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Mild, efficient and selective hydrolysis of polymer-supported methyl esters using trimethyltin hydroxide

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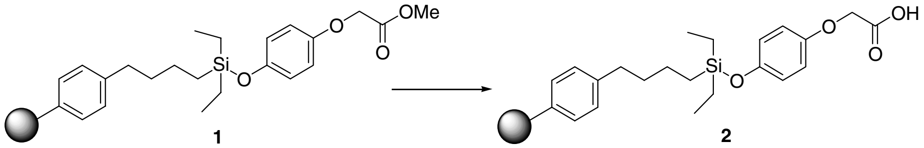
Abstract—An efficient and selective procedure for a rapid access to polymer-supported carboxylic acids from their corresponding methyl esters using trimethyltin hydroxide is described. Silyl and benzyl ether, and Rink amide linkers are stable to the reaction conditions.

Solid-phase organic synthesis (SPOS) is a widely used tool for the preparation of a large number of structurally diverse compounds for combinatorial libraries.[1] SPOS offers a number of indisputable advantages as compared to solution chemistry. Purification is facilitated by simple filtration, avoiding time-consuming separation techniques, subsequent building blocks and reagents can be added in excess in order to drive reactions to completion. Also, the 'pseudo-dilution' effect,[2] which is the result of using the polymeric solid support, makes intramolecular macrocyclization a suitable reaction that could be carried out efficiently on solid-phase rather than in solution. Therefore, there is a growing need to enhance the variety of synthetic transformations and organic structures that can be achieved through solid-phase methodologies.

Mild, efficient and selective hydrolysis of esters is of prime importance in organic synthesis.[3] However, apart from those methods directed towards the cleavage of ester linkage to the resin, investigations on the hydrolysis of esters on solid support have been scarce. In the course of our studies on the application of solid-phase methodologies to the synthesis of biologically interesting compounds,[4] we encountered great difficulty in the hydrolysis of a methyl ester linked to (4-diethylsilylbutyl)polystyrene resin (**1**) (Scheme 1). Our first option was potassium trimethylsilanoate which has been the reagent of choice for the hydrolysis of resin-bound esters.[5] In our case, treatment of ester **1** with 10 equiv of potassium trimethylsilanoate in dichloromethane at room temperature for 12 h, caused the Si–O bond to break. Hydrolysis with sodium hydroxide in THF/H_2O (9:1)[6] did not proceed at all, probably due to the poor swelling properties of the polystyrene–divinylbenzene resin.

In the search for an alternative procedure of the hydrolysis of resin-bound methyl ester **1**, we have considered the use of trimethyltin hydroxide (TMTOH). TMTOH has been reported by us as an effective reagent for the hydrolysis of alkyl esters[7] and for the cleavage of phenacyl ester anchored amino acids from polystyrene resin.[8]



Scheme 1.

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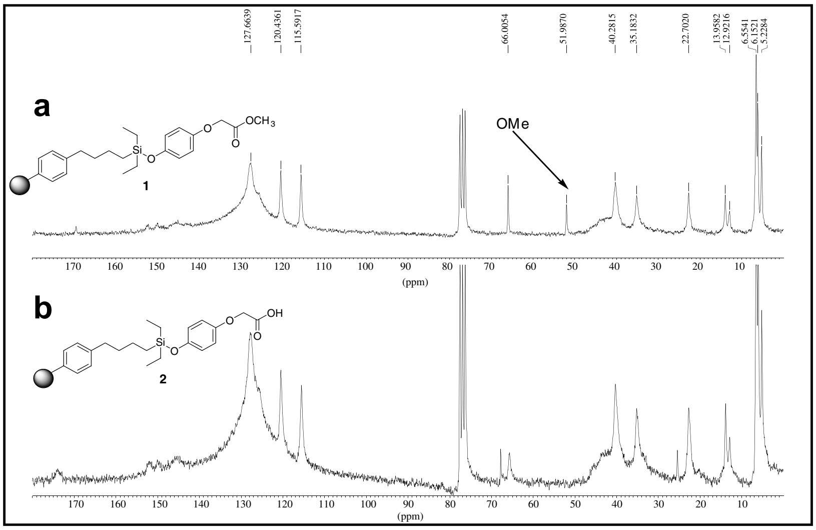


Figure 1. Gel phase ^{13}C NMR at 50 MHz of (a) methyl ester **1** and (b) carboxylic acid **2**.

