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# TiCl<sub>4</sub>, Dioxane—A Facile and Efficient System for De-O-Benzylation, De-O-Allylation, and De-O-Xylylation of Phenolic Ethers

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# TiCl<sub>4</sub>, Dioxane—A Facile and Efficient System for De-O-Benzylation, De-O-Allylation, and De-O-Xylylation of Phenolic Ethers

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# ABSTRACT

Simultaneous de-O-xylylation and reductive coupling was observed when 1 equiv. of the dialdehyde 2a/2b was treated with 5 equiv. of each TiCl<sub>4</sub> and Zinc which lead to the development of TiCl<sub>4</sub> in dioxane as a new system for the facile deprotection of phenolic ethers 4a-4d, 5a-5d, and 6a-6c.

Natural product synthesis plays a predominant role in organic synthesis in which protection and deprotection<sup>[1]</sup> occupy indispensable role. The development of new reagent for the deprotection of functional

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groups continues to be a significant aspect in the synthetic chemistry of polyfunctional molecules. In continuation of our studies<sup>[2]</sup> on the synthesis of novel cyclophanes, we recently focused our attention on the synthesis of stilbenophanes **1a** having 4,4'-dioxa-*cis*-stilbene spacer.<sup>[3]</sup> Application of McMurry coupling technology<sup>[4]</sup> for the synthesis of cyclophanes has extensively studied. With a view to synthesize stilbenophane **1a/1b**, 1 mol of the dialdehyde **2a/2b** was treated with 5 equiv. of each TiCl<sub>4</sub> and zinc in dioxane. However treatment of **2a/2b** with TiCl<sub>4</sub>, Zn in dioxane resulted in de-*O*-xylylation and McMurry coupling in one pot to give **3**.



Scheme 1.

The formation of *cis*-stilbene diol **3** from the dialdehyde 2a/2b is a novel observation which opens new dimension in the chemistry of Ti(II) in dioxane solution. We report herein the use of TiCl<sub>4</sub> in dioxane as a new deprotection protocol for benzylic, allylic, and xylylic ethers of phenol and cresol.

There are many reagents available for de-*O*-benzylation such as  $Rh/Al_2O_3$ ,<sup>[5]</sup> Na/NH<sub>3</sub>,<sup>[6]</sup> Ph<sub>3</sub>C<sup>+</sup>BF<sub>4</sub>,<sup>[7]</sup> *t*-BuMgBr,<sup>[8]</sup> dimethyldioxirane,<sup>[9]</sup> Li-naphthanalide,<sup>[10]</sup> NIS followed by hydrolysis,<sup>[11]</sup> CrCl<sub>2</sub>-LiI-Et-*O*-Ac(H<sub>2</sub>O).<sup>[12]</sup> Catalytic hydrogenation<sup>[13]</sup> can be also used for de-*O*-benzylation.<sup>[14]</sup> Lewis acids such as BCl<sub>3</sub>,<sup>[15]</sup> BBr<sub>3</sub>,<sup>[16]</sup> AlCl<sub>3</sub><sup>[17]</sup> are also known to act as reagents for de-*O*-benzylation. Recently Gurjar et al.<sup>[18]</sup> has used TiCl<sub>4</sub> for de-*O*-benzylation in the total synthesis of microcarpalide. De-*O*-allylation has been reported by Chen et al.<sup>[19]</sup> using tetra butyl ammonium peroxy disulphate. TiCl<sub>3</sub>-Li-I<sub>2</sub><sup>[20]</sup> can also function as a reagent for de-*O*-allylation. There are only few reagents for de-*O*-xylylation.<sup>[21]</sup>

Though  $TiCl_4^{[22]}$  in  $CH_2Cl_2$  has been reported in the literature for deprotection of benzylic ethers in carbohydrate substrates, but however requires longer reaction time (6–16 h). The reaction of benzylic ether 4

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with  $TiCl_4$  in THF did not yield any deprotected product but afforded 4-chlorobutanol due to the cleavage of THF by  $TiCl_4$ . Hence THF could not function as solvent during deprotection of benzylic ethers with  $TiCl_4$ .

When the benzyl phenyl ether 4a (1 equiv.) was subjected to debenzylation using TiCl<sub>4</sub> (5 equiv.) in dioxane, phenol was obtained in 85% yield after purification of the crude product by column chromatography. The purpose of selecting dioxane is many fold. It can act as nucleophilic reagent to cleave the *O*-TiCl<sub>3</sub> intermediate complex. The good solubilizing power of dioxane and its stability towards TiCl<sub>4</sub> are the salient features of dioxane. Dichloromethane and ether are the usual solvents while using TiCl<sub>4</sub>, however the high boiling point of dioxane and its easy removal after the reaction makes it as the best solvent for de-*O*-benzylation studies.

Facile debenzylation was also observed even while using 1 equiv. of  $TiCl_4$  in dioxane. However, unsuccessful debenzylation with catalytic amount of  $TiCl_4$  (0.1 equiv.) in dioxane indicated the importance of  $TiCl_4$  in stoichiometric quantity.

In order to test the generality of TiCl<sub>4</sub>-dioxane system for de-*O*-benzylation, de-*O*-allylation, and de-*O*-xylylation various phenolic ethers obtained by simple alkylation of substituted phenol were subjected to deprotection using TiCl<sub>4</sub>-dioxane (Sch. 2).

