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Highly regio- and chemoselective silylation of diethyl α-hydroxyphosphonates, alcohols and phenols in the presence of solid $TiCl_3(OTf)$ as a catalyst with hexamethyldisilazane (HMDS) at room temperature in the absence of solvent

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ABSTRACT

Solid trichlorotitanium(IV) trifluoromethanesulfonate [$TiCl_3(OTf)$] is an easily prepared compound from the reaction of $TiCl_4$ with trifluoromethanesulfonic acid. This solid Ti(IV) based compound is used as a catalyst for highly efficient silylation of diethyl α-hydroxyphosphonates, alcohols and phenols with hexamethyldisilazane (HMDS) at room temperature under solvent-free conditions. Chemo- and regioselectivity for masking different hydroxyl functional groups were observed in the presence of this catalyst.

1. Introduction

Silylation of α-hydroxyphosphonates to result α-siloxyphosphonates is of great importance from different aspects. They are attractive in biology, industry and they are useful precursors for the preparation of organic compounds [1]. α-Trimethylsiloxyphosphonates contain an α-hydrogen with reasonable acidity. These can be deprotonated with bases to generate carbanions, which are important synthons to acyl anions and can take part in carbon–carbon bond forming reactions [2]. They can be easily transformed to α-hydroxy ketones after alkaline hydrolysis of Si–O bond followed by elimination of dialkyl phosphate [2]. They can react with various acylating agents to produce the α-acylated products. β,γ-Unsaturated ketones, carboxylic acids, and unsymmetrical ketones can be prepared by alkylation of the carbanions formed in the reaction mixture [3–5]. However, by paying attention to the versatile applications of α-trimethylsiloxyphosphonates, the importance of silylation of α-hydroxyphosphonates becomes obvious in organic synthesis.

Masking of hydroxyl groups of alcohols with silylating agents is a popular strategy for protection of this functionality against the other functionality in the synthesis of complex organic molecules especially in natural product synthesis [6]. Silyl ethers are usually obtained by the reaction of alcohols with silyl halides in the presence of a stoichiometric amount of a base [7]. However, removing ammonium salt, which is produced during this silylation reaction, is sometimes a time-consuming process. In order to improve the method, the other silylating agents such as allylsilane and silyl enol ethers under the influence of a catalytic amount of *p*-toluenesulfonic acid [8], trifluoromethanesulfonic acid [9] and $Sc(OTf)_3$ [10], $R_3Si–H$ activated by dirhodium(II) perfluorooctanoate $\{Rh_2(PFO)_4\}$ [11], $Ph_2P–SiEt_3$ in the presence of diethyl azodicarboxylate (DEAD)/pyridinium *p*-toluenesulfonate (PPTS) [12] and hexamethyldisilane using $[PdCl(\eta^3–C_3H_5)]_2–PPh_3$ [13] have been reported. Although these procedures provide improvements in many cases, they suffer from expensive silylating agents and catalysts, using hazardous and not easily available chemicals such as DEAD and using moisture sensitive compounds.

One of the most popular and practical method for protection of –OH functionality is its conversion to $–OSiMe_3$ by using commercially available, inexpensive and easy handling hexamethyldisilazane (HMDS). The only by product of the reaction is ammonia, which is easily removed from the reaction media. The main limitation of HMDS is its poor silylating property, especially for sterically hindered –OH groups, which requires harsh reaction conditions or long reaction times [14]. However, in order to eradicate or diminish the encountered shortcoming, various acid catalysts have been

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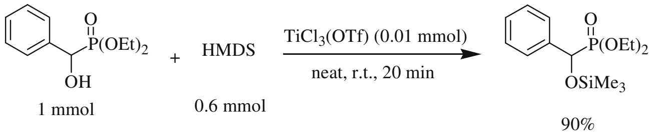
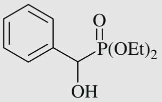
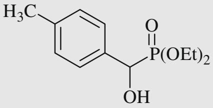
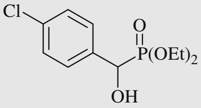
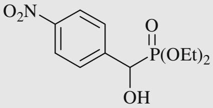
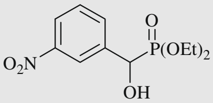
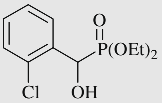
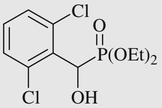
introduced for this purpose [15–29]. Although the silylation ability of HMDS has been promoted in the presence of these catalysts, yet some of the presented methods suffer from long reaction times, drastic reaction conditions and sometimes, a tedious workup is required. In addition, in most of the reported methods, selectivity of the protocols is either poor or is not reported properly.

