A New and Convenient Synthesis of *N*-Substituted Perhydroazepines from Adipaldehyde and Primary Amines with Tetracarbonylhydridoferrate, $HFe(CO)_4^-$, as a Selective Reducing Agent

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Ethanolic tetracarbonylhydridoferrate combined with adipaldehyde is very efficient for the selective transformation of an amino group into perhydroazepine. A large variety of both aliphatic and aromatic amines react with adipaldehyde in the presence of tetracarbonylhydridoferrate at room temperature and carbon monoxide to give the corresponding *N*-alkyl- and *N*-arylperhydroazepines in good to excellent yields.

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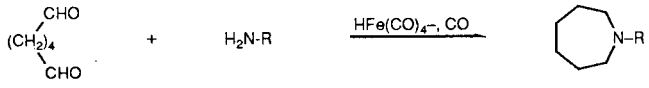
The synthesis of perhydroazepine or *N*-substituted perhydroazepine can be usually achieved by reduction of various kinds of ϵ-caprolactams [1-2] or by other sources [3-5]. But most product have some limited applicabilities and require drastic conditions. For example, the hydrogenation of ϵ-caprolactam to perhydroazepine using Raney-Cobalt under hydrogen atmosphere showed an excellent activity and selectivity. Accordingly, with this catalyst, *N*-isopropylperhydroazepine from perhydroazepine was obtained in good yield at 190° for 10 hours in the medium of isopropyl alcohol [1]. And also lithium aluminum hydride efficiently performs reduction of carbonyl group of ϵ-caprolactam and 2- or 4-methylcaprolactams. And the reaction of 2,2-diphenyl-4-(1-perhydroazepinyl)valeonitrile with methyl iodide gave the corresponding quaternary iodide and this substance was heated with a mixture of silver oxide and water whereby 1,1-diphenyl-1-cyano-2-butene and *N*-methylperhydroazepine were formed. But this reaction was no practical use in synthesis because of the poor yield. Nucleophilic displacement of halogen by nitrogen for haloamines follows an SN_2 mechanism and thus reaction of the salt gave *N*-substituted perhydroazepine. Little attention, however, has been paid to the normal reductive amination of adipaldehyde.

In this communication, we wish to report a new and convenient synthesis of *N*-substituted perhydroazepine from adipaldehyde and primary amines using tetracarbonylhydridoferrate, $HFe(CO)_4^-$, as a selective reducing agent. This reagent has been shown to be efficient for the alkylations of amine [6], ketone [7], the reductive amination of organic azide [8], ester [9], and *N*-heterocyclization [10]. A large variety of primary amines were converted into the corresponding *N*-substituted perhydroazepines in good to excellent yields with tetracarbonylhydridoferrate-adipaldehyde at room temperature under carbon monoxide for 24 hours. The results are described in the experimental part and the reaction pathways are depicted in Scheme 1.

Scheme 1

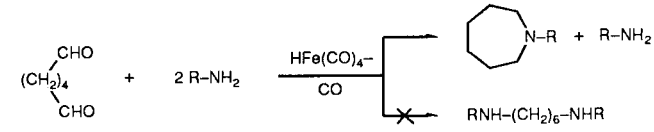


Compound	R =	Compound	R =
1	benzyl	6	4-chlorophenyl
2	phenyl	7	4-methylbenzyl
3	4-methylphenyl	8	2-phenylethyl
4	3-methylphenyl	9	1-phenylethyl
5	4-methoxyphenyl	10	cyclohexyl
		11	2-hydroxyethyl

First, we obtained pure adipaldehyde from the cleavage of 1,2-cyclohexanediol in dry benzene solution in the presence of lead tetraacetate-potassium carbonate. When adipaldehyde was mixed with a primary amine in ethanol, an intractable condensation material was obtained after solvent was evaporated. But the ferrate-adipaldehyde-amine system gives *N*-substituted perhydroazepine. The ferrate acts as an efficient and highly selective reducing agent to give the *N*-heterocycles as the sole product.

The reaction proceeds smoothly with an absorption of carbon monoxide and with a gradual colour change from pale yellow to dark red and has a great tendency to undergo heterocyclization at the nitrogen atom of the amines, even at the ferrate-adipaldehyde-amine molar ratio of 1.0:1.0:2.0, at this ratio, *N,N'*-disubstituted hexanediamine is expected to be formed, but *N*-heterocycles and the remained primary amine is identified [Scheme 2].

