

[Hydroxy(organosulfonyloxy)iodo]arenes in Organic Synthesis

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Abstract: In Part I of this Account, the utility of [hydroxy(sulfonyloxy)iodo]benzenes, $\text{PhI}(\text{OH})\text{OSO}_2\text{R}$, and closely related sulfonyloxyiodinanes for the oxysulfonylation, aryliodination, and oxidation of organic molecules is reviewed. Not only is the work from the research groups of the principal authors covered, but also that of other major researchers in the field. These hypervalent iodine reagents have been employed for the preparation of α -sulfonyloxy carbonyl compounds (ketones, esters, lactones), *vic*-ditosyloxyalkanes, 1,4-disulfonyloxyalkenes, tosyloxylactones, bislactones, ketolactones, isoflavones, and alkynyl- and vinylodonium salts. The functionalization of cubanes, the direct conversion of carboxamides to alkylammonium tosylates and various oxidative rearrangements are also described. Some underlying and unifying mechanistic interpretations are presented with particular emphasis on the stereo- and regiochemistry attending the aforementioned transformations. In Part II one of the authors (GFK) documents the role of serendipity in a number of discoveries achieved by his group in this area.

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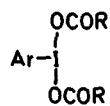
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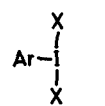
1. Introduction

In recent years, there has been considerable interest in hypervalent iodine(III) compounds as reagents for organic synthesis.¹⁻¹⁵ Prior to 1970, most known tricoordinate iodine compounds of general structure ArIL_1L_2 possessed identical heteroatom ligands, i.e., $\text{L}_1 = \text{L}_2 = \text{RCO}_2$, Cl, F, (1 and 2). In 1970, Neiland and Karele reported the synthesis of the less symmetrical iodine, [hydroxy(tosyloxy)iodo]benzene (3, HTIB).¹⁶ Koser and co-workers subsequently explored the efficacy of HTIB as a reagent for the phenyliodination and oxytosylation of a range of organic substrates, and HTIB is sometimes referred to as "Koser's Reagent" (e.g., *Aldrich Catalogue*, 1990-1991). A remarkable feature of HTIB is its ability to introduce the formal equivalent of the tosyloxonium ion (i.e., TsO^+) directly

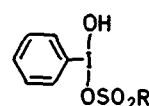
onto carbon. For example, ketones and silyl enol ethers react with HTIB to give α -tosyloxy ketones.^{17,18} More recently, the preparation and chemistry of [hydroxy(mesyloxy)iodo]benzene (4, HMIB)¹⁹⁻²¹ and [hydroxy((+)-10-camphorsulfonyl)oxy]iodo]benzene (5)²² have attracted interest. In this article, the literature on the synthesis and reactions of 3, 4, 5, and the structurally related iodine, μ -oxobis[(trifluoromethanesulfonato)(phenyl)iodine] (6),²³ are reviewed.



1 R = alkyl, CF_3 , aryl



2 X = Cl, F



3 R = *p*-tolyl

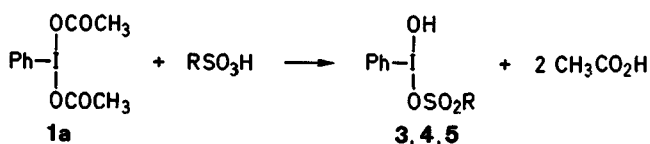
4 R = Me

5 R = 10-camphoryl

2. Synthesis and Structure of

[Hydroxy(organosulfonyloxy)i]darenes

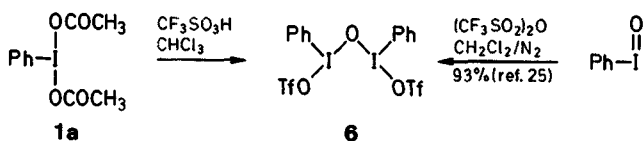
[Hydroxy(tosyloxy)i]darene (3) can be prepared by the treatment of (diacetoxi)idarene (1a) with *p*-toluenesulfonic acid monohydrate in organic solvents (e.g., $\text{ClCH}_2\text{CH}_2\text{Cl}$, MeCN), and it can be recrystallized from acetonitrile.^{16,24} [Hydroxy(mesyloxy)i]darene (4)^{19–21} and the chiral analog, [hydroxy[(+)-10-camphorsulfonyl]oxy]i]darene (5),²² can be made in the same way from 1a and the appropriate sulfonic acids. The sulfonyloxyiodinanes are stable crystalline solids and may be stored.



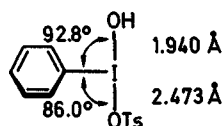
product	R	solvent	yield (%)
3	<i>p</i> -tolyl	$\text{ClCH}_2\text{CH}_2\text{Cl}$ or MeCN	82, ¹⁶ 93 ²⁴
4	Me	CHCl_3 or MeCN or MeCN + H_2O	70–87
5	10-camphoryl	MeCN + H_2O	80

HTIB (3) and its benzenesulfonate, *p*-chlorobenzenesulfonate and *p*-nitrobenzenesulfonate analogs have also been synthesized from (dichloro)idarene, PhICl_2 , and the appropriate silver arenesulfonates, $\text{Ag}^+ \text{ArSO}_3^-$, in acetonitrile,²⁴ but the diacetate/sulfonic acid method is more convenient and provides higher yields of products.

The treatment of 1a with triflic acid does not give [hydroxy-(trifluoromethylsulfonyloxy)i]darene (7), $\text{PhI}(\text{OH})\text{O}_3\text{SCF}_3$. When 1a is mixed with trifluoromethanesulfonic acid in chloroform, the anhydride of 7, μ -oxobis[trifluoromethanesulfonato(phenyl)iodine] (6) is obtained instead.²³ The treatment of iodosobenzene with triflic anhydride also affords 6.²⁵ The oxygen-bridged ditriflate 6 is a yellow solid, characteristic of some μ -oxoiodinanes,²⁶ and can be kept for months under nitrogen.²⁵



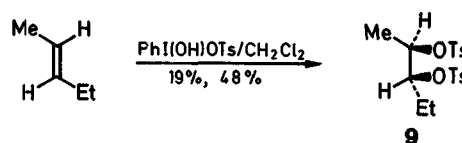
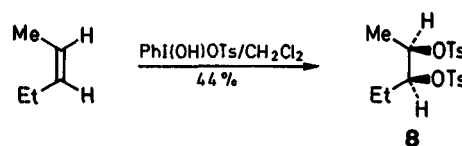
The structure of HTIB has been established by single-crystal X-ray analysis.²⁷ As expected, the iodine(III) atom is T-shaped about the iodine(III) atom. The electronegative heteroligands are colinear, and the I–OTs bond (2.473 Å) is substantially longer than the sum of the iodine and oxygen covalent radii (1.99 Å) thus indicating that it is endowed with ionic character. In contrast, the I–OH bond (1.94 Å) is a bit shorter than predicted from covalent radii.



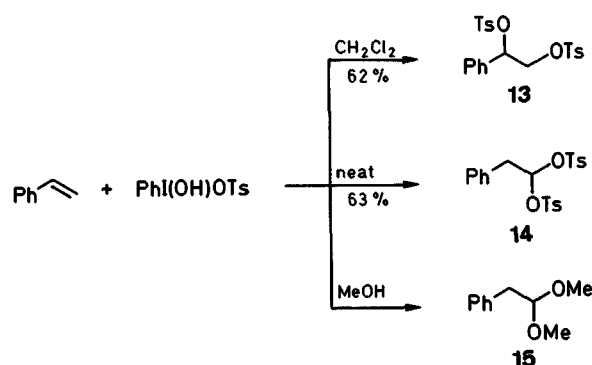
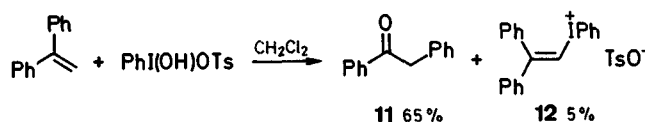
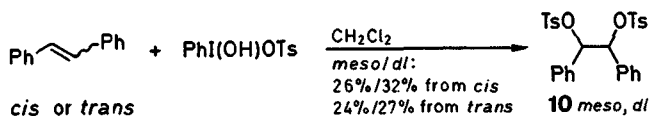
3. Synthesis of *vic*-Ditosyloxyalkanes, *vic*-Dimesyloxyalkanes and *vic*-Bistrifloxyalkanes from Alkenes

vic-Ditosyloxyalkanes are produced in moderate yields (16–69%) when various alkenes are mixed with HTIB in

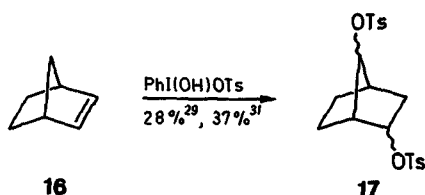
dichloromethane.^{28,29} Cyclohexene, *cis*- and *trans*-2-butene, *cis*- and *trans*-2-pentene, *cis*-3-hexene, and *cis*-4-octene all react stereospecifically and afford ditosyloxyalkanes derived from the *syn* addition of the tosyloxy ligands to the double bond.²⁹ For example, *cis*-2-pentene gives (\pm)-*erythro*-2,3-ditosyloxy-pentane (8) with HTIB while *trans*-2-pentene affords (\pm)-*threo*-2,3-ditosyloxy-pentane (9).²⁹ The ditosyloxylation process is typically accompanied by the production of *p*-toluenesulfonic acid, which arises from an unidentified side reaction involving the reductive decomposition of HTIB.²⁹



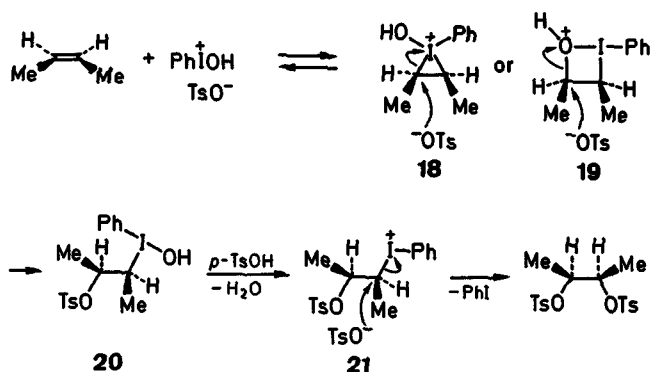
The placement of phenyl substituents on the carbon–carbon double bond either destroys the stereospecificity of ditosyloxylation or promotes molecular rearrangements.^{28,29} Thus, *cis*- and *trans*-stilbene react with HTIB much more slowly than alkyl-substituted alkenes do and give mixtures of *meso*- and (\pm)-1,2-diphenyl-1,2-ditosyloxyethane (10) in both cases. 1,1-Diphenylethylene affords deoxybenzoin (11) as the major product and a low yield of β , β -diphenylethenyl(phenyl)iodonium tosylate (12). The products derived from styrene with HTIB depend upon the reaction medium. When dichloromethane is employed as solvent, the “normal” product, 1-phenyl-1,2-ditosyloxyethane (13), is produced, but in the absence of solvent, rearrangement occurs and 1,1-ditosyloxy-2-phenylethane (14) is obtained.²⁹ The treatment of styrene with HTIB in methanol yields phenylacetaldehyde dimethyl acetal (15).³⁰



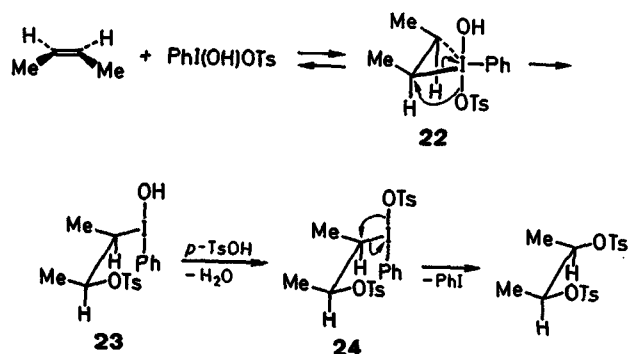
Rearrangement also occurs when norbornene (**16**) is the substrate, and a diastereomeric mixture of 2,7-ditosyloxy-norbornanes (**17**) is obtained.^{29,31} A similar rearrangement has been observed in the reaction of norbornene with [hydroxy(mesyloxy)iodo]benzene.¹⁹



The stereospecificity of ditosyloxyalkane formation from alkyl-substituted alkenes can be accommodated by a polar mechanism in which HTIB behaves, at least formally, as an ion pair (i.e., PhI^+OH , TsO^-).^{28,29} This is illustrated below for the ditosyloxylation of *cis*-2-butene. Electrophilic *anti* addition of HTIB to the alkene double bond via the bridged periodonium tosylate **18** or the protonated cyclic alkoxyiodinane **19** to give the hydroxyiodinane **20** seems plausible. Dehydroxylation of **20** at the iodine atom with tosic acid would give the phenyl(β -tosyloxyalkyl)iodonium tosylate **21**. Nucleophilic displacement of iodobenzene from carbon by the tosylate ion in **21** with inversion of configuration would deliver the *vic*-ditosyloxyalkane with overall *syn* stereochemistry.

