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Synthesis of Pyrazole Carboxylic Acid via Cobalt-Catalyzed Liquid Phase Oxidation

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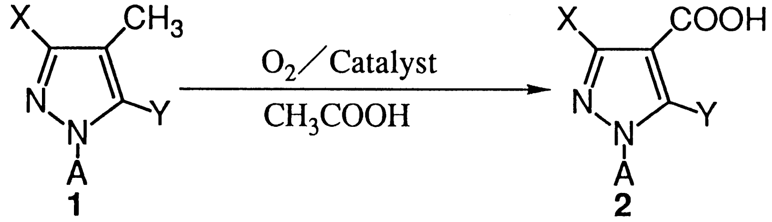
In the presence of catalytic amount of cobalt acetate(II) , manganese acetate(II) and bromide ion, the selective oxidation of 3,5-dichloro-1,4-dimethylpyrazole with molecular oxygen afforded 3,5-dichloro-1-methylpyrazole-4-carboxylic acid in more than 95% yield.

The pyrazole carboxilic acids were useful intermediates for fine chemicals,[1)] and the development of its synthetic process has been a subject of practical interest. Heretofore the permanganic acid oxidation method has been used to prepare pyrazole carboxilic acids from arkylpyrazoles.[2)] However, the demerits of this method are the use of excess amount of permanganate, extremely poor yield of the acids, and production of large amounts of undesired waste water contaminated with manganese. On the other hand, the liquid phase oxidation of substituted methylbenzenes is widely performed industrially and laboratory-scale synthesis.[3)] Also heretofore heterocyclic acids which have pyridine or quinoline group, have been prepared by cobalt-catalyzed liquid phase autoxidation method.[4)] However, there has not been reported a method wherein only a 4-methyl group of 1,4-dimethylpyrazoles is selectively oxidized to yield pyrazole carboxylic acids. In this communication, we would like to describe a convenient method for the preparation of pyrazole carboxylic acids from methylpyrazoles by cobalt-catalyzed liquid phase oxidation.

A typical procedure for the preparation of 3,5-dichloro-1-methylpyrazole-4-carboxylic acid is as follows. A 100ml hasteroy autoclave was charged with 3,5-dichloro-1,4-dimethylpyrazole (7.27 mmol), $Co(OAc)_2 \cdot 4H_2O$ (0.218 mmol), $Mn(OAc)_2 \cdot 4H_20$ (0.0545 mmol), NaBr (0.436 mmol) and 50ml of acetic acid. Air was introduced at 70 kg/cm^2 at ambient temperature, and the mixture was heated with stirring. When the temperature of the reaction mixture reached 130 °C, the partial pressure of oxygen was regulated at 20 kg/cm^2. The conversion ratio was estimated by HPLC with acetonitrile-water (1/1) as eluants. After diazomethane treatment, the products were isolated by purification and characterized by MS and NMR.

Table 1. Oxidation of 4-methylpyrazoles with Co-Mn-Br catalyst[a)]



Entry	**1**			Time	Conv of **1**	Yield of **2**	Catalyst
	A	X	Y	h	%	%	
1	CH_3	Cl	Cl	1	99.7	96.3	Co - Mn - Br
2	CH_3	Cl	Cl	1	0	0	Co - Br
3[b)]	CH_3	Cl	Cl	1	10.1	3.0	Mn - Br
4	CH_3	Cl	Cl	1	7.5	2.1	Co - Mn
5	CH_3	H	Cl	2	97.8	93.3	Co - Mn - Br
6	CH_3	H	H	1	98.7	94.4	Co - Mn - Br
7	CH_3	Br	Br	1	53.2	41.7	Co - Mn - Br
8	H	Cl	Cl	4	94.1	82.7	Co - Mn - Br
9	H	H	Cl	1	93.8	90.8	Co - Mn - Br

a) Reaction conditions : **1** 7.27 mmol, $Co(OAc)_2$ 0.218 mmol, $Mn(OAc)_2$ 0.0545 mmol, NaBr 0.436 mmol, CH_3COOH 40 ml, O_2 20 kg/cm^2, temp 130 °C.

b) $Mn(OAc)_2$ 0.273 mmol.