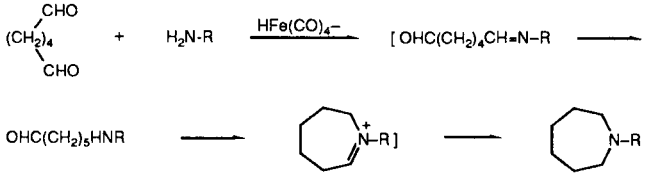
Scheme 2



This method can be applied to both aliphatic and aromatic amines with different functional groups. In the case

of substituted anilines, such substituents as methyl, methoxy, and chloro groups have almost no effect on the formations of heterocycles when located at the 4-position, but no heterocyclization occurred when the substituent was located at the 2-position. Such result from the reaction of 2-substituted anilines seems to be due to the steric hindrance. This cyclization reaction seems to proceed *via* Schiff base and immonium salt and to include the reduction of carbon nitrogen double bond [Scheme 3] [11].

Scheme 3



EXPERIMENTAL

The glpc analysis was made using internal standard; a stainless steel column (0.3 cmϕ, 3m) packed with 10% Versamid on Neopak 60-80 mesh. The melting and boiling points were uncorrected. The ir spectra were measured on a Hitachi Model 215 grating spectrophotometer. The ^{1}H nmr spectra were obtained at 60 MHz with a Varian EM-60 or at 300 MHz with a Nicolet NT spectrometer. The ^{13}C nmr spectra were determined at 25.05 MHz with JEOL pulsed FT-spectrometer, model FX-100. Samples were dissolved in deuteriochloroform, and chemical shifts were expressed in relative to TMS as an internal standard. Elemental analyses were performed at the microanalytical center of Kyoto University. The ms spectra were recorded on a A. E. T. MS 902 spectrometer.

The potassium tetracarbonylhydridoferrate was prepared according to the method described in a previous paper [12]. Tetracarbonylhydridoferrate (22 mmoles) was used in each run. Iron pentacarbonyl, amines, and other compounds employed were all commercial products which have been proved to be sufficiently pure. Adipaldehyde was prepared according to the previous report [13].

Typical reaction procedure for *N*-benzylperhydroazepine is as follows. To a mixture of iron pentacarbonyl (22 mmoles), ethanolic 1*M*-potassium hydroxide (66 ml), ethanol (44 ml), and benzylamine (22 mmoles), adipaldehyde (22 mmoles) was added dropwise for 10 minutes. The mixture was stirred under an atmosphere of carbon monoxide at room temperature for 24 hours. The reaction proceeded smoothly and then the absorption of carbon monoxide ceased in about 10 hours or longer times. The mixture was exposed on air to be oxidized, filtered, and the solvent was then evaporated. The residual oily material was distilled under vacuum to give a colourless liquid with the following yields and spectral data. The same procedure was applied to the syntheses of the following *N*-substituted perhydroazepines.

N-Benzylperhydroazepine (**1**).

This compound was obtained in 90% yield, bp 75°/0.25 Torr; ^{1}H nmr (carbon tetrachloride): δ 1.59 (m, 8H, 4CH$_2$), 2.57 (m, 4H, 2CH$_2$), 3.60 (s, 2H, CH$_2$), 7.29-7.33 (m, 5H, Ar); ^{13}C nmr (deuteriochloroform): δ 25.32 (t, 2CH$_2$), 30.87 (t, 2CH$_2$), 54.19 (t, N-CH$_2$), 55.18 (t, N-(CH$_2$)$_2$), 126.79 (d, CH), 128.06 (d, 2CH), 128.31 (d, 2CH), 140.59 (s, C); ms: m/e 189 (M$^+$).

Anal. Calcd. for $C_{13}H_{19}N$: C, 82.48; H, 10.12; N, 7.40. Found: C, 82.49; H, 10.10; N, 7.41.

N-Phenylperhydroazepine (**2**).

This compound was obtained in 70% yield, bp 66°/0.18 Torr; ^{1}H nmr (carbon tetrachloride):δ 1.01-1.57 (m, 8H, 4CH$_2$), 2.56 (m, 4H, 2CH$_2$), 6.52 (m, 3H, 3CH), 7.03 (m, 2H, 2CH); ms: m/e 175 (M$^+$).

Anal. Calcd. for $C_{12}H_{17}N$: C, 82.29; H, 9.71; N, 8.00. Found: C, 82.27; H, 9.75; N, 7.98.

N-(4-Methylphenyl)perhydroazepine (**3**).