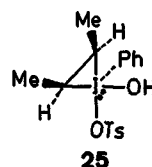


An alternative mechanism, and one which may have general applicability, entails an initial oxidative addition of HTIB to the alkene to give the iodine(V) species **22**, a fully coordinated, non-ionic variant of **18**. Coupling of an equatorial carbon atom with the axial tosylate ligand in periodinane **22** with *retention* of configuration to give the hydroxyiodinane **23** is proposed. Ligand exchange (i.e. tosyloxy for hydroxy) in **23** to give **24** followed by a second ligand coupling in **24**, again with retention of configuration



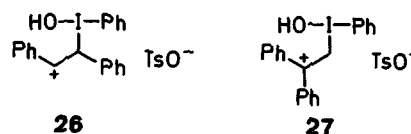
at carbon, and the reductive elimination of iodobenzene would complete ditosyloxyalkane formation by an overall *syn* addition.

Stable pentacoordinate iodine(V) compounds are generally thought to be square pyramidal about the iodine atom with two pairs of colinear ligands.² Thus, the C–I–C angle strain in the trigonal bipyramidal species **22** might well drive the initial ligand-coupling step (i.e., **22** → **23**). Alternatively, ligand coupling may proceed via the less strained (but still strained) square pyramidal periodinane **25**.

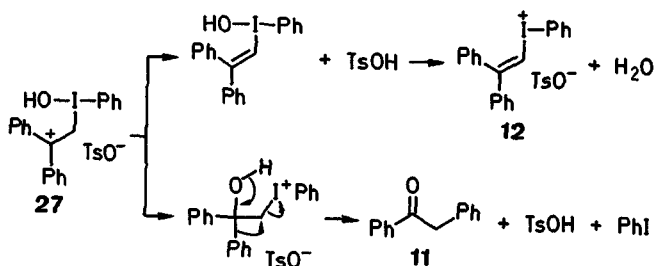


In summary, the *syn* ditosyloxylation of alkenes with HTIB is accounted for by two inversion steps in the polar mechanism and two retention steps in the oxidative addition/reductive elimination mechanism.

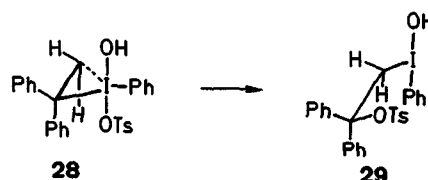
The non-stereospecific ditosyloxylation of the stilbenes and the conversion of 1,1-diphenylethylene to **11** and **12** with HTIB is consistent with a polar mechanism in which the open carbenium ions **26** and **27**, instead of bridged periodonium species such as **18**, play a key role.

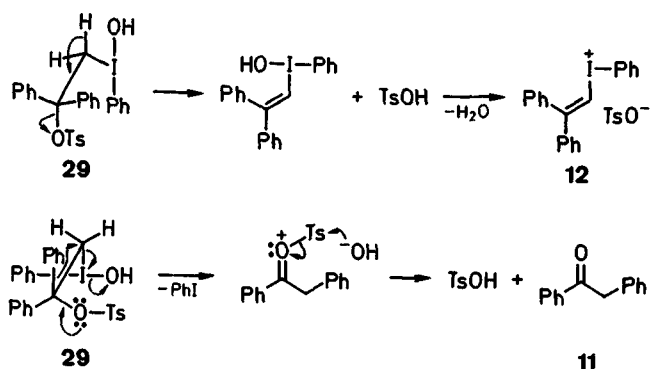


Thus, β -proton elimination from **27** followed by dehydroxylation at iodine would afford **12**, while intramolecular capture of the carbenium center by the hydroxyl group in **27** followed by 1,2-phenyl migration with loss of iodobenzene would give **11**.



The oxidative addition of HTIB to 1,1-diphenylethylene to give the periodinane **28** also seems plausible. Ligand coupling in **28** would afford the hydroxyiodinane **29**, which might either eliminate tosic acid to give **12** or rearrange with the reductive elimination of iodobenzene to give **11**.

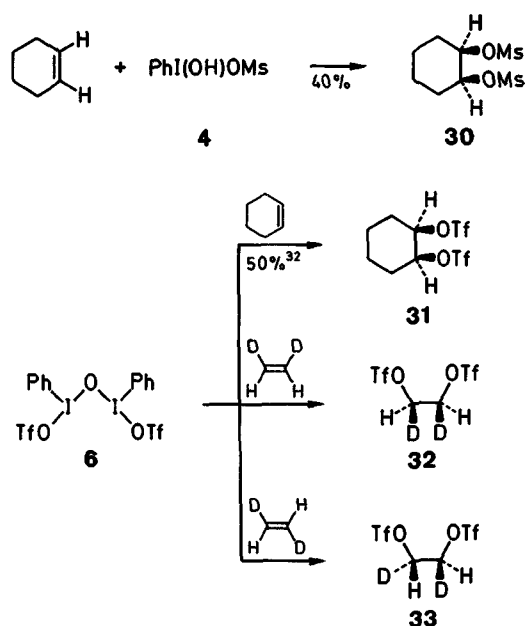




In principle, these mechanisms could be distinguished by the use of HTIB labeled at the hydroxyl oxygen atom with ^{18}O . If the oxidative addition/reductive elimination sequence is correct, unlabeled deoxybenzoin should be produced, but if the polar mechanism is operative, ^{18}O -labeled deoxybenzoin should be obtained.

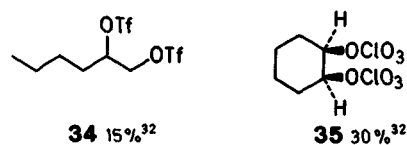
The rearrangements of styrene and norbornene with HTIB can be explained by similar mechanisms.

The reactions of selected alkenes with [hydroxy(mesyloxy)-iodo]benzene (4) to give *vic*-dimesyloxyalkanes^{19,32,33} and with μ -oxobis[(trifluoromethanesulfonyl)(phenyl)iodine] (5) to give *vic*-bis(trifluoromethylsulfonyloxy)alkenes^{23,25,32} have also been investigated. The introduction of the sulfonyloxy ligands into the alkene double bond with *syn* stereospecificity has been demonstrated for both reagents. Thus, cyclohexene reacts with both 4 and 6 to give the corresponding *cis*-1,2-disulfonyloxycyclohexanes 30³³ and 31.^{23,32} The treatment of *cis*-1,2-dideuteroethylene with the μ -oxotriflate 6 affords *meso*-1,2-bis(trifluoromethylsulfonyloxy)[1,2- $^2\text{H}_2$]ethane (32), while *trans*-1,2-dideuteroethylene affords the (\pm)-diastereoisomer 33.²⁵



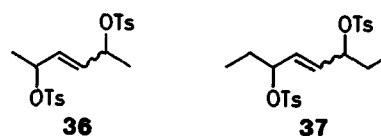
An interesting variant of the foregoing reactions is the functionalization of alkenes with HTIB in the presence of nucleofugic anion salts.^{32,34} For example, when 1-hexene is mixed with HTIB in the presence of a fivefold excess of lithium trifluoromethanesulfonate, a low yield of the ditriflate 34 is produced. Similar treatment of cyclohexene with

HTIB in the presence of lithium perchlorate affords the *cis*-diperchlorate 35.

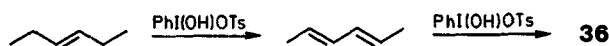


4. Synthesis of 1,4-Ditosyloxyalkenes and 1,4-Bistrifloxyalkenes from Conjugated Dienes

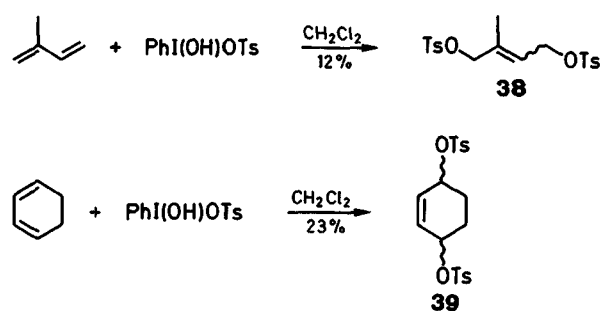
The reactions of *trans*-3-hexene and *trans*-4-octene with HTIB follow a different course than those of the corresponding *cis*-alkenes and afford low yields of 2,5-bis(tosyloxy)-3-hexene (36) and 3,6-bis(tosyloxy)-4-octene (37).²⁹



That the *trans*-alkenes are first oxidized to dienes which then undergo conjugate ditosyloxylation with HTIB is indicated by the identification of *cis,trans*- and *trans,trans*-2,4-hexadienes in the *trans*-3-hexene reaction mixture and by the conversion of authentic *trans,trans*-2,4-hexadiene to 36 in 35% yield with HTIB.²⁹

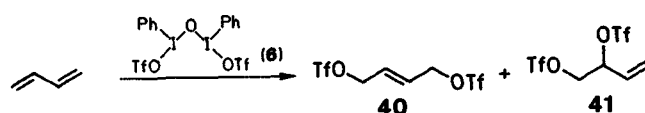


This method for the synthesis of 1,4-ditosyloxyalkenes from conjugated dienes is not very efficient and far from universal, but it does exhibit some generality.³⁵ For example, isoprene affords 1,4-ditosyloxy-2-methyl-2-butene (38) with HTIB, while 1,3-cyclohexadiene gives 1,4-ditosyloxy-2-cyclohexene (39).³⁵



The geometries (i.e., *E*, *Z*) of the acyclic ditosyloxyalkenes have not yet been determined nor has the stereochemistry of the conjugate ditosyloxylation process.

The reaction of 1,3-butadiene with μ -oxobis[(trifluoromethanesulfonyl)(phenyl)iodine] (6) has also been studied and affords an 89:11 mixture of the 1,4- and 1,2-ditriflates 40 and 41.²⁵ Treatment of the 1,4-ditriflate with tetraethylammonium bromide gives (*E*)-1,4-dibromo-2-butene.²⁵



converted to the (\pm)-bislactone **50**, thus confirming the *syn* stereospecificity of the bislactonization process.³⁷

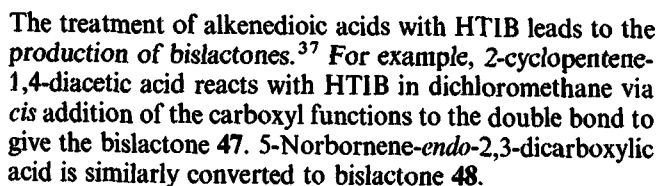
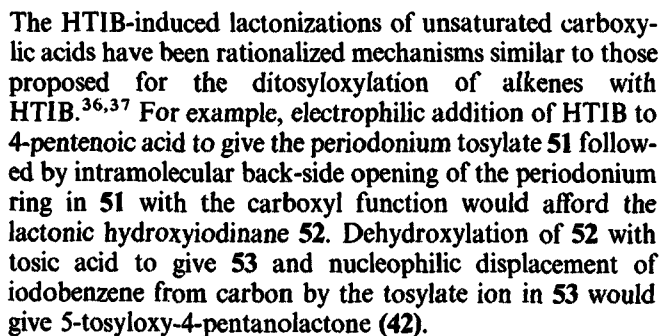
OC(=O)C/C=C/C(=O)O
 $\xrightarrow[\text{64 \%}]{\text{PhI(OH)OTs/CH}_2\text{Cl}_2}$
O=C1OC2C(=O)OC(=O)C2C1

49

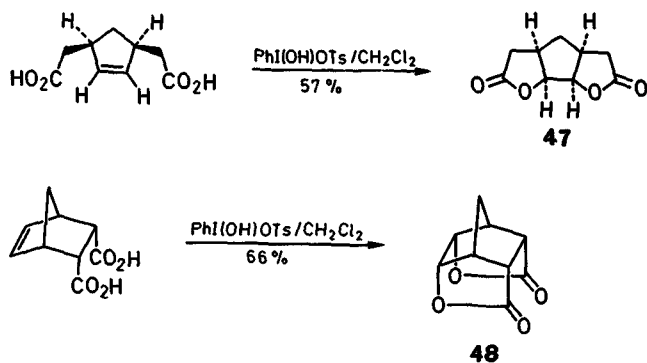
OC(=O)C/C=C\CCCC(=O)O
 $\xrightarrow[\text{CH}_2\text{Cl}_2]{\text{PhI(OH)OTs}}$
O=C1OC2C(=O)OC(C1)C2

 64%

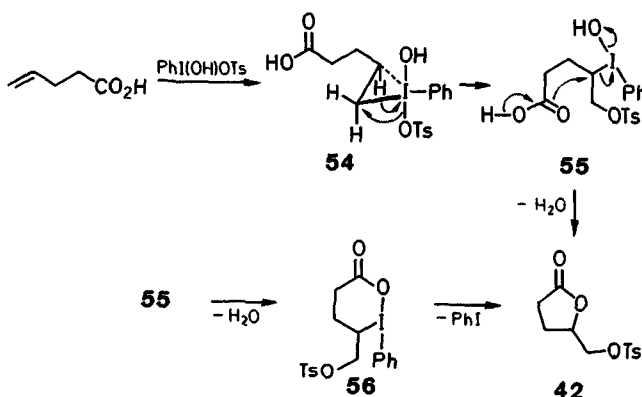
50



A sequence initiated by the oxidative addition of HTIB to 4-pentenoic acid to give the fully coordinated periodinane **54** followed by front-side carbon–tosylate ligand coupling in **54** to give the acyclic hydroxyiodinane **55** also seems plausible. Cyclization of **55** with the concomitant reductive elimination of iodobenzene would afford **42**. A possible variant of this mechanism is one in which the lactonic iodinane **56** intervenes and collapses to **42** and iodobenzene via front-side ligand coupling.

