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Metal-Promoted Thiyl Radical Cyclizations in β-Lactam Antibiotics

Walter Cabri,* Ilaria Candiani and Angelo Bedeschi*

Farmitalia-Carlo Erba S.r.l., R&D, via Giovanni XXIII,23
20014-Nerviano(MI), Italy

Roberto Santi

Istituto G.Donegani via Fauser,4 28100-Novara, Italy

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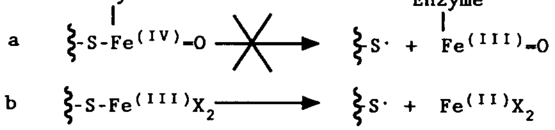
Abstract: Intramolecular thiyl radical addition to a double bond promoted by Fe(III) and Mn(III) is described. The stabilized radical intermediate afforded by subsequent hydrogen abstraction cephams **4** and **5**.

The intriguing studies of Baldwin on the biosynthesis of penicillins and cephalosporins[1] appear to exclude the formation of thiyl radicals in the INPS(isopenicillin synthase)-catalyzed formation of the sulphur containing ring. In particular, the bond between the sulphur and the ferryl-oxo specie, postulated to play a key role in the active site of the enzyme, does not undergo homolytic cleavage (**a**, Scheme 1).[2]

Scheme 1



$$\text{a}\quad \text{-S-}\overset{\text{Enzyme}}{\overset{|}{\text{Fe}^{(IV)}}}\text{-O} \;\not\longrightarrow\; \text{S}\cdot + \overset{\text{Enzyme}}{\overset{|}{\text{Fe}^{(III)}}}\text{-O}$$

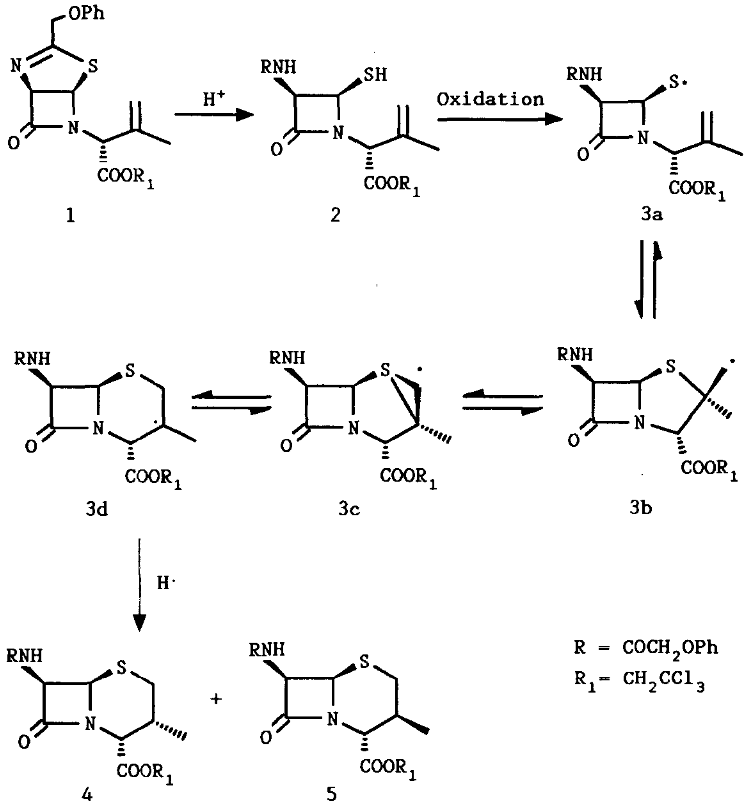
$$\text{b}\quad \text{-S-Fe}^{(III)}\text{X}_2 \longrightarrow \text{S}\cdot + \text{Fe}^{(II)}\text{X}_2$$

However, this intermediate suggested to us an approach for the synthesis of the sulphur containing ring based on the formation of the thiyl radical by using the metal in a lower oxidation state[3] (**b**, Scheme

1). In fact, the sulphur centered radical can give, by intramolecular addition to a double bond in a 5-exo fashion, rearrangement and hydrogen abstraction, the corresponding cephams (Scheme 2).[4,5]

The reaction of **2**, obtained by acidic treatment of thiazoline **1**,[6] with stoichiometric amounts of Fe(III) salts in CH_3CN at 0-5 °C afforded a mixture of cephams **4** and **5** (80/20 ratio) in moderate overall yields from **1** (Table I).[7]

Scheme 2



Among the Fe(III) salts tested, $Fe(ClO_4)_3$ $9H_2O$ in the presence of Ac_2O [$Fe(OAc)_3$] gave the best performances (entries 2). It is worth noting that the addition of three equivalents of 1,10-phenanthroline (entry 4) as well as the use of Fe(citrate) as a promoter (entry 11) suppressed the reaction. These results suggest that the oxidation took place through complexation of the thiol onto the metal followed by homolytic cleavage of the S-Fe(III) bond (**b**, Scheme 1).

