5-Acyl-1, 2, 4-oxadiazoles **6** can also be prepared in a similar manner from the reaction of 5-ethoxycarbonyl-1, 2, 4-oxadiazole **5**[2a] with organomagnesium reagents. In contrast to the previous reaction for the preparation of 3-acyl-1, 2, 4-oxadiazole, which provided only one product, the reaction of **5** with Grignard reagents provided adduct **7** occured at 4-double bond of oxadiazole along with adduct **6**. The formation of **7** may be rationalized by the greater resonance effect of negative charge on 4-nitrogen as compared with that on 2-nitrogen. The similar result was observed in the rection of 3-methyl-5-phenyl-1, 2, 4-oxadiazole with n-BuLi[13].

R' =CH₃	75 %	10 %
n-C₃H₇	70 %	18 %
C₄H₉	69 %	19 %
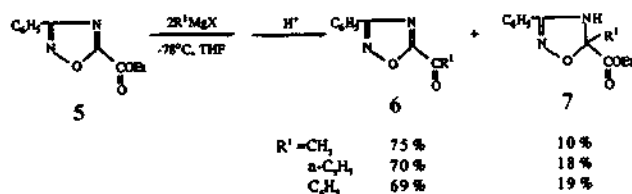
In a typical procedure, a 50 m*l* two-neck flask, equipped with a septum port, a magnetic stir bar, and a nitrogen tee connected to a source of nitrogen, was charged with 3-ethoxycarbonyl-5-phenyl-1, 2, 4-oxadiazole (0.654 g, 3 mmole) and 30 m*l* dry THF. The reaction mixture was cooled to $-78°C$ by using Dry-Ice/isopropanol slush and 3 m*l* (6 mmole) of propylmagnesium chloride (2 M solution) was added dropwise at $-78°C$. After stirring at $-78°C$ for 1 hour, the reaction mixture was quenched with HCl saturated ether solution. The mixture was poured into 30 m*l* of H_2O, extracted with ether (30 m*l*×2) and dried the ether layer with anhydrous $MgSO_4$. Column chromatography (25% ethylacetate in hexane) provided 0.55 g (85% yield) of 3-butanoly-5-phenyl-1, 2, 4-oxadiazole: mp 38-39°C; ^{1}H NMR (CDCl₃) δ 8.25-7.90 (m, 2H), 7.60-7.27 (m, 3H), 3.05 (t, J=7.3 Hz, 2H), 1.80 (m, J=7.3 Hz, 2H), 1.02 (t, J=7.3 Hz, 3H); IR (KBr) 1705 (C=O); MS 216 (M⁺, parent ion).

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Sodium Halates-Halotrimethylsilanes. New Reagents for Aromatic Halogenation Reactions

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There have been many recent reports on the halogenation of aromatic compounds using inorganic halogen compounds in the presence of various oxidizing agents[1]. Nitric acid[2], hydrogen peroxide and peracids[3], halates and perhalates[4], and transition metal compounds of higher oxidation states[5] are among such oxidizing agents used for this purpose.

In connection with the continued search for the new reagents utilizing each pairs of inorganic compounds and halotrimethylsilanes[6], we found that sodium chlorate, bromate and iodate in combination with the corresponding halotrimethylsilane serves as efficient halogenating agents. We now wish to report our preliminary results on nuclear halogenation reactions of aromatic compounds using these pairs of reagents.

$$X = Cl, Br, I \qquad (1)$$
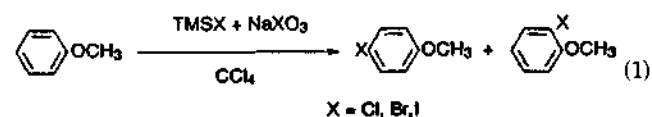
When one to the three equivalents of chlorotrimethylsilane were reacted with the 3:1 mixture of toluene and sodium chlorate in dichloromethane at room temperature, a mixture of *o*- and *p*-chlorotoluene was formed. The ratio of the *o*- and *p*-chlorotoluene turned out to be 35:66 and did not vary significantly depending upon the ratio of sodium halate and halotrimethylsilane. Similar *o*- and *p*- isomeric ratios were exhibited for chlorinations of toluene by Cl_2-Fe pair or sulfuryl chloride as the chlorinating agent[7]. Little or no side chain chlorination was observed. Various xylenes produced expected monochloroxylene. Introduction of the second chlorine into the aromatic rings turned out to be much more difficult than the first chlorination. Anisole also reacted with chloro-

