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OXIDATION OF ISOXAZOLINES BY PERACIDS - A USEFUL ROUTE TO β-HYDROXY KETONES AND ACYLATED DIOLS

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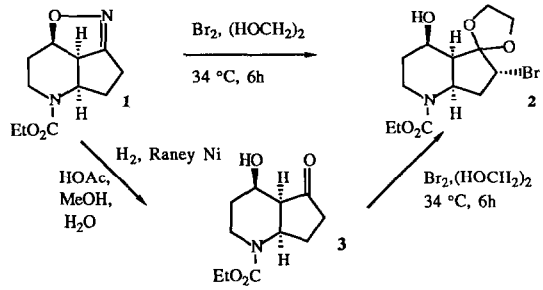
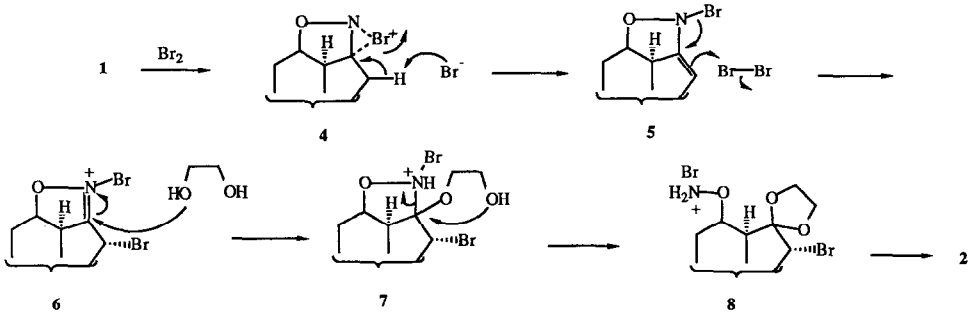
SUMMARY: A method for bringing about the ring cleavage of isoxazolines by the use of peracids is described.

During studies directed toward the total synthesis of the alkaloid natural product streptazolin,[1] we discovered that the isoxazoline intermediate **1** could be transformed directly into the α-bromo ketal **2** by reaction with bromine in ethylene glycol at 34 °C for 6 h.[2] The structure of **2** was readily confirmed by comparison with an authentic sample prepared from the hydroxy ketone **3** formed in the hydrogenolysis reaction of **1**.



A possible mechanism for the conversion of **1** to **2** is provided below. Initial electrophilic attack of bromine at the C=N bond can lead to the enamine structure **5** by loss of a proton. This intermediate might then engage in a further reaction with bromine to provide an iminium ion species **6** which is trapped by ethylene glycol. The resulting hemiaminal **7** can undergo an internal exchange reaction to provide the ketal **8** which ultimately provides the α-bromo ketal **2** by rupture of the N-O bond.

SCHEME 1. A Mechanism for Bromine Promoted Isoxazoline Ring Cleavage.



In light of this interesting finding, we decided to explore the reaction of isoxazolines with another type of oxidant, the peracids, as a possible new approach to isoxazoline ring cleavage. Indeed, when **1** was treated with MCPBA in ethylene glycol at room temperature for 12 h, the β-hydroxy ketone **3** was isolated in lieu of the ketal **2**.

While the transformation of isoxazolines to β-hydroxy ketones has been achieved by catalytic hydrogenation, chemical reduction (Ti^{+3}) and by ozonolysis,[3] the ability to accomplish this conversion by use of a peracid may prove valuable in certain synthetic undertakings. Additionally, we anticipated that peracid treatment of an isoxazoline might also afford a direct route to an acylated vicinal diol by subsequent Baeyer-Villiger oxidation of the β-hydroxy ketone.

In the reaction of **1** with MCPBA we found that a minimum of three equivalents of the peracid was required to achieve a reasonable conversion to **3**. A variety of other isoxazolines whose structures can be found in Table 1 were examined in their reaction with peracids. In most cases, the use of peroxytrifluoroacetic acid or 3,5-dinitroperoxybenzoic acid was found advantageous due to the low reactivity of MCPBA.