More recently, Nicolaou and co-workers have extended the scope to a mild and selective hydrolysis of esters present within complex and sensitive substrates.[9]

Thus, treatment of resin **1** with 10 equiv of TMTOH in 1,2-dichloroethane at 85 °C for 48 h (with an additional 5 equiv of TMTOH added after 24 h) led to the free carboxylic acid **2**, which was evident from the absence of the methyl carbon signal (51.98 ppm) in gel phase ^{13}C NMR (Fig. 1). This promising initial test prompted us to investigate this reaction in more detail. The results obtained in these studies are summarized in Table 1.[10]

Application of the TMTOH conditions to other methyl esters linked to the (4-diethylsilylbutyl)polystyrene resin, such as compound **3**, yields the desired carboxylic acid **4** (entry 2). Methyl ester hydrolysis was corroborated by the cleavage from the resin with TBAF to obtain 3-hydroxybutyric acid. Methyl esters bound to Wang resin by a benzyl ether linkage were also evaluated. In

Table 1. Hydrolysis of polymer-supported methyl esters using trimethyltin hydroxide[a]

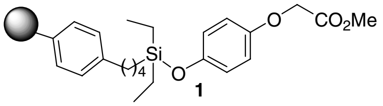
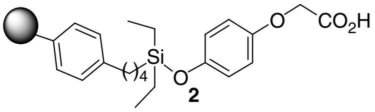
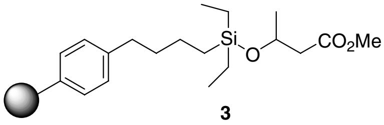
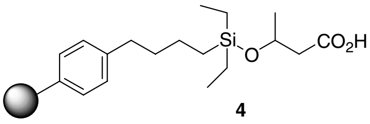
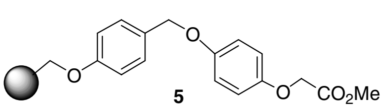
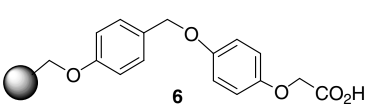
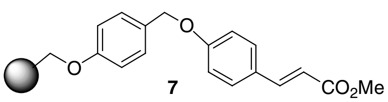
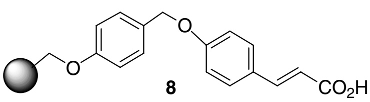
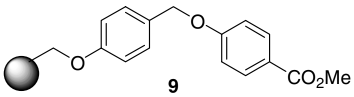
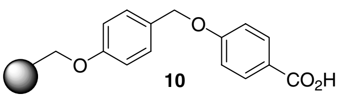
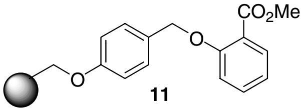
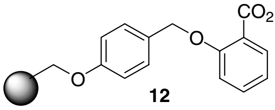
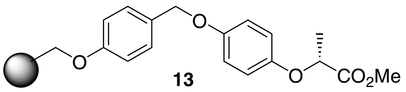
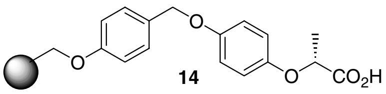
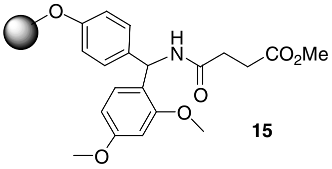
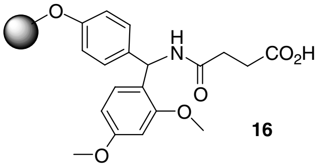
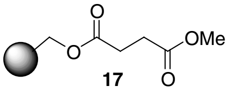
Entry	Substrate	Product[b]	Gel phase ^{13}C NMR peaks for methyl esters (ppm)
1	 **1**	 **2**	δ 51.98
2	 **3**	 **4**	δ 51.27
3	 **5**	 **6**	δ 51.78
4	 **7**	 **8**	δ 51.45
5	 **9**	 **10**	δ 51.69