This compound was obtained in 67% yield, bp 62°/0.12 Torr; ^{1}H nmr (carbon tetrachloride): δ 1.03-1.65 (m, 8H, 4CH$_2$), 2.24 (s, 3H, CH$_3$), 2.90 (m, 4H, 2CH$_2$), 6.53 (m, 2H, 2CH), 6.89 (m, 2H, 2CH); ^{13}C nmr (deuteriochloroform): δ 21.05 (q, CH$_3$), 25.34 (t, 2CH$_2$), 30.90 (t, 2CH$_2$), 55.21 (t, N-(CH$_2$)$_2$), 128.01 (d, 2CH), 129.00 (d, 2CH), 136.19 (s, C), 137.64 (s, C); ms: m/e 189 (M$^+$).

Anal. Calcd. for $C_{13}H_{19}N$: C, 82.54; H, 10.05; N, 7.41. Found: C, 82.50; H, 10.08, N, 7.42.

N-(3-Methylphenyl)perhydroazepine (**4**).

This compound was obtained in 65% yield, bp 71°/0.10 Torr; ^{1}H nmr (carbon tetrachloride): δ 1.06-1.65 (m, 8H, 4CH$_2$), 2.23 (s, 3H, CH$_3$), 3.03 (m, 4H, 2CH$_2$), 6.34 (m, 3H, 3CH), 6.88 (m, 1H, CH); ms: m/e 189 (M$^+$).

Anal. Calcd. for $C_{13}H_{19}N$: C, 82.54; H, 10.05; N, 7.41. Found: C, 82.64; H, 10.02; N, 7.34.

N-(4-Methoxyphenyl)perhydroazepine (**5**).

This compound was obtained in 55% yield, bp 87°/0.24 Torr; ^{1}H nmr (carbon tetrachloride): δ 1.06-1.67 (m, 8H, 4CH$_2$), 2.90 (m, 4H, 2CH$_2$), 3.74 (s, 3H, OCH$_3$), 6.54 (m, 4H, Ar); ^{13}C nmr (deuteriochloroform): δ 21.67 (t, 2CH$_2$), 34.66 (t, 2CH$_2$), 47.07 (t, 2CH$_2$), 55.66 (q, OCH$_3$), 114.31 (d, 2CH), 114.81 (d, 2CH), 142.85 (s, C), 153.04 (s, C); ms: m/e 205 (M$^+$).

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.10; H, 9.27; N, 6.83. Found: C, 76.05; H, 9.24; N, 6.85.

N-(4-Chlorophenyl)perhydroazepine (**6**).

This compound was obtained in 50% yield, bp 75°/0.16 Torr; ^{1}H nmr (carbon tetrachloride): δ 1.04-1.67 (m, 8H, 4CH$_2$), 2.78 (m, 4H, 2CH$_2$), 6.54 (m, 2H, 2CH), 7.03 (m, 2H, 2CH); ms: m/e 209 (M$^+$), 211 (M$^+$+2).

Anal. Calcd. for $C_{12}H_{16}ClN$: C, 68.90; H, 7.65; N, 6.70. Found: C, 68.82; H, 7.66; N, 6.72.

N-(4-Methylbenzyl)perhydroazepine (**7**).

This compound was obtained in 91% yield, bp 71-72°/0.12 Torr; ^{1}H nmr (carbon tetrachloride): δ 1.05-1.72 (m, 8H, 4CH$_2$), 2.24 (s, 3H, CH$_3$), 2.54 (m, 4H, 2CH$_2$), 7.23 (s, 4H, Ar); ^{13}C nmr (deuteriochloroform): δ 20.62 (t, 2CH$_2$), 26.63 (t, 2CH$_2$), 28.04 (q, CH$_3$), 55.08 (t, CH$_2$NCH$_2$), 62.25 (t, N-CH$_2$), 128.21 (d, CH), 128.34 (d, 2CH), 135.42 (s, C), 136.55 (s, C); ms: m/e 203 (M$^+$).

Anal. Calcd. for $C_{14}H_{21}N$: C, 82.76; H, 10.34; N, 6.90. Found: C, 82.77; H, 10.32; N, 6.91.

N-(2-Phenylethyl)perhydroazepine (**8**).

This compound was obtained in 85% yield, bp 71-72°/0.18 Torr; ^{1}H nmr (carbon tetrachloride): δ 1.05-1.72 (m, 8H, 4CH$_2$), 2.14-2.93 (m, 8H, (CH$_2$)$_2$N(CH$_2$)$_2$), 7.24 (s, 5H, Ar); ^{13}C nmr (deuteriochloroform): δ 25.24 (t, 2CH$_2$), 30.83 (t, 2CH$_2$), 36.08 (t, 2CH$_2$), 51.20 (t, N(CH$_2$)$_2$), 54.42 (t, N-CH$_2$), 125.90 (d, CH), 128.34 (d, 2CH), 128.52 (d, 2CH), 139.84 (s, C); ms: m/e 203 (M$^+$).

