

Synthesis of Vicinal Bis(alkylthio) Derivatives by Reductive Coupling of Dithioacetals Derived from Aromatic Aldehydes with Low Valent Titanium Iodide Species

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Reduction of dithioacetals derived from aromatic aldehydes with low valent titanium iodide species in situ formed by treatment of titanium(IV) iodide with zinc in a mixed solvent of dichloromethane and pivalonitrile at room temperature afforded coupling products, vicinal bis(alkylthio) derivatives, in good to high yields.

Synthesis of pinacols by reductive coupling of carbonyl compounds is an important tool for the formation of vicinal diols. Of various reducing reagents, low valent titanium compounds proved to be particularly effective and are being studied intensively.¹ Recently, it was reported from our laboratory that a newly utilized low valent titanium iodide species in situ formed by treating titanium(IV) iodide with copper was an effective reductant to afford various vicinal diols from various aromatic and aliphatic aldehydes in good to high yields with good to high diastereoselectivities under mild conditions.² Also from our laboratory in 1978, it was reported³ that various vicinal dialkoxy derivatives or olefins were obtained by treating acetals, which were usually considered as protected aldehydes under basic conditions,⁴ with low valent titanium chloride species prepared from titanium(IV) chloride and lithium aluminum hydride in THF at room temperature.

In order to apply the newly utilized low valent titanium iodide species to various synthetic reactions, a reductive coupling of dithioacetals, the protected aldehydes,⁴ was focused as our next target. Meanwhile, Takeda and co-workers reported a preparative method of titanium-carbene complexes generated by reductive desulfurization of the two alkylthio groups of the dithioacetals with low valent titanocene species $\text{Cp}_2\text{Ti}[\text{P}(\text{OEt})_3]_2$.⁵ The above complexes have effectively been employed to date in many useful synthetic reactions. To the best of our knowledge, however, there are no examples reported on the formation of coupling products, vicinal bis(alkylthio) derivatives, from dithioacetals by desulfurization of one of the alkylthio groups.⁶ In this communication, we would like to report an efficient method for the preparation of various vicinal bis(alkylthio) derivatives by reductive coupling of dithioacetals derived from aromatic aldehydes with low valent titanium iodide species.

At first, reductive coupling of benzaldehyde diethyl dithioacetal was tried by using reactive low valent titanium iodide species which were generated by treating titanium(IV) iodide with copper or zinc⁷ in a mixed solvent of dichloromethane and pivalonitrile at room temperature (summarized in Table 1). In the case of using copper, the desired vicinal bis(alkylthio) derivative, 1,2-bis(ethylthio)-1,2-diphenylethane, was not obtained at all, while it afforded the desired products in moderate to good yields by way of reductive elimination of one alkylthio group when low valent titanium iodide species generated from more than double molar amounts of zinc and titanium(IV) iodide were used (entries

Table 1. Reductive coupling reaction of benzaldehyde diethyl dithioacetal promoted by low valent titanium iodide species

Entry	M ¹ (x)	M ² (y)	Temp. / °C	Time / h	Yield ^a / %	[dl / meso] ^b
1	none	none	rt	6	N. R.	[-]
2	Cu (2.0)	none	rt	6	N. R.	[-]
3	Zn (1.0)	none	rt	1	N. R.	[-]
4	Zn (2.0)	none	rt	1	36	[51 / 49]
5	Zn (2.0)	none	rt	16	61	[52 / 48]
6	Zn (3.0)	none	rt	1	70	[51 / 49]
7	Zn (5.0)	none	rt	1	67	[53 / 47]
8	Zn (2.0)	Zn (1.0)	rt	1	52	[51 / 49]
9	Zn (2.0)	Zn (2.0)	rt	1	95	[49 / 51]
10	Zn (2.0)	Zn (3.0)	rt	1	91	[50 / 50]
11	Zn (1.0)	Zn (2.0)	rt	1	75	[52 / 48]
12	Zn (3.0)	Zn (2.0)	rt	1	86	[51 / 49]
13	Zn (5.0)	Zn (2.0)	rt	1	95	[51 / 49]
14	Zn (2.0)	Cu (2.0)	rt	6	N. R.	[-]
15	Zn (2.0)	Mg (2.0)	rt	6	17	[46 / 54]
16	Zn (2.0)	Mn (2.0)	rt	6	trace	[-]
17	Zn (2.0)	Zn (2.0)	0	1	94	[51 / 49]
18	Zn (2.0)	Zn (2.0)	-23	9	27	[52 / 48]
19	Zn (2.0)	Zn (2.0)	-78	9	23	[51 / 49]

