Pergamon

Tetrahedron Letters, Vol. 37, No. 30, pp. 5229-5232, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01071-4

Cleavage of Carboxylic Esters Effected by Organotin Oxides and Hydroxides Under Classical Heating and Microwave Irradiation. A Comparative Study.

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Abstract: We describe some recent findings on similarities and differences in the cleavage of selected carboxylic esters from the viewpoint of reactivity effected by organotin oxides and hydroxides, under different modes of heating (oil bath or microwave irradiation). These studies complement earlier use of bis(tributyltin) oxide and provide a simple and efficient procedure of cleavage of carboxylic esters in apolar aprotic or without solvent, under mild conditions with readily available organotin reagents. Copyright © 1996 Elsevier Science Ltd

Selective protection and deprotection of functional groups is of prime importance in organic synthesis.[1] We have been working in the development of new methodologies towards the cleavage of carboxylic esters to afford the corresponding acids. We have reported the use of bis(tributyltin) oxide (BBTO) (**1**) for the chemoselective cleavage of primary alkyl and aromatic carboxylic esters, double esters such as (pivaloyloxy)methyl carboxylates[2] as well as phenacyl, benzyl and methyl esters of *N*-protected amino acids and dipeptides and *N*-protected amino acid benzyl esters linked to resins.[3] In this paper, we report an extention of this methodology, to the deprotection of carboxylic esters with BBTO and other trialkyltin, triaryltin and dialkyltin oxides as well as triaryltin and trialkyltin hydroxides,[4] such as bis(chlorodibutyltin) oxide (**2**), bis(triphenyltin) oxide (**3**), dibutyltin oxide (**4**), triphenyltin hydroxide (**5**)[5] and trimethyltin hydroxide (**6**). Table 1 summarizes products of the reactions of these organotin reagents with methyl phenylacetate (**7**) and isopropyl phenylacetate (**8**).

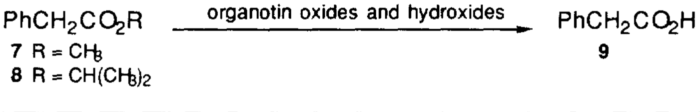
When **7** was heated at 200°C or 100°C without solvent with 2 or 1 equivalents of BBTO (**1**), it was converted into the phenylacetic acid (**9**) in quantitative yield (entries 1, 2 and 3). Upon treatment of a 0.5 M toluene solution of ester **7** with 1 equivalent of organotin oxides **3**, **4** and hydroxides **5** and **6**, at 100°C for 6.0 h (entries 5, 6, 7 and 8), the acid **9** was produced in high to moderate yield. These results indicate that an excess of the reagent is not neccesary and rule out the path b on the mechanism II for the conversion of esters to acids with BBTO as was previously considered.[6] It is now clear that the oxygen atom of the carbinol center does not undergo coordination with a second molecule of BBTO.

When **5** is used as reagent (entry 7), yield of **9** higher than 50% indicates that, although oxide **3** can be formed *in situ*,[5] hydroxide **5** is itself a reactive specie. Experiment with trimethyltin hydroxide (**6**) (entry 8), which is remarkably difficult to dehydrate[4a] allows us to conclude that a second atom of tin is not neccesary to accomplish the cleavage reaction.[7] When the ester **7** was treated with bis(chlorodibutyltin) oxide (**2**), remained unaffected even over a longer period of heating (entry 4, see also entry 6 in Table 2). Presumably, the strongly electron withdrawing nature of the chlorine atoms would affect the nucleophilicity of the oxygen atom bonded to two tin atoms (-Sn—O—Sn-) in this compound. The Lewis acidity of reagents **1** and **2** coordinated with triphenylphosphine oxide were determined by recording the P=O IR frequencies relative to triphenylphosphine oxide.[8] Thus, the $Ph_3P=O$ frequency shifts suggest an ordering of Lewis acid strengths **2** > **1**. This is a logical order, because the presence of the electronegative chlorine substituent enhance the Lewis acidity of the tin.

