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Nonacarbonyldiiron-, Pentacarbonyliron-, or Hexacarbonylmolybdenum-induced Reactions of 4,5-Polymethylene-substituted 2-Isoxazolines[1]

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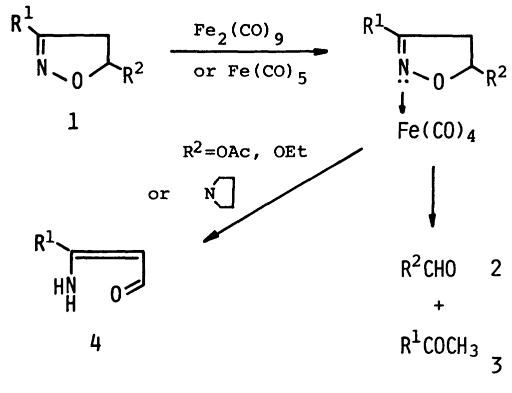
The reaction of 4,5-polymethylene-substituted 2-isoxazolines, 3-phenyl-3a,5,6,7a-tetrahydro-4*H*-pyrano-[3,2-*d*]isoxazole or 3-phenyl-3a,4,5,6a-tetrahydrofuro[3,2-*d*]isoxazole, with $[Fe_2(CO)_9]$, $[Fe(CO)_5]$, or $[Mo(CO)_6]$ resulted in the formation of 5-hydroxy-1-phenyl-1-pentanone or 4-hydroxy-1-phenyl-1-butanone, *via* the N–O and C–C bond cleavage of the 2-isoxazoline ring and the subsequent hydrolysis. The similar reaction of 7a-morpholino- and 7a-(1-pyrrolidinyl)-3-phenyl-3a,4,5,6,7,7a-hexahydro-1,2-benzoisoxazoles undergoes the N–O bond cleavage and, the subsequent elimination of the amino group or the C-3a–C-7a bond fission. Although the reaction of 6a-morpholino- and 6a-(1-pyrrolidinyl)-3-phenyl-3a,4,5,6a-tetrahydro-4*H*-cyclopent[*d*]isoxazoles with $[Mo(CO)_6]$ undergoes the N–O bond cleavage, and the subsequent elimination of the amino group or the C-3a–C-6a bond fission, the reaction of those 2-isoxazolines with $[Fe_2(CO)_9]$ proceeds very slowly. The mechanisms are proposed for these reactions.

The 2-isoxazoline ring systems have been a subject of great synthetic interest, and they have been used for the synthesis of β-amino alcohol,[2] α,β- or β,γ-unsaturated oximes,[3] and β-hydroxy ketones.[4] The versatility of 2-isoxazolines as precursors for a number of classes of compounds was also demonstrated recently.[5] Previously, it has been shown that the reaction of 3,5-disubstituted 2-isoxazolines **1** with $[Fe(CO)_5]$ under photoirradiation, or with $[Fe_2(CO)_9]$ under thermal conditions undergoes the N–O bond and C-4–C-5 bond cleavage to give aldehydes **2** and ketones **3**, which are derived from reduction and the subsequent hydrolysis of the postulated vinylnitrene complexes.[6] Furthermore, 2-isoxazolines bearing substituent such as an acetoxy or ethoxy group at C-5, undergo the N–O bond cleavage and the concomitant elimination of the acetoxy or ethoxy group leading to β-amino enones **4**.[6] However, in the case of 2-isoxazolines bearing 1-pyrrolidinyl group at C-5, the N–O and C-4–C-5 bond cleavage giving **2** and **3** predominates over elimination of the C-5-substituent giving **4**.[6] The facile metal carbonyl-induced N–O bond cleavage of 2-isoxazolines has a strong resemblance to the photochemically[7] induced N–O bond fission of the various 2-isoxazolines. This fact seems to suggest the p-d electron delocalization from the central metal to the π^* (LUMO) orbital of the C=N–O moiety of the complexed 2-isoxazolines.[6] This effect would weaken the N–O bond to undergo a facile cleavage.

