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α, β-不飽和 카르보닐化合物의 還元 아미노화反應

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Reductive Amination of α, β-Unsaturated Carbonyl Compounds with Tetracarbonylhydridoferrate as a Reducing Agent

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요 약. 세개의 α, β-불포화알데히드, 신남알데히드, 크로톤알데히드, 아크로레인을 여러가지 일차 아민 존재하에서 테트라카르보닐철산염으로 환원시켜 상당히 다른 수득률로 N-알킬아민을 합성하였다. 보통, $KHFe(CO)_4$ (22 mmole)와 일차아민 (22~44 mmole)과 α, β-불포화 알데히드 (22 mmole)를 에탄올 용매에 넣고 일산화탄소 분위기하에 실온에서 9~60시간 자석 젓개로 저어주면 일산화탄소를 천천히 흡수하면서 반응이 진행된다. 생성물은 가스크로마토그래피, 질량분석스펙트럼, 핵자기공명스펙트럼, 적외선스펙트럼 등으로 그 구조를 알았다.

ABSTRACT. The reductive amination of three α, β-unsaturated aldehydes, cinnamaldehyde, crotonaldehyde, and acrolein are carried out successfully by tetracarbonylhydridoferrate in the presence of various primary amines. In a typical reaction, a mixture of potassium tetracarbonylhydridoferrate (22 mmole), an amine (22~44 mole) and α, β-unsaturated aldehyde (22 mmole), in ethanol (30~50 m*l*) was stirred for 9~60 hours at room temperature under carbon monoxide atmosphere. All the products were characterized as secondary amines by mass, infrared, and nmr spectra as well as gas chromatographic data.

INTRODUCTION

Potassium tetracarbonylhydridoferrate prepared from iron pentacarbonyl and alkali metal hydroxide has been shown to be a useful reducing agent for a variety of organic functional groups[1]. There has been considerable recent interest in the use of the tetracarbonylhydridoferrate anion generated in *situ*, $[HFe(CO)_4]^-$, for effecting reductive alkylation[2~4], amination[5~9], hydroacylation[10], dehalogenation[11,12], desulfurization[13], and for hydrogenation of the carbon-carbon double bond of an α, β-unsaturated carbonyl[14]. The ferrate, however, has little

activity for the reduction of carbonyl group. Although a reducing power of the ferrate is not strong, the ferrate appears to have a wide applicability as a selective reducing agent.

The synthesis of several N-alkyl and N-arylamines is, therefore, studied by the reductive amination of α,β-unsaturated aldehyde with tetracarbonylhydridoferrate as a reducing reagent.

EXPERIMENTAL

General. Commercial $Fe(CO)_5$ (Stream Chemicals Inc.) was used without further purification, and the other compounds employed in this study were obtained commercially.

Nuclear magnetic resonance (nmr) spectra were measured on a Varian T-60A spectrometer in $CDCl_3$ or in CCl_4 with TMS (tetramethylsilane) as internal standards. Mass spectra were obtained on a Hitachi RMU-7M mass spectrometer at 30 eV. Infrared spectra were measured on a Perkin Elmer Model 267 spectrophotometer in CCl_4 or $CHCl_3$ solvents. Potassium bromide pellets were also used. Gas chromatography was performed on a Varian Aero 2800 Model with flame ionization detector and He carrier gas. The columns (3 mm×3 m) used were 10 % Versamid on Neopak 60/80 mesh. Melting points are uncorrected and were determined on a Thomas Melting Point Apparatus.

Preparation of Potassium Iron Carbonylates, $KHFe(CO)_4$, and $K_2Fe(CO)_4$. The alcoholic solutions of these salts were prepared by the method described by Krumholtz and Stettiner[15]. A 200 *ml* three-necked flask, fitted with a magnetic stirrer and a rubber stopper, was connected with a pressure equalizing gas buret and then flushed with nitrogen or carbon monoxide. By the use of a hypodermic syringe, 66 *ml* of a 1 *N* potassium hydroxide solution in ethanol, 34 *ml* of ethanol, and 3.0 *ml* of iron pentacarbonyl (22 mmole) were placed in the flask and then stirred vigorously for 2 hours at room temperature to give a brown solution with a white precipitation. Iron pentacarbonyl is toxic, and great care must be exercised in its handling.

