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Catalytic carbon–sulfur bond formation by amphoteric vanadyl triflate: exploring with thia-Michael addition, thioacetalization, and transthioacetalization reactions

Chien-Tien Chen *, Yow-Dzer Lin, Cheng-Yuan Liu

Department of Chemistry, National Taiwan Normal University, Taipei 11650, Taiwan, ROC

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ABSTRACT

A series of thiols have been examined as protic nucleophiles for Michael-type additions to α,β-unsaturated carbonyls as well as double nucleophilic condensations with aldehydes, ketones, and acetals catalyzed by amphoteric, water-tolerant vanadyl triflate under mild and neutral conditions. The newly developed C–S bond formation protocols were carried out smoothly in good to high yields in a highly chemoselective manner.

1. Introduction

Carbon–sulfur bond formation is an important methodology in organic synthesis[1] in view of many decent sulfur-containing natural and pharmaceutical products, which reveal potent antibiotic, antimicrobial, analgesic, anti-inflammatory, antipsychotic, anti-HIV, and anti-tumor activities.[2] Conjugate 1,4-addition of a thiol nucleophile to an alkene or alkyne acceptor activated by an electron-withdrawing group (e.g., ketone, ester, amide, nitrile, nitro, sulfonate, or phosphonate), namely the thia-Michael addition, constitutes one of the most efficient C–S bond-forming strategies in synthetic organic chemistry.[3] Beside some conventional conjugate additions performed in basic media, a myriad array of metal-centered Lewis acid catalysts has been developed in view of the potential applications in asymmetric variants.[4]

On the other hand, double addition of a thiol or dithiol nucleophile to an aldehyde or ketone with concomitant water stripping to form a dithioacetal, namely the thioacetalization, is a versatile functional group protection tactic.[5] The resultant aldehyde-derived dithioacetals serve as masked acyl anion equivalents[6] or zwitterion synthons,[7] allowing for subsequent reductive desulfurization to the corresponding methylene groups,[8] transformation of carbohydrates to carbocycles,[9] and titanium-alkylidene mediated carbonyl olefination[10] in delicate natural product syntheses.[11]

Due to the broad spectrum of dithioacetals in organic syntheses, thioacetalization of acetals, ketals, acylals, *S*,*O*-acetals, oximes, hydrazones, and enamines[12] (i.e., transthioacetalization) leads to their direct access to dithioacetals without resorting to a conventional deprotection–protection sequence from these compounds. Additional applications of transthioacetalization involving deprotection of acetonide and benzylidene functional groups are also documented.[5,13]

Thiols and sulfides are well known to poison metal catalysts due to their strong coordination and adsorptive properties, which results in hampering or paralyzing metal-centered catalysis.[14] Therefore, significant efforts toward developing sulfur-tolerant metal catalysts have been made. In the past decade, metal salts or complexes derived from Al(III),[15] Bi(III),[16] Cu(II),[17] Fe(III),[18] In(III),[19] Mo(VI),[20] Ni(II),[21] Ru(III),[22] Sc(III),[23] Ti(IV),[24] and Zn(II)[2b,13b,25] are the most extensively identified. However, only a couple of these catalysts can be applied to all the three different reaction types mentioned above. Consequently, an ideal neutral, water and functional group-tolerant, catalyst remains to be explored. As part of our ongoing programs by using vanadyl and oxometallic species in catalyzing C–C and C–X bond formation,[26a–e] asymmetric aerobic oxidation,[26f–h] DNA photocleavage,[26i] and directed assembly,[26j] we recently succeeded in using amphoteric vanadyl triflate to catalyze Michael reactions with *N*-, *P*-, and *C*-centered protic nucleophiles.[26a] With the preliminary success, we sought to evaluate the feasibility of thia-Michael addition, thioacetalization, and transthioacetalization reactions catalyzed by the same catalyst.[27] Namely, the partial positively charged V center in V=O is Lewis

* Corresponding author. Tel.: +886 2 29331186x121; fax: +886 2 29324249.
E-mail address: chefv043@ntnu.edu.tw (C.-T. Chen).

