Samarium Diiodide-Mediated Reaction of Organic Halides with Carbonyl Compounds

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Abstract: The following three types of samarium diiodide mediated reactions of organic halides and carbonyl compounds are discussed: 1) Samarium-mediated highly stereoselective reaction of 1,1-dihaloalkanes with aldehydes. 2) Stereoselective reaction with configurationally stable α-phenylthioalkylsamarium compounds. 3) Preparation and reaction of α-samarium enolate equivalent of β-ketoester.

1. Introduction

In 1980 Kagan reported effective use of lanthanides in organic reactions (ref. 1). Since then, lanthanide-mediated reactions have attracted considerable attention of organic chemists (ref. 2). One of the most attractive synthetic usages is the formation of a powerful nucleophilic species by the reduction of organic compounds with low-valent salts or metals. Among such metal reagents, samarium diiodide has been recognized as an effective electron donating reagent in reductive coupling of organic halides with carbonyl compounds, both Barbier type reactions and Reformatsky type reactions. Those have been performed by treatment of a mixture of carbonyl compounds and organic halides with samarium diiodide (SmI\(_2\)) producing the corresponding alcohols. Attempts to prepare organosamarium(III) species from •SmI\(_2\) and organic halides before an addition of carbonyl compounds, often afforded unsatisfactory results (ref. 3). One main reason may be the instability of samarium(III) species. In these transformations, it has also been well argued whether the reaction proceeds via the organosamarium species or radical species, and the recent work show the possibility the existence of the organosamarium species depending on the reaction condition (ref. 4). We tried to react SmI\(_2\) with various organic halides and to prepare stereoselective and functionalized organosamarium species. The following three types of organosamarium species were prepared to perform novel selective transformations.

2. Samarium-Mediated Highly Stereoselective Reaction of 1,1-Dihaloalkanes with Aldehydes (ref. 5)

Reaction of α-heteroatom substituted alkylmetal reagents with carbonyl compounds has been studied and used to prepare β-substituted alkanols (ref. 6). Among several α-heteroatom substituted alkylmetal reagents, halogen-substituted ones have been extensively studied, since reaction of these α-haloalkylmetals with carbonyl compounds yields β-haloxydrins of high synthetic potential. Synthesis of stereodefined haloxydrins needs both stereoselective generation of α-haloalkylmetals and a diastereoselective reaction with carbonyl compounds. Many reported results related to these transformations have focused on the use of lithium or magnesium as key metals (ref. 7). Diastereoselective formation of α-haloalkyl-lithium/magnesium reagents from the corresponding gem-
Dihaloalkane and organometalics offered a functionalized building block in the reaction with carbonyl compounds. While these diastereoselective formations of α-haloalkylmetals have been well investigated, enantiotopic transformation of 1,1-diiodoalkanes into optically active α-haloalkylmetals is still an undeveloped and challenging problem. Considering the high reducing power of SmI₂, we selected samarium as a key metal (ref. 8).

The reaction of 1,1-diiodoethane (1a) with SmI₂ gives α-iodoethylsamarium equivalent (2a) which reacts with decanal (3a) affording (2RS,3RS)-2-iodo-3-dodecanol (4a) with excellent diastereoselectivity (Scheme 1). Reactions using diiodoalkanes and aldehydes yield the corresponding iodohydrins in a diastereoselective manner. Results are summarized in Table 1.

Scheme 1. Diastereoselective Synthesis of 4

Achiral aldehydes possessing a substituent at the α- or α,α-position also produced the corresponding iodohydrins in a highly diastereoselective manner (entries 2 and 3). Reaction of 2a with racemic aldehydes containing a stereogenic center at the α-position (3d and 3e; entries 4,5) gave the corresponding iodohydrins 4d,e in a diastereoselective manner (4d,e: >98%de; related to the α-stereogenic center and hydroxyl, and >94%de related to the hydroxyl substituted carbon and iodo group). The reaction of 2a with β-substituted aldehyde 3f afforded halohydrin 4f; the stereoselectivity between iodine and hydroxyl was extremely high (>98%de) but no diastereoselectivity was observed between the β-substituted and hydroxyl group. A diastereodefined building block can be generated from β-substituted iodide 1b in the reaction with acetaldehyde 3g to give iodohydrin 4g in a diastereoselective manner (entry 7) (ref. 9). The SmI₂-mediated reaction of α-substituted aldehyde 3e with β-substituted diiodide 1b proceeded in a good diastereoselective manner to give halohydrin 4h that possesses four adjacent stereogenic centers.
When the reaction was carried out with optically active aldehydes (ent-3d,e), the adduct was obtained in a diastereo- and enantioselective manner. The yield and selectivity were not affected by changing the ratio of the reagents (Table 2). The result ruled out the possibility of kinetic resolution of a racemic α-haloalkylmetal species and implies that the prochiral 1,1-diiodoalkane was almost quantitatively converted into the optically pure α-halometal equivalent (ref.10,11).

