JOC*Note*

Hafnium Trifluoromethanesulfonate (Hafnium Triflate) as a Highly Efficient Catalyst for Chemoselective Thioacetalization and Transthioacetalization of Carbonyl Compounds

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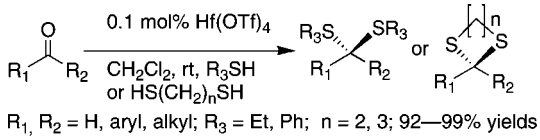

A range of carbonyl compounds including aliphatic and aromatic aldehydes and ketones were converted to the corresponding thioacetals in high yields in the presence of a catalytic amount of hafnium trifluoromethanesulfonate (0.1 mol %, room temperature). The mild conditions tolerated various sensitive functional and protecting groups and were racemization-free when applied to α-aminoaldehydes. Transacetalization and chemoselective thioacetalization of aromatic aldehydes in the presence of aliphatic aldehydes and ketones were also documented.

Thioacetals are useful carbonyl protecting groups thanks to their inherent stability under both acidic and basic conditions.[1] In addition, 1,3-dithianes have been widely used in organic synthesis as masked acyl anions[2] or masked methylene functions[3] in carbon−carbon bond-forming reactions. Generally, they are prepared by condensation of carbonyl compounds with thiols or dithiols in the presence of protic[4] and Lewis acids.[5,6] These methods often required long reaction time, drastic reaction conditions, and stoichiometric amount of catalyst and failed to protect deactivated aromatic substrates. Furthermore, many reported methods were incompatible with sensitive functional and protecting groups and displayed poor aldehydes versus ketones chemoselectivity. We report herein that $Hf(OTf)_4$ is a highly efficient, racemization-free catalyst for the thioacetalization of carbonyl compounds.

In connection with our synthetic program dealing with the synthesis of tetrahydroisoquinoline-containing alkaloids,[7,8] we observed that hafnium trifluoromethanesulfonate [$Hf(OTf)_4$] is an efficient catalyst for transforming the aminal to aminothioether, a key intermediate in the synthesis of antitumor antibiotic (−)-quinocarcin.[9] The high oxophilicity[10] and low thiophilicity[11] of $Hf(OTf)_4$ led us to hypothesize that it could potentially act as an efficient catalyst for the conversion of carbonyl compounds to the corresponding thioacetals/thioketals. Indeed, simply stirring a dichloromethane solution of 4-nitrobenzaldehyde (**1a**) and ethanethiol (**2a**) at room temperature in the presence of 0.1 mol % of $Hf(OTf)_4$ afforded the corresponding thioacetals (**3a**) in 99% yield (Table 1). This reaction, completed within 5 min, is extremely easy to perform without the need of using anhydrous solvent and inert atmosphere.

This simple procedure turned out to be applicable to a wide range of carbonyl compounds including racemization-prone α-aminoaldehydes. The results are summarized in Table 1. Reaction of ethanethiol with both electron-rich and electron-poor aromatic aldehydes afforded the corresponding thioacetals

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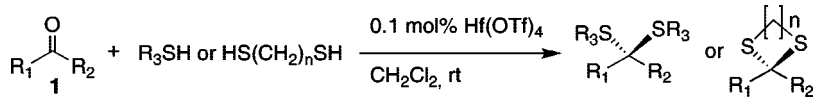
TABLE 1. Hf(OTf)$_4$-Catalyzed Thioacetalization of Aldehydes and Ketones to Thioacetals[a]



