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Chemical Transformations Induced by Hypervalent Iodine Reagents

Anastasios Varvoglis
Department of Chemistry
Thessaloniki University
Thessaloniki 540 06, Greece

Key Words: Iodobenzene derivatives, Iodanes, Iodonium compounds, Hypervalent iodine

***Abstract**: The main features of hypervalent iodine chemistry are presented with an emphasis on recent synthetic applications. Reactions are loosely grouped together according to the type of substrate and/or transformation.*

Contents

A. GENERAL CONSIDERATIONS

1. Introduction

Since the first preparation of (dichloroiodo)benzene, $PhICl_2$, by C. Willgerodt, in 1886, a great number of organic polyvalent iodine compounds have been discovered[1]. These belong to a variety of classes of iodine (III) and (V) compounds and include well over 1000 individual members. The expression "polycoordinated iodine compounds" is often used to describe them collectively; in parallel, the term "hypervalent" is becoming increasingly popular: it refers to bonding and includes all classes of polycoordinated iodine. In these compounds, apart from an ordinary σ- bond, there are also one to four hypervalent bonds of two types. The first type is found in systems with monovalent ligands X, such as RIX_2 or RIX_4, where X is an electronegative ligand (atom or group). These contain one or two linear triads X-I-X in which bonding involves four electrons and three atoms (three centre- four electron, 3c-4e, bonds). The second type is found in RIZ or $RIZX_2$ or RIZ_2 systems and involves bivalent ligands forming with iodine "double" bonds(formally I=Z but actually polar, e.g. RI^+-Z^-); these are two centre-four electron (2c-4e) bonds, where Z is oxygen or an organic electronegative group linked to iodine with carbon or nitrogen.

The collective name for all non-charged species according to IUPAC is iodanes, which may be λ^3-, for iodine (III) derivatives or λ^5-, for iodine (V) derivatives. Formal removal of one monovalent ligand from iodine (III) or (V) compounds, either as an anion or as a cation, gives rise to ionic species, some of which are of special interest. The various compounds may be classified in families according to the N-X-L designation, in which N is the number of electrons formally assignable to the valence shell of the central atom X, and L is the number of ligands. The most important classes and some of their parent members are shown below, all derived from iodobenzene. Iodanes derived from some aliphatic and perfluoroalkyl iodides are also known[1].

N-X-L Type	*Example*	*Common name*
10-I-3	$PhICl_2$	(dichloroiodo)benzene
10-I-3	$PhI(OAc)_2$	(diacetoxyiodo)benzene
10-I-3	PhI(OH)OTs	[hydroxy(tosyloxy)iodo]benzene

8-I-2	Ph_2I^+	diphenyliodonium
8-I-2	PhI^+Rf	perfluoroalkyl phenyliodonium
8-I-2	$PhI^+CH{=}CH_2$	alkenyl phenyliodonium
8-I-2	$PhI^+C{\equiv}CH$	alkynyl phenyliodonium
10-I-2	PhI=O	iodosylbenzene
10-I-2	PhI=CXY	phenyliodonium methylides
10-I-2	$PhI{=}NSO_2Ph$	(phenylsulfonyliminoiodo)benzene
12-I-3	$PhIO_2$	iodylbenzene
12-I-5	Dess-Martin reagent	(see section 7. 1)

There is not always a clear distinction between ionic and hypervalent structures, whereas in some compounds misleading representations are used, for example PhI(OH)OTs is actually ionic ($PhI^+OH\ TsO^-$), and $Ph_2I^+Cl^-$ is not. Apart from cations, iodate anions such as (diacetoxy)iodate, $I(OAc)^-_2$, a 10-I-2 species, and tetrachloroiodate, ICl^-_4, a 12-I-4 species, also have hypervalent bonding. Tetracoordinated iodates are intermediates during bimolecular reactions of λ^3-iodanes with nucleophiles. These and some related cations or dipoles are not discussed here. As for nomenclature, several names are in current use; in this report names as close as possible to IUPAC rules are used.

For several decades, iodanes were mere chemical curiosities, devoid of any synthetic utility. However, the situation changed and presently many individual compounds as well as a number of classes are emerging as new valuable reagents in organic synthesis; among them are several heterocycles, the chemistry of which is often of exceptional interest. It is the purpose of this report to highlight their potential, with an emphasis on the numerous recent synthetic applications. Because of the multitude of new reactions, a somewhat enhanced degree of selectivity was inevitable. Therefore, some topics such as halogenation and perfluoroalkylation are not discussed. A book[1] and several recent review articles[2-10] are available for more detailed information. Another forthcoming book deals also specifically with synthetic applications.[11]

2. Preparative Methods for Reagents

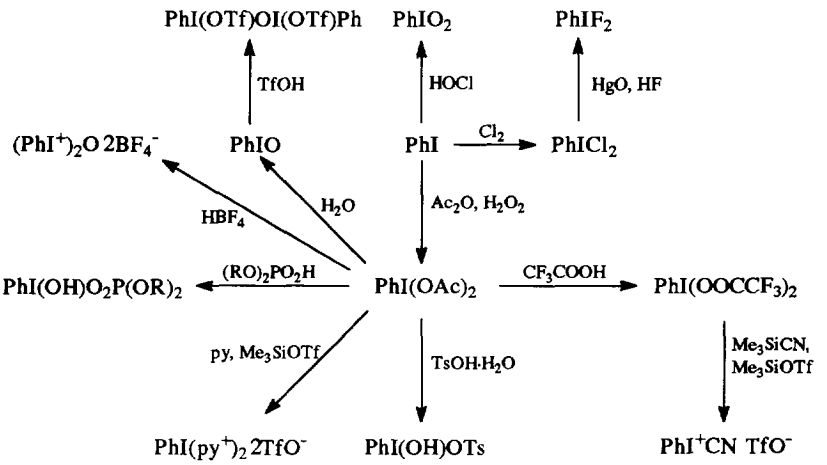
Virtually all hypervalent iodine compounds of synthetic utility are derived from iodobenzene or some ring-substituted analogues; 2-iodobenzoic acid is the

starting material for most heterocyclic iodanes. Several compounds are commercially available, but generally their preparation, with few exceptions, presents no special problems; most of them can be safely assigned to undergraduate classes.

Scheme 1 illustrates the main preparative approaches for iodobenzene derivatives. Some of them, such as $PhICl_2$, PhIO, $PhIO_2$ and $PhI(OAc)_2$ appear in *Organic Syntheses*. Interconversions among them occur readily and in several instances they offer improved procedures.

Scheme 1

Preparative Methods for Hypervalent Iodine Reagents Derived from Iodobenzene



(py=pyridine; Tf=CF_3SO_2)

Apart from individual members, reagents of interest are found in several classes; new methods for their preparation have been developed recently, especially for various iodonium salts.[10,11] Some relevant generalised synthetic approaches appear in scheme 2.

Scheme 2

Preparative Approaches for Some Important Classes of 8-I-2 Phenyliodonium Reagents

Ar_2I^+ : from ArH + ArI + oxidant; or $PhIL_2$ + ArH

PhI^+R_f : from C_6H_6 + R_fIL_2

$PhI^+CH{=}CHR$: from silyl or stannyl alkenes + $PhIL_2$

$PhI^+C{\equiv}CR$: from silyl or stannyl alkynes + $PhIL_2$

PhI^+C^-XY : from CH_2XY and $PhIL_2$

$PhI^+N^-SO_2R$: from NH_2SO_2R and $PhIL_2$

(for other dipoles, see text)

It is emphasised that, with few exceptions, most functional groups are compatible with the phenyliodonio functionality. Also, virtually any alkene or terminal alkyne can be converted through a silyl or stannyl derivative to, respectively, alkenyl or alkynyl iodonium salts; even ethylene gave in this way $PhI^+CH{=}CH_2$ TfO^-, whereas acetylene afforded both $PhI^+C{\equiv}CH$ TfO^- and $PhI^+C{\equiv}CI^+Ph$ $2TfO^-$. Non-nucleophilic anions stabilise these rather labile but isolable salts, whereas the much more stable diaryliodonium salts can tolerate almost any anion. The preparation of iodonium salts and some other important reagents will be mentioned as appropriate, along with some reagents prepared *in situ*.

3. Patterns of Reactivity

The prominent feature of iodanes is their ready exchange reactions with nucleophiles, due to the highly electrophilic character of iodine (III) and (V). Even in nucleophilic solvents such as water, alcohols or acids, stable new species incorporating the solvent may be formed and isolated; in other instances mixtures of mono- and bis-substituted non-isolable species are formed, which have a different reactivity from their precursors. Solvent effects are sometimes very pronounced and the solvent itself may arise in the

final product, for example in the reactions of the system $PhI(OAc)_2$ / MeOH / KOH with ketones (section 10.1).

Most reactions involve oxidisable or nucleophilic substrates. The former are usually converted to the expected products, while the latter form intermediates, sometimes isolable, which eventually undergo a variety of transformations. Reactivity is widened when iodanes are used in combination with other reagents, for example in the system $PhICl_2$ / $Pb(SCN)_2$ for aromatic thiocyanation[12] or $PhI(OOCR)_2$ / I_2 /ROH (section 7.2). From a mechanistic point of view, heterolytic pathways are often involved but they are not dominant; in several instances homolytic pathways can also operate, the reactive species being either PhI˙L or L˙. The efficiency of all these reactions is due not only to the highly electrophilic character of iodine, but also to the superleaving group ability of the phenyliodonio group, which in a particular reaction with an alkenyl phenyliodonium salt has been estimated to be 10^6 times greater than the triflate group.[13]

Apart from photochemical methods, with or without co-reagents, catalysis is important in many reactions: Brönsted acids, metal salts and metal complexes may exert a profound effect on reactivity. All these factors extend greatly the usefulness of primary iodine reagents, and eventually an impressive array of new reagents are now available for numerous transformations, some of which are impossible by other means.

Oxidation in its general sense dominates the reactivity of iodanes. It includes oxidative processes such as functionalisation and degradation, and also rearrangements, cyclisations and other less conventional transformations. A remarkable feature observed in several nucleophilic substrates is that they form unstable iodanes, the intermediacy of which brings about a reversal in their reactivity, permitting many interesting reactions. From a practical point of view, most reactions are exceedingly simple. They are usually performed at room temperature, in ordinary solvents, without special precautions for the exclusion of oxygen or humidity. The work up normally involves chromatographic separation and the yields are mostly satisfactory. Iodobenzene is almost always a by-product and is recyclable and environmentally safe.

An idea about reactivity modes and outcomes can be formed from an inspection of the following list, which shows how iodanes may be involved.

Types of reactions

Substitution at sp^3, sp^2 and sp carbon; allylic, nucleophilic, aromatic; transylidation.

Addition to double and triple bonds; elimination.

Ring formation: carbocycles, ethers, amines, lactones, heterocycles; cycloaddition.

Degradation: fragmentation, deprotection, ring-opening, decarboxylation.

Rearrangements: Claisen, Hofmann, Pummerer, Smiles, ring-transformations.

Types of monofunctional substrates undergoing transformation

Alkanes, unsaturated compounds, alcohols, carbonyl compounds, acids, esters, amines, amides, nitriles, oximes, nitroalkanes, sulfur compounds, aromatics, heterocycles, silyl compounds, phosphorus (III) compounds, boranes, organometallics.

Types of products

Simple and functionalised derivatives of alkenes, alkynes, carbonyl compounds, ethers, acids and aromatics; heterocycles, esters, amines, enynes, Diels-Alder products, etc.

Introduction of groups

Halogens, N_3, SCN, OR, SR, SeR, OAc, OSO_2R, $OPO(OR)_2$, vinyl, allyl, alkynyl, perfluoroakyl, aryl, hetaryl.

Intermediates involved

Carbenes, alkylidene carbenes, nitrenes, arynes, dehydrothiophene, aryl oxenium and nitrenium cations, free radicals ($R^{\cdot}$, $RCOO^{\cdot}$, $RCH^{\cdot}OH$, $RO^{\cdot}$, $ArO^{\cdot}$, $Cl^{\cdot}$, $N_3^{\cdot}$, $PhI^{\cdot}Cl$), radical cations, etc.

B. CHEMICAL TRANSFORMATIONS

4. Simple Oxidations

All iodanes are good oxidants and several among them have been used in various types of more or less conventional oxidations, notably $PhICl_2$, PhIO, $PhIO_2$, $PhI(OAc)_2$, $PhI(OOCCF_3)_2$ and PhI(OH)OTs; these reagents can bring about many useful transformations, generally, and specifically oxygenations and dehydrogenations. A limited number of such reactions will be discussed briefly; their selection was based on either novelty or potentially general applicability. An important advantage in choosing iodine reagents is that one

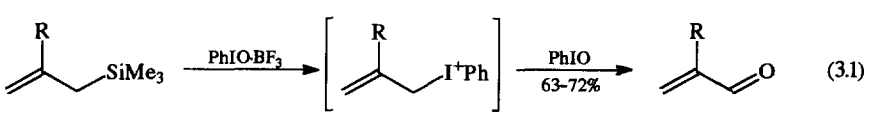
avoids the use of toxic compounds of heavy metals, such as lead, thallium, mercury and chromium, which traditionally have been applied to many analogous reactions. Oxidation modes of alcohols and phenols are discussed separately.

4.1. Oxygenation at carbon

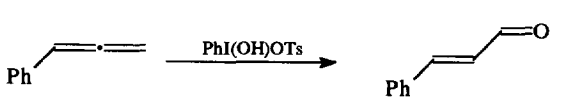
Iodosylbenzene epoxidises electron-deficient olefins such as tetracyanoethylene and ketenes under mild conditions.[14] Ordinary alkenes undergo epoxidation only upon catalysis by metal porphyrins or simple analogues.[1,11,15] Such reactions have revealed many interesting mechanistic and stereochemical features. Some ingeniously-tailored catalysts have high chemo-, regio- and stereoselectivity, but these reactions are hardly of preparative significance. In combination with BF_3 (or sometimes SO_3), and also in water, the reactivity of PhIO is considerably increased and instead of epoxidation it brings about other transformations in alkenes, e.g. cyclohexene was converted by $PhIO.BF_3$ to formylcyclopentane, in 60% yield.[16]

A general method for the preparation of allylic aldehydes (propenals) was based on the oxidation of allylsilanes with two equivalents of $PhIO.BF_3$ (eq. 3. 1) ; in this reaction PhIO reacts first as an iodine electrophile and then as an oxygen nucleophile. Allyliodonium intermediates are initially formed serving as allylic cations which are attacked nucleophilically by PhIO. The side-chain alkyl may contain a double bond which remains unaffected; also, no allylic rearrangement takes place.[17]Propenals were also formed from phenylated allenes, in their reaction with PhI(OH)OTs. The same reagent converted 1-alkoxyallenes to 2-alkoxy-3-tosyloxypropanals; these substrates with $PhI(OAc)_2$ were transformed to 3-acetoxy-3-alkoxypropynes.[18]

Scheme 3



(3.1)



(3.2)

$$RCH{=}CHCH_2R \xrightarrow[(2\text{-}pySe)_2\ (cat.)]{PhIO_2} RCH{=}CHCOR \qquad (3.3)$$

Allylic ketones were formed from several olefins, such as *trans*-5-decene, β-pinene and geraniol acetate upon oxidation with $PhIO_2$ catalysed by 2,2'-dipyridyl diselenide, in refluxing benzene (eq. 3.3). The mechanism of this useful transformation involves the intermediacy of 2-pyridylseleninic anhydride which was the actual oxidising species.[19]

Alkynes are reactive towards iodanes and give different products, depending on reagents and conditions. For instance, upon heating in methanolic PhI(OH)OTs, they underwent oxidative rearrangement to furnish methyl carboxylates (eq. 4 .1).[20] Terminal alkynes were transformed to α-hydroxyketones by $PhI(OOCCF_3)_2$ in refluxing aqueous acetonitrile (eq. 4.2).[21] Other alkynes were converted to α-diketones by the same reagent;[22] functionalised alkynes were similarly transformed to α-diketo derivatives, at room temperature, using PhIO which becomes a strong oxidant with ruthenium catalysis (eq. 4.3).[23]

Scheme 4

$$PhC{\equiv}CMe \xrightarrow[\substack{MeOH,\ \Delta \\ 66\%}]{PhI(OH)OTs} PhCH(Me)COOMe \qquad (4.1)$$

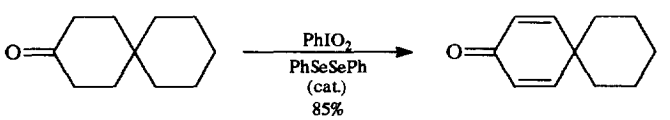
$$RC{\equiv}CH \xrightarrow[aq.\ MeCN,\ \Delta]{PhI(OOCCF_3)_2} RCOCH_2OH \qquad (4.2)$$

$$RC{\equiv}CNR_2 \xrightarrow[RuCl_2(Ph_3P)_3,\ (cat.)]{PhIO} RCOCONR_2 \qquad (4.3)$$

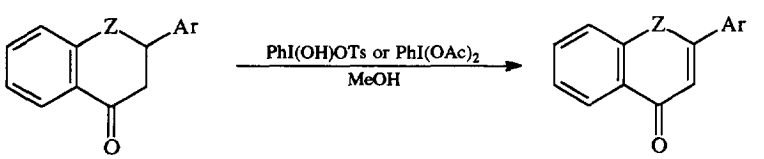
4.2. Dehydrogenation

Dehydrogenations, especially from two carbon atoms or one carbon and one heteroatom, are of considerable importance. Steroidal ketones and other cyclic keto substrates were efficiently converted to 1,4-dien-3-ones[24] by benzeneseleninic anhydride, generated *in situ* from $PhIO_2$ and PhSeSePh (an example is shown in eq. 5.1). The use of 3-iodylbenzoic acid, instead of $PhIO_2$, was preferable because its reduction product (3-iodobenzoic acid) is easily recovered; with this reagent chromatographic separation is avoided. Flavanones upon reaction with PhI(OH)OTs in methanol afforded similarly dehydrogenated products, i.e. flavones;[25] a similar dehydrogenation occurred in 2-aryl-tetrahydroquinolones[26] when treated with $PhI(OAc)_2$ in methanolic KOH (eq. 5.2). In contrast, flavanones and thioflavanones under such conditions were converted to α-hydroxy dimethyl acetals[27] (see also section 10.1). An intermolecular dehydrogenation occurred in the dimerisation of 5-alkyl-isopropylidene malonates (Meldrum's acid derivatives) by $PhI(OAc)_2$.[28]

Scheme 5



(5.1)

