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RESEARCH ARTICLE

Dichloro-*bis*(trifluoromethanesulfonate)titanium(IV) ($TiCl_2(SO_3CF_3)_2$) as a stable and a non-corrosive solid catalyst for the efficient and highly selective protection of carbonyl groups as their 1,3-dithianes and 1,3-dithiolanes under solvent-free conditions at room temperature

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$TiCl_2(SO_3CF_3)_2$ as a non-corrosive solid catalyst has been applied for the efficient and highly regio- and chemoselective protection of carbonyl groups as their 1,3-dithianes and 1,3-dithiolanes under solvent-free conditions at room temperature in excellent yields.

Keywords: *S*,*S*-Acetals; Dithioacetals; 1,3-Dithianes; 1,3-Dithiolanes; Solvent-free; Titanium (IV); Carbonyl compounds; Catalyst

1. Introduction

Selective functional group protection strategies are of great importance for the synthesis of complex target molecules [1–3]. One of the most abundant functional groups in natural products and man-made organic molecules is carbonyl functionality. Facile manipulation of this functional group in the course of synthesis of organic molecules with complex structure is very important. One of the most useful strategies for the protection of carbonyl groups is to convert this functionality to its *S*,*S*-acetals [1–3] which act as precursors of acyl carbanion equivalents [4–6], or as electrophiles catalyzed by Lewis acids [7–10]. Generally, *S*,*S*-acetals are prepared by the condensation of carbonyl groups with thiols catalyzed by Lewis and Brønsted acids [11–26], solid supported reagents [27–33], I_2 [34], triflates [35–40], heteropoly acids [41], LiBr [42], dodecylbenzenesulfonic acid (DBSA) [43,44], WCl_6 [45], $Cu(BF_4)_2.xH_2O$ [46], $HClO_4$-SiO_2 [47], etc. However, these methods have some drawbacks such as low

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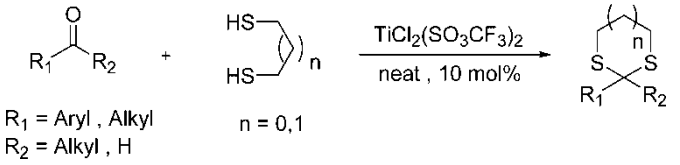


SCHEME 1

yields of products, elongated reaction times, using stoichiometric amounts of the catalyst, requirement of a high temperature and hazardous organic solvents. Solvent-free reactions often lead to a decrease in reaction times, increased yields, easier workup, compliance with green-chemistry protocols and more often with enhancement of the regio- and stereoselectivity of the reactions [48]. In this paper, we have presented a stable solid titanium (IV) based Lewis acid catalyst for the efficient and selective protection of carbonyl groups as their 1,3-dithianes and 1,3-dithiolanes using corresponding dithiols at room temperature under solvent-free conditions.

2. Results and discussion

In this paper, we have introduced dichloro-*bis*(trifluoromethanesulfonate)titanium(IV); $TiCl_2(SO_3CF_3)_2$ as a stable, non-corrosive and easy handling titanium (IV)-based catalyst for the efficient and highly selective protection of carbonyl groups by 1,3-propanedithiol and 1,2-ethanedithiol under solvent-free conditions at room temperature (scheme 1).

For optimization of the reaction conditions, we have studied the reaction of acetophenone with 1,2-ethanedithiol in the presence of this catalyst at room temperature. We found that the optimized molar ratio of acetophenone/1,2-ethanedithiol/cat. was 1/1.2/10 mol% and after 10 min, the desired product was isolated in 97% yield. In order to show the general catalytic ability of $[TiCl_2(SO_3CF_3)_2]$ for the protection of carbonyl functional group, we have applied similar reaction conditions for the preparation of structurally diverse dithioacetals from different carbonyl compounds. The desired S/S-dithioacetals were isolated in excellent yields and the reactions proceeded from immediate to 15 min (table 1).

In order to show the merit of this catalytic method, we have compared the results of the reaction of acetophenone with 1,2-ethanedithiol (table 2) and 1,3-propanedithiol (table 3) with some other catalysts used for the same reactions. As it is evident from the results tabulated in the tables 2 and 3, $TiCl_2(SO_3CF_3)_2$ is a more efficient catalyst than the others presented in the tables. $TiCl_2(SO_3CF_3)_2$ which is a stable, non-fuming and a non-corrosive solid Ti(IV) compound is even more efficient than $TiCl_4$ for the preparation of *S*,*S*-acetals from carbonyl compounds and in addition, its handling is much easier than $TiCl_4$ which is a fuming and a highly corrosive liquid.

Selectivity of the method is important from different views, especially when it is applied for the synthesis of multifunctional molecules. However, in several competitive reactions, we have shown that *S*,*S*-acetalization of carbonyl groups in the presence of this catalyst proceeded with high chemo-and regioselectivity at room temperature under solvent-free conditions (scheme 2). As presented in scheme 2, high selectivity between aldehydes and ketones, acyclic ketones and cyclic ketones, esters and aldehydes, 1,2-ethanedithiol and 2-mercaptoethanol were observed in the presence of this catalyst. We have also shown that high chemoselectivity is observed well in a molecule carrying two different carbonyl groups.

