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Contribution

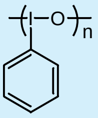
Utilization of Iodine Resources
Syntheses & Reactions of Hypervalent Organoiodanes

Masahito Ochiai, Professor,
Faculty of Pharmaceutical Sciences,
University of Tokushima

As Japan is not blessed with abundant natural resources, the Japanese are dependent on the importation of the majority of our raw materials from overseas. However, Japan can be proud for its production of iodine, where it is a leading manufacturer in the world. Fossil seawater obtained from underground is the material for producing industrial iodine. More than 80% of the produced iodine is exported to various countries of the world. However, we have to rely on the United States and Europe for importation of the majority of the products into which iodine is incorporated, for instance, an X-ray contrast medium or a photosensitive agent for photographic film. Because of this, our iodine resource is not fully utilized. Accordingly, it becomes very important to develop an effective method for utilization of iodine to its full extent by producing high value organoiodane. Our attention has been directed to trivalence hypervalent organoiodanes (λ^3-organoiodane) with low toxicity and we are making a study of its full use in the synthetic organic chemistry.

Iodine is large-sized halogen element, easily polarizable and low in electronegativity. It forms hypervalent organoiodanes beyond the octet theory by readily extending its valence.

The representative λ^3-organoiodanes are iodosylbenzene (polymer) **1**, (diacetoxyiodo)benzene **2**, [bis(trifluoroacetoxy)iodo]benzene **3**, [hydroxy(tosyloxy)iodo]benzene (Koser reagent) **4**, *o*-iodosylbenzoic acid **5**. They have been widely used as oxidants for active methylene groups, double and triple bonds, alcoholic and phenolic hydroxyl groups, sulphur and amino compounds [1]. More than twenty kinds of λ^3-organoiodanes including the above-noted iodanes, are available from Tokyo Kasei Kogyo Co. Ltd.



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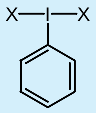
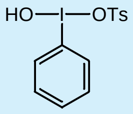


2: X = OAc
3: X = $OCOCF_3$



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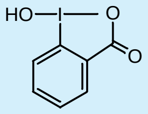

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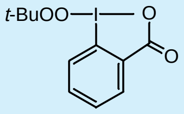


6

The λ^3-organoiodane which contains an alkylperoxy group as a ligand has not been synthesized probably because of its high tendency to decompose. We have recently found [2] that the Lewis acid-catalyzed ligand exchange of 1-hydroxy-1,2-benziodoxol-3(1*H*)-one **5** with *tert*-butyl hydroperoxide affords the crystalline peroxyiodane **6**. The peroxyiodane **6** is very stable in the solid state, no decomposition whatever is found, and its cystalline form stores well at room temperature for over one year. This product is an interesting compound since it contains *tert*-butylperoxy group and a trivalent iodine atom, in the same molecule, both of which are powerful oxidants. The purpose of this review is to describe the usefulness of λ^3-peroxyiodanes and their wide applications as radical oxidants.

1. Syntheses & Reactions of Alkenyliodanes and Alkynyliodanes

In 1985 it was found that when iodosylbenzene **1** was activated with BF_3 in dichloromethane, and is reacted with vinylsilane or vinylstannane, the silicon or tin is replaced with trivalent iodine and λ^3-alkenyliodane **7** can be synthesized in good yield (Figure 1) [3]. The generation of λ^3-alkenyliodane is stereospecific and the stereochemistry of vinylsilane or vinylstannane is maintained. The λ^3-alkenyliodane **7** can also be obtained through boron-iodine exchange reaction, employing vinylboronic acid as a substrate [4].

