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Highly Regio- and Stereoselective Iodohydroxylation of Non-Heteroatom-Substituted Allenes: An Efficient Synthesis of 4-[3′-Hydroxy-2′-iodoalk-1′(*Z*)-enyl]-2(5*H*)-furanone Derivatives

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Abstract: An efficient protocol for the highly regio- and stereoselective synthesis of 4-(3′-hydroxy-2′-iodoalk-1′(*Z*)-enyl)furan-2(5*H*)-one derivatives *via* selective iodohydroxylation of non-heteroatom-substituted allenes, i.e., 4-allenyl-2(5*H*)furanones, has been developed. The regio- and stereoselectivity of this reaction may be controlled by the electronic and steric effects of the furanone ring.

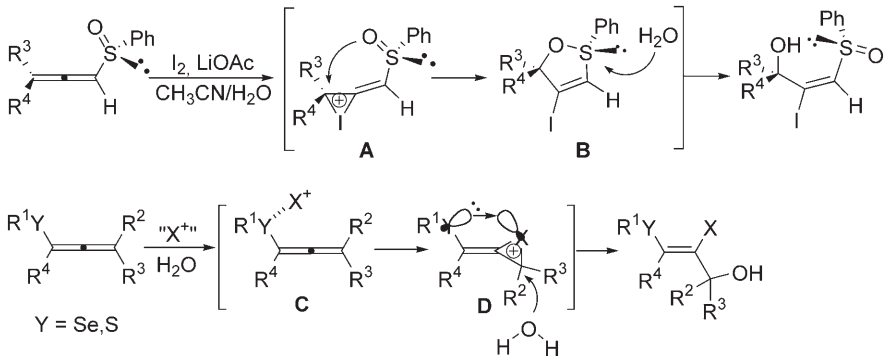
Keywords: allenes; electrophilic addition; hydroxylation; regioselectivity; steric hindrance

Electrophilic additions of allenes are synthetically attractive since two functionalities are introduced in one step.[1,2] However, the regio- and stereoselectivity, which depend on the steric and electronic effects of the substituents of the allenes and the nature of the electrophiles, are usually poor.[3] For example, the reaction of phenylallene with Br_2 in MeOH afforded a mixture of 3-methoxy-3-phenyl-2-bromo-1-propene and 1-methoxy-3-phenyl-2-bromo-2-propene with a ratio of 84:16 while in non-polar solvents, such as CS_2, CH_2Cl_2, etc., the reaction was highly regioselectively and gave a *Z/E* mixture of 1-phenyl-2,3-dibromo-1-propene in 98% yield.[4] The iodomethoxylation of "symmetric" 2,3-pentadiene afforded 3-iodo-4-methoxy-2-pentene in a *Z/E* ratio of 9:1.[5] Methoxymercuration of 2,3-pentadiene also produced a mixture of *Z/E* isomers.[6] To the best of our knowledge, there are only two examples of the highly stereoselective electrophilic addition of simple allenes: the reaction of phenylallene with 2,4-dinitrobenzenesulfenyl chloride affords 3-phenyl-2-arylthio-2(*Z*)-propenyl chloride exclusively[7] and "symmetric" 2,3-pentadiene reacts readily with IN_3 in CH_3CN to give exclusively 3-iodo-4-azido-2(*Z*)-pentene in 80% yield.[8]

