

RING CLEAVAGE REACTIONS OF SUBSTITUTED 2-ISOXAZOLINES BY
PENTACARBONYLIRON UNDER ULTRAVIOLET IRRADIATION

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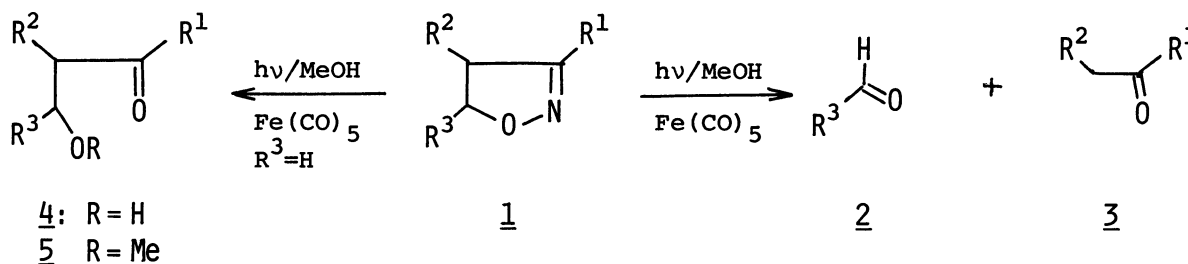
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The photoirradiation of 3,5-disubstituted 2-isoxazolines and $\text{Fe}(\text{CO})_5$ in MeOH causes the N-O and $\text{C}_4\text{-C}_5$ bond cleavage to give two fragments of aldehydes and ketones, while that of 2-isoxazolines having no substituent at 5-position gives additional β -hydroxy- and β -methoxyketones.

Heterocyclic systems have been used as the substrates to construct functionalized carbon skeletons. Previously we have reported that $\text{Fe}(\text{CO})_5$ or $\text{Mo}(\text{CO})_6$ causes an efficient reductive cleavage of the N-O bond of isoxazoles to give β -aminoenones under photoirradiation or heating in the presence of water.^{1,2)} 5-Substituted 2-isoxazolines are readily accessible under mild conditions by 1,3-dipolar cycloaddition of nitrile oxides to monosubstituted or 1,1-disubstituted alkenes³⁾ with complete regioselectivity, and they have been used for the synthesis of γ -aminoalcohols,⁴⁾ α,β - or β,γ -unsaturated oximes⁵⁾ and β -hydroxyketones.⁶⁾

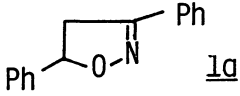
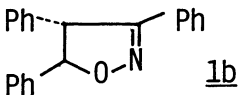
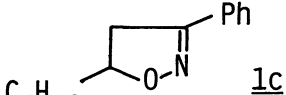
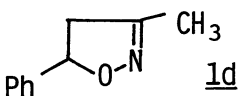
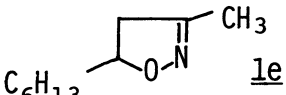
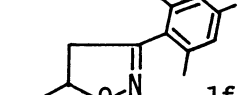
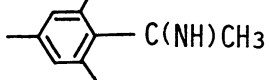
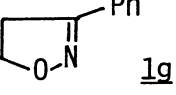
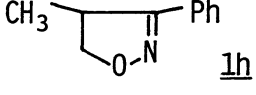
In search for further utilities of the isoxazolines and in connection with the previous studies,^{1,2)} we have found that the photoirradiation of the 3,5-disubstituted 2-isoxazolines 1a-f with $\text{Fe}(\text{CO})_5$ in MeOH causes the N-O and $\text{C}_4\text{-C}_5$ bond cleavage to give two fragments of aldehydes 2 and ketones 3, while that of 2-isoxazolines 1g,h having no substituent at 5-position, gives β -hydroxy- and β -methoxyketones, 4 and 5, in addition to 2 and 3 as shown in Scheme 1.⁷⁾

Photoirradiation of 1a,b,c (Table 1, entries 1-3) afforded the corresponding aldehydes and ketones.⁸⁾ Benzaldehyde and acetophenone is slightly labile under the present conditions (to give less than 85% of the recovery after irradiation for 24 h) and the yields are rather low, although the reactions seem to be very selective and the other product was not detected. The photoreactions of isoxazolines such as 1a,⁹⁾ 1b¹⁰⁾ and other derivatives¹¹⁾ have been known. Since the irradiation of 1a or 1b