These results indicate that the alternative mechanism IIa[2] which was based on Lewis acid complexation of BBTO at the carboxyl oxygen atom must be ruled out.

Treatment of **8** with 1 molar equivalent of **1** or **6** (entries 9 and 12), afforded **9** in high yield. This result indicates that, in these cases, the steric demand of the secondary alkyl group is not important. However, for organotin oxide **3** and hydroxide **5** (compare entries 5 and 10; 7 and 11) this steric hindrance appears to be important.

Table 1. Cleavage of carboxylic esters by organotin oxides and hydroxides under classical heating.



$$\underset{\substack{\mathbf{7}\ R = CH_3\\ \mathbf{8}\ R = CH(CH_3)_2}}{PhCH_2CO_2R} \xrightarrow{\text{organotin oxides and hydroxides}} \underset{\mathbf{9}}{PhCH_2CO_2H}$$

entry	ester	reagent (mol. eq.)/time/temp.[a]	solvent[b]	yield of **9** (%)[c]
1	**7**	**1**; 2; 0.5; 200	---	100
2	**7**	**1**; 1; 0.5; 200	---	100
3	**7**	**1**; 1; 2.5; 100	---	100
4	**7**	**2**; 1; 20; 100	toluene	0
5	**7**	**3**; 1; 6.0; 100	toluene	94
6	**7**	**4**; 1; 6.0; 100	toluene	65
7	**7**	**5**; 1; 6.0; 100	toluene	60
8	**7**	**6**; 1; 2.5; 100	toluene	96
9	**8**	**1**; 1; 6.0; 100	---	82
10	**8**	**3**; 1; 6.0; 100	toluene	27
11	**8**	**5**; 1; 6.0; 100	toluene	22
12	**8**	**6**; 1; 6.0; 100	toluene	84

[a] time in hours; refer to heating in an oil bath at the temperature in degree centigrade. [b] solutions 0.5 mmol/ml. of organotin reagents. [c] values represent isolated yields. The IR, and ^{1}H NMR of the isolated phenylacetic acid (**9**) were in agreement with these of an authentic sample.

Microwave irradiation[9] has recently found application in performing important accelerations of reaction rate for the cleavage of benzyl,[10] acetyl[11] and pivaloyl[12] ester groups. We were interested to investigate the applicability of microwave irradiation and decided to check its effect on the cleavage of carboxylic esters by organotin oxides and hydroxides on apolar aprotic solvents with low dielectric constant, such as toluene solutions, or in solvent-free mixtures. Bose *et al.*[13] have developed a convenient methodology, termed microwave-organic reaction enhancement (MORE) which employs polar, high boiling solvents in open vessels.[14] The results obtained with a primary alkyl and a secondary alkyl carboxylic esters and one or two molar equivalents of **1**-**5** are summarized in Table 2. It is clear from these experiments the influence that the concentrations of the solutions have on the yield and selectivity of the cleavage of esters **7** and **8** by **1**, **3** and **5**. Reaction of ester **7** with **1** under concentrated toluene solution or under solvent-free conditions, when subjected to microwave irradiation[15] resulted in the rapid formation (20 minutes or less) of **9** in quantitative yields (entries 3, 4 and 5). With ester **8** and neat BBTO (**1**), the yield of **9** was excellent (entry 10), meanwhile with bis (triphenyltin) oxide (**3**) and triphenyltin hydroxide (**5**) (entries 11 and 12) no reaction was observed in either case.