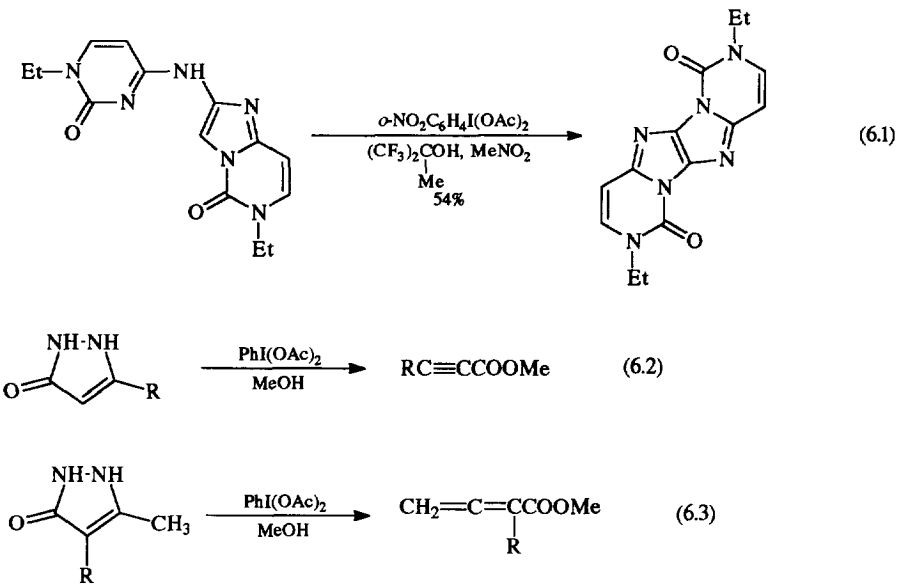


(5.2)

(Z=O or NH)

Several intramolecular cyclisations involving carbon-nitrogen bond formation were realised uniquely through $PhI(OAc)_2$ or its 2-nitro-analogue in non-nucleophilic solvents. Typical substrates were 2° amines in which their nitrogen was linked to two *N*-containing rings, as exemplified in eq. 6. 1.[29] Generally, dehydrogenation in compounds with N-H bonds is very easy. Many reactions of this kind were successfully performed using various iodanes;[1] simple examples can be found in sections 10.4 and 15.1. More unusual was the fragmentation of two types of pyrazolone derivatives: this was accompanied by loss of dinitrogen and solvent participation, resulting in the formation of acetylenic or allenic esters (eqs. 6.2 and 6.3).[30]

Scheme 6



5. Transformations of Alkenes

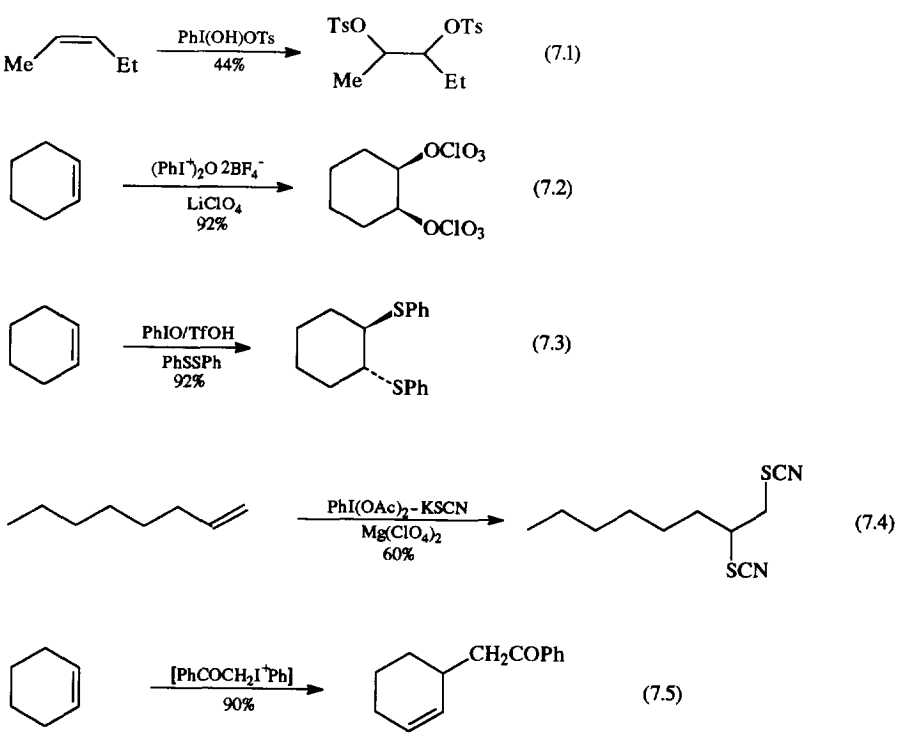
In addition to the oxygenation reactions already mentioned, and also azidation, cyclopropanation and aziridination (sections 9.1, 13.1 and 13.2), alkenes afford a variety of products with iodine reagents, either alone or in combination with nucleophiles. Simple substrates undergo addition which may be followed by elimination; in functionalised alkenes subsequent cyclisation or rearrangement may also occur. Vinylic substitution is another important transformation effected through the intermediacy of isolable alkenyl iodonium salts.

5.1. Addition to alkenes and dienes

The two ligands L of iodanes $PhIL_2$ are often added to the double bond, notably chlorine and trifluoroacetoxy groups (but not acetoxy) to give mainly *trans*-adducts. An exception is the stereoselective *cis*-addition of two tosyloxy groups coming from PhI(OH)OTs; for example, *cis*-2-pentene was converted to *erythro(dl)*-2,3-bis(tosyloxy)pentane (eq. 7.1), in an ionic reaction involving probably a cyclic iodonium intermediate and requiring two equivalents of reagent.[31] Alternatively, and more efficiently, *cis*-addition was effected using Zefirov's reagent, i.e. PhI(OTf)OI(OTf)Ph; for example, *cis*-1,2-bis-trifyloxycyclohexane was obtained from cyclohexene in 60% yield and 99%

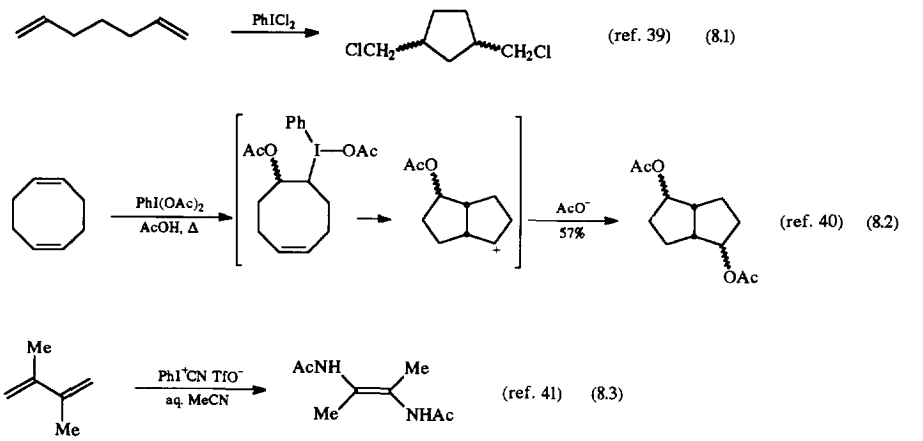
stereoselectivity.[32] Similar μ-compounds of the general formula $(PhI^{+})_2O\ 2X^{-}$ (X= BF_4, PF_6, SbF_6) in presence of external nucleophiles such as methanol, acetic acid and even lithium perchlorate gave also *cis*-adducts (eq. 7.2).[33] Addition to alkenes of other nucleophiles proceeded also successfully through either iodanes formed *in situ* or free radicals. In the first mode, the combination of PhIO and triflic acid and then PhSSPh yielded the trans-adduct with cyclohexene (eq. 7.3).[34] Thiocyanation of electron-rich olefins by $PhI(OAc)_2$ and KSCN in acetonitrile, *via* a radical process, resulted in the formation of 1:1 mixtures of *cis*-and *trans*-adducts.[35] Olefins such as 1-octene and cyclohexene gave no reaction; however, in presence of $Mg(ClO_4)_2$ or the stable free radical TEMPO (2, 2, 6, 6-tetramethyl-piperidine-*N*-oxyl) good yields of the appropriate adducts were obtained (eq. 7.4). Phenylated alkenes afforded mostly rearranged products with iodanes. For example, styrene upon treatment with PhIO in acidified methanol was transformed[36] to $PhCH_2CH(OMe)_2$, whereas with *p*-$ClC_6H_4IF_2$ it gave $PhCH_2CHF_2$.[37] Addition followed by elimination occurred when the unstable $PhI^{+}CH_2COCH_3$ (formed *in situ* from $PhC(OSiMe_3)=CH_2$ and PhIO) reacted with alkenes (eq. 7.5).[38]

Scheme 7



Additions to dienes can lead to interesting transformations; some of them,[39-41] apart from the expected chlorination and acetoxylation are illustrated in

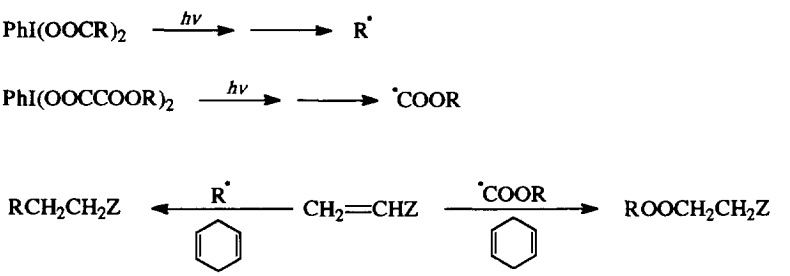
Scheme 8



5.2. Addition to electron-deficient or functionalised alkenes

Electron-deficient alkenes such as methyl acrylate and phenyl vinyl sulfone, undergo an interesting type of addition upon photochemical treatment with a range of [bis(acyloxy)iodo]benzenes, coming from either simple acids, of the general formula $PhI(OOCR)_2$, or from half-esters of oxalic acid, i.e. $PhI(OOCCOOR)_2$. These reagents produced free radicals, either R· or ·COOR, respectively, which in presence of a hydrogen donor such as 1,4-cyclohexadiene reacted with olefins to furnish reductive addition products[42] (scheme 9).

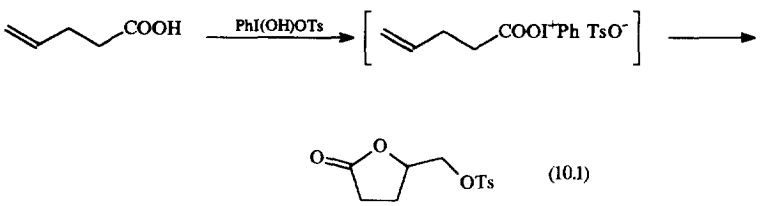
Scheme 9



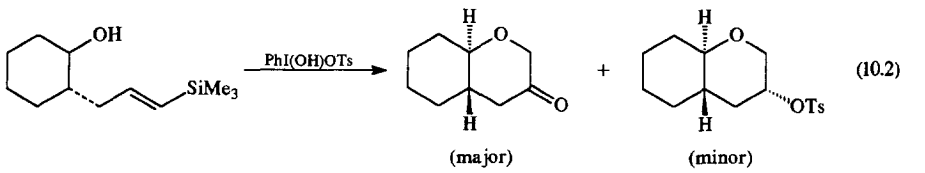
(R = ethyl, 1-adamantyl, cyclohexyl, 2-phenylethyl, (-)-menthyl, etc.
(Z = S(O)Ph, $S(O)_2Ph$, COOMe, $PO(OEt)_2$)

Unsaturated acids[43] reacted with PhI(OH)OTs affording mainly tosyloxylated lactones; here the hydroxyl function participates first in an exchange reaction, followed by intramolecular attack from the double bond and final combination with the tosyloxy group (eq. 10.1). Silyl-substituted δ, ε-unsaturated cyclohexanols[44] gave with PhI(OH)OTs two products, a pyranone and a tosyloxy-tetrahydropyran (eq. 10.2) with a vinyliodonium species being probably the key intermediate.

Scheme 10



(10.1)



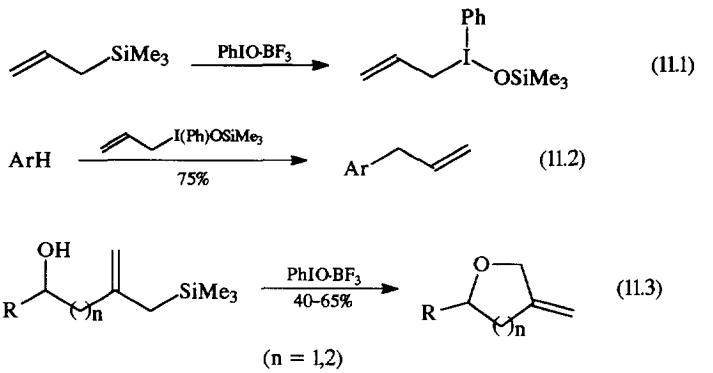
(major) (minor)

(10.2)

5.3. Transfer of the allyl group

The reaction of allyltrimethylsilane with $PhIO.BF_3$ is believed to form a reactive intermediate (eq. 11.1) which behaves as an allyl cation equivalent. This umpolung of reactivity has synthetic implications, as for instance the Friedel-Crafts allylation of electron-rich aromatics (eq. 11.2).[45] Also, oxygen nucleophiles such as alcohols or carboxylic acids react readily with this intermediate furnishing allyl ethers or esters. Hydroxy allylsilanes underwent intramolecular cyclisation upon reaction with $PhIO.BF_3$ to afford 5- or 6-membered β-methylene cyclic ethers (eq. 11.3).[46] It is of interest to note that allyltrimethylsilane in its reaction with "PhI^+CH_2COPh" transfered the allyl group as an anion, producing the unsaturated ketone $CH_2{=}CHCH_2CH_2COPh$, in 63% yield.[38] Reactions of alkenes and allylsilanes with iodine reagents in combination with azido compounds are discussed separately in section 9.

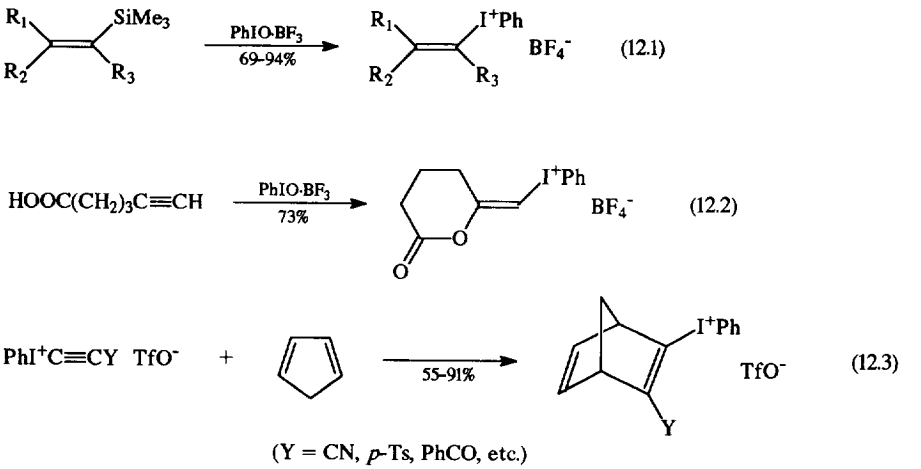
Scheme 11



5.4.Transformations through alkenyl iodonium salts

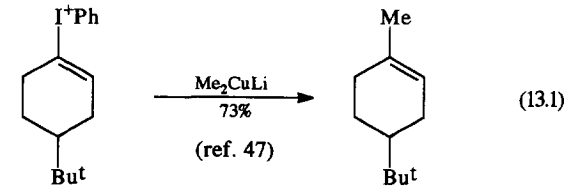
Alkenes undergo many interesting transformations through alkenyl phenyliodonium salts. These reactive compounds may be considered as vinyl cation equivalents and/or vinylidene carbene precursors. Indeed, nucleophilic vinylic substitution and 1,1-elimination dominate their reactivity. The simplest way to prepare alkenyl iodonium salts is *via* alkenylsilanes and $PhIO.BF_3$; the products are formed stereospecifically (eq. 12.1).[47] Stannylated alkenes are sometimes preferable; for example,[48] $PhI^+CH{=}CH_2$ TfO^- was obtained from $CH_2{=}CHSnBu_3$ and PhI^+CN TfO^-. Functionalised olefins, such as methyl 3-aminocrotonate[49] and 2-amino-1,4-naphthoquinone,[50] afforded iodonium salts directly with PhI(OH)OTs. Other approaches involved addition to the triple bond of alkynes or alkynyl iodonium salts. For instance, 4- and 5-alkynoic acids upon treatment with $PhIO.BF_3$ afforded lactonic iodonium salts[51] (eq. 12.2), whereas several alkenyl mono- and bis-phenyliodonium salts were obtained through 1,3-dipolar or Diels-Alder cycloadditions,[52] as exemplified in eq. 12.3.

Scheme 12

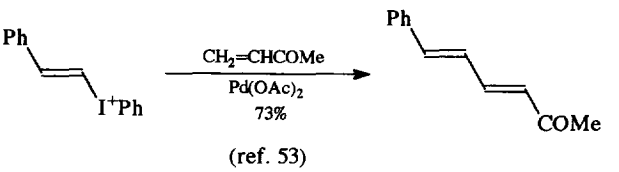


Nucleophilic vinylic substitution in alkenyl iodonium salts served for the synthesis of many alkenes, dienes and enynes or enediynes, under milder conditions than those needed for vinyl iodides. Carbon nucleophiles of various types were used for the transfer of alkyl,[47] alkenyl,[53,54] alkynyl[55,56] and aryl[47] group, several of which were organometallics. Alkenes and alkynes reacted in a similar fashion, with palladium catalysis. Such reactions, some of which are illustrated in scheme 13, proceeded with a high degree of stereoselectivity. In an analogous way, intramolecular cyclisation in several arylalkenyl iodonium salts of the general formula $PhI^{+}CH{=}CHCH_2CH_2Ar\ BF_4^-$ occurred upon gentle heating, providing access to dihydronaphthalenes.[57]

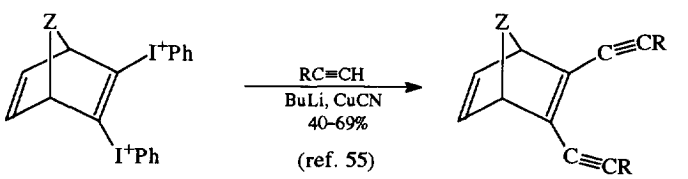
Scheme 13



(13.1)



(13.2)



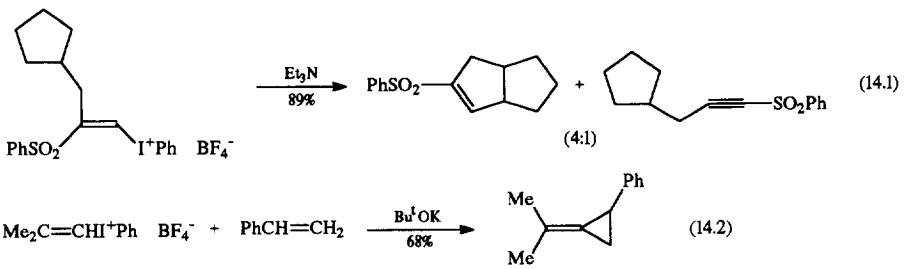
(13.3)

(Z = CH_2, O)

Other nucleophiles[47,58,59,60] which underwent alkenylation through alkenyl iodonium salts were NO_2^-, $ArSO_2^-$, and halides. Depending on the conditions, haloalkenes produced from *E*-alkenyl precursors were either in the *Z*-(with Bu_4NX) or in the *E*- (with CuX and KX) configuration.

