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A DIRECT SYNTHESIS OF O,S-ACETALS FROM ALDEHYDES [1]

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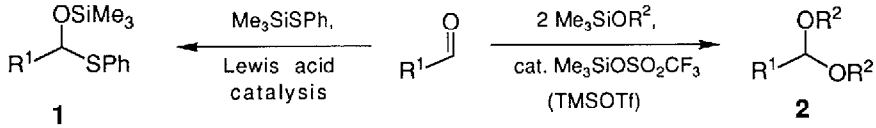
Summary: In the presence of catalytic to stoichiometric amounts of trimethylsilyl triflate, 1:1:1 mixtures of silyl ethers, phenyl(trimethylsilyl)sulfide, and aldehydes give O,S-acetals in fair to good yields.

O,S-Acetals are an increasingly important class of compounds in organic synthesis, uses ranging from protecting group chemistry (MTM ethers [2]) to oligosaccharide synthesis [3]. In 1980, Cohen and Matz showed that O,S-acetals give α-lithioethers upon treatment with lithium naphthalenide and related reductants [4]. This finding entailed numerous synthesis applications including stereoselective alkylations [5], the stereocontrolled synthesis of tetrahydrofurans [6] or protected 1,3-diols [7], and the initiation of [2,3]-Wittig [6,8] or reverse Brook rearrangements [9].

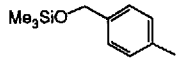
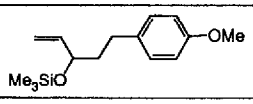
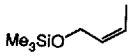
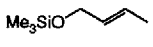
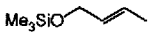
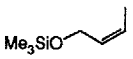
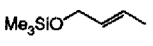
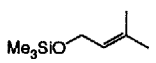
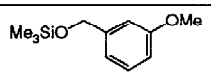
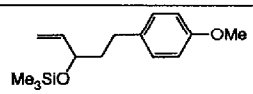
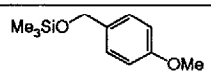
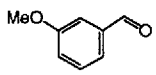
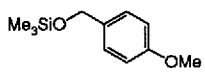
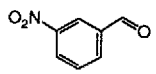
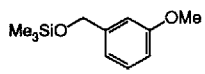
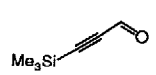
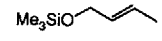
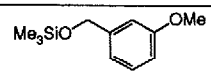
O,S-Acetals can be prepared from α-chloro sulfides [10] and alcohols by various protocols [11]. However, Williamson type syntheses are feasible only for primary [2] and not for secondary alcohols [12]. In fact, most current preparations of O,S-acetals start from O,O-acetals, appropriate reagents being $RSH/BF_3{\cdot}OEt_2$ [13], $PhSH/MgBr_2$ [14], $PhS\text{-}SiMe_3/ZnI_2/Bu_4NI$ [15], $(iPrS)_2BBr$ [16], $Me_2BBr/RSH/NEtiPr_22$ [17], $Bu_{4-n}Sn(SPh)_n/BF_3{\cdot}OEt_2$ [18], or Et_2AlSPh [19]. Lactols [20] or glycosyl acetates [21] have been converted into O,S-acetals by related procedures. In addition, enol ethers are known precursors of O,S-acetals [22], as are S,S-acetals [23], α-acyloxy sulfides [24], thionolactones [25], and other compounds [26].

To date, no *direct* conversion of carbonyl compounds into O,S-acetals has been described. This gap is filled by the present communication.

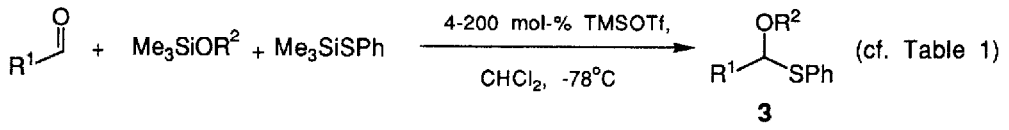


Our method represents a combination of the reaction conditions of Evans' Lewis acid catalyzed preparation of silylated O,S-acetals **1** from aldehydes + Me_3SSiPh [27], and of Noyori's trimethylsilyl triflate (≡TMSOTf) mediated synthesis of O,O-acetals **2** from aldehydes + silyl ethers [28]. When we reacted, in the presence of varying amounts of TMSOTf, aldehydes at dry ice temperature in CH_2Cl_2 with 1 equiv *each* of Me_3SSiPh [29] and a silyl ether, we isolated O,S-acetals **3** as the major reaction product.