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Table 1. Halogenation of Aromatic Compounds with Halotrimethylsilane-Sodium Halate Pairs in Dichloromethane and Carbon Tetrachloride

Substrate	Halogenating Agent[a]	Reaction Conditions[b]	Product[c]	% Yield[d]
benzene	TMSCl+NaClO₃	rt, 11 h	chlorobenzene	0
	TMSI+NaIO₃	reflux, 16 h	iodobenzene	0
toluene	TMSCl+NaClO₃	rt, 14 h	p-chlorotoluene (34:66)	(90)
	TMSBr+NaBrO₃	rt, 6.5 h, dark	benzyl bromide	85
	TMSCl+NaIO₃	rt, 10 h	p-chlorotoluene[e]	78
	TMSCl+I₂O₅	rt, 7 h, CCl₄	p-iodotoluene (2:98)	85
	TMSI+NaIO₃	reflux, 16 h	p-iodotoluene	0
o-xylene	TMSCl+NaClO₃	rt, 13 h	4-chloro-1,2-xylene	90
m-xylene	TMSCl+NaClO₃	rt, 12 h	4-chloro-1,3-xylene	80
p-xylene	TMSCl+NaClO₃	0℃-rt, 17 h	2-chloro-1,4-xylene	77
	TMSBr+NaBrO₃	rt, 12 h	4-(bromomethyl)toluene[f]	70
ethylbenzene	TMSBr+NaBrO₃	rt, 12 h	α-phenylethyl bromide	96
anisole	TMSCl+NaClO₃	rt, 10 h	p-chloroanisole (9:91)	(70)
	TMSBr+NaBrO₃	rt, 6 h	p-bromoanisole (7:93)	(85)
	TMSCl+NaClO₃+NaI	rt, 14 h CCl₄	p-iodoanisole (2:98)	85
	TMSI+NaIO₃	rt, 8 h	p-iodoanisole (2:98)	(91)
	TMSCl+NaIO₃	rt, 20 h	p-iodoanisole (2:98)	(90)
o-chloroanisole	TMSCl+NaClO₃	rt, 10 h	2,4-dichloroanisole	90
	TMSBr+NaBrO₃	rt, 10 h	4-bromo-2-chloranisole	94
p-chloroanisole	TMSCl+NaClO₃	rt, 17 h	2,4-dichloroanisole	90
	TMSBr+NaBrO₃	rt, 17 h, CCl₄	2-bromo-4-chloroanisole	94
phenol	TMSCl+NaClO₃	rt, 2 h	p-chlorophenol (3:97)	75
	TMSBr+NaBrO₃	rt, 1.5 h	p-bromophenol (2:98)	84
p-cresol	TMSCl+NaClO₃	rt, 5 h	2,6-dichloro-4-methylphenol	55[f]
	TMSBr+NaBrO₃	rt, 12 h	2,6-dibromo-4-methylphenol	74[g]
chlorobenzene	TMSCl+NaClO₃	rt, 16 h	NR[h]	
	TMSI+NaIO₃	reflux, 14 h	NR[h]	
bromobenzene	TMSCl+NaClO₃	rt, 14 h	NR[h]	
	TMSBr+NaBrO₃	rt, 14 h	NR[h]	
iodobenzene	TMSI+NaIO₃	rt, 6 h	NR[h]	
nitrobenzene	TMSCl+NaClO₃	rt, 17 h	NR[h]	
	TMSCl+NaIO₃+NaI	reflux, 17 h	NR[h]	
naphthalene	TMSCl+NaClO₃	rt, 22 h	unknown products	
	TMSBr+NaBrO₃	rt, 1.5 h	1-bromonaphthalene	87