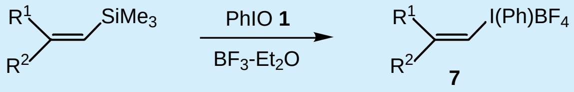


Fig.1

The trivalent iodine group exhibits very high leaving group ability and, therefore, nucleophilic substitution reactions of alkenyliodane **7** at vinylic carbons proceed at room temperature under mild conditions. Enolate anions, R_2CuLi, CuCN, ArSNa, n-Bu_4NCl, etc. act as good nucleophiles in these reactions. Especially, an S_N2 reaction at vinylic carbons accompanied by the stereochemical inversion of configuration, which was regarded as not to proceed before, is made possible through use of alkenyliodane **7**. In alkenyliodane **7**, the acidity of α-hydrogens is high enough for the α-elimination to take place followed by reductive elimination of iodobenzene, in the presence of a base, leading to the generation of an alkylidene carbene in good yield 5).

In a similar way as the synthesis of alkenyliodanes, alkynyliodane **8** can be synthesized from alkynylsilane and stannane (Figure 2). Synthesis of alkynyliodanes can also be performed directly from the terminal alkyne 5). The Michael addition reaction of the alkynyliodane **8** with enolate anions, leads to the formation of cyclopentene skeletons. As shown in Figure 2, the alkynyliodane **8** (R=H) is a good ethynylation reagent 6) and available from Tokyo Kasei. The alkylidene carbene is a reaction intermediate and an ethynylated product can be obtained via 1,2-hydrogen rearrangement of the α-hydrogen.

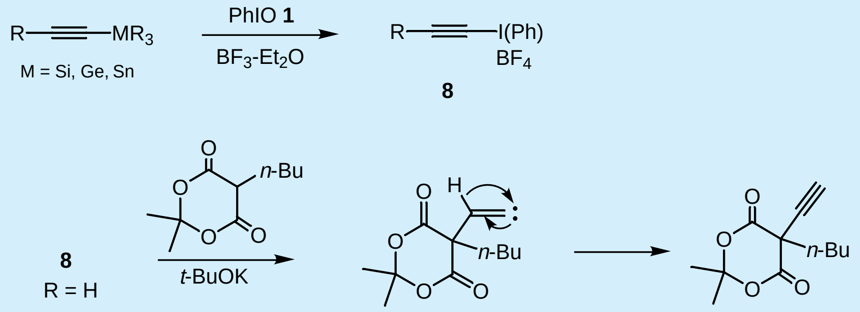


Fig.2

2. Generation of Allenyliodanes & Their Reductive Iodonio-Claisen Rearrangement

The application of the silicone-iodane exchange reaction to propargylsilane leads to the generation of λ^3-allenyliodane via an S_E2' reaction. When (diacetoxyiodo)benzene **2** was treated with propargylsilane **9** in the presence of BF_3, the propargyl group was introduced at the ortho-position of iodobenzene and *o*-propargyliodobenzene **10** was obtained in high yields 7) (Figure 3). After a number of other reactions were studied, the followiing observations were made:

1) The trivalent iodine is always reduced to univalent iodide.
2) Regioselective propargylation occurs at the ortho-position of iodoarenes.
3) The new carbon-carbon bond is formed regioselectively at the α–carbon of the propargyl group.
4) The reaction proceeds at a low temperature.
5) Propargylgermane and stannane can also be used.
6) Hydroxy- and acetoxy-propargylsilanes can be used.

