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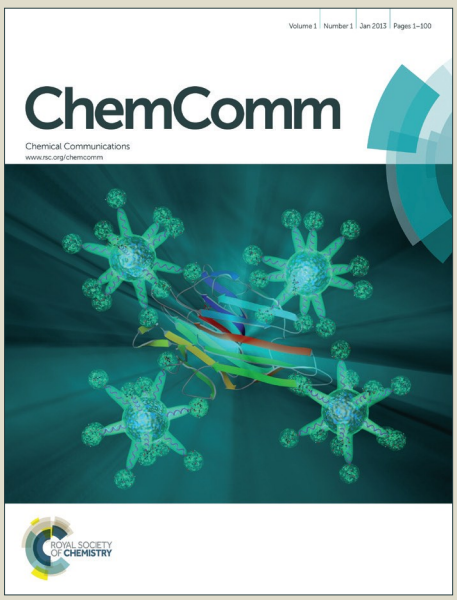

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ARTICLE TYPE

MnO_2-Promoted Carboesterification of Alkenes with Anhydrides: A Facile Approach to γ-Lactones

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An efficient carboesterification of alkenes with anhydrides promoted by MnO_2 has been developed to afford functionalized γ-lactones in good to excellent yields. This method shows a broad substrate scope and provides a valuable and convenient synthetic tool for constructing γ-lactones.

γ-Lactone skeleton is an important moiety in natural products, many of which show exceptional biological and pharmaceutical properties.[1] Representative γ-lactones are found in natural products and biologically active molecules, such as (+)-harzialactone A,[2] longilactone[3] and plakolide A[4], as shown in Figure 1. In addition, alkane γ-lactones can also be widely used as ingredients in perfumes and food additives due to their pleasant odor.[5] Over the past few decades, many methods for obtaining γ-lactones have been developed through constructing a single ester bond (Scheme 1a).[6] So γ-lactones could be obtained from linear substrates such as carboxylic acids,[7] hydroxyl nitriles,[8] keto esters,[9] and so on.[10] In recent years, impressive achievements have also been achieved in the asymmetric synthesis of γ-lactones.[11] In particular, the direct preparation of enantioenriched lactones from keto alcohols via ketone hydroacylation has attracted much attention.[12] Despite the significant progress that has been achieved along these lines, the main restrictive limitation is that the linear substrates were obtained by multiple steps. So the simple and available substrates are highly desirable.

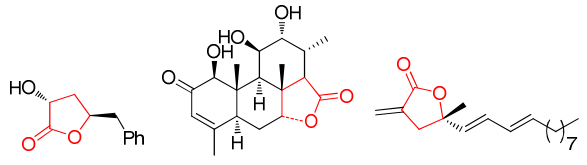
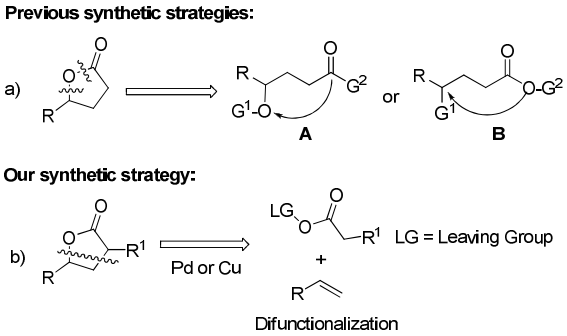


Figure 1. γ-Lactone-containing natural products

Difunctionalization of alkenes is a very important reaction in organic synthesis because of their high potential for application in natural product and drug synthesis.[13, 14] Recent progress in this research area has also been reported with regard to carboamination,[15] carbohalogenation[16] and carbocyclization[17] of alkenes by transition metal catalysis. Among these alkene difunctionalization reactions, carboesterification of alkenes is a useful approach to γ-lactones (Scheme 1 b).[18] The pioneering

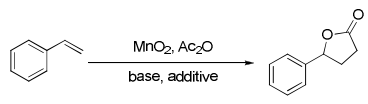


Scheme 1. Synthetic strategies of γ-lactones

works of radical addition of acetic acid to alkenes to construct γ-lactones in the presence of Mn(III) were reported by Heiba and Bush.[19] As our continued interest in synthesizing heterocyclic compounds,[20] we reported several new strategies for γ-lactones. One efficient method is palladium-catalyzed intermolecular or intramolecular carboesterification of alkenes with alkynes.[21] Another interesting method is the Cu-catalyzed carboesterification of alkenes with acetic anhydride under O_2, however, the nonterminal alkenes showed low reactivities.[22] Herein, we would like to report a new method for the formation of γ-lactones directly from alkenes and anhydride in a single step promoted by MnO_2. Relatively low cost of MnO_2 and broad substrate scope are the important merits of this reaction.