Reaction Procedures. All the reductions were carried out in a similar manner. To the solution of potassium iron carbonylate obtained as described above, 22 mole of primary amine and 22 mmole of α, β-unsaturated aldehyde were added simultaneously. The mixture was stirred vigorously from 9 to 60 hours at room temperature, under one atmosphere of carbon monoxide. After the reaction is completed, the reaction mixture was acidified with hydrochloric acid, and solvents were concentrated after the separation of a precipitated material. A residue was extracted with ether or chloroform in the presence of sodium hydroxide, and dried over anhydrous sodium carbonate. After evaporating the solvent, distillation at reduced pressure gave N-alkylated amines.

RESULTS AND DISCUSSION

The in *situ* generated tetracarbonylhydridoferrate reacted with mixture of α, β-unsaturated aldehydes, such as cinnamaldehyde, crotonaldehyde and acrolein, and various primary amines under carbon monoxide to give the corresponding saturated secondary amine derivatives. The reaction proceeds smoothly at room temperature with an absorption of carbon monoxide after a certain induction period and with color change from pale brown to dark red. The results are summarized in *Table* 1.

Several primary aromatic amines were butylated by the reaction with crotonaldehyde in the presence of tetracarbonylhydridoferrate. *o*-Methoxy and *m*-methyl groups hinder the butylation. The butylation of *o*-methoxyaniline

Table 1. N-Alylation of primary amines with $KHFe(CO)_4$-α,β-unsaturated carbonyl compounds.[a]

$$RNH_2+R'CH=CH-CHO \xrightarrow{KHFe(CO)_4} R'CH_2CH_2CH_2NHR$$

Exp. No.	R (RNH_2)	R' (R'CH=CHCHO)	Reaction time (hr)	Absorbed[b]	Product (%)[c]
1	t-$(CH_3)_3C$	C_6H_5	23	1.0	N-*t*-Butyl-3-phenylpropanamine, 48
2	CH_3	C_6H_5	20	1.0	N-Methyl-3-phenylpropanamine, 45
3	$C_5H_5CH_2$	C_6H_5	8.5	0.9	N-Benzyl-3-phenylpropanamine
4	p-$CH_3C_6H_4$	C_6H_5	20	0.7	N-*p*-Methoxyphenyl-3-phenylpropanamine
5	p-$CH_3OC_6H_4$	CH_3	24	1.3	N-Butyl-*p*-anisidine, 46
6	o-$CH_3OC_6H_4$	CH_3	42	1.3	N-Butyl-*o*-anisidine, 48
7	m-$CH_3CH_6H_4$	CH_3	42	2.0	N-Butyl-*m*-toluidine, 49
8	p-$CH_3C_6H_4$	CH_3	28	1.7	N-Butyl-*p*-toluidine, 44
9	$C_6H_5CH_2$	CH_3	26	1.7	N-Butylbenzylamine, 43
10	p-ClC_6H_4	CH_3	60	0.8	N-Butyl-*p*-chloroaniline, 26
11	2-Aminopyridine	CH_3	28	1.3	N-Butyl-2-amincpyridine, 30
12	2-Aminopyridine	CH_3	50	1.8	N-Butyl-2-aminopyridine, 57
13	3-Aminopyridine	CH_3	35	1.4	N-Butyl-3-aminopyridine, 27
14	4-Aminopyridine	CH_3	24	1.3	N-Butyl-4-aminopyridine, 21
15	p-$CH_3OC_6H_4$	H	24	1.2	N-propyl-*p*-anisidine, 62

[a]At room temperature under carbon monoxide. Molar ratio $KHFe(CO)_4$/R'CH=CHCHO/RNH_2=1 : 1 : 1; [b]Mole/mole-$KHFe(CO)_4$; [c]Isolated yield; [d]Crotonaldehyde $\xrightarrow{KHFe(CO)_4}$ butyraldehyde+ amine $\xrightarrow{KHFe(CO)_4}$ Product.