### 3. Stereoselective Reaction with Configurationally Stable α-Phenylthioalkylsamarium Compounds (ref. 12)

The property of α-sulfur-substituted alkylsamarium reagents will be attractive, although several examples of the reaction of α-sulfur-substituted alkylmetals with aldehydes showed the diastereoselective formation of β-(alkylthio)alkanols (ref. 13). The configurational instability of α-sulfur-substituted alkyllithium in the reaction with various electrophiles has been shown already (ref. 14). The reaction of methylthiomethyl chloride with carbonyl compounds mediated by SmI₂ has also been also reported, but any stereochemistry has not been shown (ref. 15).

The SmI₂ mediated reaction of alkyl halides with carbonyl compounds in THF has been performed...
in Barbier type manner (a mixture of an alkyl halide and a carbonyl compound was added to a THF solution of SmI₂), as the intermediary organosamarium is not stable enough to carry out the reaction in Grignard reaction manner (a carbonyl compound is treated with a reagent prepared from an alkyl halide and a THF solution of SmI₂) except a few examples. At first, the Barbier type reaction was tried: A treatment of a mixture of aldehydes 1 and 1-chloroethyl phenyl sulfides 6 with SmI₂ in THF afforded β-(phenylthio)alkanols in good yields with syn-selectivity (Scheme 2).

\[
\begin{align*}
RCHO + \text{PhSCHClCH}_3 & \xrightarrow{\text{SmI}_2 (4.0 \text{ mmol})} \text{THF, RT} \rightarrow R \begin{array}{c}
\text{CH}_3 \\
\text{OH}
\end{array} + R \begin{array}{c}
\text{CH}_3 \\
\text{OH}
\end{array} \\
1 \text{ (2.0 mmol)} & 6 \text{ (2.0 mmol)} \\
R = \text{Cyclohexyl} & 95\% \ (86 / 14) \\
\text{t-Bu} & 86\% \ (97 / 3)
\end{align*}
\]

Scheme 2

To carry out the reaction, the intermediary organosamarium species should have a certain life time under the reaction conditions with various electrophiles (ref. 3). They were revealed to be relatively stable, as they can be trapped with D₂O to give 1-deuterioethyl phenyl sulfide in 53% yield (10, 82% D; Scheme 3). The same intermediate reacted with aldehydes yielding the corresponding β-(phenylthio)alkanols with syn selectivity (Scheme 4).

\[
\begin{align*}
\text{PhSCHClCH}_3 + 2 \text{SmI}_2 & \xrightarrow{0 \degree C} \text{THF, 1 h} \rightarrow \begin{array}{c}
\text{PhS} \\
\text{CH}_3 \\
\text{Sml}_2
\end{array} \rightarrow \text{D}_2O \rightarrow \text{PhSCHDCH}_3 \\
6 & \rightarrow 10 \ 53\% \ (82\% \text{D})
\end{align*}
\]

Scheme 3

\[
\begin{align*}
\text{PhSCHClCH}_3 + 2 \text{SmI}_2 & \xrightarrow{0 \degree C} \text{THF, 1 h} \rightarrow \begin{array}{c}
\text{PhS} \\
\text{CH}_3 \\
\text{Sml}_2
\end{array} \rightarrow \text{D}_2O \rightarrow \text{PhSCHDCH}_3 \\
6 \text{ (2.0 mmol)} & 1 \text{ (1.0 mmol)} \rightarrow \text{RCHO} \rightarrow \begin{array}{c}
\text{PhS} \\
\text{CH}_3 \\
\text{Sml}_2
\end{array} \rightarrow \text{D}_2O \rightarrow \text{PhSCHDCH}_3 \\
6 \text{ (2.0 mmol)} & 1 \text{ (4.0 mmol)} \rightarrow \text{RCHO} \rightarrow \begin{array}{c}
\text{PhS} \\
\text{CH}_3 \\
\text{Sml}_2
\end{array} \rightarrow \text{D}_2O \rightarrow \text{PhSCHDCH}_3 \\
R = n-\text{Pentyl} & > 99\% \ (84 / 16) \\
\text{Cyclohexyl} & 82\% \ (87 / 13)
\end{align*}
\]

