

Reduction of Organic Halides with Sodium and Potassium Gallium Hydrides and Chemoselective Reduction of Organic Halides with Potassium Gallium Hydride in Multifunctional Compounds

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The discovery of sodium borohydride¹ and lithium aluminum hydride² has revolutionized the procedures utilized for the reduction of organic functional groups. Since then, a number of methods for the effective reduction of alkyl halides have been modified with various hydride reagents.³ But most of them have been reducing agent containing boron or aluminum. In general, it has been known that somewhat powerful agents are necessary to reduce organic halides. This means practically very difficult to reduce halogen group selectively in organohalogen compounds containing other functional groups. During the reaction rate studies of metal gallium hydrides on various functional groups, we found that lithium, sodium, and potassium gallium hydride exhibited excellent reducing power for the reduction of alkyl halides to the corresponding alkane, although the hydrides showed mild reducing characteristics to reduce only aldehydes and ketones.^{4,5} The above results strongly suggest that the gallium hydrides could be possible to reduce organic halides selectively in the presence of other functional groups except aldehydes and ketones.

In this study, we tested these possibilities by employing the selective reduction of halides in multifunctional compound with NaGaH₄ and KGaH₄.

Results and Discussion

To evaluate the reducing power of the reagents to organic halides with different structural features more in detail, we first carried out the reduction of 1-chlorooctane selected as representative. Thus, the halide was reacted with NaGaH₄ and KGaH₄ in THF at 65 °C. The reductions with NaGaH₄ and KGaH₄ were converted to the octane in 95 and 82% of yields for 24 h, respectively. On the other hand, 1-bromooctane and 1-iodooctane were quantitatively reduced for 0.5 h by both NaGaH₄ and KGaH₄. Like the reactivity pattern observed in the S_N2 reaction, we observed slower reduction rate of 2-bromooctane, secondary alkyl bromide than that of 1-bromooctane, primary alkyl bromide. In this case, the reductions with NaGaH₄ and KGaH₄ were converted to the octane in 96% of yield for 12 h. For the reduction of chlorocyclohexane with NaGaH₄ were converted to the cyclohexane in 13% for 24 h, while the reaction of KGaH₄ was essentially inert. NaGaH₄ showed moderate reduction rate of bromocyclohexane, *i.e.*, 94% yield for 24 h, while KGaH₄

showed show rate 32% yield for 24 h. On the other hand, 99% of iodocyclohexane was reduced for 1 h by NaGaH₄, while 45% of that was reduced for 24 h by KGaH₄.

To evaluate the reduction rate of aromatic halide, we employed chlorobenzene, 4-chlorotoluene, and 4-chloroanisole. Both NaGaH₄ and KGaH₄ were essentially inert for all of them.

Aromatic bromides, such as bromobenzene, 4-bromotoluene, and 4-bromoanisole were reacted with NaGaH₄. The reductions with NaGaH₄ were converted to benzene, toluene, and anisole in 91, 84 and 83% of yields, respectively, while 34, 26, and 22% by KGaH₄ for 24 h.

Aromatic iodides, such iodobenzene, 4-iodotoluene and 4-iodoanisole were reacted with NaGaH₄. The reductions with NaGaH₄ were converted to benzene, toluene, and anisole in 95% of yield for 3, 6, and 6 h, respectively. In the case of KGaH₄, iodobenzene was quantitatively reduced for 12 h, but 4-iodotoluene and 4-iodoanisole having electron releasing group showed 38 and 34% yield, respectively. For benzyl halide, we did not see the difference in reduction rate between chlorine and bromine. They were quantitatively reduced for 0.5 h by NaGaH₄. All these results were summarized in Table 1.