Table 2. NMR analysis of N-alkylated amines.

Exp. No.	b.p or m.p	NMR ($CDCl_3$, CCl_4) ppm
1	196 °C	1.4(*s*, 9H) 2.4~3.0(*m*, 6H) 7.2(*s*, 5H, Ar) 8.3(*s*, 1H, NH)
2		2.2(*m*, 2H) 2.55(*s*, 3H, N-CH_3) 2.6~3.0(*m*, 4H) 7.1(*s*, 5H, Ar) 8.1(*s*, 1H, NH)
3	77/0.1 mmHg	1.0(*s*, 1H, NH), 1.7(*q*, 2H) 2.5(*m*, 4H), 3.7(*s*, 2H) 7.2(*d*, 10H, Ar)
4	155/0.15 mmHg	0.9(*q*. 2H), 2.65(*t*, 2H) 2.9(*s*, 1H, NH) 3.1(*t*, 2H) 3.7(*s*, 3H, O-CH_3) 6.5(*q*, 4H, Ar) 7.15(*s*, 5H, Ar)
5	158/0.2 mmHg	1.0(*m*, 3H), 1.3~1.9(*m*, 4H) 3.0(*t*, 2H), 3.35(*s*, 1H, NH) 3.7(*s*, 3H, OCH_3) 6.45~6.95(*q*, 4H, Ar)
6		1.0(*m*, 3H), 1.3~1.8(*m*, 4H) 3.1(*t*, 2H), 3.8(*s*, 4H, OCH_3, NH) 6.45~6.95 (*m*, 4H, Ar)
7		1.0(*m*, 3H), 1.3~1.9(*m*, 4H), 2.25(*s*, 3H), 3.0(*t*, 2H), 3.28(*s*, 1H, NH) 6.17~7.15(*m*, 4H)
8	59/0.3 mmHg	1.0(*m*, 3H), 1.3~1.9(*m*, 4H), 2.20(*s*, 3H), 3.0(*t*, 2H), 3.25(*s*, 1H, NH), 6.28~7.0(*q*, 4H, Ar)
9	236 °C	0.9(*m*, 3H), 1.05~2.0(*m*, 4H), 2.0(*t*, 2H), 4.05(*s*, 1H, NH), 7.3~7.7(*m*, 5H, Ar)
10	66/0.3 mmHg	1.0(*m*, 3H), 1.2~1.7(*m*, 4H), 3.05(*t*, 2H), 3.5(*s*, 1H, NH), 6.4~7.2(*s*, 4H, Ar)
11&12		0.85(*m*, 3H), 1.1~1.7(*m*, 4H), 3.15(*t*, 2H), 4.9(*s*, 1H, NH), 6.2~6.6(*m*, 2H, *m*-H), 7.15~7.5(*t*, 1H, *p*-H), 8.0(*d*, 1H, O-H)
13		1.0(*m*, 3H), 1.15~7.75(*m*, 4H), 3.15(*q*, 2H), 4.5(*s*, 1H, NH), 6.9(*m*, 2H, *m*, *p*-H) 8.0(*m*, 2H, *o*-H)
14	147 °C	1.0(*m*, 3H), 1.15~1.18(*m*, 4H), 3.2(*q*, 2H), 5.0(*s*, 1H, N-H), 6.8(*d*, 2H, *m*-H) 8.0(*d*, 2H, *o*-H)
15		1.0(*m*, 3H), 1.2~1.9(*m*, 2H), 3.0(*t*, 2H), 3.35(*s*, 1H, NH), 3.7(*s*, 3H, OCH_3) 6.8(*q*, 4H, Ar)

required 42 hrs for completion, but that of *p*-methoxyaniline only 24 hrs. Such a substituent effect may be attributed to a steric hindrance. *p*-Chloro group highly inhibit the butylation requiring 60 hrs for complete butylation of *p*-chloroaniline and the yield is low. Chlorine withdraws the electron from the nitrogen atom in tne ring decreasing the nucleophilicity of the nitrogen atom. When aminopyridines are used as primary amines, the yield decreases in the order of 2-, 3-, and 4-aminopyridines.