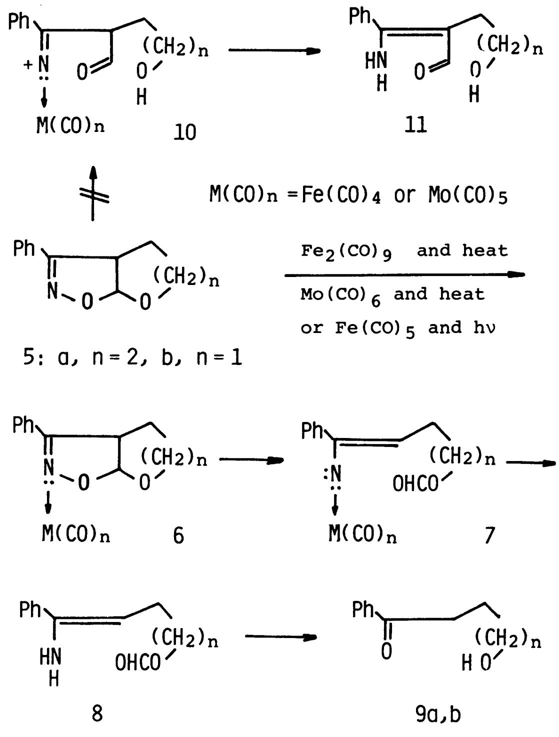


Scheme 1.

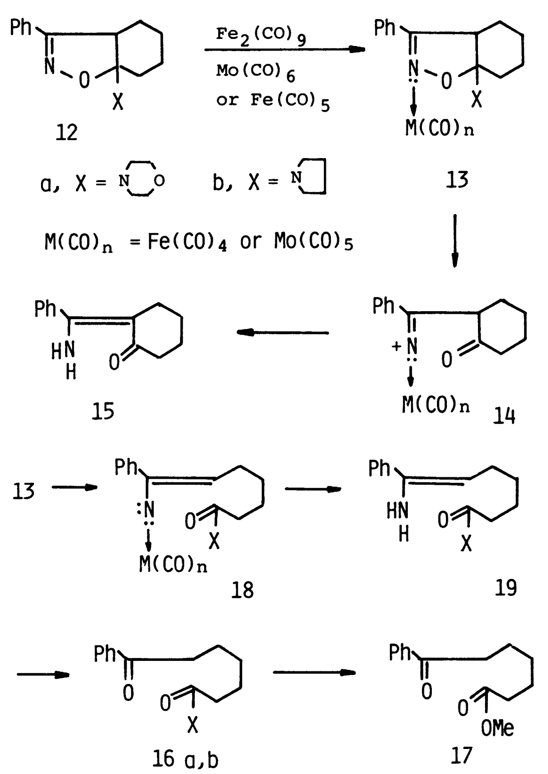
In search for further synthetic utilities of the 2-isoxazoline ring system and in connection with the previous studies,[6] we have investigated the reaction of 4,5-polymethylene-substituted 2-isoxazolines in the presence of $[Fe_2(CO)_9]$, $[Fe(CO)_5]$, or $[Mo(CO)_6]$. The results are presented in this paper.

The thermal reaction of 2-isoxazolines **5a**[8] and **5b**[8] with 1.2 molar equivalent amounts of $[Fe_2(CO)_9]$ in anhydrous methanol for 24 h and separation by TLC afforded 5-hydroxy-1-phenyl-1-pentanone (**9a**) and 4-hydroxy-1-phenyl-1-butanone (**9b**) in moderate yields. The photoirradiation of **5a,b** with $[Fe(CO)_5]$ also afforded the similar results. In addition, the reaction of **5a,b** with $[Mo(CO)_6]$ in anhydrous methanol was also found to result in the formation of **9a** and **9b**. The yields and the reaction conditions are listed in Table 1. The products are known compounds and were identified by comparison of the spectral properties with those reported in the literature.[9]

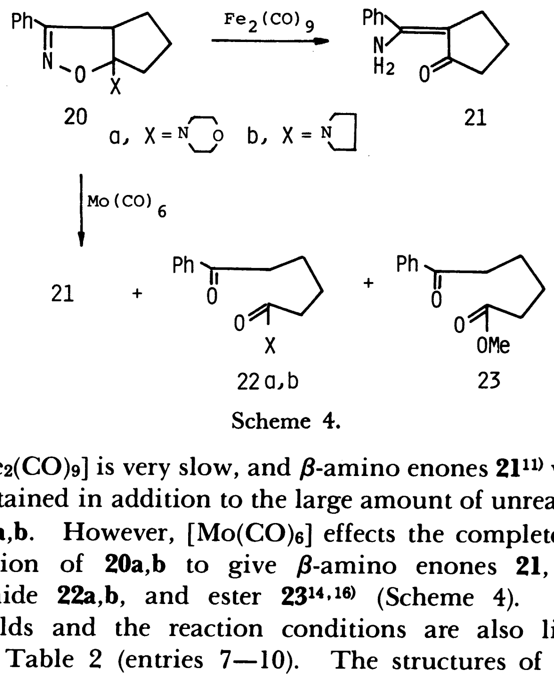
The reaction seems to be selective and no other product was detected. The products obtained in these reactions correspond to those formed by the N–O and C–C bond cleavage of the 2-isoxazoline ring. Free or solvated $[Fe(CO)_4]$ species is generally assumed to be the common intermediate in thermolysis (≥80 °C) or photolysis of $[Fe(CO)_5]$ and thermolysis of $[Fe_2(CO)_9]$ (≥20 °C).[10] $[Mo(CO)_6]$ has also been shown to give an N-donor complex of isoxazoles.[11] Therefore the initial step is N-donor complexation of **5a,b** to give **6**. The following ring cleavage of **6** gives the complexed nitrene **7**, the reduction of which gives enamine **8**.[12] The enamine moiety of **8** as well as the ester moiety would be hydrolyzed to give **9a,b** under the reaction conditions in the presence of stray water or under workup condi-



