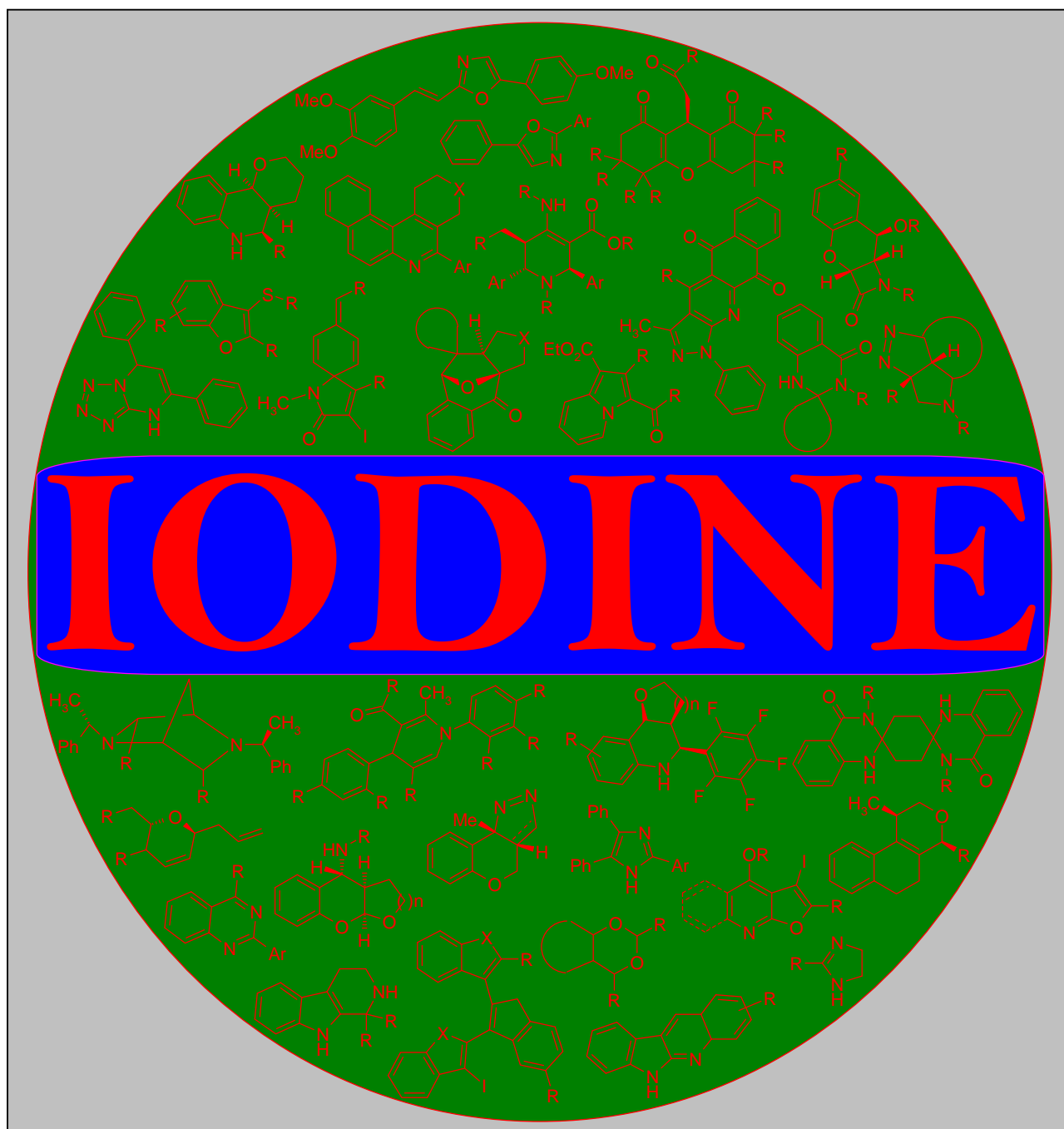


# Recent Developments in the Synthesis of Five- and Six-Membered Heterocycles Using Molecular Iodine

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**Abstract:** Heterocyclic scaffolds represent the key structural subunits of many biologically active compounds. Over the last few years, iodine-mediated reactions have been extensively studied due to its low cost and eco-friendliness. This review covers the advances in the field of iodine-mediated synthesis of heterocyclic compounds

since 2006, especially with emphasis on mechanism of ring formation. In this article, synthesis of different heterocycles is classified based on the manipulation of functional groups.

**Keywords:** Catalysis, heterocycles • multicomponent • iodine • one-pot.

## Introduction

Iodine is a non-metal under Group VII A of the periodic table. Though relatively a rare element, the high solubility of its compounds in water has contributed to its enrichment in the oceans. It is the heaviest micronutrient element essential for all living organisms, with its deficiency known to cause severe health problems in animals and human beings. Iodine provides the substrate for synthesis of the thyroid hormones, thyroxine and triiodothyronine, which are crucial for normal growth and development. Deficiency of this element is known to cause goiter and even mental retardation.

Iodine is non-combustible, but it is a strong oxidizer, especially for the conversion of –SH groups into disulfides and iodination of aromatic rings of tyrosine and histidine in proteins. Due to this oxidizing ability, iodine is widely used in several disinfectants (*viz.*, tincture of iodine, povidone-iodine, *etc.*).

In organic chemistry, the alkaline solution of iodine has been used for the detection of acetyl group and is known as the Lieben iodoform reaction. Iodine is used as a universal stain during thin-layer chromatography, besides for activation of magnesium during preparation of Grignard reagents. The major industrial application of iodine is as a co-catalyst for the production of acetic acid by the Monsanto and Cativa processes.

The use of iodine as an inexpensive, non-toxic and a readily available catalyst for various organic transformations have recently been well reviewed<sup>[1,2]</sup>, covering literature upto the year 2006. It is also been reviewed for iodocyclization,<sup>[3]</sup> in the protection – deprotection<sup>[4]</sup> of functional groups, electrophilic iodination<sup>[5]</sup> of organic compounds and transformation of molecules containing oxygen functional groups.<sup>[6]</sup> Iodine has high tolerance to air as well as moisture and can be easily removed from the reaction mixture by washing with reducing agents. The development of safe, atom efficient acid-catalyzed organic process is one of the most important challenges for green chemistry. While acid catalysis remains the most widely used type of catalysis, the commonly used acid catalysts continue to pose serious health and safety problems. Moreover, the mild Lewis acidity of iodine has enhanced its utility for several organic transformations starting from minor catalytic amounts to higher stoichiometric levels.

Many of the iodine-mediated reactions are well known for mild reaction conditions, greater stereo- and regioselectivities, and short reaction times. Most of these reactions are carried out *via* multicomponent and/or domino reaction sequence. Multicomponent<sup>[7-11]</sup> and domino<sup>[12-18]</sup> reactions allow the creation of several bonds in a single operation and are one of the important synthetic tools for the creation of molecular diversity and complexity.<sup>[13,14]</sup> They are also extremely user and environment-

friendly due to the step reduction and high atom-economy associated to their use.

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In this review, we focus on the use of molecular iodine for the construction of various five and six member heterocyclic compounds with one or two heteroatom either as a single ring system or condensed to other ring with emphasis on the mechanism of ring formation. Heterocyclic rings occur as the key structural subunits in numerous biologically active natural

products and has also been used as chiral auxiliaries, chiral catalysts and ligands for asymmetric catalysis. Many important heterocycles, such as benzofurans, furans, benzothiophenes, thiophenes, benzopyrans, benzoselenophenes, selenophenes, indoles, quinolines, isoquinolines,  $\alpha$ -pyrones, isocoumarins, isoxazoles, chromones,  $\beta$ -lactams, 2,3-dihydropyrroles, pyrroles, furopyridines, furanones, isochromenes etc. have been prepared *via* iodine-mediated domino or one-pot multicomponent reactions.