Scheme 4

A reaction of 9 with a chiral aldehyde was also tried to obtain some information on the configurational stability which reflects the diastereomer distribution of the product. Reaction of 9 with racemic 3e afforded racemic 11a, out of four possible stereoisomers 11a-d, predominantly, whereas
that with (S)-3e showed lower diastereoselectivity. Use of excess organosamarium reagent did not show considerable improvement of diastereoselectivity. These results suggested that the configuration of the organosamarium reagent is stable and kinetic resolution for selection of one diastereomer did not operate under the reaction conditions. The reason for the disability of kinetic resolution might be due to an aggregation of the organosamarium species (ref. 16).

\[
\begin{align*}
\text{PhSCHClCH}_3 &+ \text{Sml}_2 \xrightarrow{\text{0 \degree C, THF, RT}} \left[ \begin{array}{l}
\text{PhS} \\
\text{Sml}_2
\end{array} \right] \xrightarrow{\text{CH}_3} \text{PhCHO 3e} \\
\end{align*}
\]

\[
\begin{array}{c}
\begin{array}{cccc}
\text{9} & \text{racemic - 3e} & \text{11a-d (ratio)} \\
\hline
1.0 \text{ mmol} & 1.0 \text{ mmol} & 65\% (83:10:6:1) \\
2.0 & 1.0 & >99\% (83:11:5:1)
\end{array}
\end{array}
\]

\[
\begin{array}{c}
\begin{array}{ccc}
\text{9} & (S)-3e & \text{ent- 11a-d} \\
\hline
1.0 \text{ mmol} & 1.0 \text{ mmol} & 54\% (59:31:11:<1) \\
2.0 & 1.0 & 87\% (63:23:12:2)
\end{array}
\end{array}
\]

Scheme 5

\[
\begin{align*}
\left[ \begin{array}{l}
\text{PhS} \\
\text{Sml}_2
\end{array} \right] & \xrightarrow{\text{TDA-1}} \begin{array}{c}
\text{PhCHO 3e} \\
\text{THF, 20 \degree C}
\end{array} \\
\end{align*}
\]

\[
\begin{align*}
9 (1.0 \text{ mmol}) & \text{TDA-1 (1.0 mmol) racemic-3e (1.0 mmol) : 90 \% (55:32:12:2)} \\
9 (1.0 \text{ mmol}) & \text{TDA-1 (1.0 mmol) (S)-3e (1.0 mmol) : 59 \% (38:41:7:14)} \\
9 (3.0 \text{ mmol}) & \text{TDA-1 (3.0 mmol) (S)-3e (1.0 mmol) : 98 \% (59:31:8:2)}
\end{align*}
\]

TDA-1: Tris[2-(2-methoxyethoxy)ethyl]amine

Scheme 6
An attempt to modify the organosamarium reagent with a multi-dentate ligand, which might make the organosamarium species monomeric, showed a possibility of kinetic resolution. A TDA-1, tris[2-(2-methoxyethoxy)ethyl]amine (ref. 17), mediated 9 reacted with racemic 3e in good yields to give a mixture of four diastereomers. Reaction with excess (S)-3e yielded almost the same distribution of 4 diastereomers, whereas the reaction with equimolar (S)-3e showed much less diastereoselectivity. These data suggested improvement of diastereoselectivity by the design of an appropriate ligand.

4. Reaction of Ethyl Bromoacetate with Samarium Diiodide (ref. 18)

We assumed that the reactive intermediate generated by the treatment of α-bromoesters with SmI₂ might be either Sm-version of Reformatsky-type reagents or samarium enolates (ref. 1,19). The formed intermediate, however, was not the expected ones, but δ-diiodosamario-β-oxobutanoates, a dimeric species of the starting bromoester, which can be used as a highly nucleophilic species for introducing 3-oxobutanoate moiety into carbonyl compounds.

First, the SmI₂-mediated reaction of ethyl bromoacetate with cyclohexanone was performed at different temperatures by Grignard-type procedure. The distribution of the products strongly depends on the reaction temperature (Table 3).

Table 3. SmI₂-Mediated Reaction of Ethyl Bromoacetate with Cyclohexanone

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (T °C)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-78</td>
<td>12</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>-50</td>
<td>13</td>
<td>&gt;98</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>14</td>
<td>80</td>
</tr>
</tbody>
</table>

a A THF solution of SmI₂ (2 eq.) was added to a THF solution of ethyl bromoacetate (1 eq.). b Isolated yield.

