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$Ti(O\text{-}i\text{-}Pr)_4/Me_3SiCl/Mg$-Mediated Reductive Cleavage of Sulfonamides and Sulfonates to Amines and Alcohols

Noriaki Shohji, Tsuyoshi Kawaji, and Sentaro Okamoto*

Department of Material and Life Chemistry, Kanagawa University, 3-27-1 Rokkakubashi, Kanagawa-ku, Yokohama 221-8686, Japan

okamos10@kanagawa-u.ac.jp

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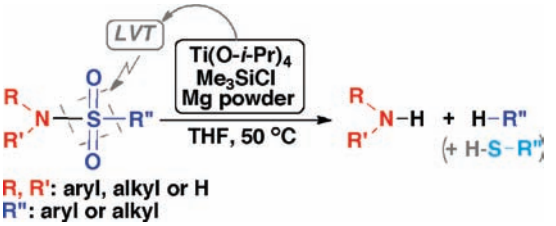
ABSTRACT



A low-valent titanium generated *in situ* from $Ti(O\text{-}i\text{-}Pr)_4$, Me_3SiCl, and Mg powder in THF reacted with aryl- and alkyl-sulfonamides of aryl and alkyl amines in a reductive N–S/S–O/S–C bond cleaving pathway to provide the corresponding amines and hydrocarbons (and thiols) derived from the sulfonyl moiety. The reagent could also cleave sulfonates to the corresponding alcohols.

Protection/deprotection of amine functionality is of importance for synthesizing nitrogen-containing compounds involving biologically active substances. One of the most versatile protecting groups for amines is based on formation/disconnection of sulfonamides,[1] which are readily prepared, often bring an easiness of purification, and have reasonable stability under various reaction conditions. However, the requirement of the robust conditions for their deprotection is a major disadvantage. The traditional way is hydrolysis with strong acids such as HBr or $HClO_4$. Reductive cleavage through a single-electron transfer (SET) process from alkali metals is commonly used. However, these suffer from harsh reaction conditions, which often affect other functional groups present in the substrate. The methods reported to mediate *p*-toluenesulfonamide (Ts-amide) cleavage under milder conditions are as follows: electrolysis,[2] $Ni(acac)_2/i\text{-}PrMgCl$,[3] $n\text{-}Bu_3SnH/AIBN$,[4] $TiCl_4/Zn$,[4a] $TiCl_3/Li$,[5a] mischmetal/$TiCl_4$,[5b] Mg/MeOH,[6] Mg/Me_3CoLi,[7] alkali metals on silica,[8] TMSI,[9] SmI_2,[10] photolysis,[11] TBAF,[12] and phase-transfer catalyst.[13] However, many of these methods are not necessarily general

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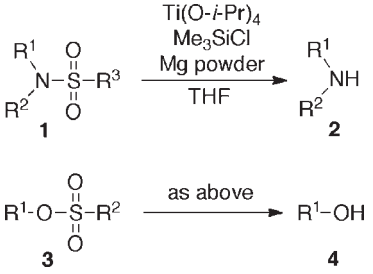
and/or require toxic, expensive reagents and special equipment.

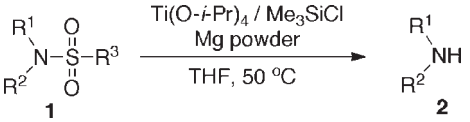
Recently, we have developed a new protocol for deallylation and depropargylation of allyl and propargyl ethers to the parent alcohols by employing a low-valent titanium (LVT)[14] derived *in situ* from Ti(O-*i*-Pr)$_4$, Me_3SiCl, and Mg powder in THF.[15] The reaction proceeded with a stoichiometric or catalytic amount of the LVT reagent at room temperature. We now found that a Ti(O-*i*-Pr)$_4$/Me_3SiCl/Mg reagent reacts with sulfonamides **1** to produce the corresponding amines **2** in good to excellent yields, where the sulfonyl moiety was reduced to hydrocarbons and/or thiols (Scheme 1). The reagent also cleaved sulfonates **3** to **4**.