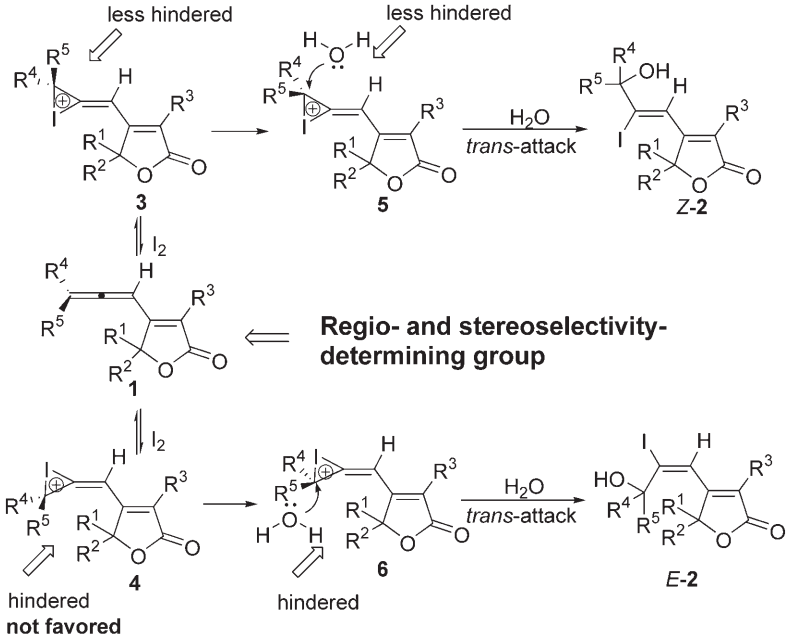
Recently, we observed the highly regio- and stereoselective halohydroxylation of 1,2-allenyl sulfoxides,[9] sulfides and selenides,[10] where the sulfoxide, sulfide or selenide groups are believed to serve as a stereochemistry-determining functionality. With sulfoxides, the participation of the oxygen atom formed the five-membered intermediate **B**, which led to the exclusive formation of the *E* products. With sulfides and selenides, the soft Lewis acid-base interaction between X^+ and S or Se in the intermediate **D** determined the *Z*-selectivity (Scheme 1). Herein, we report a highly regio- and stereoselective iodohydroxylation reaction of furanone-substituted allenes by applying such steric and electronic effects.

Our research in this area originated from the study on the reactivity of allenes, i.e., 4-(3′-methylbuta-1′,2′-dienyl)-5-phenyl-3-propylfuran-2(5*H*)-ones **1**, which may be conveniently prepared by the method recently developed in our laboratory[11a] and has already shown some potential in organic synthesis.[11a,b] A protocol was envisioned for its highly regio- and stereoselective iodohydroxylation (Scheme 2). The electron-withdrawing nature of the furanone skeleton may lead to the regioselective interaction of I_2 with the relatively electron-rich C=C bond remote from the furanone group, forming intermediate **3**. The formation of **4** may be highly unfavorable due to the steric interaction of R^4, R^5 with the furanone skeleton, which may also deter the *trans*-attack of water to *E*-**2**. Thus, the stereoselectivity may be determined by the steric bulkiness of the furanone group, which made the *trans*-attack of H_2O at the three-membered ring in **3**, producing *Z*-**2** highly stereoselectively.[6,12]

In fact we were quite happy to observe that the reaction of **1a** with 4.0 equivs. of I_2 for 1 h in CH_3CN/



Scheme 1.



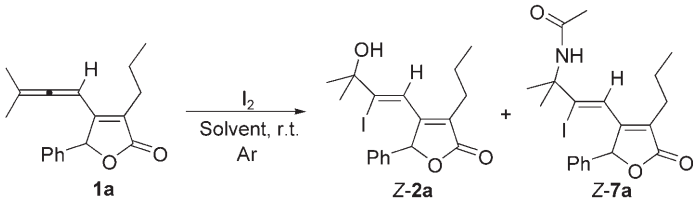
Scheme 2.

H_2O in open air did afford product *Z*-**2a** in 51% yield as the only stereoisomer as expected! However, the product was contaminated with a more polar Ritter-type iodoamidation product *Z*-**7a** in 13% yield (entry 1, Table 1).[10c] Under an argon atmosphere, only 4% of *Z*-**7a** was formed and the yield of *Z*-**2a** was 59% (entry 2, Table 1). The reaction become very clean when $CH_3NO_2/H_2O = 5:1$ was used as the solvent with the yield of *Z*-**2a** being improved to 71% (entry 3, Table 1). CH_3NO_2 is better than other solvents, such as THF and CH_2Cl_2 (entries 4 and 5, Table 1). Using 4 equivs. of I_2 is not necessary since 1.5 equivs. of I_2 afforded *Z*-**2a** in 77% yield (entries 6 and 7, Table 1). No better results were achieved by changing the ratio of CH_3NO_2/H_2O (entries 8 and 9, Table 1). Thus, we have established a protocol for the highly regio- and stereoselective iodohydroxylation of non-heteroatom-substituted allenes.

