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Lewis acid-catalyzed reduction of dithioacetals by 1,4-cyclohexadiene

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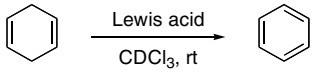
Abstract—Dithioacetals were reduced by 1,4-cyclohexadiene in the presence of a catalytic amount of Lewis acid to afford the corresponding sulfides in good yields.

The oxidation of 1,4-cyclohexadiene (1,4-CHD) derivatives to afford benzene derivatives is a useful aromatization method in organic reactions.[1] Various oxidants such as chloranil,[1,2] DDQ,[1,3] trityl salts,[1,4] and oxygen[5] have been used for this purpose. The oxidation of 1,4-CHD after deprotonation by *n*-BuLi/*N*,*N*,*N*′,*N*′-tetramethylethylenediamine is also reported.[1,6] Furthermore, Pd/C is the effective catalyst for the aromatization of 1,4-CHD.[1,3a,7] Although Lewis acid-catalyzed aromatization of 1,4-CHD and related hydrocarbons has been extensively studied, selective aromatization reactions using Lewis acids are very limited.[1,8] Since the aromatization of 1,4-CHD formally leads to the concomitant formation of two hydrogen atoms, 1,4-CHD may have the potential usefulness as the reductant. However, examples of the reduction using 1,4-CHD are rare. For example, catalytic hydrogenation using 1,4-CHD as hydrogen source is performed typically by Pd/C.[9] 1,4-CHD has also been used as the radical hydrogen donor,[10] especially in Bergmam cyclization.[11] In this Letter, we wish to report a novel finding that various Lewis acids smoothly induce the dehydrogenation of 1,4-CHD, and more interestingly, 1,4-CHD acts as the reductant for dithioacetal to monosulfide transformation in the presence of these Lewis acids.

1,4-CHD was treated with aluminium(III) chloride at room temperature in $CDCl_3$, and the reaction was monitored by ^1H NMR. The signals of 1,4-CHD immediately disappeared, and the signals of benzene and complex aliphatic hydrocarbons which might be formed by cationic oligomerization accompanied with aromatization appeared with the evolution of gas (Table 1, entry 1). The dehydrogenation proceeded even in the presence of a catalytic amount of Lewis acids (entries 2 and 6). When ethylaluminum dichloride and gallium(III) chloride were used, complex aromatic compounds were obtained probably because of Friedel–Crafts reaction (entries 3 and 5). Although indium(III) chloride, zinc(II) chloride and zinc(II) iodide showed lower activity for the aromatization, the selectivity was high (entries 7, 9 and 10).

Table 1. Aromatization of 1,4-CHD



Entry	Lewis acid (mol %)	Time	Yield[a] (%)	Conv.[a] (%)
1	$AlCl_3$ (100)	8 min	31	100
2	$AlCl_3$ (12)	30 min	37	100
3	$EtAlCl_2$ (100)	11 min	—[b]	100
4	$BF_3{\cdot}OEt_2$ (100)	7 d	30	96
5	$GaCl_3$ (100)	8 min	—[b]	100
6	$GaCl_3$ (10)	10 min	15	100
7	$InCl_3$ (100)	7 d	2	2
8	$TiCl_4$ (91)	21 h	42	91
9	$ZnCl_2$ (140)	7 d	5	5
10	ZnI_2 (100)	12 d	97	100

[a] Determined by ^1H NMR.
[b] Complex aromatic compounds were observed.

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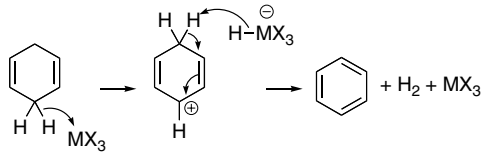


Scheme 1. Plausible reaction mechanism of aromatization.

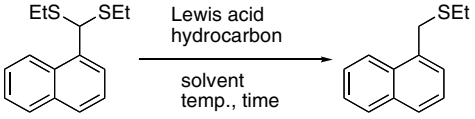
Plausible mechanism of this aromatization is shown in Scheme 1. Lewis acid abstracts hydride[8b,12] from 1,4-CHD to form intermediary hydride complex and cyclohexadienyl cation. The deprotonation of the cation by the hydride affords benzene. We were prompted to use intermediary hydride complex as the reductant.