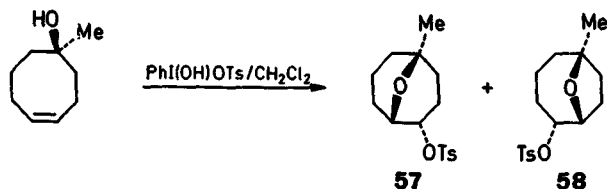


The stereochemistry of the bislactonization reaction has been established by the selection of diacids in which the carboxyl groups are not geometrically restricted for *cis* addition as they are in the foregoing substrates. The treatment of *cis*-4-octene-1,8-dioic acid with HTIB affords the *meso*-bislactone **49**, while *trans*-4-octene-1,8-dioic acid is

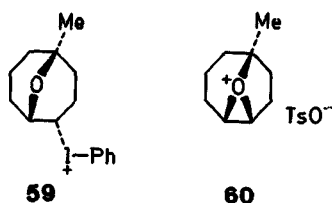


5.2. Participation of the Hydroxyl Group

[Hydroxy(tosyloxy)iodo]benzene effects the oxidative cyclization of 1-methyl-4-cycloocten-1-ol in dichloromethane to a mixture (55% yield) of the tosyloxy-9-oxabicyclononanes **57** and **58**.³⁸ Although this reaction exhibits little

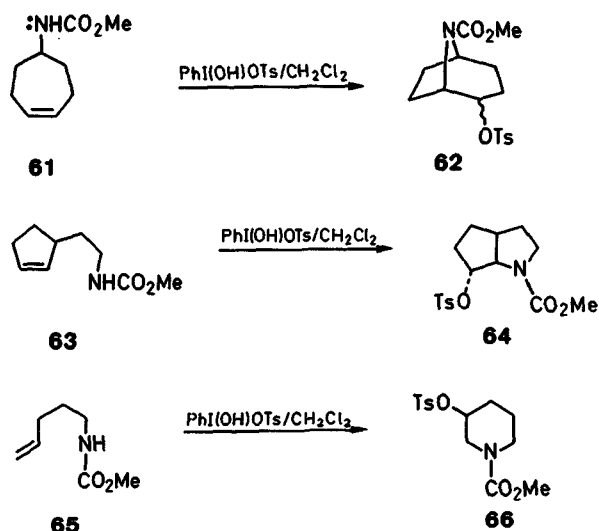


regioselectivity, the addition to the double bond proceeds with high *trans* stereoselectivity, thus providing an interesting contrast to the *cis* functionalizations of alkenes and alkenedioic acids with HTIB. The stereochemistry has been rationalized by the intermediate production of the *trans*-iodonium species **59** (and its regio isomer) from an initially formed bridged periodonium ion and its collapse to the bridged oxonium species **60** prior to the introduction of the tosyloxy ligand.³⁸

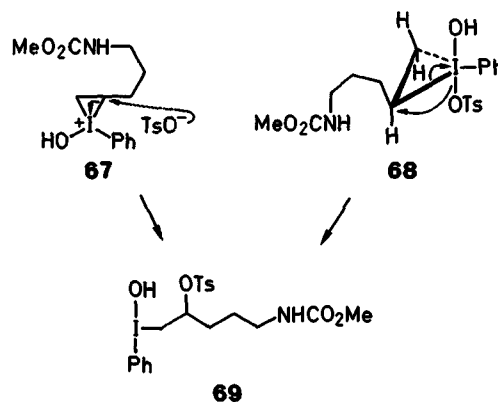


5.3. Participation of Carbamate Nitrogen

The reaction of the cycloheptenylcarbamate **61** with HTIB in dichloromethane proceeds with participation of the nitrogen atom of the carbamate function and affords *N*-methoxycarbonyl-2-tosyloxy-7-azabicyclo[3.2.1]octane (**62**).³⁹ The cyclopentenylcarbamate **63** is similarly converted to **64**, the structure of which has been established by X-ray analysis.³⁹ Treatment of the acyclic carbamate **65** with HTIB affords *N*-methoxycarbonyl-3-tosyloxypiperidine (**66**).³⁹ Compound **66** is the non-Baldwin–Eschenmoser product and may originate from a reaction sequence in

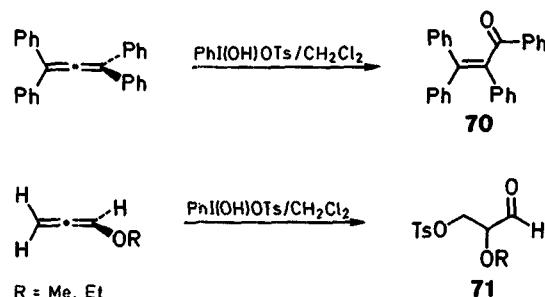


which the tosyloxy ligand is selectively introduced at the secondary carbon in cyclic hypervalent intermediates such as **67** and **68** to give the hydroxyiodinane **69** prior to carbon–nitrogen bond formation.



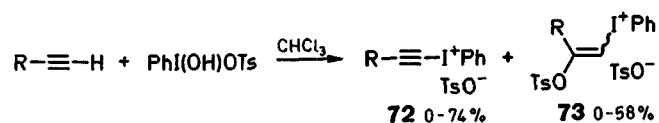
6. Reactions of Allenes with [Hydroxy(tosyloxy)iodo]benzene

Tetraphenyl-1,2-propadiene undergoes an oxidative rearrangement with HTIB in dichloromethane to give α,β -diphenylchalcone (**70**).⁴⁰ This reaction finds analogy in the HTIB-induced conversion of 1,1-diphenylethylene to deoxybenzoin (**11**) and may be rationalized in a similar way.²⁹ 1-Alkoxypropa-1,2-dienes afford 2-alkoxy-3-tosyloxypropenals **71** under similar conditions.⁴⁰



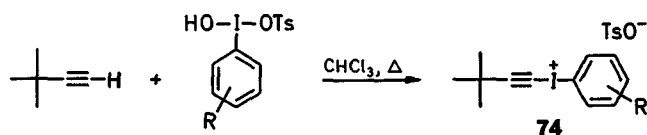
7. Synthesis of 1-Alkynyl- and 1-Alkenyliodonium Salts from Alkynes

The treatment of terminal alkynes with [hydroxy(tosyloxy)iodo]benzene in chloroform affords 1-alkynyl(phenyl)iodonium tosylates **72** and phenyl(2-tosyloxy-1-alkenyl)iodonium tosylates **73**.^{28,41,42} The product composition in these

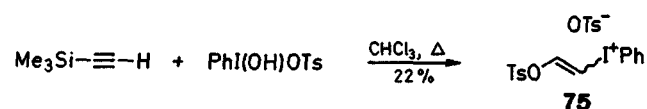


reactions appears to be regulated to some extent by the steric bulk of the R group in the starting alkyne.⁴¹ When R is large (i.e., *tert*-butyl, *sec*-butyl, cyclohexyl, cyclopentyl) or when R = aryl (i.e., Ph, *p*-tolyl), 1-alkynyliodonium salts **72** are obtained either exclusively or nearly so, but when R is small

(i.e., propyl, butyl, hexyl), (2-tosyloxy-1-alkenyl)iodonium salts **73** are formed preferentially. Alkyl groups of intermediate size (R = isopropyl, isobutyl) afford mixtures of **72** and **73**. 3,3-Dimethyl-1-butyne is an excellent substrate for the synthesis of 1-alkynyliodonium salts. Treatment of this alkyne with a series of [hydroxy(tosyloxy)iido]arenes affords a variety of aryl (3,3-dimethyl-1-butyryl)iodonium tosylates **74**, which have been isolated in yields ranging from 56 to 80%.⁴³ Trimethylsilylacetylene, on the other hand, fails to give an alkyne salt with HTIB and reacts with cleavage of the trimethylsilyl group to give a low yield of phenyl(β -tosyloxyvinyl)iodonium tosylate (**75**).⁴¹

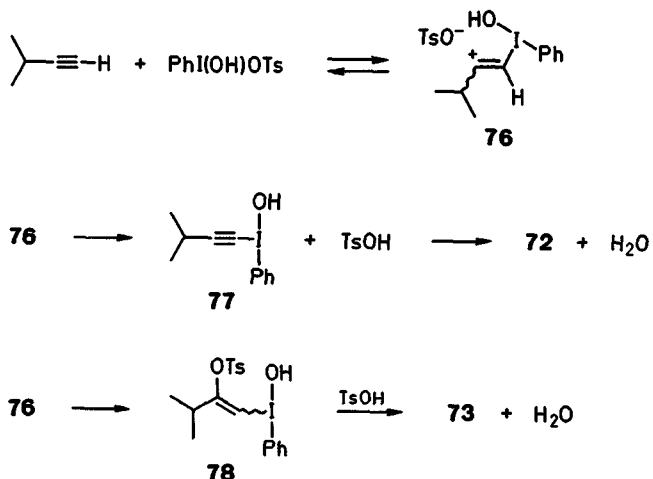


R = H, 2-Me, 3-Me, 4-Me, 2-F, 3-F, 4-F, 3-Cl, 4-Cl



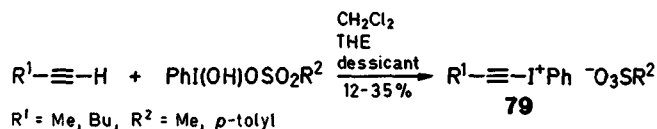
The formation of (2-tosyloxy-1-alkenyl)iodonium salts from terminal alkynes with HTIB proceeds, at least in some cases, with low stereoselectivity. Thus, mixtures of geometric isomers of **73** have been obtained from 1-pentyne and 1-hexyne, and they can be separated.⁴¹ However, their specific configurations (i.e., *E* vs. *Z*) have not yet been established.

The observed steric effect on the **72/73** ratio in these reactions and the low stereoselectivity attending the production of **73** are consistent with a polar mechanism in which **72** and **73** originate from a common intermediate, presumably an "open" carbenium ion. This is illustrated below for the reaction of isopropylacetylene with HTIB. Electrophilic attack of HTIB on the triple bond of the alkyne would give the vinyl cation **76**, which might either eliminate a proton to give **72** via the hydroxyiodinane **77** or be captured by the tosylate ion to give **73** via the hydroxyiodinane **78**.

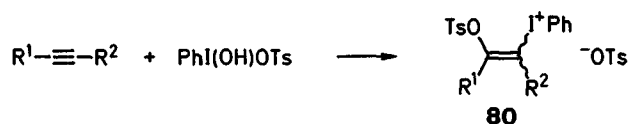


An important modification of this method for 1-alkynyliodonium salt synthesis is the treatment of terminal alkynes

with [hydroxy(sulfonyloxy)iodo]benzenes in dichloromethane in the presence of THE dessicant (i.e., silica bead).^{20,44} Under these conditions, even those alkynes with small R groups (i.e., methyl, butyl) afford 1-alkynyl(phenyl)-iodonium tosylates and mesylates **79** with HTIB (**3**) and HMIB (**4**).

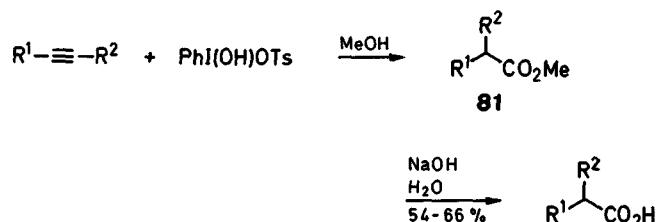


Internal alkynes (2-butyne, 2-heptyne, methylphenylacetylene) also react with HTIB to give phenyl(2-tosyloxy-1-alkenyl)iodonium tosylates **80**.²⁸ However, neither their geometric configurations nor the regiochemistry (i.e., direction of HTIB addition) of the 2-heptyne and methylphenylacetylene adducts have been elucidated.



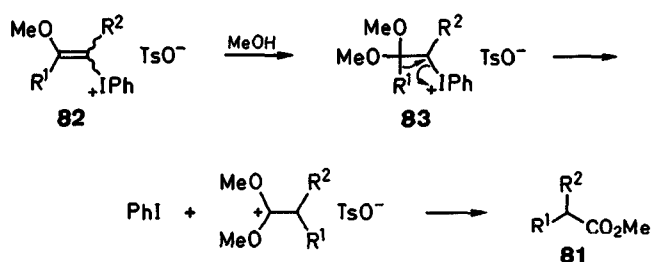
8. Oxidative Rearrangement of Alkynes to Esters

Both terminal and internal alkynes react with HTIB in methanol to give esters of carboxylic acids **81**.⁴⁵ For example, methylphenylacetylene is converted to methylphenylacetate.