With this protocol in hand, we tested the generality of this iodohydroxylation reaction with other substituted β-allenylfuranones. The substituents at the 5-position of the furanone skeleton did not have much impact on this reaction. The reaction of the substrates with R^3 being hydrogen (entries 7 and 8, Table 2), alkyl (entries 1–4, 6, 9, and 11, Table 2), allyl (entries 5, 10 and 12, Table 2) smoothly afforded the products in moderate to good yields. The rate of this reaction greatly depends on the steric hindrance of the substituents at the allenyl terminal. When $R^1 = R^2 = Et$, the reaction mixture should be stirred at room temperature for 51 h to afford *Z*-**2f** in 62% yield. The structure of the products *Z*-**2** was further established by the NOE and X-ray diffraction studies of *Z*-**2k** (Figure 1).[13]

In conclusion we have depicted an efficient synthesis of 4-[3′-hydroxy-2′-iodoprop-1′(*Z*)-enyl]furan-

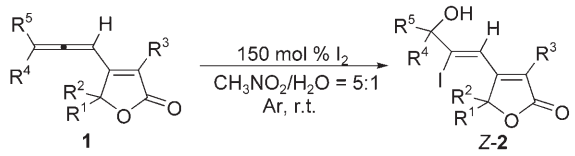
Table 1. Optimization of reaction conditions for the iodohydroxylation of I_2 with **1a**.[a]



Entry	Solvent	I_2 [equivs.]	Time [h]	Isolated yields [%]	
				Z-**2a**	*Z*-**7a**
1[b]	$CH_3CN/H_2O = 5:1$	4.0	1.0	54	13
2	$CH_3CN/H_2O = 5:1$	4.0	1.0	59	4
3	$CH_3NO_2/H_2O = 5:1$	4.0	1.0	71	-
4	$THF/H_2O = 5:1$	4.0	1.0	69	-
5	$CH_2Cl_2/H_2O = 5:1$	4.0	4.0	44	-
6	$CH_3NO_2/H_2O = 5:1$	2.0	1.0	74	-
7	$CH_3NO_2/H_2O = 5:1$	1.5	1.0	77	-
8	$CH_3NO_2/H_2O = 10:1$	1.5	1.0	72	-
9	$CH_3NO_2/H_2O = 3:1$	1.5	1.0	69	-

[a] The reaction was carried out using 0.15–0.25 mmol of **1a**.
[b] The reaction was carried out in open air.

Table 2. Iodohydroxylation of β-allenyl furanones **1**.[a]



Entry	Substrate **1**					Time [h]	Yield of *Z*-**2** [%]
	R^1	R^2	R^3	R^4	R^5		
1	Ph	H	*n*-C_3H_7	Me	Me (**1a**)	1.0	77 (*Z*-**2a**)
2	Ph	H	Me	Me	Me (**1b**)	12.5	80 (*Z*-**2b**)
3	Ph	H	Et	Me	Me (**1c**)	9.5	78 (*Z*-**2c**)
4	Ph	H	*i*-C_4H_9	Me	Me (**1d**)	4.0	70 (*Z*-**2d**)
5	Ph	H	Allyl	Me	Me (**1e**)	4.0	70 (*Z*-**2e**)
6[b]	Ph	H	Me	Et	Et (**1f**)	51	62 (*Z*-**2f**)
7	Ph	Me	H	Me	Me (**1g**)	12	76 (*Z*-**2g**)
8	Ph	Et	H	Me	Me (**1h**)	1.0	76 (*Z*-**2h**)
9	Ph	Et	Me	Me	Me (**1i**)	4.0	75 (*Z*-**2i**)
10	*p*-BrC_6H_4	H	Allyl	Me	Me (**1j**)	11	49 (*Z*-**2j**)
11	Me	Me	Me	Ph	Me (**1k**)	11	61 (*Z*-**2k**)
12	Me	Me	Allyl	Me	Me (**1l**)	11	65 (*Z*-**2l**)

[a] The reaction was carried out using 0.15–0.30 mmol of **1**, 1.5 equivs. of I_2, 4 mL of CH_3NO_2, and 0.8 mL of H_2O.
[b] 3.0 equivs. of I_2 were used.

