A Novel Transthioacetalisation: A Simple, Non-aqueous, Irreversible Transformation†

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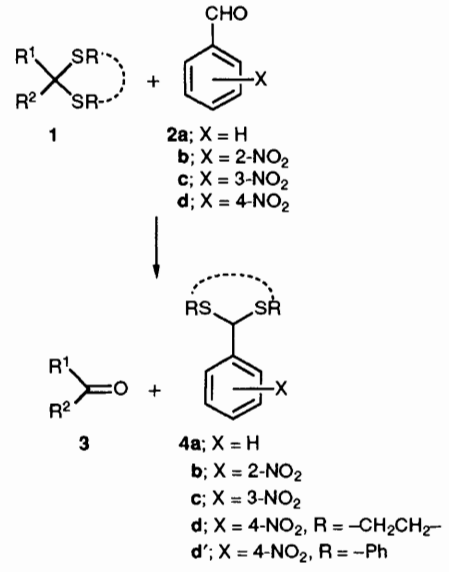
Thioacetals derived from ketones and aldehydes have been shown to undergo $CF_3SO_3SiMe_3$ or $CF_3SO_3SiBu^tMe_2$ catalysed sulphur transfer in the presence of an aldehyde to give the corresponding carbonyl compounds at room temperature.

Thioacetals have gained prominence in organic transformation because of the ease with which they act as acyl anion equivalents.[1] Synthetic chemists have used this protocol widely to metallate thioacetals and later unmask the parent carbonyl compound, in chain extension reactions. Although a wide variety of reagents[2–5] including transition metals (*e.g.* Hg^{2+}, Ag^{+}, Ce^{4+}) are available to effect this transformation, no procedure involving them is general and they require several steps or involve oxidants. In connection with our interest in the synthesis of biotin, we needed to deprotect a thioacetal (Table 1, entry 1). Existing methods were tried, but the desired carbonyl compound was obtained in fair to moderate yields. We therefore needed to develop a mild and efficient methodology to effect dethioacetalisation.

We reasoned that if thioacetals were to be treated with a more reactive aldehyde in the presence of a catalyst, it should be possible to effect an irreversible, non-equilibrium exchange (Scheme 1), and we now report a simple, mild and convenient methodology to effect transthioacetalisation. Thioacetals on treatment with a catalytic amount of $CF_3SO_3SiMe_3$ or $CF_3SO_3SiBu^tMe_2$ in the presence of aldehydes (*e.g.* benzaldehyde and 2-, 3- and 4-nitrobenzaldehyde) in dichloromethane at room temperature furnished the corresponding carbonyl compounds in good to excellent yields.‡ A wide variety of thioacetals (Table 1) were smoothly transformed to the parent carbonyl compounds using this protocol. 4-Nitrobenzaldehyde was obtained as its thioacetal in excellent yields. Of the four aldehydes tested, 4-nitrobenzaldehyde was the best, in terms of both time required as well as efficiency of sulphur transfer.

The difference in reactivity of thioacetals of aldehydes and ketones can be used to advantage in effecting selective deprotection of thioacetals derived from ketones in the presence of aldehydes. The example in Scheme 2 illustrates the difference in the rate of reaction for selective deprotection of the thioacetals derived from ketones.



Scheme 1 *Conditions*: $CF_3SO_3SiMe_3$ (cat.), CH_2Cl_2, room temp.

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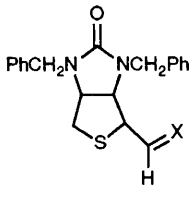
‡ *General Procedure*: To a stirred mixture of thioacetal (1 mmol) and 4-nitrobenzaldehyde (1–1.5 mmol), in dichloromethane (5 ml) under nitrogen at room temperature was added $CF_3SO_3SiMe_3$ (0.2 mmol). After completion of the reaction (TLC), saturated aqueous sodium hydrogen carbonate was added. The organic layer was separated and washed with water and dried (Na_2SO_4). Removal of the solvent under reduced pressure furnished a residue which was purified either by distillation (kugelrhor) or by chromatography (SiO_2) using 3% acetone–light petroleum as eluent to furnish the corresponding carbonyl compounds.

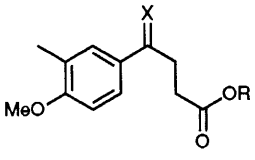
Table 1 Transthioacetalisation using aromatic aldehydes

Entry	Substrate	Product	Yield (%)	Aldehyde	Thioacetal	Yield (%)	Time/h
1	**8a**[a]	**8b**[c]	92	**2d**	**4d'**	98	4
2	**9a**[b]	**9b**	81	**2d**	**4d**	98	3
3	**10a**	**10b**[c]	96	**2d**	—	—	4
4	**11a**	**11b**	80	**2d**	—	—[d]	3
5	**12**	**11b**	78	**2d**	—	—[d]	5.5
6	**13**	**11b**	95	**2d**	—	—[d]	4.5
7	**13**	**11b**	78	**2c**	—	—[d]	12
8	**13**	**11b**	76	**2b**	—	—[d]	18
9	**13**	**11b**	28	**2a**	—	—[d]	26
10	**14a**	**14b**	73	**2d**	**4d**	97	5
11	**15**	**14b**	62	**2d**	**4d'**	95	0.67
12	**16a**	**16b**	76	**2d**	**4d'**	—	1
13	**17**	**16b**	65	**2d**	**4d**	100	5
14	**18a**	**18b**	63	**2d**	**4d**	90	0.5
15	**6**	**7**	100	**2d**	—	—[d]	4
16	**19a**	**19b**	95	**2d**	**4d**	97	0.75
17	**20a**	**20b**	83	**2d**	**4d**	88	4

