Alternative and Mild Procedures for the Removal of Organotin Residues from Reaction Mixtures

Philippe Renaud,* Emmanuel Lacôte and Laura Quaranta

Université de Fribourg, Institut de Chimie Organique, Pérolles, CH-1700 Fribourg

Abstract : Simple treatment of tributyltin halide-containing reaction mixtures with Me_3Al or aq. 1M NaOH leads after filtration through silica gel to complete removal of tin residues. The Me_3Al method is particularly convenient for polar products and the NaOH method for non-polar products.
© 1998 Elsevier Science Ltd. All rights reserved.

Due to their mildness and their compatibility with many functional groups, radical reactions became during the last fifteen years a very popular tool for organic synthesis.[1] The possibility of forming and breaking several bonds in one-step procedures (reaction cascades) offers unique advantages over classical processes. Among all the methods to carry out radical reactions, chain reactions using organotin derivative such as tributyltin hydride have a prominent place.[2] Unfortunately, tin byproducts, such as tributyltin halides, are very difficult to eliminate from the reaction products. This represents a major drawback for use of tin-mediated radical reactions, especially when testing the biological activity of the products is foreseen.

Several methods for the removal of tin residues from reaction mixtures have been described. They follow two different approaches. On one hand, new tin reagents who facilitate the separation from the reaction products have been developped, although they are potentially attractive, these methods are not routinely used.[3] On the other hand, methods for the removal of the widely used tributyltin derivatives have been elaborated and the methods we report here belongs to this second category. Extraction of the tin derivatives with hexane has been reported but is not general.[4] DBU-I_2 treatment has been investigated by Curran, however this method is severely limited by the basicity of DBU.[5] The standard treatment with KF in MeOH is not very efficient and is incompatible with silyl protecting groups (deprotection) and esters (transesterification).[6] Crich has recently proposed a useful and practical method for the removal of tin residues by reduction with $NaBH_3CN$.[7] However, this procedure required heating in refluxing *tert*-butanol, which is not compatible with heat-sensitive substrates.[8] Moreover, the separation of tin hydride from reaction products is difficult when working with apolar products. During our study of the role of Lewis acids in radical reactions,[9] we noticed that contamination by tin derivatives was not occurring when working with an excess of Me_3Al in the reaction mixture and also when the workup procedure included washing with an aqueous NaOH solution. Based on these observations, we have developed two different treatments which allow the efficient elimination of organotin residues.

Fax : 41 26 300 9739. E-mail : philippe.renaud@unifr.ch

Me₃Al workup procedure. Reactions of trialkyltin halides with Me₃Al at room temperature are known to give a rapid and clean formation of methyltrialkyltin.[10] Tetraalkyltin derivatives are highly apolar compounds that can be washed easily from silica gel with hexane. Therefore, it is possible to transform the trialkyltin halides formed during the radical reaction by a one-pot treatment with Me₃Al as shown for the reduction of **1** (eq. 1). The methyltributylstannane is easily separated from the reduced compound **2** by filtration over a short pad of silica gel with hexane as eluent followed by hexane/EtOAc 90:10 to elute the reduced product **2**.
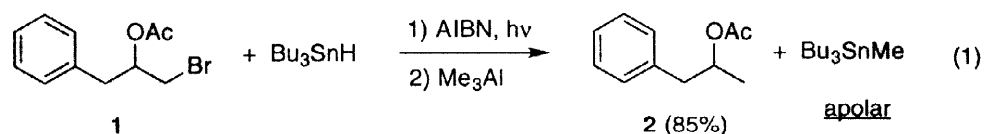
Typical procedure. A solution of **1** (257 mg, 1 mmol), AIBN (4 mg, 0.025 mmol) and Bu₃SnH (320 μl, 1.2 mmol) in dry benzene (5 ml) was irradiated at 10 °C under N_2 for 2 h. A 1M soln. of Me₃Al in hexane (1.2 ml, 1.2 mol) was then added and the reaction mixture was stirred at r.t. for 2 h. After hydrolysis with aq. 1M NaOH (10 ml), the organic layer was separated, washed with brine and dried over MgSO₄. The crude product was filtered through silica gel with hexane to remove Bu₃SnMe and hexane/AcOEt (90:10) to elute the reduced product **2** (151 mg, 85%) free of organotin residues as proved by ¹H-NMR and GC analyses.