$R^1, R^2 = \text{Bu, H; Ph, H; Pr, Me; Ph, Me; Ph, Et; } p\text{-CH}_3\text{COC}_6\text{H}_4, \text{Me; } \alpha\text{-thienyl, H}$

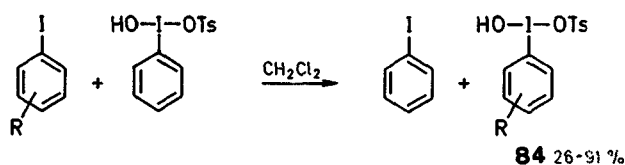
A likely mechanism for these oxidative rearrangements entails the initial formation of 2-methoxy-1-alkenyl(phenyl)iodonium tosylates **82** analogous to the production of (2-tosyloxy-1-alkenyl)iodonium salts **73** and **80** from alkynes with HTIB in non-hydroxylic solvents. Michael addition of methanol to the double bond of **82** to give **83** followed by a 1,2-shift of the R¹ group in **83** with loss of iodobenzene would ultimately afford **81**.



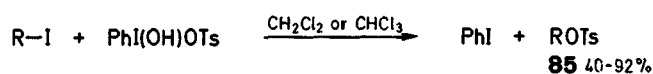
That 1-alkynyl(phenyl)iodonium salts may precede the formation of **81** when terminal alkynes are substrates is indicated by the production of methyl α -methylphenylacetate from authentic phenylethynyl(phenyl)iodonium tosylate ($\text{PhC}\equiv\text{C}^+\text{I}^-\text{Ph}^-\text{OTs}$) with HTIB in methanol under reflux.⁴⁵

9. Ligand Transfer and Oxidative Displacement Reactions of Iodoarenes and Iodoalkanes with Sulfonyloxy-iodinanes: Synthesis of Sulfonyloxycubanes and homocubanes

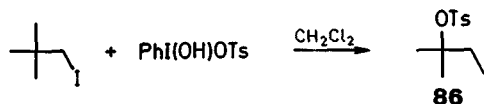
When various iodoarenes are mixed with [hydroxy(tosyloxy)iodo]benzene in dichloromethane, ligand transfer occurs, and the corresponding [hydroxy(tosyloxy)iodo]arenes **84** are obtained.⁴⁶ However, the treatment of iodoalkanes with HTIB eventuates in the production of tosyloxyalkanes **85**.^{47,48} When neopentyl iodide is the substrate, 2-methyl-2-tosyloxybutane (**86**), a product of molecular rearrangement, is obtained.⁴⁸



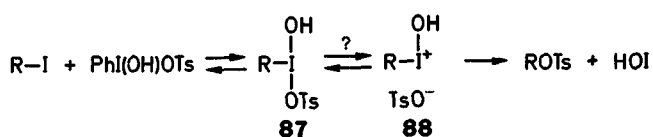
R = 4-Me, 4-Cl, 4-Br, 4-I, 4-NO₂, 4-Ph, 2-CONHMe, 2-CONHCH₂Ph, 2,3-benzo



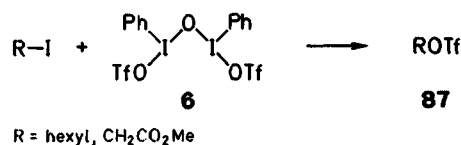
R = *i*-Pr, hexyl, octyl, (\pm)-1-methylheptyl, CH₂CO₂Me



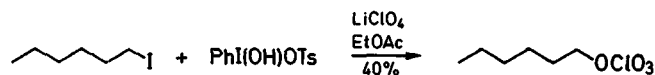
The oxidative displacement of the iodine atom from alkyl iodides with hypervalent iodine reagents [e.g., $\text{PhI}(\text{OAc})_2$, $\text{PhI}(\text{OCOCF}_3)_2$, PhICl_2 , PhIF_2 , $\text{PhI}(\text{OH})\text{OTs}$] is a general phenomenon.^{48,49} The rates of product formation from 1-iodooctane, (\pm)-2-iodooctane and neopentyl iodide appear to depend on the nature of the iodine(III)-bound heteroligands [i.e., $\text{TsO} > \text{Cl} > \text{CF}_3\text{CO}_2 > \text{F} > \text{OAc}$], and such reactions are thought to proceed by rate limiting ligand transfer from the hypervalent iodine reagent to the alkyl iodide.⁴⁸ Thus, it seems likely that the conversion of alkyl iodides to alkyl tosylates with HTIB entails the initial production of [hydroxy(tosyloxy)iodo]alkanes **87** and their subsequent nucleophilic collapse to **85** and hypoiodous acid, perhaps by way of ion pairs such as **88**.



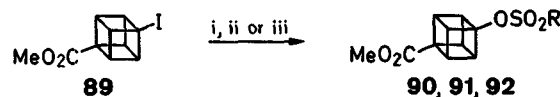
Oxidative displacements are also observed when 1-iodohexane and methyl iodoacetate are mixed with μ -oxobis-[(trifluoromethanesulfonyl)(phenyl)iodine] (**6**), the products being the corresponding alkyl triflates.⁴⁷



The treatment of 1-iodohexane with HTIB in the presence of a fivefold excess of lithium perchlorate in ethyl acetate affords hexyl perchlorate.⁵⁰

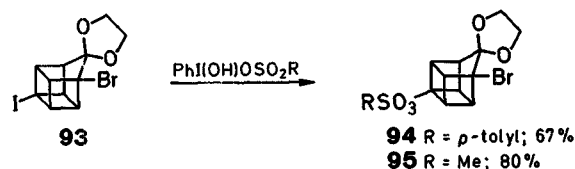


An area in which the oxidative displacement of iodine has served a key synthetic role has been in the systematic functionalization of cubane derivatives.^{51–54} 1-Iodocubane represents the epitome of bridgehead systems. A backside S_N2 displacement is impossible, and carbocation intermediates are expected to be of high energy. Yet the iodocubane system, readily obtainable from cubanecarboxylic acid, represents a synthetic point of departure for the introduction of the mesylate, tosylate and triflate ligands into the cubane skeleton. The treatment of methyl 4-iodocubanecarboxylate (**89**), either with HTIB (**3**) or HMIB (**4**) in dichloromethane, affords good yields of the cubyl tosylate **90** and the cubyl mesylate **91**.^{52,54} The cubyl triflate **92** can be prepared from **89** with iodosobenzene ($\text{PhI}=\text{O}$) in the presence of trimethylsilyl triflate.⁵²



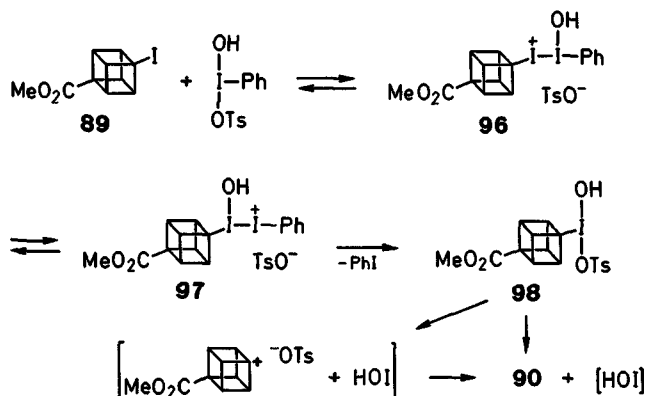
product	R	conditions	yield
90	<i>p</i> -tolyl	(i) $\text{PhI}(\text{OH})\text{OTs}/\text{CH}_2\text{Cl}_2$	75 %
91	Me	(ii) $\text{PhI}(\text{OH})\text{OMs}/\text{CH}_2\text{Cl}_2$	80 %
92	CF ₃	(iii) $\text{PhI}=\text{O}/\text{TMSOTf}$	85 % ⁵²

An analogous set of transformations has been effected in the homocubyl series. Thus, 4-iodo-1-bromopentacyclo-[4.3.0.0.2.50.3.804.7]nonan-9-one ethylene acetal (**93**) affords the homocubyl tosylate **94** and homocubyl mesylate **95** with HTIB and HMIB in dichloromethane.^{53,54}

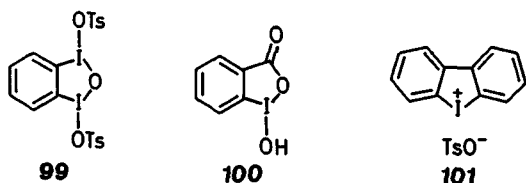


These reactions have been rationalized by the mechanism illustrated below for the conversion of **89** to **90** with HTIB.^{52,54} Electrophilic attack of HTIB on an iodine lone pair in **89** to give the iodonium tosylate **96** containing an iodine–iodine bond seems likely. Migration of the hydroxy ligand from one iodine atom to the other in **96** to give the isomeric iodonium tosylate **97** followed by the reductive

loss of iodobenzene would deliver the [hydroxy(tosyloxy)-iodo]cubane **98**. Two pathways for the collapse of **98** to **90** may be envisioned, one involving front-side coupling of the cubyl carbon with the tosyloxy ligand with loss of hypoiodous acid and the other involving ionization to an ion pair and front-side coordination of the cubyl cation with the tosylate ion.

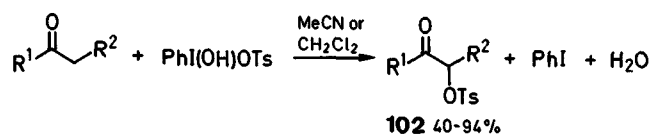


The reactions of HTIB with iodoarenes containing *ortho* functional groups sometimes lead to cyclic products.⁴⁶ For example, *o*-diiodobenzene affords the cyclic, μ -oxoiodinane **99** with HTIB, while *o*-iodobenzoic acid and *o*-iodobiphenyl give the benziodoxole **100** and dibenziodolium tosylate (**101**).⁴⁶

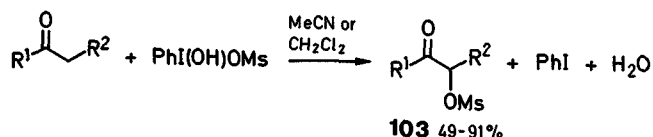


10. Synthesis of α -Sulfonyloxy Ketones and α -Sulfonyloxy β -Dicarbonyl Compounds

[Hydroxy(tosyloxy)iido]benzene is a particularly useful reagent for the direct conversion of ketones to α -tosyloxy ketones **102** in non-hydroxylic solvents.¹⁷ [Hydroxy(mesyloxy)iido]benzene can be employed for the synthesis of α -mesyloxyketones **103** under the same conditions.^{21,19}

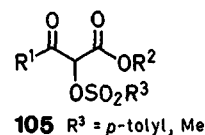
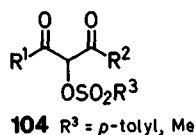


$R^1, R^2 = \text{Me, H; Et, Me; } c\text{-C}_3\text{H}_5, \text{H; Ph, H; Ph, Ph; } \alpha\text{-thienyl, H; } -(\text{CH}_2)_4-$



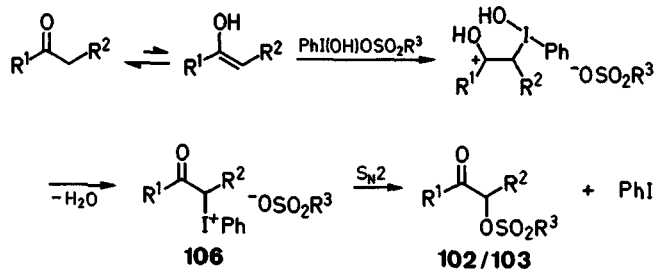
$R^1, R^2 = \text{Me, H; Et, Me; } c\text{-C}_3\text{H}_5, \text{H; Ph, H; } \alpha\text{-thienyl, H; } -(\text{CH}_2)_4-$

These transformations bear some resemblance to the α -bromination of ketones in that they require enolizable substrates and extend nicely to β -dicarbonyl compounds. Thus, the treatment of β -diketones and β -keto esters with HTIB and HMIB readily affords high yields (60–ca. 100%) of the corresponding α -sulfonyloxy derivatives **104** and **105**.^{17,21}

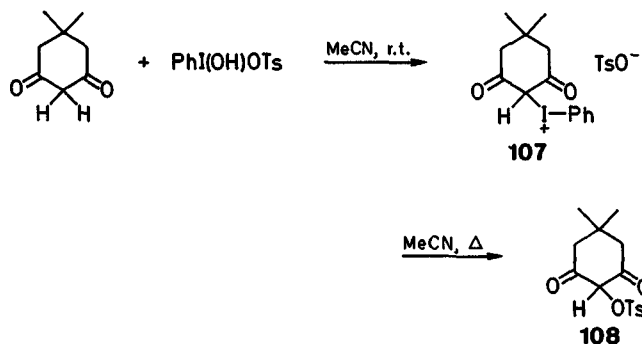


α -Mesyloxy β -dicarbonyl compounds **104** and **105** ($R^3 = \text{Me}$) may also be prepared from β -diketones and β -keto esters with iodobenzene and methanesulfonic acid in chloroform (*in situ* generation of HMIB).⁵⁵

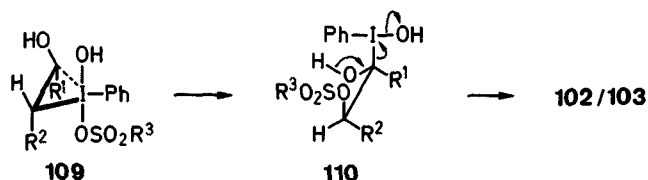
The oxysulfonylation of ketones at α -carbon has been rationalized by a polar mechanism involving electrophilic attack of HTIB or HMIB on the enol tautomer of the ketone to give the α -phenyliodonio ketone sulfonate **106**.^{17,21} S_N2 collapse of **106** with loss of iodobenzene would afford the α -sulfonyloxy ketone (**102** or **103**).



