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SYNTHESIS OF IODO(III) ENOL LACTONES VIA IODINE(III)-INDUCED LACTONIZATION OF ALKYNOIC ACIDS. STRUCTURALLY POTENTIAL SERINE PROTEASE INACTIVATORS

Masahito Ochiai,[a]* Yoshikazu Takaoka,[a] Yukio Masaki[a]
Minako Inenaga,[b] and Yoshimitsu Nagao[b]
a Gifu Pharmaceutical University, 5-6-1 Mitahora-higashi, Gifu 502, Japan
b Institute for Chemical Research, Kyoto University, Uji, Kyoto 611, Japan

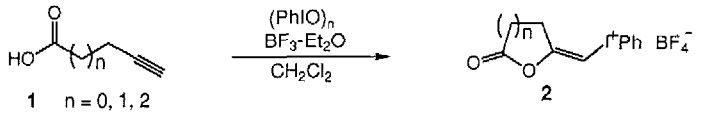
Summary: Iodine(III)-induced lactonization of 4- and 5-alkynoic acids utilizing a combination of iodosylbenzene and BF_3-Et_2O affords cyclic β-acyloxyvinyliodonium tetrafluoroborates, structurally potential serine protease inactivators.

Vinyl(phenyl)iodonium tetrafluoroborates behave similarly to the highly activated species of vinyl iodides toward the attack of nucleophiles.[1] Their α-elimination by base treatment generates alkylidenecarbenes, which undergo 1,5-C-H insertion yielding cyclopentenes.[2] The synthetic method of vinyliodonium salts, however, is limited. We report herein the first example of iodine(III)-induced lactonization[3] of alkynoic acids (1), which makes possible a stereoselective synthesis of cyclic β-acyloxyvinyliodonium salts (2).

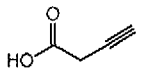
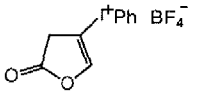
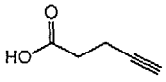
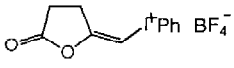
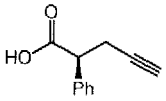
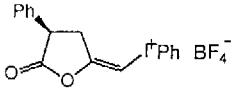
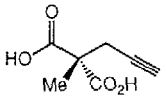
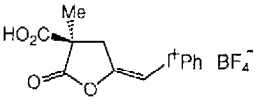
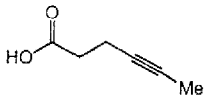
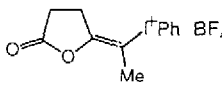
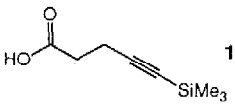
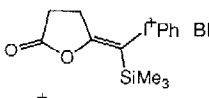
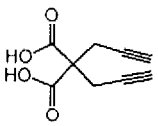
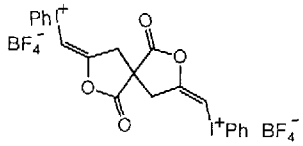
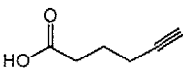
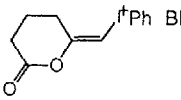
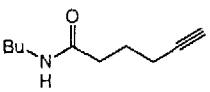
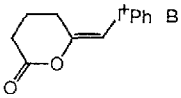
It has been reported that reaction of 1-(trimethylsilyl)-1-alkynes and 1-alkynes with iodosylbenzene (ISB) and its derivatives at room temperature affords alkynyl(phenyl)iodonium salts.[4] The reaction involves detrimethylsilylation or deprotonation of the presumed cyclic periodonium (10-I-4)[5] intermediates. With the use of alkynoic acids (1), the reaction course was dramatically altered and iodo(III)-lactonization took place under very mild conditions. When BF_3-Et_2O (2 mmol) was added to a suspension of 4-pentynoic acid (1b) (1 mmol) and ISB (1.5 mmol) in dichloromethane (20 ml) at 0 °C under nitrogen, the mixture immediately turned to a bright yellow suspension and then to a colorless solution with a concomitant precipitation of a small amount of yellow solids. After the mixture was stirred for 10 min, decantation and washing the precipitate with dry THF afforded the cyclic β-acyloxyvinyliodonium tetrafluoroborate (2b)[6] in 75% yield.

The results of the synthesis of iodo(III) enol lactones (2) are summarized in Table 1. As in the case of halolactonization of alkynoic acids with electrophilic halogenating agents,[7] the iodo(III)-lactonization of 4- and 5-alkynoic acids proceeds in an exo manner to give five- and six-membered exocyclic enol lactones, respectively, in good yields. Attempted endocyclization of 3-butynoic acid (1a) provided only unchanged 1a (run1), which is in a marked contrast with the results of the palladium(II) catalyzed endocyclization of 3-alkynoic acids reported by Utimoto and Nozaki.[8] Dicarboxylic acid (1d) afforded a good yield of the enol lactonecarboxylic acid (2d) (run 4). Reaction of the dipropargyldiacid (1g) resulted in the formation of the spiro-bis-γ-methylenebutyrolactone (2g). Amide (1i) undergoes the *O*-cyclization and no *N*-cyclization[9] to give the

Table 1. Iodine(III)-Induced Lactonization of Alkynoic Acids (**1**)



1 n = 0, 1, 2 — **2**

run	alkynoic acid	1	reactn condtns[a]	enol lactone	2	% yield[b]
1		**1a**	rt, 3d		**2a**	0
2		**1b**	0°C, 10min		**2b**	75
3		**1c**	0°C, 30min[c]		**2c**	78
4		**1d**	0°C, 25min[c]		**2d**	75
5		**1e**	0°C, 1h		**2e**	96
6		**1f**	0°C, 30min[c]		**2f**	77
7		**1g**	rt, 12h[d]		**2g**	94
8		**1h**	0°C, 10min		**2h**	73
9		**1i**	0°C, 2.5h[c]		**2h**	37

a) rt: room temperature. 1.5 - 2 mol equiv of BF_3-Et_2O were used. b) Isolated yield. c) The reaction mixture was treated with an aqueous sodium tetrafluoroborate solution. d) 3 mol equiv of ISB and 4 mol equiv of BF_3-Et_2O were used.

