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The double addition reaction of alkoxymethyl nucleophiles to esters to generate novel polyoxygenated species

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ABSTRACT

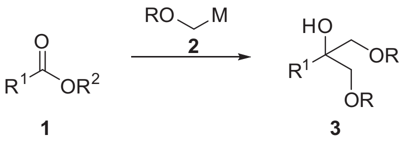
The development of a double addition reaction of alkoxylmethyl nucleophiles to a variety of functionalized aryl and alkyl esters to give polyoxygenated products is reported. Key features include broad electrophile substrate scope and good yields. Structurally diverse nucleophiles were investigated and were found to successfully undergo diaddition. This development now allows facile access to this novel class of polyoxygenated molecules.

1. Introduction

The use of organometallic alkoxymethyl species as nucleophiles in additions to carbonyl compounds is a powerful transformation, resulting in the formation of a carbon–carbon bond while concomitantly introducing an ether appendage. These reactions commonly make use of α-haloethers as substrates for either lithium–halogen exchange[1] or Grignard formation.[2] However, attempts to form these reagents through these methods are not always successful.[3] Another strategy for the generation of these nucleophiles is through synthesis of the corresponding α-stannylethers,[4] followed by facile lithium–tin exchange.[5]

While single additions of organometallic alkoxymethyl nucleophiles have been reported for a variety of eletrophiles,[6] including aldehydes,[7] ketones and enones[8] (1,2- and 1,4-addition), Weinreb amides,[1b] pyridinium cations,[3] and lactones,[9] there remains a paucity of methods for means to effect a double addition reaction for these functionalized nucleophiles. To date, there are only limited examples reported for the double addition of an organostannyl alkoxymethyl reagent to a lactone.[10] The study of the scope and generality of this transformation would be valuable, as it forms, in one step, multiple carbon–carbon bonds while also introducing additional oxygen functionality in the form of ethers (Scheme 1). Such polyoxygenated species may have important physiochemical properties, such as the ability to complex cations as crown ethers,[11] increased solubility in aqueous media, and potentially advantageous biological activity.[12] Indeed, a search through the literature reveals numerous examples describing biologically active molecules with this motif.[13] While there exists several other methods for synthesizing these types of products, such as nucleophilic addition to 3,4-dimethoxyisobutylene oxide[14] or to 1,3-dimethoxypropan-2-one,[13c,15] these procedures limit the scope of nucleophile or substrate.

In order to determine the optimal conditions for the reaction, several different conditions were screened. Initial attempts to form a nucleophile of type **2** from methoxymethyl bromide and lithium–halogen exchange or through Grignard formation failed. However, the procedure of Kaufman[4a] worked as reported to generate the stable organostannane, which was then successfully transmetallated to the organolithium species. This was observed utilizing methyl benzoate as the electrophile for double addition. While the requisite use of 2 equiv of the nucleophile at −78 °C was successful in generating the desired double addition product **6**, it was formed as an inseparable mixture with the corresponding ketone resulting from single addition (Table 1, entry 1) as well as other unidentifiable products. Increasing the equivalents of nucleophile while maintaining the temperature at −78 °C did not signif-



Scheme 1. The generation of a polyoxygenated species from the double addition reaction of an organometallic alkoxymethyl reagent.

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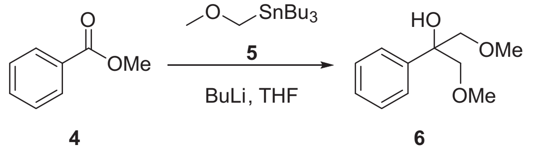
Table 1
Optimization of reaction conditions for the double addition of **5** to ester **4**



Entry	Method	Equivalents	Result
1	A	2	Mixture*
2	A	3	Mixture*
3	B	2	24%
4	B	3	56%
5	B	4	70%

Method A: −78 °C; 1.5 h. Method B: −78 °C→rt; 12 h.

* ~2:1 ratio of product to ketone by ^{1}H NMR analysis of the mixture.

icantly affect the outcome (entry 2). However, increasing the temperature over the course of the reaction eliminated this ketone side-product (method B). While the use of 2 equiv of the nucleophile led to an incomplete reaction, steadily increasing the number of equivalents of organostannane led to complete consumption of the starting material and improved yields, with 4 equiv found to give a 70% yield of the polyoxygenated product **6** (entries 3–5).

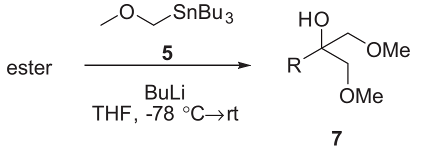
With optimized reaction conditions determined, an additional examination of aryl esters was undertaken (Table 2). Interestingly, while the presence of an electron-donating 4-methoxy group resulted in a good yield, the presence of an electron-withdrawing 4-trifluoromethyl substituent did lower the yield (entries 1 and 2). The reaction was found to be tolerant of free alcohols, as the presence of the 3-hydroxy group did not affect the outcome (entry 3), an important result that indicates the ability to circumvent protecting groups. However, *ortho*-methyl substitution of the phenyl ring resulted in a lower yield, as well as a 17% yield of the corresponding ketone. The presence of a heteroatom, a prominent motif in pharmaceutically relevant molecules, also resulted in a moderate yield (entry 5).

