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New efficient method of alkoxymethyl etherification of secondary alcohols

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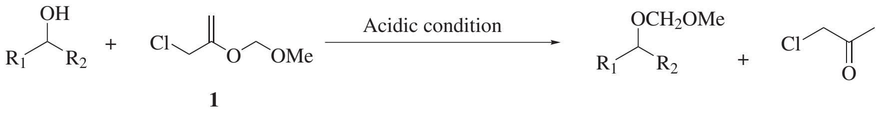
Abstract—A new efficient method of MOM etherification of secondary alcohols using 2-(chloromethyl)-3,5-dioxahex-1-ene (Okahara's reagent) is reported.

Various kinds of hydroxyl protecting groups are known. Of such groups, an alkoxymethoxy group is one of the most widely used. For the production of the alkoxymethoxy group, however, there are generally known only two methods.[1] One of them includes addition of alkoxymethyl chloride, which is highly toxic, to a small excess of diisopropylethylamine. This method is not necessarily a desirable one in view of the effects on the health of the experimenter. The other method includes an equilibrium reaction of alcohol with a large excess of dialkoxymethane under strong acidic conditions. This method cannot be used for compounds like β-hydroxy esters because β-elimination will occur, nor can it be used for compounds having functional groups unstable under strong acidic conditions.

We now report here a new type of formation of alkoxymethyl ether for secondary alcohols. We have found that 2-(chloromethyl)-3,5-dioxahex-1-ene **1**, which is well known as a reagent for acetonylation,[2] is also an efficient reagent for MOM etherification especially of secondary alcohols (Eq. 1). Table 1 shows the results achieved by applying this alcohol-protecting method to various alcohols. For secondary alcohols (entries 1–4), the corresponding MOM ethers were obtained in good yield and in an almost pure form without purification by distillation or column chromatography. At first, because compound **2** had been reported to be obtainable by a reaction of 2-benzyloxy-3-fluoro-1-propene with a corresponding alcohol (Eq. 2),[3] we anticipated the same type of reaction to mainly occur under acidic conditions. However, when secondary alcohol was used, compound **3** was not obtained but MOM ether **4** was obtained almost purely upon elimination of chloroacetone. It is noteworthy that, even in the case of β-hydroxy esters, this MOM etherification proceeded without β-elimination (entry 3). Even PPTS could catalyze this reaction, though a longer reaction time was necessary than with the use of *p*-toluenesulfonic acid.

When primary alcohol was used (entries 5–7), however, the corresponding MOM ether could not be obtained in a pure form but was obtained as a mixture. That is, compound **3** and some other byproducts accompanied by acetal and ketal exchange reactions were also obtained, though MOM ether **4** was mainly obtained. Among primary alcohols, the bulkiness



(1)

Keywords: MOM Etherification; Alkoxymethyl; Okahara's reagent; Hydroxyl protecting groups.

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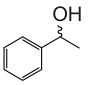
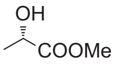
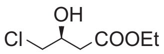
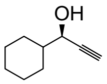
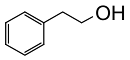
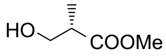
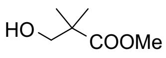
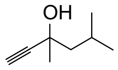
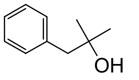
Table 1. Novel MOM etherification under acidic condition

Entry	Alcohol	Catalyst	Reaction time (h)	Yield (%)^{a}
1a		*p*-TsOH (0.5 mol%)	4	84
1b		PPTS (10 mol%)	54	85
2a		*p*-TsOH (0.5 mol%)	2	84
2b		PPTS (10 mol%)	40	86
3a		*p*-TsOH (0.5 mol%)	2	94
3b		PPTS (10 mol%)	32	95
4a		*p*-TsOH (0.5 mol%)	2	94
4b		PPTS (10 mol%)	60	98
5a		*p*-TsOH (0.5 mol%)	2	51^{b}
5b		PPTS (10 mol%)	24	44^{b}
6a		*p*-TsOH (0.5 mol%)	8	52^{b}
6b		PPTS (10 mol%)	66	59^{b}
7a		*p*-TsOH (0.5 mol%)	6	59^{b}
7b		PPTS (10 mol%)	45	72^{b}
8a		*p*-TsOH (0.5 mol%)	12	55^{b}
8b		PPTS (10 mol%)	88	83^{b}
9a		*p*-TsOH (0.5 mol%)	36	55^{b}
9b		PPTS (10 mol%)	212	57^{b,c}

[a] Isolated yield.
[b] Purified by distillation or column chromatography.
[c] Starting material was recovered (30%).

2

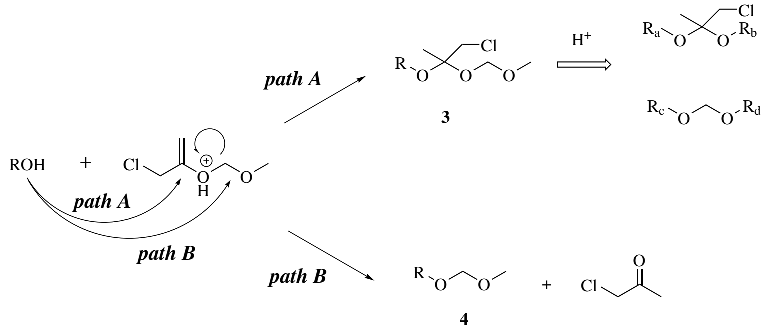
(2)

seems to have an effect on the yield of the MOM ether.

These results are recognized as follows; that is, in the case of secondary alcohol, an addition of the alcohol to the 2-position of compound **1** (path A) scarcely occurs due to the steric effect. Instead of that, an attack of the alcohol on the acetal carbon and elimination of chloroacetone (path B) occur, and MOM ether **4** would be produced. On the other hand, in the case of primary alcohols, addition of the alcohol to the 2-position of compound **1**, followed by complicated acetal and ketal exchange reactions would also occur (Scheme 1).

In the case of tertiary alcohols (entries 8 and 9), because of the lack of the reactivity, long reaction time was necessary. When PPTS was used as a catalyst, the corresponding MOM ether was almost the only product; however, when *p*-toluenesulfonic acid was used as a catalyst, the yield was less than satisfactory because byproducts were also produced.

The reactions proceeded as follows: To a mixture of alcohol (12.5 mmol), 2-(chloromethyl)-3,5-dioxahex-1-ene[4] (15 mmol) and acetonitrile (12.5 mL) was added *p*-toluenesulfonic acid monohydrate (11.9 mg, 0.063 mmol) or pyridinium *p*-toluenesulfonate (314 mg, 1.25 mmol). The mixture was stirred at room temperature for 2–212 h. The reaction mixture was added to saturated $NaHCO_3$ solution (25 mL) and extracted with EtOAc (25 mL). The extracted organic layer was washed with saturated $NaHCO_3$ solution (25 mL) and dried over anhydrous $MgSO_4$ (2.5 g). After filtration, the filtrate was concentrated under reduced pressure to give the corresponding MOM ether. When primary alcohol or tertiary alcohol (entries 5–9) was used, column



Scheme 1. Proposed reaction mechanism for MOM etherification.

chromatography or distillation was necessary to obtain pure MOM ether.

We have hereby noted a possibility that 2-(chloromethyl)-3,5-dioxahex-1-ene may be a new efficient reagent for MOM etherification. We are also studying a new environmentally suitable method for synthesizing 2-(chloromethyl)-3,5-dioxahex-1-ene and will report the outcome in the near future.

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References and notes

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