of diphenyl disulfide (1.0 equiv.) (0-20 °C, 1 h) gave exclusively syn-sulfenylated oximes 4a-c in 70-75% yields.

Hydrolysis of the sulfenylated oximes 4a-c with (titanium trichloride-ammonium acetate)-50% aqueous acetic acid[4] produced the more substituted α-sulfenyl ketones 5a-c in 90-93% yields.



1 2a-c 3a-c 4a-c 5a-c

a $R=CH_3$; b $R=CH_2CH=CH_2$; c $R=C_6H_5CH_2$

The dianions 7a-d, generated by treating the oximes 6a-d of cyclic ketones with LDA (2.4 equiv.), reacted with diphenyl disulfide in **THF** at 0 °C for 1-4.5 h to give oximes 8a-d, sulfenylated exclusively at the syn α-carbons, in 79, 94, 81, and 60% yields, respectively. The regiochemistry of the products 8a-d was confirmed by comparison of the nmr spectra with those of the authentic anti oximes 9a-d, prepared from 2-phenylthiocycloalkanones and hydroxylamine.[5]

α-Methylation of the α-sulfenylated oxime 8b was accomplished smoothly by treating with n-butyllithium (2.4 equiv.), followed by addition of methyl iodide (1.2 equiv.) (at 0 °C for 0.5 h), affording 12 in 87% yield.

The regioselective methylation of the oxime dianion 7b with methyl iodide (1.2 equiv.)(at 0 °C for 4.5 h and at room temperature for 1 h) gave the syn α-methylated oxime 14 in 86% yield.[3b] No syn-sulfenylation of this syn-methylated oxime 14 could be observed, because of the steric hindrance, but the anti α-carbon of 14 was sulfenylated regioselectively in the presence of excess bases. Treatment of 14 with sec-butyllithium (3.6 equiv.) at 0 °C for 2 h, followed by addition of diphenyl disulfide (3.6 equiv.) (at 0 °C for 18 h and at room temperature for 1 h) provided exclusively the anti-sulfenylated oxime 15 in 55% yield.

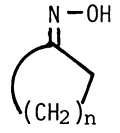
This regioselective sulfenylation was executed in the same way for anti substituted oximes. The oxime 18, derived from 2-benzylcyclohexanone and hydroxylamine, was treated with LDA (2.4 equiv.) at 0 °C for 1 h and then reacted with diphenyl disulfide at 0 °C for 2 h to afford the syn-sulfenylated oxime 19 in 90% yield. This oxime was easily alkylated with methyl iodide, ethyl bromide, n-propyl iodide, and methyl bromoacetate to give 20a-d in 81, 45, 45, and 41% yields, respectively.[6]

Heating of the α-sulfenylated oximes 8a-d obtained above in pyridine with mesyl or tosyl chloride underwent a Beckmann fragmentation[7] to give

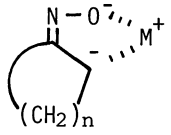
10a-d in 73, 36, 38, and 48% yields, besides with lactams 11a (5%), 11b (38%), 11c (39%), and 11d (42%), respectively. The reactions of other sulfenylated oximes 12, 15, 19, and 20a-d under the same conditions produced 13 (90%), 16 (47%; 17 11%), 21a (72%), 21b (47%), 21c (50%), 21d (55%), and 21e (48%), respectively.[8]

Thus, the present method provides a synthetically useful tool for regioselective carbon-carbon bond fission, remaining valuable functionalities. Namely, we can cleave the C_1-C_2 or C_1-$C_{2'}$ bond in 22 selectively, by subjection of initial sulfenylation or alkylation (path a or b) to oxime dianions 23.

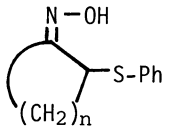
We are now on a way for applying this method to the synthesis of biochemically valuable compounds.



