The Many Paths of Hypervalent **Iodine Reactions** n











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Dr. Robert M. Moriarty, (Center), (University of Illinois) receiving the Award for Creative Research from the president of SQM (Left) and the president of the ACS (right) in 2005.

Outline

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- E. Elaborations with oxidized phenols

III. Radical Reactions of Hypervalent lodine

- A. Oxidations of Anisoles
- B. Radical Chemistry of IBX C. Radical Chemistry of Iodine (III)

IV. C-C Bond Formation with Hypervalent lodine

- A. Ligand Coupling of Enolates
- B. Cyclopropanation
- C. Wolff Rearrangements
- D. Vinyl lodonium Chemistry
- E. Alkynyl Iodonium Salts

V. Conclusion

Reviews: 1. Moriarty, R. M. *J. Org. Chem.*, **2005**, *70*, 2893. 2. Togo, H.; Katohgi, M. *Synlett*, **2001**, *5*, 565. 3. ARKIVOC, **2003**, issue vi. (see URL below)

4. Topics in Current Chemistry, 2003, 224 (book) http://www.arkat-usa.org/ark/journal/2003/I06_Varvoglis



Dr. Hideo Togo, (Chiba University)





What is Hypervalency?

-Hypervalent Compounds contain a central atom bearing more than 8 valence electrons. -The lodine hypervalent bonds involve a formal 3-center-4-electron bond with both ionic and covalent character. -The Martin-Arduengo nomenclature system has traditionally been used to describe such compounds:



Bonding In Hypervalent Iodine Compounds

-Hypervalent iodine compounds will arange themselves so that the least electronegative group occupies an equatorial position. Both calculations and X-Ray structures support this fact.



-The process of interconverting axial and equatorial ligands on hypervalent iodine is called pseudorotation (Ψ). Little is known of the mechanism of this process.

-Additionally, the two substituents in 3-center-4-electron bond will be 180° apart, so as to occupy the same hybrid orbital on the iodine atom.



-This is one reason for the unusual geometries encountered with hypervalent iodine compounds.

Bonding In Hypervalent Iodine Compounds

-In cases where the least electronegative group on iodine CANNOT occupy an equatorial position, intermolecular bonding arises, forming aggregates.



-Additionally, some 8-I-2 compounds CANNOT have two electronegative groups to stabilize the hypervalent bond, so they will spontaneously polymerize.



-In the ground state, Oxo and Imido ligands on iodine situate themselves so that no lone pairs are 180° away from the I-Oxo or I-Imido bond. Kiprof, P., Zhdankin, V. ARKIVOC, 2003, 6, 170.

Why IBX may have been Ignored for so Long

-Although IBX was discovered in 1893, little was done with it until the 1980's.

-Possible Reasons why : Problem

♦IBX is insoluble in just about everything!

There were few ways to make it



Greenbaum, F. R. Am. J. Pharm. 1936, 108, 17.

IBX Goes BOOM!



Plumb, J. B.; Harper, D. J. J. Chem. Eng. News 1990, July 16, 3.

Solution

Is a stress of the solvent

Chaudari, S. *Synlett* **2000**, *2*, 278. and Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2001**, *123*, 3183.

Try Oxone in Water!



Santagostino, M., et.al. J. Org. Chem. 1999, 64, 4537.





Chem. Abstr. 2002, 137, 109123.

A Use is Finally found for IBX

-Finally in 1983, Dess and Martin found a good use for IBX: Conversion to what became known as Dess-Martin Periodinane (DMP), a powerful alcohol oxidant.



-DMP became a method of choice for oxidations of primary and secondary alcohols:



-The reaction can be accelerated in the presence of protic acids, and is largely functional-group-tolerant.

A Comparison of IBX and DMP

-The two comounds have been compared by experimental studies, NMR spectroscopy, and theoretical calculations, and there are numerous differences.

- 1. IBX is highly functional-group tolerant, but DMP will oxidize sulfides and amines.
- 2. Alcohol oxidation by IBX is adversely affected by water: Rate α [H₂O]⁻¹. IBX Alcohol oxidations are both first-order in substrate and first-order in IBX: Rate α [Alc] * [IBX]
- If DMP and 1 equivalent of alcohol are mixed, quantitative ligand exchange occurs at iodine, but with with IBX, the exchange is reverible. In Both cases, the alcohol comes in anti to the benzoic acid carboxylate.