The second major pathway in the reactions of alkenyl iodonium salts involves base-induced α-elimination of hydrogen and iodobenzene, with generation of alkylidene carbenes, $R_2C{=}C{:}$. A prominent feature of these species is intramolecular 1,5- carbon-hydrogen insertion leading to cyclopentenes or 5-membered heterocycles from appropriate precursors. A competing pathway is rearrangement to alkynes,[61] as illustrated in eq. 14.1. In some favourable cases alkynes were formed exclusively. Alkylidene carbenes can also add to ethylenic double bonds, as exemplified[62] in the reaction between styrene and $Me_2C{=}CHI^+Ph\ BF_4^-$, in presence of *t*-BuOK (eq. 14.2).

Scheme 14



More reactions with akylidene carbenes generated from akynyl iodonium salts are described in next section.

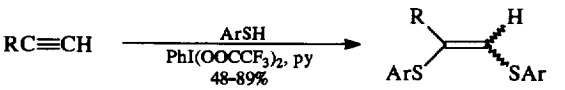
6. Transformations of Alkynes

Apart from oxygenation reactions, already discussed, alkynes undergo a plethora of transformations by iodine reagents, including addition, substitution and some rearrangements. Most of these reactions often involve isolable alkynyl phenyliodonium salts.

6.1 Additions, substitutions and rearrangements

Addition of chlorine to the triple bond is efficiently performed using $PhICl_2$, under photochemical conditions; *trans*-1,2-dichloroalkenes are thus produced with good stereoselectivity in high yield.[63] Another addition involved terminal alkynes which with 2, 3, 5, 6-tetrafluorothiophenol in presence of $PhI(OOCCF_3)_2$ and pyridine afforded mixtures of *E, Z*-adducts (eq. 15.1).[64] The reaction is thought to proceed through unstable $PhI(SAr)_2$, with formation of either alkenyl or alkynyl iodonium intermediates. Terminal alkynes can also give substitution products through non-isolable alkynyl iodonium salts; for example, with PhSeSePh and $PhI(OAc)_2$ alkynyl phenyl selenides were produced in varying yield (15-81%).[65] Alkynyl phosphates, $RC{\equiv}COPO(OR)_2$, could be obtained using $PhI^+(OH)[(PhO)_2POO^-]$, although esters of 1-alkynols generally are prepared more conveniently from isolable alkynyl iodonium salts.[66] 1-Alkynes and 1-stannylated alkynes may also react with alkenyl and alkynyl iodonium salts affording various unsaturated compounds (sections 5.4 and 6.2).

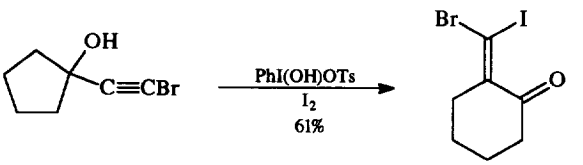
Scheme 15



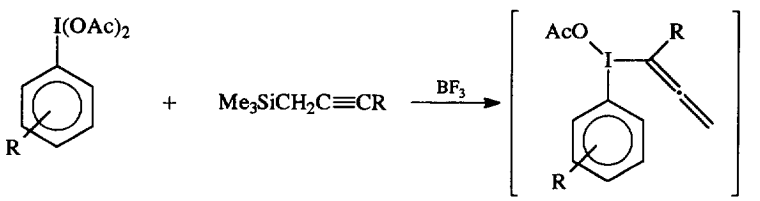
(15.1)

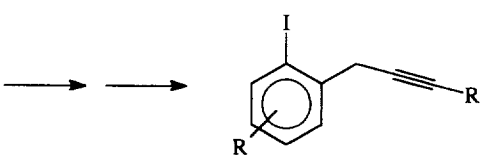
(R = C_6H_{13}, Ph, OEt, SPh, etc.; E : Z = 43-98 : 57-2)

(Ar = 2,3,5,6-tetrafluorophenyl)



(15.2)





(15.3)

A group of alkynols exhibited interesting reactivity both from mechanistic and synthetic viewpoint, in reactions involving PhI(OH)OTs, either in stoichiometric or catalytic quantities. The products were olefinic iodocarbonyl compounds of considerable structural diversity; an example is shown in eq. 15.2.[67] Alkynes of various types upon heating with methanolic PhI(OH)OTs underwent oxidative rearrangement, with solvent participation, affording methyl carboxylates (eq. 4.1).[20] A different rearrangement in which the triple bond was regenerated occurred in propargylsilanes; their treatment with $PhI(OAc)_2$ (or some ring-substituted analogues) led through unstable allenyl intermediates to *o*-iodopropargylarenes (eq. 15.3). Similar reactivity was shown by various iodosylarenes, ArIO, including the cyclic "2-iodosylbenzoic acid"; the latter was transformed to 3-propargyl-2-iodobenzoic acids. These reactions constitute a type of reductive iodonio-Claisen rearrangement of the allenyl

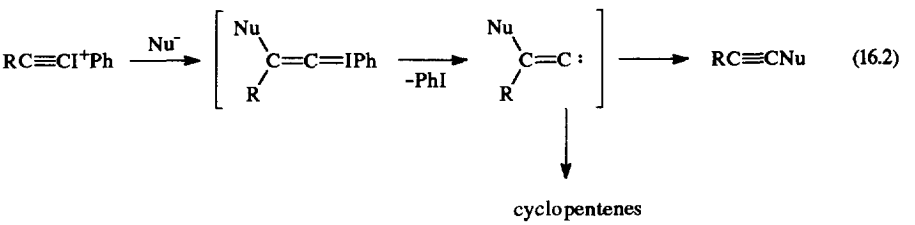
intermediates.[68] In some instances deviations were noted, resulting in the formation of *ipso*-substitution products; for example, the 2,6-dimethyl-4-methoxy analogue of $PhI(OAc)_2$ was transformed to 1-propargyl-2,6-dimethyl-4-methoxybenzene.[69] Degradation of alkynes with cleavage of the triple bond and formation of acids occurred upon heating them with $C_6F_5I(OOCCF_3)_2$ in benzene-water.[70]

6.2. Reactions through alkynyl iodonium salts

Most terminal alkynes, including acetylene and many of its monofunctionalised derivatives, have been converted to alkynyliodonium salts. For best results the use of 1-silyl- or stannylalkynes is preferable; these upon reaction with $PhIO.BF_3$ are cleanly converted to alkynyl iodonium salts, which are usually obtained as tosylates[66] or triflates[3] (eq. 16.1). The group R, apart from hydrogen, alkyl and aryl, can be also Me_3Si, CN, Cl, PhCO, Ts, etc.[71] In some cases only stannylated alkynes gave satisfactory results, in combination with $PhI^+CN\ TfO^-$, for example for the preparation of bis phenyliodonium salts $PhI^+C{\equiv}CI^+Ph\ 2TfO^-$[72] and 1,4-$(RC{\equiv}C)_2C_6H_4\ 2TfO^-$.[73]

Scheme 16

$$RC{\equiv}CSiMe_3 \xrightarrow[2.\ TsONa]{1.\ PhIO{\cdot}BF_3} RC{\equiv}CI^+Ph\ TsO^- \qquad (16.1)$$



The reactivity pattern of alkynyl iodonium salts is of particular interest, since they constitute strong electrophiles with tetraphilic character: in their reactions with nucleophiles both *sp* carbons, iodine and *ipso* carbon of the phenyl ring may be attacked. Also, they serve as good dienophiles and 1,3-dipolarophiles.[3] The great majority of useful transformations involve nucleophilic attack at β-*sp* C; the allenic intermediate initially formed expels iodobenzene and a vinylidene carbene is generated; this either cyclises to cyclopentene derivatives or rearranges to alkynyl derivatives, so that eventually all terminal alkynes through this umpolung may furnish a great variety of alkynyl compounds (eq. 16.2). Several carbon, oxygen, sulfur, nitrogen, phosphorus and arsenic

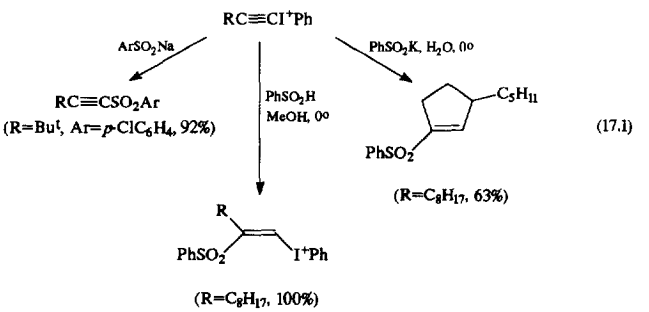
nucleophiles, some of which appear below, have undergone alkynylation in this way. It is worth noting that the various alkynoic esters were not previously known and they are prepared uniquely through alkynyl iodonium salts.

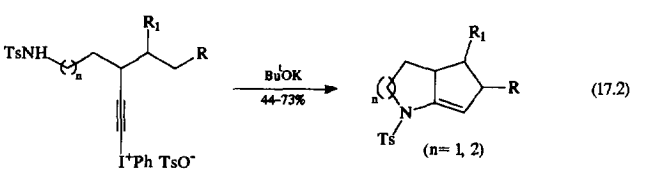
Nucleophiles in substitution reactions with alkynyl iodonium salts

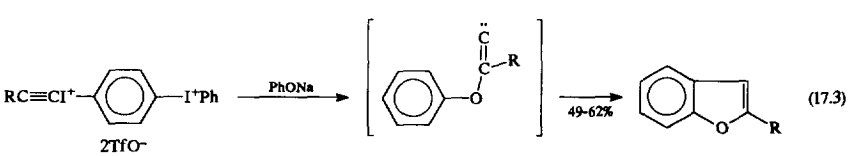
$(RCH{=}CH)_2CuLi$,[74] $(RC{\equiv}C)_2CuLi$,[75] CO and ROH,[76] $PhC(OSiMe_3){=}CH_2$,[72] $ArCOONa$,[66] $PhOLi$,[72] $KSCN$,[77] $ArSO_2Na$,[78-80] Ph_2NLi,[81] Ph_3P,[82] $(MeO)_3P$,[83] Ph_3As.[84]

The reaction of sulfinic salts or their free acids is of interest, since it may lead to substitution, addition or annulation. Depending on the substrates and the conditions, alkynyl sulfones, *Z*-β-phenylsulfonyl-alkenyliodonium salts or cyclopentenyl sulfones are formed, as illustrated in eq. 17.1. Among carbon nucleophiles, not listed above, are β-diketones,[85] β-ketoesters,[85] malonates,[86] nitrocyclohexane,[85] etc. With compounds such as β-$PhCOCH_2SO_2Ph$, and the appropriate alkynyl iodonium salt, furan derivatives may also be formed. Some nucleophiles under suitable conditions bring about addition rather than substitution; for example, Ph_3P with $RC{\equiv}CI^+Ph$ gave the expected substitution product[82] but with $PhI^+C{\equiv}CI^+Ph$ it afforded the adduct[72] *E*-$Ph_3P^+CH{=}CHP^+Ph_3$ 2 TfO^-.

Scheme 17







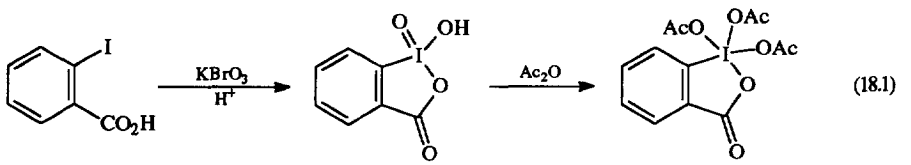
Generally, competition between the alkyl groups of the alkynyl iodonium salt and those of the nucleophile may lead to the formation of two cyclopentenes. The tandem reactions of some tosylamino alkynyl iodonium salts with *t*-BuOK served as a good approach for the synthesis of bicyclic tosyl enamides: initial attack from N to β-sp C resulted in the generation of a heterocyclic alkylidene carbene which subsequently underwent annulation (eq. 17.2).[87] Another interesting reaction was reported between alkynyl (*p*-phenylene) bis iodonium triflates and sodium phenoxide: here the alkylidene carbene underwent preferably aromatic 1,5- C-H insertion resulting in the formation of benzofurans (eq. 17.3).[88] A related reaction between $Ar_2C(OH)C{\equiv}CI^+Ph\ TfO^-$ and *p*-$TolSO_2Na$ afforded indenes.[89]

7. Oxidation of Alcohols

7.1. Oxidation to carbonyl compounds

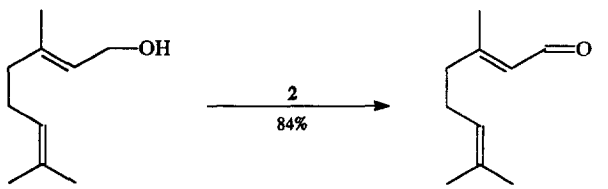
Several iodine reagents oxidise alcohols to carbonyl compounds, under various conditions. Among them, Dess-Martin reagent, **2**, is by far superior; introduced in 1983, it has become one of the best oxidants presently available. It is readily prepared from 2-iodobenzoic acid in a two-step procedure involving its initial oxidation to the isolable **1**, often called 2-iodylbenzoic acid, and subsequent reaction with acetic anhydride (eq. 18.1).[90,91] This reagent oxidises equally effectively and cleanly 1° and 2° alcohols to aldehydes and ketones, at room temperature. It is compatible with many oxidisable groups, as illustrated in the examples of scheme 18.

Scheme 18

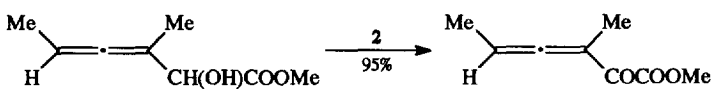


(18.1)

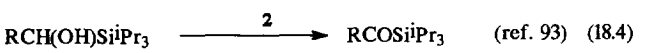
1 2



(ref. 91) (18.2)



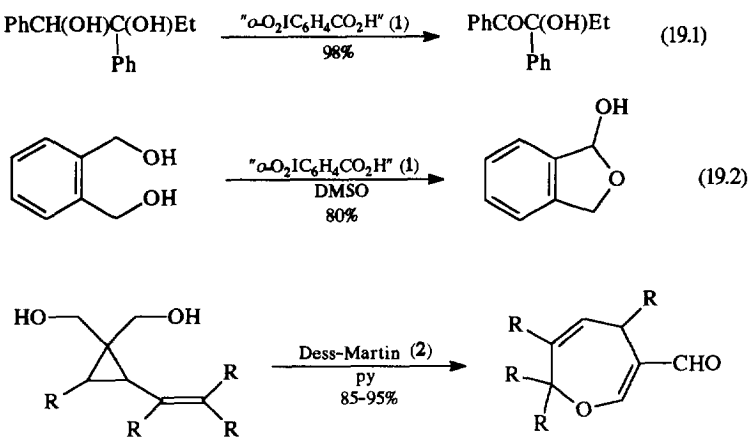
(ref. 92) (18.3)



(ref. 93) (18.4)

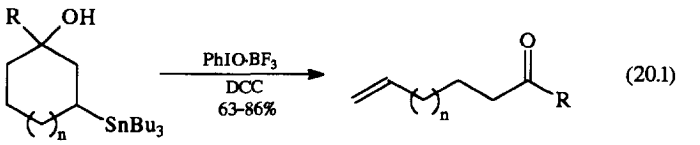
High yields were normally obtained even in multifunctional intermediates during numerous natural products syntheses. In a few cases, though, erratic results were reported. These led to a detailed investigation of the reaction, including the improved preparation of **1** and **2**; the conclusion was that small amounts of water are beneficial, increasing yields and decreasing reaction time; the active species is actually the partially hydrolysed **2**, or acetoxylated **1**, i.e. 1-oxo-1-acetoxy-benziodoxole.[91] Compound **1** in some instances was a better alternative to **2**. Its main applications involved two special oxidations: the first was the conversion of 1,2-diols to α-ketols or α-diketones, without the usual cleavage of the glycol C-C bond (eq. 19.1);[94] the other was the selective conversion of 1,4-diols such as 1,2-bis-hydroxymethylbenzene to cyclic hemiacetals (eq. 19.2).[95]

Scheme 19



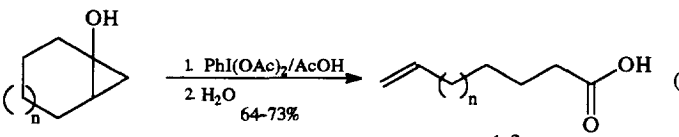
1,-3 Propanediols bearing a 2-(2-vinylcyclopropyl) moiety, and also some related substrates in which a hydroxymethyl group was replaced by a cyano or phenylsulfonyl group, underwent by **2** oxidation accompanied by ring expansion to afford 3-formyl-dihydro-oxepins (eq. 19.3).[96] Further oxidations using **2** included β-hydroxycarbonyl-, α-phenylthio-β-carbonyl- and β-dicarbonyl compounds which were converted to 1, 2, 3-triketones.[97] Iodosylbenzene in combination with equimolecular quantities of $BF_3.Et_2O$ and DCC is an efficient reagent for the oxidative fragmentationn of cyclic γ-stannylated alcohols, as illustrated in eq. 20.1; the substrates are readily available from 2-unsaturated cycloalkanones. This variation of Grob's fragmentation proceeded stereospecifically, where appropriate, through an O-I intermediate.[98] Bicyclic alcohols having either a free or, better, a silylated hydroxyl at the bridgehead of a bicyclo [n.1.0] skeleton (n= 1, 2, 3) were efficiently converted by $PhI(OAc)_2$ in acetic acid to mixed anhydrides which hydrolysed to alkenoic acids, as exemplified in eq. 20.2.[99] By contrast, 1-silyloxy-bicyclo[n.1.0] alkanes (n=4-7) upon treatment with PhIO followed by Bu_4NF gave mixtures of cyclic unsaturated ketones.[100] Apparently, a common pathway operates in both cases involving C-I intermediates and cleavage of either one or two C-C bonds in the cyclopropane ring.