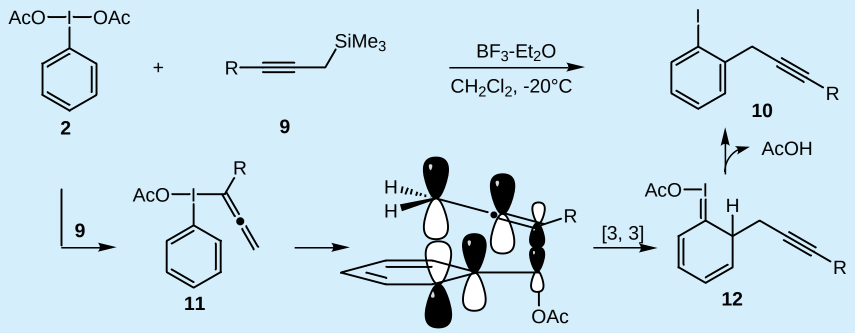


Fig.3

The reaction mechanism, taking into account the above observations, is shown in Figure 3. Reactions of propargylsilane with electrophiles, such as halogens and acyl chlorides, are known to proceed via S_E2' process. To start with, the reaction affords λ^3-allenyliodane **11**. Subsequently, a propargyl group is introduced regioselectively at the ortho-position via intramolecular [3,3]sigmatropic rearrangement, and acetic acid is then released by means of the subsequent reductive elimination of **12** with the formation of the *o*-propargyliodobenzene **10**. Intramolecular nature for the rearrangement of λ^3-allenyliodane **11** is strongly supported by the cross reaction in the presence of univalent iodoarene. Although heating at 150-250°C is required for ordinary Claisen rearrangement reactions, the reductive iodonio-Claisen rearrangement proceeds at a low temperature. The rate determining step of the reaction is presumed to be a [3,3]sigmatropic rearrangement of the λ^3-allenyliodane **11**. The lower activation energy associated with the iodonio-Claisen rearrangement of **11** can be interpreted in terms of the small bond energy needed to break the apical carbon-iodine(III) bond. In general, aryliodanes $ArIX_2$ adopt a T-shaped geometry, the hypervalent I(III)-X bonds being well overlapped with the aromatic π bond. This favorable orbital interaction could facilitate the rearrangement of **11**.

In the above reductive iodine(III) Claisen rearrangememt reaction, we had no direct evidence for the generation of λ^3-allenyliodane **11**, which has been considered to be an intermediate. Therefore, we have carried out the reaction of dimethylpropargylsilane **13** with hydroxyiodane **5** in order to isolate or detect the intermediate, allenyliodane **14** (Figure 4). It seems reasonable to assume that the [3,3]-sigmatropic rearrangement of allenyliodane **14** proceeds with difficulty, probably because the hypervalent C-I(III) bond being cleaved during the [3,3]-sigmatropic rearrangement could not overlap with the aromatic π orbitals and because of the steric hindrance of the terminal two methyl groups and their electronic effects. As expected, no propargylation at the ortho-position by [3,3] sigmatropic rearrangement was observed. To our regret, we could not detect the generation of allenyliodane **14**. Contrary to our expectation, the present reaction generated alkylperoxyiodane **15** 8). Peroxyiodane **15** has an alkylperoxy group and hypervalent iodine(III) in a same molecule, both acting as oxidants, but is stable in a solid state. X-ray analysis revealed that the iodine atom has a typical T-shaped geometry specific to hypervalent compounds with some distortion in shape.

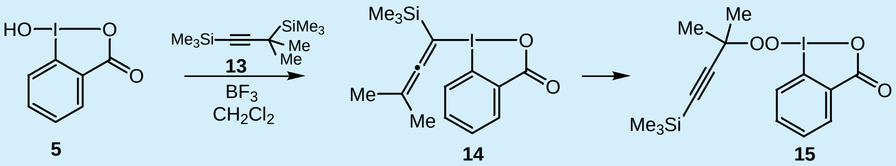


Fig.4

3. Synthesis of *tert*-Butylperoxyiodanes

Hypervalent λ^3–organoiodanes having an alkylperoxy group as a ligand are very unstable. In 1968 Milas and Plesnicar reported that reaction of iodosylbenzene **1** with *tert*-butylhydroperoxide in methylene chloride at -80°C generated *tert*-butylperoxy radical and iodobenzene . It was assumed that in this reaction, an initial ligand exchange on the iodine atom afforded bis(alkylperoxy)iodane, which was so unstable, resulting in homolytic bond cleavage of the hypervalent O-I bond, even at -80°C, to give a *tert*-butylperoxy radical. Accordingly, isolation of alkylperoxyiodane **15** is very interesting because it is stable even at room temperature. This is attributed to fixation of both the apical heteroatom ligands and equatorial aromatic ligand in the same plane by the formation of five-membered heterocycles. This arrangement to form an iodoxolone leads to enhanced stability of the alkylperoxyiodanes **15** because orbital interaction between the easily cleaved I-O bond and π-orbitals of phenyl group is not feasible.