Table 1: O,S-Acetals **3**

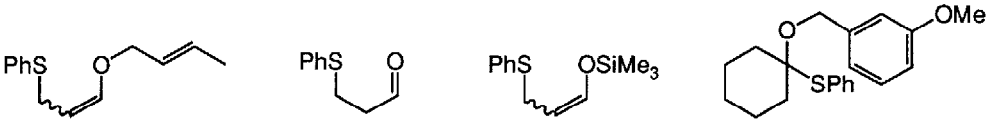
Entry	R^1	Me_3SiOR^2	Mol-% TMSOTf	h at -78°C	Yield **3**	R^1, OR^2, SPh, δ [ppm]
1			4	2	81% [a]	4.95
2			12	1	88% [b]	4.68 and 4.70
3			5	0.3	93%	4.63
4			5	0.9	89%	4.64
5			50	1.2	47% [c]	4.87
6			100	0.5	62% [d]	4.64 (4.75) and 4.54 (5.03) [e]
7			100	0.5	78% [d]	4.64 (4.75) and 4.55 (5.03) [e]
8			200	1	52% [d]	4.63 (4.73) and 4.55 (5.04) [e]
9			10	23	68% [f]	4.53
10			12	21	71% [b]	4.57 and 4.59
11			4	18	37% [g]	4.51
12			4	18	40%	5.80
13			10	20	63%	5.91
14			100	0.3	64%	5.55
15			10	2	49% [h]	-

[a] Along with 9% O,O-acetal.- [b] Isolated as a 1:1 mixture of diastereomers.- [c] Along with 34% of Evans-type product.- [d] Isolated as a 2:1 mixture of diastereomers.- [e] $\delta_{major\ isomer}$ and $\delta_{minor\ isomer}$; the acetal proton could not be distinguished from the benzylic doublet of doublets.- [f] Along with 19% O,O-acetal.- [g] Not completely separated from 19% [(4-methoxyphenyl)methyl]phenylsulfide.- [h] Along with 5% O,O-acetal.



3

Yields of **3** [30] were fair to good (37 - 93%; cf. Table 1). While most of the tested silyl ethers stemmed from primary alcohols, silylated secondary alcohols worked, too (entries 2, 10). Compatible with our scheme were primary, secondary, tertiary, aromatic, and propargylic aldehydes. Usually, 4-10 mol-% of TMSOTf were sufficient to promote complete conversion. However, $Me_3Si\text{-}C{\equiv}C\text{-}CHO$ (entry 14) or aldehydes with an oxygen or a selenium atom β to the carbonyl group (entries 5-8) required 0.5 - 2 equiv of the triflate to avoid formation of Evans-type products. Acrolein gave, upon work-up by flash chromatography, 13% of the vinylogous O,S-acetal **4** as a 91:9 *trans*:*cis* mixture ($J_{olefinic}$ = 12.5 and 6.1 Hz, respectively) along with 70% of compound **5** (presumably formed by hydrolysis of the Evans-type addition product **6**). Acetone was also amenable to O,S-acetalization (entries 15, 16). However, from cyclohexanone, Me_3SiOCH_2-*m*-C_6H_4OMe, Me_3SiSPh, and TMSOTf, only 2% O,S-acetal **7** were obtained ($\delta_{benzylic\ hydrogens}$ = 4.81 ppm in $CDCl_3$) along with 32% O,O-acetal ($\delta_{benzylic\ hydrogens}$ = 4.68 ppm).



4 **5** **6** **7**

In summary, we have found a short route to O,S-acetals derived from aldehydes R^1-CHO with $R^1 \neq H$. Such acetals have not been accessible as easily with existing methodology [31, 32].

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30) All new compounds gave satisfactory combustion analyses and ^1H-NMR spectra.

31) 1,3,5-trioxane did not act as a formaldehyde equivalent under the same reaction conditions, i.e., no O,S-acetals $CH_2(OR^2)(SPh)$ could be isolated.

32) Typical procedure: To TMSOTf (0.25 ml of a 0.5 M solution in CH_2Cl_2, 0.13 mmol, 5 mol-%) and CH_2Cl_2 (1 ml) were added, at -78°C, *Z*-1-(trimethylsilyloxy)-2-butene (361 mg, 2.50 mmol) in CH_2Cl_2 (1 ml), phenyl(trimethylsilyl)sulfide (456 mg, 2.50 mmol), and propanal (145 mg, 2.50 mmol) in CH_2Cl_2 (1 ml). After 20 min, pyridine (0.1 ml) was added. The mixture was distributed between satd. aq. $NaHCO_3$ (20 ml) and ether (3 × 20 ml). Flash chromatography (SiO_2; petroleum ether:ether 150:1 → 100:1) gave 1-(*Z*-2-butenyloxy)-1-(phenylthio)-propane (518 mg, 93%).- ^1H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, J = 7.4 Hz, 3-H_3), 1.67 (bd, J = 6.7 Hz, 4'-H_3), 1.69-1.85 (m, 2-H_2), AB signal (δ_A = 4.20, δ_B = 4.42, J_{AB} = 11.9 Hz, in addition split by $J_{A,2'}$ = 7.2 Hz, $J_{B,2'}$ = 6.2 Hz, 1'-H_2), 5.51-5.60 and 5.65-5.75 (2m, 2'-H, 3'-H), 7.26-7.32 and 7.47-7.50 (2m, H_5C_6S).

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