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Distannoxane-Catalyzed Acetalization of Carbonyls

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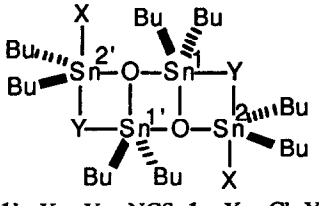
Abstract: 1,3-Disubstituted tetrabutyldistannoxanes catalyze acetalization of carbonyl compounds under mild conditions. Thorough investigations of factors influencing this reaction are given. A variety of synthetically useful carbonyl compounds are efficiently converted to acetals. In particular, acetalization of cyclic α,β-unsaturated ketones is readily achieved which have met with only limited success so far.

INTRODUCTION

1,3-Disubstituted tetrabutyldistannoxanes (**1**) are synthetically useful catalysts for transesterification,[1] esterification,[1c,2] deacetalization,[3] and deprotection of silyl ethers[3] under mild conditions. Two key steps are crucial for the readiness with which the above carbonyl group transformations are effected. (1) The Y group in **1** is readily replaced by alcohol. (2) The Sn(2) atom in the alkoxy distannoxane thus formed (Y = OR in **1**) undergoes facile coordination by carbonyl oxygen because the electronegative X group is bonded to this tin atom.[4] Consequently, both activated reactants, alcohol and carbonyl, are allowed to interact with each other on the distannoxane template. These mechanistic considerations led us to find that acetalization occurred as well when aldehydes or ketones were employed as a carbonyl component.[5]



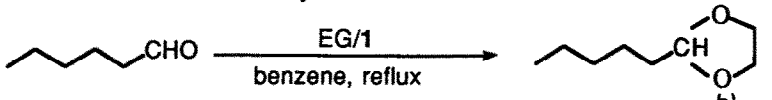
1a: X = NCS, Y = OH, **1b**: X = Y = NCS, **1c**: X = Cl, Y = OH, **1d**: X = Y = Cl

Acetalization, one of the most important functional group modifications in organic synthesis, is usually conducted under acidic conditions.[6] Despite many efforts devoted to overcome this drawback, there still remain significant limitations from the synthetic point of view. We report here that the distannoxane protocol complements the ever existing methods a great deal, particularly for acetalization of cyclic α,β-unsaturated carbonyl compounds.

RESULTS AND DISCUSSION

We first screened factors affecting the reaction by employing hexanal, which was treated with ethylene glycol (EG) (20 equiv) in the presence of **1** (0.005 equiv) in a refluxing solvent using a Dean-Stark apparatus. The influences of solvent as well as the substituents, X and Y, are summarized in Table 1. Of the solvents screened, benzene was found to be the best. Apparently, there are small but definite differences between the distannoxane catalysts, and **1a** has proved to be superior to the others. We previously disclosed the higher catalytic activity of isothiocyanato distannoxanes for the reaction between phenyl isocyanate and 1-butanol and concluded that partial ionization of the isothiocyanate group facilitated the coordination of the carbonyl oxygen of phenyl isocyanate.[7]

Table 1. Effects of Catalysts and Solvents on the Acetalization[a)]

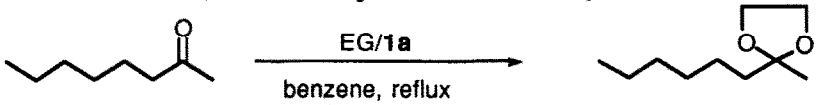


entry	1	reaction time, min	yield, %	τ_0[b)]
1	**1a**	30	100	5.1
2	**1a**[c)]	60	88	18.7
3	**1a**[d)]	30	61	25.6
4	**1b**	80	94	12.9
5	**1c**	120	86	44.6
6	**1d**	80	97	24.7

a) Reaction conditions: Hexanal : $HOCH_2CH_2OH$: **1** = 1 : 20 : 0.005.
b) τ_0 designates the time (min) for 50% yield.
c) In refluxing CCl_4. d) In refluxing hexane.