Table 1. Protection of carbonyl groups with dithiols under solvent -free conditions catalyzed by $TiCl_2(SO_3CF_3)_2$.

Entry	Substrate	Dithiol	Time (min)	Isolated yield (%)[a]	References to the products[b]
1	Acetophenone	$HSCH_2CH_2SH$	10	97	[41, 32]
2	*p*-MeO-acetophenone	$HSCH_2CH_2SH$	12	97	-[c]
3	*p*-Br-acetophenone	$HSCH_2CH_2SH$	10	99	[32]
4	*p*-Cl-acetophenone	$HSCH_2CH_2SH$	10	98	[32]
5	Cyclohexanone	$HSCH_2CH_2SH$	1	95	[32]
6	*p*-Me-acetophenone	$HSCH_2CH_2SH$	1	99	[32]
7	Acetophenone	$HSCH_2CH_2CH_2SH$	10	99	[44]
8	*p*-Cl-acetophenone	$HSCH_2CH_2CH_2SH$	10	93	[44]
9	*p*-NO_2-acetophenone	$HSCH_2CH_2CH_2SH$	15	94	[44]
10	Benzaldehyde	$HSCH_2CH_2CH_2SH$	-[d]	92	[41, 44]
11	*p*-MeO-benzaldehyde	$HSCH_2CH_2CH_2SH$	-[d]	88	[41, 44]
12	*p*-Me-benzaldehyde	$HSCH_2CH_2CH_2SH$	-[d]	90	[44]
13	*p*-Cl-benzaldehyde	$HSCH_2CH_2CH_2SH$	2	98	[41, 44]
14	*p*-NO_2-benzaldehyde	$HSCH_2CH_2CH_2SH$	7	95	[44]
15	4-Heptaneone	$HSCH_2CH_2SH$	1	81	[32]
16	2-Hexanone	$HSCH_2CH_2SH$	1	88	[32]
17	1-Phenyl-propan-2-one	$HSCH_2CH_2SH$	1	96	[32, 41]
18	Heptanal	$HSCH_2CH_2SH$	-[d]	80	[32]
19	Cinnamaldehyde	$HSCH_2CH_2SH$	-[d]	97	[32, 41]

[a]The purity of the products were determined by ^{1}HNMR, ^{13}CNMR and GC analysis.
[b]References for the known compounds.
[c]Spectral data for compound (Entry 2).
[d]Upon immediate analysis.

Table 2. Comparison of the reaction of acetophenone with 1,2-ethanedithiol catalyzed by $TiCl_2(SO_3CF_3)_2$ and some other catalysts used for the similar reaction.

Entry	Catalyst	(Mol%)	Time (min)	Yield (%)	Ref.
1	$TiCl_2(SO_3CF_3)_2$	10	10	97	–
2	$TiCl_4$[a]	13	180	96	[11]
3	$Cu(SO_3CF_3)_2$- SiO_2	10	300	92	[28]
4	$H_3PW_{12}O_{40}$	2	70	98	[41]
5	H_2SO_4	5	120	49	–
6	I_2-Al_2O_3	10	35	87	[33]
7	TfOH	5	120	50	–
8	WCl_6	10	4500	65	[45]

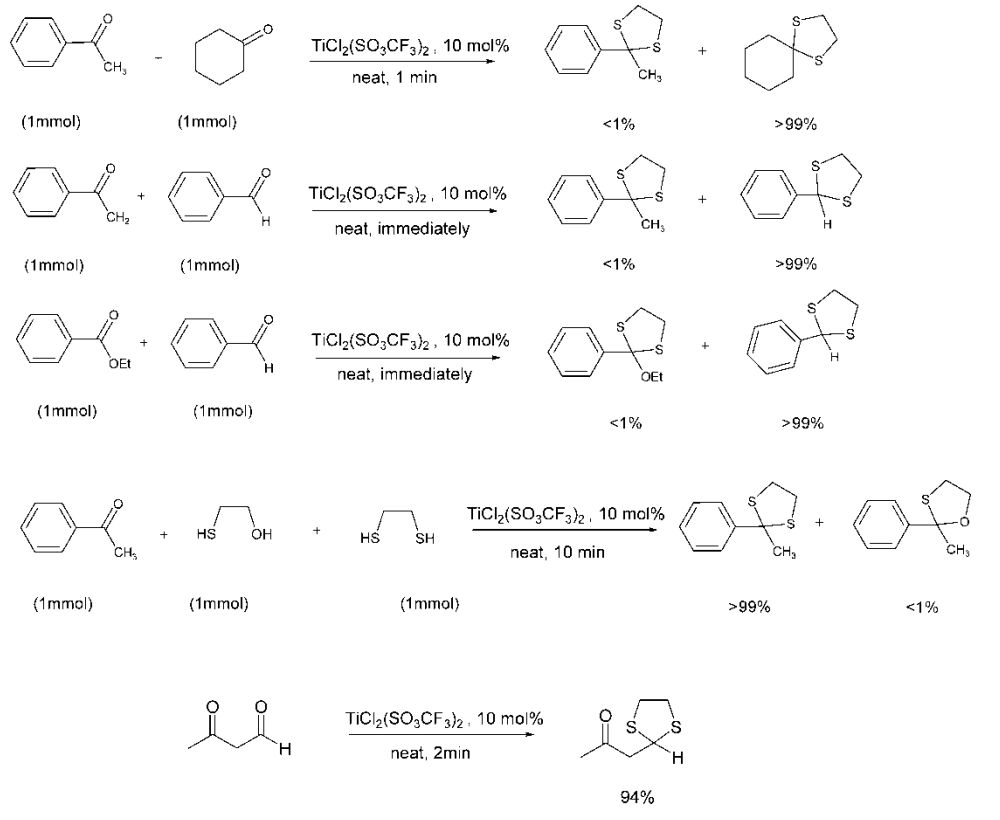
[a]Using $CHCl_3$ as solvent at −10 °C.