Table 2. Cleavage of carboxylic esters by organotin oxides and hydroxides under microwave irradiation.

entry	ester	reagent (mol. eq.)/time[a]/pot.[b]	solvent[c]	yield of **9** (%)[g]
1	**7**	**1**; 2; 20; 900	toluene[d]	13
2	**7**	**1**; 2; 20; 900	toluene[e]	49
3	**7**	**1**; 2; 20; 900	toluene[f]	100
4	**7**	**1**; 2; 16; 900	---	100
5	**7**	**1**; 1; 29; 500	---	100
6	**7**	**2**; 1; 45; 750	toluene[d]	0
7	**7**	**3**; 1; 45; 750	toluene[d]	20
8	**7**	**4**; 1; 45; 750	toluene[d]	7
9	**7**	**5**; 1; 45; 750	toluene[d]	14
10	**8**	**1**; 2; 20; 900	---	83
11	**8**	**3**; 1; 45; 750	toluene[d]	0
12	**8**	**5**; 1; 45; 750	toluene[d]	0

[a]After 7 minutes of heating we discontinued the microwave irradiation and cooled the toluene solution in order to avoid excessive evaporation of the solvent. This protocol is repeteated until reaching an overall heating time as indicated. [b]time in min; potency in watts. [c]solutions in mmol/ml of organotin reagents. [d] 0.5; [e] 0.9; [f] 2.0; [g]values represent isolated yields.

The order of reactivity of these organotin reagents for deesterification of methyl and isopropyl phenylacetate was found to be: **1**≅ **6** > **3** > **5** ≅ **4** >> **2**.

In conclusion, the studies outlined above complement earlier reports on the cleavage of carboxylic esters by BBTO and expand the versatility of the methodology for the deprotection of esters under mild conditions into other readily available organotin reagents. Microwave irradiation offers advantages over conventional heating because reaction rates are increased. An order of reactivity has been established for the various organotin reagents used. Trimethyltin hydroxide (**6**) can be used for the cleavage of acetates and benzoates of alcohols, since it is easy to remove tin byproducts into water phase giving an organic solution of the pure product. The workup procedure is very simple, compared with that of BBTO.[2]

Cleavage of methyl phenylacetate with 1, under microwave irradiation: In a typical experiment, methyl phenylacetate **6** (120 mg, 0.79 mmol), and BBTO (0.41 ml, 0.79 mmol) were mixed in a tube. The tube was covered with an inverted funnel, and placed in a domestic microwave oven and irradiated at 500 watts for the time listed in Table 2. It was found to be convenient to irradiate at intervals of 7 minutes. In all the cases the time of reaction was established by frequent monitoring of the reaction by TLC. After cooling, the residual oil was dissolved in hexane (10 ml) and extracted with 5% aqueous solution of $NaHCO_3$ (3 x 5 ml). The aqueous phase was acidified to pH 4.5 with HCl (0.5 N solution), the resultant mixture was extracted with ethyl acetate (3 x 5 ml), and the combined organic phases were washed with aqueous solution of NaCl (2 x 5 ml), dried with Na_2SO_4 and evaporated to yield pure phenylacetic acid **9** as a white solid. A similar protocol as described above, in toluene solution, was used for organotin reagents **2-6** which are all in solid state. In the reactions with hydroxide **6**, we have observed that the purification procedure by extracting the organotin residues into the aqueous phase gave a clean organic phase. In the case of **6** the progress of the reaction was monitored by TLC (silica gel GF_{254}, eluent: hexane-ethyl acetate-formic acid, 70:30:0.1).

Acknowledgements. The authors would like to thank CONICET for financial support and fellowship (R. F.)

