The Facile Synthesis of *N*-Substituted Piperidines from Glutaraldehyde and Primary Amines with Tetracarbonylhydridoferrate

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Ethanolic tetracarbonylhydridoferrate solution combined with glutaraldehyde is very efficient for the selective transformation of an amino group into a piperidine ring. A large variety of both aliphatic and aromatic amines react with the ferrate-glutaraldehyde at room temperature under carbon monoxide to give the corresponding *N*-alkyl- and *N*-arylpiperidines in good to excellent yields.

A large variety of methods are available for building up the piperidine ring.[1] Most of these feature the closing of the piperidine ring at the nitrogen atom. In these methods, 1,5-dihalids, 1,5-halogeno amine, 1,5-amino alcohol, 1,5-diamine, 1,3-dinitrile, pyridines, tetrahydropyran, and *N*-arylglutarimide are used as the starting materials. The major portion of the synthetic problem is the preparation of a suitable starting material. The double Mannich condensation of glutaraldehyde, amine, and acetonedicarboxylic acid provides an elegant classical synthesis of tropinone.[1b] Little attention, however, has been paid to the normal reductive amination of glutaraldehyde. Recently, sodium cyanohydroborate has been shown to be effective to be a selective reducing reagent in the preparation of *N*-heterocycles with 5- and 6-membered rings by the reductive amination of dicarbonyl compounds.[2]

The present paper will deal with the facile synthesis of a variety of *N*-alkyl- and *N*-arylpiperidines by the reductive amination of glutaraldehyde with tetracarbonylhydridoferrate as a highly selective reducing reagent; this reagent has been shown to be efficient for the reductive alkylation of amines, ketones, and indole.[3] A preliminary report of this work was published elsewhere.[3e]

Experimental

The potassium tetracarbonylhydridoferrate was prepared according to the method described in a previous paper;[4] 11—22 mmol of the ferrate was used in each run. The pentacarbonyliron, amines, aqueous glutaraldehyde (45%), and the other compounds employed were all commercial products.

Reaction Procedure. To a mixture of pentacarbonyliron (11—22 mmol), a 1 M-potassium hydroxide (33—66 mmol) solution in ethanol, and a primary amine (11—22 mmol), we added, drop by drop, 45% aqueous glutaraldehyde (11—22 mmol) for 5—10 min; the mixture was then stirred for 5—72 h at room temperature under carbon monoxide.

TABLE 1. THE PREPARATION OF *N*-SUBSTITUTED PIPERIDINES FROM GLUTARALDEHYDE AND PRIMARY AMINES USING TETRACARBONYLHYDRIDOFERRATE

Exp. No.	Amine	Reaction conditions[a]		*N*-Substitued piperidine	
		Time (h)	Carbon monoxide absorbed[b]	R[R-N $(CH_2)_5$]	Yield (%)[c]
1	Aniline	5	1.5	Phenyl	78
2	*p*-Toluidine	7.5	1.7	*p*-Tolyl	81
3	*p*-Methoxyaniline	6.5	2.1	*p*-Methoxyphenyl	79
4	*p*-Chloroaniline	7.5	1.8	*p*-Chlorophenyl	89
5	*o*-Toluidine	20	1.5	*o*-Tolyl	77
6	*o*-Methoxyaniline	18	1.6	*o*-Methoxyphenyl	82
7	*o*-Chloroaniline	72	0.4	—	—
8	1-Naphthylamine	13	1.3	1-Naphthyl	80
9	Benzylamine	5	1.6	Benzyl	90
10	α-Methylbenzylamine	5	1.5	α-Methylbenzyl	85
11	Phenethylamine	5	1.2	Phenethyl	55
12	Furfurylamine	5	1.3	Furfuryl	72
13	Cyclohexanamine	9.5	1.7	Cyclohexyl	51
14	1-Butanamine	7	1.2	Butyl	54
15	1-Hexanamine	7	1.1	Hexyl	60
16	1-Octanamine	5.5	1.1	Octyl	43
17	2-Aminoethanol	5.5	0.9	2-Hydroxyethyl	41
18	*N*,*N*-Dimethylethanediamine	5.5	1.1	2-(Dimethylamino)ethyl	47
19	Glycine methyl ester	5	1.3	$-CH_2COOCH_3$	45

a) At room temperature under carbon monoxide. Molar ratio: ferrate-glutaraldehyde-amine, 1.0 ; 1.0 ; 1.0.
b) Mol/mol-ferrate, c) Isolate yield, Based on the amount of the ferrate used,