- 4. In the presence of Diols, IBX forms a monodentate complex reversibly, But when diols are mixed with DMP, a bidentate chelate forms, and the process is irreversible.
- 5. As a consequence of all these rules, IBX fails to cleave diols, while DMP succeeds in this reaction.

IBX does the Twist

-Once an alcohol has bound IBX, a series of events occur, leading to oxidation of the substrate:



-Groups ortho to iodine on the phenyl ring are hypothesized to influence the rate of twisting.

Goddard, W. A., III; and Su, J. T., unpublished results.

Diol and Amino-Alcohol Oxidation by IBX

-When diols are oxidized by IBX there can be a number or outcomes, none of which involve C-C bond scission.



Corey, E. J.; Palani, A. *Tetrahedron Lett.* **1995**, *36*, 3485. (Lactol Synthesis) Bose, D. S.; Srinivas, P.; Gurjar, M. K. *Tetrahedron Lett.*, **1997**, *38*, 5839. (Aminal Synthesis)

α -Oxidation of Ketones

-Although PhIO is an insoluble polymeric solid, addition of MeOH and KOH forms a soluble, reactive derivative:



-When ketones are treated with this reagent, α-hydroxy dimethyl acetals are formed:



Moriarty, R. M. J. Org. Chem. 2005, 70, 2893.

α -Oxidation of Ketones

-Mechanism is thought to begin with trapping of the ketone enolate with hypervalent iodide:



-The "lodobenzene leaving group" is projected to be 10⁶ times faster than triflate as a leaving group.

α-Sulfonyloxylation of Enolates

-Silyl Enol Ethers can be used as electrophiles in Hypervalent lodine-mediated oxidations:



-A variety of different enolates can be used as starting materials.



-PhI(OH)OTs is sometimes referred to as "Koser's Reagent"

Koser, G. F., et. al. J. Chem. Soc., Perkin Trans. 1 1994, 1375.

Aziridination Using Hypervalent Iodine

-Using metal catalysts, and PhINTs, nitrenes can be generated for oxidative heteroatom transfer:

Review on PhI=NR: Dauben, P.; Dodd, R. H. Synlett 2003, 11, 1571.



-DuBois has shown that nitrenes can be made to perform C-H activation, giving varying ring sizes.



Espino, C. G.; Wehn, P. M.; Chow, J.; DuBois, J. J. Am. Chem. Soc. 2001, 123, 6935.

Selective o-Oxidation of Phenols to Quinones

-IBX has been shown to oxidize certain phenols to o-quinones.

-Most of these reactions were done in NMR tubes, but the unstable products could be converted to more stable species.



Magdziak, D.; Rodriguez, A. A.; Van De Water, R. W.; Pettus, T. R. R. Org. Lett. 2002, 4, 285.

Substituent Effects in the Oxidation of Phenols



-Chemists hypothesized that for some oxidants, a phenoxenium cation would be produced



AM1 Mulliken Charge Distributions

Substituent	C-2	C-4	C-6	Oxygen
Н	0.030	0.213	0.030	0.067
2-Me	0.143	0.184	-0.279	-0.094
4-Me	0.007	0.282	0.005	0.089
2-OMe	0.235	0.121	-0.010	-0.091
4-OMe	-0.003	0.335	-0.003	-0.110

LUMO Coefficients of the Phenoxenium Ion

Substituent	C-2	C-4	C-6
н	-0.476	0.606	-0.477
2-Me	0.535	-0.573	0.409
4-Me	-0.451	0.618	-0.444
2-OMe	0.558	0.505	0.329
4-OMe	-0.437	0.588	-0.401

The bottom-line <u>prediction</u> is that if a phenol has one **ortho** or **para** substituent, then **ipso** oxidation will be observed at the position of that group.

In practice, ipso oxidation is what occurs!

Another Phenol Oxidation Pathway

-In one case, Pettus reported an unusual product in one of his reactions:



-The product was supposedly formed by an intermolecular Diels-Alder dimerization.



Dimerization Transition State



Magdziak, D.; Rodriguez, A. A.; Van De Water, R. W.; Pettus, T. R. R. Org. Lett. 2002, 4, 285.

Application of Phenol Oxidations to Natural Product Synthesis



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Further Chemistry with Oxidized Phenols

-Hypervalent iodine can form substrates that undergo intramolecular Michael additions.



