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TITANIUM TETRACHLORIDE, AN EFFICIENT AND CONVENIENT REAGENT FOR THIOACETALIZATION[1,2]

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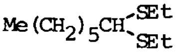
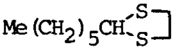
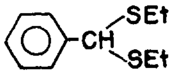
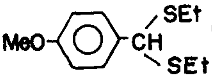
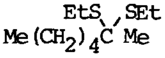
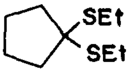
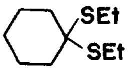
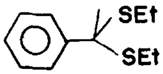
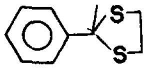
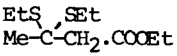
Summary: Aldehydes and ketones, when exposed to alkyl thiols or suitable alkane dithiols in presence of titanium tetrachloride, furnish near quantitative yields of the corresponding thioacetals.

The stability exhibited by dithioacetals and 1,3-dithiolanes (1,3-dithianes) under usual acid or basic conditions[3] has led to their synthetic utility as carbonyl protecting groups[3,4] and as synthons in a variety of synthetic operations;[5] in addition, these derivatives have served as intermediates in the conversion of a carbonyl function to a hydrocarbon derivative.[6] In general, such thioacetals have been obtained by acid-catalyzed condensation of thiols with carbonyl compounds,[3,4] or by reaction of carbonyl compound with ortho-thioboric esters[7] or thiosilanes[8] (and a Lewis acid), or by exchange reaction of derived acetals with thiols.[9]

For condensation with thiols and dithiols, acid catalysts such as concd HCl aq., $ZnCl_2$ or $BF_3.Et_2O$ have been invariably used.[3,4] Recently,[10] anhydrous $AlCl_3$ has been successfully employed as a convenient reagent, and has been shown to be superior, especially for thioacetalization of less reactive aromatic ketones. However, carbonyl compounds with an α-proton gave only moderate yields (∿50%), when reacted with a monothiol in presence of $AlCl_3$. Our interest in this area led us to investigate the catalytic activity of two other Lewis acids: $FeCl_3$ and $TiCl_4$. While $FeCl_3$ proved inferior to $AlCl_3$, $TiCl_4$ has shown excellent

Table 1. Thioacetals by $TiCl_4$ method: yields and other relevant data

No	Product (Ref)[a]	B.p./mm	Yield[b]	Reaction time (hr)	^{1}H-NMR[c], δ (ppm)		
					$\mathrm{SCH_2C\underline{H}_3}$[d]	$\mathrm{SC\underline{H}_2C}$	$\mathrm{\underline{H}C}\begin{smallmatrix}\text{S}\\\text{S}\end{smallmatrix}$
1	 $\mathrm{Me(CH_2)_5CH}\begin{smallmatrix}\text{SEt}\\\text{SEt}\end{smallmatrix}$ (14)	120-23°/5	95	1.0	1.28	2.70 (m)	3.72 (t) (J=6.5Hz)
2	 $\mathrm{Me(CH_2)_5CH}\begin{smallmatrix}\text{S}\\\text{S}\end{smallmatrix}$ (18)	115-18°/4	95	0.5	-	3.18 (s)	4.40 (t) (J=7Hz)
3	 (8)	125-30°/5	95	1.0	1.22	2.5 (m)	4.89 (s)
4	 (15)	150-51°/6	99	1.0	1.25	2.56 (m)	4.90 (s)
5	 $\mathrm{Me(CH_2)_4\overset{EtS\ \ SEt}{C}\ Me}$ (16)	135-36°/7	98	6.0	1.28	2.60 (q) (J_1=7.5Hz)	-
6	 (17)	110-11°/6	98	6.0	1.25	2.60 (q) (J_1=7.5Hz)	-
7	 (8)	125-30°/6	98	6.0	1.20	2.67 (q) (J_1=7.5Hz)	-
8	 (16)	145-50°/6	90	12.0	1.30	2.62 (q) (J_1=7.5Hz)	-
9	 (17)	140-42°/5	96	3.0	-	3.18 (s)	-
10	 (16)	185-90°/1	90	12.0	1.50	2.30 (q) (J_1=7.5Hz)	-
11	 $\mathrm{Me{-}\overset{EtS\ \ SEt}{C}{-}CH_2.COOEt}$	130-35°/10	98	6.0	1.22	2.50 (q) (J_1=7.5Hz)	-

[a] Except for entry 11, all compounds have been described in the literature and a relevant reference is given. Analytical data for entry 11: Found: C, 50.42; H,8.52; S, 26.30. $C_{10}H_{20}O_2S_2$ requires: C, 50.79; H, 8.53; S, 27.08%).

[b] Isolated yield of distilled product; GLC purity >98%.

[c] Spectra were recorded on $CDCl_3$ soln with TMS as internal standard.

[d] triplet, J = 7.5Hz

activity and the present Communication reports results of this investigation.

Titanium tetrachloride is known to have a strong affinity for oxygenated organic compounds, and also possesses powerful dehydrating action.[11] In view of these characteristics, $TiCl_4$ appeared to be a promising reagent for the purpose on hand.[12] In practice, reactions catalysed by $TiCl_4$ turned out to be clean and efficient (Table 1). Even carbonyl compounds having an α-proton gave excellent yields with ethyl thiol (Table 1: entries 1, 5, 6, 7), in contrast to the performance of $AlCl_3$ catalysis.[10] Enolizable carbonyl compounds have been noted[10] to furnish only vinyl sulphides with thiols under $AlCl_3$ catalysis. In contrast, with $TiCl_4$, even the highly enolizable ethyl acetoacetic ester (the only case examined) gave a near quantitative yield of the thioacetal with ethyl thiol (Table 1: entry 11). Yields of thioacetate from aromatic ketones (Table 1: entries 8, 9, 10) were equally excellent.

Thus, $TiCl_4$ has been demonstrated to be a useful catalyst for thioacetalization.

General experimental procedure

A soln of the carbonyl compound (10 mmole) and the desired monothiol (25 mmole) or dithiol (12.5 mmole) in $CHCl_3$ (5 ml) is cooled to -10° to -15°, and $TiCl_4$ (0.25 g, $\approx$1.3 mmole) introduced with stirring and the reaction temp allowed to attain room temp (28-30°) during the next few minutes. After stirring at this temp for an additional one hr[13] (in case of aldehydes) or 6-12 hr (for ketones) in the case of monothiol or half these times for the dithiol, water (5 ml) is introduced and the $CHCl_3$ layer separated. The aq. phase is extracted with $CHCl_3$ (5 ml x 3) and the combined extracts washed with water, brine and dried (Na_2SO_4). After removal of solvent the product can be purified by the usual methods. In the present case, all compounds were distilled.

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