DECHLORINATION OF CHLOROPYRAZINE N-OXIDES

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Abstract —— By heating chloropyrazine N-oxides with palladium catalysts and potassium acetate in N,N-dimethylformamide under a hydrogen stream, the chlorine atom was readily removed without deoxygenation of the N-oxide group.

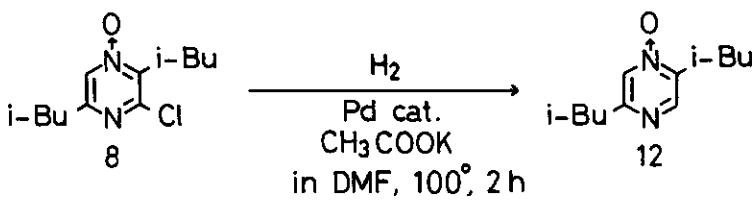
As metal catalyst for the carbon-carbon coupling reaction, palladium catalysts are specially useful[1]. Palladium catalysts also have some effects on dechlorination of aryl halides[2]. The authors already reported that chloropyrazine N-oxides are dechlorinated with sodium formate and a palladium catalyst, giving the mother pyrazine N-oxides without deoxygenation[3]. Recently, we found that the hydrogen-palladium catalyst system is very useful for dehalogenation of aryl halides[4]. The present report constitutes a continuation of the investigation on dehalogenation of aryl halides, and describes the application of the hydrogen-palladium catalyst system to the dehalogenation of chloropyrazine N-oxides. Sodium formate used in the previous work[3] behaves as both a base and a reducing agent[2]. In the present work, potassium acetate and hydrogen were used as a base and a reducing agent, respectively. Namely, the reaction was accomplished by heating chloropyrazine N-oxides with palladium catalysts and potassium acetate in N,N-dimethylformamide (DMF) under a stream of hydrogen.

For the purpose of dechlorinating chloropyrazine N-oxides without deoxygenation, the efficiency of various palladium catalysts was first examined. A DMF solution of 2-chloro-3,6-diisobutylpyrazine 4-oxide (8)[5] and potassium acetate was heated at 100°C under a hydrogen stream in the presence of various palladium catalysts. As shown in Table I, tetrakis(triphenylphosphine)palladium gave specially good results, while palladium chloride and 10% palladium-carbon did not always give satisfactory results. A mixture of palladium chloride-triphenylphosphine was also

effective, and these results suggest that tetrakis(triphenylphosphine)palladium might be formed on the way of the reaction.

Upon examination of solvents and reaction temperatures (DMF-room temperature, DMF-100°C, benzene-reflux, acetonitrile-reflux, and tetrahydrofuran-reflux), heating at 100°C in DMF was chosen as the reaction conditions. The general procedure for dechlorination is as follows: A mixture of a chloropyrazine N-oxide (1 mmol), potassium acetate (147 mg, 1.5 mmol) and a palladium catalyst (0.05 mmol) in DMF (5 ml) was heated at 100°C on an oil bath for 2 h under a hydrogen stream. After being concentrated in vacuo, the reaction mixture was triturated with water (5 ml) and extracted with Et_2O (10 ml x 3). The Et_2O layer was dried over sodium sulfate and the solvent was evaporated to give the product, which was purified by column chromatography on silica gel (Wakogel C-200, 6 g), eluting with hexane containing increasing amounts of AcOEt.

Table I. Dechlorination of
2-Chloro-3,6-diisobutylpyrazine 4-Oxide with Various Catalysts



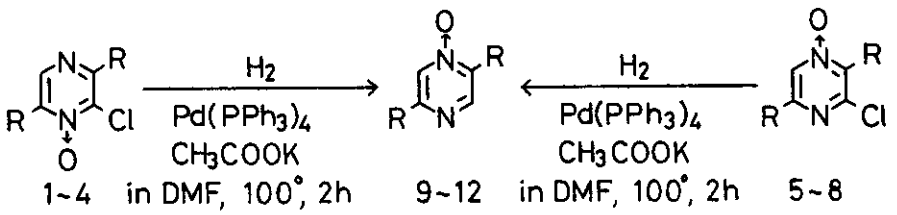
Catalyst	molar ratio	Yield (%)
$Pd(PPh_3)_4$	0.05	90
$Pd(PPh_3)_4$	0.01	82 (9[a])
$Pd(PPh_3)_2Cl_2$	0.05	56 (29[a])
$Pd(PPh_3)_2Cl_2$ + CuI	0.05 + 0.05	39
$PdCl_2$	0.05	33 (63[a])
$PdCl_2$ + $4PPh_3$	0.05 + 0.2	90
10% Pd-C	0.04	35 (58[a], 6[b])

a) The starting material b) 2-Chloro-3,6-diisobutylpyrazine[5]

In Table II, the results of dechlorination of some 2-chloro-3,6-dialkylpyrazine 1- and 4-oxides are illustrated. In all cases, tetrakis(triphenylphosphine)palladium was used as catalyst, and all the products were obtained in satisfactory yields.