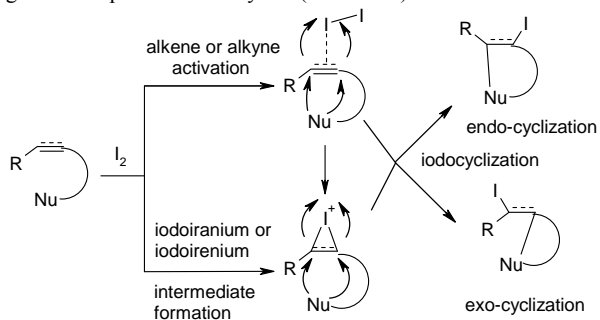
Iodine-mediated synthesis of different heterocycles is classified into following categories based on the manipulation of functional groups.

- i) Activation of carbon-carbon double bond
- ii) Activation of carbon-carbon triple bond
- iii) Activation of enamine, thioamide and hydrazone
- iv) Activation of carbonyl and imine
- v) Activation of orthoformate

## General Mechanism

### Activation of carbon-carbon double or triple bond

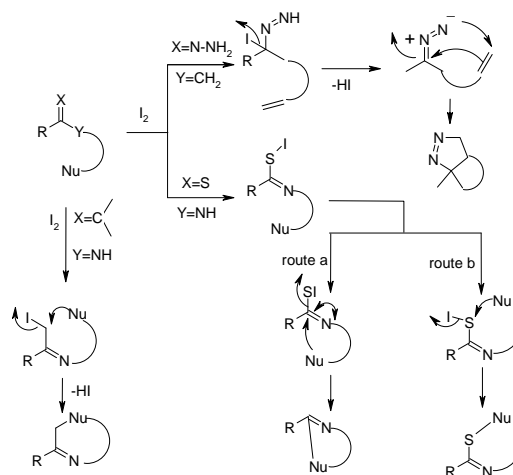
The reaction proceeds through the initial activation of the  $\pi$ -bond either through a charge transfer complex or *via* an iodoiranium / iodoirenium intermediate. This is followed by intramolecular attack by a nucleophile (Nitrogen-, Oxygen- or Sulphur-) either in a *endo* or *exo* fashion depending upon the substrate geometry to give the respective heterocycles (Scheme A).



Scheme A

### Activation of enamine, sulphonamide and hydrazone

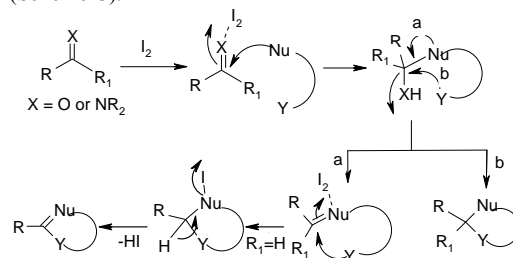
The reaction proceeds through initial iodination of an enamine or hydrazone or a thioamide to give an iodo intermediate. The iodo intermediate then can undergo nucleophilic substitution or nucleophilic addition followed by elimination or expel of HI to generate a polar intermediate which leads to heterocycle formation (Scheme B).



Scheme B

### Activation of carbonyl and imine

Iodine with its low lying  $d^*$  orbital can accept an electron pair from a heteroatom of carbonyl or an amine to act as Lewis acid. This activated carbonyl or imine is then attacked by a nucleophile (Nitrogen-, Oxygen- or Sulphur-) either in an intramolecular or intermolecular manner to give the corresponding heterocycles (Scheme C).



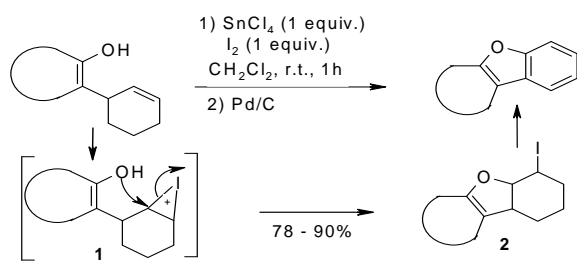
Scheme C

The activation of carbonyl could also take place by the liberated HI. The liberated HI is known to undergo easy air oxidation to give back molecular iodine thus making a catalytic cycle possible. Further, orthoformate can also be activated by an analogous process. The oxidation ability of iodine is also exploited for *in situ* oxidation of alcohol, chalcogen,  $sp^3$ -CH activation of benzylic carbon etc.

## 1) Activation of a carbon-carbon double bond *via* iodoiranium intermediate

### i) Five-membered heterocycles

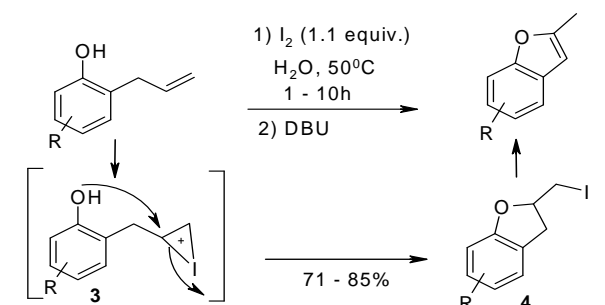
Majumdar and co-workers<sup>[19]</sup> presented an efficient method for the synthesis of furan fused heterocycles *via* 5-*exo-trig* cyclization (Scheme 1) from *ortho*-cyclohexenyl phenol and *ortho*-cyclohexenyl enol derivatives of coumarins, uracil, dimedone and pyrone.



Scheme 1

Iodoiranium intermediate **1** formed *in situ* undergoes 5-*exo-trig* cyclization to form the products **2** in good to excellent yields. These products are then aromatized using Pd-C.

Tripathi and others<sup>[20]</sup> have used 5-*exo-trig* cyclization for the synthesis of dihydro-benzofurans from *o*-allyl phenols in water (Scheme 2).

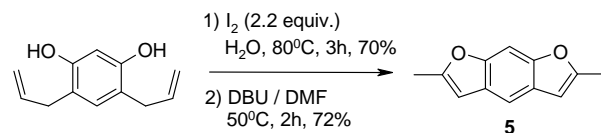


R = 4-Cl, 2,4-Cl<sub>2</sub>, 2,3-Me<sub>2</sub>, 2,5-Me<sub>2</sub>, 3-Me-4-Cl, 4-CN, 4-CHO

Scheme 2

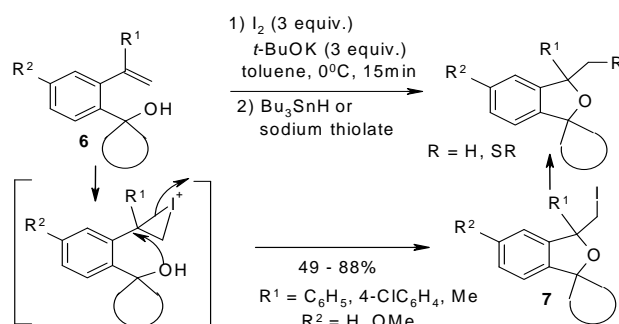
Formation of iodoiranium intermediate **3** followed by 5-*exo-trig* cyclization results in products **4**. The strategy works for phenols having electron donating as well as withdrawing groups. The dihydrofurans obtained are then dehydrohalogenated using DBU to get benzofurans.

In an interesting example double iodocyclisation was achieved for the synthesis of **5** (Scheme 3).



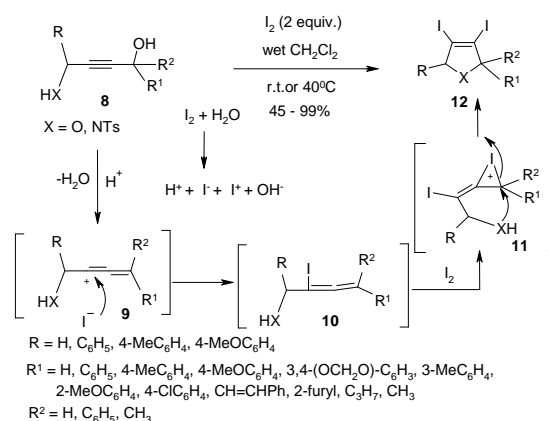
Scheme 3

Kobayashi and co-workers<sup>[21]</sup> have presented 5-*exo-trig* cyclisation for the preparation of 1,3-dihydroisobenzofurans **7** from *o*-vinylbenzyl alcohols **6** obtained from reaction of 2-vinyl phenyl lithium with carbonyl compounds (Scheme 4). In case of electron donating group (R<sub>2</sub> = OMe) on the aryl ring, the yield was found to decrease. The resulting (1-iodomethyl)-1,3-dihydroisobenzofurans are then either reduced with tributyltinhydride or alkylated with sodium thiolate.



