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# The Reductive *N*-Methylation of Amines with Tetracarbonylhydridoferrate-Formaldehyde

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Alcoholic tetracarbonylhydridoferrate combined with formaldehyde is an excellent reagent for reductive *N*-methylation of amines. The effects of reaction conditions such as temperature, atmosphere, and molar ratio (ferrate/formaldehyde/amine) on the reaction have been examined. The optimum condition for *N,N*-dimethylation of aniline is at 60 °C, under carbon monoxide, and at 1.0/2.2/1.0 for the molar ratio.

Recently, tetracarbonylhydridoferrate prepared from pentacarbonyliron and alkali metal hydroxide1) has been shown to be a convenient, selective reagent for carbonylation and/or reduction of a variety of organic functional groups such as a nitro group,2) an acetylenic bond,2) olefinic bonds3) of conjugated diene, enamine, and $\alpha,\beta$-unsaturated carbonyl compound, alkyl halides,4) and olefin oxides.5) More recently, several works have demonstrated that the ferrate is effective for reductive alkylation of amines6) and ketones7) with carbonyl compounds. Several methods for the synthesis of *N*-alkylamines from amines and carbonyl compounds have been reported.8) These methods generally give satisfactory results, but have limited applicabilities. For example, the Clarke-Eschweiler reaction, a simple method for *N*-methylation of amines using formaldehyde/formic acid, can be applied successfully only to aliphatic amines.

The present investigation deals with the reductive *N*-mono- and *N,N*-dimethylation of amines using the tetracarbonylhydridoferrate–formaldehyde system with a view to determine the factors affecting the reaction in some detail. A preliminary report of this work was published elswhere.6b,c)

## Experimental

Potassium tetracarbonylhydridoferrate was prepared according to the method described in a previous paper:4a) 3.7—11 mmol of the ferrate was used in each run. Pentacarbonyliron, amines, and the other compounds employed were all commercial products.

*Reaction Procedure.* To the alcoholic ferrate, determined amounts of amines and aqueous formaldehyde were added at 50—78 °C under carbon monoxide or argon. After a certain reaction time, the reaction mixture was submitted to analysis.

*Analytical Procedure.* *N,N*-Dimethyl derivatives of aniline, toluidines, anisidines, benzylamine, and 2-aminoethanol were analyzed by GLPC using internal standards: a column (0.3 cm $\phi$, 3 m) packed with 10% Versamid on Neopak 60—80 mesh. Other reaction products were isolated and identified by means of IR and NMR spectra, which were recorded on a 215 Hitachi grating spectrophotometer and a JEOL model 3H 60 NMR spectrometer, respectively. Products were isolated as follows: the reaction mixture was acidified with hydrochloric acid and solvents were evaporated to dryness. A residue was extracted with ether in the presence of sodium carbonate. The extract gave *N*-methylated amines after evaporating the solvent, and the amines were purified by vacuum distillation: *N*-methyl-2-aminopyridine, bp 57—58 °C/2 mmHg, yield 65%, NMR($CDCl_3$) $\tau$ 2.0 (m, 1H, $\alpha$-H), 2.6 (m, 1H, $\gamma$-H), 3.5 (m, 2H, $\beta$-H), 5.0 (m, 1H, N–H), and 7.0 (m, 3H, N–$CH_3$); *N,N*-dimethyl-*o*-anisidine, bp 48—49 °C/2—3 mmHg, 82%, NMR($CDCl_3$) $\tau$ 3.25 (s, 4H, aromatic), 6.25 (s, 3H, O–$CH_3$), and 7.3 (s, 6H, N($CH_3)_2$).

## Results and Discussion

N-*Methylation of Aniline.* Aniline was converted into *N*-methyl- and *N,N*-dimethylaniline with tetracarbonylhydridoferrate–formaldehyde under different con-

TABLE 1. *N*-METHYLATION OF ANILINE WITH $KHFe(CO)_4$–HCHO

| Exp. No. | Reaction Conditions | | | CO Absorbed b) | Product (%) e) | |
|---|---|---|---|---|---|---|
| | Ratio a) | Temp (°C) | Time (h) | | *N*-Methylaniline | *N,N*-Dimethylaniline |
| 1 | 1.0/2.2/1.0 | 60 | 9 | 1.8 | ~0 | ~100 |
| 2 c) | 1.0/2.2/1.0 | 60 | 0.5 | — | 52 | 10 |
| | | | 9 | — | 48 | 32 |
| 3 d) | 1.0/2.2/1.0 | 60 | 9 | ~0 | 30 | 70 |
| 4 | 1.0/2.2/1.0 | 50 | 9 | 1.6 | 7 | 93 |
| 5 | 1.0/2.2/1.0 | 70 | 9 | 0.6 | 19 | 78 |
| 6 | 1.0/2.2/1.0 | Reflux | 9 | ~0 | 30 | 70 |
| 7 | 1.0/4.0/4.0 | 60 | 3.5 | 1.4 | 210 | 38 |
| 8 | 1.0/4.4/2.0 | 60 | 4 | 1.1 | 98 | 50 |
| 9 | 1.0/6.6/3.0 | 60 | 3 | 1.8 | 116 | 50 |
| | | | 18 | 1.8 | 115 | 82 |

a) Molar ratio; ferrate/formaldehyde/aniline. b) Mol/mol-$KHFe(CO)_4$. c) Under argon atmosphere. d) Water, 10 mol/mol-$KHFe(CO)_4$, was added. e) Determined by GLPC. Based on the amount of the ferrate used.

