A Facile Route to the Deprotection of Sulfonate Esters and Sulfonamides with Low Valent Titanium Reagents

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Abstract: A novel method for the cleavage of *N/O*-tosyl bonds by low-valent titanium is reported. TBDPS ether, THP ether, and olefin are found to be compatible under the reaction conditions.

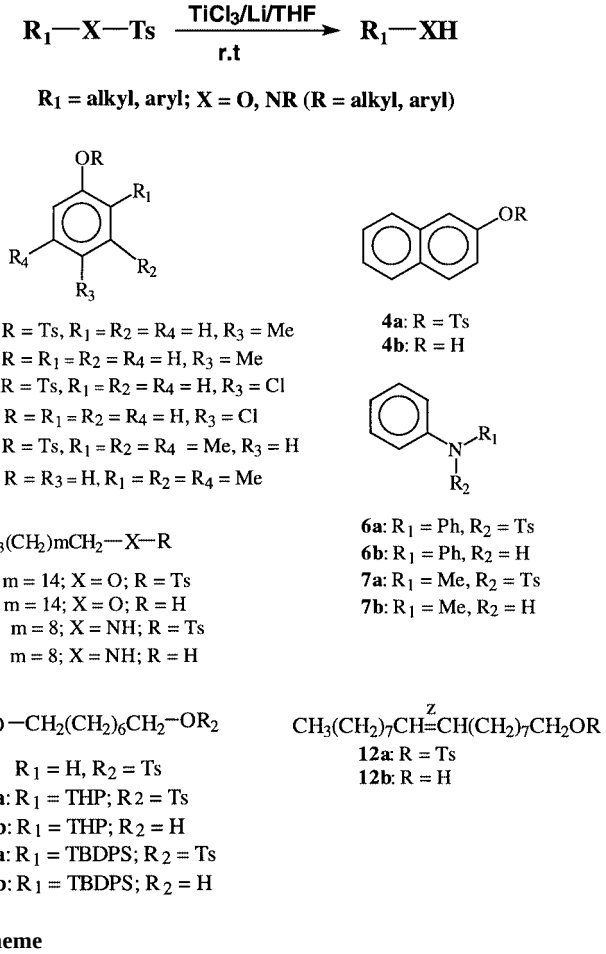
Key words: *p*-toluenesulfonate ester, *p*-toluenesulfonamide, deprotection, low-valent titanium, TBDPS ether, THP ether

Development of mild and selective methods for protection of functional groups and deprotection of protected derivatives continue to be significant aspects in the synthesis of polyfunctional molecules. Alcohols and amines are often protected by *p*-toluenesulfonyl (Ts) group due to the crystalline nature of these derivatives. However, methods for their deprotection usually suffer from poorer yields or harsh reaction conditions.[1] Therefore, there has been considerable interest in the development of facile methods for the deprotection of tosylate esters and tosylamides. Consequently, some useful reagents such as TMsCl/NaI,[2] SmI_2,[3] TBAF,[4] etc. have been developed for this purpose in recent years. This paper reports a new protocol for the facile deprotection of tosylate esters and tosylamides using low-valent titanium reagents (Scheme) at ambient temperature.

Reductive deoxygenation of carbonyl compounds to olefins under the influence of low-valent titanium (LVT) reagents, commonly referred to as "McMurry reaction", has been tremendously exploited by synthetic chemists since its debut in the early 1970s.[5] In our continuing exploration of the synthetic utility of LVT reagents, we have discovered that these reagents are also equally efficient in the deprotection of benzyl/allyl/propargyl ethers and amines[6] (by SET mechanism). As an extension of this work, it was of interest to investigate the effect of LVT reagents on other SET mediated reactions.