More Applications to Natural Products

-The oxidation of a phenol with hypervalent iodide can be followed up by an Intramolecular Diels-Alder reaction:



-This reaction was utilized in a total synthesis of (±)-Reserpine:



Chu, C. -S.; Liao, C. -C.; Rao, P. D. Chem. Commun. 1996, 1537.

Single Electron Transfer Oxidation of Anisoles

-Whereas unprotected phenols undergo oxidation at the most substituted position, presumably through a phenoxenium cation, protected phenols are oxidized via a different mechanism:



R = OMe, Me, *i*-Pr, *t*-Bu, Br, Cl, CH_2CO_2Me , CH_2CN , etc.

-This reaction is reported to work with p-substituted phenol ethers, but not with other substitution patterns.



-Using Hückel molecular orbital calculations, and EPR, support was found for a Single Electron Transfer (SET) mechanism involving an aryl cation radical.

Kita, Y.; Takada, T.; Tohma, H. Pure & Appl. Chem. 1996, 68, 627.

Synthesis of α,β –Unsaturated Compounds

-It was found that IBX could oxidize both alcohols and carbonyl compounds to unsaturated deriviatives:





Nicolaou, K. C.; Zhong, Y. L.; Baran, P. S. J. Am. Chem. Soc. 2000, 122, 7596.

-Initially a polar mechanism was invoked to rationalize the desaturation steps.



-Studies were later performed that pointed toward a Single-Electron-Transfer Mechanism.

Nicolaou, K. C.; Montagnon, T.; Baran, P. S. J. Am. Chem. Soc. 2002, 124, 2245.

Benzylic Oxidations with IBX

-It was reasoned that if SET pathways were happening in the desaturation reaction that they might be applicable in other types of reactions:



-Indeed, this type of reactivity proved possible for a number of different substrates; in some cases there were interesting outcomes:



Nicolaou, K. C.; Montagnon, T.; Baran, P. S. J. Am. Chem. Soc. 2002, 124, 2245.

Radical Cyclizations Using IBX

-Once the SET mechanism had become better understood, it was applied to other types of substrates:



-Experiments run in plain DMSO and deuterated THF gave deuterated product, but running the reaction in deuterated DMSO with plain THF gave no deuterium incorporation.

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Nicolaou, K. C., et. al. J. Am. Chem. Soc. 2002, 124, 2233.

Subtrate Scope of the IBX-Anilide Cyclization



The Radical Chemistry of Iodine (III)

-lodine (III) Compounds such as PIFA have 2 modes of reactivity, the first being charge-separation.



-However, in the second mode, the lodine (III) reagent itself may also undergo radical mediated decomposition before it ever encounters any substrate, especially under thermal, photochemical, or radical-initiated conditions.



-Acyl Hypoiodite was recently observed by ¹H NMR (Courtneidge, J. L.; Lusztyk, J. Tetrahedron Lett. **1994**, *35*, 1003.)

Togo, H.; Katohgi, M. Synlett, 2001, 5, 565.

Radical-Mediated Bond Formations

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-The decomposition of carboxyl radicals with loss of CO₂ is better known as the Hunsdiecker Reaction.

-This reaction can be mediated by hypervalent iodine:

$$2 \xrightarrow{O}_{R} \xrightarrow{Phl(OAc)_{2}} \xrightarrow{-2 \text{ HOAc}} \xrightarrow{-2 \text{ HOAc}} \xrightarrow{-2 \text{ HOAc}} \xrightarrow{-2 \text{ R}} \xrightarrow{-2 \text{ CO}_{2}} 2 \text{ R}$$

-The Hunsdiecker Reaction has seen many synthetic applications:



-The radical decarboxylation of alkyl carboxyls is roughly 10⁴ times faster than the decarboxylation of aroyl groups.

Togo, H.; Katohgi, M. Synlett, 2001, 5, 565.

Generation of Alkoxyl Radicals

-If no carboxylate groups are available, but there are free alcohols, PIDA can form alkoxyl radicals in the presence of I_2 and hv.



Other Reactions of Alkoxyl Radicals

-If an alkoxyl radical has no ô-hydrogens accessible for abstration, it will attempt to access other reactive groups:



-In the event that no reactive groups are in the vicinity, β-scissions occur, provided that the forming radical is stable.



Togo, H.; Katohgi, M. Synlett, 2001, 5, 565.