2(5*H*)-one derivatives *via* the highly regio- and stereoselective iodohydroxylation of non-heteroatom-substituted allenes, i.e., 4-allenyl-2(5*H*)furanones. It is believed that the regio- and stereoselectivity may be controlled by the electronic and steric effects of the furanone ring. This reaction may lead to new protocols for highly regio- and stereoselective electrophilic addition of allenes. Further investigations in this area are being pursued in our laboratory.

Experimental Section

Typical Procedure for the Iodohydroxylation of 4-Allenyl-2(5*H*)-furanone

Under an argon atmosphere, a mixture of 3-propyl-4-(3′-methylbuta-1′,2′-dienyl)-5-phenyl-2(5*H*)-furanone **1a** (63 mg, 0.24 mmol), I_2 (90 mg, 0.35 mmol), CH_3NO_2 (4 mL), and H_2O (0.8 mL) was stirred at room temperature for 1 h.

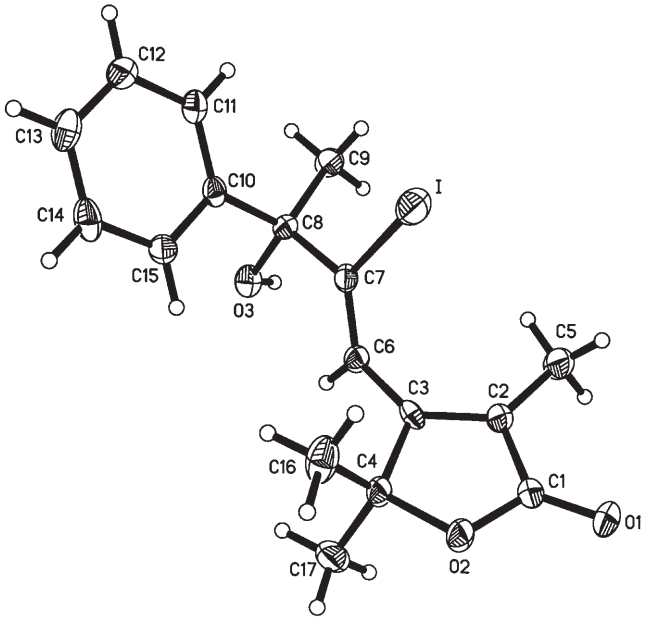


Figure 1. ORTEP representation of *Z*-**2k**.

After being treated with saturated aqueous $Na_2S_2O_3$ solution, the mixture was extracted with ether. The organic layer was subsequently washed with water and brine and dried over Na_2SO_4. After evaporation, the residue was purified *via* flash chromatography on a silica gel (petroleum ether/ethyl acetate = 10/1) to afford *Z*-**2a** as an oil; yield: 75 mg (77%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.40$–7.28 (m, 3H), 7.27–7.17 (m, 2H), 6.71 (s, 1H), 6.09 (s, 1H), 2.30 (t, $J = 7.5$ Hz, 2H), 2.25 (br, 1H), 1.68–1.50 (m, 2H), 1.434 (s, 3H), 1.428 (s, 3H), 0.91 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 14.0$, 20.6, 26.9, 29.5, 29.8, 75.5, 82.2, 124.4, 126.4, 126.7, 128.7, 129.1, 134.7, 159.6, 173.9; MS (ESI): $m/z = 430$ $[M+NH_4]^+$, 413 $[M^+ + 1]$; IR (neat): $\nu =$ 3447, 1743, 1670, 1496, 1456, 1363, 1118 cm^{-1}; HR-MS: $m/z = 413.0618$, calcd. for $C_{18}H_{22}O_3I$ $[M^+ + 1]$: 413.0608.

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[13] Crystal data for *Z*-**2k**: $C_{17}H_{19}IO_3$, MW = 398.22, monoclinic, space group *P*21/*n*, final *R* indices $[I > 2\sigma(I)]$, $R1 = 0.0967$, $wR2 = 0.2989$, *R* indices (all data) $R1 = 0.1075$, $wR2 = 0.3078$, $a = 9.3955(18)$ Å, $b = 17.296(3)$ Å, $c = 10.376(2)$ Å, $\beta = 98.905(3)^o$, $V = 1665.9(6)$ Å^3, $T = 293(2)$ K, $Z = 4$, reflections collected/unique: 8524/3087 ($R_{int} = 0.1101$), number of observations $[> 2\sigma(I)]$ 2492, parameters: 195. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center. CCDC 642223.