References and Notes

1. For a recent review, see: Jarowicki, K.; Kocienski, P. J. *Contemporary Organic Synthesis* **1995**, *2*, 316 and references cited therein.
2. Salomon, C. J.; Mata, E. G.; Mascaretti, O. A. *J. Org. Chem.* **1994**, *59*, 7259.
3. Salomon, C. J.; Mata, E. G.; Mascaretti, O. A. *J. Chem. Soc., Perkin Trans 1* **1996**, 995.
4. The chemistry of organotin oxide and hydroxides has been reviewed rather extensively, see: a) Bloodworth A. J.; Davies, A. G. In *Organotin Compounds*; Sawyer, A. Ed.; vol 1; M. Dekker: New York, **1971**, pp. 158-252. b) Davies, A. G.; Smith, P. G. In *Comprehensive Organometallic Chemistry*; Wilkinson, G.; Stone, F. G. A.; Abel, E. W. Eds.; vol. 2; Pergamon Press: Oxford, **1982**, pp. 519-627. c) Davies, A. G. In *Comprehensive Organometallic Chemistry* II, Abel, E. W.; Stone, F. G. A.; Wilkinson, G.; Eds.; vol. 2; Elsevier: Oxford, **1995**, pp. 217-303. d) Pereyre, M.; Quintard, J.; Rahm, A. *Tin in Organic Synthesis*; Butterworth: London, **1987**. e) Omae, I. *Organotin Chemistry*; Elsevier: New York. **1989**. f) Harrison, P. G. *Chemistry of Tin*, Blackie: Glasgow **1989**.
5. In solution, triphenyltin hydroxide is in equilibrium with bis(triphenyltin) oxide and water. See 4a, p. 195.
6. See path b on the mechanism II of reference 2. One of the referees pointed out this alternative path for mechanism II. Now, we can rule out this possibility.
7. In view of these results, we now note that the lack of ester cleavage, reported in Salomon, C. J.; Mata, E.. G. Mascaretti, O. A. *Tetrahedron* **1993**, *49*, 3691, which we believed and indicated was brought about by using trineophyltin hydroxide $(PhC(CH_3)_2CH_2)_3SnOH$, incorrectly assigned by Reichle, W. T. *Inorg. Chem.* **1966**, *5*, 87, was effectively carried out with bis(trineophyltin) oxide. For the correct structure and physical and spectroscopic properties see: Zimmer, H; Homberg, O. A.; Jayawant, M. *J. Org. Chem.* **1966**, 31, 3857. We now suggest that the lack of reactivity of bis(trineophyltin) oxide should be attributed to the steric restriction of the very bulky neophyl groups.
8. For Lewis acidities estimation by using the phosphine oxide IR frequency shift method, see: a) Vedejs, E.; Erdman, D. E.; Powell, D. R. *J. Org. Chem.* **1993**, *58*, 6162. b) Frazer, M. J.; Gerrard, W.; Patel, J. K. *J. Chem. Soc.* **1960**, 726.
9. For recent reviews on theoretical concepts, equipment design and applications of microwave energy in organic chemistry, see: a) Strauss, C, R.; Trainor, R. W. *Aust. J. Chem.* **1995**, *48*, 1665. b) Caddick, S. *Tetrahedron* **1995**, *38*, 10403. c) Abramovich, R. A. *Org. Prep. Proced. Int.* **1991**, *23*, 683. d) Mingos, D. M. P.; Baghurst, D. R. *Chem. Soc. Rev.* **1991**, *20*, 1.
10. Varma, R. S.; Chatterjee, A. K.; Varma, M. *Tetrahedron Lett.* **1993**, *34*, 4603.
11. Varma, R. S.; Varma, M.; Chatterjee, A. K. *J. Chem. Soc., Perkin Trans 1* **1993**, 999.
12. Ley, S. V.; Mynett, D. M. *Synlett* **1993**, 793.
13. Bose, A. K.; Manhas, M. S.; Ghosh, M.; Shah, M.; Raju, V. S.; Bari, S. S.; Newaz, S. N.; Banik, B. K.; Chaudhary, A. G.; Bakarat, K. J. *J. Org. Chem.* **1991**, *56*, 6968.
14. Despite the convenience of the MORE technique we use toluene which is a solvent with a low dielectric constant and fairly transparent to microwave irradiation because we have made an extensive use of this solvent for the cleavage of carboxylic esters by BBTO under conventional heating. See, references 2 and 3.
15. Reactions were conducted in a commercial microwave oven without any modification. The approximate temperature was 103°C. Measurements of temperatures induced by microwave heating by using a commercial microwave oven are not exact. For a procedure of measurement, see reference 13.

(*Received in USA* 27 *February* 1996; *revised* 28 *May* 1996; *accepted* 29 *May* 1996)