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Low temperature syntheses of thioketals from enol ethers and carbonyl compounds

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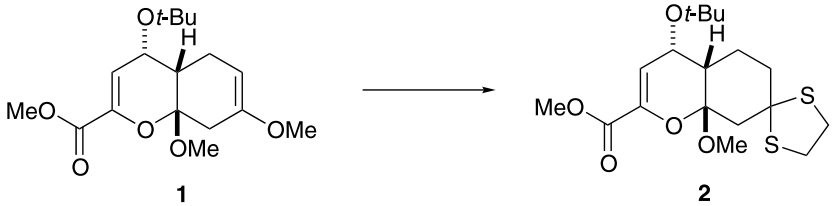
Abstract—A dithioacetalisation procedure at low temperature using TMSOTf as the promoter is described. This method proved highly efficient for unprecedented transprotection of ketone enol ethers and was successfully applied to polyfunctional sensitive substrates.

Thioacetalisation of aldehydes and ketones is often employed in the course of the synthesis of multifunctional target molecules.[1] In this very active area of protection chemistry applied to free carbonyl compounds, numerous recent reports concern the development of simple procedures using smooth catalysts ($LiBF_4$,[2] LiBr,[3] LiOTf,[4] $Cu(OTf)_2$-SiO_2,[5] I_2,[6] trichlorocyanuric acid,[7] $InCl_3$[8]), even under solvent-free conditions.[3–5] On the other hand transprotection methods mainly refer to transdithioacetalisation of *O*,*O*- and *O*,*S*-acetals.[3,4,9–12] Sudalai and co-workers[10] also described the transdithioacetalisation of oximes, enamines, and tosylhydrazones using a kaolinitic clay as the catalyst, but, to our knowledge, transprotection of ketone enol ethers have only been reported for simple substrates using harsh acidic conditions (gaseous HCl in chloroform).[13]

We report here a general dithioacetalisation procedure with 1,2-ethanedithiol at low temperature (−78°C) using TMSOTf as the promoter. This method proved to be particularly efficient for the transprotection of enol ethers.

In the course of an ongoing program,[14] we had to perform the selective transformation of enol ether **1** into dithioketal **2**[15] (Scheme 1). Due to the presence of *O*,*O*-ketal or *tert*-butoxy group, which are labile under acidic conditions, conventional methods (gaseous HCl in chloroform)[13] led only to degradation products when applied to enol ether **1**. Nearly the same result was observed when using strong Lewis acids ($TiCl_4$, $BF_3{\cdot}Et_2O$), and $Zn(OTf)_2$ was ineffective at room temperature. Use of 20 mol% $SnCl_4$ gave the desired transprotected compound **2**, but only in moderate yield.

At −10°C, a significant degradation of **1** occurred. This problem was solved at −60°C, but yield of **2** was still restricted by competitive formation of the bridged,



Scheme 1. *Reagents and conditions*: 1.0 equiv. $HSCH_2CH_2SH$, 1.25 equiv. TMSOTf, CH_2Cl_2, −78°C, 4 h (80%).

Keywords: thioacetals; transprotection; enol ethers; TMSOTf.

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di-*O*,*S*-acetalic, regioisomer. These last experiments proved that the Lewis acid-mediated methods classically used for the transformation of ketones into thioketals either (1) cannot be applied to the transformation of enol ethers into thioketals or (2) could allow this transprotection, but only in the case of rather simple substrates, which are deprived of any other acid labile functional group. Indeed, the Lewis acid used must respect some conditions. First, it must lead to a protic acid in situ, in order to perform the protonation of the double bond, and, above all, it must have a great affinity for oxygen in order to promote the ejection of the alkoxy group. In the special case of **1**, conditions used must be also non-degradative and selective. Trimethylsilyl trifluoromethanesulfonate (TMSOTf) appeared to be the ideal reagent. Indeed, the use of a slight excess of this reagent in CH_2Cl_2 at −78°C led after 4 h to the clean and regioselective protection of the enol ether moiety. The desired crystalline thioketal **2** was isolated after chromatography in 80% yield on a 1–10 mmol scale.[16]