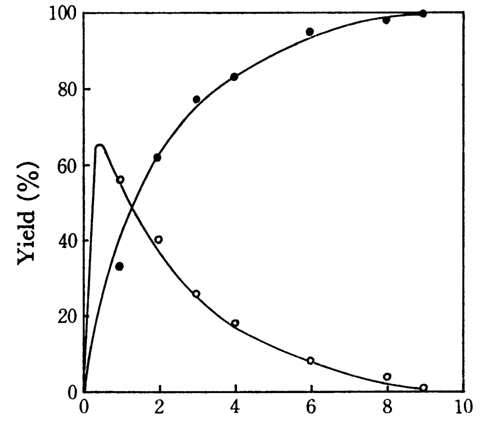


Fig. 1. *N*-Methylation of aniline with $KHFe(CO)_4$–HCHO. At 60 °C under carbon monoxide. Molar ratio, ferrate/formaldehyde/aniline, 1.0/2.2/1.0. ○: *N*-Methylaniline. ●: *N*,*N*-Dimethylaniline.

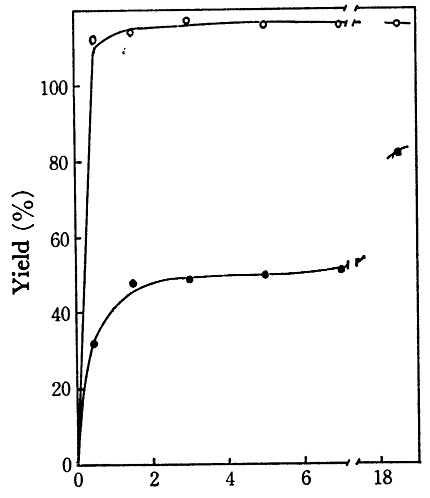


Fig. 2. *N*-Methylation of aniline with $KHFe(CO)_4$–HCHO. At 60 °C under carbon monoxide. Molar ratio, ferrate/formaldehyde/aniline, 1.0/6.6/3.0. ○: *N*-Methylaniline. ●: *N*,*N*-Dimethylaniline.

ditions. The formation of *N*-methylated anilines was highly affected by such reaction variables as reaction temperature, atmosphere, molar ratio (the ferrate/formaldehyde/aniline), and the addition of water. The results are shown in Table 1 and Figs. 1 and 2.

As Fig. 1 shows, *N*-methylaniline is dominant at first and then *N*,*N*-dimethylaniline dominates when aniline is methylated at 60 °C under carbon monoxide at 1.0/2.2/1.0 of the molar ratio. This fact shows that aniline is almost quantitatively converted into *N*,*N*-dimethylaniline *via* *N*-methylaniline under this condition. The reaction proceeds smoothly with an absorption of carbon monoxide; the gas absorbed amounts to 1.8 mol/mol-ferrate.

The reaction condition optimum for preparation of *N*,*N*-dimethylaniline is that of Exp. No. 1: at 60 °C under carbon monoxide in moist ethanol when the molar ratio is fixed at 1.0/2.2/1.0. Lower or higher temperatures, argon atmosphere, and addition of excess water are less favorable for the dimethylation and give *N*-methylaniline in considerable yields. (See Exps. 1—6). Higher temperatures (70 °C and reflux in ethanol) have an inhibitory effect on the dimethylation and carbon monoxide absorption is significantly retarded. By addition of excess water, the gas absorption is also retarded. Under argon, the reaction stops at the first stage to give *N*-methylaniline. These results show that the reducing power of the ferrate increases with an absorption of carbon monoxide.

*N*-Methylaniline predominates as the reaction product at 1.0/40/4.0 of the molar ratio (Exp. 7). The reaction appears to be completed in 2—3 h and the yields of *N*-methyl- and *N*,*N*-dimethylaniline are 210 and 38%, respectively. Accordingly the selectivity for mono- and dimethylation can be readily controlled by the ferrate/aldehyde/aniline ratio, and one mole of the ferrate has the power to methylate about 2.8 N–H bonds at maximum. Therefore, one mole of the ferrate corresponds to about 1.4 mol of aniline for dimethylation. The machanism of the reaction is not clear, but the reduction seems to proceed *via* Schiff bases and immonium salts and to include the reduction of carbon-nitrogen bonds.

$$\text{-NH}_2 + \text{HCHO} \longrightarrow$$

$$[\text{-NH-CH}_2\text{OH} \longrightarrow \text{-N=CH}_2] \xrightarrow{\text{KHFe(CO)}_4} \text{-NHCH}_3$$

Table 2. *N*-Methylation of primary amines with $KHFe(CO)_4$–HCHO[a)]