The following tabular column shows the versatility of the reagent TiCl<sub>4</sub>-dioxane for effective deprotection (Table 1).

In conclusion a facile, simple methodology for de-O-benzylation, de-O-allylation, and de-O-xylylation has been developed using TiCl<sub>4</sub> in dioxane.

# **EXPERIMENTAL SECTION**

All the melting points are uncorrected. The IR spectra were recorded using Shimadzu FT-IR 8300 instrument. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded in  $CDCl_3/DMSO-d_6$  using Jeol GSX 400 (400 MHz) NMR spectrometer. The mass spectra were recorded using

$$R-O-R'$$
  $\xrightarrow{\text{TiCl}_4}$   $R-O-H$   
reflux  $R-O-H$ 

Scheme 2.

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R	$R^{\prime}$	Compound number	Reaction time	Product	Yield (%)
C <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	<b>4a</b> <sup>[23]</sup>	40 min	Phenol	80
o-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	$CH_2C_6H_5$	<b>4b</b> <sup>[23]</sup>	45 min	o-Cresol	85
m-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	$CH_2C_6H_5$	<b>4c</b> <sup>[23]</sup>	50 min	m-Cresol	80
p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	$CH_2C_6H_5$	<b>4d</b> <sup>[23]</sup>	60 min	p-Cresol	90
$C_6H_5$	$CH_2CH = CH_2$	<b>5</b> a <sup>[24]</sup>	45 min	Phenol	80
o-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	$CH_2CH = CH_2$	<b>5</b> b <sup>[24]</sup>	50 min	o-Cresol	85
m-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	$CH_2CH = CH_2$	<b>5</b> c <sup>[24]</sup>	55 min	<i>m</i> -Cresol	80
p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	$CH_2CH = CH_2$	<b>5d</b> <sup>[24]</sup>	60 min	p-Cresol	90
C <sub>6</sub> H <sub>5</sub>	o-CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	<b>6a</b> <sup>[25]</sup>	10 h	Phenol	80
C <sub>6</sub> H <sub>5</sub>	m-CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	<b>6b</b> <sup>[25]</sup>	10 h	Phenol	90
$C_6H_5$	p-CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	<b>6c</b> <sup>[25]</sup>	10 h	Phenol	78

*Table 1.* Effective deprotection using TiCl<sub>4</sub>-dioxane.

Jeol (EI, 70 eV, and FAB-MS). Silica gel (100–200 mesh) was used for column chromatography.

### Procedure for the Synthesi of cis-Stilbene Diol 3

A solution of titanium[0] was prepared by the treatment of  $TiCl_4$  (0.96 g, 5 mmol) with zinc (0.33 g, 5 mmol) in dry dioxane (100 mL) under nitrogen atmosphere at  $0^\circ C.$  The reaction mixture was allowed to attain room temperature and then its was refluxed for 1 h. A solution of dialdehyde 2a/2b (0.35 g, 1 mmol) in dioxane (50 mL) was added slowly to the reaction mixture at reflux during a period of 16 h. The reaction mixture was refluxed for 24 h and then quenched with saturated K<sub>2</sub>CO<sub>3</sub> solution. Then reaction mixture was filtered and the residue was extracted with THF (100 mL). Evaporation of the solvent afforded a residue which was then dissolved in CHCl<sub>3</sub> (200 mL), washed with water  $(2 \times 50 \text{ mL})$ , brine (50 mL), and dried  $(Na_2SO_4)$ . Crude product obtained after evaporation of CHCl<sub>3</sub>, was purified by column chromatography. Elution with hexane:CHCl<sub>3</sub> (1:4) afforded the stilbenediol 3 as a colorless solid. Yield: 40% (from 2a), Yield: 40% (from **2b**). M.p.:  $240^{\circ}$ C. <sup>1</sup>H NMR (DMSO- $d_6$ , 400 MHz):  $\delta$  6.74 (d, 4H, J = 7.8 Hz), 6.99 (s, 2H), 7.34 (d, 4H, J = 7.8 Hz), 9.54 (s, 2H, exchanged with D<sub>2</sub>O). <sup>13</sup>C NMR:  $\delta$  115.6, 125.3, 127.4, 128.7, 156.8. m/z: 212 (M<sup>+</sup>100%). Elemental analysis: Calcd. for C<sub>14</sub>H<sub>12</sub>O<sub>2</sub>: C, 79.22; H, 5.70. Found: C, 79.16; H, 5.67.

SM1

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# General Procedure for De-O-Benzylation, De-O-Allylation, and De-O-Xylylation

A solution of benzylic ether (2.71 mmol) in dry dioxane (100 mL) was treated with TiCl<sub>4</sub> ((2.71 mmL for de-*O*-benzylation and de-*O*-ally lation)/5.42 mmol (for de-*O*-oxylylation)) under nitrogen atmosphere. The reaction mixture was refluxed for the period specified in Table 1. The reaction mixture was poured over ice and extracted with ethyl acetate ( $4 \times 50$  mL), washed with water, and finally with brain solution. The combined organic layer was then dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to give the crude product, which on chromatographic purification on silica gel with hexane:EtOAc (7:3) as eluent gave the respective phenolic product as shown in the Table 1.

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