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Direct oxidative lactonization of alkenoic acids mediated solely by NalO₄: beyond oxidant

Yan-Biao Kang, * Xian-Min Chen, Chuan-Zhi Yao, and Xiao-Shan Ning

Received 00th January 20xx, Accepted 00th January 20xx DOI: 10.1039/x0xx00000x

www.rsc.org/

Published on 08 April 2016. Downloaded by University of Wollongong on 11/04/2016 03:41:05.

A triflic acid–catalyzed direct oxidative lactonization of alkenioc acids mediated solely by NalO₄ without halogen salts is described. Sodium periodate works not only as an oxidant, but also an active reagent directly mediates the lactonization. A new cheap, green, and practical oxidative lactonization approach has been developed using NalO₄ as the solely reagent.

Oxidative lactonization¹ is useful organic transformation for synthesis of lactones from alkenoic acids. As an intramolecular version of diacyloxylation² reaction, lactonization is an approach for five- or six-membered lactone rings. Prévost-Woodward reaction³ and Upjohn reaction conditions⁴ can sometimes be applied for oxidative lactonization, but stoichiometric silver carboxylates or toxic osmium is involved. Stoichiometric NaIO4 and LiBr has been established as a modification for Prévost-Woodward reaction, however a twostep procedure is still necessary.⁵ In the transition-metal free conditions, PhI(OAc)26 and peracids have been developed as highly efficient methods for diacetoxylation or lactonization of alkenes.^{7,8} In the hypervalent iodine mediated dihydroxylation or diacetoxylation of alkenes, stoichiometric or sometimes substoichiometric additives such as LiBr, KI or PhI were used as reagent for in situ generate of halogen anion of PhI(OAc)₂ which work as active reagents. On the basis of our research on the discovery of new reactions,9 we developed a NaIO₄-mediated transition-metal-free oxidative lactonization of alkenoic acids without halogen additives where NaIO₄ works beyond oxidant.

Initially, substoihiometric KI was used as catalyst for the oxidative lcatonization of **1a** to **2a**. Surprisingly, the control reaction without of KI could also give the same conversion (Scheme 1). KI has been believed to be a necessary additive to generate iodium to form intermediate **3a**. However, **2a** was supposed to be coverted from **3a** in typical Prévost–Woodward reaction conditions.

Center of Advanced Nanocatalysis, Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, China

* E-mail: ybkang@ustc.edu.cn

Electronic Supplementary Information (ESI) available: [Experimental procedure, spectra]. See DOI: 10.1039/x0xx00000x

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Next, the reaction conditions were investigated. Various Brønsted acids were screened and triflic acid proved to be the optimized catalyst (Table 1, Entries 2–6). Acetic ahydride is a necessary acetyl reagent for high conversions, which works also as a co-solvent (Entries 2, 7–8). In the absence of Ac_2O , 68% of **1a** was recovered (Entry 7). Finally, a standard condition is established and used to investigate the reaction scope (Entry 9).

Table 1.	Reaction conditions.
-	

		cat. (5 mol%		
	CO ₂	H NalO ₄ (0.5-1.25 o AcOH, Ac ₂ C 70 °C, 14 h	equiv)	`OAc
entry ^a	cat.	NalO₄ (equiv)	solvent	2 a (%) ^b
1	_	1.2	AcOH–Ac ₂ O	26
2	TfOH	1.2	AcOH-Ac ₂ O	74 (64 ^c)
3	TsOH	1.2	AcOH-Ac ₂ O	64
4	CF ₃ CO ₂ H	1.2	AcOH-Ac ₂ O	62
5	HCI	1.2	AcOH-Ac ₂ O	42
6	HCO₂H	1.2	AcOH-Ac ₂ O	62
7	TfOH	1.2	AcOH	15 ^d
8	TfOH	1.2	Ac ₂ O	0
9	TfOH	1.25	AcOH−Ac ₂ O	76
10	TfOH	0.25	AcOH-Ac ₂ O	29 ^e
11	TfOH	0.50	AcOH-Ac ₂ O	52 ^f
12 ^{<i>g</i>}	TfOH	1.2	other	trace
13 ^{<i>h</i>}	TfOH	1.2	AcOH–Ac ₂ O	59 (63)
14 ⁱ	TfOH	1.2	AcOH–Ac ₂ O	69

^{*a*} Conditions: **1a** (1 mmol), acid (5 mol%), NaIO₄, AcOH–Ac₂O (2/1, v/v, 2 mL), 70 °C. ^{*b*} By ¹H NMR (400 MHz) using ethyl 3-phenylpropionate as the internal standard. ^{*c*} Using 10 mol% of TfOH. ^{*d*} With 5% of **3a** and 68% of **1a**. ^{*e*} With 23% of **3a** and 35% of **1a**. ^{*f*} With 39% of **3a**. ^{*g*} When THF, DMF, DMSO or CH₃CN was used as solvent **1a** was recovered. ^{*h*} At 60 °C (80 °C). ^{*i*} For 10 hours.