[a] Substrate : TMSX : NaXO₃=1:3:1, unless otherwise mentioned. [b] The reaction mixture was stirred for the shown period. CH₂Cl₂ was used as a solvent for most reactions. [c] The ratios of ortho and para isomeric products shown in the parenthesis were determined by GC. [d] GC yields are in the parenthesis. [e] Chlorotoluenes and iodotoluenes were produced in a 95:5 ratio. [f] 1,4-Di(bromomethyl)benzene was also formed in 24% yield. [g] 20-25% of monohalogenated products were also formed as minor products. [h] Starting material was recovered unreacted.

trimethylsilane-sodium chlorate to produce p-chloroanisole as a major product. Phenol gave a mixture of o- and p-chlorophenol in very good yield. Other oxidation products were produced but in less than 3% yields. A fair amount of dichlorophenol formation (10-20%) was observed. The amount of these dichlorinated products was larger for electron rich aromatic compounds such as anisole and phenol, but optimum monochlorination can be achieved by adjusting the amount and/or the ratio of sodium chlorate and chlorotrimethylsilane. Naphthalene seems to be readily oxidized, but no chloronaphthalene was detected. The products and reaction conditions of the chlorination reactions are listed in Table 1.

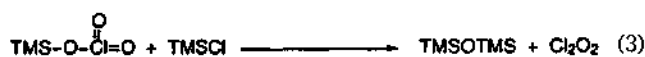Bromotrimethylsilane and sodium bromate pair in either

dichloromethane or carbon tetrachloride also produced exclusively ring brominated products when reacted with aromatic compounds bearing electron donating substituents. Anisole, for example, reacted with sodium bromate and bromotrimethylsilane to produce p-bromoanisole along with a small amount of o-bromoanisole. Naphthalene was easily brominated to 1-bromonaphthalene. Deactivated aromatic compounds such as bromobenzene and nitrobenzene were not ring brominated neither at room temperature nor at elevated temperature (40-60℃).

Toluenes, on the other hand, underwent mainly benzylic bromination when reacted with sodium bromate and bromotrimethylsilane pair. Instead of bromotoluene benzyl bromide

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were produced in very high yields. Similarly ethylbenzene was brominated at the side chain and α-phenylbromoethane was the only brominated product. This side chain bromination could not be supressed even in the absence of light. Even when the reaction flask was wrapped with aluminium foil, less than 1% of total brominated products turned out to be bromotoluenes and 99% of the products was benzyl bromide. The reason for this is yet to be understood.

Iodination of aromatic rings is by far the most difficult halogenation reaction and only a limited number of reagents have been reported in the literature[8]. Like chlorination and bromination, a reaction of aromatic compounds with iodotrimethylsilane and sodium iodate were expected to produce iodoaromatic compounds in good yields. Aromatic compounds and sodium iodate were added to the premixed solution of hexamethyldisilane and molecular iodine. Unlike other halogenation agents, this sodium iodate and iodotrimethylsilane combination was effective for the iodination of only very highly activated aromatic compounds. Anisole reacted to produce the corresponding iodoanisole in good yield. Other aromatic compounds (even toluene) failed to give iodination products.

Iodine pentoxide was found to be more or equally effective as sodium iodate. Toluene. for example, produced iodotoluene in good yield when reacted with iodine pentoxide and iodotrimethylsilane in carbon tetrachloride[9]. Halogenation reactions using sodium iodate and chlorotrimethylsilane were also attempted. When toluene was treated with chlorotrimethylsilane and sodium iodate, chlorotoluene and iodotoluene were produced in a 95:5 ratio. In contrast, the reaction of anisole with chlorotrimethylsilane and sodium iodate combination produced iodoanisole as a major halogenation product. Chloroanisole accounted less than 2% of total halogenation products. Furthermore. a reaction of anisole with a mixture of chlorotrimethylsilane, sodium chlorate and excess sodium iodide also produced *p*-iodoanisole in good yield[10]. We do not have any explanation of this strange phenomena, yet.