We further studied KGaH₄ for the chemoselective reduction of the organic halides in multifunctional compounds containing ester, nitrile, lactone, and various of organic halides. The study was focused on organic bromide. In order to optimize competitive reduction yield of halide in multifunctional compound, we evaluated the reduction of ethyl 3-bromopropanoate at various reaction temperatures. Thus, it was reacted with KGaH₄ in THF at 65, 25, and 0 °C. The reductions with KGaH₄ were converted to ethyl benzoate in 60, 62, and 91% of yields for 12 h, respectively. The explanation of the lower yields at 65 and 25 °C could be due to partial reduction product of ester. Based on the results, we carried out selective and competitive reduction of multifunctional group by KGaH₄ at 0 °C through the experiment. As shown in Table 2, all of the ethyl 2-haloalkanoate showed low selective reduction, while the ethyl 3-haloalkanoate such as ethyl 3-chloropropanoate, and ethyl 3-bromopropanoate showed high yield. Their yields for 12 h were 63 and 91%, respectively. But ethyl and aromatic ester such as ethyl 4-bromobenzoate or ethyl 4-iodobenzoate showed extremely low yield. The nitrile groups, such as 3- and 4-

Table 1. Reduction of Alkyl Halides with Metal Gallium Hydrides in Tetrahydrofuran (THF) at 65 °C^a

Compound	Reducing agent	Product	Reaction time(h)	Yield ^b (%)
1-Chlorooctane	NaGaH ₄	Octane	24	95
	KGaH ₄		24	82
Chlorocyclohexane	NaGaH ₄	Cyclohexane	24	13
	KGaH ₄		24	tr
Benzyl chloride	NaGaH ₄	Toluene	0.5	100
	KGaH ₄		0.5	98
Chlorobenzene	NaGaH ₄	Benzene	24	7
	KGaH ₄		24	tr
4-Chlorotoluene	NaGaH ₄	Toluene	24	tr
	KGaH ₄		24	tr
4-Chloroanisole	NaGaH ₄	Anisole	24	tr
	KGaH ₄		24	tr
4-Bromooctane	NaGaH ₄	Octane	0.5	100
	KGaH ₄		0.5	99
2-Bromooctane	NaGaH ₄	Octane	12	98
	KGaH ₄		12	98
1-Bromocyclohexane	NaGaH ₄	Cyclohexane	24	94
	KGaH ₄		24	32
Benzyl bromide	NaGaH ₄	Toluene	0.5	100
	KGaH ₄		0.5	100
1-Bromobenzene	NaGaH ₄	Benzene	24	94
	KGaH ₄		24	34
4-Bromotoluene	NaGaH ₄	Toluene	24	84
	KGaH ₄		24	26
4-Bromoanisole	NaGaH ₄	Anisole	24	83
	KGaH ₄		24	22
4-Iodoctane	NaGaH ₄	Octane	0.5	99
	KGaH ₄		0.5	99
Iodocyclohexane	NaGaH ₄	Cyclohexane	1	99
	KGaH ₄		24	45
Iodobenzene	NaGaH ₄	Benzene	3	99
	KGaH ₄		12	99
4-Iodotoluene	NaGaH ₄	Toluene	12	96
	KGaH ₄		24	38
4-Iodoanisole	NaGaH ₄	Anisole	12	97
	KGaH ₄		24	34

^aSolutions were 0.125 M (8 mL, 1 mmol) in metal gallium hydride and organic halide. ^bYields were determined by GC using a suitable internal standard.

bromobutyronitrile were reacted with KGaH₄ in THF at 0 °C. The reductions with KGaH₄ were converted to the butyronitrile in 79 and 82% of yields for 12 h, respectively. The α -bromo-*p*-tolunitrile was reacted fastly with KGaH₄, and was converted to *p*-tolunitrile in 86% of yield for 1 h. But we obtained low yield from 4-bromobenzonitrile which is an aromatic nitrile. Employing α -bromo- γ -butyrolactone as a halo-lactone, we obtained γ -butyrolactone quantitatively for 0.5 h.