Table 1 summarizes the results of the oxidations of six pyrazole derivatives. It is obvious that the Co-Mn-Br catalyst system is effective system. The major product was pyrazole-4- carboxylic acid **2** and the yield of pyrazole-1-carboxylic acids were less than 0.1%. Aldehydes, acetates and organic bromides were obtained in 0.2, 1.5, 1.8% yields, respectively (Entry 1). In the absence of one component of this catalyst system the reaction proceeded slightly. (Entries 2-4)

Figure 2 shows the effect of Mn/Co ratio on the activity of the catalyst upon addition of $Mn(OAc)_2$ to $Co(OAc)_2$ at a constant concentration of bromide ion, where the maximum reaction rate was obtained at the ratio of 0.2-0.3. At the ratio lower than 0.2, the activity was very low. On the other hand, when the ratio exceeded 0.3, the activity was gradually reduced.

The effect of the bromide ion concentration on the catalyst activity in the presence of cobalt and manganese was investigated (Fig.2). The maximum reaction rate was obtained at the ratio of 2.0. Without bromide ion, alkylpyrazoles could not be oxidized.

The effect of temperature on the reaction rate was also studied. Although methylbenzenes were easily oxidized under 100 °C in Co-Mn-Br system, the rate constants for the oxidation of the methylpyrazoles were extremely small even if at 120 °C. The value of the activation energy was calculated to be about 16 kcal/mol.

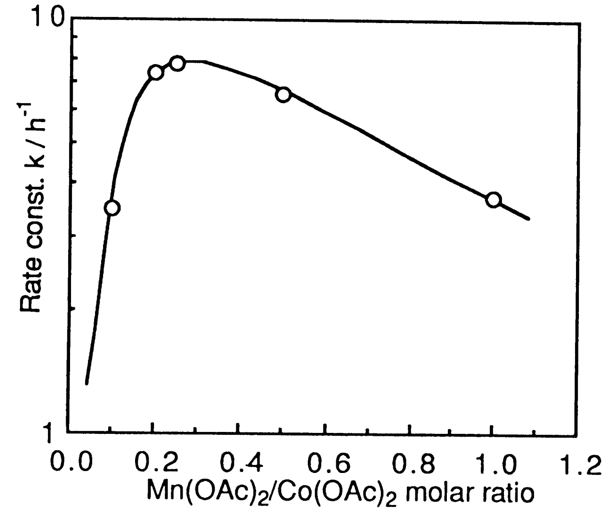


Fig. 1. Effect of Mn/Co ratio.

Reaction conditions : **1** (X=Y=Cl) 7.27 mmol, Co(OAc)$_2$ 0.218 mmol, NaBr 0.436 mmol, AcOH 40 ml, temp 130 °C, O_2 20 kg/cm^2. k is rate constant for oxidation of **1**.

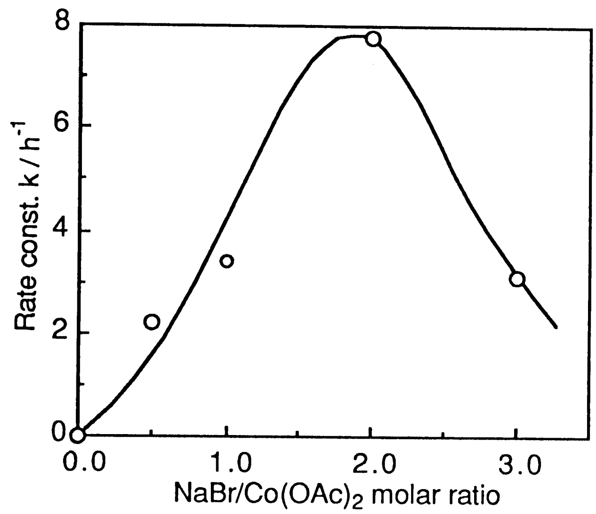
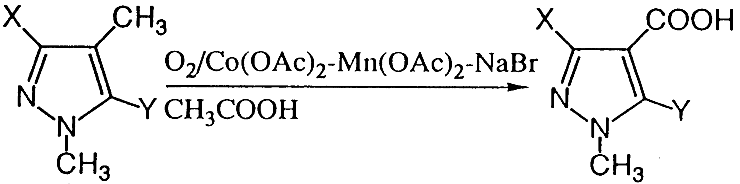


Fig. 2. Effect of Br/Co ratio.