Since we previously reported the reduction of thioacetals by gallium(II) chloride,[13] we tried to use the above aromatization system for the reduction of thioacetals. When 1-naphthaldehyde bis(ethylthio)acetal was treated with 2.0 equiv of 1,4-CHD in the presence of 10 mol % of aluminium(III) chloride, ethyl (1-naphthyl)methyl sulfide was obtained in 84% yield. Since the selective reduction of thioacetal to sulfide without the formation of hydrocarbon is a rare transformation,[14] we optimized the reduction conditions for the efficient transformation of thioacetals to sulfides. The results are shown in Table 2. First, the reduction was carried out using various unsaturated hydrocarbons. Hydrocarbons with 1,4-CHD structure showed reducing activity, and 1,4-CHD was the most effective reductant (entries 1–3). Reduction proceeded effectively by even 1.0 equiv of 1,4-CHD.[15] 1,3-CHD did not work at all because cationic polymerization of 1,3-CHD preferentially occurred (entry 4). Lewis acid greatly affected the yield of sulfide. The Lewis acids that were active in aromatization were generally effective in reduction. The highest yield was obtained with ethylaluminum dichloride (entry 7). The yield increased at the higher temperature (entries 6, 14 and 15). Since the reaction proceeded even at lower temperature, further experiments were carried out at room temperature. Sulfide was obtained in high yield when nonpolar solvent was used (entries 16–18). Since the acidity of a Lewis acid is suppressed in a polar solvent, the Lewis acidity of the catalyst seems to be the essential factor in this reduction.

The reduction of various thioacetals was investigated with 1,4-CHD in the presence of ethylaluminum dichloride or gallium(III) chloride. The results are summarized in Table 3.[16,17] Aromatic thioacetals were reduced smoothly to afford the corresponding sulfide in good to excellent yields (entries 1–3 and 6). For the reduction of less reactive thioacetals such as aliphatic thioacetal, cyclic thioacetal, and thioketal, the use of gallium(III) chloride instead of ethylaluminum dichloride provided better results (entries 4, 5, 7–9). Surprisingly, in the case of cyclic thioacetal (entry 8), 1,3-bis(benzylthio)propane was obtained as the major product while 3-(benzylthio)propane-1-thiol was not detected. It can be deduced that facile acetal exchange reaction was accompanied with the reduction. Gallium(III) chloride was also effective when dimethylacetal was used as the substrate (entries 10–12).

A plausible reaction mechanism is illustrated in Scheme 2. Lewis acid has two roles: activation of thioacetal and abstraction of hydride from 1,4-CHD to form hydride complex. Sulfide is obtained by the

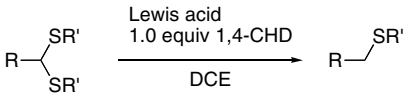
Table 2. Optimization of the reaction conditions

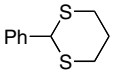
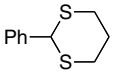


Entry	Lewis acid (mol %)	Hydrocarbon (1.0 equiv)	Solvent[a]	Temperature (°C)	Time (h)	Yield[b] (%)
1	$AlCl_3$ (10)	1,4-CHD	DCE	rt	6	94
2	$AlCl_3$ (10)	γ-Terpinene	DCE	rt	6	60
3	$AlCl_3$ (10)	9,10-DHA[c]	DCE	rt	6	65
4	$AlCl_3$ (10)	1,3-CHD	DCE	rt	6	Trace
5	$AlCl_3$ (10)	Cyclohexene	DCE	rt	6	2
6	$AlCl_3$ (5)	1,4-CHD	DCE	rt	5	81
7	$EtAlCl_2$ (5)	1,4-CHD	DCE	rt	5	94
8	Et_2AlCl (5)	1,4-CHD	DCE	rt	5	33
9	$BF_3{\cdot}OEt_2$ (5)	1,4-CHD	DCE	rt	5	73
10	$GaCl_3$ (5)	1,4-CHD	DCE	rt	5	82
11	$InCl_3$ (5)	1,4-CHD	DCE	rt	5	50
12	$TiCl_4$ (5)	1,4-CHD	DCE	rt	5	72
13	$ZnCl_2$ (5)	1,4-CHD	DCE	rt	5	1
14	$AlCl_3$ (5)	1,4-CHD	DCE	80	5	95
15	$AlCl_3$ (5)	1,4-CHD	DCE	0	5	63
16	$AlCl_3$ (5)	1,4-CHD	PhH	rt	5	81
17	$AlCl_3$ (5)	1,4-CHD	AN	rt	5	2
18	$AlCl_3$ (5)	1,4-CHD	THF	rt	5	Trace