Scheme 20



(20.1)

(n = 1, 2; R = H, alkyl, phenyl)



(20.2)

n = 1-3

Alcohols react generally with iodine (III) or (V) reagents affording initially alkoxy iodanes; these intermediates are sometimes observable by NMR. Methanol under anhydrous conditions causes depolymerisation of PhIO with formation of the isolable $PhI(OMe)_2$.[101] This compound is mildly explosive but it can safely be used when generate *in situ*. It has been used for the preparation of some iodonium-nitrogen ylides.[102]

7.2 Oxidation through alkoxy radicals

Oxidation of alcohols to alkoxy free radicals is effected very efficiently using iodine reagents; in numerous substrates cyclisation with functionalisation at an sp^3 carbon atom and/or fragmentation follow. The best reagent for these transformations is $PhI(OAc)_2$ and elemental iodine, under photochemical conditions (Suarez reagent).[103] The initially formed acetyl hypoiodite converts alcohols to alkyl hypoiodites and these upon irradiation with visible light generate the alkoxy radicals (scheme 21).

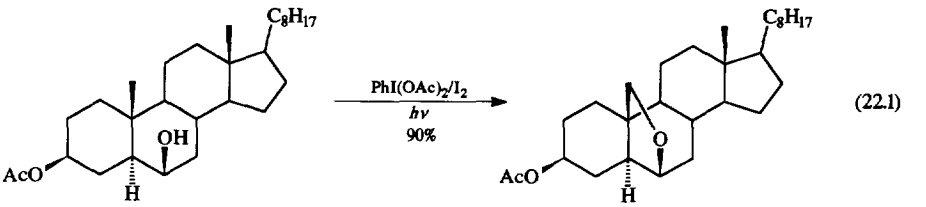
Scheme 21

$$PhI(OAc)_2 + I_2 \longrightarrow PhI + 2AcOI$$

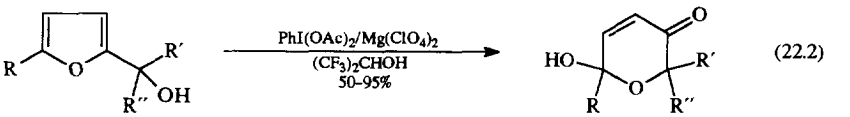
$$AcOI + ROH \longrightarrow AcOH + ROI$$

$$ROI \xrightarrow{h\nu} RO^{\bullet} + I^{\bullet}$$

Scheme 22



(22.1)



(22.2)

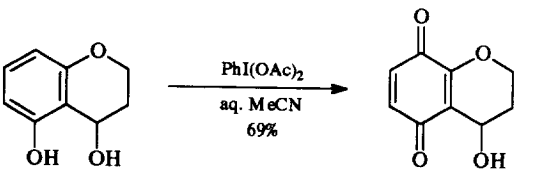
Alkoxy radicals generated in this way have been used for remote functionalisation by intramolecular abstraction of a hydrogen atom resulting in the formation of cyclic ethers (eq. 22.1).[104] In some instances unexpected products were obtained, especially with steroidal substrates and complex alcohols related to natural products. When reactions of lactols were performed in presence of oxygen, fragmentation prevailed, with formation of peroxylactones. Cyclisation was extended to nitrogen-containing steroids such as cyanamides and lactams which afforded *N*-substituted pyrrolidines.[1] A different type of reactivity in simple alcohols involved the generation of carbon-centered free radicals, as discussed in the section of azide functionality. Oxidative fragmentation has also been effected using either $PhI(OAc)_2$ or PhIO and iodine under non-photochemical conditions; examples of this reactivity can be found in some unusual transformations of carbohydrates (section 14). The oxidation of several 2-furyl alcohols, 2° and 3°, using a combination of $PhI(OAc)_2$ and $Mg(ClO_4)_2$ proceeded through alkoxy free radicals and was accompanied by ring expansion, affording eventually pyran-2(6*H*)-ones.[105] Best yields, up to 99%, were obtained in $(CF_3)_2CHOH$ but moist acetonitrile was sometimes equally satisfactory, at pH 7. In this solvent the use of another iodine reagent, [bis(pyridinium)iodo]benzene triflate,[106] resulted in excellent results concerning reaction time and yield (eq. 22.2).[107] Similar improvements can be achieved by changing anumber of variables: variations either in the substitution of the benzene ring or in the ligands attached to iodine, in combination with changes of solvents, can often bring about substantial improvements, or even a complete change of the reaction outcome.

8. Phenolic Oxidation

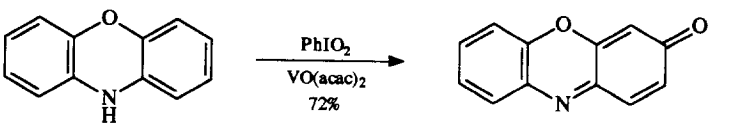
8.1 Oxidation to quinones

A great deal of work has been done in the field of phenolic oxidation using specifically either $PhI(OAc)_2$ or $PhI(OOCCF_3)_2$. Although the latter is a stronger oxidant, better results were often obtained with the former, for example, in oxygenation reactions such as the conversion of various phenols to 1,4-benzoquinones[108] (eq. 23.1). Oxygenation of phenothiazines and related systems to quinone imines,[109] however, was effected using $PhIO_2$ and catalysis by $VO(acac)_2$ (eq. 23.2).

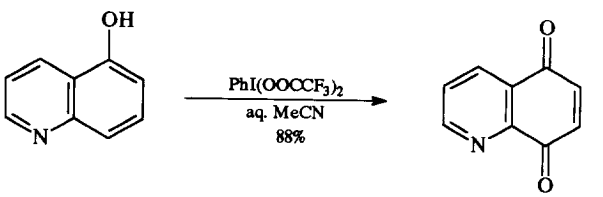
Scheme 23



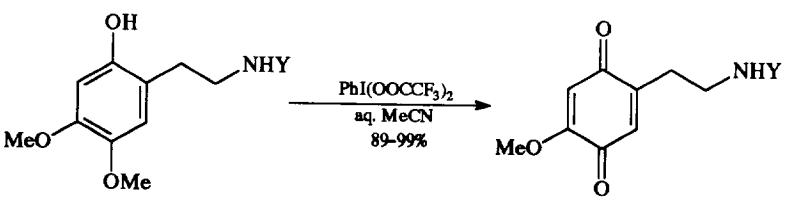
(23.1)



(23.2)



(23.3)



(23.4)

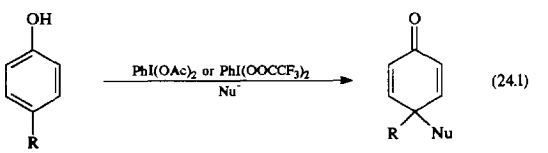
For dehydrogenations of 1,4-dihydrobenzene derivatives to 1,4-benzoquinones, $PhI(OOCCF_3)_2$ was the reagent of choice, where other oxidants failed.[1] The same is true for the conversion of naphthols and naphthylamines to 1,4-naphthoquinones; this transformation was extended successfully to various hydroxy- and aminoquinolines and isoquinolines (eq. 23.3).[110] It is worth noting that a 4-aminoindole derivative was efficiently oxidised in this way to an

indolo *p*-quinone (a mitomycin C analogue).[111] Similar reactivity was noted with more complex derivatives of *p*-alkoxyphenols (eq. 23.4).[112]

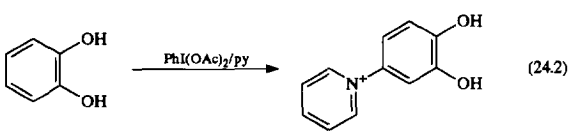
8.2. Oxidations accompanied by bond formation

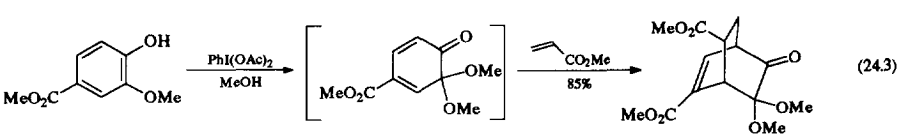
Oxidative pathways with important synthetic applications involve reactions accompanied mainly by inter- or intramolecular carbon-oxygen or carbon-carbon bond formation. Several 4-alkyl-phenols in nucleophilic solvents were converted in this way to quinols[113] (with water) or quinol ethers[114] (with alcohols); also, quinol acetals were obtained from 4-alkoxyphenols and $PhI(OAc)_2$ or $PhI(OOCCF_3)_2$. A related reaction with pyridinium polyhydrogen fluoride afforded 4-fluoroderivatives (eq. 24.1).[115] *O*-Silylated phenols were shown to be better substrates in these reactions.[113]

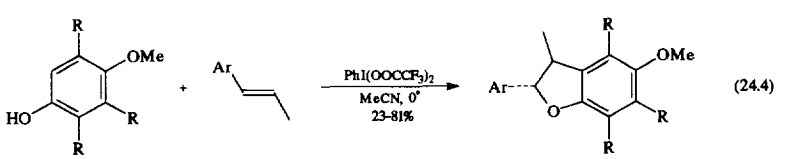
Scheme 24



(R=alkyl or alkoxy; Nu=HO, RO, F)





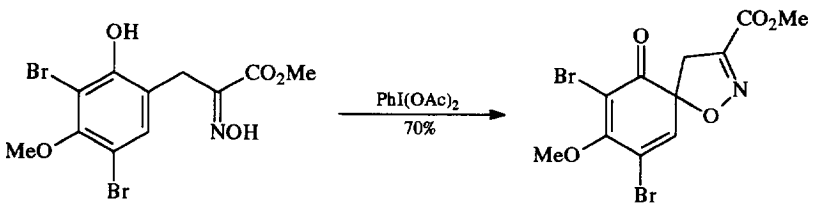


Pyrocatechol[116] and diethyl hydroquinone-2,5-dicarboxylate[117] upon reaction with, respectively, $PhI(OAc)_2$ and $PhI(OOCCF_3)_2$ in pyridine, gave 4-(*N*-pyridinio)pyrocatechol or hydroquinone derivatives, either as betains or as salts (eq. 24.2). 1,2-Benzoquinone acetals, prepared *in situ* from suitable precursors such as methyl vanillate, served as reactive 1,3-dienes in Diels-Alder reactions[118]

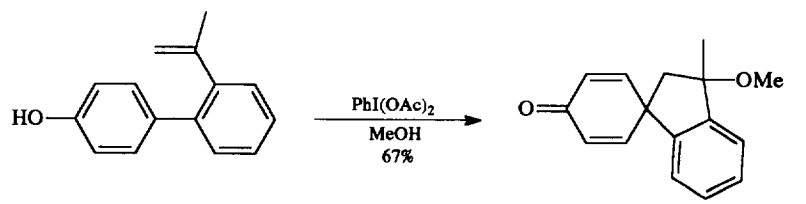
(eq. 24.3). Other quinone acetals, also formed *in situ*, afforded hydroxyanthraquinones on reaction with 3-cyanophthalide.[119] 4-Methoxyphenols and styrene or propenylbenzenes upon oxidation with $PhI(OOCCF_3)_2$ afforded dihydrobenzofuran derivatives (eq. 24.4).[120]

Intramolecular reactions of similar type involved carbon-carbon or carbon-oxygen bond formation. Substrates such as *N*-acetyltyramines and oxime derivatives were transformed to spiro derivatives with a C-O bond, as exemplified in eq. 25.1.[121] Spiroannulation with C-C bond formation occurred in some 4-hydroxy-2-alkenyl-biphenyls (eq. 25.2).[122] Exceptionally good results were obtained from *O*-silylated phenols bearing an aminoquinone moiety at 4-position (eq. 25.3); those having the same moiety at *C*-3 afforded phenolic products containing a 2,3-dihydro-1*H*-azepine ring.[123]

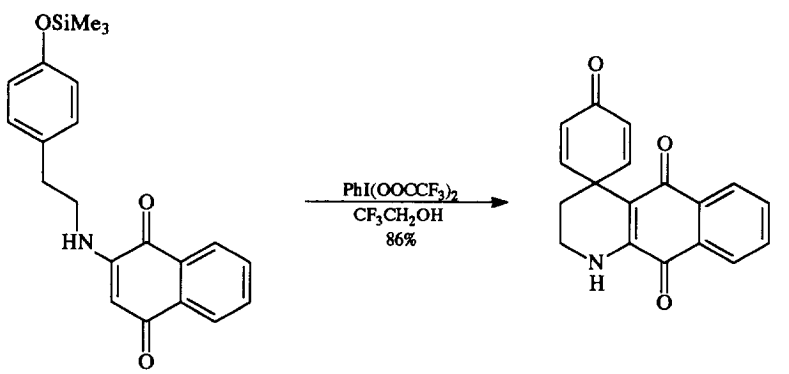
Scheme 25



(25.1)



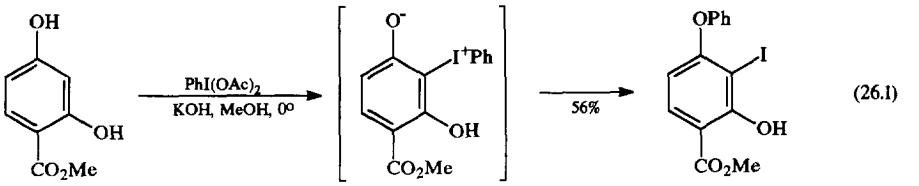
(25.2)



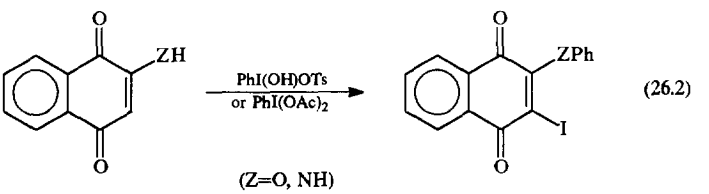
(25.3)

Phenols with strong electron-withdrawing groups undergo a different transformation upon reaction with $PhI(OAc)_2$ or $PhI(OOCCF_3)_2$: they are first converted to isolable phenyliodonium zwitterions or salts which rearrange spontaneously[124] or thermally[125] to iodo-diaryl ethers of considerable diversity; an example is illustrated in eq. 26.1.[124] Similar reactivity was exhibited by 2-hydroxy- and 2-amino-1,4-naphthoquinones (eq. 26.2) and 1,4-benzoquinones.[50,126] Further examples of phenolic oxidation may be found in section 16.

Scheme 26



(26.1)



(26.2)

9. The Case of the Azide Functionality

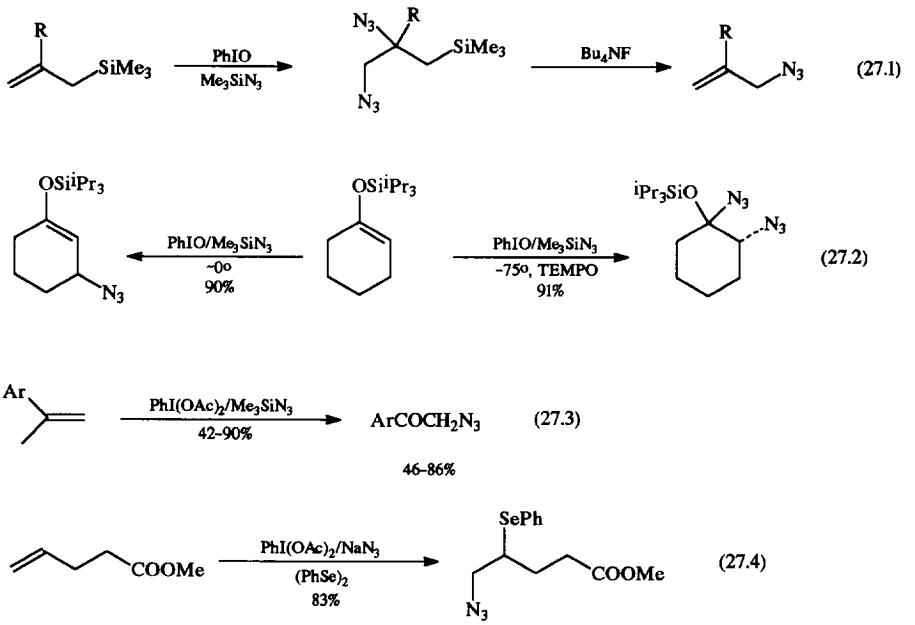
Several iodine (III) species form with NaN_3 or Me_3SiN_3 azido-substitutted iodanes. Those in which one azido group is attached to iodine participating in a heterocyclic ring[127,128] are stable (see for example eq. 284), whereas non-cyclic compounds such as $PhI(N_3)OAc$ or $PhI(N_3)OSiMe_3$ are not; the iodane $PhI(N_3)_2$ is not only unstable but also explosive in presence of humidity and traces of oxygen, even in solution.[129] These unstable reagents, often in combination with other additives, are reactive towards a wide range of substrates.