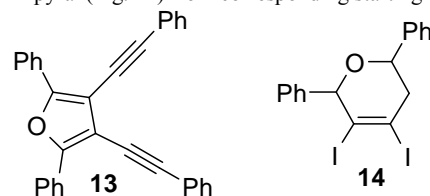
Scheme 4

Ji *et al.*<sup>[22]</sup> demonstrated the iodine-induced tandem cyclization process for the preparation of 3,4-diiodoheterocyclic compounds from but-2-yne-1,4-diol and 4-aminobut-2-yn-1-ol derivatives (Scheme 5).

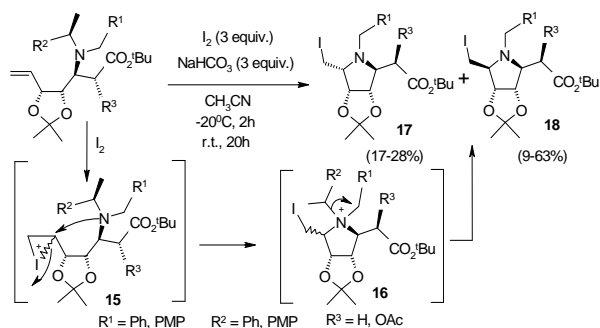


Scheme 5

Traces of water present in CH<sub>2</sub>Cl<sub>2</sub> reacts with the I<sub>2</sub> to produce H<sup>+</sup>, I<sup>-</sup>, I<sup>+</sup> and OH<sup>-</sup>. In presence of H<sup>+</sup>, compound **8** loses the hydroxyl group as water to generate allene cation intermediate **7**. The attack of I<sup>-</sup> on intermediate **9** followed by generation of iodoiranium intermediate **11** by coordinating I<sub>2</sub> with the resultant iodo-intermediate **10** and subsequent intramolecular attack of the heteroatom in an *endo-trig* fashion yielded the cyclised products **12**. Of the different solvents tested moist CH<sub>2</sub>Cl<sub>2</sub> was found to give optimum yield. The reaction works well with aromatic substituents. Electron rich aryl groups showed better results than electron withdrawing aryl groups. Aliphatic substituents also gave corresponding product. Spiro products were also obtained in good yields. The potential of the further elaboration of the diiodoheterocyclic compound was demonstrated by one example of Sonagashira coupling (Fig.13). Also the same protocol was extended in moderate yield to obtain 4,5-diiodo-2,6-diphenyl-3,6-dihydro-2*H*-pyran (Fig. **14**) from corresponding starting material.



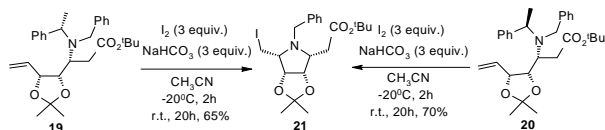
Davies *et al.*<sup>[23]</sup> described a novel ring-closing alkene iodoamination reaction for the synthesis of polyhydroxy pyrrolidines (Scheme 6).



Scheme 6

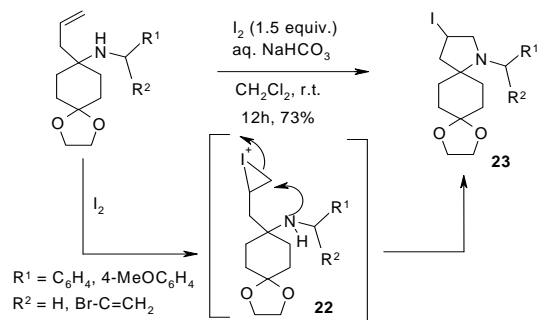
Iodoiranium intermediate **15** generated *in situ* undergoes intramolecular cyclization to give the intermediate **16** which loses *N*- $\alpha$ -methyl-benzyl protecting group *via*  $S_N1$  to yield the corresponding iodomethyl pyrrolidines **17** and **18**. Functional group manipulations with AgOAc proceeds *via* the corresponding aziridinium ion. Further deprotection gave access to polyhydroxylated pyrrolidines.

Interestingly, iodocyclization of (3*R*)-configured  $\beta$ -amino esters (3*R*, $\alpha$ *S*)-**19** and (3*R*, $\alpha$ *S*)-**20** gave the single diastereoisomer **21** (Scheme 7).



Scheme 7

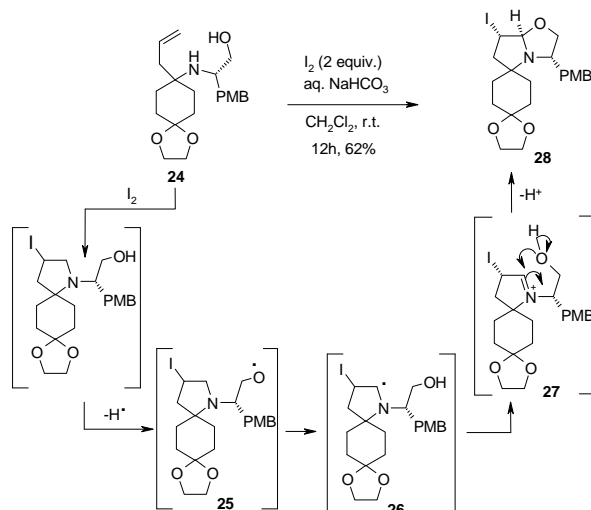
Diaba *et al.*<sup>[24]</sup> reported the 5-*endo-trig* iodoaminocyclization reaction for the preparation of azaspiro ring system (Scheme 8) found in some natural products.



Scheme 8

Iodine activates the C-C double to form the iodoiranium intermediate **22**, which undergoes 5-*endo-trig* cyclization to yield the corresponding azaspiro compound **23**.

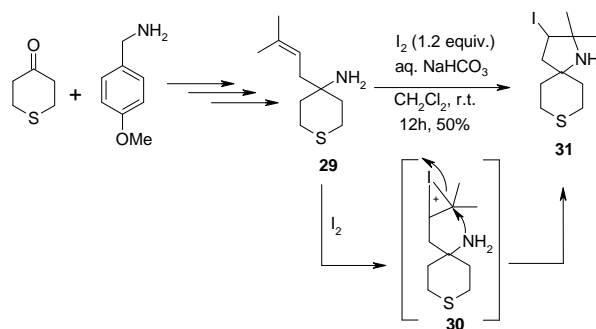
When the same reaction was carried out with amino alcohol **24** with two equivalents of  $I_2$ , an unexpected tricyclic oxazolidine **28** was obtained in 62% yield (Scheme 9).



Scheme 9

The formation of the product **28** was accounted by the authors by an initial 5-*endo-trig* cyclization to afford azaspiro ring followed by a neighbouring hydroxyl group oxidation of the amine to give an iminium intermediate **27** (a possible interpretation is that - a primary alkoxy radical **25** was initially formed by iodine, which then evolved through an intramolecular 1,5-hydrogen abstraction to an  $\alpha$ -aminoalkyl radical **26** that was easily oxidized in the reaction medium to the iminium salt **27**) which, is trapped by the hydroxyl group to form the oxazolidine ring.<sup>[25, 26]</sup>

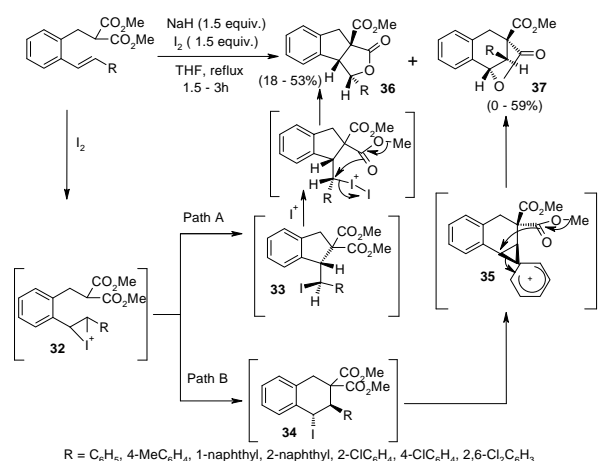
Fang and co-workers<sup>[27]</sup> described an aminocyclization reaction for the synthesis of 3-amino-2,2-dimethyl-8-thia-1-azaspiro[4.5]decane (Scheme 10).