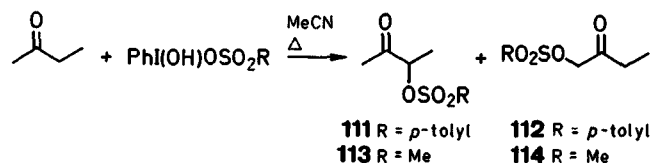
The viability of this mechanism is attested to by the production of 2-dimedonyl(phenyl)iodonium tosylate (**107**) from dimedone and HTIB in acetonitrile at room temperature.¹⁷ When **107** is heated at 70–74°C in the same solvent, 2-tosyloxydimedone (**108**) is obtained.¹⁷ However, dimedone



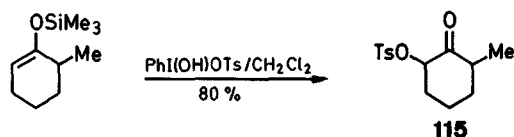
is a β -dicarbonyl compound and may not be representative of typical monoketones. The production of α -sulfonyloxy ketones via the oxidative addition of HTIB or HMIB to the enol to give the fully coordinated periodinane **109** also seems plausible. Front-side coupling of the sulfonate ligand with the " α -carbon" atom in **109** to give **110** followed by the reductive elimination of iodobenzene from **110** would afford **102** or **103**.



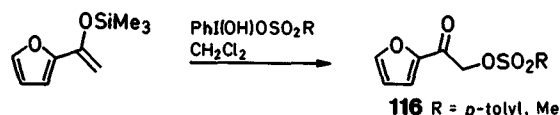
The oxysulfonylations of monoketones with HTIB and HMIB proceed with low regioselectivity. 2-Butanone reacts with HTIB in acetonitrile under reflux to give a 1.57:1.00 mixture of 3-tosyloxy- and 1-tosyloxy-2-butanones (**111** and **112**).¹⁷ The treatment of 2-butanone with HMIB under



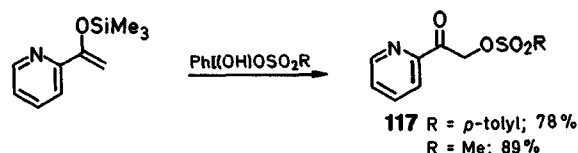
similar conditions gives a 1.26:1.00 mixture of the 3- and 1-mesyates **113** and **114**.²¹ However, silyl enol ethers are readily transformed to α -sulfonyloxy ketones with HTIB and HMIB and may be employed to control the regiochemistry of oxysulfonylation.¹⁸ Thus, 2-methyl-6-tosyloxycyclohexanone (**115**) can be prepared regioselectively from 1-trimethylsilyloxy-6-methylcyclohexene with HTIB in dichloromethane.¹⁸



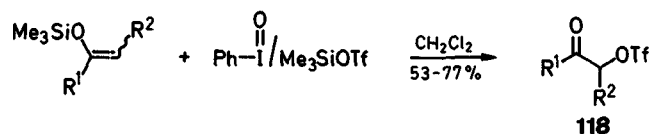
In some cases, silyl enol ethers afford higher yields of α -sulfonyloxy ketones than those associated with direct reactions. For example, α -tosyloxycyclohexanone has been obtained in 85% yield from 1-trimethylsilyloxycyclohexene with HTIB¹⁸ and in only 40% yield from cyclohexanone with HTIB.¹⁷ Similarly, α -mesyloxyacetophenone ($\text{PhCOCH}_2\text{OMs}$) has been obtained in 89% yield from the silyl enol ether (CH_2Cl_2 , room temperature)¹⁸ and in 62.5% yield from the ketone (MeCN, reflux).²¹ A third advantage of the silyl enol ether approach is that it permits the preparation of α -sulfonyloxy ketones with acid-sensitive or oxidizable ring systems. For example, the (sulfonyloxy)-methyl 2-furyl ketones **116** have been obtained in high yields (88–90%) from the appropriate silyl enol ether with either HTIB or HMIB in dichloromethane.¹⁸



The (sulfonyloxy)methyl-2-pyridinyl ketones **117** can be made in the same way.¹⁸



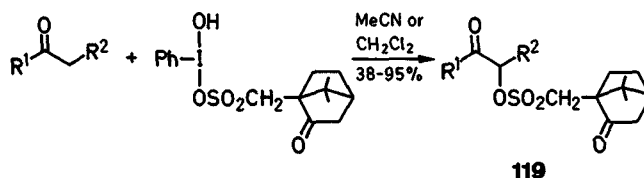
The treatment of silyl enol ethers with iodosobenzene in the presence of trimethylsilyl triflate in dichloromethane affords good yields of α -(trifluoromethanesulfonyloxy) ketones **118**.⁵⁶



R¹, R² = Ph, H; 4-ClC₆H₄, H; Ph, Me; 2-furyl, H; 2-thienyl, H; $-(\text{CH}_2)_4-$; $-(\text{CH}_2)_5-$

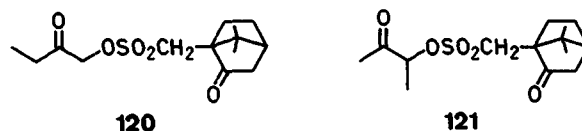
It seems likely that the active reagent in these reactions is [trimethylsilyloxy(trifluoromethanesulfonyloxy)iodo]benzene, $\text{PhI}(\text{OSiMe}_3)\text{OTf}$.

The direct functionalization of ketones with {hydroxy[(+)-10-camphorsulfonyl]oxy}iodo}benzene (**5**) to give α -(+)-10-camphorsulfonyloxy ketones **119** has recently been reported.²²

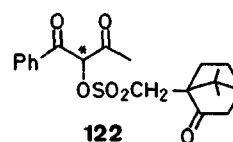


R¹, R² = Me, H; Me, Me; *i*-Bu, H; $-(\text{CH}_2)_4-$; Ph, H

An interesting feature of this reagent is the steric bulk of the camphorsulfonate ligand, which exerts a marked influence on the regioselectivity of oxysulfonylation. Whereas the oxytosylation¹⁷ and oxymesylation²¹ of 2-butanone with HTIB and HMIB occur with low preference at C-3, the oxycamphorsulfonylation of 2-butanone with **5** proceeds preferentially at C-1 to give a 2.3:1.0 mixture of the 1- and 3-camphorsulfonates **120** and **121**.²² Although two diastereoisomers of **121** are expected, they were not distinguished by 80 MHz ¹H NMR analysis. The more hindered ketone, 4-methyl-2-pentanone, apparently gives only the C-1 camphorsulfonate with **5**.²²

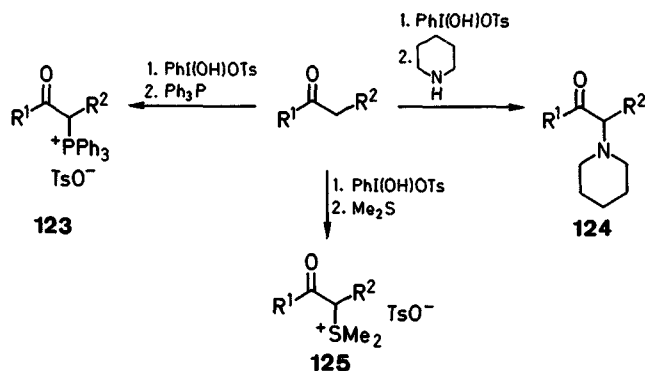


β -Diketones, β -keto esters, and diethylmalonate also react with **5** to give the corresponding (+)-10-camphorsulfonate derivatives.²² In the case of benzoylacetone, the crude product **122** was determined to be a 3:1 mixture of diastereoisomers. However, an attempt to separate them by chromatography on silica gel resulted in isomerization and returned a nearly 1:1 mixture.²²

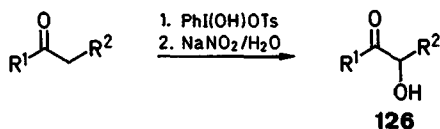


11. Synthesis of α -Substituted Ketones, Thiazoles and Selenazoles

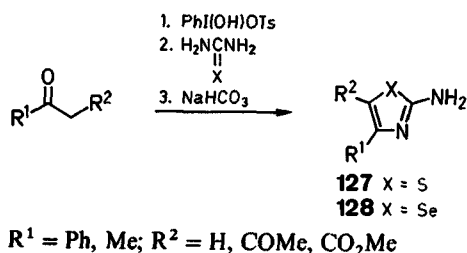
Nucleophiles such as amines, sulfides, and phosphines, which themselves undergo oxidations with hypervalent iodine reagents, cannot be used directly with HTIB for the α -substitution of ketones. However, the synthesis of α -substituted ketones **123**, **124**, and **125**, derived from such species, may be effected by the initial treatment of ketones with HTIB in acetonitrile followed by the introduction of the appropriate nucleophile.⁵⁷



In a similar sequence, the treatment of ketones first with HTIB in acetonitrile and then with saturated aqueous sodium nitrite affords good yields of α -hydroxy ketones **126** via intermediate α -nitrito esters.⁵⁸

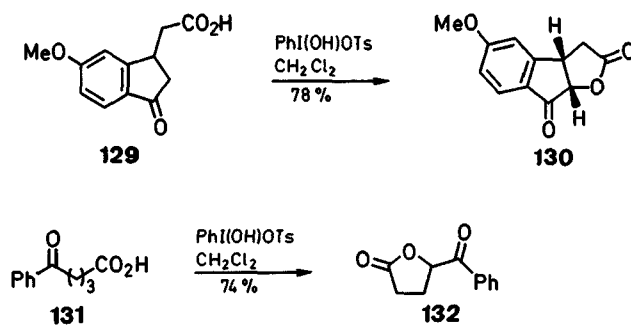


A simple synthesis of thiazoles **127** and selenazoles **128** has been achieved by the initial treatment of ketones with HTIB and the subsequent addition of thiourea and selenourea.⁵⁹ This sequence is a modification of the Hantzsch synthesis.

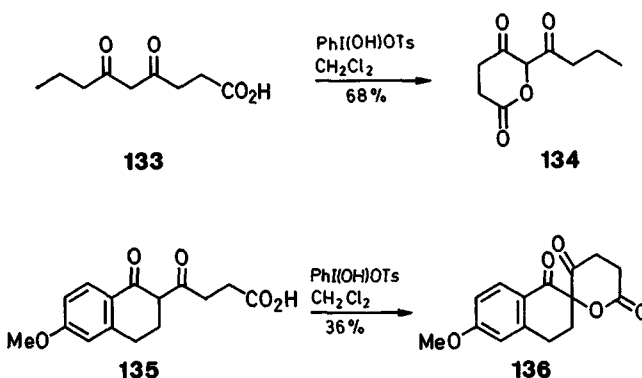


12. Intramolecular Participation of the Carboxyl Group in the Oxidation of Ketones with (Hydroxy(tosyloxy)iodo]benzene. Synthesis of Oxolactones

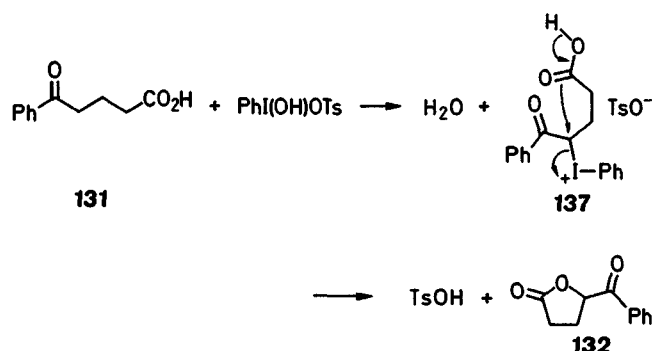
5-Oxo carboxylic acids react with HTIB in dichloromethane to give oxo- γ -lactones.⁶⁰ For example, 5-methoxy-1-indanone-3-acetic acid (**129**) affords the γ -lactone **130**, while 4-benzoylbutyric acid (**131**) is converted to the γ -lactone **132**.⁶⁰



When 4,6-dioxo carboxylic acids are the substrates, dioxo- δ -lactones are obtained.⁶⁰ This is illustrated below for the synthesis of the δ -lactones **134** and **136** from the dioxo acids **133** and **135**.⁶⁰

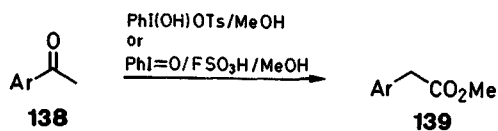


One explanation for these reactions is that they proceed via the initial phenyliodination of the oxo acid at the α -carbon atom of the ketone function to give an iodonium tosylate **137** (analogous to the polar mechanism for the α -oxytosylation of ketones with HTIB). Intramolecular nucleophilic displacement of iodobenzene in **137** by the carboxyl function and concomitant loss of tosic acid would deliver the oxolactone. This is illustrated here for the conversion of 4-benzoylbutyric acid to **132**.