9.1. Transformations of olefinic compounds

The transfer of one or two azido groups to a great variety of olefins has been studied. Ordinary alkenes afford with PhIO and Me_3SiN_3 or NaN_3 mixtures of *cis*- (minor) and *trans*- (major) vicinal diazides.[130] The adducts of allylsilanes could be converted *in situ* to allylazides upon treatment with $PhIO/MeSiN_3$ followed by Bu_4NF (eq. 27.1);[131] the same reaction was performed directly using $PhIO.BF_3/Me_3SiN_3$.[132] An interesting dichotomy was detected in

cyclic triisopropyl enol ethers: these substrates could be converted to either *trans*-1,2-diazides, streoselectively, or to 3-azido-derivatives (eq. 27.2). Allylic azidation was favoured at 0°, whereas addition dominated at -78°; the presence of catalytic amounts of TEMPO increased considerably the yield of the adducts.[133]

Scheme 27

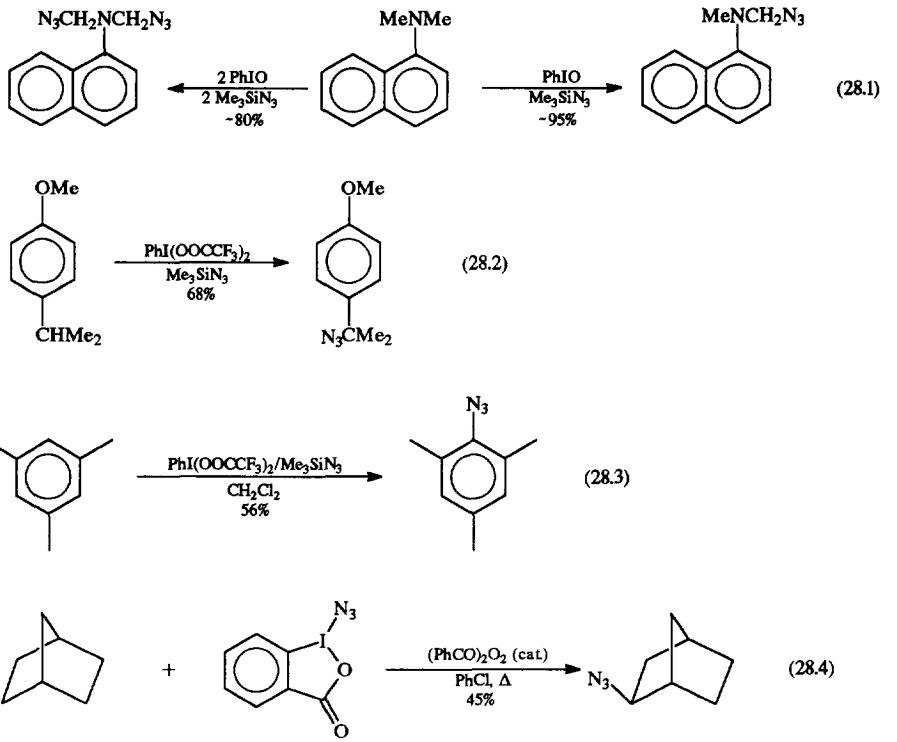


Different products were formed from olefins and $PhI(OAc)_2/Me_3SiN_3$: here, substrates with either nucleophilic or electrophilic double bonds yielded α-azido carbonyl compounds (eq. 27.3);[134] cyclic olefins, such as $\Delta^{5,6}$-cholestenes, however, were cleaved to ω-formyl-nitriles.[135] The same steroids with $PhIO/NaN_3$ in acetic acid yielded 7α-azido-$\Delta^{5,6}$-derivatives, after spontaneous elimination of HN_3 from the initially formed 5,6-*vic*-diazide and further reaction with azide anion.[136] From a mechanistic viewpoint, several pathways may operate in these reactions. Bis azidation can be either ionic, the addition proceeding in some instances through triazole intermediates, or homolytic. In silyl enol ethers (eq. 27.2) the addition is an azide radical process, while substitution involves ionic dehydrogenation. The system $PhI(OAc)_2/NaN_3$ in presence of PhSeSePh brought about azido-phenylselenylation of alkenes; good yields were obtained, with anti-Markovnikov regioselectivity, because of the operation of a homolytic pathway (eq. 27.4).[137] Important applications of these reactions have been reported in glycal chemistry (section 14).

9.2. Substitution involving the azido group

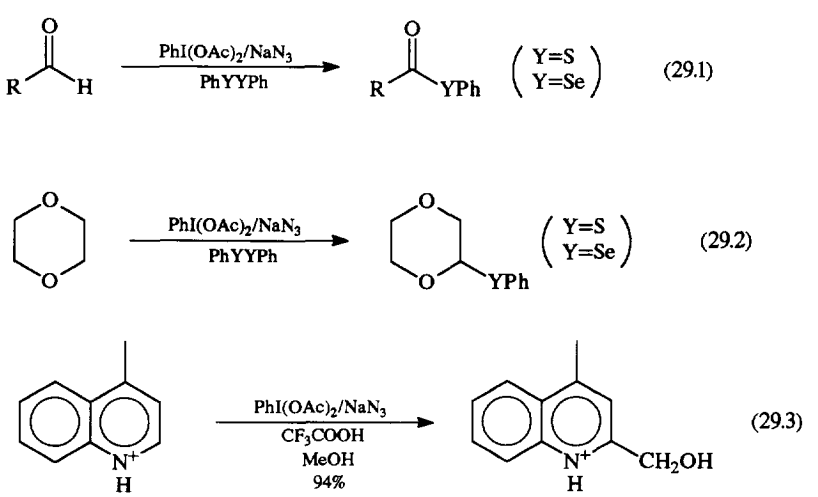
The azido group, either as a reactive electrophilic free radical or as a nucleophilic anion, can effect useful substitutions in several types of nucleophilic substrates other than olefins. For example, β-dicarbonyl compounds with $PhIO/Me_3SiN_3$ in refluxing chloroform were converted to α-azido derivatives.[138] Under milder conditions, the same reagents served for the *N*-methyl azidation of 3° amines, mostly *N,N*-dimethylarylamines (also trimethylamine). The azides were too unstable to be isolated but some of them were readily transformed to stable compounds. It is noted that 1-dimethylamino-naphthalene gave either a mono- or a bis-azido product (eq. 28.1).[139] Amides, carbamates, ureas and *L*-proline methyl ester derivatives were similarly azidated at a sp^3 carbon adjacent to nitrogen in clean reactions.[140,141] A series of 4-alkylanisoles and related aromatics were azidated also at sp^3 carbon, probably through $PhI^{\cdot}N_3$, generated from $PhI(OOCCF_3)_2$ and Me_3SiN_3 in acetonitrile (eq. 28.2); the products were stable enough to be isolated.[142] The same 4-alkyl-anisoles afforded with $PhI(OOCCF_3)_2/Me_3SiN_3$ 2-azido derivatives from the benzene ring by simply changing the solvent from acetonitrile to hexafluoro-2-propanol.[143] Azide reacts here as a nucleophile with aryl cation radicals formed through initial electron transfer with $PhI(OOCCF_3)_2$. Several electron-rich aromatics have undergone this nucleophilic aromatic substitution, not only in hexafluoro-2-propanol but also in methylene chloride; for example, mesitylene (eq. 28.3), 1,4-dimethoxynaphthalene (azidated at *C*-2, 85%), and naphthalene (at *C*-1, 49%). Some thermally stable 1-azidobenziodoxoles have been used for the azidation at high temperature in presence of benzoylperoxide of polycyclic hydrocarbons (eq. 28.4).

Scheme 28



Further substitutions of free radical character were performed with the tertiary system $PhI(OAc)_2/NaN_3/PhSSPh$ (or PhSeSePh) in aldehydes and ethers (eqs 29.1-2); these substrates were transformed, respectively, to phenyl esters of thio (or seleno)carboxylic acids and mixed acetals.[145]

Scheme 29



9.3. Substitution not involving directly the azido group

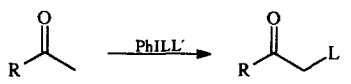
Several carbon centered free radicals were generated in ternary systems of $PhI(OAc)_2/NaN_3$ and various solvents such as alcohols, ethers, 1,4-dioxane, even formamide and propanal. All these solvents, represented as RH, produced in their interaction with the azide radical solvent derived radicals R· which were trapped by protonated lepidine, with formation of 2-substituted lepidines, as illustrated in eq. 29.3.[146]

10. Transformations of Carbonyl Compounds

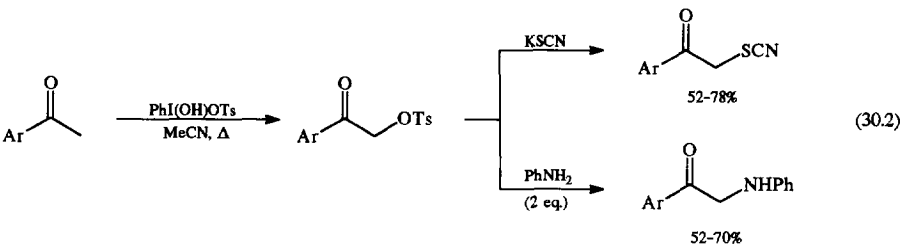
10.1. α-Substitution in ketones

α-Functionalisation of simple ketones and various keto compounds mediated by iodanes constitutes a fairly general type of reaction with many variations and extensions. In this way were directly introduced chlorine, acetoxy, azido, (diphenylphosphoryloxy) and various imidyl and organosulfonyloxy groups (eq. 30.1).

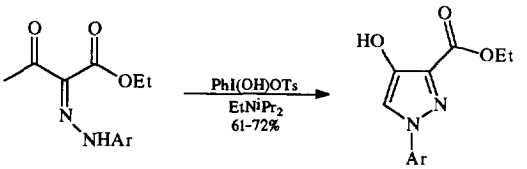
Scheme 30



(30.1)



(30.2)



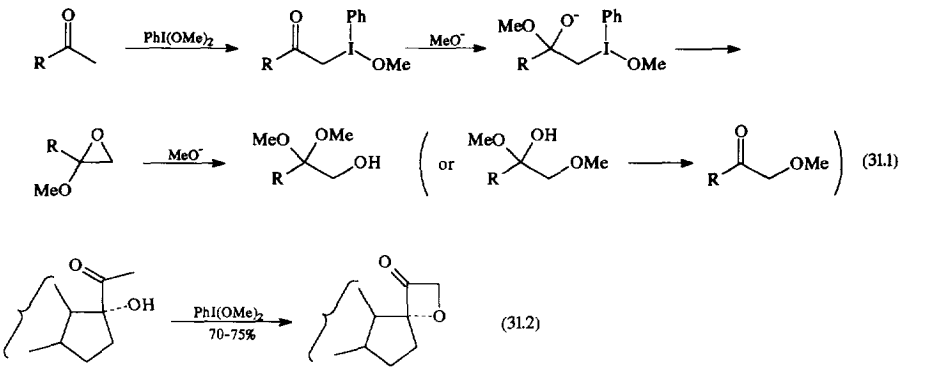
(30.3)

Organosulfonyloxylation and especially tosyloxylation have been much studied, because of the importance of their products.[4,5] α-Tosyloxyketones are useful, since they react with nucleophiles and may advantageously be used in place of α-chloroketones. In this way α-tosyloxy-acetophenones, formed *in situ* upon brief heating of acetophenones with PhI(OH)OTs, have been used for the preparation of α-anilino-[147] and

thiocyanato-[148]derivatives (eq. 30.2). In an analogous manner, several 5-membered heterocycles were obtained in one-pot syntheses from acetophenones by treatment with PhI(OH)OTs, and subsequent addition of ureas, thioureas, thioamides, etc. In some cases, the functionality needed for cyclisation was incorporated in the ketone, as in the example of eq. 30.3.[149] A related cyclisation involved 5-ketoacids which were converted by PhI(OH)OTs to lactones, e.g. 4-benzoylbutanoic acids afforded 5-benzoyl-butyrolactone; similarly, 4,6-diketoacids furnished diketo-δ-lactones.[150] In these transformations an iodane from the carboxy group, i. e. $RCO(CH_2)_3COOI(OH)Ph$, appears more likely to be involved than an α-tosyloxy intermediate. Sonication promotes significantly the efficiency of tosyloxylation, notably with otherwise unreactive cycloalkanones.[151]

Direct α-hydroxylation of ketones[152] is possible when they are heated in aqueous acetonitrile at reflux with $PhI(OOCCF_3)_2/CF_3COOH$. A more important variation of this reaction is the conversion of ketones to their α-hydroxy dimethylacetals upon treatment with $PhI(OAc)_2$ and methanolic KOH, at room temperature.[153] Its mechanism (eq. 31.1) proceeds through *in situ* formed $PhI(OMe)_2$ which reacts with the ketone first an intermediate iodane (or iodonium salts) having a C-I bond; this upon methoxide attack at the carbonyl C cyclises to an oxirane which normally with more methoxide is eventually transformed to the α-hydroxy-dimethylacetal. In sterically hindered substrates methoxide attacks the methylene C of the oxirane ring, with eventual formation of an α-methoxyketone.[154] Other deviations were reported in some steroidal substrates: a Favorskii-type rearrangement occurred in 3-ketosteroids resulting in ring-contraction of ring A to a carbomethoxy cyclopentane,[155] whereas in 17-hydroxy-17-acetyl derivatives intramolecular cyclisation prevailed, with formation of 2-oxetanones (eq. 31.2).[156]

Scheme 31

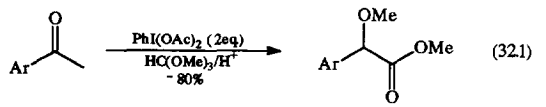


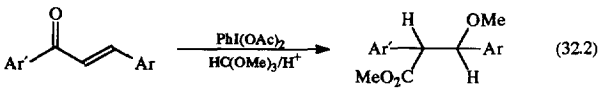
α-Phenylation of ketones is possible, using preferably their silyl enol ethers (section 12); these substrates, and also propiophenones, may be converted to α-methoxyketones (sections 10.2 and 10.3).

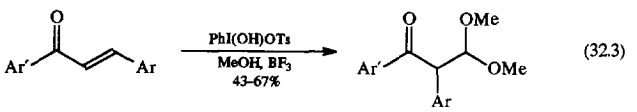
10.2. Rearrangements of ketones

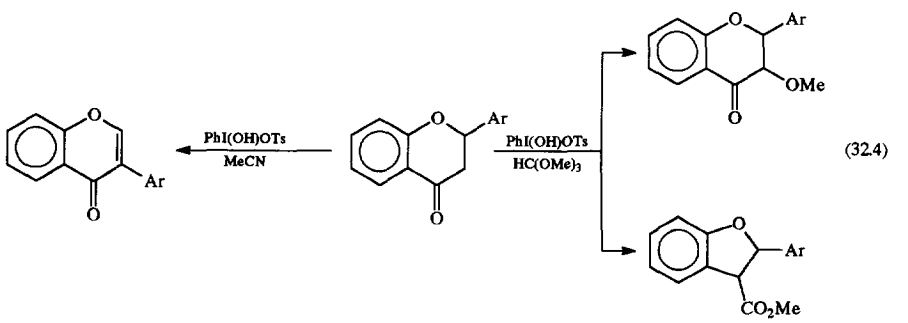
Some unexpected transformations have been noted in different types of ketones. Acetophenones when heated with $PhI(OAc)_2$ in methanol-sulfuric acid were converted to mixtures of α-methoxyacetophenones (minor product) and rearranged esters, $ArCH_2COOMe$ (major product). Two equivalents of $PhI(OAc)_2$ in trimethyl orthoformate-sulfuric acid resulted in their clean transformation to methyl α-methoxyarylacetates, at room temperature (eq. 32.1).[157] Propiophenones with $PhI(OAc)_2/MeOH/H_2SO_4$ gave rearranged esters,[158] ArCH(Me)COOMe and a similar rearrangement in 3-aroyl-propionic acids, resulted in the formation of dimethyl succinates,[159] $ArCH(COOMe)CH_2COOMe$.

Scheme 32









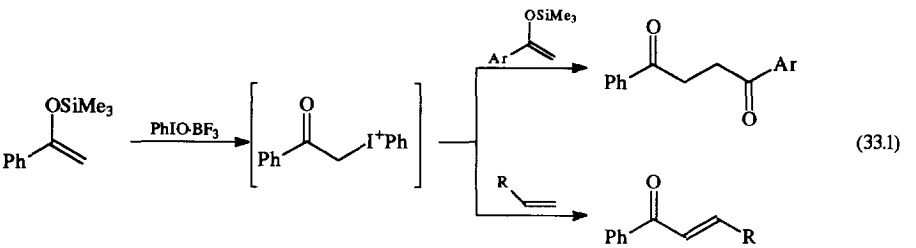
Methoxylation acompanied by rearrangement occurred in chalcones which were converted by $PhI(OAc)_2$ diastereoselectively to 2,3-diaryl-3-methoxypropanoates (eq. 32.2).[160] Chalcones reacted with PhI(OH)OTs to give either the same products as in eq. 32.2, or to *vic*-tosyloxy- adducts or to rearranged acetals (eq. 32.3), depending on the conditions.[161] Flavanones gave also different products with PhI(OH)OTs, depending on the solvent: in methanol they underwent dehydrogenation to flavones (not shown), whereas in acetonitrile they afforded rearranged isoflavones and in trimethyl orthoformate mixtures of dihydrobenzofuran derivatives (main product) and methoxy-flavanones (eq. 32.4).[162]

10.3. Transformations through silyl enol ethers

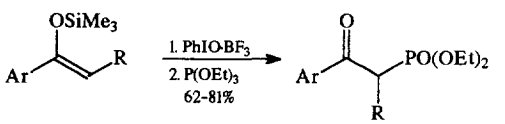
These substrates, the azidation of which was discussed in section 9.1, are more reactive than ketones and give α-substitution products either with retention of the silyl group or with simultaneous conversion to ketones. The

first type of reaction is exemplified in 1-trimethylsilyloxy-cyclohexene which afforded with $PhI(OAc)_2$ at room temperature without acid catalysis its 2-acetoxy-derivative.[163] Functionalisation follows usually the second route: even at -50° C, an unstable iodonium salt was initially formed upon reaction of acetophenone silyl ether with $PhIO.BF_3$; this reacted with more substrate or a different silyl enol ether to afford symmetrical or non-symmetrical 1,4-diketones (eq. 33.1).[164]

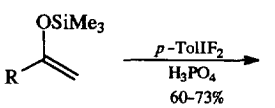
Scheme 33



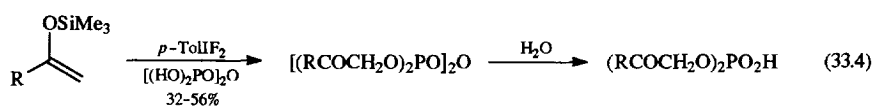
(33.1)



(33.2)



(33.3)



(33.4)

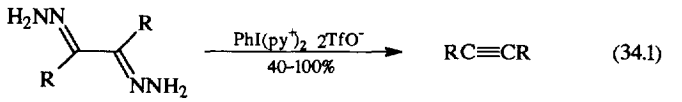
Other reagents such as $(PhI^+)_2O\ 2BF_4^-$[33] (prepared from $PhI(OAc)_2$ and HBF_4) and $PhIF_2.BF_3$[165] afforded similarly 1,4-diketones in better yields, up to 90%, from the same precursors. The iodonium intermediate of acetophenone, resulting from its silyl ether and $PhIO.BF_3$, reacted also with several added nucleophiles, especially alkenes or allylsilanes which were benzoylated to furnish unsaturated ketones (eq. 33.1).[38] Reactions of silyl enol ethers with other nucleophiles such as water, methanol or trimethylsilyl triflate afforded, respectively, α-hydroxyketones,[166] α-methoxyketones[167] and α-triflates;[168] α-

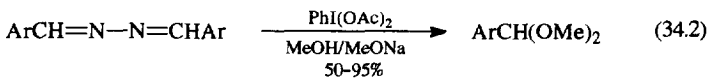
phosphonates[169] were obtained with triethyl phosphite (eq. 33.2). Silyl enol ethers coming from diverse ketones gave with *p*-TolIF$_2$ or PhI(OAc)$_2$ and phosphoric acid directly tris-ketol phosphates, even with a 1:1 stoichiometry of reactants (eq. 33.3).[170] The same methodology, using pyrophosphoric acid, resulted in the synthesis of isolable tetrakis-ketol pyrophosphates, which were hydrolysed to bis-ketol hydrogen phosphates (eq. 33.4).[171] The reaction of silyl enol ethers with PhI(OH)TsO gave α-tosyloxy-ketones, often in better yields and improved regioselectivity,[172] in comparison with the direct tosyloxylation of ketones. The related α-tosylamination is discussed in section 13.2.