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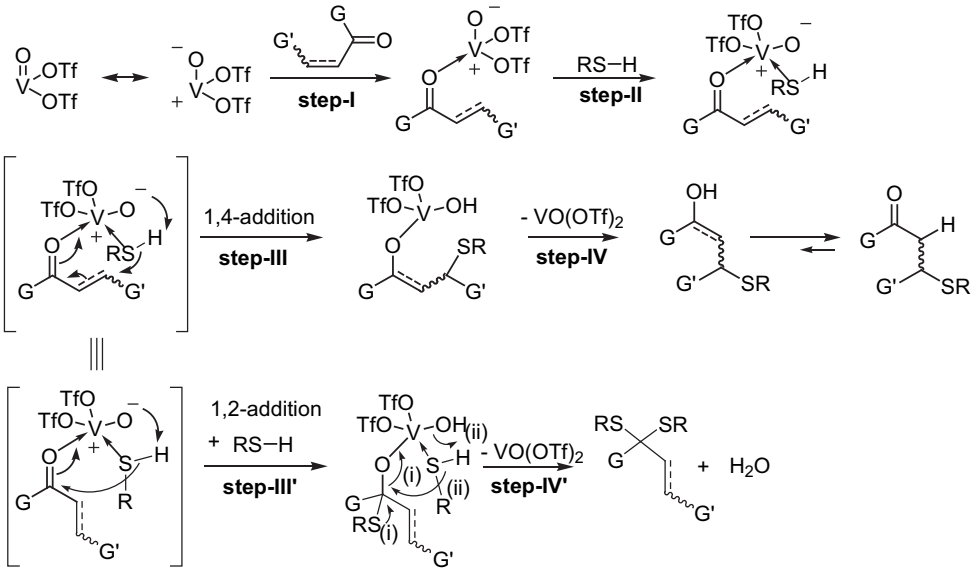


Scheme 1. Postulated mechanisms for thia-Michael-type 1,4-addition and thioacetalization (1,2-addition) to a given α,β-enone catalyzed by amphoteric vanadyl triflate.

acidic enough to first activate a carbonyl electrophile (step I in Scheme 1). Conversely, the partial negatively charged O center in V═O serves as a Lewis base to promote a subsequent proton transfer of a coordinated, protic sulfur nucleophile (step II) during the 1,4- or 1,2-addition event (step III or III′). The resultant *S*,*O*-acetal in the 1,2-addition undergoes a second 1,2-addition to a thioxocarbenium ion intermediate leading to the corresponding dithioacetal (Step-IV′). In both scenarios, the reactions proceed in a sequential push–pull type pathway toward the substrate pair (Scheme 1). Herein we disclose our complete account toward these ends.

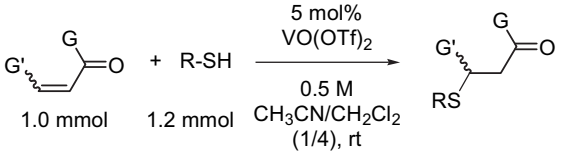
2. Results and discussion

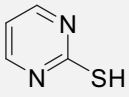
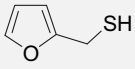
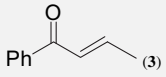
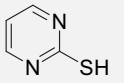
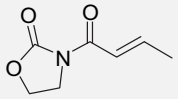
2.1. Thia-Michael addition

Conjugate additions of thiols to α,β-unsaturated carbonyl compounds were first examined. 2-Cyclohexenone (**1**) and 1-phenyl-but-2-en-1-one (**3**) were chosen as test Michael acceptors and 4-*t*-butyl-benzenethiol (or benzenethiol) (1.2 equiv) was used as a test Michael donor. The model additions were performed in the presence of catalytic $VO(OTf)_2$ (5 mol %) in various solvent systems. It was found that the conjugate additions proceeded smoothly in 3.5–4 h in 0.5 M of CH_3CN/CH_2Cl_2 (1:4) at ambient temperature. The corresponding thia-Michael adducts **1a**′ and **3a**′ were isolated in 98 and 96% yields, respectively, without any ketone protection by-products (entries 1 and 10, Table 1). To extend substrate scope, aromatic, heteroaromatic (e.g., naphthalene-2-thiol and pyrimidine-2-thiol), and functionalized aliphatic thiols (e.g., benzyl mercaptan and 2-mercaptoethanol) were further explored under the optimal reaction conditions. All the reactions were complete in 3–9 h in 87–98% yields (entries 2–7, 11–12 in Table 1). Notably, pyrimidine-2-thiol is amenable to the conjugate additions (entries 5 and 11), thus excluding the possibility of any HOTf-mediated catalysis. Furthermore, 2-mercaptoethanol can be applied to the new catalytic protocol without discernible alcohol addition (entries 7 and 12). Notably, the conjugate addition adduct, 3-(2-hydroxyethylsulfanyl)-cyclohexanone (**1g**′) (entry 7) is a valuable precursor toward the synthesis of 4-hydroxybenzothiophene, which can be further converted to the corresponding carbamate insecticides.[28] Furthermore, the highly chemoselective conjugate addition by 2-mercaptoethanol is consistent with the amphoteric character of $VO(OTf)_2$, by which the more acidic thiol end gets activated more efficiently than the corresponding alcohol end.