Since the cleavage of *O*-tosyl and *N*-tosyl bonds by Na/liquid ammonia is reported,[7] these bonds, in principle, should be cleaved by LVT reagents which are rich source of electrons. Thus, a model reaction was carried out with 4-methyl-(4-methylphenylsulfonyloxy)benzene (**1a**) and LVT reagent (prepared from $TiCl_3$-Mg-THF) under refluxing conditions (18 hours) when a mixture of the deprotected product **1b** (32%) along with the starting material **1a** (48%) was isolated (Table, entry 1). The result was encouraging albeit the yield of the reaction was modest. Earlier, we have observed that the activity of LVT reagents largely depends on their method of preparation (reducing metal, solvent, external ligands, etc.).[8] Keeping this in view, other LVT reagents were used to improve the yield of the above reaction. It was observed that with LVT reagent (prepared from $TiCl_3$-Li-THF), **1a** underwent complete deprotection to yield **1b** in good yield (76%) under refluxing conditions (Table, entry 2). Moreover, a comparable yield (75%) of **1b** was also achieved when the reaction was carried out at ambient temperature (Table, entry 3). These results are in contrast to the reported compatibility of tosylate esters with LVT reagents.[9] Based on the above result, subsequent studies were carried out with LVT reagent generated from $TiCl_3$-Li-THF.

To explore the synthetic scope of this LVT reagent, various other substrates were used. Thus, 4-chloro-(4-methylphenylsulfonyloxy)benzene (**2a**), 2,3,5-trimethyl-(4-methylphenylsulfonyloxy)benzene (**3a**) and 2-(4-



Scheme

Table Deprotection of Tosylate Esters and Tosylamides with Low-Valent Titanium Reagent

Entry	Substrate	Reagent (Conditions)	Product (% Yield)[a]
1	**1a**	$TiCl_3$-Mg-THF (reflux, 18 h)	**1b** (32)[b]
2	**1a**	$TiCl_3$-Li-THF (reflux, 18 h)	**1b** (76)
3	**1a**	$TiCl_3$-Li-THF (25 °C, 18 h)	**1b** (75)
4	**2a**	$TiCl_3$-Li-THF (25 °C, 18 h)	**2b** (83)
5	**3a**	$TiCl_3$-Li-THF (25 °C, 18 h)	**3b** (91)
6	**4a**	$TiCl_3$-Li-THF (25 °C, 18 h)	**4b** (61)
7	**5a**	$TiCl_3$-Li-THF (25 °C, 18 h)	**5b** (67)
8	**6a**	$TiCl_3$-Li-THF (25 °C, 18 h)	**6b** (72)
9	**7a**	$TiCl_3$-Li-THF (25 °C, 18 h)	**7b** (78)
10	**8a**	$TiCl_3$-Li-THF (25 °C, 18 h)	**8b** (43)
11	**10a**	$TiCl_3$-Li-THF (25 °C, 18 h)	**10b** (73)
12	**11a**	$TiCl_3$-Li-THF (25 °C, 18 h)	**11b** (76)
13	**12a**	$TiCl_3$-Li-THF (25 °C, 18 h)	**12b** (68)

[a] Isolated yield.
[b] 48% of **1a** was recovered.

methylphenylsulfonyloxy)naphthalene (**4a**) underwent smooth deprotection in good to high yields (Table, entries 4−6) with LVT reagent. Similarly, aliphatic tosylate ester such as 1-(4-methylphenylsulfonyloxy)hexadecane (**5a**) underwent facile deprotection to **5b** in good yield (Table, entry 7).

Influence of LVT on sulfonamides was also investigated. Thus, *N*,*N*-diphenyl-4-methylbenzenesulfonamide (**6a**) and *N*-methyl-*N*-phenyl-4-methylbenzenesulfonamide (**7a**) could be easily deprotected with LVT to give the amines **6b** and **7b**, respectively, in good yields (Table, entries 8 and 9). Similarly, aliphatic sulfonamide *N*-decyl-4-methylbenzenesulfonamide (**8a**) was deprotected to *n*-decylamine (**8b**) in modest yield (entry 10).

