$Mo(CO)_6$-INDUCED N-O BOND CLEAVAGE OF ISOXAZOLES. A CONVENIENT ROUTE TO PYRIDIN-4(1H)-ONES

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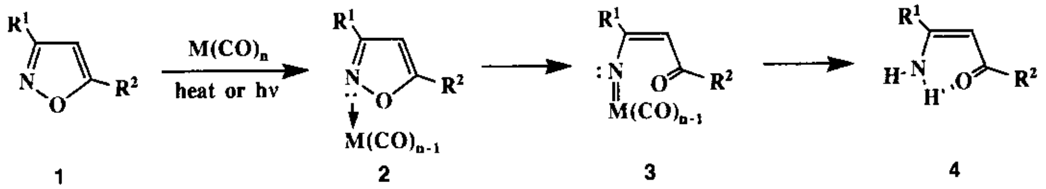
Abstract---The $Mo(CO)_6$-induced reaction of 3-methyl-5-(2-oxoalkyl)isoxazoles, which are derived through proton-abstraction of 3,5-dimethylisoxazole followed by treatment with esters, gave pyridin-4(1H)-ones in good to modest yields in a single step.

We have previously found the optimum conditions for the metal-carbonyl-induced [$Mo(CO)_6$,[1] $Fe(CO)_5$,[2] and $Fe_2(CO)_9$[2]] facile N-O bond cleavage of the isoxazole (1).[2,3] Concerning the complexed isoxazole **2**, a possible delocalization of a π-d electron from the central metal to the LUMO of the isoxazole is expected to facilitate the N-O bond cleavage under mild conditions to give the vinylnitrene complex **3**, which would give β-amino enone (**4**) in the presence of water.[2,3] The reaction has been successfully applied for the synthesis of several interesting compounds, which are not available by using the catalytic hydrogenation of isoxazole ring giving β-amino enones (Scheme 1).[4]

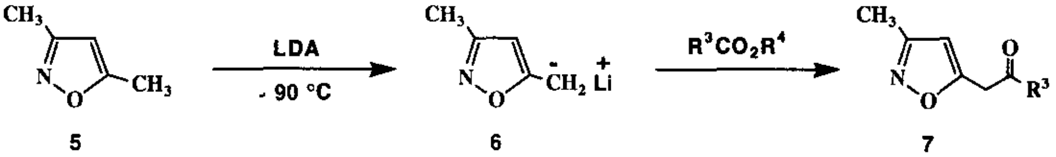
Recently, 1-substituted pyridin-4(1H)-ones and pyran-4-ones have been conveniently prepared through the electrophilic attack of esters to the α'-position of dianions of β-monosubstituted-amino-α,β-unsaturated ketones and the subsequent cyclization of the



Scheme 1. $M(CO)_n = Mo(CO)_6, Fe_2(CO)_9, Fe(CO)_5$

products.[6] Although many synthetic methods of pyridin-4(1H)-ones have appeared, the study prompted us to report our results concerning the preparation of pyridin-4(1H)-ones via isoxazole route.

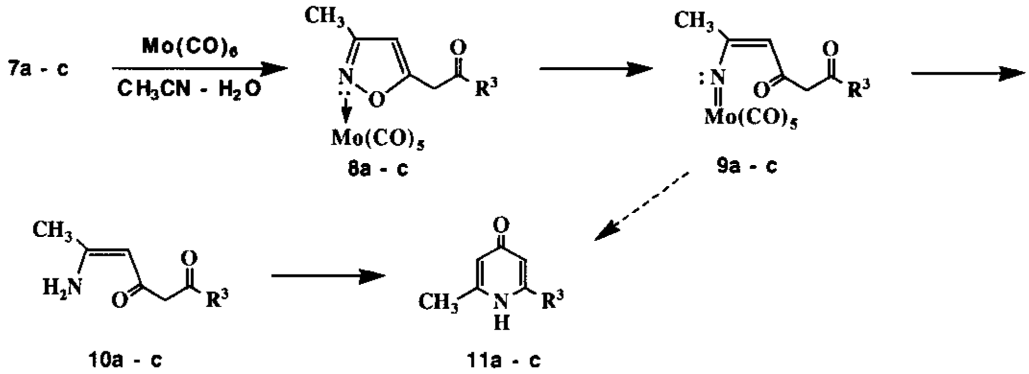
It is well known that the regiospecific reaction of 3,5-dimethylisoxazole with various electrophiles including esters in the presence of alkali metal amide in liquid ammonia occurs at the methyl group at the 5-position.[7] Thus we applied a modified method for the preparation of 3-methyl-5-(2-oxoalkyl)isoxazoles **7a–c**. After a solution of of 3,5-dimethylisoxazole was treated with lithium diisopropylamide in tetrahydrofuran, esters were added to the cold (-90 °C) solution. Then the usual workup afforded 3-methyl-5-(2-oxoalkyl)isoxazole **7a**,[7] **7b**,[8] and **7c**[9,10] in 44%, 64%, and 30% yields, respectively (Scheme 2). The highest yield was obtained in the reaction with methyl benzoate. This fact implies a trans-metalation reaction, which would occur between the isoxazole anion and the ester having acidic hydrogen at the α-position.



Scheme 2. a: R^3 = CH_3, R^4 = Et; b: R^3 = Ph, R^4 = CH_3; c: R^3 = $CH_3(CH_2)_{10}$, R^4 = CH_3

The thermally induced reaction of isoxazoles **7a–c** with $Mo(CO)_6$ in acetonitrile was carried out under reflux. The reaction mixture was then purified by tlc on silica gel to give pyridin-4(1H)-ones **11a**,[9] **11b**,[10] and **11c**. The products **11a** and **11b** are known, and the structures were confirmed on the basis of comparison of the physical data with those reported in the literatures. The compound **11c** is new and the structure was also assessed on the similarity of the spectral data with those of **11a,b**. The reaction conditions and the yields of the products are summarized in Table 1.