Two representative oxygen-containing thiols, 4-methoxybenzenethiol and furan-2-yl-methanethiol, were further examined by

Table 1
Thia-Michael additions catalyzed by $VO(OTf)_2$



Entry	Michael acceptor	R-SH	Time (h)	Product yield[a] (%)
1	2-Cyclohexenone (**1**)	C_6H_5SH	4	98 (**1a**′)
2		4-$MeOC_6H_4SH$	4.5	90 (**1b**′)
3		4-ClC_6H_4SH	5	92 (**1c**′)
4		2-NpSH	5	97 (**1d**′)
5[b]			9	87 (**1e**′)
6		$C_6H_5CH_2SH$	3	98 (**1f**′)
7[c,d]		$HOCH_2CH_2SH$	8	89 (**1g**′)
8	2-Cyclopentenone (**2**)	4-$MeOC_6H_4SH$	4.5	93 (**2b**′)
9			3.5	94 (**2f**′)
10	 (**3**)	4-*t*-BuC_6H_4SH	3.5	96 (**3a**′)
11[b]			7	93 (**3e**′)
12[c,d]		$HOCH_2CH_2SH$	5	94 (**3g**′)
13[c]	 (**4**)	C_6H_5SH	12	93 (**4a**′)

[a] Isolated and purified yield.
[b] 0.5 M CH_3CN/CH_2Cl_2 (1:1).
[c] 1.0 M CH_3CN/CH_2Cl_2 (1:1).
[d] 2.0 equiv of R-SH was employed.

using 2-cyclopentenone as the Michael acceptor. Both catalytic conjugate additions went to completion in 4.5 and 3.5 h, respectively, in 93–94% yields (entries 8 and 9).

N-But-2-enoyl-1,3,2-oxazolidinone (**4**), which is a less reactive acceptor than **3** was also tested. It was found that the addition by benzenethiol proceeded smoothly in 93% yield albeit at much slower rate than that for **3** (entries 10 and 13). No nucleophilic acyl substitution product was noted under the reaction conditions.

2.2. Thioacetalization of aldehydes

Dithioacetals such as 1,3-dithianes, 1,3-dithiolanes, 1,3-oxathiolanes, *S*,*S*′-diethyl acetals, and *S*,*S*′-diphenyl acetals are the most widely used protective groups for carbonyl compounds.[5] Therefore, we move on to evaluate the versatility of $VO(OTf)_2$ in catalyzing thioacetalization of benzaldehyde with five different thiols. It was found that all the reactions proceeded smoothly by using 5 mol % of $VO(OTf)_2$ in 0.25 M of CH_3CN/CH_2Cl_2 (1:7) at ambient temperature with dithiol or thiol nucleophiles (1.2 equiv). The resultant thioacetalization adducts **5a**–**5e** were isolated in high yields of 96–99% in 1–2 h (entries 1–5, Table 2). Five different *para*-substituted aromatic aldehydes of varying electronic demands (e.g., methoxy, hydroxy, bromo, nitro, and dimethylamino groups) were tested by using the optimal catalytic conditions with propane-1,3-dithiol. In general, an electron-donating group at the *para*-position tends to slow down the reaction (entries 6–10). In particular, *p*-*N*,*N*-dimethylaminobenzaldehyde reacts much more sluggishly and leads to product **10** in 60% yield even with higher dithiol (1.5 equiv) and catalyst (15 mol %) loading in a prolonged reaction time (14 h), entry 10. Nevertheless, the reactivity profile is better than that from $RuCl_3$-catalyzed reaction (20 mol % catalyst, 24 h, 10% yield)[22b] and is comparable to that with $Yb(OTf)_3$/ionic liquid conditions.[29] Notably, the new catalytic protocol tolerates free phenolic group as demonstrated in the case of 4-hydroxybenzaldehyde (entry 7). The reaction was complete in 2 h and in 95% yield. A couple of heteroaromatic aldehydes (e.g., furan- and thiophene-carbaldehyde) possessing chelation attributes were also amenable to the new catalytic thioacetalization (entries 11 and 12).