The generality of this workup procedure was tested by treating 1:1 mixtures of Bu₃SnI and compounds **3-10** in benzene with AlMe₃ according to the above procedure. After filtration through silica gel, compounds **3-8** free of organotin residues were isolated in good yields. However, as expected, aldehyde **9** and ketone **10** react with AlMe₃ and were not recovered.

3 (>98%)   **4 (>98%)**   **5 (>98%)**   **6 (>98%)**

7 (>98%)   **8 (82%)**   **9 (0%)**   **10 (0%)**
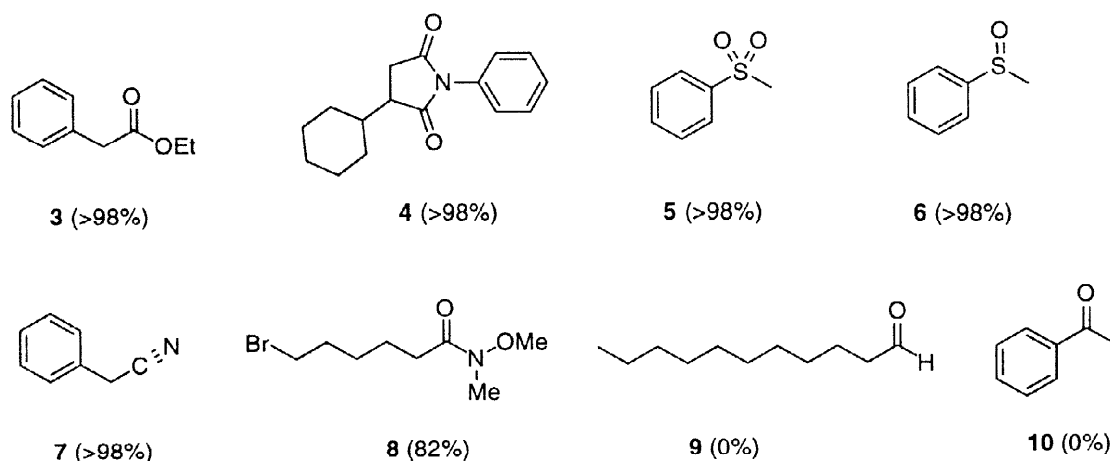
NaOH workup procedure. As anticipated from our observation in Lewis acid controlled reactions, washing of the reaction mixture with a 1M aq. NaOH solution reduces drastically the amount of tin halides. In a preliminary experiment, we have observed that washing of an etheral solution of Bu₃SnBr with a 1M aq. NaOH solution gives an emulsion containing a mixture of tributyltin hydroxide and bistributyltin oxide in equilibrium.[11]

Organotin hydroxides and oxides are not eluted on silica gel with commonly used chromatography solvents (mixture EtOAc/hexane) and could be efficiently removed by filtration through silica gel. The reaction depicted in equation 1 was performed again without the AlMe3 treatment. The crude reaction mixture was treated in the reaction flask with an aqueous 1M NaOH solution, after 1 h of vigorous stirring, the phase were separated and the organic layer was filtered through silica gel as above to yield the organotin free reduced product 2 (see Figure 1 for purity check). A related method based on DBU mediated hydrolysis of Bu3SnX has already been reported by Curran.[5] However, the biphasic method presented here proved to be much milder and convenient for base sensitive compounds. It has been applied routinely in our laboratory to many base- and hydrolysis-sensitive compounds without observation of degradation.
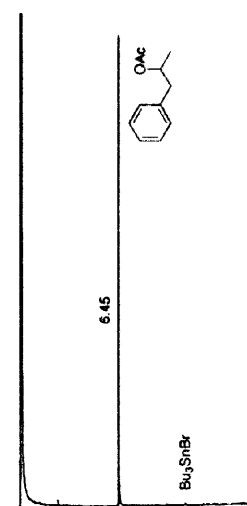

Figure 1. Purity test of crude **2** after NaOH workup and filtration through silica gel [column SE 54; 80 °C (2 min) - 200 °C (10 °C/min)]