Selectivity in the deprotection of tosyl group in the presence of other functional groups was also investigated. Thus, 1-(4-methylphenylsulfonyloxy)-8-(2-tetrahydropyranyloxy)octane (**10a**) and 1-((1,1-dimethylethyl)diphenylsilyloxy)-8-(4-methylphenylsulfonyloxy)octane (**11a**) underwent facile deprotection to 8-(2-tetrahydropyranyloxy)octan-1-ol (**10b**)[10] and 8-((1,1-dimethylethyl)diphenylsilyloxy)octan-1-ol (**11b**),[11] respectively, in good yields (entries 11 and 12). The *p*-toluenesulfonate ester of oleyl alcohol (**12a**) was deprotected to oleyl alcohol (**12b**) in good yield (entry 13). The above experiments clearly indicate the compatibility of THP ether, TBDPS ether, and olefin functionalities during the cleavage of *O*-Ts bonds with LVT reagent.

In conclusion, a facile route to the hitherto unknown cleavage of *O*-tosyl and *N*-tosyl bonds of tosylate esters and tosylamides with LVT reagent at ambient temperature has been demonstrated. Selective deprotection of tosyl group in the presence of THP ether, TBDPS ether, and olefin was also observed. Thus, the present method further enhances the utility of LVT reagents in organic synthesis.

FT-IR spectra were obtained on a Nicolet spectrophotometer (model 410). ^{1}H NMR were recorded on a Bruker AC 300 (300 MHz) or Varian EM 360 (60 MHz) spectrometer with TMS as internal standard. Microanalyses were performed with a Carlo Erba elemental analyser (model 1110). All reactions were carried out under Ar atm. $TiCl_3$ was obtained from Aldrich Chemical Co. U.S.A. THF was distilled freshly from Na-benzophenone ketyl prior to use. The tosylate esters and tosylamides were prepared according to the literature procedure.[12]

Sulfonate Esters and Sulfonamides; Typical Procedure

A solution of 4-methylphenol (**1b**) (1.08 g, 10 mmol) in $CHCl_3$ (10 mL) was cooled in an ice bath, dry pyridine (1.6 mL, 20 mmol) was added, followed by the addition of *p*-toluenesulfonylchloride (2.29 g, 12 mmol) in small portions. The reaction mixture was stirred at ice temperature and completed after 3 h (monitored by TLC). Ether (30 mL) and H_2O (10 mL) were added, the organic layer was washed successively with 2 N HCl (5 mL), 5% $NaHCO_3$ (5 mL), H_2O, brine, and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude tosylate was crystallised from MeOH to yield **1a**.

4-Methyl-(4-methylphenylsulfonyloxy)benzene (1a)

Colourless solid; yield: 2.3 g, 88%.

Mp: 67−68°C (Lit.[13] mp: 68−69°C).

IR (KBr): ν = 1376, 1175 cm^{-1}.

^{1}H NMR (60 MHz, CCl_4): δ = 2.37 (s, 3H), 2.50 (s, 3H), 6.73−7.80 (m, 8H)

4-Chloro-(4-methylphenylsulfonyloxy)benzene (2a)

Yield: 85%.

Mp: 71°C (Lit.[13] mp: 73°C).

IR (KBr): ν = 1399, 1173 cm^{-1}.

^{1}H NMR (60 MHz, CCl_4): δ = 2.47 (s, 3H), 6.73−7.63 (m, 8H).

2,3,5-Trimethyl-(4-methylphenylsulfonyloxy)benzene (3a)

Yield: 85%.

Mp: 81°C.

IR (KBr): ν = 1364, 1190 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.92 (s, 3H), 2.17 (s, 3H), 2.21 (s, 3H), 2.45 (s, 3H), 6.67 (s, 1H), 6.86 (s, 1H), 7.31 (d, 2H, J = 8 Hz), 7.74 (d, 2H, J = 8.2 Hz).

Anal. Calcd for $C_{16}H_{18}O_3S$: C, 66.2; H, 6.24; S, 11.03. Found: C, 66.5; H, 6.22; S, 10.96.

2-(4-Methylphenylsulfonyloxy)naphthalene (4a)

Yield: 82%.