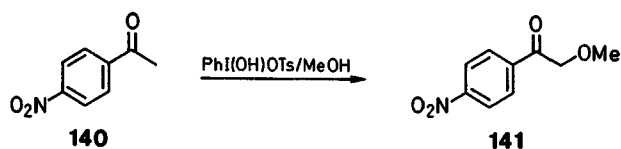


13. Oxidative Rearrangement of Aryl Ketones to Esters

The treatment of alkyl aryl ketones **138** with iodosobenzene and fluorosulfonic acid in methanol or with [hydroxy(tosyloxy)iodo]benzene in methanol containing triflic acid as a catalyst promotes oxidative 1,2-aryl migrations, and methyl α -arylalkanoates **139** are obtained.^{30,61}

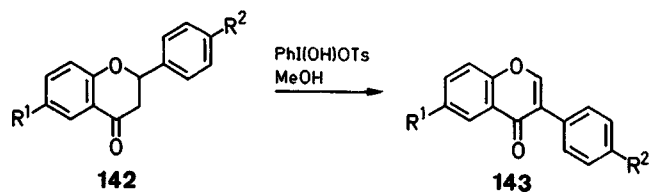


It is interesting to note, however, that 4-nitroacetophenone (**140**) gives α -methoxy-4-nitroacetophenone (**141**) with HTIB in methanol and not the product of oxidative rearrangement.⁶¹



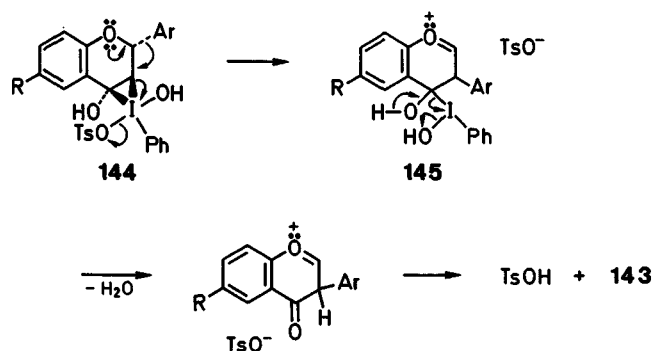
14. Synthesis of Isoflavones and 2,3-Dimethoxy-3-hydroxyflavanones

The oxidation of flavanones **142** with [hydroxy(tosyloxy)iodo]benzene in methanol does not afford α -tosyloxy derivatives.⁶² Instead, a 1,2-shift of the aryl group to the α -carbon atom of the ketone function occurs thus providing a new route to the isoflavones **143**.⁶²

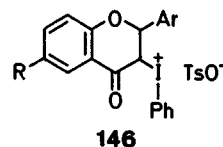


$\text{R}^1, \text{R}^2 = \text{H, H; H, OMe; Cl, H; Cl, Me}$

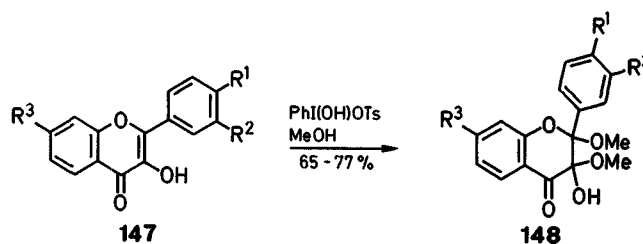
The production of **143** may be explained by the oxidative addition of HTIB to the enol tautomer of **142** on the face of the molecule *anti* to the C-2 aryl ring to give the periodinane **144**. Migration of the C-2 aryl group in **144** with opening of the periodinane ring and loss of the tosylate ion to give **145** followed by the reductive elimination of iodobenzene would give the isoflavone.



The conversion of **142** to **143** via the α -phenyliodonio ketone tosylate **146** is a plausible alternative mechanism.



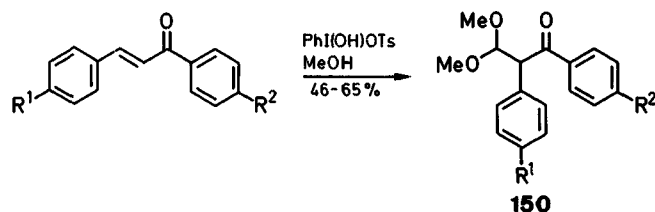
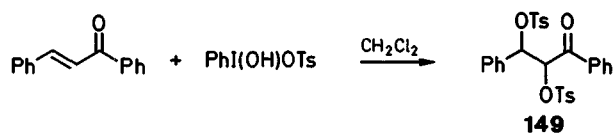
The oxidation of flavonols **147** with HTIB in methanol proceeds with the introduction of two methoxy groups into the carbon-carbon double bond, and 2,3-dimethoxy-3-hydroxyflavanones **148** are obtained.⁶³ In some respects, this transformation is analogous to the ditosyloxylation of alkenes with HTIB²⁹ and is an example of a "solvolysis-periodination" reaction.



147, 148	R ¹	R ²	R ³
a	H	H	H
b	H	H	OMe
c	OMe	H	H
d	OMe	H	OMe
e	OMe	OMe	H
f	Cl	H	H

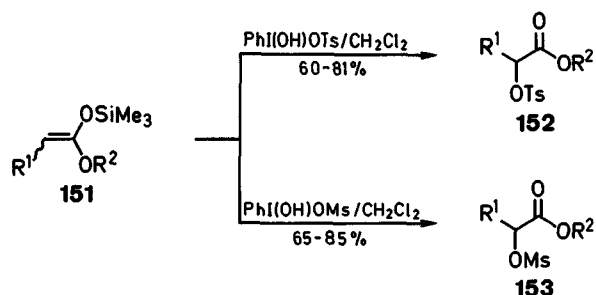
15. Reactions of Chalcones with [Hydroxy(tosyloxy)iodo]benzene

When chalcone is mixed with HTIB in dichloromethane, the *vic*-ditosylate **149** is obtained.²⁹ However, the treatment of various chalcones with HTIB in methanol affords the rearrangement products **150** containing a dimethyl acetal function.³⁰



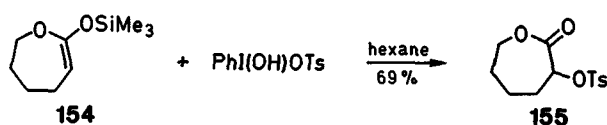
16. Synthesis of Sulfonyloxy Esters and Lactones

Silyl ketene acetals **151** react with [hydroxy(tosyloxy)iodo]benzene and [hydroxy(mesyloxy)iodo]benzene in dichloromethane to give α -tosyloxy and α -mesyloxy esters **152** and **153**.¹⁸

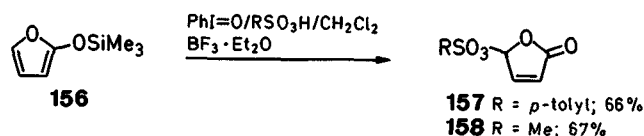


$\text{R}^1, \text{R}^2 = \text{Ph, Me; Ph, Et; Et, Me}$

Similar treatment of the cyclic silyl ketene acetal **154** with HTIB in hexane affords α -(tosyloxy)- ϵ -caprolactone (**155**).¹⁸

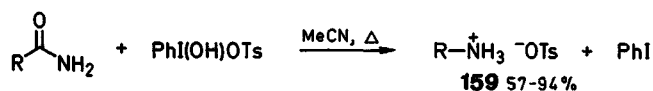


When 2-(trimethylsilyloxy)furan (**156**) is mixed with iodo-sobenzene and either *p*-toluenesulfonic acid or methanesulfonic acid in dichloromethane followed by the addition of ether-boron trifluoride complex, the 5-sulfonyloxy-2(5*H*)furanones **157** and **158** are obtained.⁶⁴



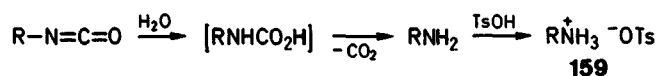
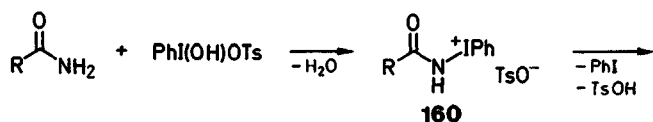
17. [Hydroxy(tosyloxy)iodo]benzene as a Hofmann Reagent. Synthesis of Amines from Carboxamides

[Hydroxy(tosyloxy)iodo]benzene has emerged as an excellent "Hofmann reagent" for the conversion of primary carboxamides to amines.^{65,66} Such reactions are conducted in acetonitrile, and the amines separate from the solvent as their hydrogen tosylate salts **159**. Long-chain aliphatic amides that respond either poorly or not at all under classical Hofmann conditions give high yields of alkylammonium tosylates with HTIB in acetonitrile.⁶⁶



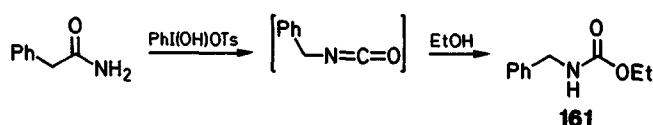
R = Me, Et, *i*-Pr, *t*-Bu, allyl, PhCH_2 , *c*- C_4H_7 , *c*- C_6H_{11} , $\text{CH}_3(\text{CH}_2)_n$ [$n = 4, 6, 10, 11, 12, 13, 14, 15, 16, 20$], *trans*- $\text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_7$, *cis*- $\text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_{11}$

The production of an alkylammonium tosylates from carboxamides with HTIB proceeds via initial formation of *N*-phenyliodonio carboxamide tosylates **160**, which rearrange with loss of iodobenzene and tosic acid to give isocyanates.⁶⁵

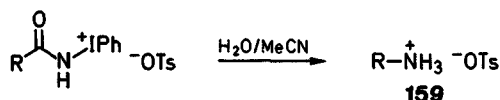
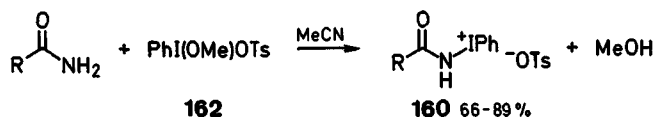


Support for this mechanism is based on two lines of evidence.

(1) When phenylacetamide is mixed with HTIB in ethanol, ethyl benzylcarbamate (**161**) is obtained, a product which presumably arises via the capture of benzyl isocyanate with the solvent.⁶⁵



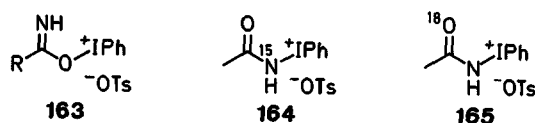
(2) A variety of *N*-phenyliodonio carboxamide tosylates **160** have been prepared from primary carboxamides with [methoxy(tosyloxy)iodo]benzene (**162**, MTIB)⁶⁷ in acetonitrile at room temperature.⁶⁸ Hydrolysis of the *N*-phenyliodonio amides with water in acetonitrile gives good yields of alkylammonium tosylates **159**.⁶⁸



R = Me, *i*-Pr, *t*-Bu, pentyl, benzyl

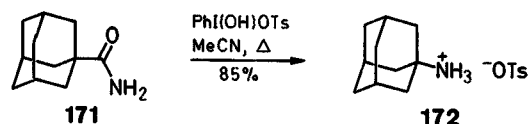
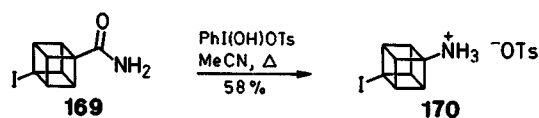
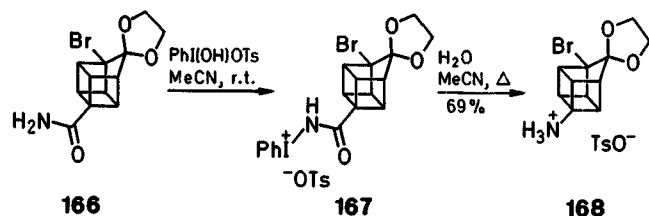
Evidence for the intermediacy of isocyanates in these reactions has been provided by the conversion of *N*-phenyliodonio phenylacetamide tosylate **160** (R = benzyl) to ethyl benzylcarbamate in hot ethanol and by the spectroscopic observation of benzyl isocyanate, $\text{PhCH}_2\text{N=C=O}$, when the iodonio amide is "dissolved" in CDCl_3 .⁶⁸

That the *N*-phenyliodonio amide tosylates do not exhibit the isomeric *O*-phenyliodonio imide structure **163** has been verified by FT-IR analysis of the ¹⁵N and ¹⁸O isotopomers **164** and **165** of *N*-phenyliodonio acetamide tosylate.⁶⁸