Next, effect of catalyst concentration was investigated by using 2-octanone whose reaction rate was moderate so that the clear difference could be detected (Table 2). The τ_0 values are slightly dependent on the

Table 2. Dependence of τ_0 Values on the Catalyst Concentration



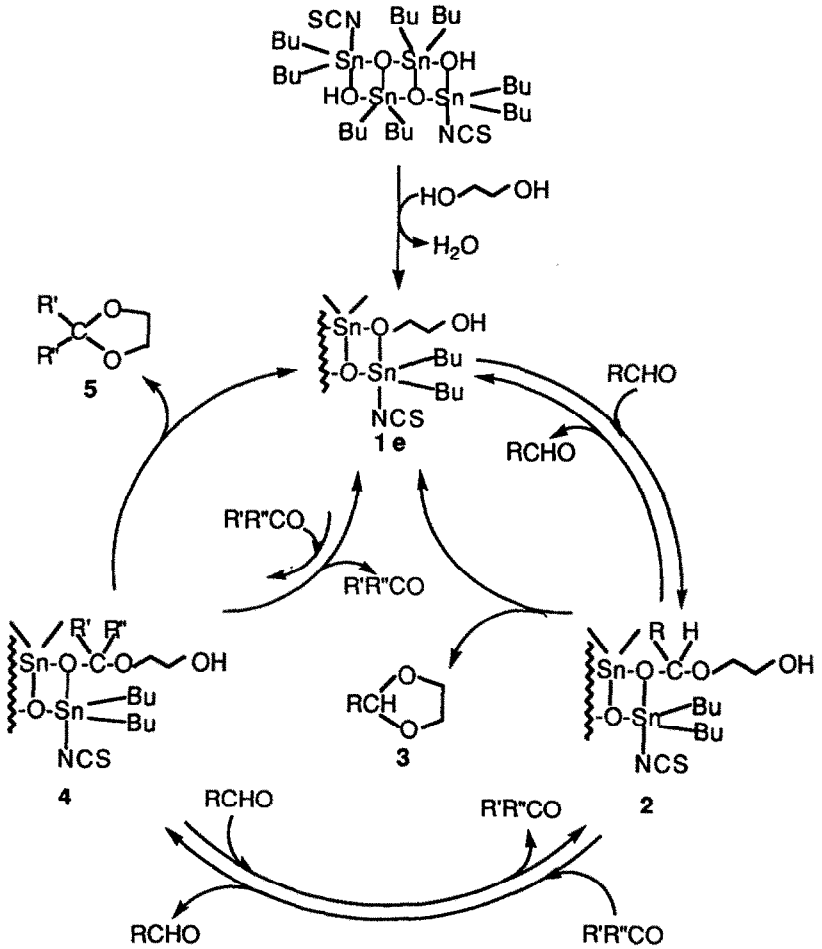
1a[a)]	τ_0
0.0005	184
0.0010	158
0.0030	143
0.0050	142
0.0100	150
0.0200	155

a) Molar equivalent to the ketone.

catalyst concentration and show the minimum at around 0.3-0.5 mol% relative to the ketone. The remarkably high catalytic activity should be noted. We accordingly have determined to employ 0.5 mol% **1a** and benzene as solvent under the standard conditions in this study.

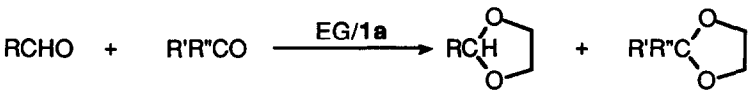
We noted that the reaction of ketones as well as aldehydes with an electron-withdrawing group was, in general, slow and that addition of an equimolar amount of alkanal dramatically accelerated the reaction rate.[5] This unique acceleration was interpreted in terms of novel transcarbonylation as shown in Scheme 1. The initial step is formation of (β-hydroxyethoxy)distannoxane **1e** (X = NCS, Y = $O(CH_2)_2OH$), which preferentially incorporates more reactive aldehyde to give an addition product **2**. In the absence of ketone, **2** is solely converted into acetal **3**. When a ketone coexists, the exchange reaction leading to the ketone adduct **4** competes with the aldehyde acetal formation. This transcarbonylation proceeds more rapidly than the direct addition of ketone to **1e**. Finally, a ketone acetal **5** is extruded from **4** with concomitant regeneration of **1e**.