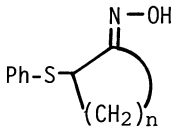
6a-d



7a-d

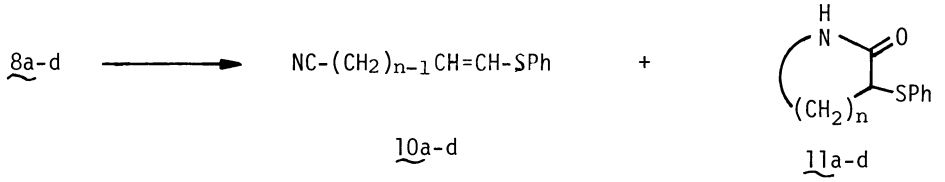


8a-d

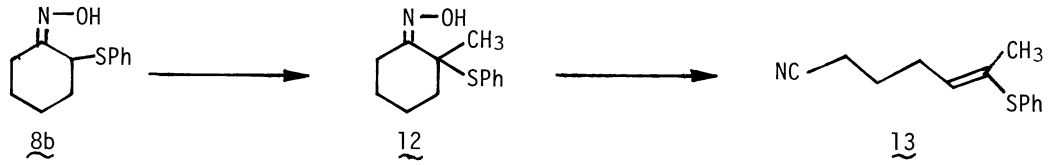


9a-d

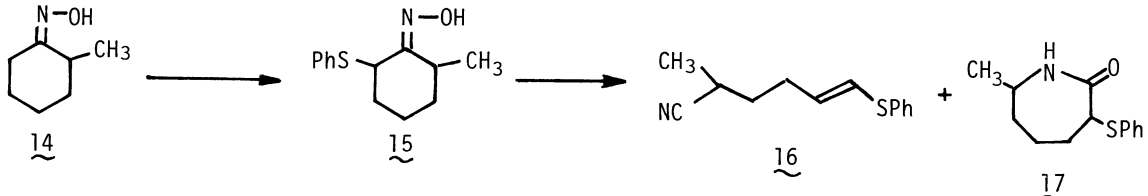
a n=3 ; b n=4 ; c n=6 ; d n=10



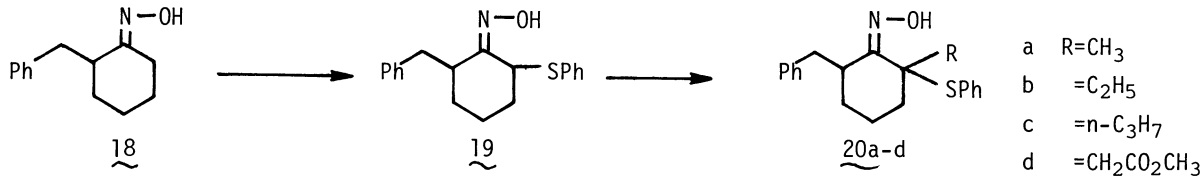
8a-d → NC-(CH2)n-1CH=CH-SPh + 10a-d; 11a-d



8b → 12 → 13

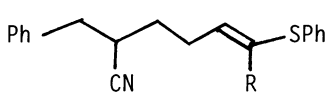


14 → 15 → 16 + 17



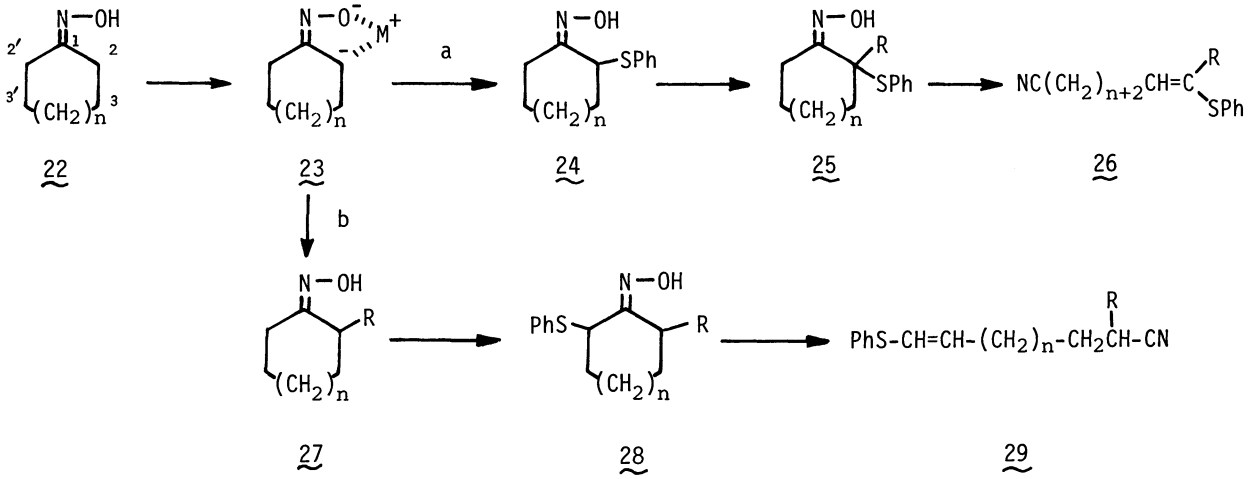
18 → 19 → 20a-d

a R=CH3
b =C2H5
c =n-C3H7
d =CH2CO2CH3



21a-e

a R=H
b =CH3
c =C2H5
d =n-C3H7
e =CH2CO2CH3



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3) a) M.E. Jung, P.A. Blair, and J.A. Lowe, Tetrahedron Lett., 1976, 1439; b) W.G. Kofron and M.-K. Yeh, J. Org. Chem., 41, 439 (1976).

4) G.H. Timms and E. Wildsmith, Tetrahedron Lett., 1971, 195.

5) In the nmr spectra of the anti-sulfenylated oximes (9a-d), the protons α to the phenylthio groups appeared at δ 4.05 (t), 3.85 (t), 3.60-4.00 (m), and 3.70-4.00 (m), while those in the syn-sulfenylated oximes (8a-d) shifted to a little lower fields by the anisotropy of the syn hydroxy groups of the oximes, and appeared at δ 4.43 (t), 4.90 (t), 4.56-4.93 (m), and 4.90-5.16 (m), respectively.

6) The stereochemistry of 15, 19, and 20a-d could not be determined exactly,however a thermodynamically more stable isomer would be prepared in every case.

7) R.K. Hill and R.T. Conley, J. Am. Chem. Soc., 82, 645 (1960); R.K. Hill, J. Org. Chem., 27, 29 (1962); M. Ohno, N. Naruse, S. Torimitsu, and I. Terasawa, J. Am. Chem. Soc., 88, 3168 (1966); M. Ohno and I. Terasawa, ibid., 88, 5683 (1966); R.L. Autrey and P.W. Scullard, ibid., 90, 4924 (1968); R.K. Hill and D.A. Cullison, ibid., 95, 2923 (1973).

8) The geometry of the olefins in the ring cleaved products would be the more stable E regarding to the phenylthio groups as depicted in the scheme, from the mechanistic points of view.[7)]

(Received September 26, 1985)