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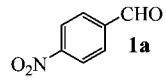
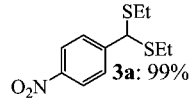
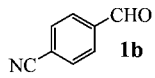
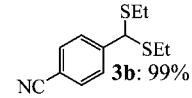
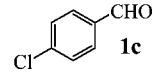
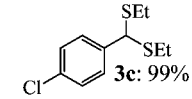
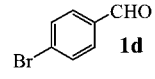
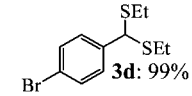
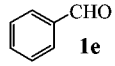
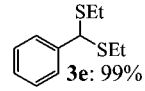
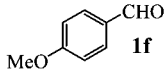
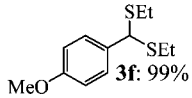
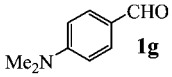
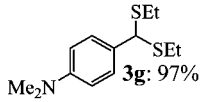
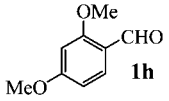
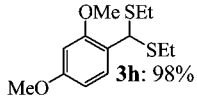
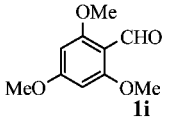
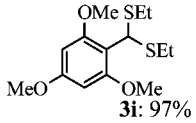
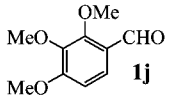
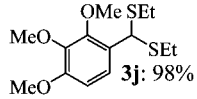
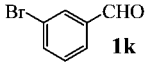
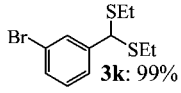
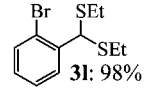
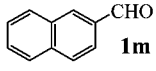
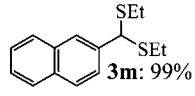
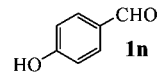
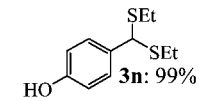
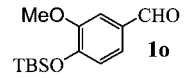
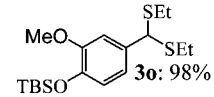
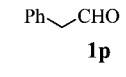
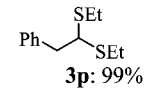
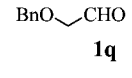
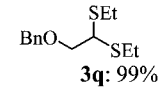
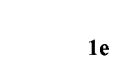
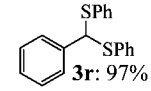
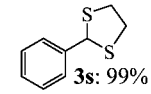
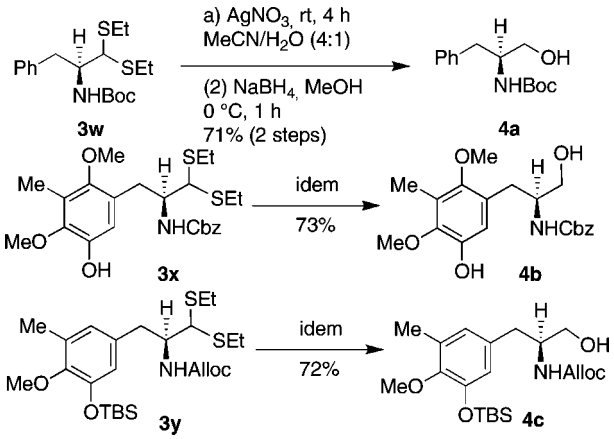
1	 **1a**	EtSH (**2a**)	5	 **3a**: 99%
2	 **1b**	**2a**	5	 **3b**: 99%
3	 **1c**	**2a**	5	 **3c**: 99%
4	 **1d**	**2a**	5	 **3d**: 99%
5	 **1e**	**2a**	5	 **3e**: 99%
6	 **1f**	**2a**	5	 **3f**: 99%
7	 **1g**	**2a**	5	 **3g**: 97%
8	 **1h**	**2a**	10	 **3h**: 98%
9[c]	 **1i**	**2a**	15	 **3i**: 97%
10	 **1j**	**2a**	10	 **3j**: 98%
11	 **1k**	**2a**	5	 **3k**: 99%
12	 **1l**	**2a**	8	 **3l**: 98%
13	 **1m**	**2a**	5	 **3m**: 99%
14	 **1n**	**2a**	5	 **3n**: 99%
15	 **1o**	**2a**	5	 **3o**: 98%
16	 **1p**	**2a**	20	 **3p**: 99%
17	 **1q**	**2a**	20	 **3q**: 99%
18	 **1e**	PhSH **2b**	10	 **3r**: 97%
19	**1e**	 **2c**	5	 **3s**: 99%
20	**1e**	**2d**	5	**3t**: 99%
21	**1r**	**2a**	30	**3u**: 98%
22	**1s**	**2a**	120	**3v**: 98%
23	**1t**	**2a**	240	**3w**: 92%
24	**1u**	**2a**	240	**3x**: 93%
25	**1v**	**2a**	240	**3y**: 94%

[a] General conditions: **1** (1.0 mmol), **2a**−**2b** (2.0 mmol) or **2c**−**2d** (1.0 mmol), and Hf(OTf)$_4$ (0.001 mmol) in CH_2Cl_2 (2 mL) at room temperature. [b] Minutes. [c] One mole percent Hf(OTf)$_4$ was used. TBS = *tert*-butyldimethylsilyl; Bn = benzyl; Boc = *tert*-butylcarbonyl; Cbz = benzyloxycarbonyl; Alloc = allyloxycarbonyl.

in excellent yields within less than 15 min (Table 1, entries 1−15). The highly deactivated and sterically hindered 2,4,6-trimethoxybenzaldehyde (**1i**) that resisted most of the thioacetalization conditions was converted to thioacetal **3i** in excellent yield (97%, entry 9). Aliphatic aldehydes (**1p,q**, Table 1, entries 16 and 17) reacted equally well with EtSH to afford the corresponding thioacetals (**3p,q**) in high yields. Other thiols such as benzenethiol (PhSH, **2b**), 1,2-ethanedithiol (**2c**), and 1,3-propanedithiol (**2d**) participated in the thioacetalization of aldehydes uneventfully (entries 18−20). Aromatic ketone (**1r**,