Scheme 1



As we already presented thorough data on the rate acceleration and discussed the validity of the transcarbonylation process, it is unnecessary to advance further comments here. However, if this mechanism indeed operates, one may presume that the rate of ketone acetal formation slows down after consumption of an aldehyde counterpart. In other words, it is rather difficult to get high yield of the ketone acetal when the aldehyde acetal formation is much faster than the transcarbonylation. Table 3 shows that this is true in some cases. The $\tau_{(rel)}$ value represents ratio of the time for 50% yield in the simple acetalization and crossover acetalization, respectively. Thus, in the crossover reaction employing hexanal and 2-octanone, the reaction rate of the former component is twice slower than that in the absence of the ketone. Inversely, the reaction of 2-octanone is accelerated 5.7 times in the presence of the aldehyde. However, the yield of ketone acetals does not amount to 100% when an aldehyde component has disappeared. After this stage, the remaining ketone is acetalized slowly through direct reaction with **1e**. The reaction completes after 210 min.

Table 3. Crossover Acetalization of Carbonyl Compounds[a)]



3 **5**

R	R'	R"	$\tau_{3\,(rel)}$ [b)]	$\tau_{5\,(rel)}$ [b)]	reaction time, min	yield, %[c)]	
						3	**5**
n-C_5H_{11}	*n*-C_6H_{13}	CH_3	0.5	5.7	60	100	60
					210		95
n-C_7H_{15}	*n*-C_6H_{13}	CH_3	0.8	5.4	60	93	64
n-C_6H_{11}	*n*-C_5H_{11}	CH_3	1.0	3.6	120	100	81
n-C_5H_{11}	C_6H_5	CH_3	0.2	18	100	95	65

[a)] Reaction conditions: RCHO : R'R"CO : EG : **1a** = 1 : 1 : 10 : 0.005, benzene, reflux.

[b)] The $\tau_{n\,(rel)}$ value of compound **n** is ratio of the τ value obtained by the simple acetalization over that obtained by crossover acetalization.

[c)] Based on GLC.

Fig. 1 illustrates time-conversion curves for the reaction of 2-octanone in the presence of hexanal. When an equimolar mixture of these two reactants were subjected to acetalization, hexanal was completely consumed after 40 min (curve 1) and then the reaction rate of 2-octanone decreased rapidly (Curve 2). It is noteworthy that when one more equivalent of hexanal was added to the reaction mixture at the stage where the aldehyde had disappeared (at 55 min), the reaction of 2-octanone was revived and the corresponding acetal was obtained in 99% yield after 120 min (curve 3). These results unambiguously support the novel transcarbonylation process. More importantly from the synthetic point of view, reation rate as well as yield of acetalization can be increased by slow addition of an aldehyde component.

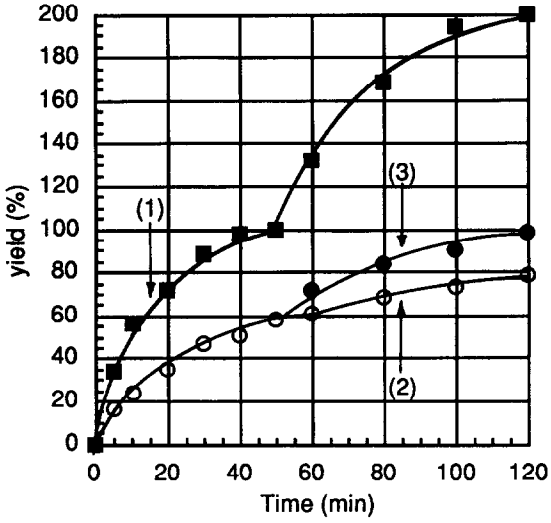
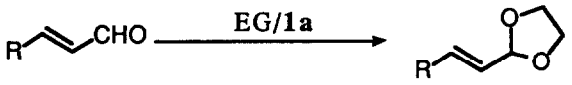


Fig. 1. Time-conversion Curves of the Crossover Acetalization Employing an Equimolar Mixture of Hexanal and 2-Octanone. (1) Hexanal. (2) 2-Octanone in the presence of an equimolar amount of hexanal. (3) 2-Octanone after addition of another equivalent hexanal.

