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Catalytic Hydrogenation of Diacetyl Monoxime to Tetramethylpyrazine with the Soluble Transition Metal Catalysts

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Abstract: Catalytic hydrogenation of diacetyl monoxime to tetramethylpyrazine, by the homogeneous catalysts generated *in situ* from some transition metal chlorides with triphenylphosphine in ethanol under H_2 pressure of 0.6～4.6 MPa at 100～150℃, has been studied. The optimum H_2 partial pressure was observed at about 1.3 MPa. The maximum conversion of diacetyl monoxime and yield of tetramethylpyrazine were 97% and 90%, respectively.

Keywords: Diacetyl monoxime, catalytic hydrogenation, tetramethylpyrazine.

Tetramethylpyrazine (TMP) is a useful compound in food industry[1]. In recent years it has been found as an active ingredient in Chuanxiong (*ligusticum wallichii franch*), which is a traditional Chinese herb. Now TMP has been widely used in the treatment of patients with cerebral ischemic diseases in China[2]. One of the important methods for the preparation of tetramethylpyrazine is the self-condensation of two molecules of 2-amino butanone to 2, 5-dihydrotetramethlipyrazine and subsequent oxidation to TMP[3]. 2-Amino butanone is prepared usually *in situ via* the reduction of the corresponding diacetyl monoxime by reducing agents, such as zinc-alkali, zinc-acetic acid, *etc*[3]. Whereas homogeneous catalytic hydrogenation routes of diacetyl monoxime (DAM) have been scarcely explored. In the present work, we wish to report the synthesis of tetramethylpyrazine *via* catalytic hydrogenation of diacetyl monoxime using homogeneous transition metal catalysts.

IR spectra were obtained on a MAGNA IR-560 spectrometer. ^1H NMR spectra were determined with $Me_3Si\text{-}SiMe_3$ as an internal standard in CCl_4 solvent on a PMX-60M Hz instrument. UV-VIS spectra were recorded with a Shimadzu UV-2401 spectrophotometer. MS spectra were determined with a Finnigan Mat Magnum GC/MS ion trap system.

The catalytic hydrogenation was carried out in a 24 ml glass-lined stainless steel autoclave. A mixture of $PdCl_2$ (2.91 mg, 1.63×10^{-2} mmol), PPh_3 (6.3 mg, 2.45×10^{-2} mmol), DAM (0.5 g, 4.89 mmol) and ethanol (6 ml) were added into the autoclave. The reactor was purged five times with hydrogen, before setting the required H_2 pressure. Hydrogen up to 1.3 MPa was introduced and the reaction vessel was placed in a preheated thermostatic oven which could be agitated by shaking (12 times / min.). The reaction mixture was kept at 150 ℃ for 6 h. After being cooled to room temperature, the reaction solution was immediately analyzed and identified by GC-MS and UV-VIS. In the meantime, the products were isolated and purified by preparative TLC on silica gel (Cyclopentane: ethyl acetate = 2:1), and further identified by H^1-NMR, IR and melting point determining. The data of TMP are in accord with refs[3, 4].

During our investigation of the catalytic hydrogenation of DAM with hydrogen using homogeneous palladium chloride-triphenylphosphine catalytic systems, we found incidentally that the reaction shown by **Scheme 1** could take place more easily to TMP under lower H_2 pressure[5]. Besides $PdCl_2$-PPh_3, Co, Ni, Pt, and Fe analogues can also be used as catalysts (**Table1**). But the $PdCl_2$ - PPh_3 catalytic systems gave the maximum yield 90% of TMP. The activities of the various transition metals are in the order: Pd > Pt> Co > Ni >Fe > Ru. The tendency appears to be related to the stability of the complexes generated from the corresponding transition metal chlorides with DAM. Atchay *et al* reported that $Pd^{(II)}$, $Co^{(II)}$, $Ni^{(II)}$ and $Fe^{(II)}$ could form unstable complexes with DAM[5,6], the stability of these complexes were in the opposite order: Pd < Co <Ni <Fe. In order to find out whether the metals could form the complexes with DAM during the reaction, we determined the electronic spectra of their reaction mixtures (**Figure1)**. Most of catalytic systems had no absorption band in the region of 400～600 nm, but the peaks at 279 and 295 nm were assigned to the characteristic absorption of TMP[4]. Only Ru-PPh_3 reaction system had two absorption peaks at 439 and 500 nm, which were assigned to the absorbance of charge-transfer transition bands from $Ru^{(II)}$ to DAM in the complexes[8]. This result indicated that the formation of stable Ru-DAM complexes retarded the further reaction proceeding. So the $RuCl_3$ -PPh_3 catalytic system displayed