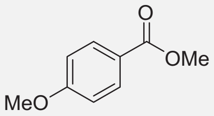
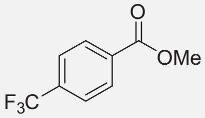
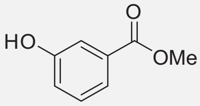
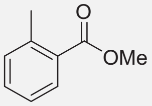
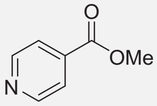
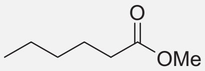
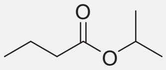
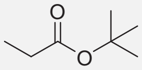
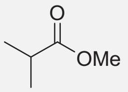
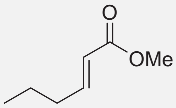
In addition to aryl esters, alkyl esters also successfully underwent double addition (Table 2). Use of methyl hexanoate gave a 76% yield of the polyoxygenated product (entry 6). Impressively, the reaction was tolerant of a sterically more demanding isopropyl ester (80% yield), while even use of a bulky *tert*-butyl ester gave an acceptable 65% yield (entries 7 and 8). As well as steric bulk in the ester substituent, α-branching substituents on the alkyl group were also well tolerated (entry 9). In addition to the use of saturated alkyl esters, an α,β-unsaturated ester was utilized as the electrophile. Methyl 2-hexenoate underwent 1,2-double addition, though with a slight loss in yield (entry 10).

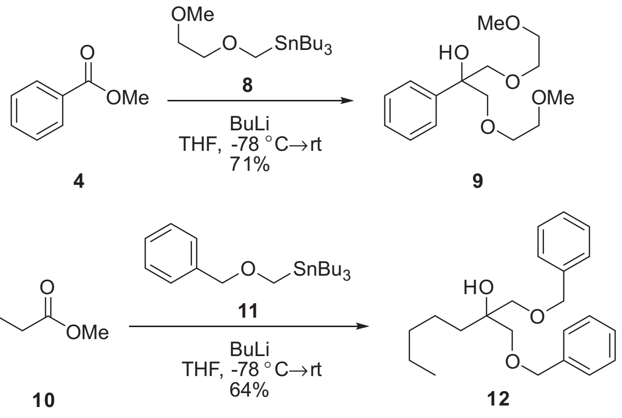
With broad substrate scope tolerability achieved, additional structurally diverse alkoxymethyl nucleophiles were examined (Scheme 2). The diether organostannane **8**, upon lithium–stannane exchange, smoothly underwent double addition to methyl benzoate to give the densely oxygenated alcohol **9**. Double addition of the nucleophile derived from **11** to the alkyl ester **10** provided dibenzyl ether **12** in an acceptable yield. The addition of the benzyl ethers is significant, as these types of products can be easily converted to the polyol via benzyl deprotection.

In conclusion, the development of a novel double addition reaction of alkoxymethyl nucleophiles to aryl and alkyl esters has been achieved in good to acceptable yields. The reaction shows broad substrate scope, amenable to sterically challenging aryl and alkyl esters, as well as to the presence of acidic protons and α,β-unsaturation. Further expansion of this reaction led to the use of more complex organostannanes as nucleophiles, including polyethers as well as benzyl ethers, notable for their ability to be further

Table 2
Substrate scope of the double addition of **5** to a variety of aryl and alkyl esters



Entry	Ester	Yield
1		70
2		53
3		68
4		47
5		50
6		76
7		80
8		65
9		81
10		55



Scheme 2. Use of organostannanes **8** and **11** in the double addition reaction.

derivatized. Significantly, the development of this reaction allows for the formation, in one step, of multiple carbon–carbon bonds and concomitant introduction of new oxygen-containing functionalities. Products resulting from this new reaction have the potential to impart novel physiochemical and biological properties in the synthesis of complex molecules.

2. General procedure

The organostannane (2 mmol, 4 equiv) was dissolved in THF (5 mL) in a nitrogen-flushed round-bottomed flask and cooled to −78 °C. *n*-Butyl lithium (2 mmol, 4 equiv, 1.6 M in hexanes) was added dropwise and the reaction was allowed to stir for 15 min at −78 °C. The ester (0.5 mmol) was dissolved in THF (2.5 mL) and added dropwise to the flask. The reaction was allowed to stir at −78 °C for 1 h, then allowed to stir for 11 h as the flask warmed to rt. The reaction was quenched with satd aq NH_4Cl (10 mL) and diluted with H_2O (25 mL). The solution was extracted with EtOAc (2 × 75 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified via flash column chromatography (EtOAc/hexanes) to give the desired product as colorless oil. No other identifiable products were isolated.

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