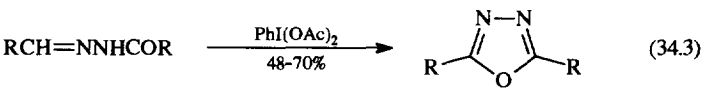
10.4. Transformations of nitrogen and sulfur derivatives

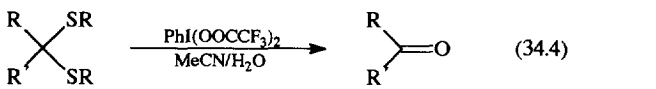
Numerous nitrogen-containing derivatives of carbonyl compounds have been oxidised by iodanes, undergoing diverse transformations; some of the more recent ones are briefly discussed. A number of these reactions are similar to those effected using lead tetraacetae. For example, reaction with PhICl$_2$ and pyridine converted aldoximes to nitrile oxides,[173] while ketoximes were deoximated.[174] Iodanes, generally, have the advantages of easier work-up and often better yields, while their use avoids the objectional lead. Simple keto derivatives such as oximes,[175] tosylhydrazones[176] or semicarbazones[177] were converted by PhI(OAc)$_2$ under mild non-acidic conditions to the parent ketones in high yield. The same oxidant was used for the *in situ* generation of nitrilimines from hydrazones of aldehydes;[178] ketohydrazones were oxidised to diazocompounds, including substrates where other oxidants failed.[179] Phenylhydrazones of ketones and α-ketoesters were converted to the parent compounds in excellent yield[180] with either PhI(OH)OTs or PhI(OOCCF$_3$)$_2$. Bis hydrazones of 1,2-diketones were cleanly oxidised to alkynes,[106] at room temperature, by the strong oxidant PhI(py$^+$)$_2$ 2TfO$^-$ (eq. 34.1).

Scheme 34









Aldazines from aromatic aldehydes were converted by $PhI(OAc)_2$ in methanolic sodium methoxide to their dimethylacetals (eq. 34.2).[181] The stronger $PhI(OOCCF_3)_2$ was used for the transformation of aliphatic ketoximes to *gem*-nitroso-trifluoroacetoxy-alkanes.[182] More complex *N*-derivatives underwent more drastic transformations, notably cyclisation to various heterocycles. For example, several types of *N*-acylhydrazones were oxidised by $PhI(OAc)_2$ with concomitant cyclisation to 1,3,4- oxadiazole or oxadiazoline derivatives,[183] as shown for one family[184] in eq. 34.3. An unusual type of reaction involved the high-yielding application of $PhI(OAc)_2$ for the oxidation of *o*-hydroxyaryl ketone acylhydrazones to 1,2-diacylbenzenes, as well as related transformations.[185,186] An efficient method for dethioacetalisation of thioacetals coming from a wide range of aldehydes and ketones has found numerous applications: it uses $PhI(OOCCF_3)_2$, under mild conditions, and results in the formation of the deprotected carbonyl compound in excellent yield (eq. 34.4).[187] The same substrates were also deprotected using $PhIO_2$ and *p*-toluenesulfonic acid,[188] whereas upon reaction with *p*-$TolIF_2$ they were converted to *gem*-difluoroalkanes.[189]

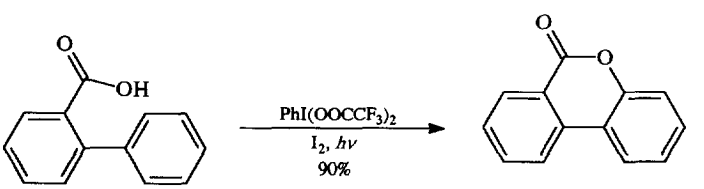
11. Transformations of Acids and Derivatives

11.1. Transfer of acyloxy groups

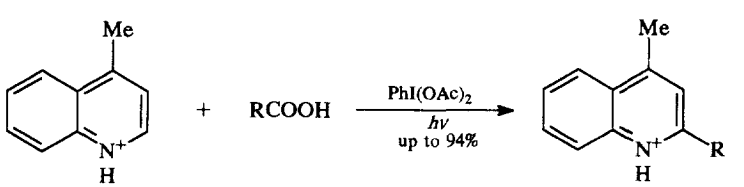
Most acids form stable diacyloxy iodanes upon reaction with either $PhI(OAc)_2$ or PhIO. These compounds may be used for the transfer of their

acyloxy groups to various nucleophiles, either ionically or through free radicals. For example, the conversion of *cis, cis*- 1,5-cyclooctadiene to 2,6-diacetoxy-*cis*-bicyclo[3.3.0]octanes follows a follows a heterolytic pathway (see eq. 8.2).[40] Also, the preparaion of alkynyl esters, RCOOC≡CR, by reaction of $PhI(OOCR)_2$ with sodium acetylides is a process involving a $RC{\equiv}CI^{+}Ph\ RCOO^{-}$ intermediate; an alternative approach for these interesting esters was the reaction of acids through their sodium salts with alkynyl iodonium salts.[66] Homolytic acetoxylation and acyloxylation has also been effected in assorted substrates, such as arylacetonitriles[190] which gave with $PhI(OAc)_2$, in presence of dibenzoylperoxide , ArCH(OAc)CN. An intramolecular example is the photochemical lactonisation of 2-alkyl or 2-arylbenzoic acids mediated by $PhI(OOCCF_3)_2$ and iodine (eq. 35. 1).[191]

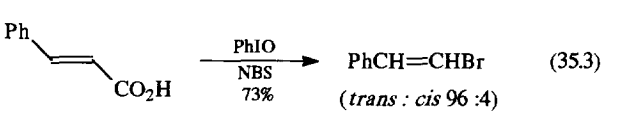
Scheme 35



(35.1)



(35.2)



(35.3)

11.2. Decarboxylation

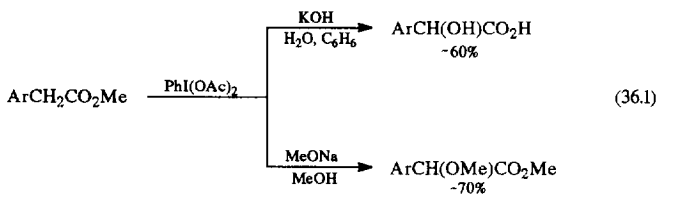
Stable diacyloxy iodanes may produce directly acyloxy radicals thermally or photochemically; these are normally decarboxylated to alkyl free radicals (section 5.2). A related method involved the *in situ* formation of diacyloxy iodanes, from $PhI(OAc)_2$ and carboxylic acids, from which free radicals were photochemically generated and used for the alkylation of several protonated pyridines, aza-pyridines and quinolines (eq. 35.2).[192] Another way to

generate R· from $PhI(OOCR)_2$ was through the reaction with iodine, leading to the formation of acyl hypoiodites, RCOOI, which were spontaneously decarboxylated to alkyl iodides.[193] This modified Hunsdiecker degradation was applied for the conversion of aryloxyacetic acids to $ArOCH_2I$;[194] under photochemical conditions, steroidal,[193] aromatic[195] and cubane carboxylic acids[196] afforded similarly and efficiently the corresponding iodides. The oxidative halo-decarboxylation of α,β-alkenoic acids is not feasible under Hunsdiecker conditions, however, the combined action of of PhIO and NBS (or NCS, or NIS) , proceeding *via* diacyloxy iodanes, resulted in the formation of alkenyl halides, as exemplified in eq. 35.3.[197] The combination of $PhI(OOCCF_3)_2$ and iodine makes a good reagent for aromatic iodination, which proceeds ionically through CF_3COOI. Substrates iodinated in this way include tetraphenylmethane,[198] thiophenes[199] and porphyrins.[200]

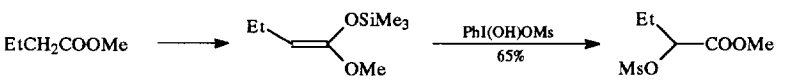
11.3. Transformations of esters

Methyl esters, mostly from arylacetic acids, have been converted to either α-hydroxy acids or to α-methoxy esters,[201] upon treatment, respectively, with $PhI(OAc)_2$/KOH or $PhI(OAc)_2$/MeONa (eq. 36.1).

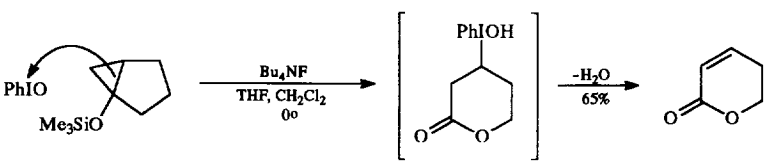
Scheme 36



(36.1)



(36.2)



(36.3)

These reactions proceed through an oxirane intermediate, just like those between ketones and $PhI(OAc)_2$ in alkaline conditions (section 10.1). Treatment of the methyl ester of 2-carboxymethyl-pyridine, 2-py-CH_2COOMe, simply with $PhI(OAc)_2$ in dichloromethane for two days at room temperature resulted in its acetoxylation at CH_2, in 90% yield.[202] The ester $MeSCH_2COOMe$ gave with $PhI(OOCCF_3)_2$ the non-isolable salt MeS^+=CHCOOMe CF_3COO^- which was converted in methanol quantitatively to the methoxy derivative MeSCH(OMe)COOMe; the same intermediate in *p*-xylene afforded a 2-(*p*-xylyl) derivative of the ester.[203] Esters in the form of silyl enol ethers reacted with either PhI(OH)OTs or PhI(OH)OMs to afford α-sulfonyloxy derivatives (eq. 36.2). A similar product was obtained from the silyl ether of ε-caprolactone, i.e. its 3-tosyloxy derivative.[172] Lactones in the form of silyloxy cyclopropanols were transformed by PhIO and Bu_4NF to unsaturated lactones *via* an iodonium intermediate (eq. 36.3).[100] Xanthate esters of the general formula ROC(S)SMe were transformed by *p*-$TolIF_2$ under mild conditions, at 0°, to alkyl fluorides; a range of products were obtained in good yields, such as 2-adamantyl and steroidal fluorides.[204]

11.4. The Hofmann rearrangement in modern version

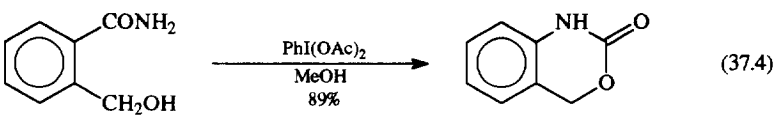
Primary carboxamides undergo readily a Hofmann-type rearrangement with several iodanes, leading to amines or some of their derivatives. The conditions are generally mild and yields good to excellent, surpassing those traditionally obtained . The reagent of choice for this rearrangement appears to be $PhI(OOCCF_3)_2$, which was used with a large number of aliphatic amides, cycloalkane carboxamides, amides of arylalkanoic acids and substrates of a more complex nature. The reaction is performed at room temperature in aqueous acetonitrile, at pH 1-3, and proceeds through alkyl isocyanates; their hydrolysis is usually followed by addition of hydrochloric acid for isolation of the amine hydrochloride (eq. 37.1). The preparation of cyclobutylamine hydrochloride according to this methodology has been described in *Organic Syntheses*.[205]

Scheme 37

$$RCONH_2 \xrightarrow[\text{aq. MeCN}]{PhI(OOCCF_3)_2} RN{=}C{=}O \xrightarrow[HCl]{H_2O} \overset{+}{R}NH_3\ Cl^- \qquad (37.1)$$

$$AcNHCH(R)CONH_2 \xrightarrow[2.\ HCl]{1.\ PhI(OOCCF_3)_2} AcNHCH(R)CH_2\overset{+}{N}H_3\ Cl^- \qquad (37.2)$$

$$RCONH_2 \xrightarrow[\substack{MeOH,\ KOH\\ 70\text{-}97\%}]{PhI(OAc)_2} RNHCOOMe \qquad (37.3)$$



(37.4)

For this transformation $PhI(OAc)_2$ is also effective but the use of $PhI(OOCCF_3)_2$ has the advantage that the liberated trifluoroacetic acid helps the reaction by protonating the amine, which then does not react with the alkyl isocyanate to give unwanted dialkylureas; also, it catalyses the hydrolysis of isocyanates. These may be isolated under appropriate conditions, since they hydrolyse more slowly than they are formed. Numerous applications of the degradation have been reported from the field of peptide chemistry. For example, from *N*-protected amides of aminoacids and oligopeptides were obtained *gem*-aminoamides which constitute building units for the synthesis of retro-inverso peptides (eq. 37.2).[206] Also, this reaction, with either $PhI(OOCCF_3)_2$ or $PhI(OAc)_2$, was a key-step in peptide sequencing: the *gem*-diamino derivative formed was hydrolysed with base to a peptide-amine and an easily identifiable aldehyde, or was converted to a thiazolidine derivative.[207] In some instances $PhI(OAc)_2$ was preferable to $PhI(OOCCF_3)_2$, especially when it was desirable to intercept the isocyanates. Thus, a high-yield preparation of urethanes from amides was performed with $PhI(OAc)_2$ in methanolic KOH (eq. 37.3).[208] A related reaction accompanied by cyclisation occurred in some *ortho*-substituted benzamides (eq. 37.4). Similarly, benzouracil was obtained from phthalamide; aliphatic diamides such as malonamides yielded 5-membered cyclic analogues.[209] It is noted that normally benzamides do not undergo the transformation to anilines, because as soon as these are formed they are

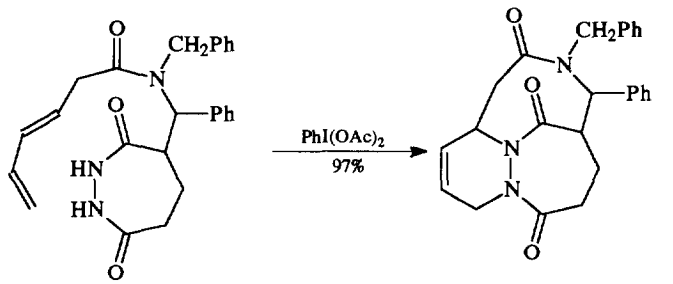
oxidised. Other iodanes used in amide degradations are PhI(OH)OTs and PhIO; the former was suitable for some bridgehead[210] or long-chain[211] aliphatic amides, otherwise unreactive; the latter was found to be preferable, in formic acid, with some carboxamides containing a phosphate group, for example for the preparation of $(HO)_2P(O)CH_2CH(Me)NH_2$.[212]

All these reactions proceed through N-I intermediates; indeed, using PhI(OMs)OTs, several aliphatic and aromatic amides delivered isolable *N*-phenyliodonium salts,[213] of the general formula RCONH-I^+Ph TsO^-. Some of them have been used in reactions with sulfides for the preparation of amidosulfonium tosylates, RCONH-S^+R_2 TsO^-.[214]

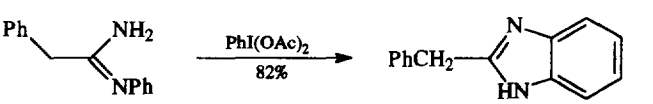
11.5. Further transformations of nitrogen derivatives

Not only amides but also *N*-methoxyamides were reactive toward $PhI(OOCCF_3)_2$, affording initially unstable *N*-phenyliodonio intermediates, the intra- or intermolecul reaction of which with an aromatic ring, probably through nitrenium ions, afforded *N*-aryl-*N*-methoxyamides,[215] e.g. MeCONHOMe in benzene was phenylated to MeCON(Ph)OMe, in 70% yield. Using *N*-methoxyamides of 6-methoxy-1,2,3,4-tetrahydroisoquinolinyl-1-acetic acids, ring expansion occurred leading to 1,5-benzodiazonine derivatives.[216] Several kinds of hydrazides were transformed to various products by iodanes. Simple hydrazides from aromatic acids were converted to methyl esters by $PhI(OAc)_2$ in methanol,[217] and 1,1-phthaloyl-hydrazide was uniquely oxidised by $PhI(OAc)_2$ to a tetrazane.[218]

Scheme 38



(38.1)



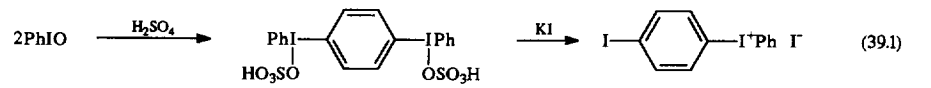
(38.2)

Bis hydrazides of the general formula RCONHNHCOR were oxidised to azo-compounds; in some cyclic hydrazides the azo functionality generated *in situ* underwent intramolecularly Diels-Alder reaction with a 1,3-dienyl moiety(eq. 38.1).[219] *N*-Phenyl-*C*-alkyl amidines were converted by $PhI(OAc)_2$ to benzimidazoles by way of ylidic N-I intermediates (eq. 38.2). The nature of the substituents and the temperature influenced greatly the reaction course, resulting in the formation of either *N*-acetylureas of the general formula RNHCON(R)COMe or simply *N,N'*-disubstituted ureas. Further transformations were also possible; in this way, *N*-(α-furyl)-*C*-phenylamidine was converted in high yield to 2-acetylamino-furan.[220]

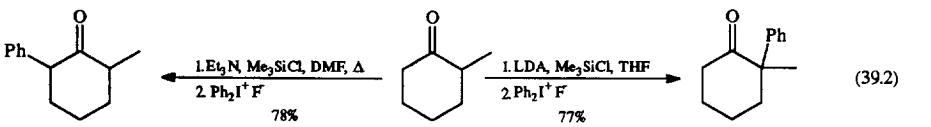
12. Arylation

Although a great deal of arylations are known, this section will be relatively short, since few new reactions in this area have been reported recently. Some of the early transformations in the field of hypervalent iodine involved arylation with iodonium salts: indeed, the conversion of a derivative of the heterocyclic dibenziodolium iodide to a 2,2'-diiodobiphenyl[221] was reported in 1933. A much older and peculiar transformation was the self-condensation of iodosylbenzene to give 4-iododiphenyliodonium iodide upon treatment with sulfuric acid, followed by aqueous potassium iodide;[222] its mechanism has been only recently elucidated: iodosylbenzene forms in sulfuric acid a bis-λ^3-derivative of 1,4-diiodobenzene which is reduced by iodide to the final product (eq. 39.1).[223]

