A new synthesis of dienone lactones using a combination of hypervalent iodine(III) reagent and heteropoly acid

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The oxidation of non-phenolic alkanoic acid derivatives to oxygen heterocycles was investigated; a new oxidative route to dienone lactones has been developed using a combination of hypervalent iodine(III) reagent, phenyliodine(III) bis(trifluoroacetate) (PIFA), and heteropoly acid (HPA).

Dienone lactone derivatives are regarded as a group of valuable compounds for the synthesis of antibiotics, such as anticapsine, aranorosine and manumysine.[1] Generally, these are synthesized by the oxidative (biomimetic) phenolic coupling reaction and a large number of reagents for this purpose have been developed.[2] Among these reagent systems, the use of hypervalent iodine(III) reagents is considered as the most effective and attractive approach to dienone lactones because their reactivities are similar to those of heavy metal reagents and anodic oxidation. They have a low toxicity, are readily available and easy to handle.[3] Previously, we have developed the hypervalent iodine oxidation of phenol derivatives to dienone lactones.[4]

In contrast to the oxidation of phenol derivatives, the reactions of phenyl ether derivatives with hypervalent iodine reagents have been limited and yielded mostly iodonium salts.[5,6] However, in the case of the *para*-substituted phenyl ethers with phenyliodine bis(trifluoroacetate) (PIFA), we originally found that the reaction with various types of nucleophiles in polar, but poorly nucleophilic solvents, such as 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), caused nucleophilic substitution on the aromatic ring.[7] A study of the reaction mechanism confirmed that it does not involve diaryliodonium salts but cation radicals as reactive intermediates, generated by a single-electron transfer (SET) from a charge-transfer (CT) complex of phenyl ethers with PIFA. Afterwards, the present methodology was used for the synthesis of some important bioactive natural product structures, such as biaryls, quinone imine derivatives and dihydrobenzithiophenes.[8] The use of phenyl ethers for the oxidative aromatic nucleophilic substitution reaction is considered to be an attractive approach, since phenyl ethers are more stable and easier to handle than phenols themselves under various reaction conditions. In this report, we describe the development of a new oxidative route to dienone lactones from phenyl ether derivatives upon treatment with a novel combination of hypervalent iodine(III) reagent and heteropoly acid (HPA)[9,10]—which is a readily available, inexpensive, easy to handle, non-corrosive, and odorless solid acid (Scheme 1).

A few investigations of the intramolecular oxidative cyclization reaction of phenyl ethers to oxygen heterocycles were reported using heavy metal reagents, such as thallium(I) trifluoroacetate.[11]

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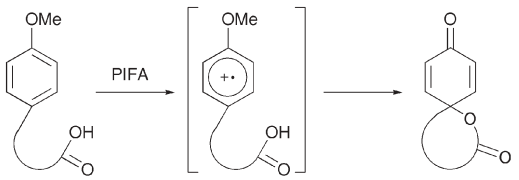


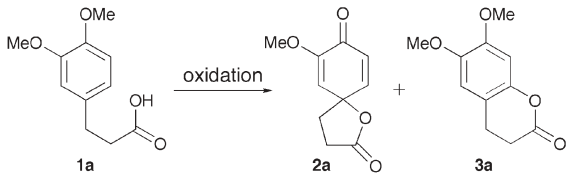
Scheme 1

However, chromanone derivatives were also obtained and both the yields and selectivities of the dienone lactones were low. Moreover, heavy metal reagents are highly toxic and must be very carefully handled. As our initial approach, the oxidation of 3-(3,4-dimethoxyphenyl)propionic acid (**1a**) using various oxidation systems was examined (Table 1). When the reaction was carried with PIFA in HFIP[7] or PIFA-$BF_3{\cdot}Et_2O$ in CH_2Cl_2,[8a,c,d] low yields and low selectivities of the dienone lactone were observed, while the reaction with a heavy metal oxidizing reagent, such as vanadium(V) oxytrifluoride, did not afford the desired product (entries 2–4). However, the addition of H_2O in the presence of activated-PIFA showed an improvement of both the selectivity and yield. The further optimization of acid activator indicates the effectiveness of the novel reagent system, PIFA-$H_4[SiW_{12}O_{40}]$,[9] in this selective cyclization (entries 6–10). Since preparation of such oxygen-substituted dienone lactones is generally difficult in spite of their synthetic utilities, it is noteworthy that the conversion was smoothly achieved using such a simple method.†

Having obtained the remarkable results described above, we further extended our procedure to other series of aromatic carboxylic acid derivatives (**1b–i**). Similarly, the significant formation of dienone lactone in good yield was observed in each case (Table 2).

A plausible reaction mechanism leading to **2a** and **3a** is envisaged as follows (Scheme 2): first the one electron oxidation of an electron-rich aromatic ring *via* the SET process leads to intermediate [A] and then intramolecular nucleophilic attack by the carboxylic acid moiety on the cation radical occurs to produce intermediate [B]. The transformation of B into **3a** occurs *via* a dienone–phenol type rearrangement with migration of the carboxylic unit, while **2a** is formed *via* hydrolysis after the nucleophilic addition of H_2O (path a). Although the direct coupling route to **3a** *via* intermediate [C] (path b) could not be rejected, it seems more reasonable to propose that **3a** is formed by path a. Additionally, the reaction of ester derivatives (R′ = Me, **4a**) with PIFA-$H_4[SiW_{12}O_{40}]$ afforded the biaryl dimer **5a** in 34% yield. This result justifies that the reaction proceeds *via* the cation radical pathway.

