AN EFFECTIVE SYNTHESIS OF 1,3-OXATHIOLANES

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2-Alkyl- or 2,2-dialkyl-1,3-oxathiolanes can be effectively prepared from aldehydes or ketones and 2-mercaptoethanol, with triisopropylsilyl triflate as a catalyst. The reaction is over within minutes and, despite the fact that water is nor removed during the reaction, the yields of products are high.
Key words: Ketone; Aldehyde; Protection; 1,3-Oxathiolane.

The acetal group belongs to the most widely used protective groups of carbonyl functionalities in aldehydes and ketones. Sometimes, however, problems may occur during their acidic deprotection and *e.g.* 1,3-dithians or 1,3-dithiolane derivatives are being used instead[1]. Relatively little attention in this respect has been paid to 1,3-oxathiolanes that can be considered, from the point of view of deprotection feasibility, as the intermediaries between both dioxa- and dithio-protection means. For instance, 1,3-oxathiolanes in contrast to 1,3-dithiolanes can be relatively easily hydrolyzed using acids[1] while other ways of their deprotection are also available, *e.g.* $TeCl_3/CH_2Cl_2$ (ref.[2]), CH_3I/acetone (ref.[3]), chloramine T/methanol (ref.[4]), benzyne (ref.[5]), $LiAlH_4$ (ref.[6]) or $KMnO_4$ (ref.[7]). Regardless of their potential as the valuable protection means and/or synthetic intermediates[8], relatively little examples of 1,3-oxathiolane preparation have been published so far, most of them addressing the protection of ketones. The reaction conditions applied in these preparations, *i.e.* elevated temperature (the azeotropic removal of water), acidic milieu [catalysis with acids (ref.[9]), $BF_3 . Et_2O$ (ref.[10]), ion-exchange resins (ref.[11]), SO_2 (ref.[12]), $ZnCl_2/Na_2SO_4$ (ref.[13])], and rather long reaction times disqualify these methods as tools for the protection of generally less stable carbonyl compounds. Some technical problem can also be encountered when the above conditions are applied to the small scale preparation. Accordingly, there is still a need for more general pathways of 1,3-oxathiolane synthesis[14–16].

In this paper we would like to report a convenient method for preparing 1,3-oxathiolanes from aldehydes and ketones by reaction with 2-mercaptoethanol using catalytic amount of triisopropylsilyl triflate.

EXPERIMENTAL

The starting aldehydes or ketones were either distilled or chromatographed on silica gel prior the use. Commercially available triisopropylsilyl triflate (TIPSOTf) was used as a catalyst for all reactions included in this paper and both TIPSOTf (24,846-0) and 2-mercaptoethanol (M370-1) were purchased from Aldrich, Czech Republic and used without any purification. For IR (CCl_4) and mass recordings, Perkin–Elmer 580 spectrometer and ZAB EQ instrument (VG, Great Britain; EI 70 eV) were used. Both ^1H and ^{13}C NMR spectra of compound **3e** were taken in $CDCl_3$ on a FT NMR spectrometer Varian UNITY-500 (499.8 MHz for ^1H and 125.8 MHz for ^{13}C, APT technique[17], solvent signal as an internal standard, δ 77.00). All other compounds were characterized using UNITY-200 spectrometer (200.04 MHz for ^1H, in deuteriochloroform with tetramethylsilane as an internal standard). The homo-correlated 2D NMR COSY spectrum[18] was obtained using the standard pulse sequence (designed by the producer) under following parameters: spectral width in both f_1 and f_2 dimensions 4 100 Hz, number of scans 4, 256 increments, recycle delay 1 s, acquisition time 0.25 s, 90° pulse 14 ms, data matrix for processing 2 048 × 2 048; processing function: sine-bell in both dimensions. The resulting spectrum was symmetrized around the main diagonal. For uninterchangeable assignment of signals in ^{13}C NMR spectrum, the hetero-correlated 2D NMR spectrum was taken by HMQC technique[19] using the standard pulse sequence (given by the spectrometer producer; following set of parameters used: spectral width in both f_1 and f_2 dimensions 4 000 and 25 000 Hz, respectively; number of scans 8, increments of f_1 300, recycle delay 1 s, acquisition time 0.2 s, 90° pulse for ^1H 29 ms, data matrix for processing 2 048 × 2 048, no weighted function). NMR data for all compounds are given in both ppm (chemical shifts) and Hz (coupling constants) units.

