JOC*Note*

An Efficient Synthesis of 4-Halo-5-hydroxyfuran-2(5*H*)-ones via the Sequential Halolactonization and γ-Hydroxylation of 4-Aryl-2,3-alkadienoic Acids

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Abstract: 4-Halo-5-hydroxyfuran-2(5*H*)-ones were synthesized via the efficient sequential halolactonization−hydroxylation reaction of 4-aryl-2,3-allenoic acids with I_2 or CuX_2 (X = Br or Cl) in moderate to good yields. The structures of the products were established by the X-ray single-crystal diffraction study of 3-methyl-4-iodo-5-phenyl-5-hydroxyl-2(5*H*)-furanone (**2a**). A rationale for this reaction was discussed based on some brief mechanistic study.

5-Hydroxyfuran-2(5*H*)-ones are an important class of compounds because they often occur in natural products and exhibit a broad range of biological activities.[1] These compounds are considered as antimutagen, bactericides, cytotoxicity, antitumor agents, allergy inhibitors, stimulatory agents, cyclooxygenase inhibitors, phospholipase A_2 inhibitors, etc.[1] Recently, much attention has been focused on the efficient and diverse synthesis of these compounds, particularly 4-halo-5-hydroxy-2(5*H*)-furanones. The typical synthetic strategies include acid-catalyzed cyclization of ketonic acids,[1k,i] autoxidation of the corresponding lactones in air,[2a,b] rearrangement reactions of α-phenylsulfinylacrylates,[2c] oxidation with chromium trioxide in acetic acid,[2d] bromination−hydrolysis of α,β-butenolides,[2e] and reaction of lithium *E*-β-bromo-β-lithioacrylates with aldehydes.[2f] Herein, we wish to report an interesting and efficient halolactonization-hydroxylation reaction of 4-aryl-2,3-allenoic acids.

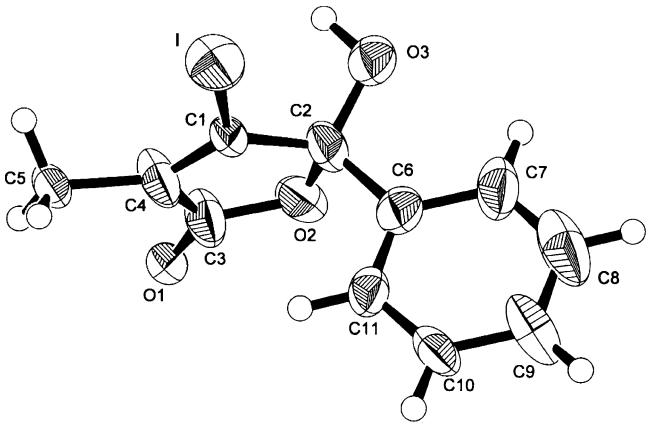
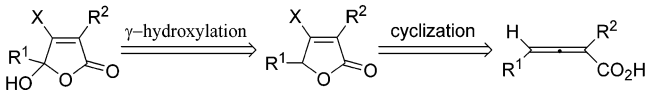
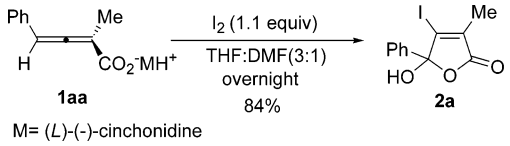


FIGURE 1. Molecular structure of **2a**.

SCHEME 1



During the course of our project aimed at the synthesis of optically active 4-iodobutenolide[3] from the optically active 1:1 salt of (L)-(−)-cinchonidine with 2,3-allenoic acid, to our surprise, racemic 4-iodo-5-hydroxy-2(5*H*)-furanone (**2a**) was formed in THF:DMF (3:1) (eq 1).



(1)

The structure of **2a** was unambiguously determined by the X-ray single-crystal diffraction study (Figure 1).[4] From this results, we envisioned that a γ-hydroxylation followed the lactonization reaction.

This result prompted us to investigate the possibility of direct synthesis of 5-hydroxy-2(5*H*)-furanones via the cyclization−hydroxylation of 2,3-allenoic acids (Scheme 1).