Scheme 2.



Scheme 3.



Scheme 4.

tions.[6,12] The N–O and C–O bond cleavage giving β-amino enone **11** *via* **10** did not occur, unlike in the case of **1** (R^2=OEt or OAc).[6]

The reaction of 7a-morpholino- and 7a-(1-pyrrolidinyl)-3-phenyl-3a,4,5,6,7,7a-hexahydro-1,2-benzoisoxazole (**12a** and **12b**)[13] with [$Fe_2(CO)_9$] at the refluxing temperature, or with [$Fe(CO)_5$] under photoirradiation, afforded the β-amino enone **15** and the ester **17**, in addition to the unreacted starting materials **12a,b** (Scheme 3). On the other hand, treatment of **12a** or **12b** with [$Mo(CO)_6$] in methanol resulted in the complete consumption of the starting material and gave **15** and **17**, in addition to the small amount of **16a** or **16b**. The reaction conditions and the yields of the products are listed in Table 2. The products **15**[11] and **17**[14] are known compounds. Furthermore, the structures of new compounds **16a,b** were confirmed by the independent preparations of the corresponding samples (see Experimental). The complexed 2-isoxazoline **13** undergoes the N–O bond cleavage and the concomitant elimination of morpholino or 1-pyrrolidinyl group to give β-amino enone **15**. The complex **13** also undergoes the N–O and C-3a–C-7a bond cleavage to give **18**, the reduction of which and the subsequent hydrolysis under the reaction conditions in the presence of stray water or under workup conditions gives **16a,b**. The compound **17** may be derived from the methanolysis of the amide group of **16** in the presence of oxidized-metal carbonyl species.

On the other hand, the reaction of 6a-morpholino- and 6a-(1-pyrrolidinyl)-3-phenyl-3a,4,5,6a-tetrahydro-4*H*-cyclopent[*d*]isoxazoles (**20a** and **20b**),[15] with [$Fe_2(CO)_9$] is very slow, and β-amino enones **21**[11] were obtained in addition to the large amount of unreacted **20a,b**. However, [$Mo(CO)_6$] effects the complete reaction of **20a,b** to give β-amino enones **21**, the amide **22a,b**, and ester **23**[14,16] (Scheme 4). The yields and the reaction conditions are also listed in Table 2 (entries 7—10). The structures of new compounds **22a,b** were also confirmed by independent preparations of the corresponding samples (see Experimental). The formation of the products are explained by the pathways, which are similar to those of **12a,b**.

Regarding the product composition for the reaction of **12a,b**, the substituent such as morpholino or 1-pyrrolidinyl groups does not affect the reaction pathways giving **15**, **16**, and **17**. However, the size of the 4,5-polymethylene chain seems to affect the reaction pathways. The N–O bond cleavage and the concomitant elimination of the morpholino or 1-pyrrolidinyl group giving β-amino enones become the major pathway for **20a,b**. The details for the ring size effect are ambiguous. Furthermore, [Mo(CO)$_6$] is found to be more efficient for the ring cleavage of the 2-isoxazolines **12a,b** and **20a,b**, as compared to [Fe$_2$(CO)$_9$].

In summary, these results demonstrate that [Fe$_2$(CO)$_9$], [Fe(CO)$_5$], and [Mo(CO)$_6$] are useful reagents for the ring cleavage reaction of the appropriately substituted 2-isoxazoline ring system. Furthermore, the ring cleavage of the present 2-isoxazolines affords a series of interesting compounds, such as **9a,b**, **16a,b**, and **17** in modest yields.