The same workup procedure was used for the reaction of cyclohexyl iodide with N-phenylmaleimide **11** (eq. 2). The addition product **4** is sensitive to weak bases such as fluoride anion. However, biphasic treatment with aqueous NaOH afforded organotin free **4** in excellent yield.
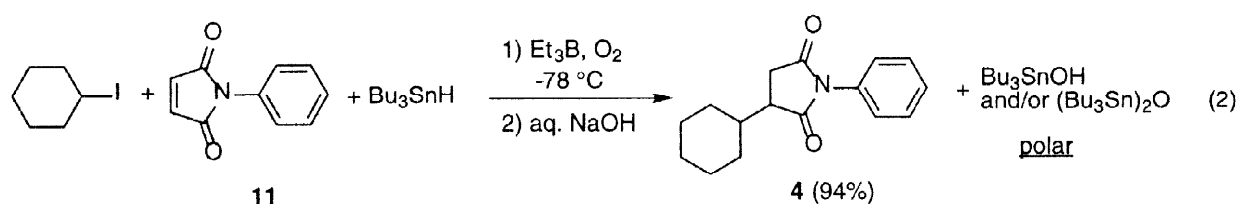
Typical procedure: To a solution of **11** (173 mg, 1 mmol) in dry dichloromethane (10 ml) at -78 °C was added Bu3SnH (540 μl, 2 mmol), cyclohexyl iodide (1.05 g, 5 mmol) and Et3B (1M solution in hexane, 2 ml, 2 mmol). O_2 was added *via* syringe pump during 4 h. Aq. 1M NaOH (10 ml) was then added and the biphasic mixture was vigorously stirred for 1 h. The organic phase was separated, washed with aq. 1M NaOH (5 ml), brine (10 ml) and dried over MgSO4. The crude product was filtered through silica gel (hexane/AcOEt 90:10) to yield **4** (242 mg, 94%) free of organotin residues as proved by 1H-NMR and GC analyses.

In conclusion, we have presented here two alternative ways of eliminating organotin halides from reaction

mixtures. The first approach is useful when the products contaminated by organotin residues are significantly more polar than Bu3SnMe. The second approach, *i.e.* washing of the crude reaction mixture with an aqueous NaOH solution is particularly simple and efficient and will be valuable for most of the reactions performed with tin derivatives. Even completely apolar substrates such as alkanes and alkenes can be freed from organotin residues.

REFERENCES AND NOTES

1. (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: Oxford, 1988. (b) Motherwell, W. B. ; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: London, 1992. (c) Curran, D. P. ; Porter, N. A. ; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996.

2. Neumann, W. P. *Synthesis* **1987**, 665-683.

3. (a) Light, J. ; Breslow, R. *Tetrahedron Lett.* **1990**, *31*, 2957-2958. (b) Gerlach, M. ; Jördens, F. ; Kuhn, H. ; Neumann, W. P. ; Petersheim, M. *J. Org. Chem.* **1991**, *56*, 5971-5972. (c) Rai, R. ; Collum, D. B. *Tetrahedron Lett.* **1994**, *35*, 6221-6224. (d) Fouquet, E. ; Pereyre, M. ; Roulet, T. *J. Chem. Soc., Chem. Commun.* **1995**, 2387-2388. (e) Clive, D. L. J. ; Yang, W. *J. Org. Chem.* **1995**, *60*, 2607-2609. (f) Curran, D. P. ; Hadida, S. *J. Am. Chem. Soc.* **1996**, *118*, 2531-2532.

4. Berge, J. M. ; Roberts, S. M. *Synthesis* **1979**, 471-472.

5. Curran, D. P. ; Chang, C. *J. Org. Chem.* **1989**, 3140-3157.

6. Leibner, J. E.; Jacobus, J. *J. Org. Chem.* **1979**, *44*, 449-450.

7. Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 7200-7201.

8. Using this approach, we observed a complete degradation of α-alkylated β-ketosulfoxides presumably *via* the thermal elimination of a sulfenic acid.

9. Renaud, P. *Chimia* **1997**, *51*, 236-238.

10. Neumann, W. P. *Liebigs Ann. Chem.* **1962**, *653*, 157-163.

11. For a discusssion of the hydrolysis products of organotin halides, see chapter 10 in: Davies, A. G. *Organotin Chemistry*; VCH: Weinheim, 1997.