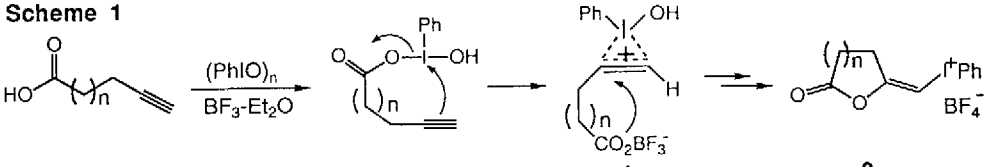
enol lactone (2h), probably produced *via* hydrolysis of the intermediate iminolactone during work up (run 9). The γ-lactones (2b-f) show the characteristic carbonyl absorption at about 1820 cm^{-1}, whereas the δ-lactone (2h) at 1795 cm^{-1}. The lactonization is stereo-

selective and *E* olefin geometry of 2 was deduced from the expected *trans* addition of a phenyliodonio group and a carboxy group to triple bonds.[10] In fact, the ^1H NMR of 2 showed no appreciable amount of NOE enhancement between the vinylic and allylic protons.

It is noted that the reaction of 5-(trimethylsilyl)-4-pentynoic acid (1f) underwent cyclization exclusively to give α-(trimethylsilyl)vinyliodonium tetrafluoroborate (2f) and formation of the corresponding alkynyliodonium salt *via* detrimethylsilylation was not observed.

On the basis of the observation that the iodo(III)-lactonization of alkynoic acids (1) is considerably more rapid than the reaction of 1-(trimethylsilyl)-1-alkynes with ISB and BF_3, we propose a reaction mechanism involving an initial activation of ISB by the depolymerization, catalyzed by BF_3, which leads to the formation of acyloxy(hydroxy)iodobenzene (3) (Scheme 1). Formation of 3 makes the subsequent electrophilic attack of trivalent iodine toward a carbon-carbon triple bond a facile intramolecular process.

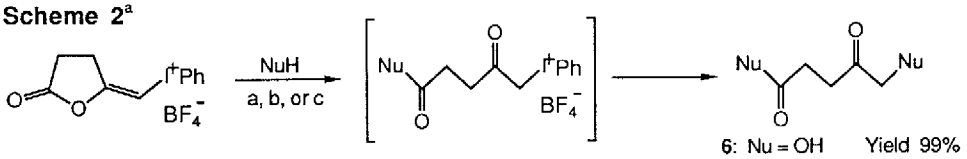
Scheme 1



1 3 4 2

Katzenellenbogen and coworkers have reported that haloenol lactones can act as effective enzyme-activated irreversible inactivators for serine proteases, such as α-chymotrypsin. Acylation of the active site serine by the haloenol lactone generates an α-haloketone, which alkylates the enzyme at the active site and inactivates the enzyme.[11] Vinyliodonium salts (2) seem to be better inactivators of serine proteases than haloenol lactones, since 2 may generate a highly reactive β-ketoiodonium group by the reaction with a serine hydroxy group. In order to gain the chemical evidence supporting this assumption, in other words, to determine whether 2 acts as ambident electrophilic species, reaction of 2 with nucleophiles was investigated. The reactions shown for 2b in Scheme 2 are representative. It was found that 2b was highly susceptible toward hydrolysis:[12] 2b on treatment with water at room temperature afforded quantitatively the ω-hydroxycarboxylic acid (6). With methanol, the α-methoxycarbonyl ester (7) was obtained in good yield. Reaction with diethylamine (3 equiv) in THF afforded the α-aminocarbonyl amide (8) under mild conditions. Sulfur nucleophiles like benzenethiol, however,

Scheme 2[a]



2b 5

6: Nu = OH Yield 99%
7: Nu = OMe 72%
8: Nu = NEt_2 67%

[a](a) H_2O, room temperature, 12h; (b) MeOH, room temperature, 24h; (c) Et_2NH (3 equiv), room temperature, 1h

did not react with 2 even on prolonged treatment at room temperature.

It is noted that the iodine(III)-induced lactonization of alkynoic acids, combined with cleavage of the resulting iodo(III) enol lactones by oxygen and nitrogen nucleophiles, offers an efficient procedure for the regiospecific transformation of alkynes into α-oxy- and α-aminoketones, respectively.

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6 2b: mp 83 – 84 °C (recrystallized from THF-hexane); IR (KBr) 1820, 1615, 1020, 905, 730 cm^{-1}; ^1H NMR (400 MHz, THF-d_8) δ 2.83 (m, 2 H), 3.43 (m, 2 H), 6.83 (t, J = 2.0 Hz, 1 H), 7.50 (m, 2 H), 7.64 (m, 1 H), 8.17 (m, 2 H); MS (FAB) m/z 301 $[(M-BF_4)^+]$. Anal. Calcd for $C_{11}H_{10}BF_4IO_2$: C, 34.06; H, 2.60; I, 32.72. Found: C, 33.98; H, 2.48; I, 32.51.

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