The reaction was readily monitored by the GLPC analysis of the primary amine used. When all of the amine had been consumed, the reaction was stopped and the potassium carbonate formed in the reaction was filtered off. The filtrate was concentrated to 3—5 ml on a rotary evaporator and/or with a Kugelrohr apparatus, and the products were separated and purified by careful vacuum distillation, and submitted to analysis.

Analytical Procedure. The GLPC analysis was made using internal standards: a column (0.3 cm ø, 3 m) packed with 10% Versamid on Neopak 60—80 mesh. The measurements of the PMR and IR spectra were made on a JOEL Model 3H 60-NMR spectrometer and a Varian HR 220 spectrometer, and on a 215 Hitachi grating spectrometer, respectively.

Results and Discussion

N-Substituted Piperidines from Primary Amines. A large variety of primary amines were converted into the corresponding *N*-substituted piperidines in good to excellent yields with tetracarbonylhydridoferrate–glutaraldehyde under mild conditions, at room temperature and under carbon monoxide. The results are listed in Tables 1 and 2.

When aqueous glutaraldehyde (45%) is mixed with a primary amine in ethanol, an intractable condensation material is obtained after evaporating the solvents, but the ferrate–glutaraldehyde–amine system gives *N*-

Table 2. Analytical data of *N*-substituted piperidines

Exp. No.	Bp (°C)	60-PMR($CDCl_3$)[a] τ	Analyses, % Found(Calcd) C	H	N
1	99/0.2 mmHg	8.40(m, 6H), 6.92(t, 4H), 2.95(m, 5H, Ar)	81.72 (81.94)	9.29 (9.38)	8.91 (8.69)
2	56/0.7	8.40(m, 6H), 6.93(t, 4H), 7.76(s, 3H, $-CH_3$), 3.10(m, 4H, Ar)	82.08 (82.23)	10.05 (9.78)	8.04 (7.99)
3	60/3	8.35(m, 6H), 6.97(t, 4H), 6.25(s, 3H, $-OCH_3$), 3.14(s, 4H, Ar)	75.30 (75.35)	8.85 (8.95)	7.30 (7.32)
4	63/0.8	8.37(m 6H), 6.85(t, 4H), 3.00(m, 4H, Ar)	67.70 (67.52)	7.47 (7.21)	7.24 (7.16)
5	44/0.2	8.40(m, 6H), 7.20(t, 4H), 7.73(s, 3H, $-CH_3$), 3.03(m, 4H, Ar)	82.37 (82.23)	9.73 (9.78)	8.22 (7.99)
6	68/0.1	8.40(m, 6H), 7.04(t, 4H), 6.18(s, 3H, $-OCH_3$), 3.10(s, 4H, Ar)	75.63 (75.35)	9.04 (8.96)	7.45 (7.32)
8	77/0.2	8.33(m, 6H), 7.03(t, 4H), 3.33(m, 7H, Ar)	85.52 (85.26)	8.09 (8.11)	6.66 (6.63)
9	49/0.1	8.50(m, 6H), 7.66(t, 4H), 6.55(s, 2H, $-CH_2-$), 2.75(s, 5H, Ar)	81.96 (82.23)	9.96 (9.78)	8.07 (7.99)
10	50/0.4	8.60(m, 6H), 7.67(t, 4H), 8.67(d, 3H, $-CH_3$), 6.67(qu, 1H, -CH), 2.76(s, 5H, Ar)	82.23 (82.48)	10.05 (10.12)	7.25 (7.40)
11	64/0.2	8.50(m, 6H), 7.00—7.70(m, 8H), 2.83(s, 5H, Ar)	82.56 (82.48)	10.31 (10.12)	7.37 (7.40)
12	66/4	8.50(m, 6H), 7.60(t, 4H), 6.50(s, 2H, $-CH_2$), 3.82(m, 2H), 2.64(s, 1H)	72.80 (72.69)	9.22 (9.15)	8.28 (8.48)
13	42/0.3	8.50(m, 17H), 7.50(t, 4H)	—	—	—
14[b]	70/34	9.10(t, 3H), 8.50(m, 10H), 7.60(t, 6H)	74.43 (76.52)	13.57 (13.56)	9.32 (9.92)
15[b]	65/5	9.10(t, 3H), 8.60(m, 14H), 7.68(t, 6H)	76.50 (78.04)	13.24 (13.69)	7.90 (8.27)
16[b]	46/0.1	9.10(t, 3H), 8.50(m, 18H), 7.70(t, 6H)	77.45 (79.12)	13.74 (13.79)	7.05 (7.10)
17[b]	58/4	8.50(m, 6H), 7.50(m, 6H), 6.50(s, 1H, -OH), 6.40(t, 2H)	63.00 (65.07)	11.56 (11.70)	10.36 (10.84)
18	29/0.8	8.50(m, 6H), 7.73(m, 8H), 7.54(s, 6H, $-N(CH_3)_2$)	62.73 (62.20)	12.69 (12.72)	15.80 (16.07)
19	47/3	8.50(m, 6H), 7.60(t, 4H), 6.83(s, 2H), 6.30(s, 3H)	61.32 (61.12)	9.87 (9.62)	8.66 (8.91)