General Procedure for Preparation of 1,3-Oxathiolanes **3a–3k**

To the stirred solution of TIPSOTf (3.1 mg, 0.01 mmol) in dioxane (0.5 ml), the mixture of aldehyde or ketone (1 mmol) and 2-mercaptoethanol (0.105 ml, 1.5 mmol) in dioxane (0.5 ml) was quickly added at room temperature. Then the reaction vessel was heated on 85 °C and stirring was continued for additional 0.5 h at this temperature. After being cooled to the room temperature, the reaction mixture was mixed up with triethylamine (4 μl, 0.03 mmol), diluted with saturated sodium hydrogencarbonate solution (2 ml), extracted with the pentane–ether mixture (1 : 1, 3 × 3 ml) and the combined extracts dried over Na_2SO_4. Simple evaporation (rotatory evaporator), chromatography on Florisil (10 times, pure pentane as a solvent) and the final evaporation at 1.6 kPa/r.t. for 45 min gave pure products **3a–3i** and **3k**. Compound **3j**, because of its low boiling point was obtained by removing pentane using 1.5 × 8 cm Vigreux column and the rest was redistilled by short-path distillation. The analytical data and the survey of structures prepared are summarized in the Table I.

1,1-Bis(2-hydroxyethylthio)-2-methylpentane (**2e**)

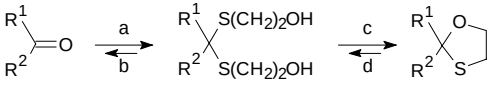
To the solution of TIPSOTf (4.6 mg, 0.015 mmol) in dioxane (0.7 ml) under the stirring at room temperature, the mixture of 2-methylpentanal (0.15 g, 1.5 mmol) and 2-mercaptoethanol (158 μl, 2.2 mmol) in dioxane (1.5 ml) was quickly added. The reaction mixture was then decomposed with saturated sodium hydrogencarbonate solution (2 ml), extracted with ether (3 × 3 ml) and the solution dried with Na_2SO_4. After evaporation of solvents, the residue was chromatographed on silica gel with the pentane–ether mixture (1 : 1). Evaporation of the solvent (rotatory evaporator), and final evaporation at 1.6 kPa/r.t. for 45 min gave 0.196 g (55%) of **2e**. ^1H NMR spectrum, 0.92 t, 3 H, J = 6.4 (CH_3CH_2); 1.08 d, 3 H, J = 6.8 (CH_3CH); 1.20–2.02 m, 4 H (CH_2); 2.72–3.01 m, 4 H (SCH_2); 3.74–3.85 m, 4 H (CH_2O); 3.89 d, 1 H, J = 3.4 (CH(O)(S)). IR spectrum: 3 381, 1 465, 1 377, 1 055 cm^{-1}. Mass spectrum, *m/z* (%): 238 (M^+, 6), 161 (37), 83 (100), 61 (15), 55 (34), 41 (28).

2-(1-Methylbutyl)-1,3-oxathiolane (**3e**) from **2e**

1,1-Bis(2-hydroxyethylthio)-2-methylpentane (**2e**, 0.166 g, 0.7 mmol) obtained by the above described procedure was dissolved in dioxane (0.7 ml) and then the solution of TIPSOTf (2 μl, 7 μmol) in the same solvent (0.3 ml) was quickly added. The reaction vessel was then transferred into the oil bath, warmed up to 85 °C beforehand, and the content stirred for additional 0.5 h at this temperature. After being cooled to the room temperature and the working up as already described in preceding paragraphs, the mixture gave yield to 79 mg (60%) of the product **3e.** The properties were in accordance with those for compound **3e** prepared without the isolation of open chain dithioacetal **2e**.