Mp: 126°C (Lit.[13] mp: 125°C).

IR (KBr): ν = 1377, 1175 cm^{-1}.

^{1}H NMR (60 MHz, CCl_4): δ = 2.40 (s, 3H), 6.90−7.77 (m, 11H).

1-(4-Methylphenylsulfonyloxy)hexadecane[14] (5a)
Yield: 78%.

Mp: 42°C.

IR (KBr): ν = 1359, 1173 cm^{-1}.

^1H NMR (60 MHz, CCl_4): δ = 0.9 (br t, 3H, *J* = 6.5 Hz), 1.20 (s, 28H), 2.37 (s, 3H), 3.83 (t, 2H, *J* = 6 Hz), 7.13 (d, 2H, *J* = 8 Hz), 7.57 (d, 2H, *J* = 8 Hz).

***N*-(4-Methylphenylsulfonyloxy)diphenylamine (6a)**
Yield: 68%.

Mp: 142°C (Lit.[13] mp: 141°C).

IR (KBr): ν = 1357, 1165 cm^{-1}.

^1H NMR (60 MHz, CCl_4): δ = 2.33 (s, 3H), 6.97−7.87 (m, 14H).

***N*-Methyl-*N*-(4-methylphenylsulfonyloxy)aniline (7a)**
Yield: 73%.

Mp: 93°C (Lit.[13] mp: 94°C).

IR (KBr): ν = 1345, 1191 cm^{-1}.

^1H NMR (60 MHz, CCl_4): δ = 2.30 (s, 3H), 3.0 (s, 3H), 6.77−7.37 (m, 9H).

***N*-(4-Methylphenylsulfonyloxy)decylamine (8a)**
Yield: 80%.

Mp: 61°C (Lit.[15] mp: 62−63°C).

IR (KBr): ν = 1327, 1161 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, 3H, *J* = 6.2 Hz), 1.20 (br s, 14H), 1.41−1.43 (m, 2H), 2.42 (s, 3H), 2.92 (q, 2H, *J* = 5.6 Hz), 4.35 (br s, 1H), 7.3 (d, 2H, *J* = 8.0 Hz), 7.74 (d, 2H, *J* = 7.9 Hz).

8-(4-Methylphenylsulfonyloxy)-1-octanol (9)
Colourless oil, yield: 70%.

IR (film): ν = 3383, 1358, 1176 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.26 (br s, 8H), 1.50−1.64 (m, 4H), 2.44 (s, 3H), 3.61 (t, 2H, *J* = 6.5 Hz), 4.0 (t, 2H, *J* = 6.5 Hz), 7.33 (d, 2H, *J* = 8.0 Hz), 7.78 (d, 2H, *J* = 7.8 Hz).

1-(4-Methylphenylsulfonyloxy)-(9*Z*)-octadecene (12a)
Colourless oil, yield 81%.

IR (film): ν = 1364, 1177 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.86 (br t, 3H), 1.25 (br s, 22H), 1.56−1.63 (m, 2H), 1.99 (br s, 4H), 2.45 (s, 3H), 4.01 (t, 2H, *J* = 6.5 Hz), 5.34 (br s, 2H), 7.34 (d, 2H, *J* = 8.0 Hz), 7.79 (d, 2H, *J* = 8.2 Hz).

1-(4-Methylphenylsulfonyloxy)-8-(2-tetrahydropyranyloxy)octane (10a)
To a solution of **9** (0.9 g, 3 mmol) and PPTS (76 mg, 0.3 mmol) in dry CH_2Cl_2 (10 mL), 3,4-dihydro-2-*H*-pyran (0.3 mL, 3.3 mmol) was added at r.t. After 30 min (monitored by TLC), the solution was diluted with Et_2O (20 mL), and washed with 50% sat. brine (to remove PPTS). The solvent was dried and evaporated to give a crude oil, which on purification by column chromatography (silica gel, hexane/EtOAc, 7:1) yielded **10a** as a colourless oil, yield 91%.