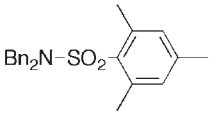
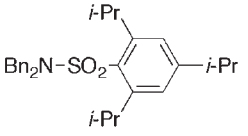
Scheme 1. Low-Valent Titanium-Mediated Cleavage of Sulfonamides and Sulfonates



The results of the reaction of amides **1** with various substituents on the nitrogen as well as on the sulfur atom are summarized in Table 1. As revealed from runs 1−8, sufonamides of dialkylamine (dibenzylamine) with a variety of sulfur substituents (R^3) reacted with a Ti(O-*i*-Pr)$_4$/Me_3SiCl/Mg (1/1.5/5) reagent to provide dibenzylamine in good to excellent yields: Amides with a bulky substituent were cleaved efficiently (run 3−5). It was noteworthy that the method could cleave aliphatic sulfonamides as shown in runs 7, 8 and 12, albeit in somewhat low yield due to slow reaction rate. In addition to sulfonamides of aliphatic secondary amines, those of aromatic secondary and primary amines (aniline derivatives, run 9 and 10) as well as aliphatic primary amines (run 11) were good substrates. Thus, the method could cleave a variety of sulfonamides reductively to amines, although the results of run 13 show a limitation of the method that aliphatic sulfonamides of aliphatic primary amines could not react.

Table 1. Reductive Cleavage of Various Sulfonamides Mediated by Ti(O-*i*-Pr)$_4$/Me_3SiCl/Mg[a]



run	substrate **1**	h[b]	yield of **2**, %[c]
1	Bn_2N-SO_2-*p*-Tol (**1a**)	12	94[d]
2	Bn_2N-SO_2-Ph (**1b**)	12	82, 72[d]
3	 (**1c**)	24	79, 60[d]
4	 (**1d**)	12	82, 80[d]
5	Bn_2N-SO_2-1-Naphthyl(**1e**)	12	82, 68[d]
6	Bn_2N-SO_2-C_6H_4-*p*-Cl (**1f**)	12	87[d]
7	Bn_2N-SO_2-CH_3 (**1g**)	24	66, 64[d,e]
8	Bn_2N-SO_2-*n*-C_8H_{17} (**1h**)	24	64, 43[d,f]
9	Ph(^{n}Bu)N-SO_2-*p*-Tol (**1i**)	24	83
10	*p*-(^{n}Bu)C_6H_4(H)N-SO_2-*p*-Tol (**1j**)	12	100, 74[d]
11	$PhCH_2CH_2$(H)N-SO_2-*p*-Tol (**1k**)	12	69
12	*p*-(^{n}Bu)C_6H_4(H)N-SO_2-CH_3 (**1l**)	24	48, 29[g]
13	$PhCH_2CH_2$(H)N-SO_2-*n*-C_8H_{17} (**1m**)	24	No reaction

[a] A mixture of **1** (1.0 mmol), Ti(O-*i*-Pr)$_4$ (1.0 mmol), Me_3SiCl (1.5 mmol), and Mg powder (5.0 mmol) in THF (5 mL) was stirred at 50 °C. [b] Reaction time. [c] Unless otherwise indicated, ^{1}H NMR yield was determined using an internal standard. [d] Isolated yield. [e] 34% of **1g** remained. [f] 13% of **1h** remained. [g] 45% of **1l** remained.

The reaction of non- and monosubstituted benzenesulfonamides (runs 1, 2 and 6) gave a mixture of the corresponding thiols and hydrocarbons as co-products. Meanwhile, interestingly, trisubstituted phenyl and naphthalene-1-sulfonamide derivatives were reduced to nearly completely produce the corresponding trisubstituted benzenes or naphthalene (runs 3−5). As illustrated in Scheme 2, after aqueous workup of the reaction mixture derived from **1d**

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and **1n**, 1,3,5-triisopropylbenzene and 1-dimethylaminonaphthalene were respectively obtained quantitatively. Thus, with choosing an appropriate sulfonyl group and reaction conditions, the method can provide a *non- (or less-)smelling deprotection procedure suitable for large-scale manufacturing* in certain cases. It was found that aliphatic sulfonamides such as **1h** (run 8) gave the corresponding thiol (35%) and *n*-hexadecane (8%), the latter of which might form through coupling of *n*-octyl radical intermediates.