Reaction conditions : **1** (X=Y=Cl) 7.27 mmol, Co(OAc)$_2$ 0.218 mmol, Mn(OAc)$_2$ 0.0545 mmol AcOH40 ml, temp 130 °C, O_2 20 kg/cm^2

The competitive oxidations of 1,4-dimethylpyrazole **1a**, 5-chloro-1,4-dimethylpyrazole **1b** and 3,5-dichloro-1,4-dimethylpyrazole **1c** were carried out using Co-Mn-Br catalyst system at 120 °C and 130 °C (Fig.3). After introducing one chloro atom in **1a** and **1b**, the reaction rates became 1/2 and 1/3 of that for **1a**, respectively. These results are in fair agreement with the Hammett's $\sigma-\rho$ relationship in the oxidation of methylbenzenes.$^{5)}$ And 3,5-dibromo-1,4-dimethylpyrazole were observed to be less reactive than **1c**. The same tendency was observed in the



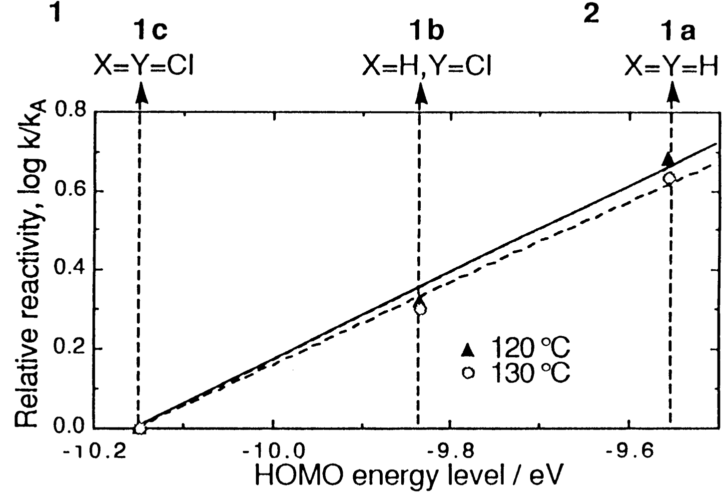


Fig. 3. Relative reactivity of 4-methylpyrazoles.

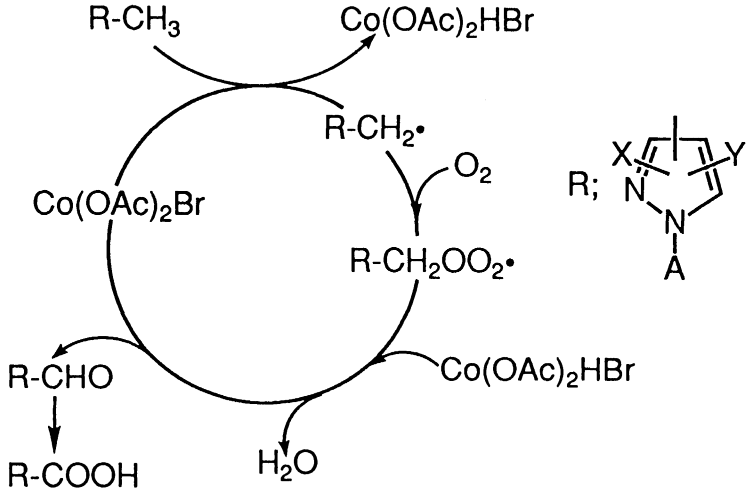
Reaction conditions : **1** each 3.63 mmol, Co(OAc)$_2$ 0.218 mmol, Mn(OAc)$_2$ 0.0545 mmol, NaBr 0.436 mmol, AcOH 60 ml, O_2 20 kg/cm^2.

HOMO energy level was calculated by MNDO method and k_A is rate constant for oxidation of **1c**.

reactions of substituted 4-methylpyrazoles.(Entries 8,9)

On the basis of these results and the previous document,[6)] the reaction profile in Scheme 1 is considered likely feasible. This scheme involves the reversible interaction of Co^{III} with **1**, leading to the formation of 4-pyrazoylmethyl radical.

And then, the radical reacts with oxygen to give a peroxyl radical, which is decomposed to an aldehyde by Co^{II} or Mn^{II}. Aldehydes were smoothly oxidized via the above path to yield acids. Mn^{III} may take part in oxidation of Co^{II} and decomposition of peroxyl radicals.



$$\text{R-CH}_2\text{OO}\bullet + \text{Mn}^{2+} \longrightarrow \text{R-CHO} + \text{Mn}^{3+} + \text{OH}^-$$

$$\text{Co(OAc)}_2\text{HBr} + \text{Mn}^{3+} \longrightarrow \text{Co(OAc)}_2\text{Br} + \text{Mn}^{2+} + \text{H}^+$$

Scheme 1.

Thus, it is noted that various pyrazole carboxylic acids were readily produced in high yields from substituted methylpyrazoles via Co-Mn-Br-catalyzed liquid phase oxidation.

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