Experimental

The IR spectra were recorded on a Shimadzu IR-400 spectrometer. The mass spectral studies were conducted using Shimadzu GCMS-QP1000 spectrometer. The NMR spectra were recorded on a Hitachi R-24 spectrometer, using tetramethylsilane as the internal standard. [Mo(CO)$_6$] and [Fe(CO)$_5$] (Strem Chemical, Inc.) were commercial samples. [Fe$_2$(CO)$_9$] was prepared by the standard method.[17] Methanol was purified and dried by the standard method. All of the reactions were carried out under a dry nitrogen atmosphere. The desired 2-isoxazolines, **5a,b**,[8] **12a,b**,[13] and **20a,b**[14] were synthesized by the 1,3-dipolar cycloadditions of benzonitrile oxide with the corresponding olefins according to the literatures.

General Procedure for the Reaction of 2-Isoxazolines 5a,b, 12a,b, or 20a,b with [Fe$_2$(CO)$_9$] or [Mo(CO)$_6$]. A solution of **5**, **12**, or **20** (1 mmol) and [Fe$_2$(CO)$_9$] (436 mg, 1.2 mmol) or [Mo(CO)$_6$] (264 mg, 1 mmol) in anhydrous methanol (20 cm^3) was refluxed for an adequate period. After evaporation of the methanol, hexane–benzene (1/1, 20 cm^3) was added to the residue and the mixture was filtered through Celite to remove insoluble material. The filtrate was concentrated, and the resulting residue was separated by TLC on silica gel using the CH$_2$Cl$_2$–AcOEt (3/1) mixture as the eluent to give the products, which are summarized in Table 1 (entries 1, 3, 4, and 6) and Table 2 (entries 1, 3, 4, and 6—10). The products **9a,b**,[9] **15**,[11] **17**,[16] **21**,[11] and **23**[14,16] are known compounds and were identified by comparison of the physical properties with those reported in the literatures. The spectral data of the products, **16a,b**, **22a,b** were identical with those of the samples which were prepared independently by the following procedures.

General Procedure for the Photoirradiation of 5a,b or 12a,b with [Fe(CO)$_5$]. A solution of **5** or **12** (1 mmol) and [Fe(CO)$_5$] (471 mg, 2.4 mmol) in anhydrous methanol (20 cm^3) was irradiated in a Pyrex vessel with RPR-350 nm lamps for an adequate period at an ambient temperature. The reaction mixture was filtered through Celite to remove insoluble material, and the filtrate was concentrated. The residue was separated by TLC on silica gel using CH$_2$Cl$_2$–AcOEt (3/1) as the eluent to give the products **9a,b**, **15**, **16a,b**, and **17** (Table 1, entries 2 and 5; Table 2, entries 2 and 5).

Independent Preparation of 16a. To a stirred dichloromethane (4 cm^3) solution of 6-benzoylhexanoyl chloride, which was prepared from 6-benzoylhexanoic acid[16] (440 mg, 2 mmol) and thionyl chloride (1.29 g, 10 mmol), morpholine (4.35 g, 50 mmol) was added. After the reaction mixture was stirred for 1 h, water was added to the reaction mixture. The product was extracted with CH$_2$Cl$_2$ and the extract was dried over Na$_2$SO$_4$. After evaporation of the CH$_2$Cl$_2$, the resulting residue was distilled to give **16a** (301 mg, 52%): bp

TABLE 1. REACTION OF 2-ISOXAZOLINES **5a,b** WITH [Fe$_2$(CO)$_9$], [Fe(CO)$_5$], OR [Mo(CO)$_6$][a)]

Entry	Compound	Conditions[b)]	Reaction time/h	Product (Yield/%)
1	**5a**	A	24	**9a** (57)
2	**5a**	B	24	**9a** (51)
3	**5a**	C	24	**9a** (61)
4	**5b**	A	24	**9b** (65)
5	**5b**	B	24	**9b** (70)
6	**5b**	C	24	**9b** (71)

a) Reactions were carried out in anhydrous methanol. b) A: 1.2 molar equivalent amounts of [Fe$_2$(CO)$_9$] were used under reflux; B: 2.4 molar equivalent amounts of [Fe(CO)$_5$] were used under photoirradiation; C: An equivalent amount of [Mo(CO)$_6$] was used under reflux.