$$TMSCl + NaClO_3 \longrightarrow TMS\text{-}O\text{-}\overset{\overset{\displaystyle O}{\|}}{Cl}{=}O \quad (2)$$

$$TMS\text{-}O\text{-}\overset{\overset{\displaystyle O}{\|}}{Cl}{=}O + TMSCl \longrightarrow TMSOTMS + Cl_2O_2 \quad (3)$$

The chemical reactions between halotrimethylsilane and sodium halate leading to the formation of the effective halogenating agent is not clear yet. The first step of the reaction could be the formation of trimethylsilyl esters of halic acids from the reaction of halotrimethylsilane and sodium halate. Further reaction of trimethylsilyl halate with another equivalent of halotrimethylsilane would remove the trimethylsilyloxy group as hexamethyldisiloxane. This could result in temporarily formation of dioxochlorine cation en route to formation of unstable dichlorine dioxide. This unstable dichlorine dioxide is believed to decompose and/or disproportionate to various chlorine and oxychlorine species. With less reactive aromatic compounds, halogen oxides seem to decompose into molecular halogen and oxygen and other halogen compounds of lower oxidation state. However, the exact pattern of this decomposition is not completely understood.

This type of replacement of trimethylsilyloxy group with

halogen to form halogen hetero atom bonds were observed for the reactions of TMS esters of chromate, chlorochromate, selenite, nitrite, and nitrate with chlorotrimethylsilane[6]. Corresponding chromyl chloride, selenium oxychloride, nitrosyl and ntryl chloride were postulated to be formed.

Excessive heating should be avoided for chlorination reactions. Raising the temperature of the chlorination mixture for less reactive aromatic compounds caused violent explosions. The formation of brominating and iodinating agents from the corresponding halotrimethylsilane and sodium halates are believed to proceed in a silmilar manner, although the decomposition and disproportionation pattern might be slightly diffierent. For bromination and iodination reactions, however, the temperature of the reaction mixture could be safely raised to 60-80℃.

These reagent combinations were found also very efficient for halogen addition to olefins and α-halogenation of carbonyl compounds[11]. We are currently investigating the mechanism of these aromatic halogenation reactions and other application of these reagents.

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9. Iodination reactions by halotrimethylsilane and iodine oxide were not further pursued.
10. The conversion of iodide ion to the active electrophilic iodine species is not understood.
11. When cyclohexene was reacted with TMSBr + NaBrO₃.

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trans-1,2-dibromocyclohexane was produced in an almost quantitative yield. TMSCl+NaClO₃ pair were found very efficient for α-chlorination of ketones.

A New Aldehyde Synthesis From Carboxilic Acid Esters With Sodium Diethylpiperidino-hydroaluminate[1]

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Partial reduction of carboxylic acid esters to the corresponding aldehydes have been accomplished successfully with various substituted metal hydrides, such as diisobutylaluminum hydride (DIBAH)[2], lithium tri-t-butoxyaluminum hydride (LTBA)[3] and diaminoaluminum hydride[4]. Of these reagents, LTBA can be applied only for phenyl esters of aliphatic acids and diaminoaluminum hydride requires longer reaction time (6-10 h), usually at elevated temperature (65°C). On the other hand, DIBAH has been generally utilized for the aldehyde synthesis from esters. However, the yields of aromatic aldehydes (48-70%) are considerably lower than those of aliphatic aldehydes (80-88%). Recently we have improved considerably (10-28%) the yields of aromatic aldehydes by adding o-anisidine to the reaction mixture[5]. But the very low temperature (−70°C) required for the DIBAH reduction is still a considerable handicap, especially for larger samples.

Recently we have found that sodium diethylpiperidinohydroaluminate (SDPA) could be prepared conveniently by reacting equimolar amount of piperidine with sodium diethyldihydroaluminate (OMH-1) in THF-toluene (1:1) cosolvent at 0°C. Reaction of excess SDPA (4 eq) with esters at 0°C showed a distinct rate break after one hydride uptake, suggesting a possibility of aldehyde synthesis (Fig. 1). Indeed we could apply this substituted aluminohydride successfully for the synthesis of aldehydes from the corresponding carboxylic acid esters. The results for representative carboxylic acid esters are summerized in Table 1.