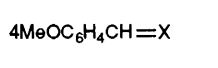
[a] The acetal **8a** was obtained in a cyclization reaction, details of which will be published elsewhere. $CF_3SO_3SiBu^tMe_2$ catalysed transthioacetalization of **8a** gave comparable yields of **8b**. [b] Acetals in entries 2–16 were prepared according to the general procedure reported in the literature.[6] [c] Ester **10b** was saponified, isolated and characterized as acid **9b**. [d] Since the carbonyl compounds were distilled, no attempt was made to isolate the thioacetals. [e] All the compounds were characterized by ^1H NMR, IR and mass spectral analysis. The carbonyl compounds, obtained by transthioacetalization, were characterized by direct comparison of their spectra with those of the starting carbonyl compounds. Selected spectral data for thioacetal **8a** (entry 1): IR (neat) ν/cm^{-1} 1700, 1615, 1595 and 1500; ^1H NMR ($CDCl_3$), δ 2.75 (dd, 1H, *J* 3.52, 12 Hz), 3.33 (dd, 1H, *J* 4.9, 12 Hz), 3.56 (d, 1H, *J* 15.5 Hz), 3.73–3.75 (m, 1H), 4.04–4.18 (m, 4H), 4.78 (d, 1H, *J* 15.5 Hz), 4.69 (d, 1H, *J* 15.3 Hz) and 7.01–7.4 (m, 20H); ^{13}C NMR ($CDCl_3$), δ 37.02(t), 45.82(t), 42.26(t), 52.72(d), 63.22(d), 64.71(d), 65.71(d) and 158.6(s); *m/z* 445 (M −109). Aldehyde **8b** (entry 1), IR (neat) ν/cm^{-1} 1705, 1695, 1605, 1595 and 1500; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.29 (1H, dd, *J* 4.78, 13.16 Hz), 2.68 (1H, d, *J* 13.15 Hz), 3.59 (1H, s), 4.09 (1H, dd, *J* 4.74, 7.78 Hz), 4.16 (1H, d, *J* 15.4), 4.34 (1H, d, *J* 7.9 Hz), 4.36 (1H, d, *J* 15.4 Hz), 4.47 (1H, d, *J* 15.4 Hz), 4.68 (1H, d, *J* 15.4 Hz), 7.18–7.83 (m, 10H, Ar) and 9.13 (1H, s); ^{13}C NMR ($CDCl_3$) δ 34.71(t), 46.42(t), 47.16(t), 59.30(d), 60.63(d), 61.96(d), 159.75(s) and 189.80(d); *m/z* 352.



8a; X = $(SPh)_2$
8b; X = O

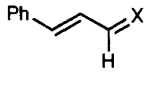


9a; R = H, X = $-SCH_2CH_2S-$
9b; R = H, X = O
10a; R = Me, X = $-SCH_2CH_2S-$
10b; R = Me, X = O

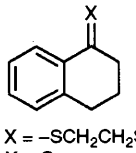


11a; X = $(SPh)_2$
11b; X = O
12; X = $-SCH_2CH_2CH_2S-$
13; X = $-SCH_2CH_2S-$

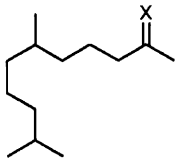
14a; X = $-SCH_2CH_2S-$
14b; X = O
15; X = $(SPh)_2$



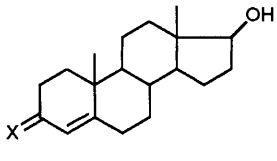
16a; X = $(SPh)_2$
16b; X = O
17; X = $-SCH_2CH_2S-$



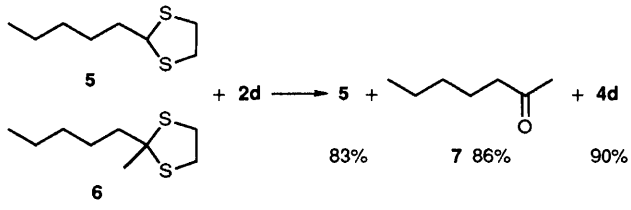
18a; X = $-SCH_2CH_2S-$
18b; X = O



19a; X = $-SCH_2CH_2S-$
19b; X = O



20a; X = $-SCH_2CH_2S-$
20b; X = O



Scheme 2 *Conditions*: $CF_3SO_3SiMe_3$ (cat.), room temp., 4 h

We believe this is the first report of a catalytic anhydrous irreversible transthioacetalisation methodology involving a double transfer of oxygen and alkanethiol. We are now attempting to extend the transthioacetalisation to acetals, oxazolidines, oxathiolanes *etc.* In view of the generality and selectivity, we feel that the method should find widespread use.

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