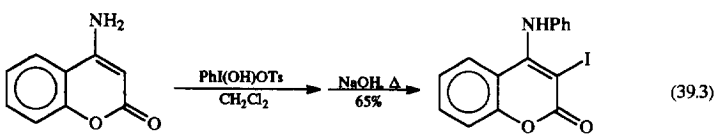
Scheme 39



(39.1)



(39.2)



(39.3)

In more detail, the initial adduct of iodosylbenzene with sulfuric acid, i. e. $PhI(OSO_3)OH$, attacks from its *C*-4 the highly electrophilic iodine of its conjugated base, i. e. $PhI(OSO_3)OH_2^+$, to give the 1,4-bis iodane. The reaction of iodosylbenzene with triflic acid furnished an isolable analogue (see eq. 17.3) which served for the preparation of several other 1,4-bis iodonium salts, such as alkenyl and alkynyl(1,4-phenylene)bis iodonium triflates.[224] Most useful arylations involve diaryl iodonium salts. A great number of substrates have been arylated at carbon, oxygen, nitrogen, and other nucleophilic sites through a well-established methodology. For example, α-arylation of 1,3-diketones is described in *Organic Syntheses*,[225] whereas the search for optimum yields and mild conditions needed for the synthesis of thyroxine analogues has resulted in the development of improved procedures for *O*-arylation of phenols.[226]

Generally, it is presently feasible to make good choices, since the basic features of reactions with iodonium salts have been delineated: a 10-I-3 intermediate is usually formed first which in some instances is isolable. This in polar reactions seems to undergo not an intramolecular aromatic nucleophilic substitution, as previously assumed, but a synchronous (cheletropic) extrusion of an iodoarene from a tetragonal pyramidal intermediate, in which both aryls, the nucleophile and iodine lie in one plane. This model explains the regio-selectivity observed in arylations with non-symmetrical diaryl iodonium salts; it takes into account the bulkiness of the aryl group (the nucleophile prefers

the bulkier), electronic factors and the size of the nucleophile; also, the decreased reactivity of certain cyclic iodonium salts can be accounted for.[227] At high temperature, a S_NAr pathway, elimination of an aryl cation or benzyne formation may also operate.[1]

With non-charged nucleophiles the intermediate iodane seems to undergo a homolytic decomposition, presumably in a solvent case involving $Ar_2I^{\cdot}$. This route was followed in the phenylation of silyl enol ethers, which with Ph_2IF give α-phenyl ketones.[228] The regiochemistry of phenylation could be controlled by appropriate choice of silyl enol ether (eq. 39.2). In ketones and sometimes in silyl enol ethers bis phenylation occurs inevitably to a substantial degree. To overcome this problem in the phenylation of hydrocodone, its lithium enolate was used.[229] Generally, addition of crown ethers[230] or 1,1-diphenylethylene[231] increased considerably the yields in several phenylations. Phenylation or arylation with palladium catalysis gave often very good results. For example, acrylic acid afforded cinnamic acids in aqueous sodium carbonate using Ar_2I^+ HSO_4^-.[232] Also, cross-coupling of an aryl group from Ar_2I^+ with a phenyl group from $NaBPh_4$ in water resulted in the formation of biaryls in excellent yields.[233] Other substrates successfully arylated included allylic cyclic carbonates,[234] allylic alcohols,[54] organotin compounds[235] and terminal alkynes;[236] the latter were also phenylated by PhI(OH)OTs or Zefirov's reagent.[56]

Direct or indirect *O*- and *N*-phenylations have been effected using iodanes. This approach was accompanied by iodination and has been applied to a great variety of cyclic 1,3-diketones, phenols, and some related amino-substituted analogues (enaminones). Indeed, their treatment with an appropriate

iodane leads initially to phenyliodination. When the precursor is fairly acidic, no catalysis is required, otherwise the presence of aqueous base is necessary. In this way were obtained either phenyliodonium salts or directly phenyliodonium dipoles (ylides); the latter are usually isolable compounds which spontaneously or upon gentle heating undergo a Smiles-type rearrangement to afford α-phenoxy-iodo derivatives of the parent substrate, as already exemplified in eq. 26.1. Similar reactivity has been reported in β-enamino ketones and related heterocyclic phenolic or amino compounds (eq. 39.4)[237]

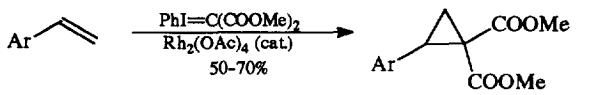
13. Generation of Reactive Intermediates

Due to the superleaving group ability of the phenyliodonio group, especially when it is linked to non-aromatic carbon, oxygen or nitrogen, many reactions with iodanes proceed through electron-deficient species, such as oxenium, nitrenium or radical cations. This section examines non-charged intermediates, other than ordinary free radicals.

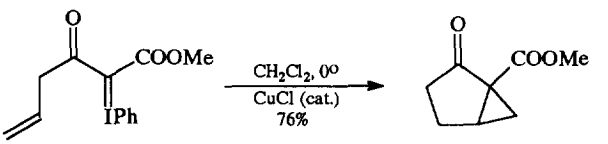
13.1 Carbenes

The generation of alkylidene carbenes from alkenyl or alkynyl iodonium salts has already been discussed (sections 5.4 and 6.2). Diacyl and related carbenes have been postulated as intermediates in several instances associated with reactions of phenyliodonium ylides. It appears that their copper- or rhodium-catalysed decomposition occurs *via* carbenes or carbenoids. This was established for $PhI{=}C(COOMe)_2$ and related ylides by comparison with similar reactions of the corresponding diazocompounds, which are known to proceed through carbenes. In all cases identical product composition for Rh(II)-catalysed decomposition of both precursors was observed using styrenes, allylbenzene and phenylacetylene, as illustrated in eq. 40.1.[238]

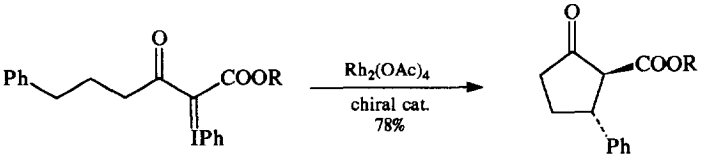
Scheme 40



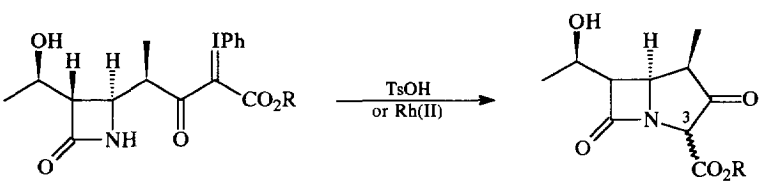
(40.1)



(40.2)



(40.3)



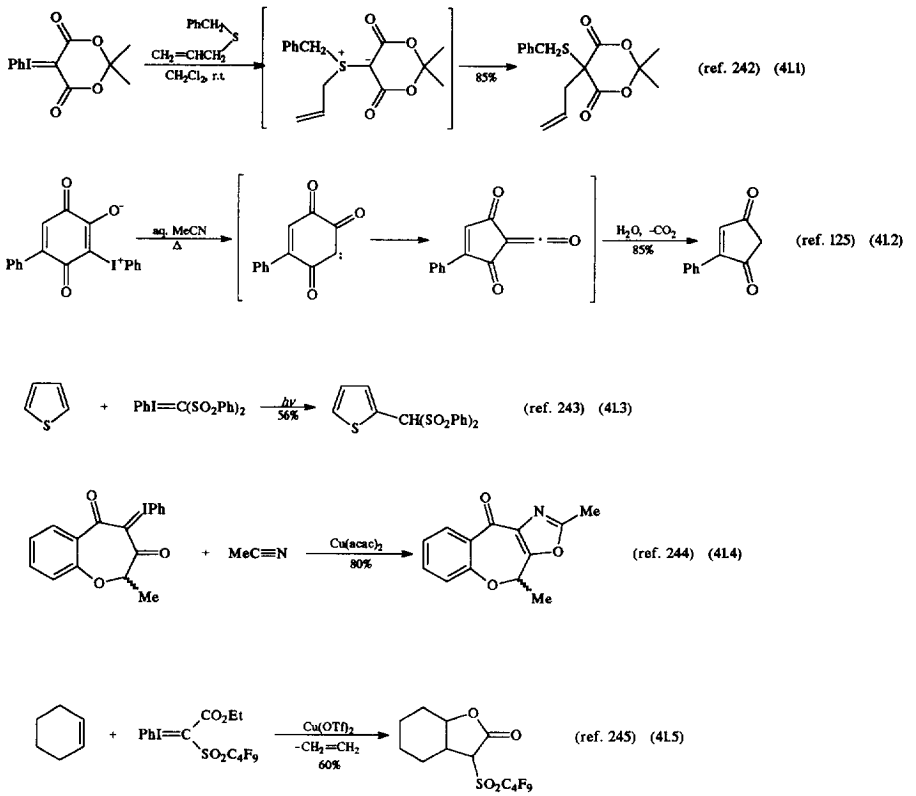
(40.4)

(TsOH: 3*S*, 94%
Rh (II): 3*R*, 86%)

Not only intermolecular but also intramolecular cyclopropanations occur (eq. 40.2).[239] In a similar reaction from a D-ribose precursor, two diastereoisomers were obtained (1:1.5), whereas the corresponding diazo-analogue showed the reverse diastereoselectivity (4.5:1).[240] It seems that internal cyclopropanation is limited to the formation of bicyclo[3.1.0] systems. Diketocarbenes undergo also C-H, O-H and N-H insertions. Cyclopentanones (also, oxa- or aza- analogues) have been obtained by intramolecular versions of this reaction and in the presence of a chiral catalyst 67% ee has been achieved (eq. 40.3).[238] The N-H insertion from an iodonium ylide intermediate was used in a synthesis 1-β-methylcarbapenems; here, both Rh(II) and acid catalysis were effective but the products had different stereoselectivity (eq. 40.4).[241] The Rh-catalysed reaction probably involved a carbenoid, whereas the acid catalysis proceeded *via* the protonated ylide. It is noted that in intramolecular reactions the iodonium ylides may be not isolated. They are normally formed upon treatment of the active methylene precursor with $PhI(OAc)_2$ in aqueous alkali.

Iodonium ylides come also from several other types of precursors. Their reactions may involve the intermediacy of carbenes; among them are cited: transylidations, Wolff-type rearrangements, C-H insertion to aromatic compounds, and 1,3-dipolar cycloaddition (to furan, alkenes, alkynes or nitriles). Some pertinent examples with various types of ylides are illustrated in scheme 41.

Scheme 41



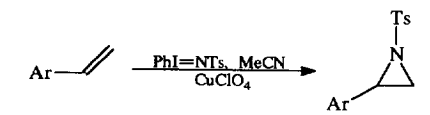
A few comments follow about these reactions. The initial transylidation in eq. 41.1 is followed by a [2, 3]-sigmatropic rearrangement. It is a rare example of transylidation under mild conditions, without a catalyst;[241] normally, these reactions are Cu-catalysed. Among iodonium ylides used in transylidations other than those coming from keto-precursors, are cited $PhI=C(NO_2)_2$, $PhI=C(SO_2R_F)_2$, and the non-isolable $PhI=C(CN)_2$, which reacted with sulfides, pyridines, triphenylphosphine, triphenylarsine, etc.[1] The transformation of eq. 41.2 constitutes a new example of an old type of reaction and has been used for the preparation of several cyclopentene-1,3-diones.[125] Benzene as well as thiophene (eq. 41.3) gave with $PhI=C(SO_2Ph)_2$ photochemically formal carbene C-H insertion products. However, these are

more likely to come from initial cyclopropanation followed by rearrangement; benzo[*b*] thiophene gave with the same ylide thermally the corresponding sulfonium ylide.[243] The last two reactions of scheme 41 have been chosen from the numerous 1,3-dipolar cycloadditions, in which the mesomeric forms of ketocarbenes are combined with dipolarophiles. An interesting reaction from $PhI{=}C(SO_2R)_2$ and thiobenzophenones leads to 2-arylsulfonyl-benzo[c]-thiophenes or heterocycle-fused[c]thiophenes.[246]

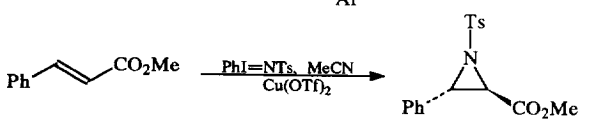
13.2 Nitrenes

Iodonium ylides from sulfonamide precursors are ideally suited for the generation under mild conditions of arylsulfonylnitrenes, $ArSO_2N$, which have been used mainly for aziridination but also for insertions into C-H bonds. Most studies were performed with the readily available PhI=NTs, which is obtained[247] from $PhI(OAc)_2$ and $TsNH_2$ in methanolic KOH. A variety of catalysts are suitable for the decomposition of PhI=NTs, the most efficient being CuOTf, $Cu(OTf)_2$ and $CuClO_4$, depending on the olefin (eqs. 42.1 and 42.2).

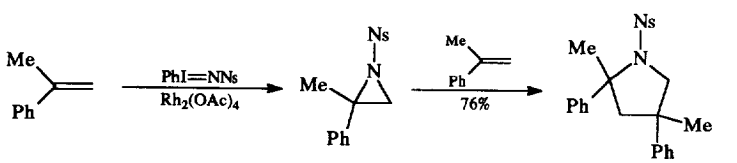
Scheme 42 [248]



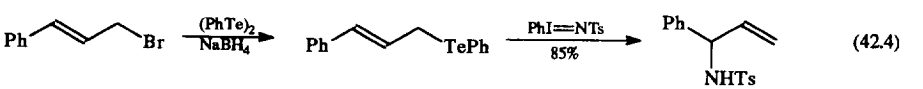
(78-90%) (42.1)



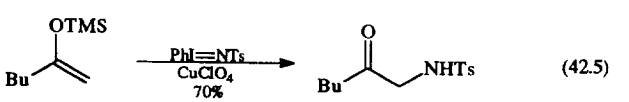
(75%) (42.2)



(42.3)



(42.4)



(42.5)

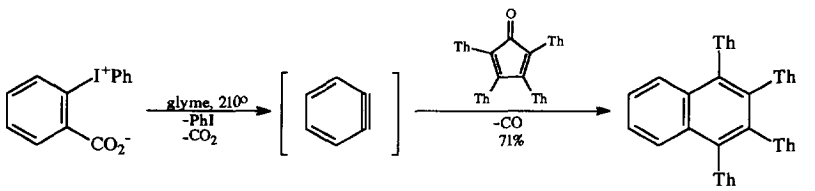
Electron-rich as well as electron-deficient olefins of considerable diversity were aziridinated under mild conditions in good yields. Also, several 1,3-dienes underwent monoaziridination and were converted to 2-alkenyl-aziridines, with the exception of 1,3-cyclooctadiene which gave a 1,4-addition product.[249] The reaction stereoselectivity in *E*- and *Z*- substrates is both catalyst and substrate dependent. By using chiral copper catalysts, especially derived from 1,2-diaminocyclohexane, asymmetric aziridination with high *ee* was achieved.[250] Another catalyst, $Rh_2(OAc)_4$, worked better in some instances, in conjunction with $PhI{=}NSO_2C_6H_4$-*p*-NO_2.[102] Using this system, the initial adduct of α-methylstyrene reacted with the olefin to give directly a pyrrolidine (eq. 42.3).[251] Several catalysts may suppress aziridination and direct the tosylamino group to an allylic position of the substrate. In this way cyclohexene afforded 3-tosylaminocyclohexene in presence of a Mn-porphyrin catalyst.[252] A more general approach for the synthesis of allylic amines in the form of *N*-tosyl derivatives is the reaction of allylic sulfides[253] or selenides[254] or tellurides[255] with PhI=NTs, without catalysis. The heteroatom gives first ylides (isolable and chiral sulfimides, $R_1R_2S^+$-N^-Ts were obtained from certain sulfides with a chiral catalyst); these undergo a [2, 3] sigmatropic rearrangement to furnish the final products. From a practical point of view, *in situ* prepared tellurides are convenient substrates (eq. 42.4). Other C-H nitrene insertions are known with silyl enol ethers which were converted to α-tosylaminoketones (eq. 42.5) and also with some silylketene acetals which gave α-tosylaminoesters.[248] Another reaction involving nitrene generated from PhI=NTs is the Pd-catalysed carbonylation leading to arylsulfonyl isocyanates.[256] Formal insertion of the TsNH group to a *B-C* bond was effected indirectly by treating trialkylboranes with PhI=NTs; the initial product, $R_2B(NTs)R$, upon hydrolysis afforded tosylamines, RNHTs.[257]

13.3 Arynes

Two kinds of iodonium compounds are suitable for the generation of arynes. The first involves 2-phenyliodonio-benzoate, the preparation[258] of which was described in *Organic Syntheses* in 1966. Its advantage is that it can be used as a benzyne precursor in Diels-Alder reactions when the diene is unreactive, since at high temperatures other precursors are destroyed (eq. 43.1).[259] By contrast, for the other benzyne precursor, i. e. 2-phenyliodonio-trimethylsilylbenzene triflate, room temperature suffices; benzyne is generated

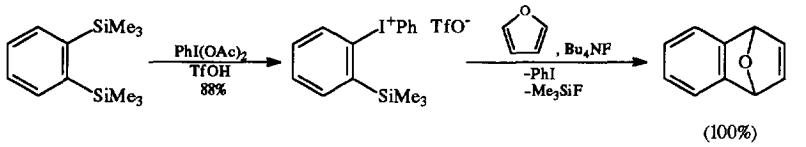
here simply upon treatment with Bu_4NF.