Na(C₂H₅)₂AlH₂ + [piperidine] →(THF-Toluene, 0 °C)→ Na(C₂H₅)₂AlH[piperidine] + H₂
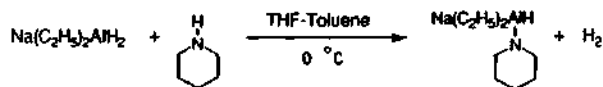
As shown in Table 1, aromatic esters were reduced almost quantitatively to the corresponding aldehydes, using 1.1 eq of SDPA. This is contrasted to the very low yield by OMH-1, as shown in the reduction of ethyl benzoate. t-Butyl benzoate was reduced very slowly, in rather lower yield (85 %) presumably due to the bulky t-butyl group. The yields of aldehydes from aliphatic esters were somewhat low compared with the aromatic aldehydes, yet the yields are comparable to the other known methods. The yields of aldehydes
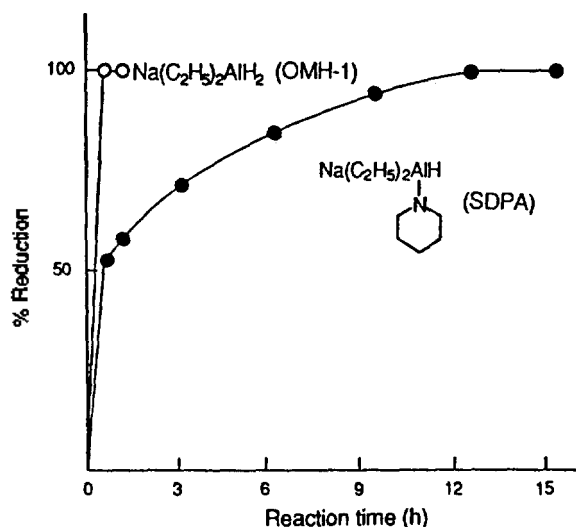
Figure 1. Reaction of OMH-1 and SDPA with Ethyl Benzoate in THF-Toluene at 0°C. ([Hydride]=0.8 M, and [Ester]=0.2 M).

Table 1. Partial Reduction of Esters to the Corresponding Aldehydes with SDPA in THF-Toluene at 0°C

Esters	Ratio of hydride/compd.	Reaction time(h)	Yield[a] of aldehyde(%)
methyl benzoate	1.1	0.5	98
ethyl benzoate	1.1	0.5	99
	(1.1)	(0.5)	(22)[c]
isopropyl benzoate	1.1	1.0	97
t-butyl benzoate	4.0	3.0	85
phenyl benzoate	1.1	0.5	97
ethyl o-toluate	1.1	1.0	60
	1.5	1.0	92
	(1.1)	(1.0)	(27)[c]
ethyl m-toluate	1.1	1.0	94
ethyl p-toluate	1.1	1.0	94
ethyl o-methoxybenzoate	1.5	1.0	96
ethyl p-methoxybenzoate	1.1	1.0	94
methyl o-chlorobenzoate	1.1	3.0	93
methyl m-chlorobenzoate	1.1	0.5	99
ethyl p-chlorobenzoate	1.1	0.5	96, 79[d]
ethyl p-nitrobenzoate	1.1	0.5	98, 77[d]
ethyl caproate	1.1	1.0	85
ethyl decanoate	1.1	1.0	90
isopropyl caproate	1.1	1.0	63
	1.1	3.0	52
	1.5	2.0	77
ethyl cyclohexanecarboxylate	1.1	3.0	47
	1.5	3.0	61
ethyl cinnamate	1.1	1.0	65

[a] 1.1 Equiv. of SDPA was added to esters in THF-Toluene at 0°C. [b] Yields were estimated by GLC. [c] Yields obtained by OMH-1 alone are shown in parenthesis. [d] Isolated yield.

from linear unhindered esters such as ethyl caproate or ethyl decanoate were good, however hindered esters such as isopropyl caproate and ethyl cyclohexanecarboxylate, and α, β-