Titanium tetrachloride ($TiCl_4$) has been extensively used as a catalyst or reagent in organic synthesis, in particular, for C–C bond formation reactions such as aldol condensation reaction, Diels–Alder cycloaddition reaction and Mukaiyama reaction [30]. Applications of $TiCl_4$ as a catalyst in the industrial processes such as polymerization reactions are also of vital importance. However, $TiCl_4$ is a highly aggressive, hygroscopic and corrosive material and its handling needs serious precautions. These put limitation on the use of this compound as a catalyst or reagent in organic reactions.



Scheme 1. Silylation reaction of diethyl α-hydroxybenzylphosphonate with HMDS in the presence of $TiCl_3(OTf)$.

Table 1
Trimethylsilylation of α-hydroxyphosphonates catalyzed by $TiCl_3(OTf)$ with HMDS under neat conditions at room temperature.

Entry	Substrate	Time (min)	Isolated yield%[a,b]
1		25	90
2		10	88
3		20	92
4		20	95
5		20	98
6		20	94
7		20	92

[a] The structures of the products were confirmed by comparison of their spectral data (^1H NMR, ^{13}C NMR) with those of known sample.

[b] The equivalent ratio of substrate/HMDS/catalyst is: 1/0.6/0.01.

Trichlorotitanium(IV) trifluoromethanesulfonate [$TiCl_3(OTf)$], a lemon yellow powder that is not stable towards water. However, it is practically much less hygroscopic than $TiCl_4$ and is a potential alternative for $TiCl_4$. We have utilized this compound as a catalyst for the conversion of epoxides to 1,3-dioxolanes [31], aldol condensation of cycloalkanones with aromatic aldehydes [32], conversion of acetophenones to 1,3,5-triarylbenzenes [33] and esterification reactions [34].

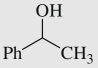
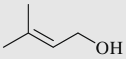
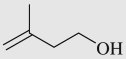
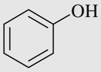
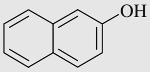
Now, in this article we report another efficient catalytic application of $TiCl_3(OTf)$ for regio- and chemoselective silylation of different hydroxyl groups including α-hydroxyphosphonates with HMDS under neat conditions at room temperature.

2. Results and discussion

Transformation of hydroxyl groups to their silyl ethers is of value from different views. This conversion enhances solubility of the compounds in non-polar solvents, increases thermal stability, and in addition, trimethylsilylation of hydroxyl compounds is used extensively to increase volatility of the compounds for gas chromatography and mass spectrometry as well. Moreover, protection of hydroxyl groups and their transformation to the corresponding silyl ethers is of vital importance in the total synthesis of complex organic molecules. For these vast applications of silyl ethers presentation of new methods, using new catalysts is of demand from industries and academia.

α-Trimethylsiloxyphosphonates are useful precursors for the preparation of organic compounds and they have found biological and industrial applications [1]. To the best of our knowledge, procedures for the silylation of α-hydroxyphosphonates are relatively

Table 2
Trimethylsilylation of alcohols and phenols catalyzed by $TiCl_3(OTf)$ with HMDS under neat conditions at room temperature.[a]

Entry	Substrate	Time	Isolated yield (%)[b]
1	$C_6H_5CH_2OH$	2 min	92
2	p-NO_2–$C_6H_4CH_2OH$	2 min	87
3	p-MeO–$C_6H_4CH_2OH$	2 min	94
4	Ph_2CHOH	2 min	92
5		2 min	87
6		5 min	95
7		5 min	90
8	$CH_3(CH_2)_6CH_2OH$	5 min	90
9	$PhCH_2CH_2OH$	1 min	94
10	$PhCH_2CH_2CH_2OH$	3 min	92
11	$CH_3(CH_2)_5CH(OH)CH_3$	10 min	88
12	Cholesterol[c]	10 min	95
13	Menthol	30 min	93
14	Adamantanol	2 h	90
15		10 min	90
16		10 min	89
17	$C_6H_5CH_2NH_2$	48 h	nr
18	$C_6H_5CH_2SH$	48 h	nr

[a] The structures of the products were confirmed by comparison of their spectral data (1H NMR, ^{13}C NMR) with those of known sample.

[b] The equivalent ratios of substrate/HMDS/catalyst are: 1/0.6/0.01.

[c] The reaction was performed in CH_2Cl_2 as a solvent.