The alkylperoxyiodanes with unique structure were expected to be utilized as new oxidants in organic synthesis. Hereby, iodane **6**, in which the *tert*-butylperoxy group was introduced, was designed as a representative compound and its synthesis attempted. Reaction of hydroxyiodane **5** with *tert*-butylhydroperoxide did not take place at room temperature and hydroxyiodane was recovered because of its poor reactivity. However, on addition of Lewis acid to the reaction mixture, the desired ligand exchange on the iodine atom proceeded effectively to afford peroxyiodane **6** in good yield (Figure 5) 2). Coordination of BF_3 on the oxygen atoms of hydroxyiodanes **5** causes activation. The product *tert*-butylperoxyiodane **6** is stable in the solid state and no decomposition is seen when the crystalline form is stored over a year at room temperature.

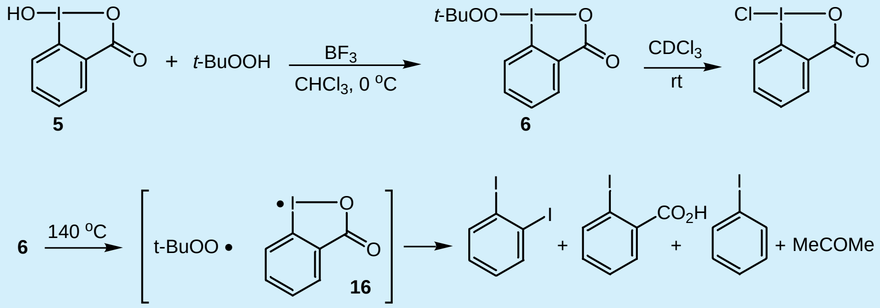


Fig.5

The peroxyiodane **6**, though stable in the solid state, is readily decomposed in solution. When the peroxyiodane **6** is dissolved in chloroform and allowed to stand at room temperature, a ligand exchange takes place to give chloroiodane, and the half life of **6** is about 4 days. Heating crystalline peroxyiodane at 140°C causes it to decompose explosively to generate 1,2-diiodobenzene (46%), iodobenzene (6%), *o*-iodobenzoic acid (14%) and acetone (43%). In this thermal decomposition reaction, the decomposition is considered to take place via the generation of *tert*-butylperoxy radical and 9-I-2 σ-iodanyl radical **16** due to cleavage of the weak hypervalent bond between the oxygen of the peroxy group and iodine atom.

4. Benzylic Oxidation Reaction by *tert*-Butylperoxyiodane [9)]

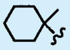
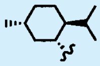
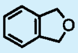
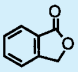
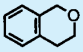
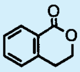
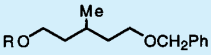
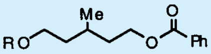
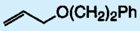
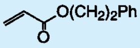
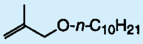
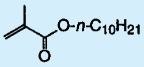
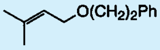
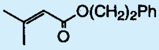
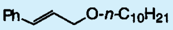
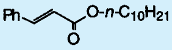
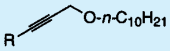
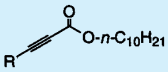
tert-Butylperoxyiodane **6** is effective for the oxidation of the benzylic methylene group of benzyl ethers **17**, to form esters of benzoic acid **18**. Reactions are performed at room temperature under a nitrogen atmosphere using a rubber balloon. The yields of esters are highly dependent upon the dielectric constant of the solvents and the best results were obtained in benzene which has a small dielectric constant, although, the reaction at room temperature was very slow. However, the reaction in benzene was considerably accelerated with the addition of alkali metal carbonates (K_2CO_3, Cs_2CO_3 *etc.*).