The reaction using a mixture of palladium chloride and triphenylphosphine ($PdCl_2$ + $4PPh_3$) gave almost the same results.

Table II. Dechlorination of 2-Chloro-3,6-dialkylpyrazine 1- and 4-Oxides



1~4 9~12 5~8

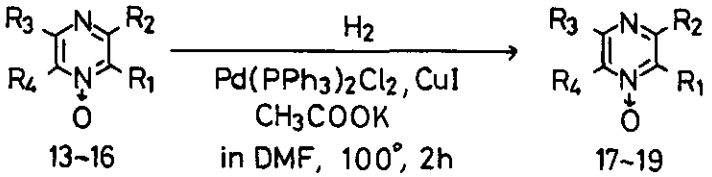
Reaction of 1-Oxides				Reaction of 4-Oxides			
Substrate	R	Product	Yield (%)	Substrate	R	Product	Yield (%)
1[7]	Me	9[13]	47 (5[a])	5[10]	Me	9[13]	83
2[8]	Et	10[11]	64 (25[a])	6[11]	Et	10[11]	87 (6[a])
3[8]	iso-Pr	11[3]	61 (2[a])	7[12]	iso-Pr	11[3]	70
4[9]	iso-Bu	12[3]	90	8[5]	iso-Bu	12[3]	87

a) The starting material

This reaction was applied to dechlorination of chloro-phenylpyrazine N-oxides. Examination of some palladium catalysts and bases ($PdCl_2$ + $4PPh_3$ + CH_3COOK, $Pd(PPh_3)_2Cl_2$ + CH_3COOK, $Pd(PPh_3)_2Cl_2$ + K_2CO_3, $Pd(PPh_3)_2Cl_2$ + CuI + CH_3COOK) in the dechlorination of 2-chloro-5,6-diphenylpyrazine 4-oxide[6] indicated that the bis(triphenylphosphine)palladium dichloride-copper(I) iodide-potassium acetate system answers also for the purpose (85% yield). On the other hand, a mixture of palladium chloride-triphenylphosphine gave unsatisfactory results (56% yield of 2,3-diphenylpyrazine 1-oxide[6], 15% yield of the starting material, and 11% yield of 2,3-diphenylpyrazine[6]). In this case, palladium chloride or palladium produced by the reduction with hydrogen might participate in the reaction, before the formation of tetrakis(triphenylphosphine)palladium.

Table III shows the results of dechlorination of some chloro-phenylpyrazine N-oxides, using a mixture of bis(triphenylphosphine)palladium dichloride-copper(I) iodide (0.05 molar equivalents of each). In all cases, the products were obtained in good yields. The reaction with tetrakis(triphenylphosphine)palladium gave almost the same results.

Table III. Dechlorination of Chloro-phenylpyrazine N-Oxides



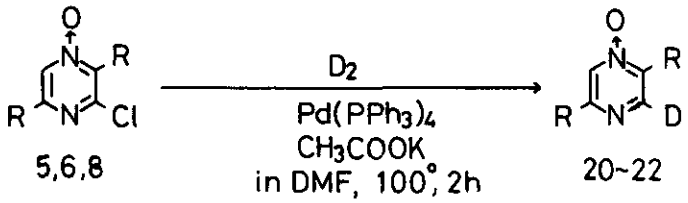
13~16 17~19

	Substrate					Product				Yield
	R_1	R_2	R_3	R_4		R_1	R_2	R_3	R_4	(%)
13[14]	Cl	H	Ph	H	17[14]	H	H	Ph	H	92
14[14]	H	Cl	Ph	H	17[14]	H	H	Ph	H	84
15[15]	Ph	H	Cl	Me	18[15]	Ph	H	H	Me	94
16[16]	Ph	Cl	Ph	H	19[16]	Ph	H	Ph	H	82 (4[a])

a) 2,5-Diphenylpyrazine[16]

Next, deuteration of the pyrazine ring will be described. The reaction mixture was heated in a stream of deuterium in the presence of 0.05 molar equivalents of tetrakis(triphenylphosphine)palladium, and the deuterium incorporation in the products was estimated by mass spectral analyses. The yields and deuterium incorporation are given in Table IV. The deuterated products are expected to be useful for the investigation of metabolism and mass fragmentation of pyrazines. Consequently, the present reaction system is very useful for the dechlorination of chloropyrazine N-oxides, especially for deuteration of pyrazine ring, and probably applicable for dechlorination of chloro derivatives of the other heteroaromatics.

Table IV. Incorporation of Deuterium into the Pyrazine Ring



5,6,8 20~22

Substrate		Product		Yield	Deuterium
	R		R	(%)	Incorporation (%)
5[10]	Me	20	Me	60	98
6[11]	Et	21	Et	92	90
8[5]	iso-Bu	22	iso-Bu	92	77

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