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Diol-tin ketal as effective catalyst in the tin mediated benzoylation of polyols

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Abstract

The monobenzoylation of 1-phenyl-1,2-ethanediol in the presence of different tin reagent has been studied. The stannylene ketal of 1-phenyl-1,2-ethanediol has been prepared and used as a catalyst or generated in situ by exchange with other mixed tin ketals. In either case, the acylation occurs rapidly with 2 mol% of the catalyst with the known selectivity. These experiments clearly establish the catalytic nature of the acylation reaction.

Keywords: Tin ketals; Diols; Monoacylation catalysis

1. Introduction

Tin mediation in the monofunctionalisation of polyols allows to reach two main objectives: high regioselectivity and rate enhancement.

In compounds containing three or more hydroxyl groups, the regioselectivity is the prevalent aspect of the reaction and it has been applied in the selective functionalisation of carbohydrates [1].

In compounds containing two hydroxyl groups functionalisation at the primary hydroxyl group prevails, but opposite selectivity can be eventually obtained with a particular reaction protocol [2].

In all cases, tin mediated reactions are much faster than reactions in normal conditions. In fact, oxygen atoms in the intermediate stannylene ketals are activated toward the nucleophilic attack on the acylating agent. When the acylating agent is an acid chloride, after the first functionalisation the tin ligand becomes chlorinated and loses its activation preventing further reaction.

The literature concerning tin mediated acylations and alkylations describes a variety of experimental conditions without specifying when a catalytic cycle can be active. Most reactions with dibutyl tin oxide (Bu_2SnO) employs reagents in a more than stoichiometric amount, but when the reaction is run in a microwave apparatus a catalytic amount of Bu_2SnO has been used [3]. This clearly indicates that a stoichiometric amount of reagent is not necessary. Also, a polymer supported tin reagent has been used in the selective functionalisation of carbohydrates using a catalytic [4] amount of tin containing resins. Recent works describe the use of dimethyltin dichloride (Me_2SnCl_2) as an effective catalyst in the monofunctionalisation described in Scheme 1 [5]. Macrolactonisation and esterification procedure with water removal are also catalysed by Bu_2SnO [7]. Recently, a thorough study of the monotosylation reaction of diols with catalytic Bu_2SnO has been published [8]. The possibility of performing reactions with non-stoichiometric amounts of reagents is highly desirable particularly in the case of highly toxic compounds difficult to remove from the reaction mixture like lipophilic alkyl tin reagents [6]. Bu_2SnO has been used in the monofunctionalisation of carbohydrates for a long time [1]. Due to solubility requirements reactions were run in methanol were Bu_2SnO is transformed into $Bu_2Sn(MeO)_2$ [1], a much more reactive specie [9]. This compound has been also employed in a stoichiometric amount for the monofunctionalisation of a series of diols [9].

2. Results and discussion

We studied the monobenzoylation of compound **1** with different tin reagents and found that a catalytic cycle can be obtained

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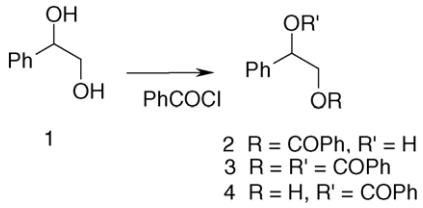


Scheme 1.

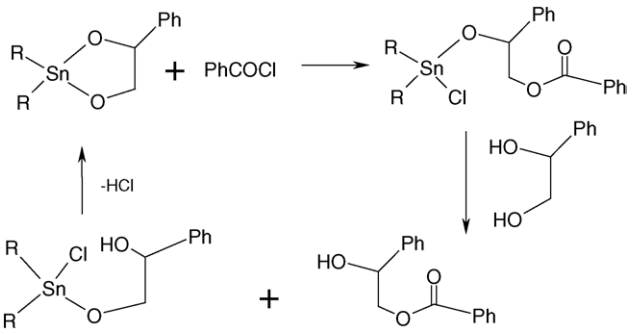
with a series of non-chlorinated tin derivatives forming the same stannylene derivative **6** as an active specie. This simple reaction allows to easily compare different reaction protocols by measuring the reaction rate and the product distribution.