It is known that slow γ-hydroxylation of butenolides may be accomplished via the treatment of furan-2(5*H*)-ones with oxygen.[2a,b] We initiated this study with the reaction of 2-methyl-4-phenyl-2,3-butadienoic acid with various bases in THF/DMF (2:1) at room temperature. Among the bases screened, the use of NaOH, K_2CO_3, Na_2CO_3, Cs_2CO_3, Li_2CO_3, NaOAc, Et_3N, and pyridine gave

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(4) Crystal data for compound **2a**: $C_{11}H_9O_3I$, MW = 316.09, monoclinic, space group $P2(1)/n$, Mo Kα, final R indices [$I > 2\sigma(I)$], R1 = 0.045, wR2 = 0.057, a = 12.900 (5) Å, b = 7.216 (2) Å, c = 13.626 (3) Å, α = 90.00°, β = 116.23 (2)°, γ = 90.00°, V = 1137.8 (6) Å^3, T = 293 K, Z = 4, reflections collected/unique 2681/2561 (R_{int} = 0.0196, no observation [$I > 2\sigma(I)$] 1868; parameters 137.

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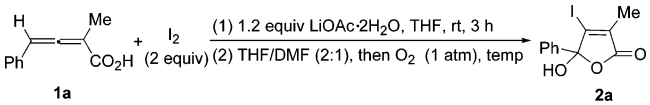
TABLE 1. The Effect of Temperature on the Iodolactonization−Hydroxylation Reaction of 2-Methyl-4-phenyl-2,3-butadienoic Acid



1a 2a

entry	temp (°C)	time (h)	yield (%)
1	13	121	89[a]
2	30	20	68
3	30	47	88
4	**40**	**36**	**87**
5	50	19	82
6	60	50	64[b]

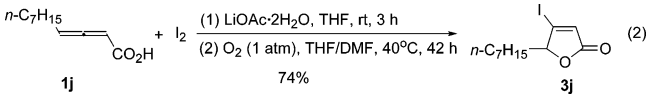
[a] Instead of O_2 (1 atm), the reaction was carried at room temperature in air. [b] Decomposition of **2a** was observed due to the higher temperature and prolonged reaction time.

complicated products. Fortunately, we were pleased to find the use of LiOAc·$2H_2O$ and CsOAc gave the desired product with the yields of 89% and 87%, respectively. However, the reaction took 6 days. Further study showed that the reaction gave the product **2a** in 87% yield at 40 °C after 36 h (entry 4, Table 1).

The results for the iodolactonization−hydroxylation reaction of differently substituted 2,3-allenoic acids with I_2 and LiOAc·$2H_2O$ in THF/DMF (2:1) under O_2 are summarized in Table 2.

From Table 2, it can be concluded that R^1 should be aryl and R^2 can be a general alkyl group or benzyl group. When the aryl group is 1-naphthyl, under the current reaction conditions the reaction afforded the desired products **2h** and **2i** with 40% and 31% yields, respectively (entries 8 and 10, Table 2). When the reaction was performed at room temperature, the yields of products **2h** and **2i** were improved to 78% and 71%, respectively (entries 9 and 11, Table 2).

However, effort for the halolactonization−hydroxylation of 4-heptadienoic acid **1j** has been unsuccessful, instead forming the iodolactonization product **3j** only (eq 2).

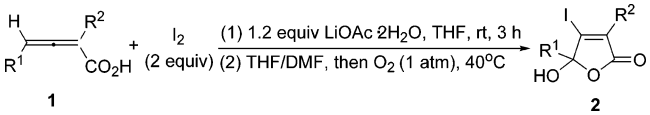


1j 3j

This group has developed a convenient and efficient method for the synthesis of 4-halobutenolides with CuX_2 (X = Br, Cl).[5] We envisioned obtaining 4-bromo- or chloro-5-hydroxyfuran-2(5*H*)-ones with this method. It is noteworthy that the γ-hydroxylation of 4-halobutenolides did not proceed in acetone/water, which was the reaction media for the halolactonization step. However, after the usual workup of the first step, the crude 4-halobutenolide obtained can be hydroxylated with LiOAc·$2H_2O$ in THF/DMF (2:1) with oxygen, leading to the desired 4-halo-5-hydroxyfuran-2(5*H*)-ones. The results are summarized in Table 3 with the yields ranging from 47% to 81%.