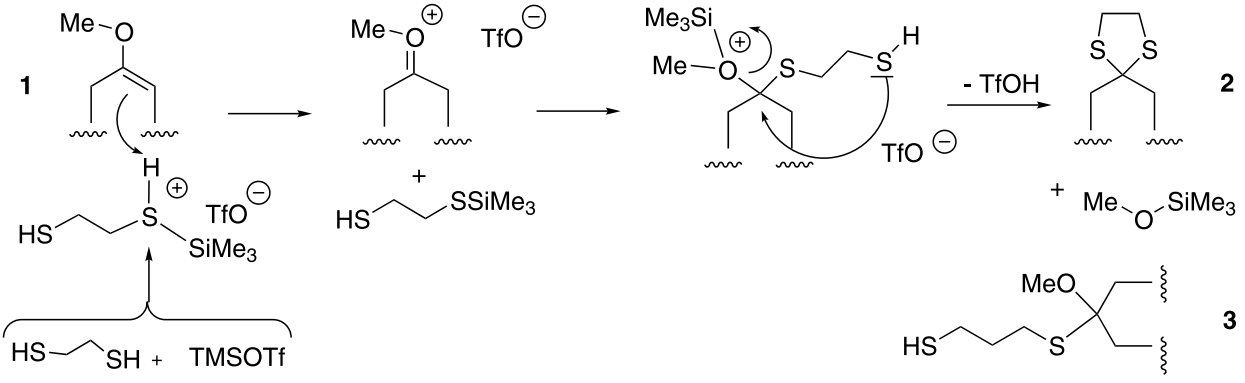
We suppose that TMSOTf and dithiol would preform a silylsulfonium intermediate, that would be acidic enough to protonate the double bond and perform the activation of enol ether **1**. Then, the co-produced thiosilane would add to the resulting oxonium. Subsequent activation of the methoxy group into a trimethylsilyloxonium would favor the final substitution by the thiol, thus leading to the thioketal **2** and methyl trimethylsilyl ether (Scheme 2). This pathway is supported by the fact that using catalytic amounts ot TMSOTf (10 mol%) under the same conditions led to a poor yield of dithiane **2** (<10%), the main reaction product being the corresponding *O*,*S*-ketal **3**.

The high reactivity of TMSOTf is crucial in our reaction and allowed us to lower significantly the temperature, thus selectively leading to the requisite thioketal without appreciable side-reactions. TMSOTf has already been used for the conversion of a ketal into a dithioketal at 0°C,[17] but these conditions rapidly led to the degradation of enol ether **1**, thus showing the significant role of temperature.

The scope of this unusual[18] thioacetalisation procedure was next explored (Table 1). First, a comparative study between cyclohexanone,[19] its corresponding acetal and its corresponding methyl and TBDMS enol ethers confirmed that both enol ethers are very convenient substrates under these conditions. Thus, TBDMS enol ethers of cyclohexanone and cyclododecanone afforded thioketals **4a** and **4b** in nearly quantitative yields. Di-protected compound **4c** was conveniently obtained from the corresponding sensitive alkyl enol ether. Another interesting feature of this reaction was the selective transprotection of enol ethers **6** and **7** (entries 9 and 10) without alteration of the α-ketoester moiety. Others experiments evidenced the convenient conversion of acyclic ketones and aldehydes under these conditions.

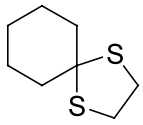
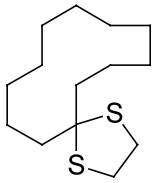
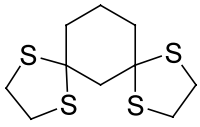
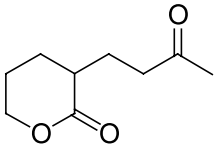
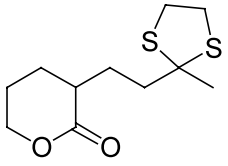
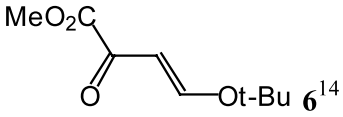
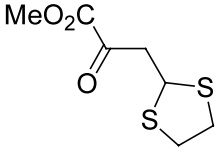
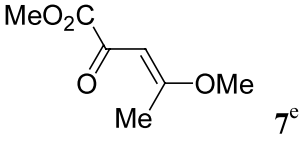
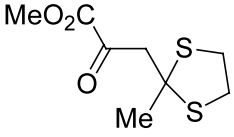
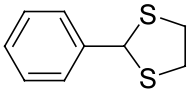
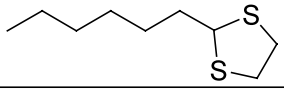
Finally, this method also enabled the transformation of bicyclic ketone **8** into dithioketal **2** (Scheme 3). The same reaction was also performed following the very mild conditions described by Evans and coworkers.[22] In the latter case, we obtained a lower yield, due to the incomplete conversion of ketone **8** (a silylhemithioketal was competitively formed). This example[23] illustrates that the use of TMSOTf at low temperature can be complementary to the method described by Evans and besides offers the benefit of the low cost of the reagents used. A similar complementarity was previously reported for the conversion of carbonyl compounds into 1,3-dioxolanes (use of 1,2-bis-(trimethylsilyloxy)ethane/cat. TMSOTf at −78°C[24] versus use of ethyleneglycol/TMSCl at 20–40°C[25] or ethyleneglycol/alkoxysilane/cat. TMSOTf at −20°C[26]).

In conclusion, enol ethers, carbonyl compounds and acetals can be converted into thioketals at low temperature using TMSOTf as a stoichiometric reagent. Although less economical for simple substrates than above-mentioned catalytic procedures,[1–12] this method



Scheme 2.