Scheme 10

Iodine coordinates with the C-C double bond of compound **29** to generate iodoiranium intermediate **30** which, undergoes 5-*endo-trig* cyclization to furnish the spiro compound **31**. The iodo group was then converted to amino functionality by usual way.

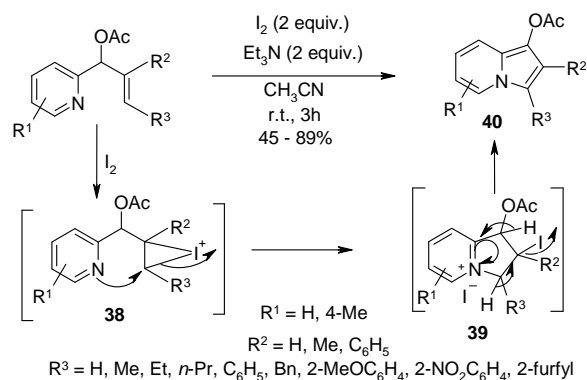
Wirth and co-workers<sup>[28]</sup> developed a novel method for the synthesis of indane-lactones and tetrahydronaphthalenes-lactones (Scheme 11).



Scheme 11

Iodoiranium intermediate **32** generated *in situ* undergoes intramolecular cyclization (5-*exo-trig* and 6-*endo-trig*) to give the intermediates **33** and **34**. Product **36** may have formed by the activation of iodine in **33** by reaction with an iodonium cation followed by cyclization *via* reductive elimination. In a similar manner, the products **37** may have formed by the activation of iodine in **34** by another iodine electrophile and then participation of the phenyl substituent to form phenonium ion intermediate **35** which opened up to furnish the products **37**.

Kim and co-workers<sup>[29]</sup> also presented the 5-*endo-trig* cyclization reaction to provide a number of highly substituted indolizines in one-pot from corresponding allyl acetates (Scheme 12).

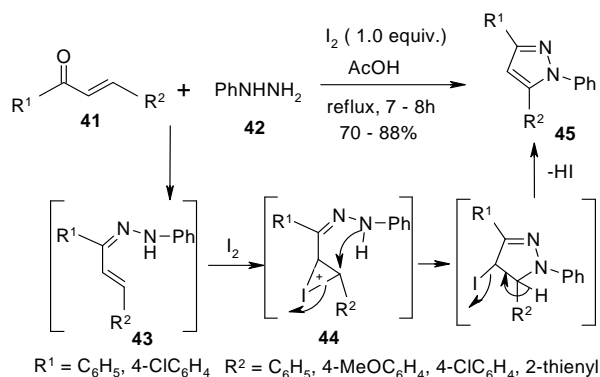


Scheme 12

Iodoiranium intermediate **38** generated *in situ* undergoes 5-*endo-trig* iodocyclization to give the intermediate **39**. Subsequent isomerization and aromatization by the loss of HI accomplished the products **40** in good yields.

Synthesis of pyrazoles **45** from phenyl hydrazine **42** and chalcones **41** by heating in acetic acid at reflux temperature

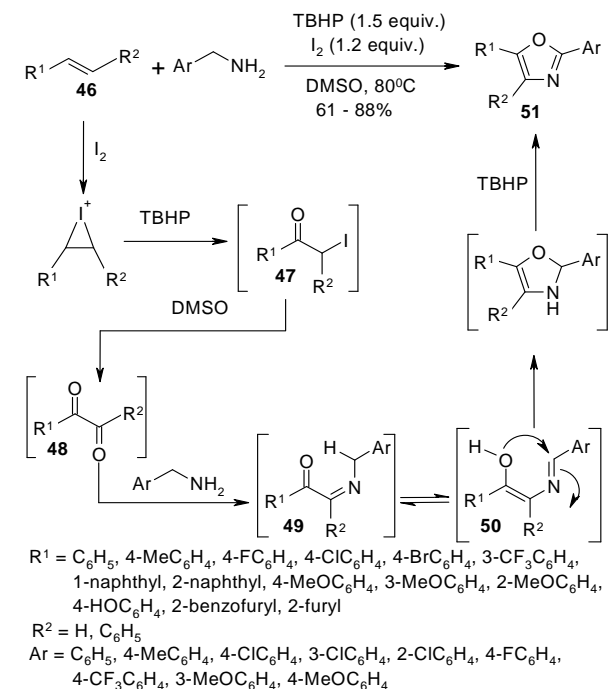
(Scheme 13) was reported by Ponnala and Sahu<sup>[30]</sup> using stoichiometric amount of iodine.



Scheme 13

Hydrazone **43** generated *in situ* by treating **41** with **42** in refluxing AcOH reacts with iodine to form the iodoiranium ion intermediate **44**. Intramolecular cyclization followed by loss of HI gave the products **45**.

Jiang and co-workers<sup>[31]</sup> demonstrated the synthesis of polysubstituted oxazoles from aryl alkenes and benzylic amines *via* TBHP/I<sub>2</sub>-mediated oxidative cyclization process (Scheme 14).



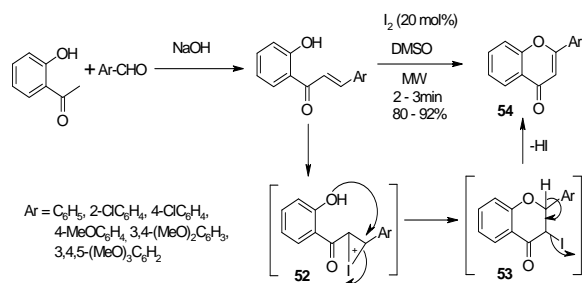
Scheme 14

TBHP/I<sub>2</sub>-mediated oxidation of **46** furnishes the intermediate **47** which is converted to **48** by DMSO *via* Kornblum oxidation. Benzylic amines then reacts with **48** to give the intermediate **49** which is in equilibrium with its enol form **50**. Intramolecular nucleophilic addition followed by deprotonation and subsequent oxidation afforded the oxazoles **51**. The reaction works well with

olefins regardless of electronic properties of the groups present on the aryl ring. Higher yields were obtained with electron withdrawing groups on the aromatic ring. If one of the substituent on the olefin was alkyl group then abysmal yield of the products were obtained. The method is restricted to benzyl amines as other alkyl amines failed to yield the products.

## ii) Six-membered heterocycles

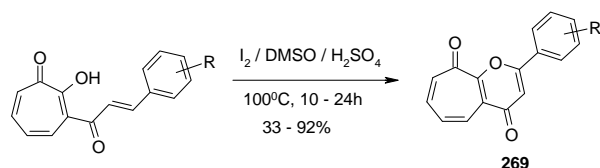
Menezes *et al.*<sup>[32]</sup> from our laboratory described a simple approach for the preparation of various flavones using 20 mol% I<sub>2</sub> under microwave irradiation (Scheme 15).



Scheme 15

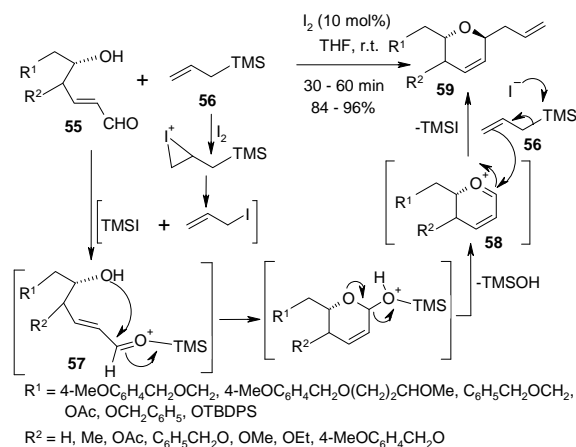
*In situ* formed iodoiranium intermediate **52** undergoes intramolecular cyclization to give intermediate **53** which, readily eliminates HI to furnish the corresponding flavones **54**. The liberated HI gets oxidized back to I<sub>2</sub> to complete the catalytic cycle.

