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Domino two-step oxidation of β-alkoxy alcohols to hemiacetal esters: linking a stoichiometric step to an organocatalytic with a common organic oxidant

Tom Targel,[a] Palakuri Ramesh,[a] and Moshe Portnoy*[a]

Abstract: Primary and secondary β-alkoxy alcohols can be cleanly and efficiently oxidized into hemiacetal esters in a cascade two-step process. *m*CPBA serves both as a stoichiometric oxidant in the first TEMPO-catalyzed step, converting alcohols to aldehydes/ketones, and as a reagent in the second Baeyer-Villiger stoichiometric oxidation, transforming the aldehydes/ketones into hemiacetal esters. The use of oxidant common to both steps enables the domino reaction to proceed under single experimental setting. Longer oxidative cascade sequences are possible, when this new methodology is applied to suitable substrates.

Introduction

The conversion of alcohols into carbonyl derivatives is one of the most frequently used transformations in organic synthesis. Oxidation of primary alcohols typically converts them into corresponding carboxylic acids or their derivatives,[1,2] while special conditions or oxidants must be used, if one desires to prevent the second oxidation, thus obtaining an aldehyde as a product.[3] On the other hand, oxidation of secondary alcohols yields ketones as end products,[3] and only through a two-step sequence, inevitably involving the Baeyer-Villiger (BV) oxidation as the concluding reaction, they could be converted to esters of carboxylic acids based on a truncated carbon skeleton.[4] Oxidation of aldehydes, however, whether using Baeyer-Villiger conditions or other oxidation technique, leads usually to carboxylic acid or their derivatives without modifying the skeleton.[5,6]

On rare occasions, BV-like skeleton-truncating oxidation of aldehydes to formate esters was reported. Such is the case of Dakin reaction of electron-rich benzaldehydes,[7] as well as the instance of aldehydes with a nitrogen- or an oxygen-substituted α-carbon.[8] On a very few occasions, such oxidation was coupled with a preceding alcohol-to-aldehyde oxidation step, thus completing oxidation of a primary alcohol to ester in two successive, but separate, steps.[8e-h] As abovementioned, in these cases, the first step must be carried out under special conditions or with special reagents (e.g., Swern oxidation,[8e,g] Dess-Martin periodinane[8h]) incompatible with the BV-like aldehyde oxidation reaction.

In this report we disclose a technically simple one-pot domino procedure, which converts β-alkoxy alcohols, whether primary or secondary,[9] into the corresponding hemiacetal esters through a two-step oxidation, involving a TEMPO-catalyzed conversion of an alcohol to an aldehyde or a ketone, followed by a stoichiometric BV-like oxidation under the same reaction settings.[10] Such experimental conditions greatly simplify the synthetic transformation and substantially shorten the overall reaction times. Hemiacetal esters are occasionally found in natural products,[11] readily undergo Lewis acid-catalyzed nucleophilic substitution,[8e,f,12] and thus constitute valuable synthetic targets and intermediates.

TEMPO-catalyzed oxidation of alcohols (TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxyl) is, nowadays, a generally accepted method that requires a stoichiometric oxidant, of which NaOCl (bleach) is the most common.[13,14] A number of other oxidants were used in conjunction with TEMPO catalyst.[15,16] Among them, *meta*-chloroperbenzoic acid (*m*CPBA) was introduced by Cella,[16a] with Rychnovsky, providing an improved experimental setting for its use.[16b]

Results and Discussion

Intrigued by an unusual pattern of TEMPO-catalyzed oxidation of a substrate, incorporating a short oligoethylene glycol substituent, we prepared a simpler substrate **1a** and tested it in a similar reaction.[17] We observed that the use of *m*CPBA as a stoichiometric oxidant leads to a unique reaction pattern with the terminal alcohol being oxidized to a formate hemiacetal ester, rather than to the corresponding aldehyde or carboxylic acid (Scheme 1). The results, summarized in Table 1, indicated that using 2 molar % of TEMPO and tetrabutyl ammonium bromide (TBAB),[18] as well as 2.2 equivalents of *m*CPBA, the model substrate is consumed quantitatively in less than 75 minutes at room temperature, forming mostly the corresponding hemiacetal formate **2a** (entries 1-2). Moreover, monitoring of the reaction using HPLC demonstrated that the substrate is fully consumed in just 10 min. It seems that the best yield is achieved immediately after full consumption of the starting material, and at longer times a slight deterioration of yield is observed. Noteworthy, without the stoichiometric oxidant there is no reaction, as expected, while without the catalyst, even after prolonged reaction times, most of the starting material remains intact, whereas some of it is converted into a complex mixture of products.[19] Thus, the chosen

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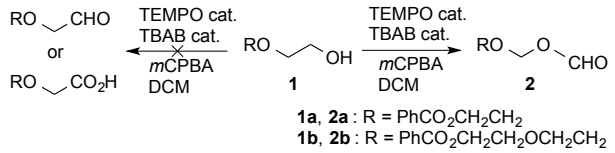
combination of the catalyst and the oxidant makes it possible to convert the aforementioned reaction sequence of two steps, into a single, fast and practically simple one-pot procedure.