To investigate the possible mechanism of the reaction, butenolide **3a** was hydroxylated in THF/DMF with

TABLE 2. Iodolactonization−Hydroxylation Reaction of 4-Aryl-2,3-allenoic Acids[a]

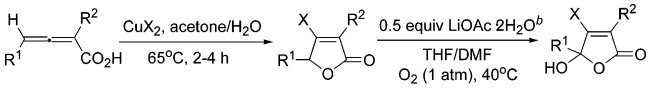


1 2

entry	R^1	R^2	time (h)	yield (%)[b]
1	Ph	Me (**1a**)	36	87 (**2a**)
2	Ph	*n*-C_3H_7 (**1b**)	34	83 (**2b**)
3	Ph	Bn (**1c**)	8	72 (**2c**)
4	*p*-$MeOC_6H_4$	*n*-C_4H_9 (**1d**)	90	54 (**2d**)
5	*p*-FC_6H_4	*n*-C_4H_9 (**1e**)	13	73 (**2e**)
6	*p*-$Pr^iC_6H_4$	*n*-C_4H_9 (**1f**)	12	70 (**2f**)
7	*p*-MeC_6H_4	*n*-C_4H_9 (**1g**)	19	73 (**2g**)
8	1-naphthyl	Me (**1h**)	34	40 (**2h**)
9[c]	1-naphthyl	Me (**1h**)	120	78 (**2h**)
10	1-naphthyl	*n*-C_3H_7 (**1i**)	50.5	31 (**2i**)
11[c]	1-naphthyl	*n*-C_3H_7 (**1i**)	120	71 (**2i**)

[a] The reaction was carried out with 2,3-allenoic acid (0.5 mmol), I_2 (1.0 mmol), and LiOAc·$2H_2O$ (0.6 mmol) in THF:DMF = 2:1 (3 mL) with O_2 (1 atm). [b] Isolated yield. [c] Instead of O_2 (1 atm), the reaction was carried out at room temperature in air.

TABLE 3. Halolactonization−Hydroxylation Reaction of 4-Aryl-2,3-allenoic Acids with CuX_2



1 4

	1		CuX_2		
entry	R^1	R^2	X =	time (h)	yield (%)[a]
1	Ph	Me (**1a**)	Cl	8.5	77 (**4a**)
2	Ph	Me (**1a**)	Br	3.5	54 (**4b**)
3	Ph	*n*-C_3H_7 (**1b**)	Cl	6	47 (**4c**)
4	Ph	*n*-C_3H_7 (**1b**)	Br	5	50 (**4d**)
5	Ph	Bn (**1c**)	Cl	4.5	79 (**4e**)
6	Ph	Bn (**1c**)	Br	3.5	49 (**4f**)
7	1-naphthyl	*n*-C_3H_7 (**1i**)	Cl	5	81 (**4g**)
8	1-naphthyl	*n*-C_3H_7 (**1i**)	Br	5	77 (**4h**)

[a] Isolated yield. [b] No improvement was observed with more than 0.5 equiv of LiOAc·$2H_2O$.

oxygen at 40 °C to yield the desired product **2a** with the addition of different additives. In the absence of lithium acetate, the hydroxylated product **2a** was formed in O_2 in 22% yield with 73% of **3a** recovered (entry 1, Table 4). With the addition of LiOAc·$2H_2O$, the reaction was faster (entries 2 and 3, Table 4). It is interesting to observe that the oxidation in the presence of LiOAc·$2H_2O$ (1.2 equiv) can be improved with the addition of I_2 (1 equiv), affording **2a** in 84% yield (entry 4, Table 4). The same reaction can also proceed in the absence of O_2 although the yield of **2a** was much lower (entry 5, Table 4). Under anhydrous conditions, the reaction was also low yielding, implying the importance of H_2O in this hydroxylation process (entries 6 and 7, Table 4). The same reaction can also proceed in THF or DMF; however, the yield of **2a** was much lower, implying the solvent effect (compare entries 4 and 5 of Table 4 with the results in Scheme 2).