Under similar fashion, Gao and others<sup>[33]</sup> prepared a wide range 2-aryl-4,9-dihydrocyclohepta[*b*]-pyran-4,9-diones from 3-cinnamoyltropones using I<sub>2</sub>/DMSO/H<sub>2</sub>SO<sub>4</sub> system (Scheme 16).



Scheme 16

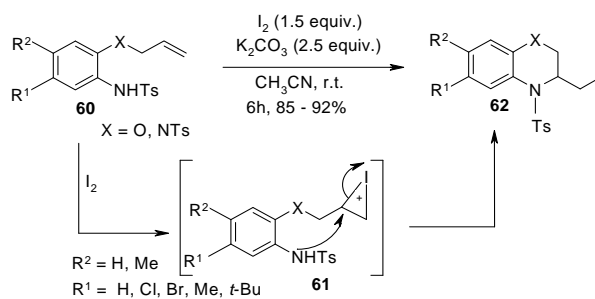
Mohapatra and co-workers<sup>[34]</sup> reported the synthesis of *trans*-2,6-disubstituted-3,4-dihydropyrans by treating  $\delta$ -hydroxy- $\alpha,\beta$ -unsaturated aldehydes with allyltrimethyl silane in presence of 10 mol% of iodine (Scheme 17).



Scheme 17

Activation of the carbonyl group of **55** by *in situ* formed TMSI generates intermediate **57**. Nucleophilic attack of hydroxyl group on activated carbonyl carbon followed by expulsion of trimethyl silyl hydroxide forms the oxonium intermediate **58**. The final products **59** were formed by the initial attack of I<sup>-</sup> on the trimethyl silyl group of compound **56** to generate nucleophile which, attacks the oxonium intermediate **58**.

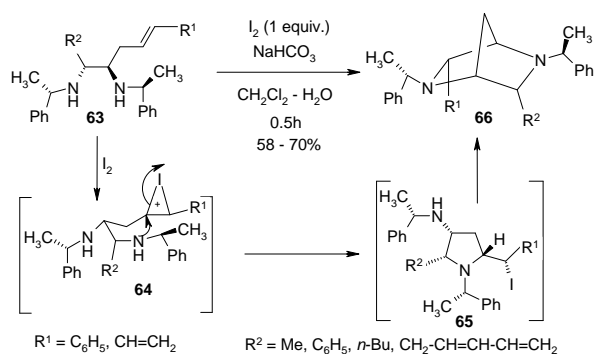
Majumdar and co-workers<sup>[35]</sup> described an efficient approach for the synthesis of 3,4-dihydro-2*H*-1,4-benzoxazine and 1,2,3,4-tetrahydroquinoxaline derivatives (Scheme 18).



Scheme 18

Iodine activates the C-C double bond of compound **60** to generate iodoiranium intermediate **61** which, underwent 6-*exo-trig* cyclization to yield the corresponding products **62**.

Alvaro *et al.*<sup>[36]</sup> achieved the synthesis of substituted 2,5-diazabicyclo[2.2.1]-heptanes **66** via iodine-mediated cyclization of **63** (Scheme 19).



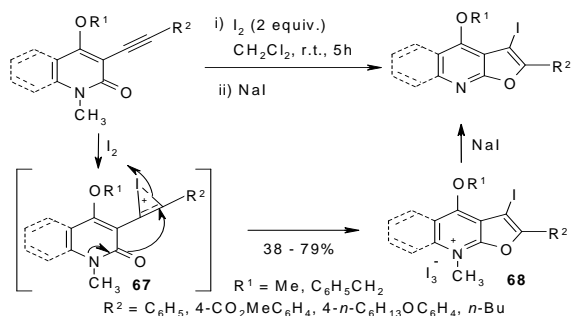
Scheme 19

Iodine activates C-C double bond of compound **63** to generate iodoiranium intermediate **64** which, subsequently underwent intramolecular cyclization to give the pyrrolidine intermediate **65**. Intramolecular substitution by the attack of the secondary amine on the highly reactive benzylic iodide yielded the bridged piperazines **66**.

## 2) Activation of a carbon-carbon triple bond via iodoiranium intermediate

### i) Five-membered heterocycles

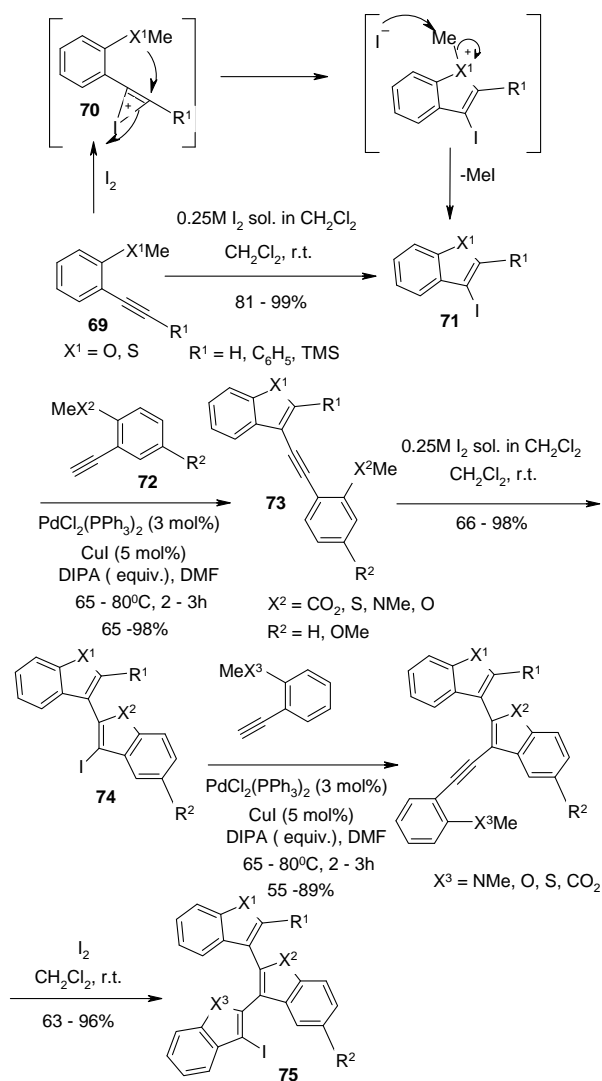
Balme and co-workers<sup>[37]</sup> demonstrated the *endo-dig* iodocyclization of 4-alkoxy-3-alkynyl-2-pyridones to give 3-iodofuro-pyridinium triiodide and iodofuro-quinolinium triiodate salts in moderate to good yields (Scheme 20).



Scheme 20

Iodine activates the C-C triple bond to form the iodoiranium intermediate **67** which, subsequently undergoes intramolecular cyclization by the attack of the carbonyl oxygen to give the pyridinium- and quinolinium-fused furans **68**. The later were then dealkylated *in situ* upon exposure to an iodide anion to get 3-iodo[2,3-*b*]pyridine-4(1*H*)-ones and furo[2,3-*b*]quinoline-4(9*H*)-ones.

Larock and Mehta<sup>[38]</sup> reported the repetitive 5-*endo-dig* iodocyclization followed by Sonogashira coupling approach for the generation of various polyheterocyclic (PHC) compounds (Scheme 21).