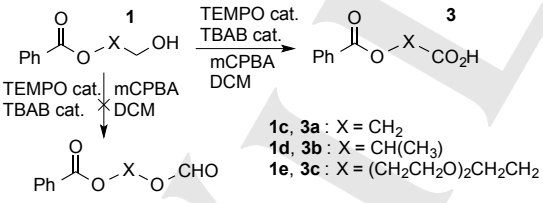


Scheme 1. Oxidation of primary β-alkoxy alcohols.

Table 1. Oxidation of primary alcohol substrates.[a]

Entry	Substrate	Product	Time	Consumption[b] (%)	Yield[c] (%)
1	**1a**	**2a**	4 h	quant.	78
2	**1a**	**2a**	75 min	quant.	80 (78)
3	**1a**	**2a**	10 min	quant.[d]	88
4	**1b**	**2b**	1.75 h	quant.	80
5	**1b**	**2b**	75 min	quant.	81 (75)
6	**1b**	**2b**	10 min	quant.[d]	86
7	**1c**	**3a**	30 min	87, 84[d]	71
8	**1c**	**3a**	4 h	quant.	79
9	**1d**	**3b**	4 h	90	78
10	**1e**	**3c**	4 h	96	94 (52)

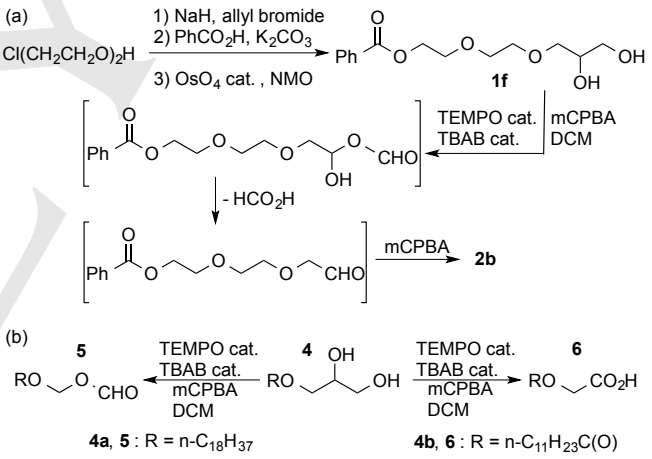
[a] Reaction conditions: 1 equiv of substrate with 2.2 equiv of *m*CPBA, 2 molar % TEMPO, 2 molar % TBAB, DCM (8 mL/mmol substrate), rt. [b] Consumption of the starting material as determined by ^{1}H NMR, quant. = quantitative. [c] As determined by ^{1}H NMR, isolated yield in parentheses. [d] Determined by HPLC.



Scheme 2. Oxidation of primary β-acyloxy and γ-alkoxy alcohols.

A similar substrate **1b**, based on a triethylene glycol unit rather than diethylene glycol, reacted in a similar way (Table 1, entries 4-6). On the other hand, ethylene glycol monobenzoate **1c** did not undergo a similar reaction, but rather the more common oxidation to carboxylic acid **3a** (Scheme 2, Table1, entries 7-8). The latter result emphasizes the major difference between the influence of the β-alkoxy and β-acyloxy substituents of the primary alcohol substrates on the course of the TEMPO/*m*CPBA oxidation. Since in the literature a few examples of Baeyer-Villiger mode of oxidation with *m*CPBA were disclosed for α-branched, α-acyloxy aldehydes,[8b] we wondered whether α-branching will redirect the reaction of β-acyloxy alcohols toward *gem*-diol diester and constructed, accordingly, substrate **1d**.[20] However, also in this case the common alcohol-to-carboxylic acid mode of oxidation was followed (Table 1, entry 9). A similar outcome, producing acid **3c**, was obtained for the γ-alkoxy substrate **1e**,[21] with the three carbons separating the alkoxy and hydroxy substituents (Scheme 2, Table 1, entry 10).