Table 1. Metal-Promoted Thiyl Radical Cyclizations.[a]

Entry	**Promoter**	**Additive(eq)**	**4+5,yield %**[b]
1	$Fe(ClO_4)_3$ $9H_2O$	-	10
2	$Fe(ClO_4)_3$ $9H_2O$	$Ac_2O(10)$	42
3	$Fe(ClO_4)_3$ $9H_2O$	AcOH(20)	30
4	$Fe(ClO_4)_3$ $9H_2O$	Phen(3)	-
5	$Fe(ClO_4)_3$ $9H_2O$[c]	$Ac_2O(10)$	7
6	$Fe(ClO_4)_3$ $9H_2O/O_2$	$Ac_2O(10)$	-
7	$Fe(NO_3)_3$ $9H_2O$	-	29
8	$Fe(NO_3)_3$ $9H_2O$	$Ac_2O(10)$	34
9	$Fe_2(SO_4)_3$ $5H_2O$	$Ac_2O(5)$	traces
10	Fe_2O_3	-	-
11	Fe(citrate)	-	-
12	$FeCl_3$	-	-
13	$Mn(OAc)_3$ $2H_2O$	-	37

a. For the Fe(III) and the Mn(III) promoted reaction procedures see respectively ref.7 and 9. b. Overall yield from **1**. c. 10mol% of promoter was used.

Manganese(III) salts were reported to promote the formation of disulphides from thiols by an ionic reaction as a result of a double single electron transfer oxidation.[8] In our case, the cyclization was faster than the thiyl radical oxidation. The reaction of **2** in the presence of $Mn(OAc)_3$ in CH_3COOH at rt afforded a mixture of cephams **4** and **5** (75/25 ratio).[9]

Other heavy metal ions in high oxidation states, such as Cu(II), Co(III), Pb(IV), and Ce(IV) were unable to promote the reaction.

Further studies in order to increase the reaction yields and determine the scope and limitation of this approach are under way.

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References and Notes

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3. Sheldon,R.A.;Kochi,J.K. *Metal-Catalyzed Oxidations of Organic Compounds*, Academic Press: London, 1981.
4. For a photochemical approach to this thiyl cyclization see: (a) Maki,Y.; Sako,M. *Tetrahedron Lett.* **1976**,4291. (b) Gordon,E.M.; Cimarusti,C.M. *Tetrahedron Lett.* **1977**,3425. Mixtures of cepham and cephem derivatives were obtained.
5. The stabilized radical specie **3** was postulated as intermediate in the biosynthetic ring expansion of penam to cepham. See: Baldwin,J.E.;Adlington,R.M.;Kang,T.W.;Lee,E.;Schofield,C.J. *Tetrahedron* **1988**,*44*,5953.
6. The cyclization of **2** under ionic conditions failed. See: Narisada,M.;Onoue,,H.;Ohtani,M.; Watanabe,F. *Tetrahedron Lett.* **1978**,1755.
7. General procedure for cyclization promoted by Fe(III) salts. Table 1, entry 2: Acetic anhydride (0.944ml,10mmol) was added to a stirred solution of $Fe(ClO_4)_3$ $9H_2O$ (516mg,1mmol) in CH_3CN (10ml) at 0°C under Ar. After 0.7 h a solution of **2** in 10ml of a 1/1 mixture of CH_3CN/CH_2Cl_2 obtained by standard procedure from **1** (0.463mg, 1mmol),[6] was dropwise added in 0.2 h. The reaction mixture was diluted after 3 h with CH_2Cl_2 (40ml) and sequentially washed with HCl 10% (15ml) and water till neutrality. The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure affording after purification by flash chromatography (hexane/ethyl acetate 7/3 by volume) 212 mg of a 80/20 mixture of **4** and **5** (42% yield). The structures have been assigned by comparison with pure samples obtained by standard procedure: Spry,D.O. *Tetrahedron Lett.* **1973**,165.
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9. General procedure for Mn(III) promoted cyclization: To a stirred suspension of $Mn(OAc)_3$ $2H_2O$ (268mg,1.0mmol) in CH_3COOH (30ml) at rt under Ar, a solution of **2** in 10 ml of CH_2Cl_2 obtained by standard procedure from **1** (0.463mg,1mmol),[6] was dropwise added in 0.5 h. After 2 h the reaction was diluted with CH_2Cl_2(40ml). Subsequent standard work-up and purification afforded 178 mg of a 75/25 mixture of cephams **4** and **5** (37% yield).

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