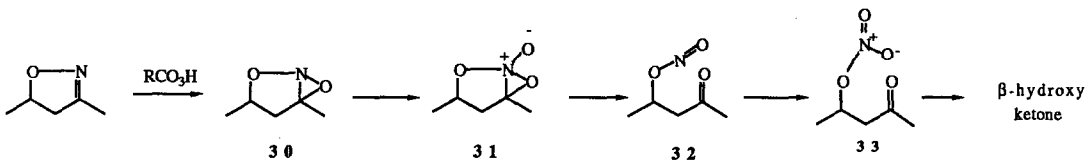
As is apparent from Table 1, the peracid cleavage can be stopped at the β-hydroxy ketone stage by using mild reaction conditions (entries 1 and 8). On the other hand, the isoxazolines **10**, **14**, **24**, and **27**, prepared from acetonitrile oxide and the appropriate olefin, provided the acetate derivatives of the diols via Baeyer-Villiger oxidation of the intermediate β-hydroxy ketones.

In these cases, acyl migration was observed, and the isolated yields ranged from 40-70%. The yields are comparable to those obtained by a two stage sequence involving hydrogenolytic cleavage of the isoxazoline ring followed by Baeyer-Villiger oxidation of the intermediate β-hydroxy ketone.

In the case of the 3-ethyl substituted isoxazoline **19**, the β-hydroxy ester derivative **20** was isolated in addition to the acylated 1,2-diols. Subjection of **1** to peroxytrifluoroacetic acid provided the fused ring lactone **9** in moderate yield.

Mechanistically, it is possible that the peracid converts the isoxazoline to an oxaziridine intermediate **30** which is further oxidized to the *N*-oxide **31**.[4] This highly reactive species then undergoes fragmentation to the keto nitrite **32**, which is further oxidized to the nitrate **33**. Cleavage of the nitrate derivative would then afford the β-hydroxy ketone.

SCHEME 2. A Possible Mechanism for Peracid Induced Isoxazoline Ring Cleavage.



30 **31** **32** **33**

A representative experimental procedure employing 3,5-dinitroperoxybenzoic acid follows: To a solution of isoxazoline **10** (71 mg, 0.4 mmol) in 25 mL of chloroform containing 4,4'-thiobis(2-*tert*-butyl-6-methylphenol, 20 mg, 0.056 mmol) was added 3,5-dinitroperoxybenzoic acid (2.11g, 95% active oxygen). The mixture was heated at reflux for 8 h, then cooled to 0 °C and filtered through a sintered glass funnel with a chloroform wash (25 mL). The filtrate was washed with 20% aqueous sodium bisulfite (3 x 10 mL), saturated aqueous sodium bicarbonate (3 x 10 mL), and saturated aqueous sodium chloride (3 x 10 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography of the residue on silica gel with 20% ethyl actetate-hexanes afforded 39.8 mg (50%) of **11** as an oil and 13.3 mg (17%) of **12** as an oil; Acetate **11**: R_f = 0.32 (silica gel, 50% ethyl acetate-hexanes); IR (thin film) 1734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52-7.22 (m, 5H), 4.98 (dd, 1H, J = 8.5, 3.2 Hz), 4.30 (A of dABq, J_{AB} = 11.6 Hz, J_{AX} = 3.2 Hz), 4.17 (B of dABq, J_{AB} = 11.6 Hz, J_{BX} = 8.5 Hz), 2.50 (br s, 1H), 2.12 (s, 3H); mass spectrum (15 eV), m/z 152 (M^+-H_2O), 150, 149, 120, 107 (base), 79, 58, 43; Acetate **12**: R_f = 0.25 (silica gel, 50% ethyl acetate-hexanes); IR (thin film) 1734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50-7.25 (m, 5H), 5.87 (dd, 1H, J = 7.4, 4.2 Hz), 3.98-3.72 (m, 2H), 2.16 (s, 3H), 1.84 (br s, 1H); mass spectrum (15 eV), m/z 162 (M^+-H_2O), 150, 149, 134, 120, 107 (base), 74, 59, 45, 31, 29.