Results shown in Table 3 suggested that each intermediate generated at individual reaction temperature might be different (Scheme 7). Reduction of bromoacetate with SmI₂ does not proceed at -78 °C; during the warming of the reaction mixture to 0 °C, Barbier type reaction occurred affording hydroxy ester 12 in good yield as reported by Kagan (entry 1). Reduction of bromoester occurred at -50 °C, initially generating a reactive species, ethyl β-diiodosamarioacetate, which reacted with ethyl bromoacetate to give a dimeric intermediate, ethyl δ-diiodosamario-β-oxobutanoate (15) or its equivalent, which coupled with cyclohexanone affording compound 13 (entry 2) (ref. 20, 21). The above reactive intermediate (15) isomerized to low-reactive intermediate, samarium acetylacetonate (16), which did not couple with cyclohexanone at 0 °C (entry 3). Detailed discussions about 15 and 16 are noted later.
Scheme 7

Table 4. Preparation of 4-Hydroxy-β-ketoesters by Selfcondensed Reformatsky Type Reagent.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Carbonyl Compounds</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>Cyclohexanone</td>
<td>0.5</td>
<td>13</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>Cyclopentanone</td>
<td>1.0</td>
<td>17</td>
<td>&gt;98</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>4-Heptanone</td>
<td>1.0</td>
<td>18</td>
<td>&gt;98</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>β-Tetralone</td>
<td>0.5</td>
<td>19</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>2-Methylcyclohexanone</td>
<td>1.0</td>
<td>20</td>
<td>95 \textsuperscript{c}</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>4-t-Butylcyclohexanone</td>
<td>1.0</td>
<td>21</td>
<td>&gt;98 \textsuperscript{c}</td>
</tr>
<tr>
<td>7</td>
<td>Me</td>
<td>Cyclohexanone</td>
<td>0.2</td>
<td>22</td>
<td>95 \textsuperscript{c}</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td>Propanal</td>
<td>1.0</td>
<td>23</td>
<td>87</td>
</tr>
<tr>
<td>9</td>
<td>H</td>
<td>Benzaldehyde\textsuperscript{d}</td>
<td>0.5</td>
<td>24</td>
<td>&gt;98</td>
</tr>
<tr>
<td>10</td>
<td>H</td>
<td>(E)-2-Hexenal\textsuperscript{d}</td>
<td>0.5</td>
<td>25</td>
<td>&gt;98</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Normal Reformatsky type reaction product (β-hydroxyester) was not detected by NMR in all cases.  \textsuperscript{b} Isolated yield.  \textsuperscript{c} Isolated as a diastereomeric mixture.  \textsuperscript{d} Side reaction caused by reduction of aldehyde was not detected.
According to the reaction conditions of entry 2 of Table 3, SmI₂-mediated reaction of α-bromoesters with various aldehydes and ketones afforded the corresponding hydroxy keto esters in good to excellent yields. Results are summarized in Table 4. α,β-Unsaturated aldehyde gave the 1,2-adduct exclusively (entry 10). It should be emphasize that easily enolizable β-tetralone gave the corresponding product in good yield (entry 4). In contrast, a dianion, obtained from ethyl acetoacetate according to the reported procedure, reacted sluggishly with β-tetralone (ref. 22).

The above described Sm-mediated bromoester-carbonyl compound coupling reaction could be applied to acid anhydrides, as carbonyl compounds, by the use of t-Bu bromoester and mixed anhydrides (Scheme 8). Reaction proceeded smoothly to give β,δ-diketoesters (ref. 23). Results are shown in Table 5.

Scheme 8

Table 5. Preparation of t-Butyl 3,5-dioxoalkanoates

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Isolated Yield (%)</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>26b</td>
<td>29a</td>
</tr>
<tr>
<td>2</td>
<td>EtOCH₂⁻</td>
<td>65</td>
<td>29b</td>
</tr>
<tr>
<td>3</td>
<td>2-tetrahydrofuranyl</td>
<td>75</td>
<td>29c</td>
</tr>
</tbody>
</table>

a t-Butyl bromoacetate (1.0 mmol), SmI₂ (2.0 mmol), and anhydride (0.48 mmol) were used. b t-Butyl 4-ethoxycarbonyl-3-oxobutanoate was also isolated in 23% yield.

In these reactions, the alkoxy group on the R moiety of substrates promoted the preferential introduction of RCO-moiety into the product; interaction between alkoxy group and samarium could select RCO moiety in preference to EtOCO moiety to give the desired products (ref. 24). Thus, β,δ-diketoesters can be obtained from easily accessible bromoacetate, mixed acid anhydrides and samarium diiodide.