When compound **1** was treated at reflux in chloroform for 30 min with a catalytic amount of $Bu_2Sn(MeO)_2$ (0.02 eq) and the resulting solution was treated with 1.1 eq of benzoyl chloride at room temperature in the presence of triethylamine (TEA) (2 eq) as a base, the benzoylation reaction was complete in 10 min [11] with a product distribution similar to the one observed with the same substrates with other reaction protocols [3,5]. Dibutyl tin diisopropoxide ($Bu_2Sn(2\text{-}PrO)_2$), prepared by refluxing Bu_2SnO in 2-propanol for 1 h and removing the solvent under high vacuum, was as effective as a catalyst for the reaction in Scheme 1. Finally, tetra butyl dimethoxide distannoxane ($Bu_4Me_2Sn_2O$) obtained by reaction of Bu_2SnO and dimethyl carbonate and further reaction with methanol [10] was prepared and the same reaction protocol was followed: **1** was refluxed for 20 min in chloroform in the presence of 0.02 eq of $Bu_4(MeO)_2Sn_2O$. The mixture was then treated at room temperature with 1.1 mol of benzoyl chloride and TEA. Analysis of samples showed that the reaction was complete in about 10 min time. These experiments strongly suggest that a common intermediate might be responsible for the catalytic cycle. It is well known that exchange reactions occur between tin alkoxides and diols thus generating the corresponding tin cyclic ketals [1,8,9].

2.1. Benzoylation catalysed by the stannylene ketal *6*

Compound **6** obtained by refluxing **1** with 1 eq of Bu_2SnO in methanol was isolated, characterised and proved to be identical with the compounds obtained from 1-phenyl-1,2-ethanediol with a stoichiometric amount of the tin reagents **7**–**10** [12]. 1-Phenyl-1,2-ethanediol **1** (500 mg, 3.6 mmol) in chloroform (20 ml) was then treated at room temperature with compound **6** (26 mg, 0.07 mmol, 0.02 eq), benzoyl chloride (509 mg, 3.6 mmol) and TEA (730 mg, 7.2 mmol). Reaction samples analysed by TLC and ^{1}H NMR showed that compound **1** was completely transformed in about 10 min [11] giving a 10:1 mixture of **2** and **3**. We believe that these results show that in all the above experiments there is an exchange reaction between the initially formed tin alkoxide and the diol to give the ketal **6**, which is the active reaction catalyst. The proposed mechanism for the catalytic cycle, is reported in Scheme 2.

We have not explored the effect of the nature and amount of base on the selectivity and the rate of the reaction. A few solvents have been tested but from previous data from the literature [8] it is reasonable to believe that the choice is much larger.



Scheme 2.

Table 1
Time of complete conversion of 1 → 2 + 3 in different conditions and 2/3 ratio

Run	Catalyst (eq)	Solvent	*t* (min)	**2**/**3**	Base (eq)
1	**6** (0.02)	$CHCl_3$	10	14	TEA (2)
2	**6** (0.02)	Toluene	14	10	TEA (2)
3	$Bu_2Sn(MeO)_2$ (0.02)	$CHCl_3$	<10	14	TEA (2)
4	$Bu_2Sn(MeO)_2$ (0.02)	Toluene	14	11	TEA (2)
5	$Bu_2Sn(2\text{-}PrO)_2$ (0.02)	2-PrOH	12	12	K_2CO_3 (2)
6	$Bu_2Sn(2\text{-}PrO)_2$ (0.02)	$CHCl_3$	16	11	TEA (2)
7	$Bu_4(MeO)_2Sn_2O$ (0.02)	$CHCl_3$	<10	9.5	TEA (2)
8	$Bu_4(MeO)_2Sn_2O$ (0.02)	Toluene	12	10	TEA (2)

Table 1 reports the data of reaction in Scheme 1 with four different tin compounds used in a catalytic amount in different solvents. *t* (min) indicates the time at which the diol is completely transformed after benzoyl chloride addition. **2**/**3** indicates the ratio between the two isomeric monobenzoates as determined by ^{1}H NMR studies.

From the preparative point of view, the use of **6** as catalyst (0.02 eq) in $CHCl_3$ proved to be the most practical protocol.

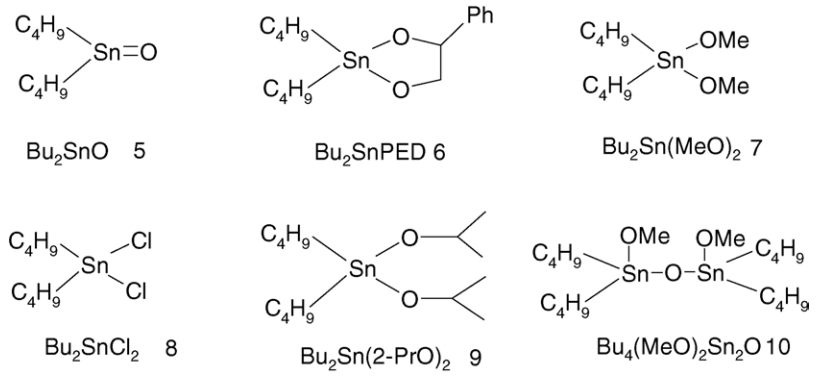
3. Conclusions

We have established for the first time the catalytic nature of the tin acetal **6** in the benzoylation of **1**. The present method has the following peculiarities:

(i) A catalytic amount of tin compound is required, not involving toxic chloro tin derivatives or microwave irradiation.
(ii) The stannylene ketal can be generated from commercially available tin species in the appropriate solvent and then used as catalyst in the benzoylation reaction in a different solvent if required.
(iii) A wide range of solvents from non-polar to isopropanol can be used allowing to work in homogeneous solution even with less soluble substrates [13].
(iv) The catalytic cycle is active with any of the tin species in Scheme 3 and the selective acylation goes to completion in 5–15 min at room temperature (>60 min without the tin catalyst).

4. Experimental

Bu_2SnO and the other dibutyl tin derivatives **7** and **8** were purchased from Sigma–Aldrich. $Bu_2Sn(2\text{-}PrO)_2$ was prepared



Scheme 3.

from Bu_2SnO in 2-PrOH as described above. $Bu_4(MeO)_2Sn_2O$ was prepared from dibutyl tin oxide and dimethyl carbonate as described in the literature [10].

4.1. Preparation of the stannylene ketal **6**

Compound **6** was prepared from each of the following stannylene derivatives: the compound prepared from Bu_2SnO **5** was isolated purified and characterised. In all other cases, the compound was not purified and used as such in the benzoylation reaction. The presence of compound **6** in the mixture was assessed by inspection of the ^1H and ^{13}C NMR spectra of the crude material.

4.1.1. From Bu_2SnO (**5**)

Compound **1** (5.0 g, 36 mmol) was dissolved in 50 ml of toluene. Dibutyltin oxide (8.9 g, 35.7 mmol) is added. The suspension was refluxed for 24 h in a Dean Stark apparatus. Compound **6** was isolated after solvent removal and stored in a dry box for further use. ^1H and ^{13}C NMR were identical with the one reported in the literature.

4.1.2. From Bu_2SnCl_2 (**8**)

Compound **1** (5.0 g, 36 mmol) was dissolved in 50 ml of toluene. Dibutyltin dichloride (11 g, 36 mmol) was added together with triethylamine (800 mg, 2 eq). The solution was refluxed for 2 h. The reaction mixture containing compound **6** was used as such for the acylation reaction.

4.1.3. From $Bu_2Sn(MeO)_2$ (**7**)

Compound **1** (5.0 g, 36 mmol) was dissolved in 50 ml of methanol. $Bu_2Sn(MeO)_2$ (10.6 g, 36 mmol) was added and the solution was refluxed for 2 h. Compound **6** was obtained after solvent removal and used as such for the acylation reaction.

4.1.4. From $Bu_2Sn(2\text{-}PrO)_2$ (**9**)

Compound **1** (0.5 g, 3.6 mmol) was dissolved in 10 ml of 2-propanol. $Bu_2Sn(2\text{-}PrO)_2$ (1.25 g, 3.6 mmol) was added and the solution was refluxed for 2 h. Compound **6** was obtained after solvent removal and used as such for the acylation reaction.

4.1.5. From $Bu_4(MeO)_2Sn_2O$ (**10**)

Compound **1** (0.5 g, 3.6 mmol) was dissolved in 25 ml of $CHCl_3$. $Bu_4(MeO)_2Sn_2O$ (1.25 g, 3.6 mmol) was added and the solution was refluxed for 2 h. Compound **6** was obtained after solvent removal and used as such for the acylation reaction.

4.1.6. (±)4-Phenyl-2,2-di-n-butyl-1,3,2-dioxa stannolan (**6**)

^1H NMR (250 MHz,$CDCl_3$): $\delta = 0.92$ (m, 6H); 1.1–2.0 (m, 12H); 3.19 (br, dd, 1H, $J = 9.5$ and 9.0); 3.79 (Br, dd, 1H, $J = 9.0$ and 4.0); 4.50 (br, dd, 1H, $J = 9.5$ and 4.0); 7.1–7.6 (m, 5H).

^{13}C NMR (250 MHz,$CDCl_3$): $\delta = 13.61$ (q); 22.36 (t); 26.87 (t); 27.36 (t); 69.28 (t); 75.74 (d); 126.76 (d); 127.64 (d); 128.21 (d); 143.02 (s).