Our initial investigation of carboesterification reactions focused on the cyclization of styrene **1a** with anhydride in the presence of MnO_2, LiBr and NaOAc (Table 1). To our delight, when **1a** was treated with MnO_2 (2.0 equiv), NaOAc (1.0 equiv) and LiBr (0.2 equiv.) in 1 mL of Ac_2O, we found that the carboesterification of styrene indeed proceeded smoothly at 120 °C to give the γ-lactone product **2a** in excellent yield (Table 1, entry 1). The reaction did not occur without MnO_2 and further investigation showed that 1.2 equiv of MnO_2 was the optimal

Table 1. Optimization of the reaction conditions [a]



1a 2a

Entry	MnO_2 (equiv)	Base	Additive	Time (h)	Yield (%) [b]
1	MnO_2 (2.0)	NaOAc	LiBr	12	93
2	--	NaOAc	LiBr	12	N.D.

3	MnO_2 (1.0)	NaOAc	LiBr	12	90
4	MnO_2 (0.5)	NaOAc	LiBr	12	37
5	**MnO_2 (1.2)**	**NaOAc**	**LiBr**	**3**	**94 (90)**
6 [c]	MnO_2 (1.2)	NaOAc	LiBr	5	70
7	MnO_2 (1.2)	--	LiBr	3	48
8	MnO_2 (1.2)	Pyridine	LiBr	3	44
9	MnO_2 (1.2)	KOH	LiBr	3	92
10	MnO_2 (1.2)	*t*-BuONa	LiBr	3	86
11	MnO_2 (1.2)	NaOAc	--	3	81
12	MnO_2 (1.2)	NaOAc	NBS	3	52
13	MnO_2 (1.2)	NaOAc	LiCl	3	82
14	MnO_2 (1.2)	NaOAc	KBr	3	91
15 [d]	MnO_2 (1.2)	NaOAc	LiBr	3	N.D.
16 [e]	MnO_2 (1.2)	NaOAc	LiBr	3	N.D.

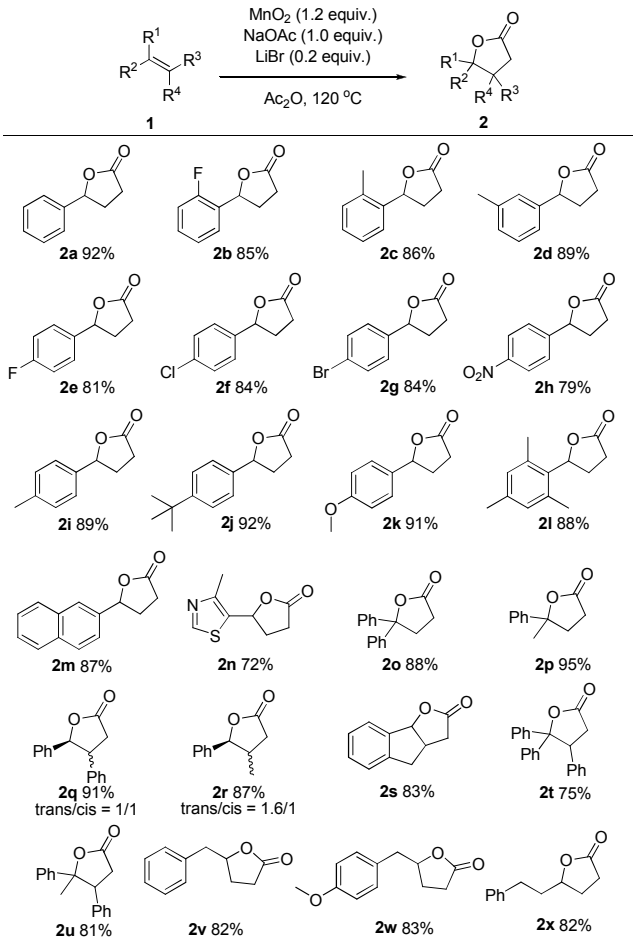
[a] The reaction was carried out with **1** (0.50 mmol), MnO_2, base (1 equiv) and additive (0.2 equiv) in Ac_2O (1.0 mL) at 120 °C. [b] Determined by GC using dodecane as the internal standard. Data in parentheses is the yield of isolated product. [c] Under 100 °C. [d] Ac_2O/DMF = 1/4 (v/v, 1 mL). [e] Ac_2O/DMSO = 1/4 (v/v, 1 mL).