The structures of organosamarium intermediates are estimated by the regioselective reaction of 3-oxobutanoate moiety with D₂O. As described earlier, the intermediate is stable under −50 °C, but the thermal isomerization was observed between −50 and 0 °C. Quenching the intermediate under −50 °C with DCl in D₂O afforded ethyl 4-deuterio-3-oxobutanoate (30) exclusively (>80% deuterated). In contrast, after warming a THF solution of the intermediate from −50 to 0 °C, quenching it with DCl in D₂O afforded ethyl 2-deuterio-3-oxobutanoate (31, >80% deuterated) almost quantitatively. NMR studies on the reaction mixture supported the above results.
Based on regioselectivity of the DCI-quenching reaction and NMR determinations, Sm-mediated reaction of α-bromo esters can be shown in Scheme 9. The initial reactive species obtained from ethyl bromoacetate can react with ester moiety to give ethyl 4-bromo-3-oxobutanoate, which reacts with SmI$_2$ affording dimeric intermediate 15. Thus formed intermediate could be stabilized by intramolecular coordination of oxygen to Sm resulting in the loss of reactivity towards ester moiety. The intermediate isomerizes to intermediate 16, probably via intra- or intermolecular rearrangement of samarium moiety from carbon to oxygen, that did not give any adduct with aldehydes or ketones (ref. 25).

Acknowledgements. Financial support from the Ministry of Education, Science, Culture and Sports, Japan (Grant-in-Aid 06403025, 07230247, 07651053, 10125217, 10132227) are acknowledged.

References and Notes


(4) Only a limited number of examples were reported that involve the relatively stable intermediary organosamarium species in THF which were able to be labelled by quenching D$_2$O. a) Kagan, H. B.; Collin, J.; Namy, J. L.; Bied, C.; Dallemer, F.; Lebrun, A. J. Alloys Comp. 1993, 192, 191. b) Namy, J. L.; Collin, J.; Bied, C.; Kagan, H.B. Synlett 1992, 733. c) Under an
1998, 37, 824.
(8) Iodoalkylation of carbonyl compounds using SmI₂ and gem-dihaloalkane has not been reported
except for iodomethylation. The structure of the intermediary species is not clear, but assumed to
be α-iodoethyldisamarium diiodide. Iodomethylation with diiodomethane and SmI₂: Imamoto, T.;
Yamaguchi, M. ibid. 1986, 27, 3891.
(9) Although the yield of the iodohydrin increased by the use of excess diiodide and SmI₂,
diastereoselectivity was unchanged. The results of the yields and diastereoselectivities (one
diastereomer / the rest of all possible diastereomers) under various equivalents of the reagent:
31% (99 / 1) (pentanal: 1.0 mmol, diiodide: 1.0 mmol, SmI₂: 2.0 mmol); 47% (99 / 1) (1.0
mmol, 2.0 mmol, 4.0 mmol); 62% (1.0 mmol, 3.0 mmol, 6.0 mmol). In the case of the use of
excess reagent, 1-iodo-2-phenylpropane and 2,5-diphenyl-3-hexene were observed as by-
products. The reduction of diastereotopic iodide may not proceed selectively and unfavorable
intermediate decomposed into these by-products.
(10) A treatment of aldehyde with 1,1-dibromoethane and SmI₂ did not afford halohydrine. A
reduction of aldehyde into alcohol was detected. An addition of catalytic amount of Co(II)
compound allowed the addition to proceed and gave iodohydrin with syn selectivity: Yoshioka,
(11) The results show that a 1,1-diiodoalkane can be used as a precursor of chiral α-iodoalkyl
building block. Since any evidence of the formation of chiral α-iodoalkylsamarium species has
not been obtained, the reaction can be explained either by enentioselective formation of α-
iodoalkylsamarium species by the reduction with SmI₂-chiral aldehyde complex system or by
facile racemization of α-iodoalkylsamarium species under the reaction with chiral aldehyde.
29, 2547; McDougal, P.G.; Condon, B.D. ibid. 1989, 30, 789; Ritter, R.H.; Cohen, T. J.
1994, 35, 5441.
653.
(16) The reason for the failure of kinetic resolution was supposed that the intermediate 9 might form
aggregates consisting from a pair of enantiomers. The ligation that breaks these aggregates
makes the kinetic resolution possible; see text.


(22) The dianion, obtained from ethyl acetoacetate and lithium diisopropylamide, acted as a strong base to β-tetralone and resulted in an enolization.


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