Subsequently, we found that more complex cascade reaction sequences for suitable substrates are enabled by the new methodology. Thus, substrate **1f** similar to **1b**, but incorporating glycerol instead of ethylene glycol terminal unit, was prepared (from **1a** via allylation-dihydroxylation sequence) and tested. This substrate situates hydroxy, rather than alkoxy substituent, in the β-to-primary alcohol position. If also in the case of β-hydroxy alcohols oxidation to carbonyl is followed by a BV-like oxidation under the indicated reaction conditions, *gem*-diol monoformate rather than hemiacetal formate formation is expected in the case of this substrate (Scheme 3a). Successively, under the reaction conditions (acidified DCM) collapse of the *gem*-diol monoester to α-alkoxy aldehyde is expected to be followed by another BV oxidation to yield the hemiacetal formate **2b** (Scheme 3a).



Scheme 3. Synthesis and oxidation of a primary β-hydroxy γ-alkoxy alcohol (a) and oxidation of other monosubstituted glycerols (b).

Indeed, subjection of substrate **1f** to the abovementioned reaction conditions, but with 3.3 equivalents of *m*CPBA instead of 2.2, due to the anticipated triple oxidation sequence, led to 85% consumption of the starting material in 4 hours with the predominant formation of **2b** (Table 2, entry 2). The same reaction but with 2.2 equivalents of the oxidant led to 51% consumption only (entry 1). In this case, the only other substantial compound in the reaction mixture (in addition to **2b**) was the starting material. The latter results indicate that, under the reaction conditions, the stoichiometric BV oxidation steps, as well as the formic acid elimination from the intermediate *gem*-diol monoester, are faster than the TEMPO-catalyzed step. Furthermore, they demonstrate that β-hydroxy alcohols react in a manner similar to that of β-

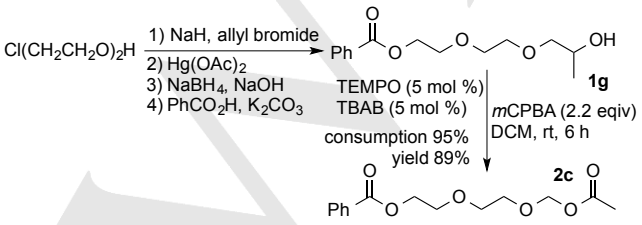
alkoxy alcohols. Batyl alcohol (**4a**), another glycerol monoether, reacted under the same conditions in a similar way (Scheme 3b), predominantly yielding formyloxymethyl ether of octadecyl alcohol (**5**, Table 2, entries 4-5). Noteworthy, structurally related monoester of glycerol **4b** also underwent triple oxidation under the reaction conditions. However, in this case the reaction mostly produced α-acyloxy carboxylic acid **6** (Scheme 3b, Table 2, entry 7), emphasizing again the difference between the reactivity patterns of α-alkoxy and α-acyloxy aldehydes. Noteworthy, the N-oxyl-catalyzed oxidative cleavage of 1,2-diols to give carboxylic acids, reported by Iwabuchi,[22] is based on a different mechanism. This was demonstrated by mechanistic studies and by the invariable formation of carboxylic acids as end products, even when 1,2-diol substrates incorporated a β-alkoxy substituent in similar to substrates **1f** and **4a**.

Table 2. Oxidation of diol substrates.[a]

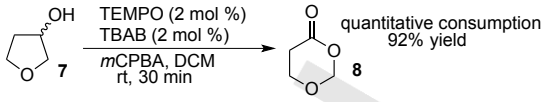
Entry	Substrate	Product	*m*CPBA (equiv)	Consumption[b] (%)	Yield[c] (%)
1	**1f**	**2b**	2.2	51	49
2	**1f**	**2b**	3.3	85	64
3	**1f**	**2b**	4.4	99	73
4	**4a**	**5**	3.3	92	71
5[d]	**4a**	**5**	3.3	96	73 (66)
6	**4b**	**6**	3.3	92	60

[a] Reaction conditions: 1 equiv of substrate, *m*CPBA, 2 molar % TEMPO, 2 molar % TBAB, DCM (8 mL/mmol substrate), 4 h, rt. [b] Consumption of the starting material as determined by ^{1}H NMR. [c] As determined by ^{1}H NMR, isolated yield in parentheses. [d] 8 h.