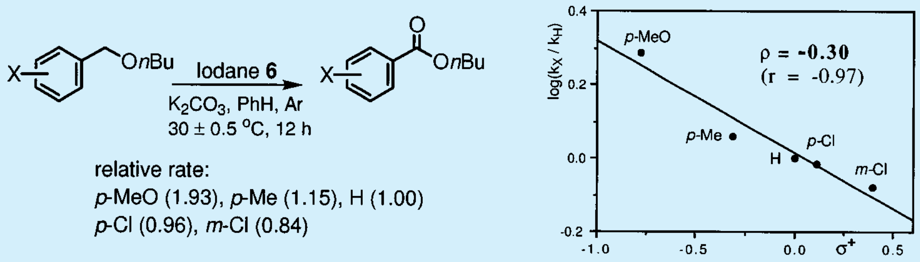
The benzyl group is frequently used as a protecting group for alcohols in organic synthesis. Since esters are readily hydrolized to alcohols, peroxyiodane **6** provides an oxidative deprotection method for the benzyl group. One of the common problems associated with deprotection reactions is their chemoselectivity. Chemoselective oxidation at the benzylic site proceeds even in the presence of MOM group, silyl group, acetyl group or tetrahydropyranyl group. The allyl group is used as a protecting group for alcohols and peroxyiodane **6** is useful for the oxidation of allyl ether to the corresponding α,β-unsaturated esters. Furthermore, the benzylic oxidations of other hydrocarbons also proceed readily and indan, tetrahydronaphthalene, dihydroanthracene, fluorene,*etc*. are efficiently oxidized. The results of these reactions are partly shown in Table 1.

Radical inhibitors such as α-tocopherol and galvinoxyl inhibit the oxidation of the benzylic methylene group, which suggests the involvement of radical species. To verify that radicals are generated at the benzylic positions, 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO), which reacts very rapidly with carbon radicals, was used as a trap for any benzylic radicals. The substituent effect on the oxidation reaction of benzyl butyl ethers **17a** was investigated (Figure 6). The introduction of electron-withdrawing chlorine in *p*- or *m*-position decreased the rate of the reaction, while introduction of *p*-MeO group or *p*-Me group accelerated the reaction. Hammett correlation was established between the relative reaction rate and substituent constant σ^+ with $\rho = -0.30$. This ρ value appears to be comparable to $\rho = -0.65$ for benzylic hydrogen abstractions from dibenzyl ethers by benzoyloxy radical. An examination of the deuterium primary isotope effect resulted in a very large value ($K_H/K_D = 12\text{-}14$). This large isotope effect also strongly indicated that the cleavage of the benzylic C-H bond is involved in the rate-determining step.

The effect of molecular oxygen on this reaction was also investigated. Very interestingly, in the presence of a large excess of benzyl butyl ether **17a** relative to the peroxyiodane **6**, the prolonged reactions (410 h) under nitrogen rubber balloons afforded more than stoichiometric amounts of benzoate ester **18a** (*ca*. 600%), while the reaction in the absence of oxygen (a degassed argon tube experiment) gave 24% of benzoate ester **18a** and 72% of peroxyacetal **19**, which has *tert*-butylperoxy group at the benzylic position. This result would indicate the formation of two kinds of reaction intermediates: the peroxyacetal **19** and hydroperoxyacetal **20** derived from the reaction with molecular oxygen. It is assumed that both of these intermediates are converted into esters of benzoic acid. The reaction mechanism is shown in Figure 7.