Scheme 2. Reaction of Aromatic Sulfonamides with Ti(O-*i*-Pr)$_4$/Me$_3$SiCl/Mg

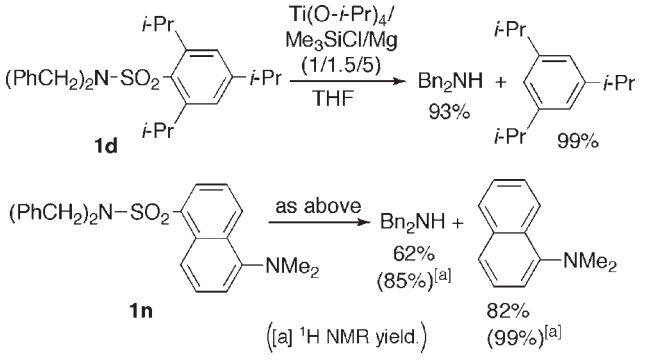
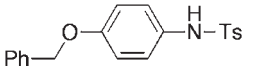
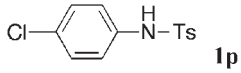
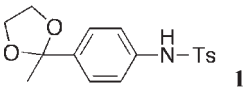
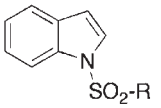
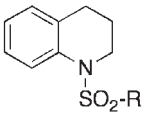
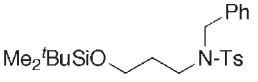


Table 2 shows the representative results of the reaction of tosylamides derived from cyclic and functionalized amines. The amides of anilines with an electron-donating and -withdrawing group were good substrates (runs 1−3). The N−S bond in sulfonamides of indole and hydroquinoline was readily cleaved (runs 4−7). Functional groups such as benzyl ether (run 1), aromatic chloride (run 2), ketal (run 3), and silyl ether (run 8) were tolerated under the conditions. It is noteworthy that the reaction conditions retained benzyl ethers of aliphatic and aromatic alcohols, which may be disconnected under the conditions by SET from alkali metals (Birch conditions). As well as tosylamides, mesitylamides (runs 5 and 7) could smoothly be deprotected.

As shown in Scheme 3, a Ti(O-*i*-Pr)$_4$/Me$_3$SiCl/Mg reagent could also cleave the O−S bond of sulfonates. *p*-Toluene sulfonate of 2-naphthol (**3a**) reacted with the reagent at 50 °C for 12 h to provide 2-naphthol in good yield. The reaction of methanesulfonate derivative **3b** also provided 2-naphthol, albeit in low yield due to the slow reaction rate. Phenol tosylates **3c** and **3d** smoothly reacted to furnish the corresponding phenols without any damage of their functional groups. Meanwhile, the reaction of tosylate of 1-octanol (**3e**) with Ti(O-*i*-Pr)$_4$/Me$_3$SiCl/Mg (1/1.5/5) yielded desired 1-octanol (**4e**) and *p*-tolyl *n*-octyl sulfide (**7e**) in a ratio of 71:27. The results can be explained by assuming that the thiolate anion, *p*-Tol-S$^-$, generated *in situ*, reacts competitively with remaining **3e**. To avoid this, excess amount of Me$_3$SiCl (4 equiv) was used, expecting the formation of non-nucleophilc silyl ether of the thiol, *p*-Tol-S-SiMe$_3$. Thus, the reaction gave quantitatively

Table 2. Reaction of Sulfonamides **1** of Cyclic and Functionalized Amines[a]

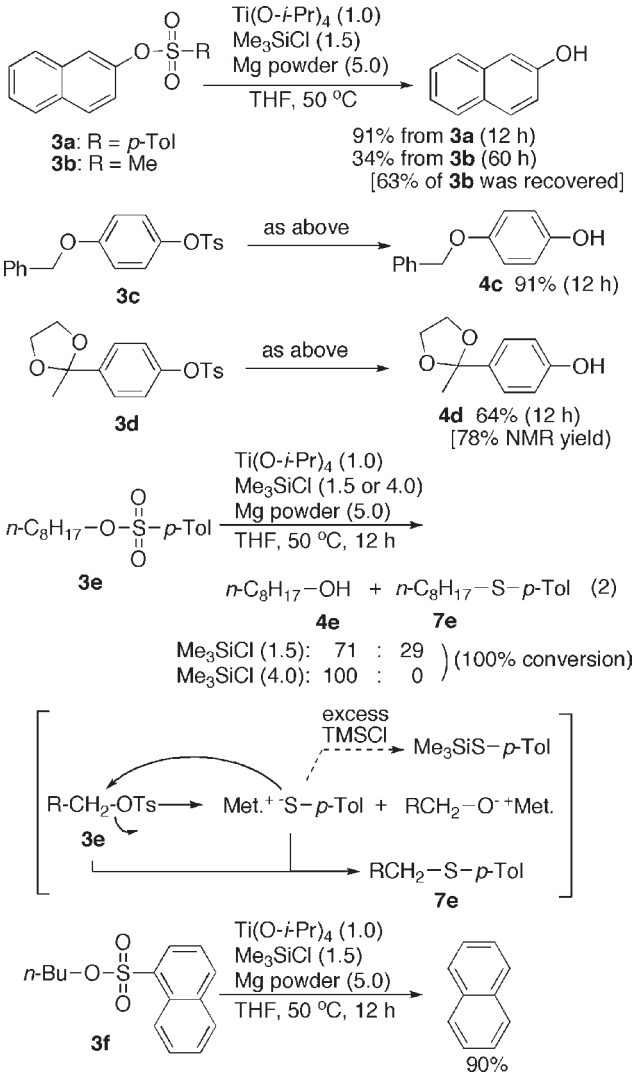
run	substrate **1**	yield of **2**, %[b]
1	 **1o**	90
2	 **1p**	49 (67)[c]
3	 **1q**	74
		