Following the series of successful single setting two-fold and three-fold oxidations of primary alcohols, we decided to extend our study to β-alkoxy secondary alcohols,[9,23] focusing first on substrate **1g**, which was synthesized via an allylation-oxymercuration-reduction-substitution sequence (Scheme 4). The substrate could be cleanly converted into the corresponding hemiacetal acetate **2c**, although for the almost quantitative conversion the catalyst loading needs to be increased to 5 molar % and the reaction time prolonged to 6 hours. With some secondary alcohols, however, the reaction is much faster. For instance, racemic 3-hydroxytetrahydrofurane underwent almost quantitative conversion to the corresponding hemiacetal lactone with 2% TEMPO in just half an hour (Scheme 5).

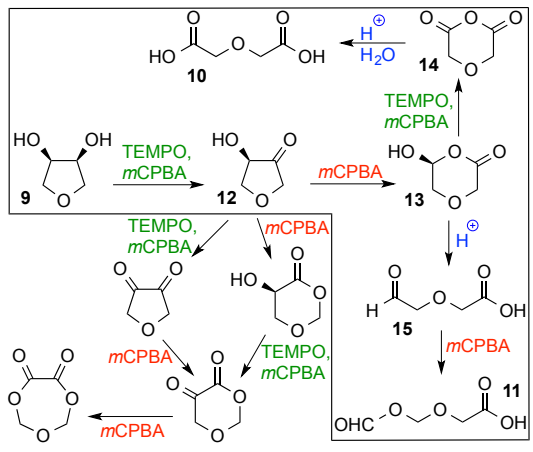


Scheme 4. Synthesis and oxidation of a secondary β-alkoxy alcohol (consumption and yield determined by ^{1}H NMR).



Scheme 5. Oxidation of a cyclic secondary alcohol (consumption and yield determined by ^{1}H NMR).

A particularly interesting reaction outcome was observed when 1,4-anhydroerythritol (**9**) was subjected to the developed reaction conditions. In the case of this *meso*-diol, each hydroxyl group is flanked by one β-hydroxy and one β-alkoxy substituents (on the opposite sides of the secondary alcohol). Accordingly, under the TEMPO/*m*CPBA oxidative conditions a plethora of cascade reaction sequences is possible, leading potentially to a range of end products (Scheme 6). Luckily, in all the experiments that we performed with this substrate, two main products were invariably formed, although a number of unidentified minor side products were always present as well (Table 3). One of the products, characterized by a single singlet signal in ^{1}H NMR, was identified as diglycolic acid (**10**), by its ^{1}H and ^{13}C NMR (including comparison to an authentic sample). Another product, producing in ^{1}H NMR a pattern of three singlets, unique among expected patterns of the potential reaction products, was identified as the hemiacetal formate **11**. As in the case of **1a**, the reaction does not proceed without the stoichiometric oxidant and slowly generates a complex mixture of products without the catalyst. If less than 3 equivalents of *m*CPBA are used, the two products are still formed, but some of the starting material **9** remains in the mixture at the end of the reaction. Moreover, the ratio between the two products depends on the respective ratio between the stoichiometric oxidant and the catalyst. Increasing the amount of *m*CPBA without changing the molar % of TEMPO favors the formation of **11** (entries 1-6). Decreasing the amount of *m*CPBA, while keeping the loading of TEMPO constant, or preserving the amount of *m*CPBA, while the loading of the catalyst is increased, favors the formation of product **10** (entry 12 vs. entry 3).[24] Furthermore, increase of the reaction time beyond the minimal period, required for the full consumption of **9**, lowers the ratio **11**:**10**, probably due



Scheme 6. Potential pathways of oxidation of 1,4-anhydroerythritol with the presumed main pathways bordered by solid line. In green – catalytic steps, in red – stoichiometric.

Table 3. Oxidation of 1,4-anhydroerythritol.[a]

Entry	*m*CPBA (equiv)	Time (h)	Consumption[b] (%)	Yield[c] **10**+**11** (%)	Ratio **10**:**11**
1	1.1	6	45	33	2.09
2	2.2	6	80	49	2.06
3	3.3	6	quant.	51	1.55
4	4.4	6	quant.	59	0.65
5	6.6	6	quant.	50	0.57
6	11	6	quant.	60	0.42
7	6.6	3	quant.	67	0.47
8	6.6	1	quant.	71	0.31
9	3.3	1	quant.	64	0.92
10	3.3	0.5	99	66	0.74
11	3.3	0.25	83	62	0.72
12[d]	3.3	6	quant.	38	5.3

[a] Reaction conditions: 1 equiv of substrate, *m*CPBA, 2 molar % TEMPO, 2 molar % TBAB, DCM (8 mL/mmol substrate), rt. [b] Consumption of the starting material as determined by ^{1}H NMR, quant. = quantitative. [c] As determined by ^{1}H NMR. [d] 5 molar % TEMPO, 5 molar % TBAB.

to the slow hydrolytic/oxidative degradation of **11**, under reaction conditions (entries 7-8 vs. entry 5, and entries 9-11 vs. entry 3).