a) 60-PMR spectra characteristic of the piperidine ring; τ around 8.3—8.6(m, 6H, $-\overset{|}{\underset{|}{N}}-CH_2-CH_2-CH_2-CH_2-CH_2-$) and around 6.8—7.7(t, 4H, $-\overset{|}{\underset{|}{N}}-CH_2-(CH_2)_3-CH_2-$). b) Somewhat unstable to be oxidized under air with a color change.

TABLE 3. THE PREPARATION OF *N*-SUBSITUTED PIPERIDINES FROM GLUTARALDEHYDE AND PHENYLENEDIAMINES USING TETRACARBONYLHYDRIDOFERRATE

Exp. No.	Amine	Reaction conditions[a]		Product	Yield[c] (%)
		Time(h)	Carbon monoxide absorbed[b]		
20	*o*-Phenylenediamine	9	1.7	*N*-(2-Aminophenyl)piperidine	63
21	*o*-Phenylenediamine	48	2.3	*o*-Dipiperidinobenzene	42
22	*p*-Phenylenediamine	5	1.8	*N*-(4-Aminophenyl)piperidine	73
23	*p*-Phenylenediamine	5	2.7	*p*-Dipiperidinobenzene	69

a) At room temperature under carbon monoxide. Molar ratio: ferrate-glutaradehyde-amine, 1.0 : 1.0 : 1.0 in Exps. 20 and 22, and 2.0 : 2.0 : 1.0 in Exps. 21 and 23. b) Mol/mol-ferrate. c) Isolated yield. Based on the amount of the amine used.

TABLE 4. ANALYTICAL DATA OF *N*-SUBSTITUTED PIPERIDINES FROM PHENYLENEDIAMINES

Exp. No.	Bp (°C)	60-PMR ($CDCl_3$) τ	Analyses, % Found (Calcd)		
			C	H	N
20[a]	57/0.1 mmHg	8.37(m, 6H), 7.18(t, 4H), 6.10(s, 2H, $-NH_2$), 3.23(m, 4H, Ar)	74.80 (74.96)	8.87 (9.15)	15.68 (15.89)
21	53/0.1	8.40(m, 12H), 7.03(t, 8H), 3.17(s, 4H, Ar)	78.52 (78.64)	9.66 (9.89)	12.17 (11.46)
22[a]	75/0.2	8.44(m, 6H), 7.03(t, 4H) 6.73(s, 2H, $-NH_2$), 3.17(m, 4H, Ar)	74.69 (74.96)	9.21 (9.15)	15.94 (15.89)
23	105/0.1	8.40(m, 12H), 7.00(t, 8H), 3.17(s, 4H, Ar)	78.37 (78.64)	9.77 (9.90)	11.69 (11.46)

a) IR(Neat), ν_{-NH_2} 3340 and 3440 cm^{-1}.