Table 1. Oxidation of Benzyl, Allyl, and Propargyl Ethers **17** with the Peroxyiodane **6**

entry	ether	17	time (h)	product	18	yield (%)
	$PhCH_2OR$			$PhCO_2R$		
1	R = *n*-Bu	**17a**	24		**18a**	95
2	*tert*-Bu	**17b**	24		**18b**	80
3	*cyclo*-C_6H_{11}	**17c**	48		**18c**	79
4		**17d**	31		**18d**	74
5		**17e**	30		**18e**	74
6		**17f**	23		**18f**	78
7		**17g**	17		**18g**	86
						
8	R = MOM	**17h**	72		**18h**	78
9	THP	**17i**	47		**18i**	61
10	TBDMS	**17j**	100		**18j**	68
11		**17k**	42		**18k**	60
12		**17l**	72		**18l**	73
13		**17m**	46		**18m**	76
14		**17n**	51		**18n**	72
						
15	R = H	**17o**			**18o**	51
16	TMS	**17p**			**18p**	65



relative rate:
p-MeO (1.93), *p*-Me (1.15), H (1.00)
p-Cl (0.96), *m*-Cl (0.84)

Fig.6

Initially, the weak hypervalent bond between the oxygen atom of the peroxy group and the iodine atom of the peroxyiodane **6** is cleaved to generate *tert*-butylperoxy radical and 9-I-2 σ- iodanyl radical **16**. The benzylic radical **21** is generated when the electrophilic iodanyl radical **16** abstracts the benzylic hydrogen of the benzyl ether **17a**. The benzylic radical **21** further reacts with the peroxyiodane **6** to yield *tert*-butylperoxyacetal **19**, which decomposes to the corresponding ester **18a**. On the other hand, in the presence of molecular oxygen in the reaction system, the reaction of the benzylic radical **21** with oxygen yields the peroxy radical **22**. The peroxy radical **22** further abstracts the benzylic hydrogen of **17a** to yield hydroperoxyacetal **20** and the benzylic radical **21** is regenerated as well. The hydroperoxyacetal **20** is converted to the corresponding ester **18a** under reaction conditions.