Reaction conditions: Low valent titanium iodide species ($[\text{TiIn}]$) was prepared by $\text{TiI}_4 / \text{M}^1 / \text{BuCN} = 1.0 / x / 4.0$ mmol in CH_2Cl_2 (0.10 M-Ti). Dithioacetal / $[\text{TiIn}] / \text{M}^2 = 0.3 / 0.3 / 0.3$ y mmol in CH_2Cl_2 (4.0 mL). ^aIsolated yield. ^bRatios were determined by ¹H NMR analysis of crude product mixture.

1–7). To improve the reactivity of low valent titanium iodide species, more reliable preparative method was then investigated. The reaction proceeded successfully to afford the corresponding coupling product in high yield when zinc was added anew to the supernatant solution of zinc-treated low valent titanium iodide species. The resulted solution was then applied to the reductive coupling,⁸ and consequently, the double molar amounts of the respective initial and additional zinc with titanium(IV) iodide promoted the reaction most effectively (entries 8–13).⁹ When other metals⁷ were used in place of the additional zinc, however, the yields of vicinal bis(alkylthio) derivative remained rather low (entries 14–16). Concerning temperatures, the reaction proceeded smoothly at 0 °C or above (entries 17–19).

Next, reductive coupling reactions of various other dithioacetals derived from aromatic aldehydes using low valent titanium iodide reducing system were examined based on the above results (summarized in Table 2). With regard to the substituents on phenyl group of dithioacetals, *para*-substituted dithioacetals except CF_3 -substituted one coupled smoothly to

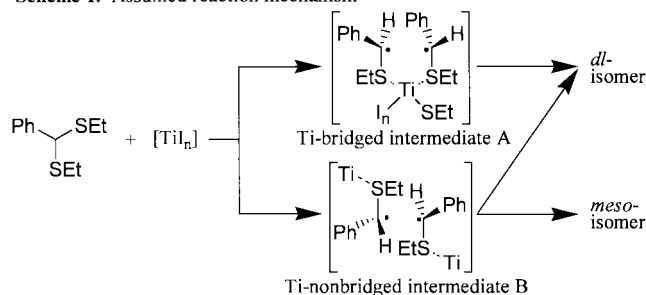
Table 2. Reductive coupling reaction of various dithioacetals derived from aromatic aldehydes promoted by low valent titanium iodide species

$\text{TiI}_4 + \text{Zn (2.0 mol. amt.)} \xrightarrow[\text{rt, 3 h}]{\text{CH}_2\text{Cl}_2-\text{tBuCN}} [\text{TiI}_n]$					
$\text{X-C}_6\text{H}_4\text{-C(R')SR} \xrightarrow[\text{CH}_2\text{Cl}_2, \text{rt}]{[\text{TiI}_n] + \text{Zn (2.0 mol. amt.)}} \text{X-C}_6\text{H}_4\text{-C(R')SR-C(R')SR-C}_6\text{H}_4\text{-X}$					
Entry	X	R	R'	Time / h	Yield ^a / % [dl / meso] ^b
1	H	Et	H	1	95 [49 / 51]
2	<i>o</i> -Cl	Et	H	1	78 [62 / 38]
3	<i>o</i> -Cl	Et	H	14	89 [63 / 37]
4	<i>m</i> -Cl	Et	H	15	70 [50 / 50]
5	<i>p</i> -Cl	Et	H	1	96 [49 / 51]
6	<i>o</i> -OMe	Et	H	1	70 [55 / 45]
7	<i>o</i> -OMe	Et	H	5	75 [55 / 45]
8	<i>m</i> -OMe	Et	H	10	83 [50 / 50]
9	<i>p</i> -OMe	Et	H	1	97 [49 / 51]
10	<i>p</i> -Me	Et	H	1	92 [49 / 51]
11	<i>p</i> -CF ₃	Et	H	8	63 [52 / 48]
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12	H	Ph	H	1	80 [43 / 57]
13	H	<i>t</i> -Bu	H	1	82 [50 / 50]
14	H	<i>c</i> -Hex	H	1	83 [56 / 44]
15	H	Et	Me	1	90 [50 / 50]