IR (film): ν = 1361, 1199 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.25 (br s, 8H), 1.53−1.83 (m, 10H), 2.45 (s, 3H), 3.34−4.03 (m, 6H), 4.56 (br s, 1H), 7.33 (d, 2H, *J* = 7.4 Hz), 7.78 (d, 2H, *J* = 6.5 Hz).

1-((1,1-Dimethylethyl)diphenylsilyloxy)-8-(4-methylphenylsulfonyloxy)octane (11a)
To a solution of **9** (0.9 g, 3 mmol) in dry DMF (1 mL), TBDPSCl (0.86 mL, 3.3 mmol) and imidazole (409 mg, 6 mmol) were added and the mixture was stirred at 25 °C. After 30 min (monitored by TLC), the solution was diluted with Et_2O (20 mL), quenched with sat. $NaHCO_3$ (2 mL), and extracted with Et_2O (2 × 10 mL). The organic layer was dried and concentrated under reduced pressure to give a thick oil, which on purification by column chromatography (silica gel, hexane/EtOAc, 6:1) yielded **11a** as a colourless oil, yield 93%.

IR (film): ν = 1361, 1177 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.05 (s, 9H), 1.21−1.65 (m, 12H), 2.44 (s, 3H), 3.64 (t, 2H, *J* = 6.5 Hz), 4.00 (t, 2H, *J* = 6.5 Hz), 7.32−7.45 (m, 7H), 7.65−7.81 (m, 7H).

Deprotection of Sulfonate Esters and Sulfonamides; Typical Procedure
A mixture of $TiCl_3$ (1.23 g, 8 mmol) and Li (196 mg, 28 mmol) in dry THF (30 mL) was refluxed (80 °C, 3 h) under Ar. The LVT reagent thus prepared[16] was cooled to ambient temperature (25 °C) and a solution of 4-methyl-(4-methylphenylsulfonyloxy)benzene (**1a**, 524 mg, 2 mmol) in THF (5 mL) was added, and the solution was stirred at 25 °C for 18 h. After completion of the reaction (TLC), the reaction mixture was diluted with Et_2O (10 mL), quenched with aqueous 10% K_2CO_3 (1 mL) and stirred (5 min). The black mixture was passed through Celite, washed with Et_2O (2 × 10 mL), and the collected extract was dried (Na_2SO_4). The solvent was evaporated in vacuo and the crude product was purified by preparative TLC (silica gel; hexane/EtOAc = 19:1) to yield pure 4-methylphenol (**1b**, 162 mg, 75%).

8-(2-Tetrahydropyranyloxy)octan-1-ol[10] (10b)
Yield: 73%.

IR (film): ν = 3397 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.33 (br s, 8H), 1.52−1.82 (m, 10H), 3.34−3.87 (m, 6H), 4.57 (t, 1H, *J* = 2.7 Hz).

8-((1,1-Dimethylethyl)diphenylsilyloxy)octan-1-ol[11] (11b)
Yield: 76%.

IR (film): ν = 3353, 1111, 702 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.04 (s, 9H), 1.25−1.38 (m, 8H), 1.53−1.58 (m, 4H), 3.63–3.67 (m, 4H), 7.37−7.42 (m, 6H), 7.65−7.68 (m, 4H).

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(16) LVT reagent was generated from the reduction of $TiCl_3$ with 3.5 equiv of Li in THF (Rieke's method). $TiCl_3$:substrate was kept at 4:1 in all the cases. Use of less than 4 equiv of $TiCl_3$ with respect to the substrate led to the isolation of unreacted starting material. This could be attributed to the consumption of LVT for further reduction of *p*-toluenesulfonyl group (formed during the cleavage) to the corresponding sulfide. After stirring the reaction mixture at 25 °C for 4 h, TLC showed about 40−50% consumption of the starting materials. No significant improvement in the reaction kinetics was observed by carrying out the reactions at reflux temperature. Therefore, in all cases, the reaction mixture was stirred overnight (18 h) at 25 °C for completion.

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