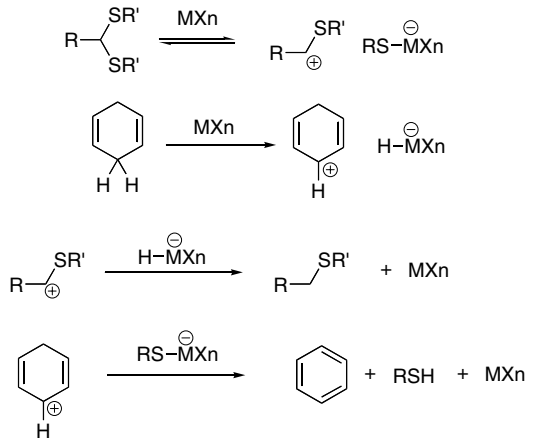
[a] DCE: 1,2-dichloroethane; PhH: benzene; AN: acetonitrile; THF: tetrahydrofuran.
[b] Determined by ^1H NMR.
[c] 9,10-DHA: 9,10-dihydroanthracene.

Table 3. Reduction of thioacetals



Entry	Substrate	Lewis acid (mol %)	Temperature (°C)	Time (h)	Yield[a] (%)
1	$PhCH(SEt)_2$	$EtAlCl_2$ (5)	rt	5.5	88
2	*p*-$MeOC_6H_4CH(SEt)_2$	$EtAlCl_2$ (5)	rt	9	87
3	*p*-$ClC_6H_4CH(SEt)_2$	$EtAlCl_2$ (5)	rt	5.5	96
4	$Me(CH_2)_{10}CH(SEt)_2$	$EtAlCl_2$ (5)	80	24	29[b]
5	$Me(CH_2)_{10}CH(SEt)_2$	$GaCl_3$ (5)	80	24	61[b]
6	$PhCH(SPh)_2$	$EtAlCl_2$ (5)	rt	3	77
7		$EtAlCl_2$ (5)	80	24	0
8		$GaCl_3$ (10)	80	40	44[b,c]
9	$PhC(Me)(SEt)_2$	$EtAlCl_2$ (5)	80	20	55[b]
10	$PhCH(OMe)_2$	$EtAlCl_2$ (5)	rt	5	0
11	$PhCH(OMe)_2$	$GaCl_3$ (5)	rt	10	28[d]
12	$PhCH(OMe)_2$	$GaCl_3$ (5)	80	21	92[b,d]

[a] Determined by ^1H NMR.
[b] 2.0 equiv of 1,4-CHD was used.
[c] The product is $PhCH_2S(CH_2)_3SCH_2Ph$.
[d] The product is $PhCH_2OMe$.



Scheme 2. Plausible reaction mechanism for the reduction of thioacetal by 1,4-CHD.

attack of the hydride complex to the activated thioacetal. The cyclohexadienyl cation reacts with thiolate complex to afford thiol and benzene with regenerating the Lewis acid.

In summary, we have developed a novel method for the reduction of thioacetal to sulfide using 1,4-CHD. The application of reduction system using 1,4-CHD is in progress.

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15. In every case, the formation of the complex hydrocarbons was not observed even when ethylaluminum dichloride or gallium(III) chloride was used as the Lewis acid. Although the formation of benzene was not confirmed because of its volatility, 4-isopropyl-1-methylbenzene and anthracene were detected when γ-terpinene and 9,10-DHA, respectively, were used.
16. In every case, the starting material was almost consumed and no hydrocarbon (over-reduction product) was observed, although the structures of by-products were not clear.
17. *Typical procedure for the reduction of dithioacetals*: Under a nitrogen atmosphere, 0.96 M ethylaluminum dichloride in *n*-hexane (50.0 μL, 48.0 μmol) was added to a solution of 1-naphthaldehyde bis(ethylthio)acetal (251 mg, 0.959 mmol) and 1,4-CHD (77.5 mg, 0.967 mmol) in 1,2-dichloroethane (7.00 mL) at room temperature, and the mixture was stirred at the temperature for 5 h. After water was added, the organic materials were extracted with chloroform. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (hexane/chloroform = 4/1) to give ethyl (1-naphthyl)methyl sulfide (182 mg, 0.904 mmol, 94%). The yields determined by ^1H NMR were based on triphenylmethane as an internal standard.