On the basis of these results, a plausible mechanism for the formation of **2a** is depicted in Scheme 3. Under a basic condition, butenolide **3a** may be deprotonated to form anion **5**, which may react with O_2 to afford the peroxy anion **6**. Protonolysis of **6** with H_2O would lead to hydroperoxide **7**, which was reduced to **2a** with HI and

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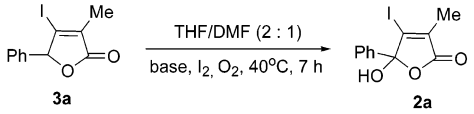
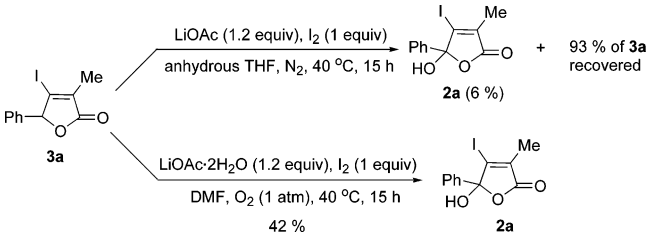
TABLE 4. The Effect of the Additive on the Hydroxylation Reaction of 3-Methyl-4-iodo-5-phenyl-2(5*H*)-furanone (3a)



entry	base (equiv)	I_2 (equiv)	O_2 (atm)	yield of **2a** (%)	**3a** (%) recovered
1	–		1	22	73
2	LiOAc·$2H_2O$ (0.2)	–	1	56	19
3	LiOAc·$2H_2O$ (1.2)		1	54	0
4	LiOAc·$2H_2O$ (1.2)	1	1	84	0
5[a,b]	LiOAc·$2H_2O$ (1.2)	1	–	51	0
6[a–c]	LiOAc (1.2)	1	–	37	17
7[a,c]	LiOAc (1.2)	–	1	43	0

[a] The reaction time was 15 h. [b] The reaction was conducted in N_2. [c] Anhydrous THF/DMF (2:1) was used.

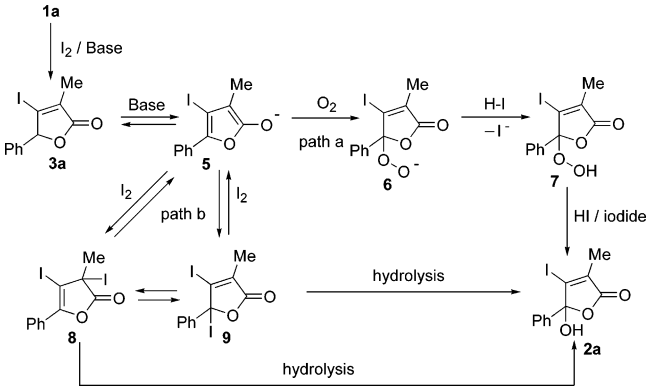
SCHEME 2



iodide (path a). Alternatively, anion **5** may also react with I_2 to afford diiodide **8** and/or **9**, which gives **2a** upon hydrolysis (path b).[6] This explains why the hydroxylation may also proceed in the absence of O_2.

In conclusion, we have observed an interesting sequential halolactonization–hydroxylation reaction[7] of 2,3-allenoic acids leading to 4-iodo-, 4-bromo-, and 4-chloro-5-hydroxyfuran-2(5*H*)-ones in moderate to good yields. Although the reaction condition is not as mild as that observed in eq 1 with the cinchonidine salt, the current hydroxylation may be useful for the efficient hydroxylation of butenolides. Further studies of the scope, mechanism, and synthetic application of this methodology are being carried out in our laboratory.

SCHEME 3



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Supporting Information Available: Typical experimental procedures, analytical data for compounds **2** and **4**, and ^1H NMR and ^{13}C NMR spectra of **2** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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