Scheme 43



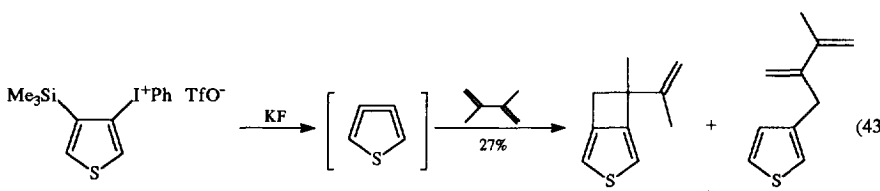
(43.1)

(Th = 2-thienyl-)



(43.2)

(100%)



(43.3)

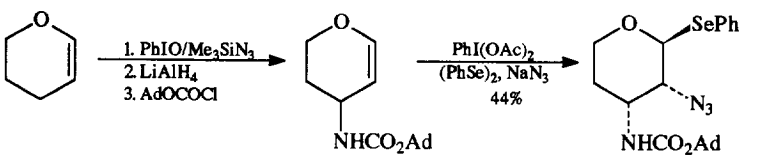
(1:1)

Very high yields of Diels-Alder adducts with several 1,3-dienes were reported, so that it can be considered as the reagent of choice for benzyne and aryne generation. Its preparation is fairly facile, from 1,2-bis-trimethylsilylbenzene and $PhI(OAc)_2$-TfOH (eq. 43.2); methyl substituted analogues were obtained in lower yields but their aryne adducts with furan were formed almost quantitatively.[260] 3,4-Didehydrothiophene has been generated from 3-phenyliodonio-4-trimethylsilylthiophene triflate; it gave not only Diels-Alder products, but also, with 2,3-dimethylbutadiene, a [2+2] cycloaddition adduct as well as an ene reaction product (eq. 43.3).[261]

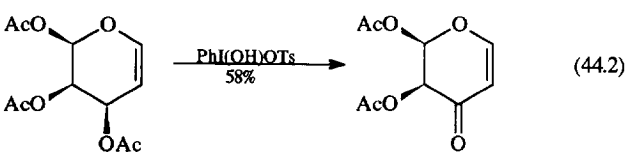
14. Transformations of Carbohydrates

A fair share in the present flourishing of carbohydrate chemistry is due to applications of hypervalent iodine reagents for transformations of glycals, thioglycosides and various simple sugars. Allylic azidation by PhIO and Me_3SiN_3 (section 9.1) has been applied to 3,4-dihydro-2*H*-pyrans and related carbohydrate based enol ethers.[129] Further transformations were possible making use of the highly regioselective azido-phenylselenylation of glycals, as illustrated in eq. 44.1.[262]

Scheme 44



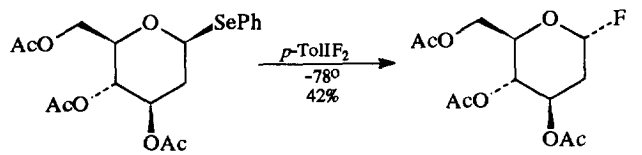
(44.1)



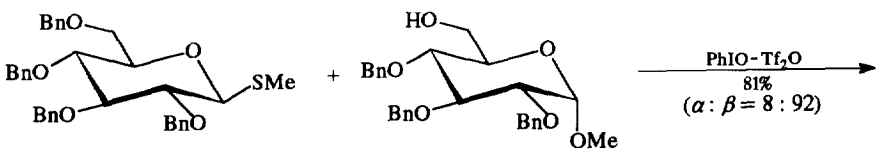
(44.2)

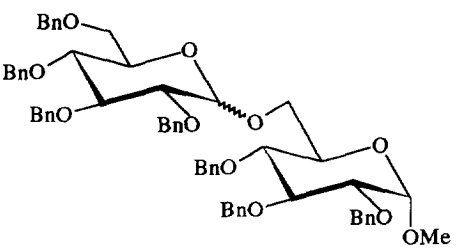
Glycals were also converted to *trans*-diazido adducts.[262] Another useful transformation of variously protected glycals was effected upon treatment with PhI(OH)OTs; irrespective of the relative stereochemistry and the nature of protection, 2,3-dihydro-4*H*-pyran-4-ones were obtained in fair yield (eq. 44.2).[263] Reaction of a complex glycal like intermediate with $PhI(OAc)_2$ in methanolic NaOH resulted in substitution with formation of a methoxy derivative.[264] Thio- and selenoglycosides upon treatment with *p*-$TolIF_2$ were converted to fluoroglycosides,[265] as exemplified in eq. 45.1.

Scheme 45



(45.1)



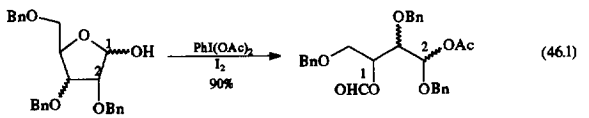


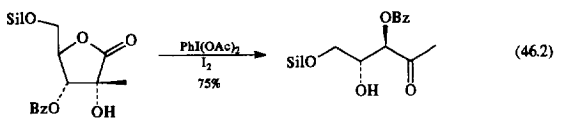
(45.2)

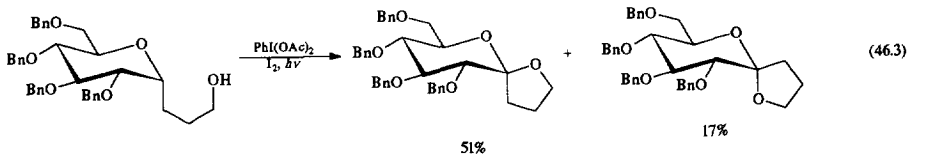
Several alkyl- and arylthioglycosides reacted with $PhI(OOCCF_3)_2$ and simple alcohols to furnish glycosides with inverted stereochemistry in excellent yields and very high stereoselectivity.[266] A reagent prepared *in situ* from PhIO and triflic anhydride or a metal triflate was similarly effective in activating thioglycosides, which were used for the preparation of several disaccharides (eq. 45.2); high α-selectivity was observed with catalysis by $SnCl_4$-$AgClO_4$ and related salts.[267]

A convenient way to descend the aldose series was *via* β-fragmentation of their anomeric alkoxy radicals, induced by $PhI(OAc)_2$ and iodine; for example, both D- and L-forms of tribenzylarabinofuranose were converted to acetoxylated D- and L-erythrose building blocks, in the form of formates (eq. 46.1).[268]

Scheme 46







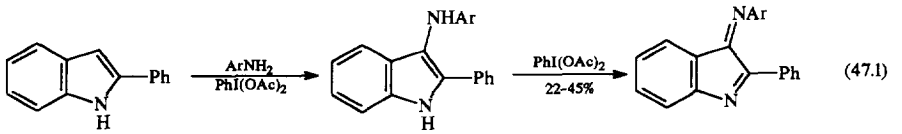
In an analogous manner, free radicals produced from uronic acids underwent β-fragmentation accompanied by 1,5- or 1,6-intramolecular cyclisation to give lactones.[269] Under the same conditions, 3-hydroxylactones underwent an unprecedented decarboxylation,[270] as exemplified in eq. 46.2. Other transformations involved the conversion of *C*-2 hydroxymethylated carbohydrates to cyclic ketoses,[271] using PhIO and iodine, and also the photochemical synthesis of chiral spiroacetals from carbohydrates by $PhI(OAc)_2$ and iodine,; an example[272] of the latter type is illustrated in eq. 46.3.

15. Miscellaneous Transformations

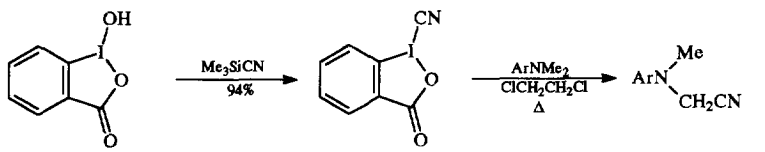
15.1 Transformations of amines

Amines react with iodanes in various ways. For example, primary and secondary aliphatic amines were dehydrogenated by PhIO to, respectively, nitriles[273] and imines;[274] cyclic secondary amines in water were converted directly to lactams.[274] Aromatic amines gave mainly azo compounds with $PhI(OAc)_2$. Some anilines reacted with indole and 2-substituted indoles in presence of $PhI(OAc)_2$ to afford 2-arylamino- or 3-aryliminoindoles in moderate yield; it was demonstrated that anilines were initially oxidised to their radical cations which through nitrenium cations, $ArNH^+$, afforded the substitution products,[275] as exemplified in eq. 47.1.

Scheme 47

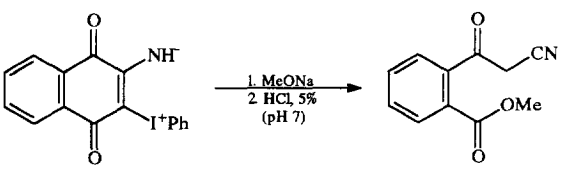


(47.1)



(47.2)

(Ar = Ph, 4-BrC_6H_4, 4-MeC_6H_4, 1- naphthyl; 80-96%)



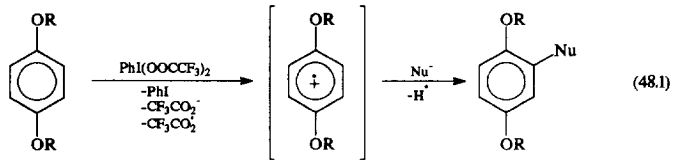
(47.3)

A new cyclic iodane, 1-cyano-benziodoxol-3-(1*H*)-one, which is readily obtained from "*o*-iodosylbenzoic acid", was exceptionally efficient as a cyanating agent for some *N,N*-dimethylarylamines (eq. 47.2).[276] This reaction follows probably a free radical pathway, analogous to azidation (section 6.2). 2-Amino-1,4-naphthoquinone gave with PhI(OH)OTs a stable phenyliodonium 1,4-dipole; this was thermally isomerised to 2-phenylamino-3-iodo-1,4-naphthoquinone,[50] whereas with an excess of sodium methoxide followed by neutralisation the unusual transformation depicted in eq. 47.3 took place.[277]

15.2 Nucleophilic aromatic substitution

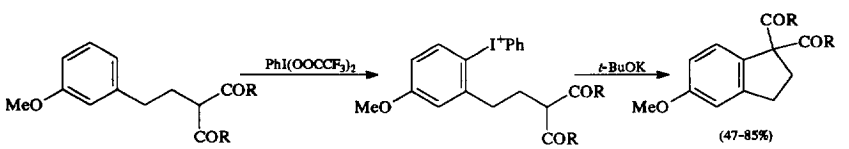
Electron rich aromatic compounds undergo substitution by nucleophiles in presence of iodanes through diverse pathways. Phenol ethers of various kinds upon reaction with $PhI(OOCCF_3)_2$ (in hexafluoro-2-propanol, at room temperature) formed initially charge-transfer complexes from which were generated radical cations, observable by EPR; in the presence of a variety of nucleophiles, substitution ensued[143,278] according to the general pattern of eq. 48.1. In a spectroscopic study, several electron rich aromatics underwent one-electron oxidation by $PhI(OOCCF_3)_2$, sometimes with formation of further transformation products.[279]

Scheme 48

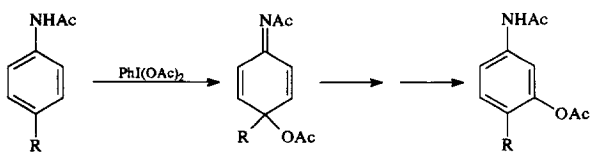


(48.1)

(Nu⁻ comes from NaN_3, Me_3SiOAc, Me_3SiNCS, β-diketones, ArSH, RSH)



(48.2)



(48.3)

An intramolecular aromatic alkylation of α -(aryl)alkyl β-dicarbonyl compounds was shown to proceed *via* phenyliodonium intermediates (eq. 48.2).[280] 4- Substituted anilides were converted by $PhI(OAc)_2$ in acetic acid, at room temperature, to 3-acetoxy derivatives, *via* nucleophilic attack of acetate on the aromatic ring; the intermediate dienoneimine (eq. 48.3), in contrast to the stable dienone analogues (section 8.2), rearranged to afford the final products.[281]

16. Applications in Natural Product Syntheses

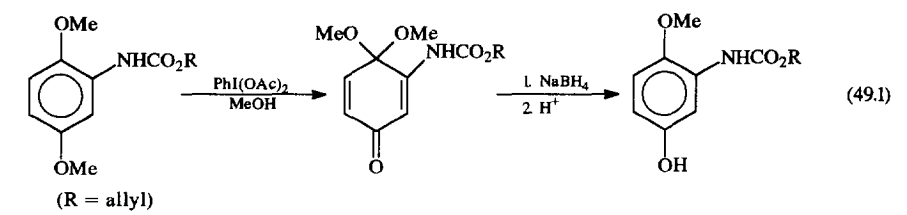
Some iodanes have gained popularity in synthetic applications in the field of natural products. Among them, the Dess-Martin reagent is presently the reagent of choice for the oxidation of alcohols to carbonyl compounds. It should be noted that a selective ketol oxidation during the synthesis of glaucarubolone[282] was uniquely successful with an analogue of "o-iodylbenzoic acid", in which the carbonyl oxygen was replaced by two trifluoromethyl groups. Another iodane, $PhI(OOCCF_3)_2$, is increasingly preferred for two different transformations: deprotection of thioacetals and amide degradation.

α-Hydroxylation of ketones using $PhI(OAc)_2$ in methanolic KOH has been widely used in several instances, for example in the synthesis of ikarugamycin,[283] cephalotaxine,[284] 2α-hydroxytropan-3-one,[285] etc. The direct

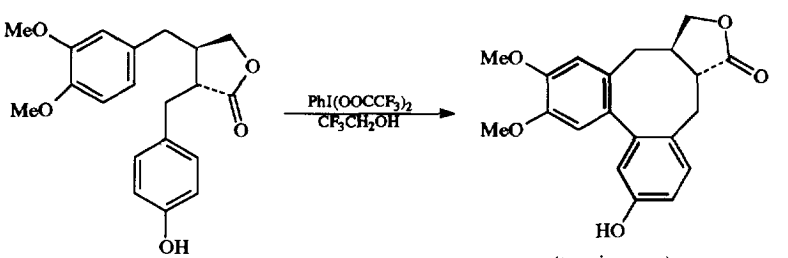
conversion of an ethynyl group to hydroxyacetyl using $PhI(OOCCF_3)_2$ (see eq. 4.2) was applied in a total synthesis of the aglycone of 11-deoxyadriamycin-type antibiotics.[21] The same oxidant brought about rearrangement of a substituted chalcone to the monoacetal of a β-dicarbonyl compound (see eq. 32.2) in a key step during the synthesis of homopterocarpin.[286] The system $PhIO_2$ / $(PhSe)_2$ was used for the introduction of oxygen functionality into *aspidosperma*-type alkaloids[287]. Lack of space will limit this section to rather few illustrated examples of further transformations.

Phenolic oxidation mediated by iodanes has been abundantly applied in the synthesis of many natural products. A good way to demethylate selectively an intermediate during synthetic studies of manumycins involved oxidation by methanolic $PhI(OAc)_2$ followed by reduction (eq. 49.1).[288]

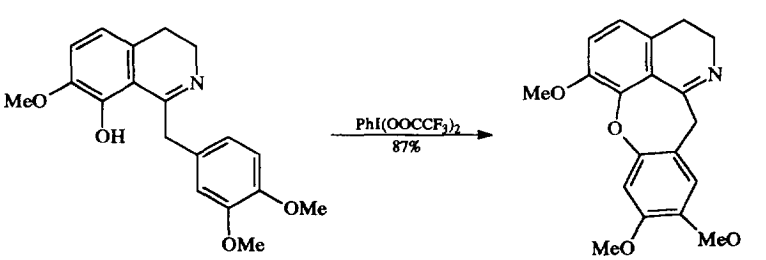
Scheme 49



(R = allyl) (49.1)



(two isomers) (49.2)



(49.3)

Oxidations of phenolic intermediates to quinone imines were effected using both $PhI(OAc)_2$ and $PhI(OOCCF_3)_2$ in a total synthesis of dynemicin A.[289] Oxidative cyclisations of phenolic compounds involving C-C bond formation have been effected by using either $PhI(OAc)_2$ or $PhI(OOCCF_3)_2$. Despite low yields, these oxidants were uniquely effective, especially in the field of morphine alkaloids; for example, in the conversion of reticuline to salutaridine[290] and related[291,292] reactions. An interesting cyclisation leading to the formation of 8-membered carbocycles was realised upon oxidation of phenolic *trans*-2,3-dibenzyl-butyrolactones to steganes and isosteganes[293] (eq. 49.2). A synthesis of discorhabdin C involved in its final stage the use of $PhI(OOCCF_3)_2$ with formation of a spirocyclohexadienone system.[294] The strong oxidant $C_6F_5I(OOCCF_3)_2$ induced C-O bond formation in phenolic precursors during synthetic studies of cularine and sarcocarpine alkaloids,[295] as illustrated in eq. 49.3. A key intermediate in a synthesis of tuberostemonine was obtained by $PhI(OAc)_2$ oxidation leading to intramolecular C-O bond formation from the hydroxyl oxygen of the carboxyl group of *N*-protected tyrosine; in alkaline environment this was transformed *in situ* to a bicyclic product with a C-N bond.[296] Direct C-N bond formation in an indolic compound was effected by $PhI(OAc)_2$ in a synthesis of sporidesmin-A.[297]

Hypervalent iodine methodology was further applied to various reactions. These include: an oxidative decarboxylation step by $PhI(OAc)_2$ /$Cu(OAc)_2$ in the synthesis of the steroid dolicholide;[298] selective chlorination in steroids[1] using $ArICl_2$ (remote chlorination); hydroxylation of the methyl group by PhIO and an iron porphyrin in pyrrole derivatives;[299] intramolecular cyclopropanation *via* an iodonium ylide in a synthesis of the 3,5-cyclovitamin D ring A synthon;[300] cyclodehydrogenation of 2-hydroxychalcones by $PhI(OAc)_2$ leading to flavones;[301] and numerous applications of the Suarez reaction (section 7.2); for example in a synthesis of 8-deoxyvernolepin[302] and in the field of steroids.[303]

17. Conclusion and Future Outlook

Hypervalent iodine reagents are coming of age. Their advantages are indeed impressive: mild reaction conditions, operational simplicity, selectivity, efficiency and diversity are combined with reasonable cost, non-toxicity and the possibility of recycling. Therefore, it is not surprising that old and new iodanes are increasingly used for a plethora of useful transformations. An extra

intriguing feature is that because of their versatility, sometimes their reactions may lead to unexpected products, not easily available otherwise. It is hoped that this report will induce more people to try their hand in the fascinating and rewarding field of hypervalent iodine compounds.

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Biographical Sketch

Anastasios Varvoglis

Anastasios Varvoglis graduated from the University of Thessaloniki in 1961. He received his PhD from Cambridge University in 1967 under the direction of professor A.J. Kirby. Since 1974 he has been Professor of Organic Chemistry at the University of Thessaloniki. For the last 25 years he has published regularly and exclusively in the field of hypervalent iodine, especially on the chemistry of iodonium dipoles and salts. He is the author of three review articles and two books on hypervalent iodine, one of which has just been published.