4.2. Benzoylation of compound **1** with benzoyl chloride in different solvents and conditions

4.2.1. With **6** as catalyst in $CHCl_3$

Compound **1** 1-phenyl-1,2-ethane diol (0.5 g, 3.6 mmol) was dissolved in 20 ml of $CHCl_3$. Compound **6** (0.026 g, 0.07 mmol, 0.02 eq) in 5 ml of $CHCl_3$ was added to the solution together with TEA (1.0 ml, 7.2 mmol) and benzoylchloride (0.42 ml, 3.6 mmol). The reaction was stirred at room temperature until the starting material had disappeared (10 min from TLC hexethyl ac. 1:1, rf PED 0.18, primary monoac. 0.34). The reaction was quenched with water (10 ml) and the two phases separated. The organic solvent was removed under vacuum to obtain a pale yellow solid directly analysed by ^1H NMR without further purification. The outcome of the reaction was determined from the integration of the benzylic proton whose chemical shifts are highlighted below. The ratio of the primary monobenzoylation to the secondary one was 14/1.

^1H NMR 1-phenyl-1,2-ethane diol ($CDCl_3$): $\delta = 3.61$–3.79 (m, 2H); **4.78–4.85** (dd, 1H); 7.29–7.39 (m, 5H).

^1H NMR 1-phenyl-1-hydroxy-2-benzoyloxy-ethane ($CDCl_3$): $\delta = 3.20$ (br, s, 1H); 4.38–4.57 (m, 2H); **5.15** (dd, 1H); 7.20–7.60 (m, 8H); 7.90–8.30 (m, 2H).

^1H NMR 1-phenyl-1-benzoyloxy-2-hydroxy-ethane ($CDCl_3$): $\delta = 2.20$ (br s, 1H); 3.90–4.15 (m, 2H); **6.05** (q, dd, 1H); 7.20–7.60 (m 8H); 7.90–8.30 (m, 2H).

^{1}H NMR 1-phenyl-1,2-dibenzoyloxy-ethane ($CDCl_3$): δ = 4.55–4.80 (m, 2H); **6.35** (t, 1H); 7.15–8.15 (m, 15H).

*4.2.2. With **6** as catalyst in toluene*

Compound **1** 1-phenyl-1,2-ethane diol (0.5 g, 3.6 mmol) was dissolved in 20 ml of toluene. Compound **6** (0.026 g, 0.07 mmol, 0.02 eq) in 5 ml of toluene was added to the solution together with TEA (1.0 ml, 7.2 mmol) and benzoylchloride (0.42 ml, 3.6 mmol). The reaction was stirred at room temperature until the starting material had disappeared (TLC, 14 min). The reaction was quenced with water and the two phases separated. The organic solvent was removed under vacuum to obtain a pale yellow solid directly analysed by ^{1}HNMR without further purification. The ratio of the primary monobenzoylation to the secondary one was 10.

*4.2.3. With **6** as catalyst in 2-propanol*

Compound **1** 1-phenyl-1,2-ethane diol (0.5 g, 3.6 mmol) was dissolved in 20 ml of 2-propanol. Compound **6** (0.026 g, 0.07 mmol, 0.02 eq) in 5 ml of 2-propanol was added to the solution together with TEA (1.0 ml, 7.2 mmol) and benzoylchloride (0.46 ml, 4 mmol). The reaction was stirred at room temperature until the starting material had disappeared (TLC, 10 min). The reaction was quenced with water and the two phases separated. The ratio of the primary monobenzoylation to the secondary one was 12.

*4.2.4. With Bu_2SnO **5** as catalyst in MeOH/$CHCl_3$*

Compound **1** 1-phenyl-1,2-ethane diol (0.5 g, 3.6 mmol) was dissolved in 20 ml of MeOH. Compound **5** (0.018 g, 0.07 mmol, 0.02 eq) was added and the suspension refluxed for 2 h. The solvent was evaporated in vacuum and the residue dissolved in 10 ml of $CHCl_3$ and treated with TEA (1 ml, 7.2 mmol) and benzoylchloride (0.42 ml, 3.6 mmol) in 2 ml of $CHCl_3$. The mixture was stirred at room temperature until the starting material had disappeared (TLC, 10 min). The reaction was quenced with water and the two phases separated. The ratio of the primary monobenzoylation to the secondary one was 14.