The present reactions are best explained by the pathways shown in Scheme 3.[3] There is a complex formation of **7a–c** with $Mo(CO)_6$ to give **8a–c**, and the subsequent N–O bond cleavage gives the complex **9a–c**. In the absence of water (Table 1, entries 1 and 3) no identified product was obtained. On the contrary, addition of water furnished the yields of **11a,b** (entries 2 and 4). The requirement of water is clearly demonstrated in the



Scheme 3. a: $R^3 = CH_3$; b: $R^3 = Ph$; c: $R^3 = CH_3(CH_2)_{10}$

Table 1. Results of the reaction of **7a–c** with $Mo(CO)_6$[a]

Entry	Substrate	Solvent	H_2O[b]	Reaction time/h	Product	Yield/%
1	**7a**	CH_3CN	none	1.0	--	--[c]
2	**7a**	CH_3CN	25	1.5	**11a**	89
3	**7b**	CH_3CN	none	1.3	--	--[c]
4	**7b**	CH_3CN	25	1.5	**11b**	32
5	**7c**	CH_3CN	10	1.0	**11c**	29
6	**7c**	CH_3CN	25	1.0	**11c**	41
7	**7c**	CH_3CN	100	1.5	**11c**	89

a. Heated under reflux until **7a–c** disappeared completely. b. Molar equivalent amounts toward **7a–c**. c. No identified material was obtained.

yields of **11c** (entries 5-7). In our previous papers, the intramolecular condensation of the complexed vinylnitrene with the carbonyl group was demonstrated.[11] However, the direct condensation of **9a–c** to give **11a–c** seems to be less important in the present reactions, and the complexes **9a–c** has to be hydrolyzed to give the enamine derivatives **10a–c**, which then undergo the condensation to give pyridin-4(1H)-ones **11a–c** in good to modest yields. The benzoyl group seems to be less reactive in the condensation reaction (entry 4).

In conclusion, since the isoxazoles having various (2-oxo)alkyl group are easily available and the M0(CO)$_6$-induced N-O bond cleavage is also simple, therefore the present reaction provides a convenient route for the preparation of pyridin-4(1H)-ones.

EXPERIMENTAL

Ir spectra were recorded on a Shimadzu IR-400 spectrophotometer. The mass and high resolution mass spectral studies were conducted using a Shimadzu GCMS-QP1000 and a JEOL DX-300 spectrometers. ^{1}H-Nmr spectra were recorded on a Hitachi R-24 spectrometer in $CDCl_3$, and chemical shifts were given in ppm (δ) relative to internal $SiMe_4$. Microanalyses were performed at the Science and Engineering research Laboratory of Waseda University. Mps were recorded on a Buchi apparatus and are uncorrected.

General Procedure for the Preparation of 7a,b,c. A solution of LDA (lithium diisopropylamide) was prepared by the reaction of diisopropylamine (2.43 g, 24 mmol) in dry THF (tetrahydrofuran) (10 ml) with butyllithium (22 mmol, 14 ml of 1.6 M hexane solution) at 0 °C. To a stirred solution of 5 (1.94 g, 20 mmol) in dry THF (40 ml) was added a solution of LDA at -90 °C over 30 min, and the mixture was stirred for another 1 h at -90 °C and warmed to room temperature. After the reaction had been quenched with hydrochloric acid (1%), the mixture was extracted with CH_2Cl_2. The extract was washed with aqueous $NaHCO_3$ solution, dried over Na_2SO_4, and evaporated. The residue was then purified by distillation or by column chromatography followed by recrystallization to give **7a** (44%), **7b** (64%), and **7c** (30%). **7a**: bp 85 °C (266.6 Pa).[7] **7b**: mp 72-73 °C (from hexane-benzene) (lit.,[8] 72 °C). **7c**: mp 60-61 °C (from EtOH); ^{1}H-nmr (60 MHz) δ 0.91 (3H, t, J=4.0 Hz), 1.26-2.45 (20H, m), 3.70 (2H, s), 5.99 (1H, s); ir (CCl_4) 1726 cm^{-1}; ms (m/z) 279 (M^+, 5), 97 (100). Anal. Calcd for $C_{17}H_{29}NO_2$: C, 73.07; H, 10.46; N, 5.01. Found: C, 72.95; H, 10.71; N, 4.89.

General Procedure for the Reaction of 7a,b,c with Mo(CO)$_6$. A solution of **7a,b,c** (1 mmol) and Mo(CO)$_6$ (132 mg,0.5 mmol)[3] in dry or moist CH_3CN (20 ml) was heated under reflux for a period indicated in Table 1. The reaction mixture was filtered through Celite to remove insoluble materials, and the filtrate was concentrated. The residue was then purified by tlc on silica gel to give the products. The reaction conditions and the yields of the products are summarized in Table 1. **11a**: mp 220-221 °C (from EtOH) (lit.,[9] 225 °C). **11b**: mp 232-233 °C (from AcOEt-EtOH) (lit.,[10] 235-237 °C). **11c**: mp 66-67 °C (from hexane-CCl_4); ^{1}H-nmr (60 MHz) δ 0.87 (3H, t, J=4.0 Hz), 1.25-2.43 (20H, m), 6.18 (2H, s); ir (CCl_4) 1625 cm^{-1}; ms (m/z) 263 (M^+, 33), 123 (100). High ms Calcd for $C_{17}H_{29}NO$: 263.4222. Found: 263.2253.

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