Scheme 1.

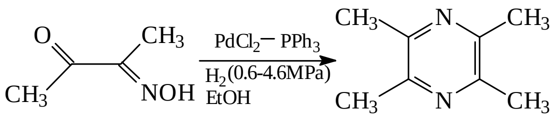


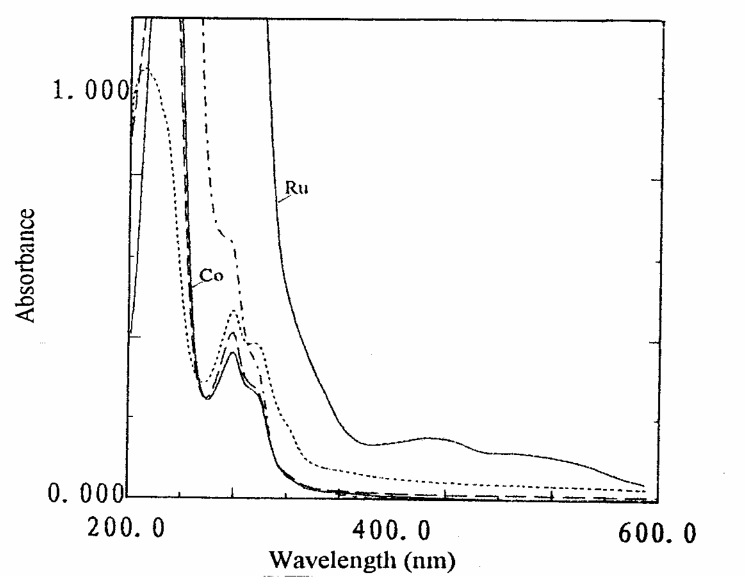
Table 1. The reaction results[a]

Catalyst precursor	PPh_3/M	T (℃)	P_{H2} (MPa)	t (h)	Conversion (%)	Yield[b](%)
$PdCl_2$, PPh_3	1.5	150	1.3	6	97	90
$PdCl_2$, PPh_3	1.5	120	4.0	6	87	53
$CoCl_2$, PPh_3	3.0	150	2.4	25	76	72
$CoCl_2$, PPh_3	3.0	100	4.0	30	67	57
$NiCl_2$, PPh_3	3.0	150	4.0	18	96	56
$NiCl_2$, PPh_3	3.0	120	4.0	26	37	31
H_2PtCl_4, PPh_3	3.0	150	4.0	6	64	49
H_2PtCl_4, PPh_3	3.0	120	3.0	16	40	40
$FeCl_3$, PPh_3	3.0	150	1.0	6	27	24
$FeCl_3$, PPh_3	3.0	120	4.0	46	25	13
$RuCl_3$, PPh_3	3.0	120	4.0	26	4	2

a. Other conditions: DAM 0.5 g, DAM/metal chloride: 300 (mole ratio), EtOH 6 ml.
b. Yields were determined by GC-MS analysis.

poor activity in the reaction.