*4.2.5. With $Bu_2Sn(MeO)_2$ **7** as catalyst in $CHCl_3$*

Compound **1** 1-phenyl-1,2-ethane diol (0.5 g, 3.6 mmol) was dissolved in 20 ml of $CHCl_3$. Compound **7** (0.021 g, 0.07 mmol, 0.02 eq) in 5 ml of $CHCl_3$ was added and the solution refluxed for 60 min. TEA (1 ml, 7.2 mmol) and benzoylchloride (0.42 ml, 3.6 mmol) in 2 ml of $CHCl_3$ were added at room temperature and stirred until the starting material had disappeared (TLC, 10 min). The reaction was quenced with water and the two phases separated. The ratio of the primary monobenzoylation to the secondary one was 14.

*4.2.6. With $Bu_2Sn(MeO)_2$ **7** as catalyst in toluene*

Compound **1** 1-phenyl-1,2-ethane diol (0.5 g, 3.6 mmol) was dissolved in 20 ml of toluene. Compound **7** (0.021 g, 0.07 mmol, 0.02 eq) in 5 ml of toluene was added and the solution refluxed for 60 min. TEA (1 ml, 7.2 mmol) and benzoylchloride (0.42 ml, 3.6 mmol) in 2 ml of toluene were added at room temperature and stirred until the starting material had disappeared (TLC, 14 min). The reaction was quenced with water and the two phases separated. The ratio of the primary monobenzoylation to the secondary one was 11.

*4.2.7. With $Bu_2Sn(2\text{-}PrO)_2$ **9** as catalyst in $CHCl_3$*

Compound **1** 1-phenyl-1,2-ethane diol (0.5 g, 3.6 mmol) was dissolved in 20 ml of $CHCl_3$. Compound **9** (0.024 g, 0.07 mmol, 0.02 eq) in 5 ml of $CHCl_3$ was added and the solution refluxed for 30 min. TEA (1 ml, 7.2 mmol) and benzoylchloride (0.42 ml, 3.6 mmol) in 2 ml of $CHCl_3$ were added at room temperature and stirred until the starting material had disappeared (TLC, 10 min). The reaction was quenced with water and the two phases separated. The ratio of the primary monobenzoylation to the secondary one was 12.

*4.2.8. With $Bu_2Sn(2\text{-}PrO)_2$ **9** as catalyst in 2-propanol*

Compound **1** 1-phenyl-1,2-ethane diol (0.5 g, 3.6 mmol) was dissolved in 20 ml of 2-propanol. Compound **9** (0.024 g, 0.07 mmol, 0.02 eq) in 5 ml of 2-propanol was added and the solution refluxed for 30 min. TEA (1.1 ml, 8 mmol) and benzoylchloride (0.46 ml, 4 mmol) in 2 ml of 2-propanol were added at room temperature and stirred until the starting material had disappeared (TLC, 12 min). The reaction was quenced with water and the two phases separated. The ratio of the primary monobenzoylation to the secondary one was 12.

*4.2.9. With $Bu_4(MeO)_2Sn_2O$ **10** as catalyst in toluene*

Compound **1** 1-phenyl-1,2-ethane diol (0.5 g, 3.6 mmol) was dissolved in 20 ml of toluene. Compound **10** (0.038 g, 0.07 mmol, 0.02 eq) in 5 ml of toluene was added and the solution refluxed for 30 min. TEA (1 ml, 7.2 mmol) and benzoylchloride (0.42 ml, 3.6 mmol) in 5 ml of toluene were added at room temperature. The reaction was stirred until the starting material had disappeared (TLC, 12 min). The reaction was quenced with water and the two phases separated. The ratio of the primary monobenzoylation to the secondary one was 10.

*4.2.10. With $Bu_4(MeO)_2Sn_2O$ **10** as catalyst in $CHCl_3$*

Compound **1** 1-phenyl-1,2-ethane diol (0.5 g, 3.6 mmol) was dissolved in 20 ml of $CHCl_3$. Compound **10** (0.038 g, 0.07 mmol, 0.02 eq) in 5 ml of $CHCl_3$ was added and the solution refluxed for 30 min. TE (1 ml, 7.2 mmol) and benzoylchloride (0.42 ml, 3.6 mmol) in 5 ml of $CHCl_3$ were added at room temperature. The reaction was stirred until the starting material had disappeared (TLC, 12 min). The reaction was quenced with water and the two phases separated. The ratio of the primary monobenzoylation to the secondary one was 10.

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[11] In the absence of the assistance of a tin intermediate the mono benzoylation of 1-phenyl-1,2-ethanediol **1** required in control experiments more than 60 min, with a statistical product distribution.
[12] Compound **6** is depicted in Scheme 2 as a monomeric compound. From spectral data in the literature [2,8] it has been proposed a multimeric structure in solution. This structure should be chemically equivalent to the monomeric one.
[13] Experiments with substrates non-soluble in organic solvents will be reported elsewhere.