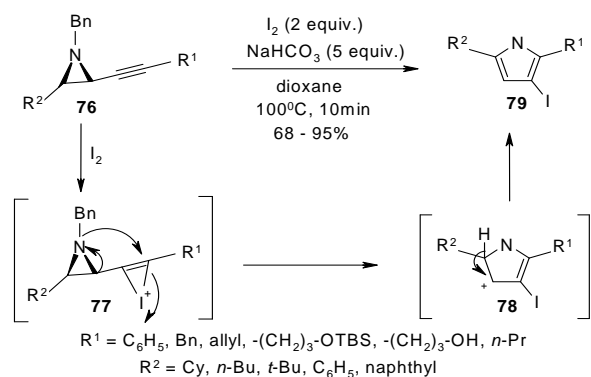


Scheme 21

Iodine activates the C-C triple bond of compound **69** to generate the iodoiranium intermediate **70**. Intramolecular cyclization and subsequent loss of methyl iodide results in the formation of compounds **71**. Pd-catalyzed coupling reaction<sup>[39]</sup> of **71** with **72** followed by iodocyclization of the resultant compound **73** yielded the respective compounds **74**. Compounds **74** on further Pd-catalyzed coupling reaction – iodocyclization sequence provided the tricyclic compounds **75**. A variety of heterocyclic units including benzofurans, benzothiophens, indoles and isocoumarin have been efficiently incorporated into the polycyclic framework.

Yoshida *et al.*<sup>[40]</sup> described the synthesis of 2,5-disubstituted -3-iodopyrroles by an iodine-promoted electrophilic cyclization (Scheme 22) of propargylic aziridines.

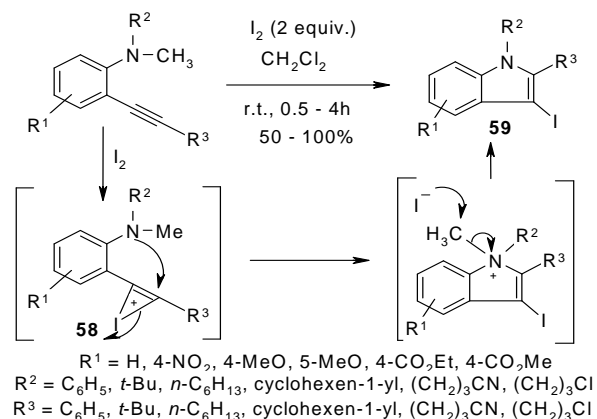




Scheme 22

Iodine coordinates with the C-C triple bond of compound **76** to form the iodoirenium intermediate **77**. The intramolecular attack of azidone nitrogen produces the intermediate **78** which, readily eliminates the proton to give the aromatized products **79** in good to excellent yields. A variety of substituted 3-iodopyrroles were prepared and usefulness of the iodo group was demonstrated by one successful example of Negishi coupling.

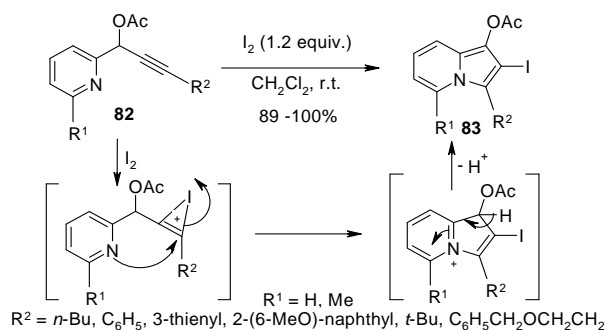
Larock and co-workers<sup>[41]</sup> prepared several 2,3-disubstituted indoles *via* iodine-mediated electrophilic cyclization (Scheme 23).



Scheme 23

Iodine coordinates the C-C triple bond to form iodoirenium intermediate **80**. Intramolecular cyclization of **80** by the nucleophilic attack of amino group followed by loss of methyl iodide yielded the corresponding indole derivatives **81**.

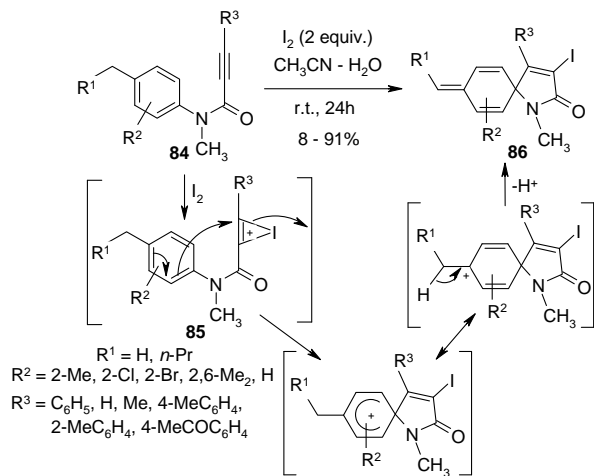
Kim and co-workers<sup>[42]</sup> reported the 5-*endo-dig* cyclization of propargylic acetates **82** to give the indolizines **83** (Scheme 24).



Scheme 24

Indolizines **83** were formed *via* initial activation of C-C triple bond by iodine and subsequent intramolecular nucleophilic attack of pyridine nitrogen followed by dehydrogenation.

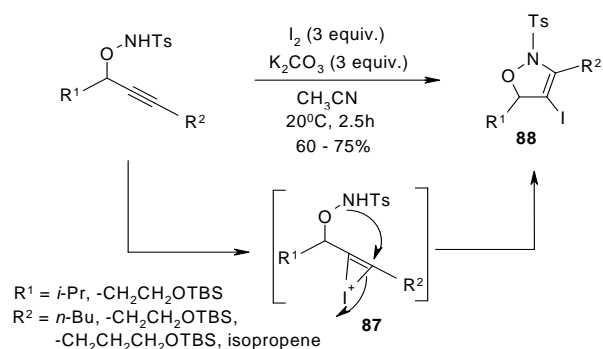
Yu *et al.*<sup>[43]</sup> described a novel intramolecular electrophilic ipso-cyclization<sup>[44, 45]</sup> for the preparation of various 8-methyleneazaspiro[4.5]trienes (Scheme 25).



Scheme 25

Iodine coordinates with the C-C triple bond of compound **84** to generate the iodoirenium intermediate **85**. Intramolecular Friedel-Crafts cyclization followed by loss of proton afforded the respective spiro-compounds **86**. Interestingly in presence of base (NaHCO<sub>3</sub>) the yield of the product was reduced. Analogous amides with methyl group replaced with hydrogen or an acyl group were found to be unsuitable substrates. With terminal acetylenes also the reaction fails. The scope of the reaction was studied with very few examples of additional substituents on phenyl ring like methyl, chloro and bromo.

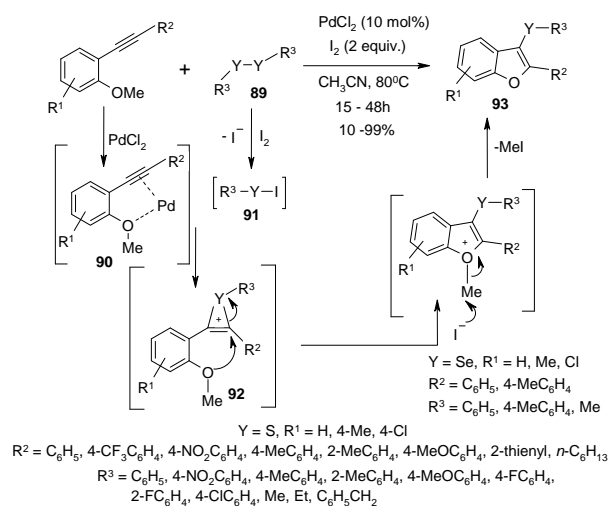
Knight and others<sup>[46]</sup> reported the synthesis of 2,5-dihydroisoxazoles *via* 5-*endo-dig* cyclization from *o*-propargylic hydroxyamines (Scheme 26).



Scheme 26

iodoirenium intermediate **87** generated *in situ* underwent 5-*endo-dig* cyclization to yield the corresponding 3-isoxazolines **88** in good yields. An exception was the failure of terminal acetylenes ( $R_2 = \text{H}$ ) to give any 3-unsubstituted isoxazolines.