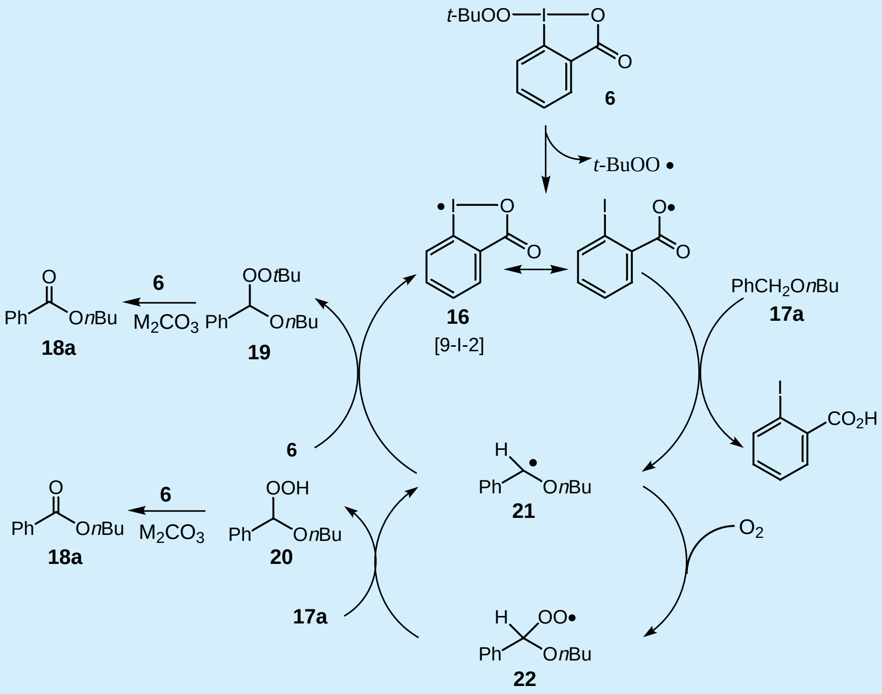


Fig.7

5. Oxidation of Sulfides by *tert*-Butylperoxyiodane 10)

tert-Butylperoxyiodane **6** oxidizes sulfides to sulfoxides. Dialkyl sulfides and alkyl aryl sulfides are converted to sulfoxides in good yields in aqueous acetonitrile (method A). Diaryl sulfides are converted in good yields to sulfoxides in dichloromethane (method C). Addition of BF_3-Et_2O (method B) to aqueous acetonitrile accelerated the reaction (Figure 8).

$$R^1\text{—S—}R^2 \xrightarrow{\text{iodane } \mathbf{6}} R^1\text{—S(O) —}R^2$$

A) CH_3CN-H_2O (5:1) / 50 °C
B) CH_3CN-H_2O (5:1) / BF_3-Et_2O (0.3) / 25 °C
C) CH_2Cl_2/25 °C / N_2

n-BuSBn, *i*-BuSBn, *s*-BuSBn, BnSBn, Me$(CH_2)_4$SPh,

CH_2=CHCH_2SPh, *p*-MeOC_6H_4SMe, *p*-MeC_6H_4SMe,

p-ClC_6H_4SMe, PhSCH_2P(O)$(OEt)_2$, PhSPh, $(p\text{-ClC}_6H_4)_2S$

Fig.8

Our studies on the substituent effects for the reaction of substituted thioanisoles in aqueous acetonitrile exhibited a large negative ρ value (-3.35) toward the substituent constants σ. The corresponding BF_3-Et_2O mediated reaction exhibited the ρ value -2.23, with a better correlation toward the substituent constants σ^+. It seems reasonable to assume that the reaction in aqueous acetonitrile is an ionic reaction from the following observations.

1) An equilibrium is in existence between the peroxyiodane **6** and hydroxyiodane **5**.
2) Use of either the hydroxyiodane **5** or the *tert*-butyl hydroperoxide as an oxidant by itself causes no reaction to occur, but the use of both in together allows the reaction to proceed almost quantitatively.
3) In addition, the effect of the added galvinoxyl which is a radical scavenger, is small.

Furthermore, it is strongly suggests that *tert*-butylperoxyiodane **6** is the active species and that a reactive intermediate with a considrable positive charge on the sulfur atom is generated . On the other hand, the reaction in dichloromethane (method C) is completely inhibited by the addition of galvinoxyl indicating that the reaction takes place by a radical mechanism.

Oxidative deprotection of dithioacetals also takes place. Treatment of dithioacetals with peroxyiodane **6** in aqueous acetonitrile reacts completely in several minutes with the generation of parent ketones in high yields. The peroxyiodane **6** is useful for the oxidation of selenides to selenoxides and phosphines to phosphine oxides. Furthermore, the peroxyiodane **6** oxidizes 2 mol of triphenylphosphines to the corresponding oxides.

6. Oxidation of Amines by *tert*-Butylperoxyiodane 11)

The *tert*-butylperoxyiodane **6** is effective for the oxidation of amines. The reaction of secondary amines with the *tert*-butylperoxyiodane **6** causes dehydration to occur, yielding imines. Addition of K_2CO_3 accelerates the reaction. In the oxidation of tetrahydroisoquinoline, dihydroisoquinoline is obtained in high yeild. When an excess amount of peroxyiodane **6** is used, isoquinoline is produced. The reaction with tertiary amines generates peroxy amino acetals with the peroxy group being introduced on the α-carbon atom of the amines (Figure 9).