This method is particularly useful for the synthesis of bridgehead amines. When the homocubane carboxamide **166** is mixed with HTIB at room temperature, the *N*-phenyliodonio amide **167** is obtained.⁶⁹ Hydrolysis of **167** in

hot acetonitrile delivers the homocubylammonium tosylate **168**.⁶⁹ Similar treatment of 4-iodocubane-1-carboxamide (**169**) with HTIB in acetonitrile affords 4-iodo-1-cubylammonium tosylate (**170**).⁶⁹ 1-Adamantanecarboxamide (**171**) gives 1-adamantylammonium tosylate (**172**).⁶⁹



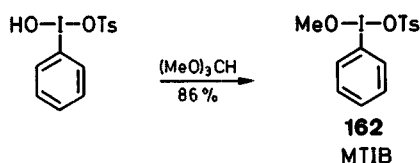
The direct synthesis of alkylammonium tosylates by this method is especially advantageous in the case of **170** because of the instability of the free cubylamine.⁶⁹

The use of HTIB as a Hofmann reagent does have limitations. Efforts to obtain ammonium tosylates from benzamide, 2-cyclopenteneacetamide, cyclopropanecarboxamide and chloroacetamide were unsuccessful.⁶⁵ The treatment of malonamide with HTIB mimics the reactions of ketones and affords α -tosyloxymalonamide (**173**).⁶⁵

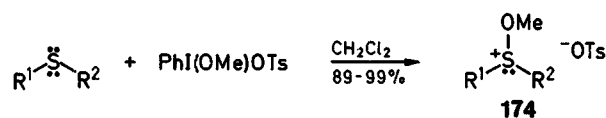


18. Oxidation of Sulfides

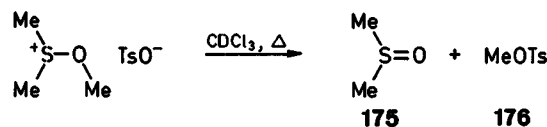
The treatment of [hydroxy(tosyloxy)]benzene with trimethyl orthoformate affords the alkoxyiodinane, [methoxy(tosyloxy)iodo]benzene (**162**, MTIB).⁶⁷



This is an interesting reagent which transfers the formal equivalent of MeO^+ to sulfides in dichloromethane to give methoxysulfonium tosylates **174**.⁷⁰ When methoxydimethylsulfonium tosylate (**174**, $\text{R}^1 = \text{R}^2 = \text{Me}$) is heated in deuteriochloroform, dimethyl sulfoxide **175** and methyl tosylate **176** are produced.⁷⁰

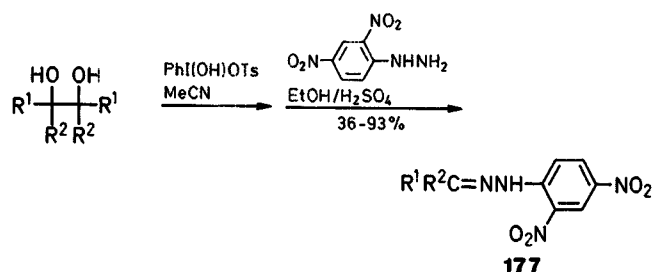


$\text{R}^1, \text{R}^2 = \text{Me, Me; PhCH}_2, \text{PhCH}_2; 4\text{-BrC}_6\text{H}_4, \text{Me; Pr, Pr}$



19. Oxidative Cleavage of Glycols

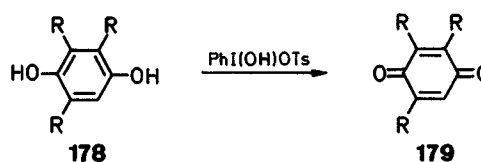
vic-Diols undergo oxidative cleavage with [hydroxy(tosyloxy)iodo]benzene in acetonitrile at room temperature to give the corresponding aldehydes or ketones. The carbonyl compounds were identified as their 2,4-dinitrophenylhydrazones **177**.³⁵



$\text{R}^1, \text{R}^2 = \text{Ph, Ph; Me, Me; Ph, Me; Ph, H}$

20. Oxidation of Hydroquinones

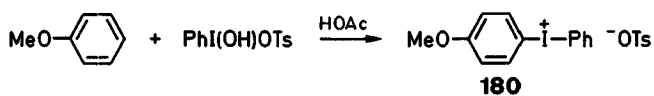
Hydroquinones **178** are oxidized to quinones **179** with HTIB.⁷¹ However, 4,4'-biphenol and 4-benzylphenol fail to give oxidation products.⁷¹



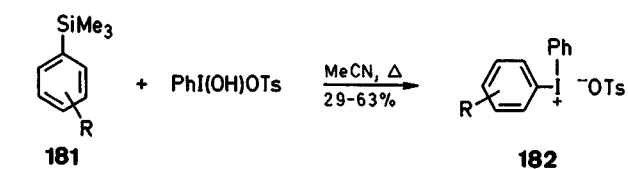
$\text{R} = \text{H, Me}$

21. Synthesis of Diaryl- and Aryl(heteroaryl)iodonium Salts

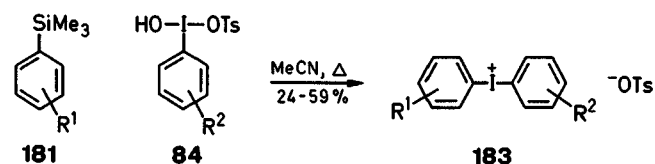
[Hydroxy(tosyloxy)iodo]benzene is moderately electrophilic at the iodine atom and reacts with anisole to give *p*-anisyl(phenyl)iodonium tosylate (**180**).¹⁶ However, neither



benzene nor toluene gives an iodonium salt with HTIB in acetonitrile.⁷² Trimethylsilylarenes **181**, on the other hand, undergo aryliodination at the silicon-bound carbon atom with HTIB and other [hydroxy(tosyloxy)iodo]arenes **84** in acetonitrile or dichloromethane thus providing a mild regioselective synthesis of diaryliodonium tosylates **182** and **183**.⁷²

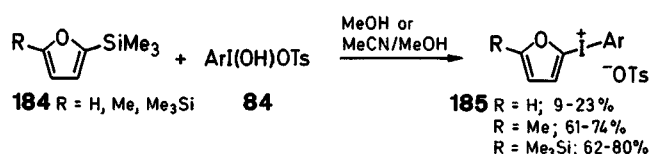


$R = \text{H}, 2\text{-Me}, 3\text{-Me}, 4\text{-Me}$

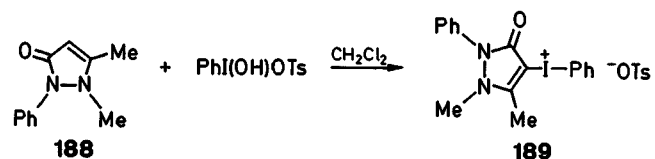
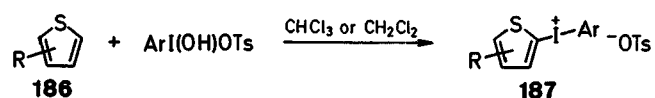


$R^1, R^2 = \text{H}, 4\text{-Me}; 2\text{-Me}, 4\text{-Me}; 3\text{-Me}, 2\text{-Me}; 4\text{-Me}_3\text{Si}, \text{H}; 3\text{-Me}_3\text{Si}, \text{H}, 4\text{-(4-Me}_3\text{SiC}_6\text{H}_4), \text{H}$

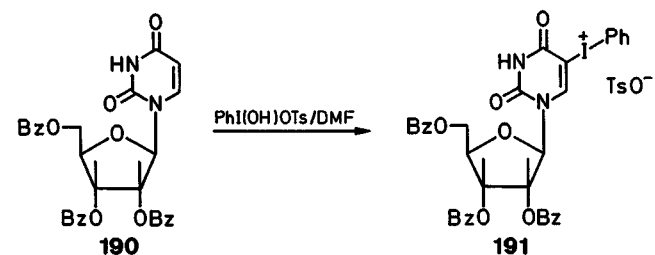
This method has also been applied to the 2-trimethylsilyl-furans **184** and affords a variety of aryl(2-furyl)iodonium tosylates **185**.⁷³



Thiophenes **186**, including those containing oxidizable functional groups (i.e. CH_2OH , CHO), undergo *direct* condensations with [hydroxy(tosyloxy)iodo]arenes to give aryl(2-thienyl)iodonium tosylates (**187**).⁷⁴ Antipyrine (**188**) is similarly reactive and is converted to the iodonium tosylate **189** with HTIB in dichloromethane at room temperature.⁷⁵

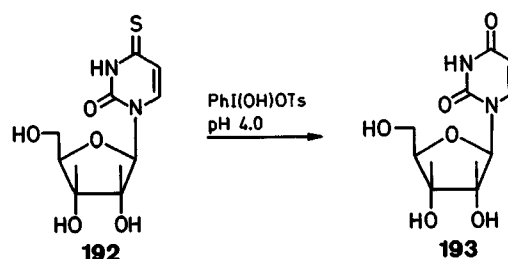


A particularly interesting application of HTIB is its use for the phenyliodination of 2'3'5'-tribenzoyluridine (**190**) in dimethylformamide to give phenyl-3-(2',3',5'-tribenzoyluridine)iodonium tosylate (**191**).⁷⁶



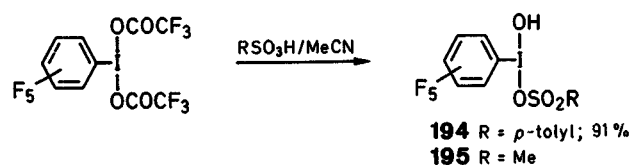
4-Thiouridine (**192**), on the other hand, is converted to uridine (**193**) with an excess of HTIB in an acetate buffered

medium (pH 4.0) instead of an iodonium salt.⁷⁷ An analogous transformation occurs (i.e., $\text{S}^4\text{U} \rightarrow \text{U}$) when tRNA (E. Coli) is treated with HTIB under similar conditions.⁷⁷ It was noted that preparative reactions require 2',3',5'-tribenzoyl-4-thiouridine as the substrate owing to the susceptibility of the diol functionality in **193** to undergo oxidative cleavage with HTIB.⁷⁷

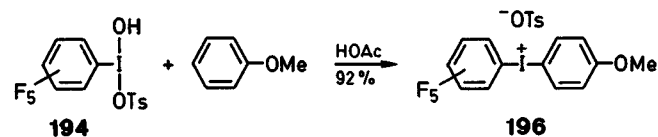


22. Synthesis and Reactivity of [Hydroxy(sulfonyloxy)iodo]pentafluorobenzenes

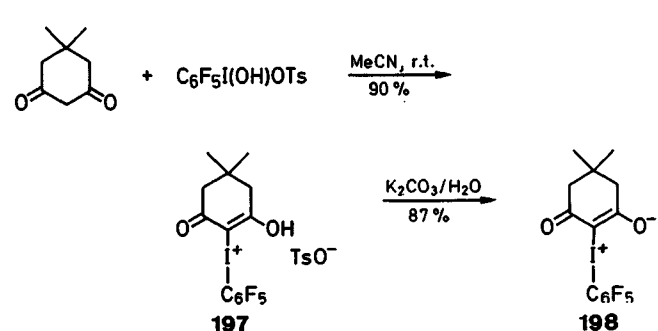
The treatment of [bis(trifluoroacetoxy)iodo]pentafluorobenzene with either *p*-toluenesulfonic acid or methanesulfonic acid in acetonitrile affords the corresponding [hydroxy(sulfonyloxy)iodo]pentafluorobenzenes **194** and **195**.⁷⁸



A preliminary study of the efficacy of **194** for the perfluorophenyliodination of organic substrates has been made. When **194** is mixed with anisole in acetic acid, *p*-anisyl-(perfluorophenyl)iodonium tosylate (**196**) is obtained.⁷⁸



Dimedone is similarly converted to the α -perfluorophenyl-iodonium tosylate **197** with **194** in acetonitrile at room temperature.⁷⁸ Treatment of **197** with aqueous potassium bicarbonate delivers the iodonium ylide **198**.⁷⁸



23. Conclusion

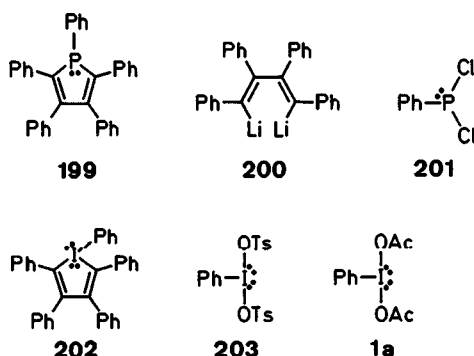
[Hydroxy(tosyloxy)iodo]benzene is a particularly useful reagent for the introduction of the tosyloxy ligand into the carbon-carbon double bond and at the α -carbon atom of carbonyl compounds. When coupled with the intramolecular participation of nucleophilic functional groups, such transformations offer promise for the straightforward synthesis of moderately complex molecules. HTIB is an excellent reagent for the Hofmann rearrangement and, in many cases, may be the reagent of choice for this important transformation. The oxytosylation of carbon via the oxidative displacement of iodine from the carbon-iodine bond with HTIB is also a useful synthetic method.