Figure 1. Electronic spectra of the reaction solution after hydrogenation of DAM catalyzed by transition metal-triphenylphosphine catalytic systems[a,b]

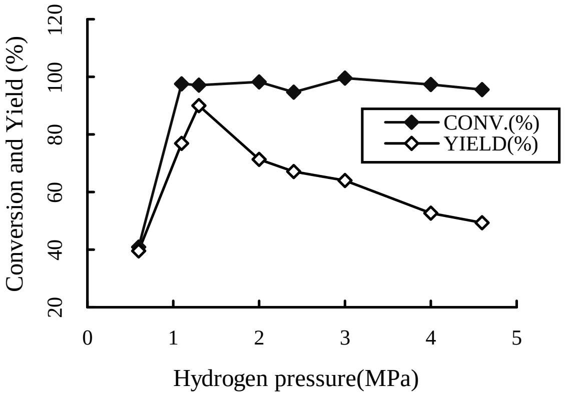


Ru-PPh_3 (Ru——), Pt-PPh_3 (– – – –), Ni-PPh_3 (······),
Pd-PPh_3 (— — —), Co-PPh_3 (Co———)

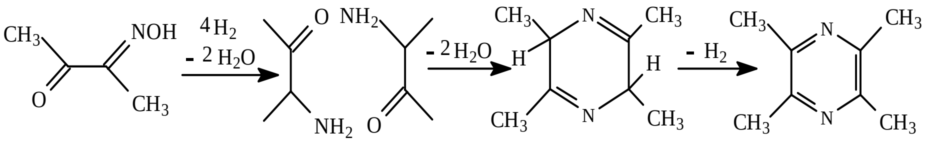
a. The electronic spectra were obtained at 25℃.
b. Reaction conditions: see experimental section

It was also found that H_2 pressure dramatically changed the reaction results shown in **Figure 2**. The conversion of DAM increased with increasing H_2 pressure in lower pressure range; while the conversion remained nearly constant when H_2 pressure is higher than 1.3 MPa. However a new trend for the yield of TMP was observed, the yield of TMP passed through a maximum at H_2 pressure of 1.3 MPa. Similar trends can be also observed in the systems of Co, Ni, and Pt. We think the phenomena match well with the following reaction path (**Scheme 2**). The conversion of DAM to TMP proceeds actually in three discrete steps: (i) hydrogenation of DAM to yield 2-amino butanone (**a**); (ii) condensation of **a** to form dihydrotetramethylpyrazine (**b**); (iii) dehydrogenation of **b** to afford TMP. It is clear that the effect of H_2 pressure on the first step is opposite to the third step. Increasing H_2 pressure is in favor of the hydrogenation of DAM to **a**, but not of the dehydrogenation of **b.** So the optimum H_2 pressure was observed at about 1.3 MPa.

Figure 2. Effect of H_2 pressure on the reaction results of $PdCl_2$-PPh_3 catalytic systems



Scheme 2.



a **b**

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References

1. (a) S. Takayaki, N. Taru, *et al.*, *Ger. offten, DE* 19 629 258, **1997**; (b) S.Shinkichi, *Japan Kokai JP* 63 162 988**; (**c) C. Tehkuei, Eur. Pat.,EP 505 891, **1992**.
2. Y. P. Ye, S. Z. Wang and J. Jiang, *Acta Academiae Medicinae Sinicae*, **1996**, *18*, 288.
3. G.B.Barlin, *The Pyrazines*, ed. A. Weissberger and E.C.Taylor, Interscience, New York, **1983**.
4. D. J. Bell, I. R. Brown, *et al., Aust. J. Chem.*, **1979**, *32*, 1281.
5. X. Y. Wang, X. M. Zheng, Z. Y. Hou, D. Z. Sun, W. M. Lu and F. Chen, *Faming Zhuanli Shenqing Shuomingshu* 98124478.5.
6. M.Y. Atchay, *et al., Indian J. Chem*., **1973**, *11*, 1015.
7. P. P. Bhargava, *Indian J. Chem*., **1986**, *25A*, 193.
8. A. R. Chakravar, *et al., J. Chem. Soc. Dalton Trans*., **1982,** 615.

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