SCHEME 1. Probing the Racemization Issue



SCHEME 2. Chemoselective Thioacetalization of Carbonyl Compounds

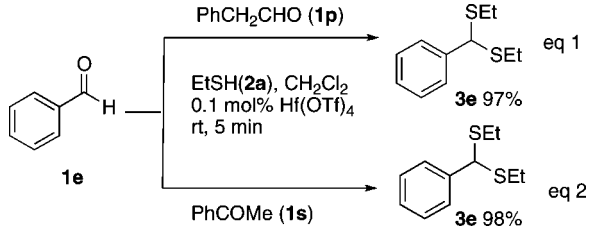
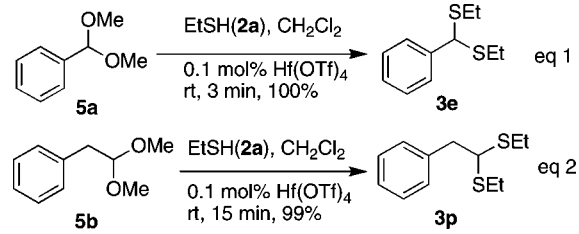


Table 1, entry 21) and aliphatic ketone (**1s**, entry 22) were similarly converted to the acetals under the standard conditions, albeit with a longer reaction time.

Finally, chiral nonracemic α-aminoaldehydes **1t**, **1u**, and **1v** were converted to the corresponding acetals **3w**, **3x**, and **3y** in excellent yields (entries 23−25). To verify if any racemization took place during thioacetalization, the thioacetals **3w**−**y** were converted back to the corresponding aminoalcohols **4a**−**c** via a sequence of dethioacetalization[12] and reduction (Scheme 1). The optical rotation ($[\alpha]_D$) of these compounds matched with those obtained by the direct reduction of chiral aldehydes **1t**−**v** ($NaBH_4$, MeOH, 0 °C, 1 h), as well as those described in the literature.[13,14]

We next examined the applicability of this protocol to the selective thioacetalization of carbonyl groups. When an equimolar mixture of benzaldehyde (**1e**) and phenylacetaldehyde (**1p**) was allowed to react with EtSH under our established conditions [0.1 mol % $Hf(OTf)_4$, CH_2Cl_2, rt], only **1e** was converted to thioacetal **3e** (98% yield) without a touch of **1p** (Scheme 1, eq 1). Similarly, selective thioacetalization of benzaldehyde (**1e**) was realized in the presence of equimolar amount of acetophenone (**1s**, Scheme 2, eq 2). We believed that such selective thioacetalization procedure would be useful in the synthesis of complex molecules.

SCHEME 3. $Hf(OTf)_4$-Catalyzed Transthioacetalization



The $Hf(OTf)_4$-catalyzed system is also suitable for transthioacetalization[15] of acetals to thioacetals. Both aromatic acetal (**5a**) and aliphatic acetal (**5b**) could be converted to the corresponding thioacetals (**3e** and **3p**) in high yields under standard conditions (Scheme 3).

We emphasize that a variety of functional and protecting groups such as nitro, cyano, dimethylamino, hydroxy, *tert*-butyldimethylsilyl, benzyloxy, *tert*-butylcarbonyl (Boc), benzyloxycarbonyl (Cbz), and allyloxycarbonyl (Alloc) are tolerated under the present thioacetalization conditions.

In summary, $Hf(OTf)_4$ is an excellent catalyst for the thioacetalization of aldehydes and ketones. The reaction took place at room temperature and displayed excellent functional group compatibility. The protocol is also very effective for the transthioacetalization of acetals to thioacetals and is racemization-free when applied to chiral nonracemic α-aminoaldehyde. Chemoselective thioacetalization of aromatic aldehyde in the presence of aliphatic aldehyde and aromatic ketone was also demonstrated.

Experiment Section

$Hf(OTf)_4$-Catalyzed Thioacetalization Procedure. A solution of 4-*tert*-butyldimethylsilyloxy-3-methoxybenzaldehyde (**1o**, 266.4 mg, 1.0 mmol), EtSH (**2a**, 0.15 mL, 2.0 mmol), and $Hf(OTf)_4$ (0.8 mg, 0.001 mmol) in CH_2Cl_2 (2 mL) was stirred at room temperature for 5 min. The reaction mixture was filtered through a short pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford thioacetal **3o** (365.2 mg) in 98% yield as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (d, 1H, J = 2.1 Hz), 6.84 (dd, 1H, J = 8.1, 2.1 Hz), 6.75 (d, 1H, J = 8.1 Hz), 4.88 (s, 1H), 3.81 (s, 3H), 2.62−2.48 (m, 4H), 1.21 (t, 6H, J = 7.4 Hz), 0.99 (s, 9H), 0.14 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.0, 144.6, 133.7, 120.3, 120.1, 111.3, 55.4, 52.4, 26.3, 25.7, 18.4, 14.3, −4.7; FTIR (film) 2956, 2927, 2855, 1508, 1463, 1415, 1282, 1249, 1236, 1206, 1148, 1122, 1036, 903, 838, 822, 804, 780, 746, 701 cm^{-1}; MS 372 (M^+), 311; HRMS (TOF MS ES$^+$) *m*/*z* calcd for $C_{18}H_{32}O_2NaSiS_2$ $[M + Na]^+$ 395.1511, found 395.1511.

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Supporting Information Available: Experimental procedures; characterization data; and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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