The Hoffmann-Löffler-Freytag Reaction

-This reaction is analogous to the reactions of alkoxyl radicals, but involves nitrogen-centered radicals instead. -Usually, an electron withdrawing group must be adjacent to the nitrogen radical for the reaction to be successful:



-The radicals formed in these reactions will obey many of the same rules that alkoxyl radicals do.



-As in the case of alkoxyl radicals, a δ-hydrogen abstraction occurs.

Radical Intermolecular C-C Bond Formations

-Heteroaromatic Bases can be alkylated:



-Such carbon-centered radicals can also undergo reductive addition to electron-poor olefins:



-When an iodobenzene dioxalate is decomposed, two equivalents of CO_2 can be produced, but formation of the second equivalent is often slower. Thus, intermediates can be trapped, giving acylation products:



Togo, H.; Katohgi, M. Synlett, 2001, 5, 565.

Non-Radical Pathways to C-C Bond Formation

-Hypervalent lodine has another mode of reactivity called Ligand Coupling.



-For two ligands to couple on a hypervalent iodine center, one must be axial, and the other equatorial.

-Diaryl iodonium salts (a class of 10-I-3 reagents) are useful for ligand coupling:



-If the anionic group of an iodonium salt is a good enough leaving group, it can switch with a carbon ligand.

Moriarty, R. M. J. Org. Chem., 2005, 70, 2893.

Coupling Reactions of Enolates

-The use of Hypervalent iodine can allow the synthesis of 1,4-Dicarbonyls



Cyclopropanations with Iodonium Salts

-When a monocarbonyl compound is treated with PhIO and base in MeOH, the outcome is usually α -oxidation, but when a β -dicarbonyl is treated under the same conditions, an isolable iodonium ylid is generated.



-Moriarty claims that the stability of these compounds relative to their monocarbonyl counterparts has to do with the bonding of the enolate oxygen atom to iodine center.

-However, cyclopropanations are known to occur with malononitrile, which has no oxygen atom to impart this stability.



-In this case, something else is actually occurring!

Cyclopropanations with Iodonium Salts

-In a system developed by Moriarty, cyclopropanation is beleived to involve an iodonium ylid.



-When the reaction is run in the absence of copper, it works, but the yield is very poor.

-It is possible that the olefin is involved in charge transfer with the iodine, similar to what is seen in the malononitrle cyclopropanations (previous slide).

-The copper may help catalyze single electron transfer processes.

-At no point in the reaction are any Wolff Rearrangement products observed.

Moriarty, R. M.; Prakash, O.; Vaid, R. K.; Zhao, L. J. Am. Chem. Soc. **1989**, *111*, 6443. Moriarty, R. M. J. Org. Chem., **2005**, *70*, 2893.

Ring Contractions of Iodonium Ylids

-Although Wolff Rearrangements are not seen under the conditions of cyclopropanation, they can arise under other conditions:



-This mode of reactivity has been utilized in the synthesis of cyclopentane diones.

Vinyl Iodonium Salts: Synthesis and Properties

-By using alkenyl stannanes of defined olefin geometry, one can prepare vinyl iodonium salts using the Stang Reagent.



-When certain vinyl iodonium salts are exposed to fragmentation conditions, a variety of products are formed:



-These products demonstrate some of the reactivity characteristics of these compounds, and a number of mechanisms have been postulated.

Hinkle, R. J.; Mikowski, A. M. ARKIVOC, 2003, 6, 201-212.

Proposed Mechanisms of Fragmentation

-4 mechanisms were originally proposed and tested with calculation and experiment:



Hinkle, R. J.; Mikowski, A. M. ARKIVOC, 2003, 6, 201-212.

Alkynyl lodonium Salts

-Alkynyl lodonium Salts can also be used to prepare the reactive vinyldenes mentioned earlier.



-The reactive vinylidene formed has found in application in total synthesis.

Feldman, K. S. ARKIVOC, 2003, 6, 179.

Alkynyl lodonium Salts

-Flash Vacuum Pyrolysis studies have indicated that 2 different products can be prepared from aryl vinylidenes:



-A model system analogous to Parietropone was tested, but favored the C-H activation over cyclopropylidenation.



Alkynyl lodonium Salts

-Although model systems did not look promising, Feldman charged onward with the real system:



Feldman, K. S. ARKIVOC, 2003, 6, 179.

A Concise Synthesis of Angel Dust



"When in doubt, think hypervalent iodine." -R. M. Moriarty