A green process for the oxidative lactonization of 1,2-benzenedimethanol by tungstic acid with aqueous H_2O_2 [†]

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A new economic and green route to synthesize phthalide from 1,2-benzenedimethanol using aqueous hydrogen peroxide as the oxidant and tungstic acid as the catalyst under organic solvent-free conditions is presented. This process proceeds with advantages from the viewpoint of green chemistry, in which the only by-product of H_2O_2 is water and the catalyst can also be easily recovered. The desired product with high purity and good yield can be conveniently obtained when cooled after reaction.

At present, the development of environmentally friendly techniques in the field of oxidation of organic compounds has attracted much attention because the reagents used in stoichiometric amounts in these reactions are sometimes wasteful and toxic. Therefore, there is an urgent need to replace the classic oxidants with "clean" oxygen donors, such as H_2O_2 . It is known that the oxidation of organic substrates using hydrogen peroxide as an oxidant has long been studied. Many useful reactions carried out with H_2O_2 have been developed, such as the oxidation of sulfides to sulfoxides and sulfones,¹ epoxidation of olefins and allylic alcohols² and the oxidative cleavage of carbon–carbon double bonds to aldehydes³ and acids.⁴ To date, the oxidation of diols to lactones with H_2O_2 has been rarely reported.

Lactones and their derivatives are ubiquitous in nature.5 Many substances containing the lactone ring show interesting biological activity.6 Lactones can also be used in the production of a variety of polymers.7 Although oxidation of alcohols has been widely used for the synthesis of lots of chemicals, the oxidation of diols to lactones usually requires fierce reaction conditions and specific oxidants. The reaction can be carried out under mild conditions in the presence of organic cooxidants which are not green oxidants, such as α,β -unsaturated ketones,⁸ PhBr,9 N-methylmorpholine N-oxide, or acetone. Mitsudome et al. recently obtained a high yield of lactones (99%) from diols using molecular oxygen as the oxidant and supported gold nanoparticles as the catalyst under mild conditions.¹⁰ However, the catalyst is expensive and cannot be easily synthesized. Among the diol oxidations to lactones, the oxidative lactonization of 1,2-benzenedimethanol to phthalide can be taken into account as a probe reaction, since phthalide and its derivatives are commonly used in the manufacturing of dyes, pharmaceuticals,¹¹ bactericides and other useful products. The oxidation of 1,2-benzenedimethanol with aqueous H_2O_2 is an effective green process for the synthesis of phthalide, owing to the avoidance of waste or pollutant.

Phthalide is traditionally synthesized by reaction of phthalic anhydride, zinc and hydrochloric acid; reaction of phthalimide and sodium hydroxide; or hydrogenation of phthalic anhydride.¹² During these processes, serious environmental pollution is generated, a low yield of phthalide is obtained, or a high reaction temperature is required, which consumes a large amount of energy.

In the present work, the optimal reaction conditions are investigated in detail by using WO₃·H₂O as the catalyst and tertbutanol as the solvent, bearing in mind that the tert-butanol-H₂O₂ system is stable and has been used in a large number of oxidation reactions.¹³ In addition, analysis by GC is very convenient in the tert-butanol-H2O2 system. Then, under the optimized conditions, a green and novel approach to produce phthalide from 1,2-benzenedimethanol by catalytic oxidation with aqueous H_2O_2 without using organic solvents is presented because the reaction conditions are similar. In particular, aqueous hydrogen peroxide as an oxidant is environmentally clean, easy to handle and tungstic acid is an inexpensive catalyst. In this study, the catalyst can be easily removed by simple filtration after reaction because little H2O2 remains after reaction and it can be decomposed when heated at 90 °C, which leads to the deposit of WO_3 ·H₂O. The desired product phthalide can be easily obtained through cooling the reaction system because phthalide undergoes thermally reversible changes between the water-soluble and water-insoluble states from hot water to warm water at room temperature.

The activity test was performed at a set temperature for a given time with magnetic stirring in a closed 25 ml regular glass reactor using 50% aqueous H_2O_2 as the oxygen-donor and *t*-BuOH as the solvent. In a typical experiment, 0.0135 g of WO₃·H₂O (0.054 mmol) and 0.67 ml of 50 wt% aqueous H_2O_2 (11.1 mmol) were introduced into the regular glass reactor at 40 °C with vigorous stirring. Then, the reaction was started after the addition of 10 ml of *t*-BuOH and 0.690 g of 1,2-benzenedimethanol (5 mmol) into the mixture, which was left for 24 h or more. The conversion of H_2O_2 was measured by a standard iodimetric titration method. The quantitative analysis of the reaction products was performed by using a GC method and the identification of different products in the reaction mixture was determined by means of GC-MS on HP 6890GC/5973 MS, and ¹H NMR on DMX 500.

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According to the GC-MS analysis, the products of the catalytic oxidation of 1,2-benzenedimethanol, as shown in Scheme 1, comprise the main product phthalide and small amounts of by-product involving phthalaldehyde, phthalic acid and 1,3-dihydroisobenzofuran. Phthalaldehyde could be oxidized to phthalic acid. The catalytic performance and the optimization of the reaction conditions are based on the yield of phthalide.