Table 1 (*continued*)

Entry	Substrate	Product[b]	Gel phase ^{13}C NMR peaks for methyl esters (ppm)
6	 **11**	 **12**	δ 51.91
7	 **13**	 **14**	δ 52.07
8	 **15**	 **16**	δ 51.56
9	 **17**	[c]	

[a] Conditions: 10 equiv of trimethyltin hydroxide in 1,2-dichloroethane at 85 °C for 48 h (with an additional 5 equiv of TMTOH added after 24 h).

[b] Determined by the disappearance of the methyl ester carbon peak in gel phase ^{13}C NMR.

[c] See text.

all cases, the corresponding carboxylic acid was obtained without affecting the linker. The success of the hydrolysis step was corroborated by releasing the corresponding carboxylic acid from the resin, using TFA 10%/CH_2Cl_2.[4h,11] The usefulness of the mild TMTOH reagent with substrates sensitive to epimerization was further demonstrated by the hydrolysis of ester **13** (entry 7), where epimerization of the chiral α carbon to the methyl ester did not occur. This observation was confirmed by measuring the specific rotation angle of the carboxylic acid after cleavage from the resin. Amide linkage was also stable to the reaction conditions allowing the hydrolysis of the methyl ester moieties linked to Rink amide (**15**) (entry 8). As expected, no selectivity was achieved in the case of a benzyl ester linkage. Thus, when mono-methyl succinate ester linked to Merrifield resin (**17**) (entry 9) was treated with 15 equiv of TMTOH at room temperature, no reaction occurred after 24 h. However, heating the substrate with more equivalents of TMTOH caused a premature release from the solid support, as was evident from the absence of the carbonyl stretch bands in the IR spectrum of the resin. Solution phase hydrolysis of different ethyl esters with TMTOH has proven to be successful, in contrast, the hydrolysis of the ethyl ester analogue of resin **9** was incomplete under our optimized solid-phase conditions, as was observed by gel phase ^{13}C NMR.

In conclusion, while we and others have already reported the usefulness of trimethyltin hydroxide in organic synthesis, in this Letter we demonstrate that this reagent is a very efficient and selective tool for the hydrolysis of polymer-supported methyl esters leading to the corresponding carboxylic acids. Due to the limited availability of related methods in the literature, we believe that this procedure will extend the application of carboxylic acids as versatile intermediates for modern solid-phase organic synthesis.

Acknowledgements

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10. In a typical reaction, the methyl ester linked to (4-diethylsilylbutyl)polystyrene resin (**1**) (157.4 mg of resin containing 1.18 mmol/g) was suspended in 1,2-dichloroethane (4 mL). TMTOH (336.3 mg, 1.86 mmol) was added and the mixture was stirred at 85 °C for 24 h. After this time, a new portion of TMTOH (168 mg, 0.93 mmol) was added and the mixture was stirred at 85 °C for another 24 h. After filtration, the resin was sequentially washed with THF–AcOH (2:1) (3×3 mL), THF (3×3 mL) and dichloromethane (3×3 mL). Finally, the resin was dried under high vaccum. The effectiveness of the hydrolysis is evident by gel phase ^{13}C NMR of the product that shows the complete disappearance of the methyl carbon signal at 51.98 ppm.
11. The reaction yields were calculated from the ratio between the loading yield for the carboxylic acid and the loading yield for the methyl ester, both calculated by releasing them from the resin. In all cases the yield was almost quantitative, except for compound **10** which was recovered in 81%.