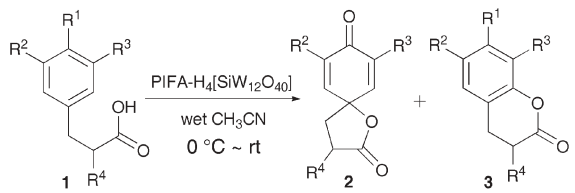
Table 1 Coupling reaction using various oxidative conditions



Entry	Reagents and solvents	Temperature	Time	Yield (%)[a] 2a	3a
1[b]	Tl_2O_3, $BF_3{\cdot}Et_2O$, TFA, TFAA, CH_2Cl_2	−20 °C	1 min	38	19
2	VOF_3, TFA, TFAA, CH_2Cl_2	−20 °C	2.5 h	—	—
3	PIFA, HFIP	0 °C	5 min	15	8
4	PIFA, $BF_3{\cdot}Et_2O$, CH_2Cl_2	−40 °C	10 min	11	9
5	PIFA, $BF_3{\cdot}Et_2O$, wet CH_3CN	0 °C ~ rt	1 h	40	12
6	PIFA, CF_3SO_3H, wet CH_3CN	0 °C ~ rt	1 h	41	9
7	PIFA, $H_3[PMo_{12}O_{40}]$,[c] wet CH_3CN	0 °C ~ rt	2 h	52	13
8	PIFA, $H_3[PW_{12}O_{40}]$,[c] wet CH_3CN	0 °C ~ rt	1.5 h	61	11
9	PIFA, $H_4[SiMo_{12}O_{40}]$,[c] wet CH_3CN	0 °C ~ rt	1 h	55	11
10	PIFA, $H_4[SiW_{12}O_{40}]$,[c] wet CH_3CN	0 °C ~ rt	0.5 h	69	11

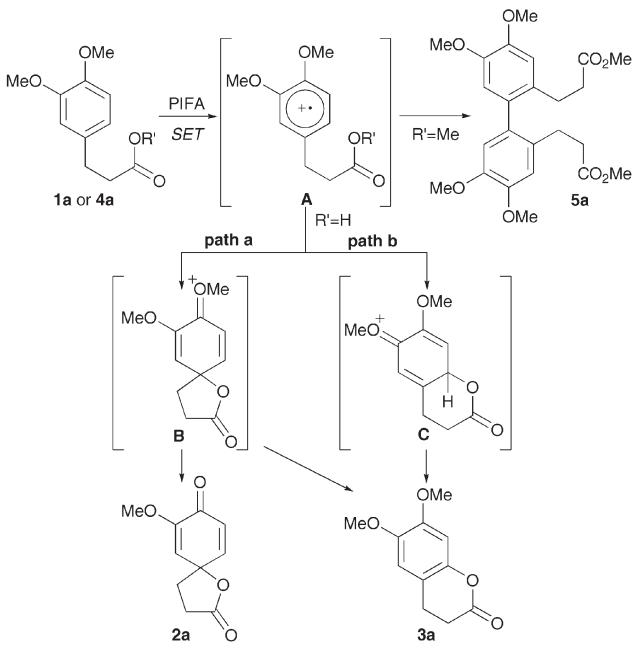
[a] Yield of isolated **2a**. [b] See reference 11. [c] PIFA (1.1 equiv.) and HPA (*ca.* 0.06 mol equiv.) were used.

Table 2 Application to various carboxylic acid derivatives



Entry	Substrate	R^1	R^2	R^3	R^4	Yield (%)[a] 2		3	
1[b]	**1b**	OMe	H	H	H	**2b**	84	—	
2[b]	**1c**	OMe	Me	H	H	**2c**	76	—	
3	**1d**	OMe	OMe	H	Me	**2d**	79	**3d**	8
4	**1e**	OMe	OMe	H	Bn	**2e**	76	**3e**	5
5	**1f**	OMe	OBn	H	H	**2f**	60	**3f**	7
6	**1g**	OBn	OMe	H	H	**2a**	69	**3g**	8
7	**1h**	OBn	OBn	H	H	**2f**	79	**3h**	9
8	**1i**	OMe	OMe	OMe	H	**2i**	63	—	
9	**1j**	3-(4-Methoxynaphthalen-1-yl)			H	**2j**	96	—	

[a] Isolated yield. [b] These reactions were carried out in dry CH_3CN.



Scheme 2 Plausible reaction mechanism.

In conclusion, a new oxidative route to dienone lactone derivatives using a combination of hypervalent iodine(III) reagent and heteropoly acid was developed. The present method is effective for the preparation of highly oxygen-substituted dienone lactone skeletons. The simple approach for such an important synthetic tool using less toxic reagent systems, may find many advantages in the synthesis of various natural and synthetic products. Further studies on the application to more valuable compounds and detailed investigations of the reaction mechanism are in progress.

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Notes and references

† A typical experimental procedure is as follows: to a stirred solution of the 3-(3,4-dimethoxyphenyl) propionic acid (**1a**, 0.20 mmol, 36.0 mg) in CH_3CN containing 2.5% water (8.0 mL), was added $H_4[SiW_{12}O_{40}]$ (40 mg) and PIFA (0.22 mmol, 94.6 mg) at 0 °C. After 0.5 h of stirring, warming from 0 °C to rt, the reaction mixture was diluted with EtOAc. EtOAc

containing 3.0% Et_3N (5.0 mL) was then added. A precipitate was observed and the solution was filtered through kieselguhr and concentrated *in vacuo*. Purification of the residue by column chromatography on silica gel produced the corresponding dienone lactone **2a** in 69% yield.

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