TABLE 2. REACTION OF 2-ISOXAZOLINES, **12a,b** AND **20a,b** WITH [Fe$_2$(CO)$_9$], [Fe(CO)$_5$], OR [Mo(CO)$_6$][a)]

Entry	Compound	Conditions[b)]	Reaction time/h	Recovery/%	Product (Yield/%)		
1	**12a**	A	24	31	**15** (26)	**16a** (—)	**17** (19)
2	**12a**	B	81	29	**15** (29)	**16a** (—)	**17** (26)
3	**12a**	C	24	—	**15** (14)	**16a** (7)	**17** (28)
4	**12b**	A	24	21	**15** (32)	**16b** (—)	**17** (26)
5	**12b**	B	67	40	**15** (38)	**16b** (—)	**17** (21)
6	**12b**	C	24	—	**15** (44)	**16b** (3)	**17** (22)
7	**20a**	A	24	77	**21** (22)	**22a** (—)	**23** (—)
8	**20a**	C	22	—	**21** (69)	**22a** (10)	**23** (—)
9	**20b**	A	24	65	**21** (32)	**22b** (—)	**23** (—)
10	**20b**	C	23	—	**21** (55)	**22b** (9)	**23** (4)

a) Reactions were carried out in anhydrous methanol. b) A: 1.2 molar equivalent amounts of [Fe$_2$(CO)$_9$] were used under reflux; B: 2.4 molar equivalent amounts of [Fe(CO)$_5$] were used under photoirradiation; C: An equivalent amount of [Mo(CO)$_6$] was used under reflux.

130—140 °C/20.0 Pa; IR ($CHCl_3$), 1679, 1625 cm^{-1}; NMR (CCl_4), δ=1.22—1.90 (6H, m), 2.05—2.47 (2H, m), 2.74—3.07 (2H, m), 3.27—3.70 (8H, m), 7.23—7.57 (3H, m), 7.75—8.04 (2H, m); MS, *m/z* (rel intensity), 289 (M^+, 11) 105 (100). Found: C, 70.94; H, 7.87; N, 4.81%. Calcd for $C_{17}H_{23}N_3$: C, 70.56; H, 8.01; N, 4.84%.

Independent Preparation of ***16b***. The similar procedure described above was applied using 6-benzoylhexanoic acid (440 mg, 2 mmol), thionyl chloride (1.298 g, 10 mmol), and pyrrolidine (3.55 g, 50 mmol) to give **16b** (475, 87%): bp 110—120 °C/13.3 Pa; IR ($CHCl_3$), 1672, 1616 cm^{-1}; NMR ($CDCl_4$), δ=1.16—2.41 (12H, m), 2.70—3.06 (2H, m), 3.16—3.52 (4H, m), 7.18—7.57 (3H, m), 7.70—7.98 (2H, m); MS, *m/z* (rel intensity), 273 (M^+, 10), 70 (100). Found: C, 74.86; H, 8.32; N, 5.33%. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12%.

Independent Preparation of ***22a***. To a stirred CH_2Cl_2 (4 cm^3) solution of 5-benzoylpentanoyl chloride, which was prepared from 5-benzoylpentanoic acid[18] (380 mg, 2 mmol) and thionyl chloride (1.29 g, 10 mmol) at an ambient temperature, morpholine (4.3 g, 50 mmol) was added. After the reaction mixture was stirred for 1 h at an ambient temperature, water was added to the reaction mixture. The product was then extracted with CH_2Cl_2 and the extract was dried over Na_2SO_4 and concentrated. The resulting residue was purified by column chromatography on alumina using benzene as the eluent to give the crude crystalline solid, which was recrystallized from a benzene-hexane (1/1) mixture to give **22a**: mp 74—75 °C; IR ($CHCl_3$), 1675, 1620 cm^{-1}; NMR (CCl_4), δ=1.50—1.97 (4H, m), 2.10—2.43 (2H, m), 2.83—3.13 (2H, m), 3.33—3.73 (8H, m), 7.40—7.63 (3H, m), 7.87—8.01 (2H, m); MS, *m/z* (rel intensity), 289 (M^+, 10), 105 (100). Found: C, 70.12; H, 7.58; N, 5.18%. Calcd for $C_{14}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09%.

Independent Preparation of ***22b***. The similar procedure described above was applied using 5-benzoyl-pentanoic acid (380 mg, 2 mmol), thionyl chloride (1.29 g, 10 mmol), and pyrrolidine (3.55 g, 50 mmol). The similar workup afforded **22b**: mp 69—71 °C (from benzene-hexane, 1/1); IR ($CHCl_3$), 1682, 1620 cm^{-1}; NMR (CCl_4), δ=1.47—2.38 (10H, m), 2.74—3.12 (2H, m), 3.12—3.57 (4H, m), 7.23—7.58 (3H, m), 7.74—8.05 (2H, m); MS, *m/z* (rel intensity), 259 (M^+, 9), 113 (100). Found: C, 74.14; H, 8.04; N, 5.05%. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40%.

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