Scheme 1 The oxidation products of 1,2-benzenedimethanol by H₂O₂.

To elucidate the reaction process, the course of the conversion of 1,2-benzenedimethanol over time is tested, as shown in Fig. 1. It is suggested that the reaction proceeds rapidly at the first 6 h and then the reaction rate decreases slowly, which can be explained by the fact that the concentration of H_2O_2 and 1,2benzenedimethanol decreases over time. Complete consumption of 1,2-benzenedimethanol is achieved when the reaction time reaches 12 h, whereas the yield of phthalide is only 72%. It is interesting to find that the yield of phthalide ascends with the prolonging of the reaction time. This phenomenon may be due to the mechanism of the oxidative lactonization of diols.¹⁴ The formation of phthalide proceeds via two steps: the initial chemoselective oxidation to 2-(hydroxymethyl)benzaldehyde, which is in equilibrium with 1,3-dihydroisobenzofuran-1-ol, and then the oxidation of 1,3-dihydroisobenzofuran-1-ol to phthalide. The phthalide would not be hydrolyzed upon continuing to elongate the reaction time under the present reaction conditions.



Fig. 1 Conversion of 1,2-benzenedimethanol and H_2O_2 and the yield of phthalide. (Reaction conditions: reaction temperature 80 °C, 1,2-benzenedimethanol 5 mmol, H_2O_2 11.1 mmol, $WO_3 \cdot H_2O$ catalyst 0.054 mmol.)

The reaction rate and the yield of products are dependant on the amount of H_2O_2 . Table 1 shows the catalytic performance of the oxidation of 1,2-benzenedimethanol with various molar ratios of H_2O_2 to 1,2-benzenedimethanol. As can be seen, the conversion of 1,2-benzenedimethanol ascends with an increase in the molar ratio of H_2O_2 to 1,2-benzenedimethanol when the ratio is lower than 2.2:1. Complete consumption of 1,2benzenedimethanol and a 90% yield of phthalide can be achieved

Table 1	Catalytic	performance	of	the	oxidation	of	1,2-benzene-
dimethar	ol with va	rious molar ra	tios	of H	₂ O ₂ to subs	trate	e ^a

	Conversion (%)		
H ₂ O ₂ :substrate	ОН	H_2O_2	Yield (%)
1.5:1	79	98	57
2:1	94	98	85
2.2:1	100	97	90
3:1	100	86	84
4:1	100	87	86

^{*a*} Reaction conditions: reaction temperature 80 °C, 1,2-benzenedimethanol 5 mmol, $WO_3 \cdot H_2O$ catalyst 0.054 mmol, reaction time 24 h, *t*-BuOH 10 ml.

Table 2 Catalytic performance of the oxidation of 1,2-benzene-
dimethanol over various temperatures^a

		Conversion (%)		
Entry	T∕°C	ОН	H_2O_2	Yield (%)
1	50	67	53	26
2	60	77	66	46
3	70	98	88	74
4	80	100	97	90

^{*a*} Reaction conditions: 1,2-benzenedimethanol 5 mmol, H_2O_2 11.1 mmol, $WO_3 \cdot H_2O$ catalyst 0.054 mmol, reaction time 24 h, *t*-BuOH 10 ml.

when the ratio of H_2O_2 to 1,2-benzenedimethanol reaches 2.2:1. Although 100% 1,2-benzenedimethanol conversion could still be retained with further increasing the molar ratio, the yield of phthalide would decrease because of the over-oxidation, which may be a result of the further oxidation of the phthalide to phthalide acid. Considering both catalytic performance and H_2O_2 utility, the 2.2:1 molar ratio of the H_2O_2 to 1,2benzenedimethanol is needed and is used in the following investigations.

It is known that the reaction temperature is essential to every reaction. As shown in Table 2, a higher temperature benefits the conversion of 1,2-benzenedimethanol and the formation of phthalide. Complete consumption cannot be achieved when the temperature is lower than 80 °C. Therefore, 80 °C was chosen as the optimal reaction temperature because H_2O_2 would decompose at temperatures higher than 80 °C.

Independent experiments were carried out to obtain an insight into the effect of the amounts of catalysts on this reaction (see Table 3). As can be seen, there is a strong dependence of the conversion of 1,2-benzenedimethanol and the yield of phthalide on the dosage of the catalysts. The importance of the use of WO₃·H₂O was evident because the reactions gave much lower conversion of 1,2-benzenedimethanol and H₂O₂, and lower yield of phthalide without any catalysts (Entry 1). In addition, it can be seen that the conversion of 1,2-benzenedimethanol increases with increasing catalyst dosage, the amounts of which range from 0 to 0.0135 g (0.054 mmol). The amount of catalyst influences the reaction rate and selectivity to the phthalide. However, when the amount is higher than 0.0135 g, the conversion of 1,2-benzenedimethanol and the yield of phthalide descends with an increase in the amount of catalyst. This is likely

 Table 3
 The effect of the amount of catalyst on the reaction^a

			Conversio	on (%)	
Entry	Amount of catalyst/g	Catalyst:substrate	СССОН ОН	H_2O_2	Yield (%)
1	0	0	31	64	7
2	0.0051	0.004	94	98	65
3	0.0135	0.011	100	97	90
4	0.0249	0.020	96	98	71
5	0.1001	0.080	93	98	46

^{*a*} Reaction conditions: reaction temperature 80 °C, 1,2-benzenedimethanol 5 mmol, H₂O₂ 11.1 mmol, reaction time 24 h, *t*-BuOH 10 ml.