Reaction conditions: Low valent titanium iodide species ([TiI_n]) was prepared by TiI₄ / Zn / ^tBuCN = 1.0 / 2.0 / 4.0 mmol in CH₂Cl₂ (0.10 M-Ti). Dithioacetal / [TiI_n] / Zn = 0.3 / 0.3 / 0.6 mmol in CH₂Cl₂ (4.0 mL). ^aIsolated yields. ^bRatios were determined by ¹H NMR analysis of crude product mixture.

afford the corresponding vicinal bis(alkylthio) derivatives in high yields, and also, the *ortho*- and *meta*-substituted dithioacetals reacted likewise to give the coupling products in good yields (entries 1–11). Then, the influence of alkylthio group on the present reaction was examined and the vicinal bis(alkylthio) derivatives were obtained in high yields irrespective of the substituents (entries 12–14). Furthermore, the reductive coupling of dithioacetal derived from acetophenone proceeded smoothly as well to afford the corresponding coupling product in high yield (entry 15) while dithioacetals derived from aliphatic aldehydes did not react under these reaction conditions.

As illustrated in Scheme 1, the reaction is assumed to proceed as follows: there are two reaction pathways of forming coupling products, namely, via a titanium-bridged intermediate A and a titanium-nonbridged intermediate B generated by reductive desulfurization of an alkylthio group. Of the two possibilities, the formation of *dl*-isomer via intermediate A might not take precedence because the sulfur–titanium–sulfur bridging interaction (coordination and coordination) is relatively weak compared with the oxygen–titanium–oxygen bridging interaction (by σ -bond and coordination) suggested in reductive

Scheme 1. Assumed reaction mechanism

coupling of aldehydes.^{2a,b} On the other hand, *meso*-isomer is considered to be preferentially produced when symmetry of intermediate B is retained. However, the symmetry is readily lost before coupling because of the poor electronic repulsion of alkylthio groups in α -(alkylthio)benzyl radicals different from the cases shown in the coupling of aldehydes. This consideration explains that a mixture of *dl*- and *meso*-diastereomers are produced by the present reaction.

Thus, reductive coupling reaction of dithioacetals derived from aromatic aldehydes was effectively achieved by the in situ formed low valent titanium iodide species in a mixed solvent of dichloromethane and pivalonitrile under mild conditions.

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- Copper powder was purchased from Soekawa Chemical Co., Ltd. and used without any treatment. Zinc powder was activated before use with 1 mol/L aqueous HCl and washed with H₂O and ether, then dried under vacuum at 100 °C. Manganese was dried under vacuum at 100 °C.
- A typical reaction procedure for the reductive coupling of benzaldehyde diethyl dithioacetal corresponding to Table 1, entry 8: to a reddish brown suspension of titanium(IV) iodide (1.11 g, 2.0 mmol) and zinc powder (0.26 g, 4.0 mmol) in dichloromethane (19.11 mL) was added pivalonitrile (0.89 mL, 8.0 mmol) under argon atmosphere. The color was changed to dark brown and the mixture was stirred for 3 h at room temperature. Resulted dark brown supernatant solution (3.0 mL, 0.3 mmol Ti) was added to additional zinc powder (0.039 g, 0.6 mmol) and the mixture was stirred for another 30 min. Then, a solution of benzaldehyde diethyl dithioacetal (0.064 g, 0.3 mmol) in dichloromethane (1.0 mL) was added. The reaction mixture was stirred for 1 h, and then phosphate buffer solution (pH = 7) was added. The mixture was filtered and extracted with CH₂Cl₂, and the organic layer was washed with saturated aqueous NaCl, dried over Na₂SO₄. After filtration and concentration, the crude product was purified by thin layer chromatography to afford the desired vicinal bis(alkylthio) derivative (0.043 g, 95% yield).
- When titanium(IV) bromide and titanium(IV) chloride were employed in place of titanium(IV) iodide using double molar amounts of the respective initial and additional zinc, the yields of vicinal bis(alkylthio) derivative a little decreased (82% [*dl* / *meso* = 49 / 51] and 92% [*dl* / *meso* = 50 / 50], respectively). On the other hand, when the procedure of ref 3 was applied, the reaction did not proceed at all.