Scheme 1

Table 1. Ring Cleavage Reaction of Isoxazolines^a

Entry	Isoxazoline	Irradiation Time (h)	Product (Yield %)
1	 <u>1a</u>	24	PhCHO (57) PhCOCH ₃ (69)
2	 <u>1b</u>	10	PhCHO (62) PhCOCH ₂ Ph (96)
3	 <u>1c</u>	24	C ₆ H ₁₃ CHO (52) PhCOCH ₃ (86)
4	 <u>1d</u>	2	PhCHO (39), (53) ^b CH ₃ COCH ₃ (—), (57) ^b
5	 <u>1e</u>	6	C ₆ H ₁₃ CHO (53), (61) CH ₃ COCH ₃ (—), (54)
6	 <u>1f</u>	6	PhCHO (58)  C(NH)CH ₃ (91)
7	 <u>1g</u>	19	PhCOCH ₃ (35) ^c PhCOCH ₂ CH ₂ OH <u>4g</u> (53) PhCOCH ₂ CH ₂ OCH ₃ <u>5g</u> (6)
8	 <u>1h</u>	5	PhCOCH ₂ CH ₃ (45) ^c PhCOCH(CH ₃)CH ₂ OH <u>4h</u> (21) PhCOCH(CH ₃)CH ₂ OCH ₃ <u>5h</u> (17)

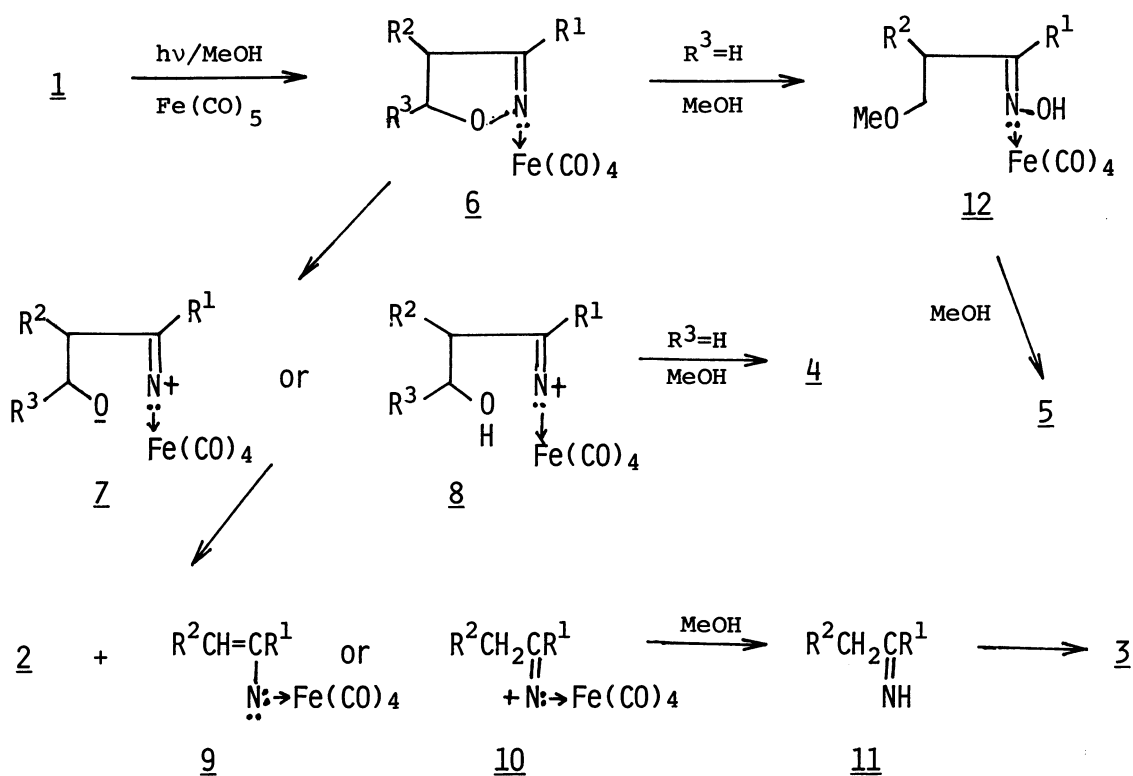
a. All isoxazolines and the products are known compounds and identified by comparison of the spectral data of those of authentic samples. b. Isolated as its 2,4-dinitrophenylhydrazone. c. The isolation of formaldehyde was not carried out.

without Fe(CO)₅ in the present conditions⁷⁾ gave no product and 1a or 1b was recovered quantitatively, therefore the light would be absorbed by Fe(CO)₅ in the present ring cleavage reactions.¹²⁾

The substituent at 3-position did not affect the reaction pathway. Thus the irradiation of 1d and 1e (entries 4 and 5) with Fe(CO)₅ in a similar way afforded the corresponding aldehydes and acetone, all of which were identified by conversion to their 2,4-dinitrophenylhydrazones. Furthermore the irradiation of 1f, which has a bulky mesityl group at 3-position, gave benzaldehyde and mesityl methyl ketimine instead of mesityl methyl ketone. These facts seem to indicate that the present reaction is general for the 3,5-disubstituted 2-isoxazolines and involves imine or enamine intermediates.