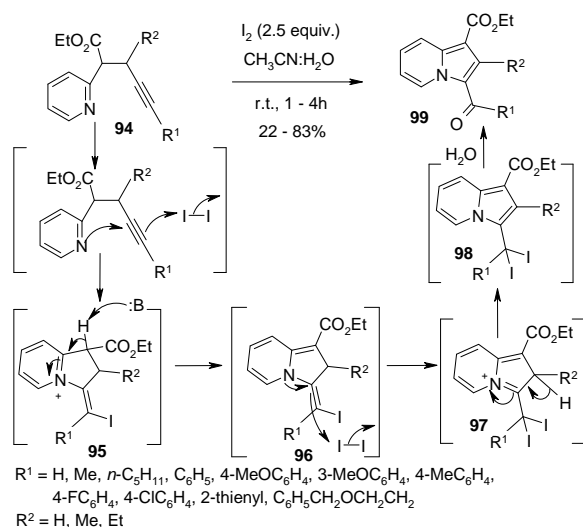
Du *et al.*<sup>[47]</sup> reported the synthesis of number of 3-chalcogenbenzo[*b*]furans in the presence of  $\text{I}_2$  and  $\text{PdCl}_2$  in moderate to excellent yields (Scheme 27).



Scheme 27

The reaction of disulfides/diselenides **89** with  $\text{I}_2$  forms the intermediate **91** *in situ* which underwent electrophilic addition with intermediate **90** to give **92** by 5-*endo-dig* manner. Annulation of **92** followed by loss of methyl group as methyl iodide furnished the 3-sulfonylbenzofurans and 3-selenylbenzofurans **93**.

Kim *et al.*<sup>[48]</sup> described a novel approach to 3-acylated indolizines **99** via iodine-induced hydrative cyclization<sup>[49]</sup> of alkynes **94** (Scheme 28).

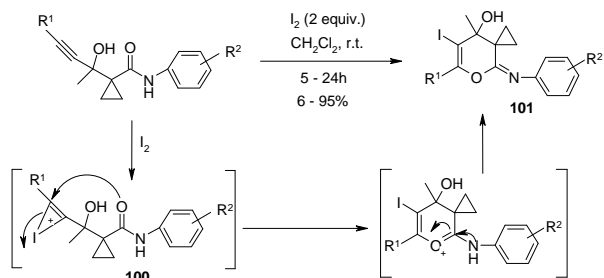


Scheme 28

Iodocyclization of **94** by the attack of pyridyl nitrogen on iodine activated C-C triple bond generates vinyl iodide **95**. Deprotonation of **95** followed by attack of enamine intermediate **96** on another molecule of iodine produces the diiodide intermediate **97** which loses proton to furnish desired indolizines **99** via hydrolysis of the diiodo group of **98** by  $\text{H}_2\text{O}$ .

## ii) Six-membered heterocycles

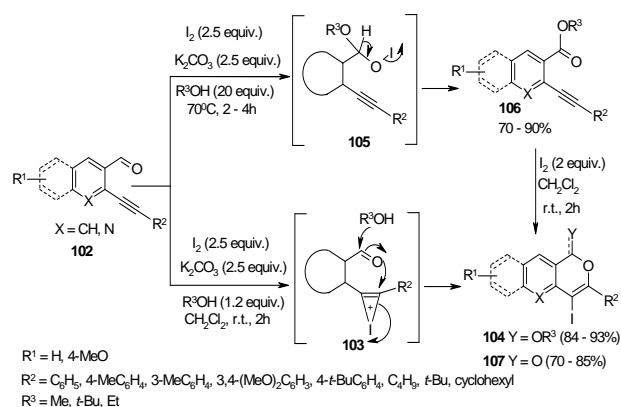
Xie and others<sup>[50]</sup> demonstrated a new approach to synthesize polysubstituted 3-iodopyrans **155** from alkyne carboxamides (Scheme 29).



Scheme 29

Formation of iodoirenium intermediate **100** followed by intramolecular nucleophilic attack of the oxygen of the carboxamide group in a 6-*endo-dig* fashion and subsequent deprotonation afforded the products **101**. Electron withdrawing groups on the *N*-aromatic ring significantly increased the yields and decreased the reaction times.

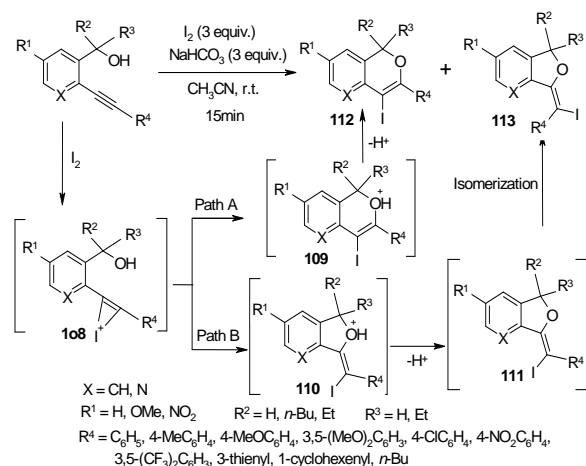
Verma and co-workers<sup>[51]</sup> presented the iodine-mediated and solvent-controlled selective synthesis of iodopyrano[4,3-*b*]quinolines and *o*-alkynyl esters under mild reaction conditions from *o*-alkynyl aldehydes (Scheme 30).



Scheme 30

Reaction of *o*-alkynyl aldehydes **102** with iodine in  $\text{CH}_2\text{Cl}_2$  provided the iodoenium intermediate **103**. Nucleophilic attack of alcohols on carbonyl carbon followed by cyclization afforded the pyrano[4,3-*b*]quinolones **104**. However, using alcohols as a solvent as well as nucleophile, *o*-alkynyl esters **106** were obtained *via* hypiodide intermediate **105** which subsequently underwent electrophilic iodocyclization to yield pyranoquinolones **107**.

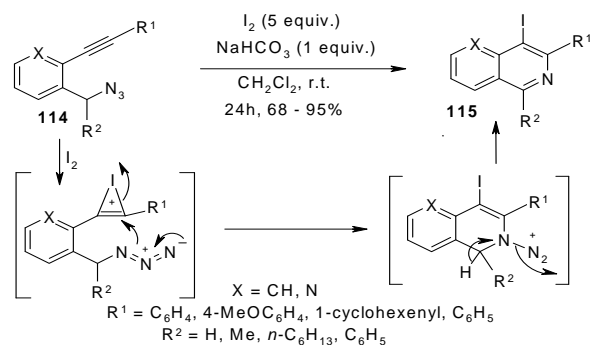
Larock and others<sup>[52]</sup> demonstrated the synthesis of five- and six-membered iodoheterocyclic compound *via* 6-*endo-dig* and 5-*exo-dig* cyclization respectively from *o*-alkynylbenzyl alcohols (Scheme 31).



Scheme 31

Iodine coordinates with the C-C triple bond to form the iodoenium intermediate **108**. Nucleophilic attack by the hydroxyl group then takes place by 6-*endo-dig* and 5-*exo-dig* cyclization to give the intermediate **109** and **110** respectively. Deprotonation of **109** lead to the products **112** while the deprotonation of **110** followed by isomerization of *E*-isobenzofuran **111** afforded the *Z*-isomer **113**.

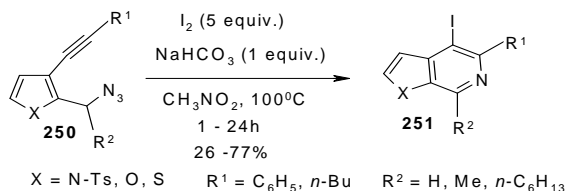
Yamamoto and others<sup>[53]</sup> demonstrated a general approach for the synthesis of highly substituted isoquinolines from *o*-alkynyl benzyl azides (Scheme 32).



Scheme 32

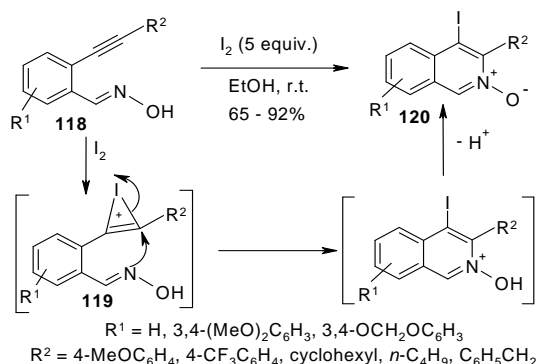
Iodine binds with the C-C triple bond of compound **114**, thereby activating it towards the nucleophilic ring closure of the azide. Subsequent elimination of  $\text{H}^+$  and  $\text{N}_2$  resulted in the formation of isoquinolines **115**.