These results could be explained in the following way. First, α-hydroxy ketone **12**, the first plausible intermediate in any chain of events proposed in Scheme 7, is preferentially oxidized into the *gem*-diol monoester **13**. This preference indicates that, again, as in the case of substrates **1f** and **4a**, the stoichiometric BV is faster than the TEMPO-catalyzed oxidation. Furthermore, it indicates that, in this particular case, the migration of hydroxyalkyl substituent in the Criegee intermediate is faster than that of alkoxyalkyl.[4,25] From presumed intermediate **13** two competitive pathways, one starting with the TEMPO-catalyzed oxidation of the monoester into diglycolic anhydride (**14**), and another beginning with the hydrolytic opening of the monoester into transient intermediate **15**, lead to products **10** and **11** respectively. The monoester opening is likely to be a reversible step, due to the favorable ring size of **13**. Thus, the higher is the ratio of TEMPO to *m*CPBA in the mixture, the more preferred is the pathway leading to **10**. On the other hand, the lower is this ratio the higher will be the relative amount of **11** in the mixture.

Conclusions

In conclusion, we devised an efficient cascade oxidation procedure, where the stoichiometric reagent of the first catalytic step serves also as the oxidant of the subsequent stoichiometric, spontaneously occurring stage. We have shown that the new methodology can be applied for fast and high-yielding conversion of primary and secondary β-alkoxy alcohols into the corresponding hemiacetal esters. Furthermore, the results achieved with substrates **1f**, **4a** and **9** demonstrated that more intricate multistep transformations leading to hemiacetal esters could be accomplished for properly functionalized substrates. Thus, the new methodology bears potential for application in total synthesis and natural products modification.

Experimental Section

Typical procedure for TEMPO/*m*CPBA oxidation: **1a** (21 mg, 1.0 equiv, 0.1 mmol) was placed in a small vial charged with a magnetic stir bar, and the solutions of TEMPO (0.1 M, 20 µL, 0.002 mmol) and TBAB (0.1 M, 20 µL, 0.002 mmol) in DCM were added by syringe at room temperature. *m*CPBA (54.2 mg, 2.2 equiv, 0.22 mmol) solution in 0.76 mL DCM was added, and the reaction was allowed to stir for 75 minutes. Aqueous saturated $NaHCO_3$ solution (2.5 mL) was added, the mixture was stirred for 5 minutes, the organic phase was separated, and the aqueous phase was extracted with DCM (4 x 2.5 mL). Subsequently, the combined organic phase was washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude was analyzed by NMR spectroscopy, and the product purified by column chromatography.

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Keywords: Domino reactions • Hemiacetal esters • Organocatalysis • Oxidations • Synthetic methods

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[23] For a single case of one-pot oxidation of secondary alcohol, lacking β-oxy substituent, to ester under similar conditions, see: J. A. Cella, J. P. McGrath, J. A. Kelley, O. El Soukkary, L. Hilpert, *J. Org. Chem.* **1977**, *42*, 2077.

[24] In the latter case a bigger amount of unidentified byproducts is also formed.

[25] V. A. Vil, G. dos Passos Gomes, O. V. Bityukov, K. A. Lyssenko, G. I. Nikishin, I. V. Alabugin, A. O. Terent'ev, *Angew. Chem.* **2018**, *57*, 3372.

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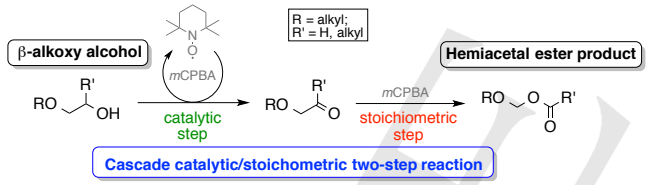

β-alkoxy alcohols are selectively oxidized into hemiacetal esters in a one-pot cascade process, combining a TEMPO-catalyzed step and a stoichiometric step with a common oxidizing reagent, *m*CPBA. Under similar reaction setting, β-alkoxy 1,2-diols also form hemiacetal ester products, undergoing multistep oxidative cascade transformation.

Hemiacetal ester synthesis

*Tom Targel, Palakuri Ramesh, Moshe Portnoy**

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Domino two-step oxidation of β-alkoxy alcohols to hemiacetal esters: linking a stoichiometric step to an organocatalytic with a common organic oxidant

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