Finally, the connection of our work with the research efforts of R. V. Hoffman (New Mexico State University, Las Cruces, New Mexico), X. Creary (Notre Dame), and G. M. Loudon (Purdue) must be acknowledged. Hoffman and his co-workers have employed *p*-nitrobenzenesulfonyl peroxide as a reagent for the synthesis of α -nosyloxy carbonyl compounds and pioneered the use of silyl enol ethers and silyl ketene acetals as substrates for such transformations.^{79,80} They have also explored the chemistry of the α -nosyloxy carbonyl compounds.⁸¹ Creary and his co-workers have conducted rigorous studies on the nucleophilic displacement and solvolytic reactions of α -sulfonyloxy ketones.⁸² Loudon and his co-workers developed the use of bis(trifluoroacetoxy)iodobenzene **1b** as a Hofmann reagent prior to our studies in this area.^{83,84}

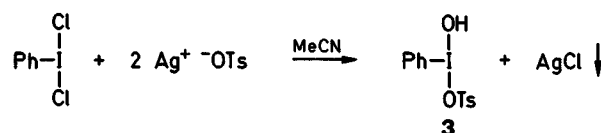
Part II. Recollections on the Role of Serendipity in Our Researches on [Hydroxy(tosyloxy)iodo]benzene (Gerald F. Koser)

24. Why [Hydroxy(tosyloxy)iodo]benzene?

As a newly appointed Assistant Professor (Fall, 1969) at The University of Akron, I was particularly interested in the development of methods for the synthesis of iodine(III) heterocycles. The preparation of pentaphenylphosphole (**199**) from 1,4-dilithiotetraphenyl-1,3-butadiene (**200**) and dichlorophenylphosphine (**201**) was known,⁸⁵ and I initiated a study of the reaction of **200** with (dichloroiodo)benzene (**2a**) as a possible approach to pentaphenylidole (**202**). I soon learned that projected analogies between phosphorus and trivalent iodine chemistry can be misleading, and the results of this investigation were equivocal at best. However, in order to retrieve something for my efforts, I decided to design an alternative iodine(III) reagent for coupling with **200**.



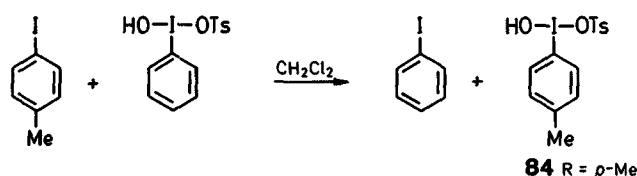
Since the tosylate ligand had been extensively employed as a leaving group for nucleophilic displacement reactions at carbon, (ditosyloxyiodo)benzene (**203**) came to mind and was slated for synthesis. I reasoned that this iodine might easily be prepared from (dichloroiodo)benzene and two equivalents of silver tosylate in acetonitrile, especially since a similar preparation of (diacetoxyiodo)benzene (**1a**) from **2a** and silver acetate was already known.⁸⁶ I first investigated this reaction in the summer of 1971 and, to my disappointment, obtained [hydroxy(tosyloxy)iodo]benzene (**3**, HTIB) instead of the *desired* ditosylate.



A more careful study of this reaction by Richard H. Wettach, a graduate student in my laboratory, revealed that silver chloride is produced in substantially lower yields (e.g., 62%) than expected, and that the formation of HTIB requires some source of moisture (i.e., atmosphere, solvent).²⁴ When the reaction was conducted under rigorously anhydrous conditions, neither HTIB nor **203** was obtained.²⁴ At some point (I'm not sure when), I became aware of a paper by Neiland and Karelc, in which the preparation of HTIB from (diacetoxyiodo)benzene and *p*-toluenesulfonic acid monohydrate and in which several of its reactions were described.¹⁶ Not only were they the first to publish on HTIB, but had also found a better method of synthesis.

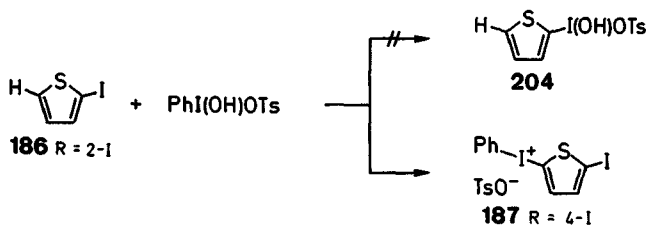
25. Mood Indigo and the Ligand-Transfer Reaction

Once we had been introduced to HTIB, I asked Rick Wettach to investigate its chemistry, in the hope that we might find something new, and to prepare some analogs with substituents in the nucleus of the phenyl ligand. One compound that we selected was the *p*-methyl analog [the methyl group would be a useful NMR "handle", an especially important feature in the days of 60 MHz spectrometers]. It was, of course, necessary to prepare *p*-iodotoluene for that purpose. Sometime after this we had a fortunate accident, and although both of our memories are vague on the details, the following account at least captures its essence. As Rich was working in the laboratory, he happened to pour an NMR sample of HTIB into what was assumed to be a clean flask, whereupon an intense blue color was generated. He then remembered that the flask had actually contained a thin layer of *p*-iodotoluene. His curiosity aroused, Rich reinvestigated the reaction under controlled conditions and discovered that HTIB transfers its ligands to *p*-iodotoluene to give *p*-[hydroxy(tosyloxy)iodo]toluene (**84**, R = *p*-Me).⁴⁶ The color change, which prompted the investigation in the first place, was unrelated to the ligand transfer reaction (see Section 9). The sample of *p*-iodotoluene had been prepared from *p*-toluidine, *p*-MeC₆H₄NH₂, some of which apparently remained as a contaminant and was oxidized by HTIB to give the colored material. When the *p*-iodotoluene was carefully purified, the color change with HTIB was no longer observed.



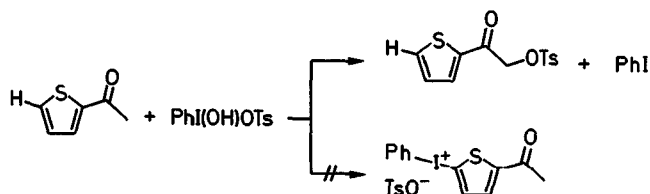
26. Will We Ever Be Able to Predict the Behavior of [Hydroxy(tosyloxy)iodo]benzene?

Once the ligand-transfer reaction was discovered, we sought to test its generality and promptly mixed HTIB with a variety of iodoarenes. Among the substrates selected for screening was 2-iodothiophene (**186**, R = 2-I), from which we expected to obtain 2-[hydroxy(tosyloxy)iodo]thiophene (**204**). However, phenyliodination occurred instead, and phenyl-2-(4-iodothiophenyl)iodonium tosylate (**187**, R = 4-I) was produced.⁴⁶



This was good news and bad news. The good news is that this reaction was subsequently developed by my graduate student, Anthony J. Margida, into a mild and general synthesis of aryl(2-thienyl)iodonium salts, a class of compounds known to be active biocides (see Section 21).⁷⁴ The bad news is that the successful preparation of **204**, which has still not been achieved, would have provided a straightforward approach to dithienyliodonium and other unusual thienyliodonium salts.

Probably the most important consequence of the errant ligand-transfer reaction was our initial impatience to test the generality of phenyliodination with any thiophene that might be available. To this end, Rich Wettach searched the lab for appropriate substrates and happened upon 2-acetylthiophene. We assumed that we had HTIB under control: surely, phenyliodination would occur. However, when 2-acetylthiophene was mixed with HTIB, an iodonium salt was not obtained! In fact, the product of this reaction, tosyloxymethyl 2-thienyl ketone, had such a simple NMR spectrum and was so unexpected that it took us awhile to figure out what it was. The oxytosylation of ketones and β -dicarbonyl compounds at α -carbon with HTIB turned out, of course, to be an important general reaction^{17,18} and was later extended by us and by others (Zefirov, Varvoglis, Moriarty) to the preparation of α -mesylates,^{18,19,21} α -camphorsulfonates²² and α -triflates⁵⁶ (see Section 10).



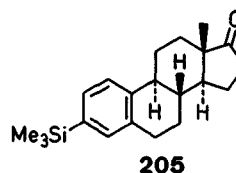
27. Is [Hydroxy(tosyloxy)iodo]benzene Soluble in Anything?

Although the functionalizations of organic compounds with HTIB proceed readily in acetonitrile, dichloromethane, or chloroform, it is not very soluble in those solvents at room temperature. Early on, Rich Wettach and I were seeking alternative solvents for HTIB (other than methanol or DMSO) and more or less randomly selected trimethyl orthoformate from the shelf. When HTIB was introduced into this solvent, we were pleased to note that it dissolved (eureka!). However, a crystalline solid soon separated and was identified in later studies as [methoxy(tosyloxy)iodo]benzene (**162**).⁶⁷ This compound has since been employed by us for the synthesis of *N*-phenyliodonio carboxamide tosylates⁶⁸ and methoxysulfonium tosylates⁷⁰ (see Sections 17 and 18).

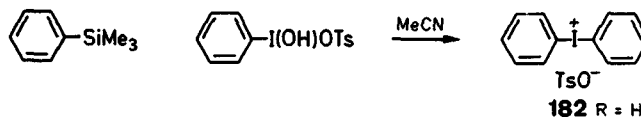


28. Make Sure that You Attend Seminars

In February of 1979, Professor Peter Vollhardt presented a seminar at The University of Akron concerning a synthetic sequence for estrone (involving some interesting cobalt chemistry), in which the penultimate product was the trimethylsilylarene **205**.⁸⁷ Dr. Vollhardt mentioned the desir-



ability of reagents that would effect the direct replacement of the trimethylsilyl group in **205** with the hydroxyl function. Since HTIB appears, at least in a formal sense, to be a stabilized "adduct" of peroxytoluenesulfonic acid, I thought that it might function as a source of $[\text{HO}^+]$ and cause the desired transformation. I asked Rich Wettach to prepare some trimethylsilylbenzene so that this idea might be tested. However, when the silane was mixed with HTIB, diphenyliodonium tosylate (**182**, R = H) was produced



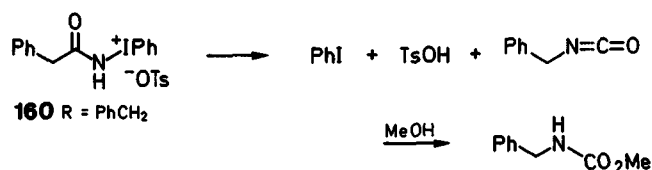
instead of phenol.⁷² The aryliodination of trimethylsilylarenes with [hydroxy(tosyloxy)iodo]arenes at the Si-C_{Ar} bond with loss of the trimethylsilyl group proved to be a general reaction and was developed into a mild, regio-specific synthesis of diaryliodonium salts.⁷² This method was subsequently extended by my graduate student, Carol S. Carman, to the (trimethylsilyl)furans and resulted in the first reported synthesis of aryl(2-furyl)iodonium salts⁷³ (see Section 21).

29. Read the Literature. Even "Me Too" Research Can Be Fruitful

The research of G.M. London and his co-workers on the use of bis(trifluoroacetoxyiodo)benzene as a Hofmann reagent^{83,84} prompted us to explore the efficacy of HTIB for the same purpose. Although this idea appeared to be decidedly mundane at the time, my graduate student, I. Mark Lazbin, obtained some interesting and unexpected results. Thus, HTIB not only promotes the conversion of carboxamides to amines in acetonitrile (no water added), but serves as an *in situ* source of *p*-toluenesulfonic acid, causing the amines to separate from the solvent as their hydrogen tosylate salts **159** ($\text{RN}^+\text{H}_3^- \text{OTs}$)^{65,66} (see Section 17).

We were particularly intrigued by the details of these reactions and speculated that they proceed via the initial condensation of the amides with HTIB to give *N*-phenyliodonio carboxamide tosylates **160** and water and the subsequent collapse of **160** to isocyanates, iodobenzene and tosic acid; hydrolysis of the isocyanates in the presence of tosic acid would ultimately yield **159**, as discussed in Section 17 above.

It was not clear to us, however, whether it was water from the proposed condensation step or adventitious moisture in the solvent (not dried prior to use) that was ultimately responsible for the hydration of the isocyanates. Obviously, isocyanates will react with water from any source, but the condensation step was only speculative at that point, and the question is not as ludicrous as it seems. In an effort to clarify this issue, Mark investigated the reaction of α -phenylacetamide with [methoxy(tosyloxy)iodo]benzene (**162**) in acetonitrile. We reasoned that the condensation of α -phenylacetamide with **162**, if it occurred, would produce methanol instead of water. If there was a sufficient quantity of water in the acetonitrile, benzylammonium tosylate would still be obtained, but, if not, any intermediate benzylisocyanate would be captured by methanol to give methyl benzylcarbamate.



To the best of my recollection, the possibility that the stable *N*-phenyliodonio amide tosylate (**160**, $\text{R} = \text{PhCH}_2$) might be isolated had not even occurred us at that time. Yet, that is exactly what happened.⁶⁸ The synthesis of *N*-phenyliodonio carboxamide tosylates from amides with HTIB proved to be general⁶⁸ (see Section 17) and this unusual class of iodonium salts has since been employed for the synthesis of amidosulfonium tosylates (see Section 18).⁷⁰

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