Furthermore, α,β-unsaturated aldehydes, such as *trans*-cinnamaldehyde and phenyl-propynal, cleanly led to the thioacetalization (i.e., 1,2-addition) products, 1,3-dithianes **13** and **14**, respectively, in 1–2 h without intervention of any conjugate addition (entries 13 and 14).

Two representative, aliphatic aldehydes, benzyloxyethanal and sterically-hindered pivalaldehyde, were selected. Both the thioacetalization reactions were finished in 1.5–2 h, leading to the condensation adducts **15** and **16** in 97% and 92% yields, respectively (entries 15 and 16). Notably, the latter case is superior to the $LiBF_4$ catalyzed one both in terms of reactivity (2 h vs 21 h) and efficiency (92% vs 84% yield).[30]

Since Lewis acids such as $AlCl_3$ and BF_3–Et_2O show no chemoselectivity between aldehyde and ketone group,[31] we further investigated intramolecular, competitive thioacetalization of 4-acetylbenzadehyde. It was found that only aldehyde protected adduct **17** was obtained in 96% yield (entry 17). Furthermore, intermolecular competitive thioacetalization between benzaldehyde and acetophenone with propane-1,3-dithiol afforded the similar chemoselective preference.[32] Therefore, overall the thioacetalizations with aromatic, α,β-unsaturated, and aliphatic aldehydes of varying steric and electronic demands (except for entry 10) show exclusive chemoselectivity and functional group compatibility in high yields (90–99%) in short reaction time (1–2.5 h) under optimal catalytic reaction conditions.

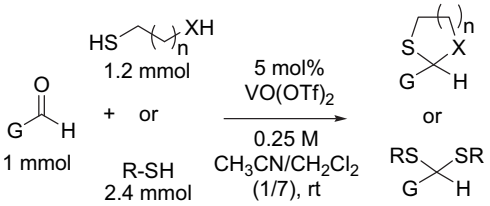
2.3. Thioacetalization of ketones

Thioacetalization of aromatic ketones are significantly suppressed in many metal-centered catalysis.[12c,15c,19b,23b,31b] After extensive optimization on the thioacetalization of acetophenone with five different dithiol or thiol nucleophiles (2.0 equiv), the reactions can be effected by using 7 mol % of $VO(OTf)_2$ in 0.17 M of CH_3CN/CH_2Cl_2 (1:3) at ambient temperature. The corresponding condensation adducts **18a**–**18e** were afforded in 84–93% yields with prolonged reaction time of 24–35 h (entries 1–5, Table 3). The reactivity profile is consistent with chemoselective thioacetalization in intramolecular competition between aldehyde and ketone moiety in 4-acetylbenzaldehyde (entry 17, Table 2) mentioned above. Cyclic, aromatic ketones are also suitable substrates under the optimal catalytic reactions with propane-1,3-dithiol. The corresponding 1,3-dithianes **19** and **20** were furnished in 90–92% yields in similar reaction time (i.e., 25–26 h), entries 6 and 7. In marked contrast, due to adverse steric and electronic effects,[33] benzophenone led to the adduct **21** in only moderate yield (65%) even under refluxed conditions (entry 8).