4	**1r** R = 4-tolyl	75
5	**1s** R = mesityl	100
		
6	**1t** R = 4-tolyl	79
7	**1u** R = mesityl	93
8	 **1v**	100

[a] A mixture of **1** (1.0 mmol), Ti(O-*i*-Pr)$_4$ (1.0 mmol), Me$_3$SiCl (1.5 mmol), and Mg powder (5.0 mmol) in THF (5 mL) was stirred at 50 °C for 12 h. [b] Isolated yield. [c] NMR yield.

1-octanol but not the sulfide. Meanwhile, the reaction of 1-naphthalene sulfonate of primary alcohol (**3f**) produced naphthalene nearly quantitatively, where C−S cleavage occurred faster than thiolate formation. This may also provide a method for desulfonation of aromatic sulfonic acid derivatives.

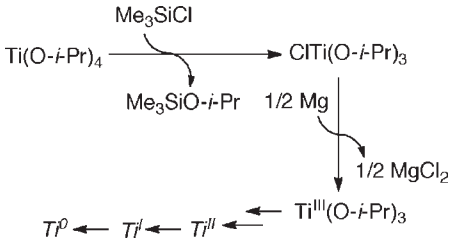
The reported LVT reagents utilized for deprotection of sulfonamides have been prepared prior to the reaction by reduction of TiCl$_4$ or TiCl$_3$ with Zn,[4a] Li,[5a] or mischmetal[5b] in THF under refluxing conditions, which are heterogeneous colloidal slurries of activated titanium. The cleavage of sulfonamides needed an excess amount (3−4 equiv) of these reagents. Meanwhile, the present method could be performed simply by mixing the substrate and the reagent comprising 1 equiv of Ti(O-*i*-Pr)$_4$ in THF at 50 °C, the mixture of which remains homogeneous, except for Mg powder, to all appearances. It can be postulated that a LVT(s) could be generated from Ti(O-*i*-Pr)$_4$/Me$_3$SiCl/Mg

Scheme 3. Reaction of Sulfonates with $Ti(O\text{-}i\text{-}Pr)_4/Me_3SiCl/Mg$



through the following reaction pathway: (i) titanium isopropoxide reacts with silyl chloride to afford a titanium chloride compound(s) and $i\text{-}PrOSiMe_3$, (ii) the resulting titanium chloride(s) can be reduced by the reaction with Mg to generate a lower-valent species, (iii) these processes may be repeated with the gradual generation of Ti(III) and lower-valent titanium species (Scheme 4). These processes might enable a facile generation of LVT(s) and an operationally simple procedure. The fact that the reaction did not proceed in the absence of Me_3SiCl may suggest that the generation of $Cl_nTi^{IV}(O\text{-}i\text{-}Pr)_{4-n}$ might be essential to reduction of the titanium by Mg.[16]

Scheme 4. Generation of LVTs



In conclusion, we have developed a mild protocol for deprotection of sulfonamide to amines, which was mediated by a low-valent titanium reagent, $Ti(O\text{-}i\text{-}Pr)_4/Me_3SiCl/Mg$, in THF at 50 °C. The method can be used for N–S cleavage of a wide range of aromatic and aliphatic sulfonamides with a reasonable functional compatibility. Choice of the appropriate sulfonyl groups and reaction conditions enables a non- (or less-)smelling deprotection procedure, which may be useful for a large-scale production in certain cases, by co-producing the corresponding hydrocarbon material instead of a thiol. The reagent could also cleave sulfonates to the corresponding alcohols.

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Supporting Information Available. Detailed experimental section including experimental procedures and spectroscopic data of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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