Anal. Calcd. for $C_{14}H_{21}N$: C, 82.76; H, 10.34; N, 6.90. Found: C, 82.81; H, 10.31; N, 6.88.

N-(1-Phenylethyl)perhydroazepine (**9**).

This compound was obtained in 73% yield, bp 64°/0.07 Torr; ^{1}H nmr (carbon tetrachloride): δ 1.04-1.70 (m, 11H), 2.25 (m, 4H, 2CH$_2$), 3.73 (q, 1H, CH), 7.24 (s, 5H, Ar); ^{13}C nmr (deuteriochloroform): δ 25.22 (q, CH$_2$), 30.81 (t, 2CH$_2$), 40.04 (t, 2CH$_2$), 53.53 (d, N-CH), 58.52 (t, N(CH$_2$)$_2$), 126.40 (d, CH), 126.57 (d, 2CH), 128.21 (d, 2CH), 145.53 (s, C); ms: m/e 203 (M$^+$).

Anal. Calcd. for $C_{14}H_{21}N$: C, 82.76; H, 10.34; N, 6.90. Found: C, 82.80; H, 10.35; N, 6.85.

N-Cyclohexylperhydroazepine (**10**).

This compound was obtained in 62% yield, bp 47°/0.08 Torr; ^{1}H nmr (carbon tetrachloride): δ 0.82-2.00 (m, 19H), 2.54 (m, 4H, 2CH$_2$); ms: m/e 181 (M$^+$).

Anal. Calcd. for $C_{12}H_{23}N$: C, 79.56; H, 12.71; N, 7.73. Found: C, 79.50; H, 12.76; N, 7.74.

N-(2-Hydroxyethyl)perhydroazepine (**11**).

This compound was obtained in 57% yield, bp 62-63°/0.34 Torr; ^1H nmr (carbon tetrachloride): δ 1.00-2.15 (m, 8H, $4CH_2$), 2.68 (m, 4H, $N(CH_2)_2$), 3.24 (m, 3H), 3.73 (t, 2H, CH_2); ms: m/e 143 (M^+).

Anal. Calcd. for $C_8H_{17}NO$: C, 67.13; H, 11.89; N, 9.79. Found: C, 67.10; H, 11.85; N, 9.81.

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REFERENCES AND NOTES

[1] T. Kamiyama, M. Inoue and S. Enomoto, *J. Synth. Org. Chem. Japan*, **36**, 65 (1978).

[2] F. F. Blicke and N. J. Doorenbos, *J. Am. Chem. Soc.*, **76**, 2317 (1954).

[3] F. F. Blicke and E. P. Tsao, *ibid.*, **76**, 2203 (1954).

[4] I. O. Sutherland in "Comprehensive Organic Chemistry", Vol **2**, D. Barton and W. D. Ollis, eds, Pergamon, Oxford, 1979, p 20.

[5] P. G. Sammes in "Comprehensive Organic Chemistry", Vol **2**, D. Barton and W. D. Ollis, eds, Pergamon, Oxford, 1979, p 594.

[6] Y. Watanabe, M. Yamashita, T. Mitsudo, M. Tanaka and Y. Takegami, *Tetrahedron Letters, 1879 (1974); Y. Watanabe, T. Mitsudo, M. Yamashita, S. C. Shim and Y. Takegami, Chem. Letters, 1265 (1974).*

[7] G. Caineli, M. Panunzio and A. Umani-Ronchi, J. Chem. Soc., Perkin Trans. I, 1273 (1975).

[8] S. C. Shim and K. N. Choi, *Tetrahedron Letters*, 3277 (1985).

[9] S. C. Shim, K. T. Huh and W. H. Park, *Tetrahedron*, **42**, 259 (1986).

[10] S. C. Shim, K. T. Huh and W. H. Park, *Synthesis*, 59 (1987).

[11] Y. Watanabe, S. C. Shim, T. Mitsudo, M. Yamashita and Y. Takegami, *Bull. Chem. Soc. Japan*, **49**, 1378, 2302 (1976).

[12] P. Krumholtz and H. M. Stettiner, *J. Am. Chem. Soc.*, **71**, 3035 (1949); Y. Takegami, Y. Watanabe, I. Kanaya, T. Mitsudo, T. Okajima, Y. Morishima and H. Masada, *Bull. Chem. Soc. Japan*, **41**, 1990 (1968).

[13] J. English, Jr. and G. W. Barber, *J. Am. Chem. Soc.*, **71**, 3310 (1949).