Aliphatic methyl ketones are much more reactive and those bearing hydroxy, acid, and ester functional groups are completely tolerant under the optimal reaction conditions. The resultant 1,3-dithianes **22**–**25** were isolated with exclusive chemoselectivity and in 87–97% yields within 15–17 h (entries 9–12). Alicyclic ketones such as cyclohexanone and 2-adamantanone undergo thioacetalization with propane-1,3-dithiol in much shorter time of 6–10 h and in high yields of 96–98% (entries 13 and 14). Conversely, thioacetalization of a sterically-hindered, cyclic α,β-enone, isophorone, was complete in 5 days, leading to **28** in fair yield of 80% without any conjugate addition product (entry 15).

To extend the application scope, we further explore the differential thioacetalization between α,β-enone and keto-groups, which is an important issue in steroid chemistry. By using 10 mol % of $VO(OTf)_2$ and 1.0 equiv of 1,2-ethanedithiol for chemoselective protection of 4-androstene-3,17-dione (entry 16), mono-protected

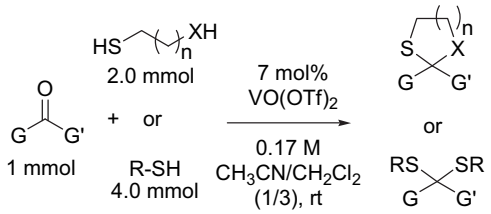
Table 2
Chemoselective thioacetalization of aldehydes catalyzed by $VO(OTf)_2$

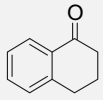
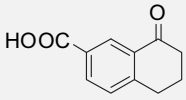
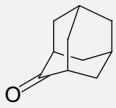
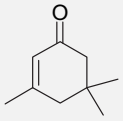
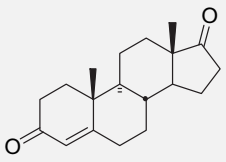
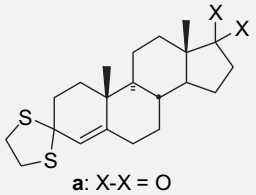
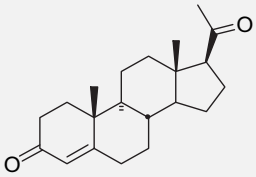
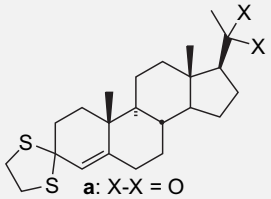


Entry	Acceptor (G)	Donor	Time (h)	Product yield[a] (%)
1	Ph	$HS(CH_2)_3SH$	1	97 (**5a**)
2	Ph	$HS(CH_2)_2SH$	1.5	96 (**5b**)
3	Ph	$HS(CH_2)_2OH$	2	97 (**5c**)
4	Ph	CH_3CH_2SH	1.5	99 (**5d**)
5	Ph	C_6H_5SH	2	96 (**5e**)
6	4-$MeOC_6H_4$	$HS(CH_2)_3SH$	2	98 (**6**)
7	4-HOC_6H_4	$HS(CH_2)_3SH$	2	95 (**7**)
8	4-BrC_6H_4	$HS(CH_2)_3SH$	1.5	99 (**8**)
9	4-$O_2NC_6H_4$	$HS(CH_2)_3SH$	1.5	97 (**9**)
10[b]	4-$Me_2NC_6H_4$	$HS(CH_2)_3SH$	14	60 (**10**)
11		$HS(CH_2)_3SH$	2	98 (**11**)
12		$HS(CH_2)_3SH$	2.5	90 (**12**)
13	*trans*-$C_6H_5CH{=}CH$	$HS(CH_2)_3SH$	2	94 (**13**)
14	$C_6H_5C{\equiv}C$	$HS(CH_2)_3SH$	1	95 (**14**)
15	$C_6H_5CH_2OCH_2$	$HS(CH_2)_3SH$	1.5	97 (**15**)
16	*tert*-Bu	$HS(CH_2)_3SH$	2	92 (**16**)
17	4-$H_3CC(O)C_6H_4$	$HS(CH_2)_3SH$	1	96 (**17**)

[a] Isolated and purified yield.
[b] 1.5 equiv of $HS(CH_2)_3SH$ and 15 mol % of $VO(OTf)_2$ were used.