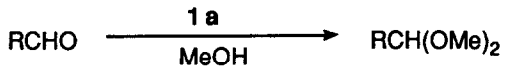
Since fundamental features of the distannoxane-catalyzed acetalization has now been disclosed, the discussion to follow is directed towards more labile α,β-unsaturated carbonyls to exemplify the synthetic potential. Acetalization of these compounds is rather difficult with conventional acid catalysts. Dauben applied the high pressure technique to this sort of reaction with considerable success.[8] Hwu et al.[9] addressed this problem by invoking the alkoxysilane/Me_3SiOTf method developed originally by Noyori et al.[10] More recently, Venanzi et al. disclosed a Rh(III) complex to be effective for cinnamaldehyde.[11] Exposure of α-enals to EG (20 equiv) in the presence of **1a** (0.005 equiv) in refluxing benzene provides good yields of acetals (eq 1).



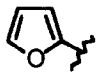
(1)

90% (cinnamaldehyde)
88% (furfural)

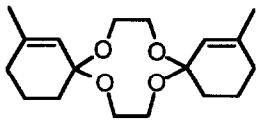
Conversion to dimethyl acetals is much simpler (eq 2). Heating of a methanol solution of an aldehyde and **1a** provides quantitative yields of the desired acetals.



(2)

R = *n*-C_8H_{17} 93%
= Ph 92%
=  85%

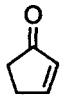
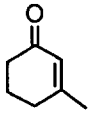
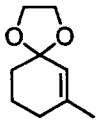
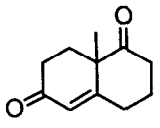
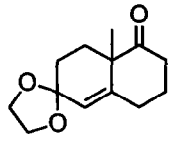
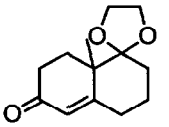
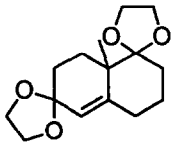
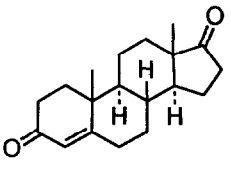
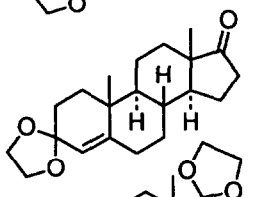
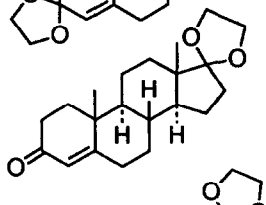
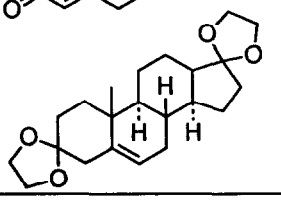
The next target is cyclic α-enones, the results of which are summarized in Table 4. A wide variety of this type of compounds are acetalized in quantitative yields. Particularly notable is the smooth reaction of 3-methyl-2-cyclohexenone. To this substrate, Dauben applied his high pressure technology.[8] Unfortunately, however, all attempts failed and even the Noyori method led to a dimerized acetal shown below. In our case, no such dimer is



formed. Another serious problem which remains to be solved is associated with polycyclic α-enones in relation to steroid chemistry. The double bonds in these α-enones are liable to shift to the β,γ-position under acidic conditions and a coexisting saturated carbonyl group also undergoes acetalization. Thus various conventional acids such as *p*-toluenesulfonic acid[12] and carboxylic acids[13] were screened but met with limited success. More recently, Paquette et al. succeeded in suppressing acetalization of the coexisting saturated carbonyl group by use of a hindered pyridinium salt but failed to avoid the double bond migration except for an α-substituted α-enone.[14] The Noyori method resulted in acetalization of the desired enone moieties (77 and 67%) and of the saturated carbonyl moieties (2.9 and 25%) for the Wieland-Miescher ketone and progestrone, respectively.[9a] The high pressure technology was successful only for α-substituted α-enones.[8] Efficacy of distannoxane is apparent from Table 4. It should be emphasized again that the double bond migration is almost suppressed.