result (Table 1, entries 7-10). Slightly lower yield was obtained without LiBr, and the reaction system became more complex. Different additives were also tested, such as NBS, LiCl, and KBr, but the reaction did not proceed well (Table 1, entries 11-14). However, when other solvents such as DMF or DMSO were used, the yield of **2a** dropped dramatically. Thus, the optimal reaction conditions were MnO_2 (1.2 equiv), NaOAc (1.0 equiv), and LiBr (0.2 equiv) in 1 mL of Ac_2O at 120 °C (Table 1, entry 5).

Under the optimized reaction conditions, we then examined the substrate scope of this alkene carboesterification reaction. As summarized in Table 2, the substituents at the *para*-, *meta*-, and *ortho*-positions of the arene ring did not affect the efficiency in this reaction system (**2b**-**2d**). A series of substituted styrenes, including some with electron-donating groups (Me, ^{t}Bu, OMe) and some with electron-withdrawing groups (F, Cl, Br, NO_2), were converted into the corresponding γ-lactones in good to excellent yields (**2a-2k**). In addition, multisubstituted styrene could be also transferred to the desired product in 88% yield (**2l**). Interestingly, good yields could be obtained when using 2-vinylnaphthalene (**2m**) and 4-methyl-5-vinylthiazole (**2n**) as the substrates. To our delight, the transformations of 1,1-disubstituted alkenes could be proceeded efficiently under the optimized conditions, affording the desired products **2o** and **2p** in 88% and 95% yields, respectively. Furthermore, good yields could be obtained when 1,2-disubstituted alkenes (**2q**-**2s**) were employed in this reaction. It is especially worth mentioning that when trisubstituted alkenes were used, the desired products **2t** and **2u** were isolated in 75% and 81% yields. Linear alkenes containing aryl groups (**2v**-**2x**) were also suitable for this reaction to give the corresponding products in good yields. Disappointingly, no desired product was observed when 1,1,2,2-tetraphenylethene was used as the substrate in this reaction.

Additionally, we examined the generality of this novel reaction process with respect to aliphatic alkenes (Table 3). Oct-1-ene and

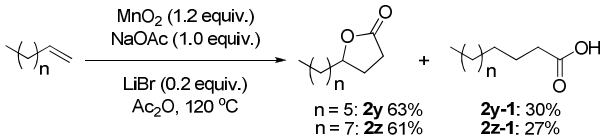
Table 2. Substrate Scope of Alkenes [a,b]



[a] Reaction conditions: **1** (0.5 mmol), MnO_2 (1.2 equiv), NaOAc (1.0 equiv), LiBr (0.2 equiv) in Ac_2O (1.0 mL) at 120 °C for 3 h. [b] Yields referred to isolated yields.

dec-1-ene were found to be the suitable substrate and converted to the corresponding cyclization products **2y** and **2z** in 63% and 61% yields, respectively. It is worth mentioning that the product **2y** and **2z** as common components were found in both white wine and red wine.[5a] Interestingly, the noncyclization byproduct acids with an unpleasant smell could be also observed (**2y-1** and **2z-1**).

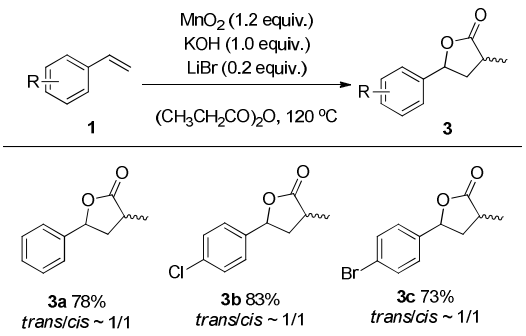
Table 3. Carboesterification of aliphatic alkenes [a]



[a] Reaction conditions: alkenes (0.5 mmol), MnO_2 (1.2 equiv), NaOAc (1.0 equiv), LiBr (0.2 equiv) in 1.0 mL of Ac_2O at 120 °C for 3 h.