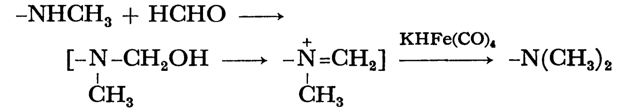
| Exp. No. | Primary amine | Reaction time (h) | CO absorbed[b)] | Product (%)[c)] *N*-Methyl-amine | Product (%)[c)] *N*,*N*-Dimethyl-amine |
|---|---|---|---|---|---|
| 1 | Aniline | 9 | 1.8 | ~0 | ~100 |
| 10 | *o*-Toluidine | 16 | 2.0 | ~0 | ~100 |
| 11 | *p*-Toluidine | 6 | 2.0 | ~0 | ~100 |
| 12 | *o*-Anisidine | 36 | 1.6 | ~0 | ~100 (82)[d)] |
| 13 | *p*-Anisidine | 7 | 1.5 | ~0 | ~100 |
| 14 | *o*-Chloroaniline | 72 | 0.4 | 56 | 33 |
| 15 | 2-Aminopyridine | 48 | 0.7 | 65[d)] | — |
| 16 | Benzylamine | 12 | 2.0 | ~0 | ~100 |
| 17 | 2-Aminoethanol | 8 | 0.6 | — | 34 |

a) At 60°C under carbon monoxide. Molar ratio: $KHFe(CO)_4$/HCHO/Amine=1.0/2.2/1.0. b) Mol/mol-$KHFe(CO)_4$. c) Determined by GLPC. Based on the amount of the ferrate used. d) Isolated yield.

TABLE 3. $N$-METHYLATION OF SECONDARY AMINES WITH KHFe $(CO)_4$–HCHO[a)]

| Exp. No. | Amine | Reaction time (h) | CO absorbed[b)] | Product (%)[c)] | |
|---|---|---|---|---|---|
| 18 | $N$-Methylaniline | 6 | 1.8 | $N,N$-Dimethylaniline | ~200 |
| 19 | $N$-Ethylaniline | 6 | 2.0 | $N,N$-Ethylmethylaniline | 195 |
| 20 | $N$-Methylbenzylamine | 3 | 1.4 | $N,N$-Dimethylbenzylamine | ~200 |
| 21 | Piperidine | 6 | 1.0 | $N$-Methylpiperidine | ~200 |
| 22 | Morpholine | 6 | 1.0 | $N$-Methylmorpholine | ~200 |
| 23 | 2-(Methylamino)ethanol | 8 | 1.5 | 2-(Dimethylamino)ethanol | ~200 |

a) At 60°C under carbon monoxide. Molar ratio: $KHFe(CO)_4/HCHO/Amine = 1.0/3.0/2.0$. b) Mol/mol-$KHFe(CO)_4$. c) Determined by GLPC. Based on the amount of the ferrate used.



$$-\mathrm{NHCH_3} + \mathrm{HCHO} \longrightarrow [-\underset{\mathrm{CH_3}}{\underset{|}{\mathrm{N}}}-\mathrm{CH_2OH} \longrightarrow -\underset{\mathrm{CH_3}}{\underset{|}{\overset{+}{\mathrm{N}}}}=\mathrm{CH_2}] \xrightarrow{\mathrm{KHFe(CO)_4}} -\mathrm{N(CH_3)_2}$$

Such a consideration may be supported by the fact that Schiff bases and immonium salts are reduced by the ferrate.[3d,6b)] As a result, $N$-methylation of the N–H bond means reduction of the $-N=CH_2$ bond with the ferrate, and one mole of the ferrate with the power to methylate 2.8 N–H bonds corresponds to about 5.6 hydrogens as a reducing reagent in the reductive methylation of amines. At 1.0/6.6/3.0 of the molar ratio, in the presence of excess aniline, $N$-methylaniline is predominant as the product. (Fig. 2). For the reduction of conjugated diene and enamine, the most effective reaction variables are the atmosphere and the amount of water present.[3a,d)] Under carbon monoxide in the presence of some water, the reaction proceeded most smoothly, and one mole of the ferrate corresponds to five hydrogens in the reduction of olefinic bonds.

N-*Methylation of Primary Amines.* Several primary amines were dimethylated under the conditions optimum for the dimethylation of aniline. The results are listed in Table 2. *o*-Methyl, methoxy, and chloro groups highly inhibit the dimethylation. For example, the dimethylation of *o*-anisidine required 36 h for completion, but that of *p*-anisidine only 7 h. Such effects of the substituents may be due to a steric hindrance, which would be the largest for the chloro group, followed by the methoxy and then the methyl group. *o*-Chloroaniline gave $N$-methyl-*o*-chloroaniline in 56% yield even after 3 days. 2-Aminopyridine gave only the $N$-monomethylated product. Benzylamine and 2-aminoethanol were dimethylated.

N-*Methylation of Secondary Amines.* As shown in Table 3, secondary amines were readily and almost quantitatively methylated to the corresponding tertiary amines by this method. The reaction completes in 3—8 h at 60 °C under carbon monoxide at 1.0/3.0/2.0 of the molar ratio.

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