On the other hand, the photoirradiation of 1g, having no substituent at 5-position, in a similar way gave acetophenone along with 3-hydroxy-1-phenyl-1-propanone (4g) and 3-methoxy-1-phenyl-1-propanone (5g) (entry 7). Similarly, 1h afforded propiophenone, 3-hydroxy-2-methyl-1-phenyl-1-propanone (4h) and 3-methoxy-2-methyl-1-phenyl-1-propanone (5h) (entry 8).

The present reactions are best explained by the mechanism in Scheme 2. This mechanism is purely speculative although mesityl methyl ketimine intermediate has been isolated. The initial step should be a N-donor complexation of 1 to the photochemically generated $\text{Fe}(\text{CO})_4$ species^{1,12)} to give 6 followed by the ring cleavage¹³⁾ to give 7 (or 8), of which reverse enamine alkylation process could give aldehyde 2 and the nitrene complex 9 (or its protonated species 10). The complexed nitrene such as 9 has been suggested to be involved in the reaction of azirines with $\text{Fe}(\text{CO})_5$ or $\text{Fe}_2(\text{CO})_9$ and, to collapse to the corresponding ketones possibly via an imine or an enamine intermediate.^{1,2,14)} The unstable imine such as 11 which is probably derived from 9 and methanol could collapse to give the ketone 3 by stray water or under the workup conditions.⁷⁾ In the case of 1g or 1h, the energy barrier causing the $\text{C}_4\text{-C}_5$ bond cleavage to give 2 and 9 (or 10) might be high as compared to those of 1a-f, because of the absence of the substituent at 5-position. Then the pathway giving 2 and 9 (or 10) could compete with the pathway giving 4g or 4h. The formation of 5g or 5h seems to involve a nucleophilic attack of MeOH to the secondary carbon atom at 5-position of 6 ($\text{R}^1=\text{Ph}$, $\text{R}^2=\text{H}$ or Me , $\text{R}^3=\text{H}$) to give the complexed oxime 12, which could undergo the N-OH bond cleavage to give 5g or 5h via the corresponding



Scheme 2

imine. Although the transformation of oximes to the corresponding ketones has been accomplished thermally by $\text{Fe}(\text{CO})_5$ ¹⁵⁾ or $\text{Fe}(\text{CO})_5\text{-BF}_3\text{OEt}_2$ ¹⁶⁾ in anhydrous conditions, it is also possible under the present reaction conditions.¹⁷⁾ Furthermore, the irradiation of 4g or 4h with $\text{Fe}(\text{CO})_5$ in MeOH could not cause the reverse aldol type reaction to give acetophenone or propiophenone along with formaldehyde (cf. entries 7 and 8), and 4g or 4h was recovered quantitatively. However, the irradiation of 3-hydroxy-1,3-diphenyl-1-propanone oxime in a similar way afforded acetophenone and benzaldehyde in 86 and 60% yields. Thus the reverse enamine alkylation process of 7 (or 8) to 9 (or 10) could be involved in the present reactions. The details of the nitrene complex 9 giving 11 are ambiguous at this stage.

The alkylation of isoxazolines at 4-position has been shown.¹⁸⁾ The present reaction might also serve as a method for the construction of functionalized carbon skeletons.

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- 7) The general procedure: A solution of isoxazoline (1 mmol) and two equivalent⁸⁾ amount of $\text{Fe}(\text{CO})_5$ in 20 cm³ of anhydrous methanol was irradiated with RPR-350 nm lamps (Rayonet RPR-100 Photoreactor, Pyrex filter) under a nitrogen atmosphere for a period indicated in Table 1. The reaction mixture was filtered through Celite to remove insoluble materials. The subsequent separation by TLC on silica gel afforded the products which were summarized in Table 1.
- 8) An equivalent amount of $\text{Fe}(\text{CO})_5$ was not enough to complete the present reaction. Furthermore, heating of 1a and $\text{Fe}(\text{CO})_5$ in MeOH for 24 h could not cause the reaction and 1a was recovered quantitatively.
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- 13) Heating of 1a and $\text{Fe}_2(\text{CO})_9$ in MeOH also gave acetophenone and benzaldehyde in 81 and 73% yields, respectively. This fact suggests that the complexed isoxazoline 6 is also involved in this reaction and its ring cleavage to give 7 (or 8) can proceed thermally.
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