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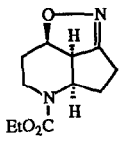
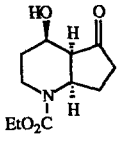
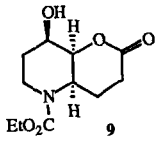
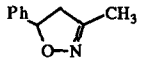
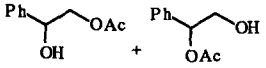
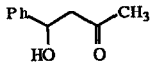
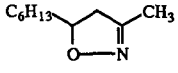
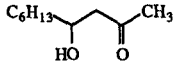
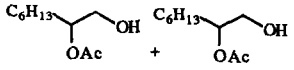
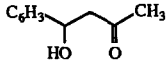
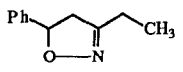
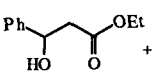
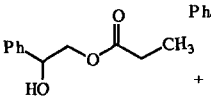
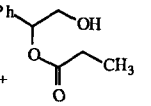
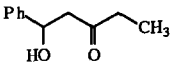
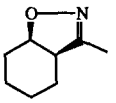
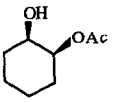
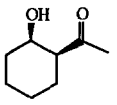
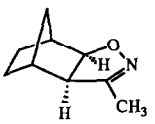
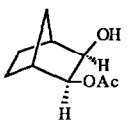
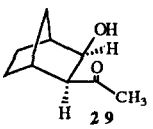
1. Kozikowski, A. P.; Park, P-u., *J. Am. Chem. Soc.*, **1985**, *107*, 1763.
2. Park, Pyeong-uk, Ph.D. Dissertation, University of Pittsburgh, 1985, pp. 131-148.
3. For reviews on isoxazoline ring cleavage, see: Kozikowski, A. P., *Acc. Chem. Res.*, **1984**, *17*, 410; Torssell, K. B. G., "Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis, Novel Strategies in Synthesis", VCH Publishers, Inc., New York, 1988.
4. For a review on *N*-oxide chemistry, see: Katritzky, A. R.; Lagowski, J. M., "Chemistry of the Heterocyclic *N*-Oxides", Academic Press, New York, 1971.

TABLE 1. Oxidations of Isoxazolines and β-Hydroxy Ketones with Peracids.

Entry No.	Substrate	Reaction Conditions (equiv)	Products	Yield (%)
1	 **1**	DNPBA[a] (4), CH_2Cl_2 rt, 21h	 **3**	(57)
2	**1**	CF_3CO_3H (10), Na_2HPO_4 (20) CH_2Cl_2, 0 °C, 4h, then 5 °C, 18h	 **9**	(42)
3	**3**	CF_3CO_3H (6), Na_2HPO_4 (12) CH_2Cl_2, 0 °C, 1h, then rt, 2h	**9**	(50)
4	 **10**	DNPBA (20), TBP[b], $CHCl_3$, reflux, 8h	 **11** + **12** 3:1	(67)
5	**10**	CF_3CO_3H (10), Na_2HPO_4 (20), CH_2Cl_2, 0 °C, 1h then rt, 2h	**11** + **12** 12:5	(45)
6	 **13**	DNPBA (5), TBP, dichlorethane, reflux, 3h	**11** + **12** 3:1	(80)
7	**13**	CF_3CO_3H (4), Na_2HPO_4 (8), CH_2Cl_2, 0 °C, 1h then rt, 2h	**11** + **12** 12:5	(50)
8	 **14**	DNPBA (5), CH_2Cl_2, rt 16 h	 **15**	(56)
9	**14**	DNPBA (20), Na_2HPO_4[d] (20), TBP, dichlorethane, reflux, 3h	 **16** + **17** 7:3	(59)
10	 **18**	DNPBA (3), Na_2HPO_4 (3), TBP, dichoroethane, reflux, 3h	**16** + **17** 7:3	(70)

11	**18**	CF_3CO_3H (3), Na_2HPO_4 (5), CH_2Cl_2, 0 °C, 1h then rt, 2h	**16** + **17** 8:3	(50)
12	 **19**	DNPBA (20), TBP, dichloroethane, reflux, 3h[e]	 **20** +  **21** +  **22**	(68)
13	 **23**	DNPBA (6), TBP, dichloroethane, reflux, 3h	**20** + **21** + **22** 7.5:2.5:1	(83)
14	 **24**	DNPBA (4), CH_2Cl_2, rt, 17h	 **25**	(41)
15	 **26**	DNPBA (2), CH_2Cl_2, rt, 17h	**25**	(41)
16	 **27**	CF_3CO_3H (10), NaH_2PO_4 (20), CH_2Cl_2, 0 °C, 1h, 5 °C, then 5 °C, 14h[f]	 **28**	(52)
17	 **29**	CF_3CO_3H (3), Na_2HPO_4 (6), CH_2Cl_2, 0 °C, 2h	**28**	(72)

[a] DNPBA = 3,5-dinitroperoxybenzoic acid
[b] TBP = 4,4'-thiobis(2-*tert*-butyl-6-methylphenol)
[c] A 10% yield of **16** and **17** was also obtained.
[d] Decomposition occurs in the absence of Na_2HPO_4.
[e] Oxidation occurs very slowly at room temperature.
[f] Decomposition occurred when this reaction was carried out using DNPBA.

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