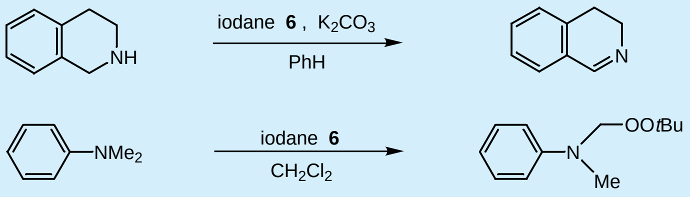


Fig.9

7. Radical Oxidation Reaction of Phenols by *tert*-Butylperoxyiodane 12)

In reactions with *p*-alkyl substituted phenols, 4-(*tert*-butylperoxy)cyclohexadienone is produced. Treatment of *p*-substituted phenols with peroxyiodane **6**, in the presence of *tert*-butyl hydroperoxide, gives *tert*-butylperoxycyclohexadienones in good yield under mild conditions (ethyl acetate/50°C). It seems reasonable to assume that this reaction is a radical reaction because the oxidation reaction in the presence of galvinoxyl was almost completely inhibited and a small amount of a dimer of *tert*-butylperoxycyclohexadienone was obtained as a by-product. The phenoxy radical, stabilized by resonance, is an intermediate, and its coupling with the *tert*-butylperoxy radical yields *tert*-butylperoxycyclohexadienone.

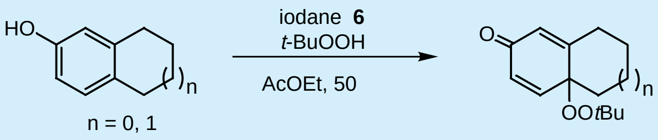


Fig.10

8. Conclusion

In *tert*-butylperoxyiodane **6**, the *tert*-butylperoxy group and the trivalent iodine atom are bonded by a hypervalent bond. An intensive survey of its structure leads us to expect its high reactivity but makes us worry about its potential for explosion. It is likely that a limited number of chemists would actually try to synthesize this compound by themselves. On the contrary, the crystalline *tert*-butylperoxyiodane **6** is a surprisingly stable compound and no decomposition occurs at room temperature. Furthermore, no radical cleavage of the hypervalent bond occurs until it is made into a solution in which case the reaction proceeds slowly. Generally, the reaction is carried out at less than 50°C and no attempts have been made beyond that temperature.

As discussed in the above, the developement of *tert*-butylperoxyiodane has been attributed to our concentrated efforts to seek for new potential utilization of iodine. The results have been generated by many careful experiments carried out by Dr. Takao Ito (Nippon Tobacco Industry K.K. Laboratory). The author wish to extend heartfelt thanks toward many of the students, for their contributions, whose names are listed in the reference literature involved in these studies.

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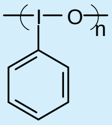
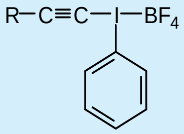
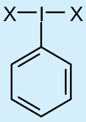
Hypervalent Organoiodanes



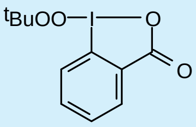
Iodosobenzene
5g JPYen9,300 (I0072)



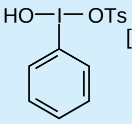
R=H
Ethynyl(phenyl)iodonium Tetrafluoroborate
1g JPYen 10,100 (E0467)
R=Me_3Si
Trimethylsilylethynyl(phenyl)iodonium Tetrafluoroborate
1g JPYen 6,850 (P1239)



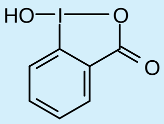
X=OAc
Iodobenzene Diacetate
25g JPYen7,650 10g JPYen3,900
(I0330)
X=$OCOCF_3$
[Bis(trifluoroacetoxy)iodo]benzene
25g JPYen 12,800 10g JPYen7,350
(B1175)



1-(*tert*-Butylperoxy)-1,2-benziodoxol-3(1*H*)-one
1g JPYen 23,800 (B2121)



[Hydroxy(tosyloxy)iodo]benzene
25g JPYen 14,500 5g JPYen 5,550
(P1015)



o-Iodosobenzoic Acid
10g JPYen 16,300 (I0073)