All the amines studied had a strong absorption band in the infrared at $3400 \pm 20\ cm^{-1}$ due to the secondary N-H stretching vibration. This is in good agreement with the previous infrared studies[16,17]. Nuclear magnetic resonance analyses of these reaction products are shown in *Table* 2[18,19].

In acidic medium, the addition of amines to α, β-unsaturated aldehydes occur at 1 and 4 positions and places amino group on the β carbon atom[20~22], while 1, 2-addition produts were isolated if the reaction is carried out in basic medium. 1, 2-Addition products were characterized by infrared and NMR spectra.

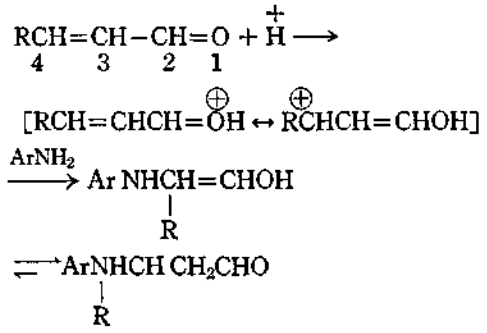
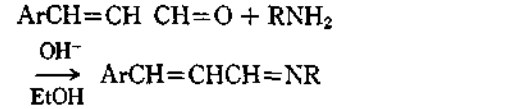
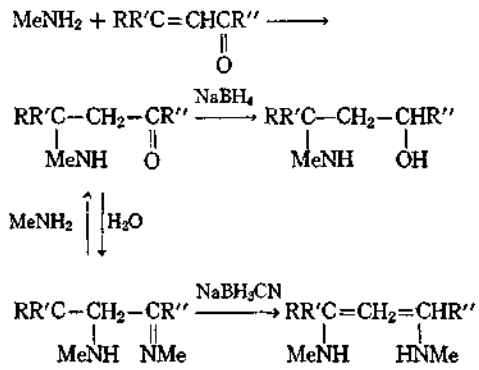


Table 3. NMR, IR data of condensation compound of *trans*-cinnamaldehyde and *t*-butyl amine.

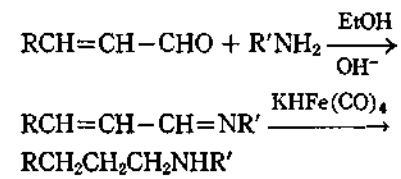
NMR (CDCl$_3$, ppm)		IR(cm^{-1})	
1.2 (*s*, 9H)	$(CH_3)_3C$-	1690	$\nu_{C=C}$
9.8 (*m*, 2H)	—CH=CH—	1640	$\nu_{C=N}$
7.2 (*m*, 5H)	Aromatic	975	$\delta_{C=C}$
7.9 (*m*, 1H)	—CH=N—		



The mechanism of the reduction of α, β-unsaturated aldehyde with amine, with sodium cyanohydridoborate ($NaBH_3CN$) has been reported as shown below[23]. The first step of the reaction is the amination of the carbon-carbon double bond of α, β-unsatusated aldehyde to form 1, 4-addition products.



However, the mechanism of the reaction under present study is not cleared. The reduction seems to proceed *via* 1, 2-addition initially followed by the reduction of carbon-carbon and carbon-nitrogen double bonds.



This mechanism is supported by the fact that Schiff bases and carbon-carbon double bonds are reduced by the ferrate[5,7,9,14].

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