Finally, We also carried out competitive reduction of halide compounds at 0 °C. From the studies on the competitive reduction between halide and ester in a mixture, the reduction of 1-chlorooctane and ethyl caproate in mixtures by

Table 2. Chemoselective Reduction of Organic Halides Containing Various Functional Groups with KGaH₄ containing in THF at 0 °C^a

Compound	Product	Reaction time(h)	Yield ^b (%)
Ethyl 2-chloropropanoate	Ethyl propanoate	24	7
Ethyl 3-chloropropanoate	Ethyl propanoate	24	63
Ethyl 2-bromopropanoate	Ethyl propanoate	24	28
Ethyl 3-bromopropanoate	Ethyl propanoate	24	91
Ethyl 2-bromoisobutyrate	Ethyl isobutyrate	24	tr
Ethyl 4-bromobenzoate	Ethyl benzene	24	tr
Ethyl 4-iodobenzoate	Ethyl benzene	24	14
3-Bromobutyronitrile	Butyronitrile	24	79
4-Bromobutyronitrile	Butyronitrile	24	82
4-Bromobenzonitrile	Benzonitrile	24	19
α -Bromo- <i>p</i> -tolunitrile	<i>p</i> -tolunitrile	24	90
1-Bromo-4-chlorobenzene	Chlorobenzene	24	3
1-Chloro-4-iodobenzene	Chlorobenzene	24	20
	Chlorobenzene	24	95 ^c
α -Bromo- γ -butyrolactone	γ -Butyrolactone	0.5	99

^aSolutions were 0.125 M (8 mL, 1 mmol) in KGaH₄ and organic halide. ^bYield were determined by GC using a suitable internal standard. ^cThe reaction carried out at 65 °C.

KGaH₄ was inert. In the mixtures of 1-bromooctane and ethyl caproate, 4-iodooctane and ethyl caproate, we observed the reduction of halide only for both cases in the yields of 91 and 93%, respectively, for 12 h. In the mixtures of benzyl chloride and ethyl benzoate, benzyl bromide and ethyl benzoate, we obtained 95 and 96% of toluene for 12 h by the reduction of halide only. Upon the reduction of mixture containing halide and nitrile, nitrile was not reduced at all, while 1-bromooctane was reduced to produce a sole product of octane in high yield of 93% for 12 h from the mixed compound of 1-bromooctane and capronitrile. In the reduction of a mixture of 1-bromooctane and benzonitrile, only 1-bromooctane was reduced to produce 89% of octane for 12 h. Upon the competitive reduction between various halides the mixture containing 1-bromooctane, 4-bromoanisole, 4-bromotoluene, bromobenzene or bromocyclohexane. From the competitive reaction of mixed compound of 1-bromooctane and bromocyclohexane, we obtained octane only with 88% yield. From all these results, it would be safe to conclude that only bromoalkane would be effectively reduced from the mixed compound containing ester, nitrile, aromatic bromide or bromocyclohexane, and bromoalkane.

In conclusion, the reducing ability of halide was NaGaH₄ > KGaH₄.

Among the organic halides, they were reduced in the order of Cl < Br < I. For the reduction of aliphatic haloester, we observed the higher selectivity with the one substituted by halogen at 3-position than the one substituted at 2-position. For aliphatic halonitrile, we observed the high yield at the substitution of halogen at 3- and 4-position.

However aromatic halonitrile showed the very low yield due to the slow reduction. α -Bromo- γ -butyrolactone was

Table 3. Chemoselective Reduction of Organic in the presence of Different Functional Group Compounds with KGaH_4 in THF at 0 °C^a

Compound	Product	Reaction time(h)	Yield ^b (%)
1-Chlorooctane	Octane	12	tr
Ethyl caproate	Capryl alcohol		0
1-Bromooctane	Octane	12	91
Ethyl caproate	Capryl alcohol		0
1-Iodoctane	Octane	12	95
Ethyl caproate	Capryl alcohol		0
Benzyl chloride	Toluene	12	95
Ethyl benzoate	Benzyl alcohol		tr
Benzyl bromide	Toluene	12	96
Ethyl benzoate	Benzyl alcohol		tr
1-Bromooctane	Octane	12	93
Capronitrile	Hexylamine		0
1-Bromooctane	Octane	12	89
Benzonitrile	Benzonitrile		0
1-Bromooctane	Octane	12	72
4-Bromobenzonitrile	Benzonitrile		26
1-Bromooctane	Octane	12	87
4-Bromoanisole	Anisole		tr
1-Bromooctane	Octane	12	90
4-Bromotoluene	Toluene		tr
1-Bromooctane	Octane	12	89
Bromobenzene	Benzene		tr
1-Bromooctane	Octane	12	88
Bromocyclohexane	Cyclohexane		0