Table 1. Thioacetalisation[a] of various carbonyl compounds, enol ethers and ketal derivatives

Entry	Starting material	Thioacetal **4**[21]		Yield (%)[b]
1	Cyclohexanone		**4a**	93
2	Cyclohexanone dimethylacetal		**4a**	89
3	1-Methoxy-cyclohex-1-ene		**4a**	90
4	1-*t*-Butyldimethylsilyloxy-cyclohex-1-ene		**4a**	92
5	Cyclododecanone		**4b**	80
6	1-*t*-Butyldimethylsilyloxy-cyclododec-1-ene		**4b**	95
7	1,5-Dimethoxy-cyclohexa-1,4-diene		**4c**	85
8	 **5**[d]		**4d**	93
9	 **6**[14]		**4e**	76[c]
10	 **7**[e]		**4f**	85[c]
11	Benzaldehyde		**4g**	94
12	Heptanal		**4h**	80

[a] Each reaction was carried out using ethanedithiol (1.0 equiv.) and TMSOTf (1.25 equiv.) in CH_2Cl_2 at −78°C for 4 h.
[b] Unoptimised yield of isolated product (after filtration over silica gel).
[c] Purified by flash column chromatography on silica gel.
[d] Prepared by PCC-oxidation of the corresponding lactol, see Ref. 20.
[e] Prepared according the procedure analogous to that used for **6**.

can be very useful for protection under highly-controlled conditions of more elaborate and/or sensitive substrates. This property was exemplified by the efficient transprotection of the polyfunctional enol ethers **1**, **6** and **7**.

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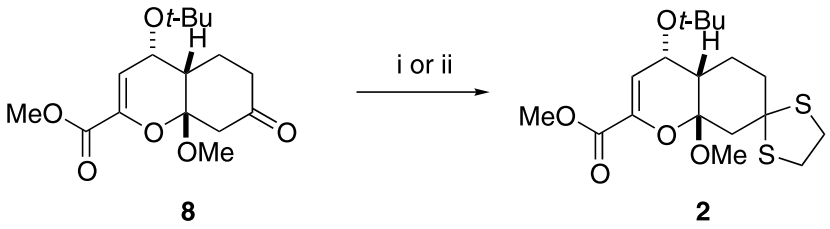

8 2

Scheme 3. *Reagents and conditions*: (i) 1.1 equiv. $Me_3SiSCH_2CH_2SSiMe_3$, 0.03 equiv. ZnI_2, Et_2O, rt, 48 h (48%); (ii) 1.0 equiv. $HSCH_2CH_2SH$, 1.25 equiv. TMSOTf, CH_2Cl_2, −78°C, 4 h (71%).

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16. *Typical experimental procedure*: To a stirred solution of starting material (1 mmol) and 1,2-ethanedithiol (84 μL, 1 mmol) in CH_2Cl_2 (5 mL), TMSOTf (240 μL, 1.25 mmol) was added under an argon atmosphere at −78°C, and the resulting mixture was stirred at −78°C. After completion of the reaction (4 h) the mixture was treated with sat. $NaHCO_3$ (3 mL). The organic layer was separated and extracted with diethylether (3×10 mL). The ether layer was separated, dried ($MgSO_4$) and filtered through a short pad of silica gel. After evaporation of the solvent in vacuo, the desired product was obtained in most cases with a high purity. Thioketals **2**, **4e** and **4f** were further purified by column chromatography on silica gel (ethyl acetate/cyclohexane: 1/9 to 2/8). Selected data for **2** (colorless oil), HRMS (EI): ($C_{18}H_{28}O_5S_2$) calcd 388.1378; found 388.1360.
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18. Known thioacetalisation procedures are typically performed at room temperature or reflux and never employed temperatures lower than −10°C.
19. A good conversion of cyclohexanone into thioketal **4a** was observed when using a catalytic amount of TMSOTf (e.g. 61% yield with 10 mol%) under the same conditions, suggesting a different mechanism than that expected when starting from enol ethers.
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21. Compounds **4a**–**c** and **4g**,**h** are known compounds. New compounds gave satisfactory spectral and elemental data. Selected data for **4d** ($C_{11}H_{18}O_2S_2$) calcd: C, 53.82; H, 7.36; S, 26.03; found: C, 53.74; H, 7.66; S ,25.51. Compound **4e** ($C_7H_{10}O_3S_2$) calcd: C, 40.75; H, 4.88; S, 31.09; found: C, 40.72; H, 4.95, S 30.76%; HRMS (EI): calcd 206.0071; found 206.0072; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.19$ (s, 4H); 3.43 (d, *J* 6.9 Hz, 2H), 3.88 (s, 3H), 4.86 (t, *J* 6.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 38.5$ (2), 46.0, 49.7, 53.1, 160.5, 191.0.
    Compound **4f** ($C_8H_{12}O_3S_2$) calcd: C, 43.61; H, 5.48; found: C, 43.86; H, 5.34%. HRMS (EI): calcd 220.0228; found 220.0219; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.89$ (s, 3H), 3.36 (s, 4H); 3.57 (s, 2H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 31.1$, 39.7 (2), 53.0, 53.2, 61.4, 161.2, 190.5.
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