RESULTS AND DISCUSSION

We have found that TIPSOTf effectively catalyzes the 2-mercaptoethanol protection of aldehydes and/or ketones despite the fact that water is not being removed during this reaction. In accordance with Djerassi who assumed initial attack of more nucleophilic thiol end in this type of reactions[23], the open chain dithioacetal **2** (Scheme 1) can be isolated as a reaction intermediate. The product ratio **2**/**3** depends on the temperature and also on the structure of starting carbonyl compound. Consequently, either open chain dithioacetal **2** or 1,3-oxathiolane **3** can be isolated under specific reaction conditions.



1 **2** **3**

a) $HS(CH_2)_2OH$, TIPSOTf, dioxane, r.t.; b) H_2O
c) TIPSOTf, dioxane, 80 °C; d) $HS(CH_2)_2OH$

1, 2, 3	R^1	R^2
a	CH_3	CH_3
b	—$(CH_2)_5$—	
c	CH_3	$(CH_3)_2CHCH_2CH_2CH_2$
d	CH_3	CH_3CH_2
e	H	$CH_3CH_2CH_2CH(CH_3)$
f	CH_3	$(CH_3)_2C{=}CHCH_2CH_2$
g	H	$C_6H_5CH_2$
h	—$CH_2CH_2CH_2CH(COOCH_2CH_3)$—	
i	H	(*Z*) $CH_3(CH_2)_3CH{=}CH(CH_2)_9$
j	H	CH_3
k	H	$(CH_3)_2C{=}CHCH_2CH_2CH(CH_3)CH_2$
l	—$CH_2CH_2CH_2C(CH_3){=}CH$—	
m	C_6H_5	C_6H_5
n	H	$CH_3CH{=}CH$
o	H	4-$CH_3C_6H_4$

SCHEME 1

TABLE I
Yields and characteristic data of 1,3-oxathiolanes **3a–3o**

	Product	Yield[a], %	IR[b] cm^{-1}	MS M^+, *m/z*	^1H NMR, δ, ppm; *J*, Hz
3a[c]	2,2-Dimethyl-1,3-oxathiolane	96	1 060	118	1.64 s, 6 H (CH_3); 3.12 t, 2 H, *J* = 6 (CH_2S); 4.17 t, 2 H, *J* = 6 (CH_2O)
3b[d]	1-Oxa-4-thiaspiro[4.5]decane	94	1 071	158	1.24–1.98 m, 10 H (CH_2); 3.03 t, 2 H, *J* = 6.1 (CH_2S); 4.17 t, 2 H, *J* = 6.1 (CH_2O)
3c[e]	2-Methyl-2-(4-methylpentyl)-1,3-oxathiolane	86	1 073	188	0.89 d, 6 H, *J* = 6.4 $(CH_3)_2$; 1.12–1.86 m, 7 H, 3 × (CH_2 + CH); 1.58 s, 3 H (CH_3CH); 3.01–3.12 m, 2 H (CH_2S); 4.06–4.25 m, 2 H (CH_2O)
3d[c]	2-Ethyl-2-methyl-1,3-oxathiolane	86	1 058	132	0.99 t, 3 H, *J* = 7.3 (CH_3CH_2); 1.57 s, 3 H (CH_3); 1.84 q, 2 H, *J* = 7.3 (CH_2CH_3); 2.98–3.12 m, 4 H (CH_2S); 4.50–4.75 m, 2 H (CH_2O)
3e[f]	2-(1-Methylbutyl)-1,3-oxathiolane	70	1 078	160	0.94 t, 3 H, *J* = 6.7 (CH_3CH_2); 0.98, 1.04, 2 × d, 3 H, *J* = 5.8 (CH_3CH); 2.65–3.15 m, 2 H (CH_2S); 3.65–3.80 m, 2 H (CH_2O); 4.25–4.41 m, 1 H (CH_2O); 4.92, 4.95, 2 × d, 1 H, *J* = 6.7 (CH(O)(S))
3f[g]	2-Methyl-2-(4-methylpent-3-enyl)-1,3-oxathiolane	58	1 080	186	1.60 s, 3 H (CH_3); 1.62, 1.69, 2 × d, 6 H, *J* = 1.2 (2 × CH_3CH=); 1.78–1.88 m, 2 H (CH_2); 2.04–2.20 m, 2 H (CH_2CH=); 3.00–3.16 m, 2 H (CH_2S); 4.06–4.26 m, 2 H (CH_2O); 5.06–5.18 m (H–CH=)
3g[h]	2-Benzyl-1,3-oxathiolane	55	1 060	180	2.98–3.31 m, 4 H (CH_2S + CH_2-benzyl); 3.71–3.88 m, 1 H (CH_2O); 4.32–4.43 m, 1 H (CH_2O); 5.30 t, 1 H, *J* = 6.4 (CH(O)(S)); 7.2–7.42 m, 5 H (H–C=)
3h[i]	Ethyl 1-oxa4-thiaspiro[4.5]decane-6-carboxylate	53	1 063	216	1.27, 1.29, 2 × t, 3 H, *J* = 7 (CH_3CH_2); 1.62–2.36 m, 8 H (CH_2); 2.92–3.18 m, 2 H (CH_2S); 3.98–4.27 m, 2 H (CH_2O); 4.17 q, 2 H, *J* = 7 (CH_3CH_2O)