In summary, distannoxanes have proved to be extremely active catalysts for acetalization. The reaction proceeds under almost neutral conditions and thus, we believe, will find practical synthetic utilities in a wide variety of fields.

Table 4. Acetalization of α-enones

α-enone	conditions	acetal(s) GLC yield (isolated yield)/%
	**1a**: 0.01 equiv; EG; 20equiv 24 h	 96(72)
	**1a**: 0.01 equiv; EG; 20equiv 22 h	 98(91)
	**1a**: 0.01 equiv; EG; 20equiv 27 h	 93(84)
	**1a**: 0.005 equiv; EG; 10equiv 30 h	 68
		 1.6
		 8.6
	**1a**: 0.01 equiv; EG; 20equiv 48 h	 82
		 4.7
		 8.3

EXPERIMENTAL SECTION

Preparation of distannoxanes has been described elsewhere.[1c] Authentic alkanal and benzaldehyde acetals were obtained by conventional methods. Ethylene acetals of cinnamaldehyde,[9b] furfural,[9b] 2-cyclohexenone,[10] Wieland-Miescher ketone,[9a,13b,14] and 4-androstene-3,17-dione[12,13a] were prepared according to literature methods. Preparation of dimethyl acetal of cinnamaldehyde has been reported.[11]

Acetalization with EG (General Procedure). A benzene solution (50 ml) of 3-methyl-2-cyclohexenone (110 mg, 1.0 mmol), EG (1.24 g, 20 mmol), and **1a** (5.6 mg, 0.01 mmol) was heated under reflux for 27 h. The benzene was evaporated and GLC analysis of the residue thus obtained revealed the desired acetal to be formed in 93% yield. The crude product was subjected to column chromatography on silica gel (95:5 hexane-ethyl acetate) to give the pure acetal (129 mg, 84%): ^{1}H NMR ($CDCl_3$) δ 1.71 (s, 3H), 1.64-1.81 (m, 4H), 1.91-1.98 (m, 2H), 3.89-4.02 (m, 4H), 5.35 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.75, 23.25, 29.76, 32.93, 64.18, 106.42, 122.18, 141.38; MS m/z (M^+) 154; HRMS *m/z* calcd for $C_7H_{10}O_2$ ($M^+ - C_2H_4$) 126.0681, found 126.0667.

Ethylene acetal of 2-cyclopentenone: ^{1}H NMR ($CDCl_3$) δ 2.04-2.08 (m, 2H), 2.38-2.43 (m, 2H), 3.94 (br s, 4H), 5.70 (dt, J = 5.7 and 1.9 Hz, 1H), 6.09 (dt, J = 5.7 and 2.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.01, 22.65, 31.58, 64.70, 130.29, 137.32; HRMS *m/z* calcd for $C_7H_{10}O_2$ (M^+) 126.0680, found 126.0678.

Acetalization with Methanol (General Procedure). A methanol solution (100 ml) of furfural (960 mg, 10 mmol) and **1a** (56 mg, 0.1 mmol) was heated under reflux for 5 h. The methanol was evaporated and GLC analysis of the residue revealed the desired acetal to be formed in 85% yield. The crude product was subjected to bulb-to-bulb distillation (80 °C/50 mm) to give the pure acetal (918 mg, 65%): ^{1}H NMR ($CDCl_3$) δ 3.36 (s, 6H), 5.44 (s, 1H), 6.35-6.38 (m, 1H), 6.41-6.43 (m, 1H), 7.41 (d, J = 1.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 52.75, 97.89, 108.37, 109.98, 142.40, 150.80; MS m/z ($M^+ - CH_3O$) 111; HRMS *m/z* calcd for $C_7H_{10}O_3$ (M^+) 142.0630, found 142.0689.

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