Table 3. Comparison of the reaction of acetophenone with 1,3-propanedithiol catalyzed by $TiCl_2(SO_3CF_3)_2$ and the other catalysts used for the similar reaction.

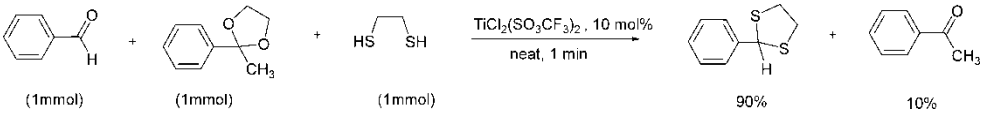
Entry	Catalyst	(Mol %)	Time (min)	Yield (%)	Ref.
1	$TiCl_2(SO_3CF_3)_2$	10	10	99	–
2	LiBr	40	180	no reaction[a]	[42]
3	LiOTf	30	1140	15[b]	[35]

[a]Reaction proceeded at 75–80 °C.
[b]Reaction performed at 110 °C.

Deprotection of *O*,*O*-acetals in the the presence of acid catalysts is a facile reaction. We have observed that in the presence of $TiCl_2(SO_3CF_3)_2$, protection of a carbonyl group with 1,2-ethanedithiol in the presence of *O*,*O*-acetal proceeds with high yields and selectivity (90%) with a fraction amount of deprotection of the *O*,*O*-acetal (10%) as shown in scheme 3.



SCHEME 2



SCHEME 3

3. Experiments

3.1 *General methods*

Chemicals were obtained from Fluka and Merck Chemical Companies. $TiCl_2(SO_3CF_3)_2$ was prepared according to the published procedure [49]. Progress of the reactions were monitored by TLC using silica gel SILG/UV 254 plates and Shimadzu GC MS-QP 1000 EX . *n*-Propanol has been employed as an internal standard for the given GC yields. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Advanced DPX-250, FT-NMR spectrometer (δ in ppm). All yields refer to the isolated products.

3.2 *General procedure*

To a mixture of a dithiol (1.2 mmol) and a carbonyl compound (1.0 mmol) at room temperature was added $TiCl_2(SO_3CF_3)_2$ (0.041 g, 0.1 mmol) [49], and the resulting mixture was stirred

for the appropriate time (table 1). Progress of the reaction was monitored by TLC or GC. After completion, the reaction was quenched with 5% solution of NaOH and extracted by continuous extraction with $CHCl_3$ (5 ml). The organic phase was separeted and dried over anhydrous Na_2SO_4 and after filtration and evaporation of the solvent the crude product was obtained. Purification was performed by column chromatography eluted with *n*-hexane or a mixture of *n*-hexane/EtOAc to afford *S*,*S*-actals in excellent yields (table 1).

Typical selected spectral data (table 1, entry 2) ^{1}H NMR (250 MHz, $CDCl_3$): δ(ppm) = 1.53 (3H, s), 3.20–3.37 (4H, complex, AA'BB'), 3.73 (3H, s), 6.78–6.90 (2H, d, J = 8.7 Hz), 7.17–7.30 (2H, d , J = 8.7 Hz), ^{13}C NMR (62.5 MHz, $CDCl_3$): δ(ppm) = 30.10, 31.06, 33.22, 55.67, 114.00, 131.23, 132.45, 159.94.

4. Conclusions

In conclusion, in this study, we have introduced a solid titanium(IV)-based compound; $TiCl_2(SO_3CF_3)_2$ as a highly efficient catalyst for the protection of carbonyl groups by dithiols under solvent-free conditions at room temperature. The method is highly selective for the preparation of *S*,*S*-acetals from aldehydes in the presence of ketones, acyclic ketones in the presence of cyclic ketones in the presence of esters and aldehydes in the presence of *O*,*O*-acetals.

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