^aA mixture of one mmol each of an organic halide and other substrate was reacted with 0.125 M (8 mL, 1 mmol) of KGaH_4 . ^bYields were determined by GC using a suitable internal standard.

quantitatively reduced to γ -butyrolactone for 0.5 h. From mixed compound containing ester and aliphatic halide, we observed reduction of halide with the damage of ester. In the case of mixed compound containing nitrile and aliphatic bromide, only halide was reduced with high yield. For the mixed compound containing aliphatic halide and aromatic halide, only aliphatic halide was selectively reduced with moderate yield. So based on the experimental results, one can employ KGaH_4 as an excellent methodology to reduce organic halide selectively under the existence of various multifunctional groups.

Experimental Section

NaGaH_4 and KGaH_4 were prepared by known method.⁶ In this experiment, we prepared a clear solution of NaGaH_4 and KGaH_4 in THF.

Reduction of Organic Halides with Metal Gallium Hydrides. The following procedure for the reduction of 1-bromooctane with NaGaH_4 was representative. An oven-dried, 50 mL-flask with a side arm capped with rubber stopple, a magnetic stirring bar and a reflux condenser connected to a mercury bubbler, was flushed with nitrogen and charged

with 1 mL of 1.00 M 1-bromooctane-THF solution. THF (5.18 mL) was introduced into the reaction flask, followed by a solution of sodium gallium hydride (1.82 mL, 0.55 M, 1 mmol) in THF, and decane as a internal standard were added and refluxed. At the appropriate interval, an aliquot of reaction mixture was hydrolyzed with 1 mL of 1 M sulfuric acid. The aqueous layer was saturated with sodium chloride, and organic layer was separated, dried with anhydrous magnesium sulfate, and finally subjected to GLC analysis on a Chromosorb-WHP, 10% SE-30, 2 m, 1/8 inch column, indicating the presence of octane in 100% yield for 0.5 h.

Chemoselective Reduction of Organic Halides Containing Various Functional Groups with KGaH_4 . The reduction of ethyl 3-bromopropanoate was described as a representative. An oven-dried 50 mL-flask with a side arm capped with rubber stopple, a magnetic stirring bar and a reflux condenser connected to a mercury bubbler, was flushed with nitrogen and charged with 1 mL of 1.00 M ethyl 3-bromopropanoate-THF solution. THF (5.11 mL) was introduced into the reaction flask, followed by a solution of KGaH_4 (1.89 mL, 0.53 M, 1 mmol) in THF, and decane as a internal standard were added at 0 °C. The reaction mixture was maintained at 0 °C. At the appropriate interval, an aliquot of reaction was hydrolyzed with 1 mL of 1 M sulfuric acid. The aqueous layer was saturated with sodium chloride, and organic layer was separated, dried with anhydrous magnesium sulfate, and finally subjected to GLC analysis on a HP-5 (50 m \times 0.32 mm \times 0.17 μ m) capillary column, indicating the presence of ethyl propionate in 91% yield for 24 h.

Chemoselective Reduction of Organic Halide in the Presence of Different Functional Group Compounds with KGaH_4 . The reduction of 1-bromooctane in the presence of ethyl caproate was carried out as a representative.

An oven-dried, 50 mL-flask with a side arm capped with rubber stopple, a magnetic stirring bar and a reflux condenser connected to a mercury bubbler was flushed with nitrogen and charged with 1 mL (1 mmol) of 1.00 M 1-bromooctane in THF and 1 mL (1 mmol) of 1.00 M ethyl caproate in THF. THF (4.11 mL) was introduced into the reaction flask, followed by a solution of KGaH_4 (1.89 mL, 0.53 M, 1 mmol) in THF, and decane as a internal standard were added at 0 °C. At the appropriate interval, an aliquot of reaction mixture was hydrolyzed with 1 mL of 1 M sulfuric acid. The aqueous layer was saturated with sodium chloride, and organic layer was separated, dried with anhydrous magnesium sulfate, and finally subjected to GLC analysis on a HP-5 (50 m \times 0.32 mm \times 0.17 μ m) capillary column, indicating the presence of octane in 91% yield for 12 h without formation of capryl alcohol.

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