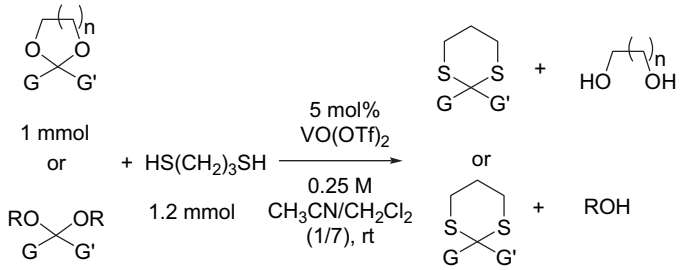
Table 3
Chemoselective thioacetalization of ketones catalyzed by $VO(OTf)_2$

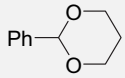
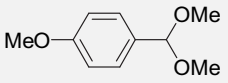
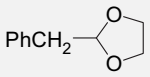
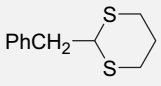
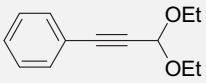
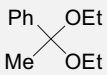
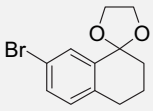
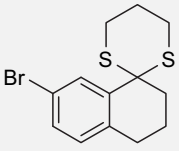
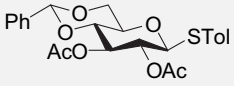
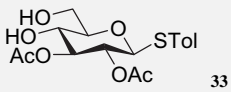
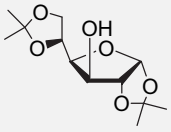
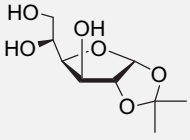


Entry	Acceptor	Donor	Time (h)	Product yield[a] (%)
1	$C_6H_5C(O)CH_3$	$HS(CH_2)_3SH$	24	93 (**18a**)
2	$C_6H_5C(O)CH_3$	$HS(CH_2)_2SH$	28	90 (**18b**)
3	$C_6H_5C(O)CH_3$	$HS(CH_2)_2OH$	32	88 (**18c**)
4	$C_6H_5C(O)CH_3$	CH_3CH_2SH	31	84 (**18d**)
5	$C_6H_5C(O)CH_3$	C_6H_5SH	35	85 (**18e**)
6		$HS(CH_2)_3SH$	25	92 (**19**)
7		$HS(CH_2)_3SH$	26	90 (**20**)
8[b]	$C_6H_5C(O)C_6H_5$	$HS(CH_2)_3SH$	30	65 (**21**)
9	$C_6H_5(CH_2)_2C(O)CH_3$	$HS(CH_2)_3SH$	15	97 (**22**)
10	$CH_3C(O)(CH_2)_3OH$	$HS(CH_2)_3SH$	17	87 (**23**)
11	$CH_3C(O)(CH_2)_2CO_2H$	$HS(CH_2)_3SH$	16	90 (**24**)
12	$CH_3C(O)CH_2CO_2CH_3$	$HS(CH_2)_3SH$	17	91 (**25**)
13	Cyclohexanone	$HS(CH_2)_3SH$	10	96 (**26**)
14		$HS(CH_2)_3SH$	6	98 (**27**)
15		$HS(CH_2)_3SH$	120	80 (**28**)
16[c]		$HS(CH_2)_2SH$	26	76 (**29a**) 5 (**29b**)  **a**: X-X = O **b**: X-X = $S(CH_2)_2S$
17[c]		$HS(CH_2)_2SH$	40	72 (**30a**) 3 (**30b**)  **a**: X-X = O **b**: X-X = $S(CH_2)_2S$

[a] Isolated and purified yield.
[b] Carried out under reflux.
[c] 1.0 equiv of $HS(CH_2)_2SH$ and 10 mol % of $VO(OTf)_2$ were used.

Table 4
Transthioacetalization of acetals catalyzed by $VO(OTf)_2$



Entry	Substrate	Time (h)	Product	Yield[a] (%)
1		1.5	**5a**	94
2		2	**6**	92
3		2	 **31**	96
4		2	**14**	97
5		3.5	**18a**	94
6		4	 **32**	95
7		0.75	 **33**	98
8		1	 **34**	92

[a] Isolated and purified yield.