TABLE I
(*Continued*)

	Product	Yield[a], %	IR[b] cm^{-1}	MS M^+, *m/z*	^1H NMR, δ, ppm; *J*, Hz
3i[j]	2-[(*Z*)-Pentadec-10-enyl]-1,3-oxathiolane	52	1 060	298	0.89 t, 3 H, *J* = 6 (CH_3); 1.22–1.52 m, 20 H (CH_2); 1.90–2.05 m, 4 H (CH_2CH=); 2.98–3.08 m, 2 H (CH_2S); 3.76, 3.80, 2 × t, 1 H (CH_2O); 4.28–4.40 m, 1 H (CH_2O); 5.06 t, 1 H, *J* = 6.1 (CH(O)(S)); 5.32–5.44 m, 2 H (H–C=)
3j[k]	2-Methyl-1,3-oxathiolane	52	1 083	104	1.58 d, 3 H, *J* = 5.8 (CH_3); 3.04–3.17 m, 2 H (CH_2S); 4.28–4.40 m, 1 H (CH_2O); 5.18 q, 1 H, *J* = 5.8 (CH(O)(S))
3k[l]	2-(2,6-Dimethylhept-5-enyl)-1,3-oxathiolane	15	1 078	214	0.95 d, 3 H, *J* = 6.4 (CH_3CH); 1.60, 1.69, 2 × d, 6 H, *J* = 1.2 (2 × CH_3CH=); 2.89–3.08 m, 2 H (CH_2S); 3.71–3.83 m, 1 H (CH_2O); 4.29–4.41 m, 1 H (CH_2O); 5.04–5.18 m, 2 H (HC= and CH(O)(S))
3l	7-Methyl-1-oxa-4-thiaspiro[4.5]dec-6-ene	0			–
3m[m]	2,2-Diphenyl-1,3-oxathiolane	0			–
3n	2-[(*E*)-Prop-1-enyl)-1,3-oxathiolane	0			–
3o[n]	2-(4-Methylphenyl)-1,3-oxathiolane	0			–