Next, the carboesterification reactions of aryl alkenes with propionic anhydride were also examined (Table 4). When the styrene was used as the substrate, 78% yield of the corresponding γ-lactone (**3a**) was obtained and the *trans*/*cis* ratio was ~1/1. The aryl alkenes with different substituents such as -Cl and -Br could be also transferred to the desired products (**3b** and **3c**) in good yields with *trans*/*cis* ratio equaling ~ 1/1.

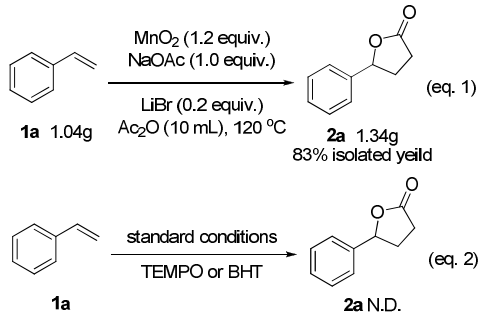
Table 4. Carboesterification of alkenes with propionic anhydride [a]



[a] Reaction conditions: alkenes (0.5 mmol), MnO_2 (1.2 equiv), KOH (1.0 equiv), LiBr (0.2 equiv) in 1.0 mL of $(CH_3CH_2CO)_2O$ at 120 °C for 5 h.

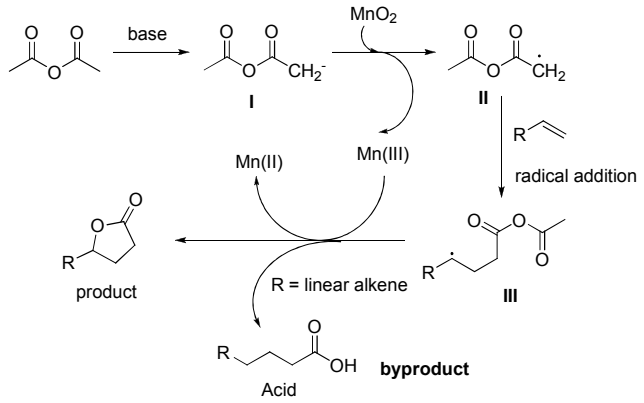
In addition, a satisfactory result (83% isolated yield) was obtained when the reaction was performed on gram-scale under the standard conditions (eq. 1).

To gain insight into the mechanism of the reaction, several control experiments were performed (eq. 2). When the radical scavengers such as TEMPO and BHT were used in the reaction system under the standard conditions, both could inhibit this carboesterification process, indicating that a radical pathway should be involved.



Based on the above results, we proposed a tentative mechanism for this MnO_2-mediated carboesterification reaction of alkenes shown in Scheme 1. Firstly, the acetic anhydride reacted with base to produce the corresponding carbanion **I**. Then, the radical intermediate **II** was obtained through the oxidation of acetic anhydride carbanions by MnO_2. Subsequently, MnO_2 was reduced to Mn(III), followed by a radical addition reaction of alkenes with intermediate **II** to produce the radical species **III**. When the R groups were aliphatic alkenes, the acid byproducts were obtained.[23a] On the other hand, an intramolecular cyclization reaction would occur to give the corresponding γ-lactone products by Mn(III). Moreover, the additives such as LiBr could play a very important role in stabilizing the free radicals in this machanism.[23b]

In summary, we have developed a new radical cyclization method for the formation of $C(sp^3)$-$C(sp^3)$ and C-O bonds via MnO_2-promoted carboesterification of alkenes with anhydrides, which provides a facile approach to γ-lactone skeletons. This radical cyclization using MnO_2 as oxidant, has a broad substrate scope, and gives γ-lactones in good to excellent yields. In addition, the readily available starting materials are the additional features of this protocol. Further study on application for the lactone products and asymmetric version of this reaction are underway in our laboratory.



Scheme 2. Plausible reaction mechanism

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental section, characterization of all compounds, copies of ^1H, ^{19}F and ^{13}C NMR spectra for selected compounds. See DOI: 10.1039/b000000x/

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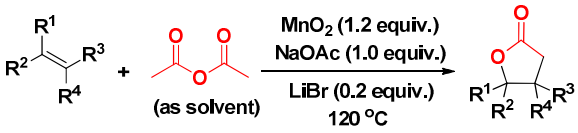

A new radical cyclization method for the formation of $C(sp^3)$-$C(sp^3)$ and C-O bonds via MnO_2-promoted alkene carboesterification with anhydrides is developed.