substituted piperidines: the ferrate acts as an efficient and highly selective reducing reagent to give the *N*-heterocycles as the only reaction products.

$$OHC(CH_2)_3CHO + RNH_2 \xrightarrow{KHFe(CO)_4} \overline{|(CH_2)_5 N-R|}$$

The reaction proceeds smoothly with an absorption of carbon monoxide and with a color change from pale yellow brown to red.

This reaction has a great tendency to undergo a heterocyclization at the nitrogen atom of the amines, even at the ferrate–glutaraldehyde–amine molar ratio of 1.0 : 1.0 : 2.0; at this ratio *N*,*N*′-disubstituted pentanediamines are expected to be formed, but the *N*-heterocycles and the unconsumed primary amines are identified.

$$OHC(CH_2)_3CHO + 2RNH_2 \begin{cases} \xrightarrow{KHFe(CO)_4} \overline{|(CH_2)_5 N-R|} + RNH_2 \\ \not\longrightarrow\ RNH(CH_2)_5HNR \end{cases}$$

This method can be applied to both aromatic and aliphatic amines with different functional groups. In the cases of substituted anilines, such substituents as the methyl, methoxyl, and chloro groups have almost no effect on the formation of the heterocycles when located at the *para* position, but they have some inhibitory effect when located at the *ortho* position. *o*-Methyl- and *o*-methoxyanilines require longer reaction times for completion, and from *o*-chloroaniline the corresponding piperidine could not be isolated even after a reaction time of 72 h. Such influence of the *ortho* substituents seems to be due to steric hindrance. Usual aliphatic amines, 1-butanamine and 1-octanamine, give the *N*-heterocyles, but this type of compound, simple *N*-alkylpiperidines, are somwhat unstable to be gradually oxidized under air with a color change from colorless to brown. Different aliphatic amines with such functional groups as the phenyl, hydroxyl, and carboxyl groups are also converted into the heterocycles with no difficulty. The successful results with the glycine methyl ester clearly indicate that this method can be applied to amino acids and their derivatives. This reaction seems to proceed *via* Schiff bases and immonium salts and seems to include the reduction of carbon-nitrogen double bonds.[3f]

$$OHC(CH_2)_3CHO + RNH_2 \longrightarrow \left[OHC(CH_2)_3\text{-}CH{=}N\text{-}R \longrightarrow OHC(CH_2)_4\text{-}NH\text{-}R \longrightarrow \overline{|(CH_2)_4 \underset{\backslash -CH^{\diagup}}{N^+}\text{-}R|} \right] \longrightarrow \overline{|(CH_2)_5 N-R|}$$

N-Substituted Piperidines from Phenylenediamines. The results for phenylenediamines are listed in Tables 3 and 4. This reaction also proceeds readily under mild conditions. In the reaction of *o*- and *p*-phenylenediamines with the ferrate–glutaraldehyde system, two types of products, *N*-(aminophenyl)piperidines and dipiperidinobenzenes, are obtainable. The types of the products sharply depend on the ferrate–glutaraldehyde–amine molar ratio. The molar ratio of 1.0 : 1.0 : 1.0 gives the *N*-(aminophenyl)piperidines selectively.

$$C_6H_4(NH_2)_2 + OHC(CH_2)_3CHO \xrightarrow{KHFe(CO)_4} C_6H_4(NH_2)[N\overline{\quad}(CH_2)_5]$$

This results also shows that this reaction has a great tendency to undergo heterocyclization at the nitrogen atom; one of the two amino groups is selectively alkylated to the piperidine ring. The molar ratio of 2.0 : 2.0 : 1.0 gives dipiperidinobenzenes; two amino groups are derived into two piperidine rings, but *o*-phenylenediamine requires a much longer reaction time than the *p*-derivative. (Exps. 21 and 23).

The results obtained here show that this method is widely applicable for the selective transformation of the amino group into the piperidine ring.

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