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The scope of this reaction was investigated and the desired products were generally obtained in moderate to good yields (Scheme 2). For example, pent-4-enoic acid **1a** was subjected the reactions to produce **2a** in 71% isolated yield. Similarly, 2,2-substituted pent-4-enoic acids such as **1b–1d** gave the desired products **2b–2d** in good yields. 4-Phenylpent-4-enoic acid **1e** is a special example because the reaction passed through a 1,2-phenium shift and an abnormal product **2e** was afforded. Ring system **1g** and **1h** resulted in the spiro lactones **2g** and **2h**. Hept-5-enoic acid **1j** was subjected to the oxidative lactonization and the target product **2j** was obtained in 67%. 2-Allylbenzoic acid **1k** gave the six-membered lactone **2k** in 91% yield. Aliphatic terminal alkene such as 1-octene **1l** gave the corresponding diacetoxyl product in moderate yield.



 $\label{eq:scheme 2. Reaction scope. Conditions: 1 (1 mmol), TfOH (5 mol%), NaIO_4 (1.25 mmol), 70 °C, 14 h, isolated yield. ° TfOH (10 mol%), 80 °C. ^b At 60 °C. ^c NaIO_4 (0.5 mmol), 80 °C. ^c$

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The reaction of **1a** to **2a** was monitored by v_{1e}^{i} HANMB, if Q determine whether **3a** is the intermediate As the whether **3a** is the intermediate As the whether **3a** is the intermediate **3a** increases at the early phase of the reaction and decreases after about 8 hours. On the contrary, product **2a** keeps increasing until the disappearance of intermediate **3a**, despite the starting material **1a** disappears after about 10 hours. This monitoring experiment directly suggests that **3a** is an essential intermediate for this oxidative lactonization of **1a**.



In Prévost–Woodward conditions, silver carboxylate (RCO_2Ag) is used to promote the substitution step to convert iodides to acetoxylation products. In current conditions, there is no silver carboxylate and the substitution of iodo-group to OAc-group seems under question. Control experiments in the presence or absence of NaIO₄ proves that the conversion of **3a** to **2a** should not be a simple S_N2 reaction (Scheme 4, Eq 1). No **3a** is converted to **2a** without NaIO₄. This means NaIO₄ is not just an oxidant for iodolactonization of **1a** to **3a**, it is also necessary for the substitution step.



The relationship between the amount of NaIO₄ and the conversion of **2a** and **3a** was investigated (Scheme 4, Eq 2). The increase of the amount NaIO₄ gives rise to the increase of conversion of **2a** as well as the ratio of **2a/3a**. Despite there is

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no trace iodide containing in the NalO₄, large amount of **3a** is still produced in 39% when 0.5 equiv of NalO₄ is used. This suggests that large amount of [I⁺] forms during the reaction process.

To confirm if trace amount of KI or other low oxidation state iodines contributes to this reaction, NalO₄ has been examined by XPS analysis. As shown in Figure 1, the elements binding energy range from 615 to 640 eV, NalO₄ was confirmed as the major component with NalO₃. Either Nal or I₂ was observed from 618 to 620 eV (Table 2).



Na I O ₄	NaIO ₄	Na IO 3	NaI	\mathbf{I}_2
$(I^{3d5/2})$	(O^{1s})	$(I^{3d5/2})$	$(I^{3d5/2})$	$(I^{3d5/2})$
623.8	531.8	623.3	618.3 ^{<i>a</i>}	619.7 ^a
Ma	jor	Minor	None	None

On the basis of control experiments, a plausible reaction working model is proposed in Scheme 5. Intermediate B generated from the acetylation of $[IO_4^-]$, followed by protonation to form C with a cationic iodine center which is captured by C=C bond to give onium intermediate D. D is converted to 2a via intermediate E and F with releasing of [IO3⁻] which repeats this process to generate another 2a and iodite anion [IO₂⁻] (Scheme 4, Eq 2). Iodite is exceeding unstable and transformed to $[IO_4^-]$ and $[I^+]$ by disproportionation. Iodine cation is captured by 1a to afford 3a, which is further converted to 2a via H or B'. Iodo lactone 3a could not directly transform to 2a through a S_N2 process (Scheme 5, Eq 1), thus an oxidationreductive elimination process is proposed. In this working model, the generation of iodine cation as well as the formation of 2a through two simultaneous pathways. Here NaIO₄ works as a direct lactonization reagent and the source of iodine cation, where it is beyond a simple oxidizing reagent.



Conclusions

In conclusion, we have developed an oxidative lactonization mediated solely by $NalO_4$, which is beyond a simple oxidant to oxidized and regenerate the reactive halogen anions or hypervalent iodanes in previous reports. This is the first time discovery of the multiple role of $NalO_4$ in lactonization. Other oxidation reactions including diacetoxylation of alkenes and iodination of esters solely using $NalO_4$ as a multiple-role reagent is undergoing in our laboratory.

Notes and references

We thank the National Natural Science Foundation of China (NSFC 21404096, U1463202), the Fundamental Research Funds for the Central Universities of China (WK2060190026, WK3430000001), Anhui Provincial Natural Science Foundation (1608085MB24) for financial support.

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