[a] Isolated yield of products **3a–3o**. [b] C–O–C vibration of 1,3-oxathiolane ring. [c] *c.f.* ref.[20]. [d] *c.f.* ref.[10]. Elemental analyses: [e] For $C_{10}H_{20}OS$ (188.3) calculated: 63.78% C, 10.70% H; found: 63.35% C, 10.47% H. [f] For $C_8H_{16}OS$ (160.3) calculated: 59.95% C, 10.06% H; found: 59.68% C, 10.04% H. [g] For $C_{10}H_{18}OS$ (186.3) calculated: 64.47% C, 9.74% H: found: 64.25% C, 9.46% H. [h] *c.f.* ref.[21]. [i] For $C_{10}H_{16}O_3S$ (216.3) calculated: 55.53% C, 7.46% H; found: 55.41% C, 7.13% H. [j] For $C_{17}H_{32}OS$ (284.5) calculated: 71.77% C, 11.34% H; found: 71.86% C, 11.27% H. [k] *c.f.* ref.[12]. [l] For $C_{12}H_{22}OS$ (214.4) calculated: 67.34% C, 10.34% H; found: 67.49% C, 10.59% H. [m] *c.f.* ref.[10]. [n] *c.f.* ref.[22].

The open chain dithioacetal **2** can be transformed to the more stable cyclic product **3** at the elevated temperature. Compounds **3a–3k** thus obtained were prepared in variable yields depending on both the structure of starting material and the type of carbonyl group. While the ketones **1a–1d** afforded generally high yields of 2,2-dialkyl-1,3-oxathiolanes, the aldehydes **1g**, **1i**, and **1j** gave the moderate yield of the products, probably due to the lower stability of starting material. This may be exemplified on 3,7-dimethyloct-6-enal (**1k**) that was preferentially converted to 5-methyl-2-(propen-2-yl)-cyclohexan-1-ol. The failure of compounds **1l–1o** to produce any acetylization products under the condition used demonstrates that α,β-unsaturated and aromatic carbonyl compounds behave exceptionally. The critical analysis of ^{1}H NMR spectra of compound **3e** revealed two sets of signals of possible diastereomers. Therefore, we have taken NMR spectra for this compound at 500 MHz. Data for both *threo* and *erythro* isomer were extracted. For uninterchangable assignment of signals the 2D NMR ^{1}H,

TABLE II
NMR data of *threo*/*erythro* isomers of compound **3e**[a]

Position	*erythro*-isomers		*threo*-isomer	
	^{1}H NMR	^{13}C NMR	^{1}H NMR	^{13}C NMR
2	4.93 d (6.1)	92, 18	4.96 d (6.3)	92, 29
4	2.93 ddd (6.2,9.2,9.9) 3.00 ddd (2.7,5.7,9.9)	32, 14	2.95 ddd (6.3,9.3,9.9) 3.00 ddd (2.6,5.7,9.9)	32, 24
5	3.74 dd (5.7,9.2) 4.36 ddd (2.7,6.2,9.2)	71, 51	3.76 dt (5.7,9.3) 4.36 ddd (2.6,6.3,9.2)	71, 54
6	0.95 d (6.8)	15, 39	1.01 d (6.8)	15, 84
7	1.84 dddq (3.4,6.1,6.8,9.3)	38, 58	1.91 dddq (4.2,6.3,6.8,9.0)	38, 3
8	1.16–1.20 m 1.43–1.48 m	35, 55	1.12–1.18 m 1.52–1.59 m	35, 97
9	1.23–1.33 m 1.38–1.48 m	20, 07	1.23–1.33 m 1.38–1.48 m	20, 07
10	0.907 t (7.2)	14, 21	0.906 t (7.1)	14, 21

^{1}H-COSY[18] spectrum was recorded and the determination of "*threo*/*erythro* configuration" based on the published similarity[24]. The integral intensities of corresponding signals reveal the ratio of *threo*/*erythro* isomers to be 1 : 1. The ^{1}H NMR data together with ^{13}C chemical shifts obtained by APT technique are given in Table II.

When compared to other synthetic procedures, the triflate-based approach gives high yields of products using a very simple reaction procedure with no need of azeotropic removal of water. The short reaction time (maximum 30 min) and the easy work up, sometimes without any chromatographic purification, affords sufficiently pure products. The amount of substrate to the catalyst ratio used is low (100 : 1), the ratio 1 000 : 1 is still effective. The method does not seem to discriminate between aldehydes and ketones and is applicable to their protection in both small and large scale.

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