Table 4 The effect of volumes of *t*-BuOH on the oxidation of 1,2-benzenedimethanol^{*a*}

Volumes of <i>t</i> -BuOH/ml	Conversion (%)			
	ОН	H_2O_2	Yield (%)	
2	100	98	87	
5	100	99	88	
10	100	97	90	
15	100	96	77	
20	99	90	72	

^{*a*} Reaction conditions: reaction temperature 80 $^{\circ}$ C, reaction time 24 h, 1,2-benzenedimethanol 5 mmol, H₂O₂ 11.1 mmol, WO₃·H₂O catalyst 0.054 mmol.

related to the consumption of H_2O_2 by the excess $WO_3 \cdot H_2O$, which decreases the utility of H_2O_2 .

The reaction results as a function of the volumes of *t*-BuOH were also studied (see Table 4). It is obvious that there is an optimum volume of *tert*-butanol at which a maximum yield of phthalide is formed. The yield of phthalide increases from 72 to 90% with a decrease in the volume of *t*-BuOH from 20 to 10 ml. Such a phenomenon is not surprising when considering the fact that the concentration of active oxidizing species that depends on the concentration of H_2O_2 is required for the formation of phthalide. When the dosage of *t*-BuOH is lower than 10 ml, there is a negligible decrease in the yield of phthalide.

Solvent also has a crucial impact on the production of fine chemicals over homogeneous catalysts, and thus it was decided to study the solvent effect. Table 5 indicates that the maximum yield of phthalide is formed when the solvent is *tert*butanol or water. Lower conversion of 1,2-benzenedimethanol was obtained in n-butanol and 2-propanol, as well as a lower yield of phthalide. It is interesting to find that the selectivity of phthalide in acetonitrile as a solvent was much lower than that in *tert*-butanol and water, although the conversion of 1,2benzenedimethanol was a little lower than that in *tert*-butanol and water. The mechanism of the catalytic oxidation in these solvents is still under investigation.

Since the yield of phthalide in water is similar to that in *t*-BuOH (see Table 5), a novel process to separate phthalide from the reaction mixture was explored in water. As we know, phthalide is soluble in water when the oxidation is carried out at 80 °C but insoluble in water at room temperature. The catalyst can be easily removed when the excess H_2O_2 is decomposed at

	Conversion (%)		
Solvents	ОН	H_2O_2	Yield (%)
n-Butanol	86	99	26
2-Propanol	27	100	7
tert-Butanol	100	98	90
Water	100	96	89
Acetonitrile	93	100	18

 $^{\rm a}$ Reaction conditions: reaction temperature 80 °C, reaction time 24 h, 1,2-benzenedimethanol 5 mmol, $\rm H_2O_2$ 11.1 mmol, solvent 10 ml.

90 °C after the reaction. The product was separated out when the filtrate was cooled to room temperature and a 77.4% yield of the separated phthalide was obtained. The melting point of the powder obtained by this route was 70.0 to 73.8 °C (Sinopharm Chemical Reagent Co., Ltd, 71.0 to 75.0 °C). The GC purity of the as-prepared phthalide was higher than 99.5%, and it can be used directly in many fields. In addition, ¹H NMR spectroscopy and the XRD pattern of the product confirmed that the structure of the powder was that of phthalide (see Figure S1 and Figure S2, ESI†).

In summary, a new, economic and efficient route for the production of phthalide by catalytic oxidation of 1,2benzenedimethanol with aqueous H₂O₂ has been developed using tungstic acid as a catalyst under organic solvent-free conditions. This process can be easily commercialized based on the following considerations. Firstly, the molar ratio of H_2O_2 to 1,2-benzenedimethanol is only 2.2:1, which is only 10% molar excess, thus the utilization efficiency of H_2O_2 is very high and this process is very economical. Secondly, the tungstic acid catalyst can be easily filtrated after reaction and the phthalide product can be removed from the reaction system after cooling the reaction mixture to room temperature. The used tungstic acid catalyst can be reused more than 6 times, thus leading to its great economical efficiency. Thirdly, the concentration of H_2O_2 is low due to the presence of water, therefore, it is safe to handle in industry. Finally, there is no need to use organic solvent in this transformation, so it is environmentally benign and low-cost. A further investigation of the present H₂O₂-tungstic acid catalytic system in many other significant transformations from α, ω -diols to lactones is currently under way.

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