A Simple Procedure for the Catalytic Acetalization of Aldehydes

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Dedicated to Professor Dr. E. Schmitz on the occasion of his 65th birthday

Acetalization provides the protection of the carbonyl function. The main problem of this reaction, however, is the removal of water in order to shift the equilibrium to the side of the products.

Many methods are available to obtain acetals in high yields, most of which are carried out under acid-catalyzed conditions [1]. For solving complicated synthetic problems (for instance molecules bearing acid-sensitive functional groups) milder methods have been developed, such as transacetalization in a non-acidic medium [2] or electrochemical acetalization [3, 4]. The acetalization in the presence of trimethylchlorosilane [5] or acetalization with trimethylsilyl alkoxysilanes at low temperatures in the presence of catalytic amounts of trimethylsilyl trifluoromethanesulfonates [6] are very mild methods.

This article describes a very simple and efficient method for synthesizing acetals under mild and neutral conditions.

$$R-CHO + Ti(OR)_4 \xrightarrow[r.t., 24]{cat. TiCl_4} R-CH(OR)_2$$

Aldehydes are treated with titanium(IV) alkoxides in the presence of catalytic amounts of titanium tetrachloride to yield the corresponding acetals.

The reaction is carried out at room temperature. Hexane or benzene are used as solvents. By using oxygen-containing solvents (diethyl ether or tetrahydrofuran) no reaction occurs. Working without solvents is possible if solubility problems are encountered with the aldehyde. The typical chemoselectivity of titanium compounds is observed [7]. Ketones are inert to these reaction conditions at room temperature. Transacetalization of acetals could not be observed under these reaction conditions.

In initial experiments we achieved the acetalization of aldehydes by using equimolar amounts of chlorotitanium triisopropoxide. Now we have found quantitative acetalization by using titanium(IV) alkoxides in the presence of catalytic amounts of titanium tetrachloride. This catalytic process even works by using 5 mol-% titanium tetrachloride without decreasing yields.

The applicability of this catalytic reaction was tested by treating benzaldehyde with different kinds of titanium(IV) alkoxides. The results are shown in Table 1.

 Table 1 Acetalization of benzaldehyde with several titanium(IV) alkoxides

C_6H_5 -CHO $-\frac{\text{Ti}(\text{OR})}{\text{cat. Ti}}$	$\xrightarrow{R)_4} C_6H_5-CH(OR)_2$			
R	Yield (%)	b.p.(°C)/ mbar	molecular formula ^b or lit. b.p.(°C)/mbar	
Et	77	110/27	221/1013 [12]	
n-Pr	89	125/27	$C_{13}H_{20}O_2$	
iso-Pr	84	130/27	234/1013 [9]	
n-Bu	78	150/27	262/1013 [12]	
$CH_2\text{-}CH(C_2H_5)\text{-}C_4H_9$	83	190/27	$C_{23}H_{40}O_2$	

^{a)} the boiling points refer to air-bath temperatures during Kugelrohr distillation

b) satisfactory microanalyses obtained: C \pm 0.43; H \pm 0.27

By treating benzaldehyde with titanium(IV) tert-butoxide in the presence of titanium tetrachloride no expected acetal could be observed. The same result was found when benzaldehyde reacted with titanium(IV) phenolate. This may be explained by the steric hindrance of the bulky groups (tertbutyl or phenyl) of these titanium(IV) alkoxides.

In other experiments different aldehydes were treated with titanium(IV) isopropoxide in order to test the application of this reaction.

The yields of the isolated acetals are generally very high (see table 1 and 2). In order to show the applicability of the described acetalization to aldehydes bearing acid-sensitive functional groups, the diisopropylacetal of the *Corey*-aldehyde **2h** was synthesized in a yield of 55%. The *Corey*-aldehyde is a very important intermediate in total synthese of prostaglandins [13]. By using other methods [5, 6], acetals of the silvlated *Corey*-aldehyde could not be observed.

 α , β -Unsaturated aldehydes, such as cinnamaldehyde or 2hexenal do not react under these conditions to give acetals, as expected [10]. The addition of the isopropylgroup to the double bond has been observed.

 α , β -Unsaturated aldehydes, products deriving from titanium alkoxide catalyzed aldol reaction [11] could not be observed. Chlorotitanium triisopropoxide is formed by an initial

	R	Yield (%)	b.p.(°C)/ mbar	molecular formula ^b or lit. b.p.(°C)/mbar
a	n-C ₃ H ₇ -	77 (20[8])	80/27	164/1013 [9]
b	$n - C_6 H_{13} -$	77 (20[8])	140/27	240/1013 [9]
с	$n - C_9 H_{19} -$	70	180/27	$C_{16}H_{34}O_2$
d	$C_{6}H_{5}-$	83	130/27	234/1013 [9]
e	tert-C ₄ H ₉ -	76	100/31	$C_{11}H_{24}O_2$
f	$C_6H_5-(CH_2)_2-$	76 (16[9])	150/30	$C_{15}H_{24}O_2$
g		77	120/27	$C_{13}H_{24}O_2$
h M	e-SiO ^w	55	145/27	C ₁₇ H ₃₂ O ₅ Si

Table 2 Diisopropylacetals 2a-h of aldehydes R-CHO prepared

^{a)} the boiling points refer to air-bath temperatures during Kugelrohr distillation

^{b)} satisfactory microanalyses obtained: C \pm 0.39; H \pm 0.34

reaction of titanium tetrachloride with titanium tetraisopropoxide. It is expected that chlorotitanium triisopropoxide is acting both as a catalyst and as a dehydrating reagent.

Experimental

¹H-NMR spectra were recorded at 80 MHz on a Tesla BS 587 A spectrometer and ¹³C-NMR spectra at 20 MHz on a Varian CFT 20 spectrometer. Low resolution electron impact mass spectra were obtained using a GC/MS-Datensystem HP 5985 B. Microanalyses were performed on a Carlo Erba autoanalyzer 1106.

General procedure for the catalytic Acetalization of Aldehydes

50 mmol of freshly distilled aldehyde were dissolved in 100 ml of abs. hexane. 14.2 g of titanium(IV) isopropoxide (50 mmol)

were added and after 15 min. 0.95 g titanium tetrachloride (5 mmol in 2 ml abs. toluene) were carefully added. The clear solution was stirred at room temperature for 24 h. Then water was added, the mixture was diluted with diethyl ether, the organic layer was separated and washed with brine. The etheral extract was dried over Na_2SO_4 , filtered and the remaining filtrate was evaporated under reduced pressure. The crude residue was purified by Kugelrohr distillation.

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