1,3-dithiolane **29a** and di-protected bis-1,3-dithiolane **29b** were isolated in 76% and 5% yields, respectively, corresponding to a selectivity of 94:6 in favor of the enone protection. On the other hand, chemoselective protection of progesterone led to **30a** and **30b** with comparable selectivity of 96:4 in 75% overall yield (entry 17).[34] These fruitful results signify a milder, easier handling, lower catalyst loading, higher chemoselectivity, and comparable yielding protocol relative to that with a recipe of $HS(CH_2)_2SH$–*p*-TsOH/AcOH (88:12, 86% and 95:5, 37%),[35a] $Bu_2Sn(SCH_2)_2$–$Bu_2Sn(OTf)_2$ (93:7, 94% and 98:2, 71%)[35b] and $TMSS(CH_2)_2STMS$–ZnI_2 (95:5, 99% and 96:4, 98%)[35c] for **29a**/**29b** and **30a**/**30b**.

2.4. Transthioacetalization

Acetals derived from aromatic, aliphatic, and alkyne-conjugated aldehydes were converted to the corresponding dithioacetals by using 5 mol % of $VO(OTf)_2$ and 1.2 equiv of propane-1,3-dithiol in 0.25 M of CH_3CN/CH_2Cl_2 (1:7) at ambient temperature. The resultant 1,3-dithianes were afforded in high yields of 92–97% in 1.5–2 h (entries 1–4, Table 4).

In marked contrast to the direct thioacetalization of aromatic ketones (reaction time 24–26 h), transthioacetalization of acetals derived from aromatic ketones proceeded efficiently in 94–95% yields with dramatically reduced reaction time (3.5–4 h), entries 5 and 6. Benzylidenes and acetonides are commonly used protecting groups for 1,2- and 1,3-diols in carbohydrate chemistry.[5] This new transthioacetalization methodology is further applied to a benzylidene-protected thioglucoside (entry 7), which leads to deprotected 1,3-diol **33** in 45 min and in 98% yield. Finally, regioselective removal of the terminal acetonide in a double isopropylidene-protected furanose was achieved in 1 h to provide adduct **34** (entry 8) in 92% yield. The present protocol is favored over that of 80% aq AcOH (at 90 °C)[36] and that of silica gel-supported $FeCl_3$.[37] It also represents an improved and alternative protocol relative to that of 20 mol % $VO(OTf)_2$/MeOH–CH_2Cl_2 (at 55 °C) reported recently by us.[38]

3. Conclusion

We have documented a new catalytic protocol for the thia-Michael addition of α,β-unsaturated carbonyls, thioacetalization of aldehydes and ketones, and transthioacetalization of acetals with high chemoselectivity (aldehyde vs ketone and enone vs ketone) and diverse functional group (i.e., hydroxy, alkoxy, acyloxy, halide, amino, nitro, pyrimidyl, acid, and ester) tolerance. In sharp contrast to those catalyzed by common Brønsted or Lewis acids, the reactions catalyzed by $VO(OTf)_2$ can be carried out at ambient temperature with catalyst loading of less than 10 mol % with straight thiol or dithiol nucleophiles, which augur well for its future application in organic synthesis.

4. Experimental

4.1. General procedure for thia-Michael addition

To a 10 mL, round-bottomed flask was placed $VO(OTf)_2$ (5 mol %), an α,β-unsaturated carbonyl (1.0 mmol) in CH_3CN/CH_2Cl_2 (1:4, 0.5 M; 1:1, 0.5 M or 1:1, 1.0 M). A given thiol (1.2–2.0 equiv) was added and the reaction mixture was stirred at ambient temperature for an appropriate reaction time as monitored by TLC (see Table 1). The resulting reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel to give the corresponding isolated product.

4.2. General procedure for thioacetalization and transthioacetalization

To a 10 mL, round-bottomed flask was placed $VO(OTf)_2$ (5–15 mol %), a carbonyl or acetal (1.0 mmol) in CH_3CN/CH_2Cl_2 (1:7, 0.25 M or 1:3, 0.17 M). A given dithiol (1.0–2.0 equiv) was added and the reaction mixture was stirred at ambient temperature for an appropriate reaction time (see Table 2–4). After the completion of reaction (as monitored by TLC), the catalyst was filtered off by a short plug of silica gel. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel to give the corresponding isolated product.

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Supplementary data

Characterization data and ^1H, ^{13}C NMR spectra for products **1a′**–**4a′** and **5a**–**34** are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.10.012.

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