The same strategy<sup>[54]</sup> was then extended for the synthesis of pyrrolopyridines **116** by iodine-mediated electrophilic cyclization of 2-alkynyl-1-methylene azide aromatics **117** (Scheme 33).



Scheme 33

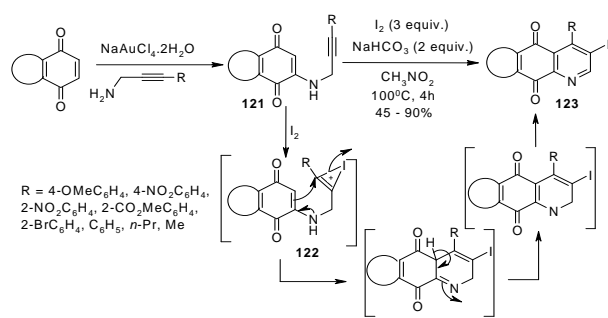
The same laboratory<sup>[55]</sup> accomplished the synthesis of iodoisoquinoline *N*-oxides **120** by reacting 2-alkynylbenzaloximes **118** with five equivalents of iodine (Scheme 34).



Scheme 34

Iodine coordinates with the C-C triple bond to form the iodoenium intermediate **119**. Intramolecular nucleophilic attack by oxime nitrogen followed by elimination of a proton resulted in the formation of iodoisoquinoline *N*-oxides **120**.

Fei *et al.*<sup>[56]</sup> developed a methodology for the construction of azaanthraquinone skeletons via 6-*endo-dig* cyclization from *N*-propargylaminoquinones (Scheme 35).



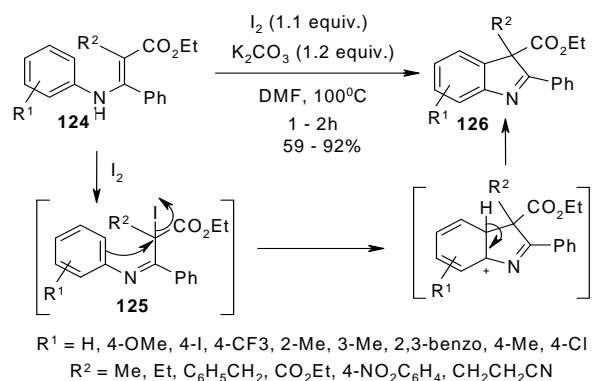
Scheme 35

Iodine coordinates with the C-C triple bond of *N*-propargylaminoquinones **121** to form an iodoenium intermediate **122** which, undergoes 6-*endo-dig* cyclization and subsequent oxidative aromatization to afford the azaanthraquinones **123**.

### 3) Activation of enamines, thioamides and hydrozones

#### i) Five-membered heterocycles

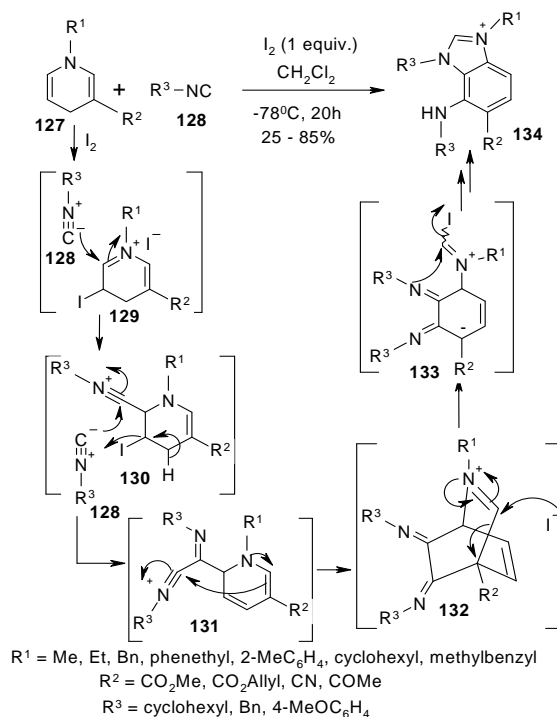
He *et al.*<sup>[57]</sup> demonstrated the iodine-promoted intramolecular cyclization of enamines **124** to give 3*H*-indoles **126** (Scheme 36).



Scheme 36

The oxidative iodination<sup>[58]</sup> of **124** generates an iodide intermediate **125** which, undergoes an intramolecular Friedel-Crafts cyclization and subsequent aromatization to yield the respective 3*H*-indoles **126**.

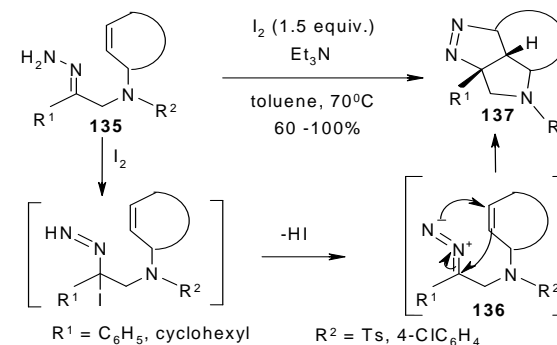
Lavilla and co-workers<sup>[59]</sup> presented an interesting protocol for the synthesis of benzimidazolium salts from dihydropyridines and isocyanides (Scheme 37).



Scheme 37

Iodine interacts with the double bond of the dihydropyridines **127** to generate  $\alpha$ -haloiminium ion **129**. The addition of isocyanides **128** forms the nitrilium ion intermediate **131** by initial nucleophilic attack of isocyanides **128** on **129** followed by another nucleophilic attack on the intermediate **130**. This intermediate is then trapped by interaction with an enamine-type double bond of the heterocyclic moiety to furnish a bicyclic system **132** which, undergoes iodine-promoted fragmentation to yield a delocalized anion **133**. Subsequent imidazole ring formation and aromatization then lead to the final products **134**.

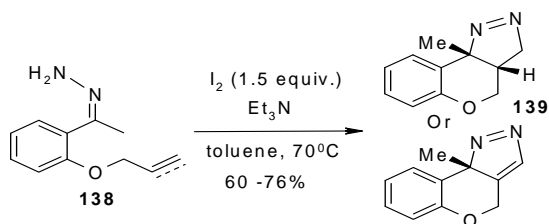
Quiclet-Sire and Zard<sup>[60]</sup> reported the reaction of hydrazones **135** with iodine to yield the fused 4,5-dihydro-3*H*-pyrazoles **137** in good to excellent yields (Scheme 38).



Scheme 38

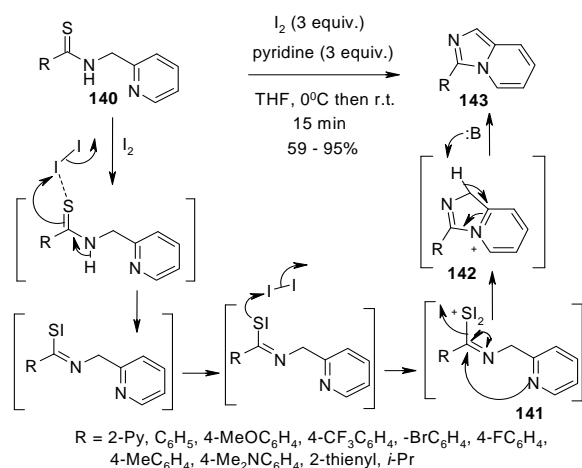
Iodination of hydrazones **135** followed by expulsion of HI gave the diazo intermediate **136**. Intramolecular cycloaddition of **136** furnished the corresponding dihydro-pyrazole derivatives **137**.

Similarly, the reaction of hydrazones **137** with iodine yielded the corresponding heterocyclic compounds **138** via intramolecular dipolar cycloaddition (Scheme 39).



Scheme 39

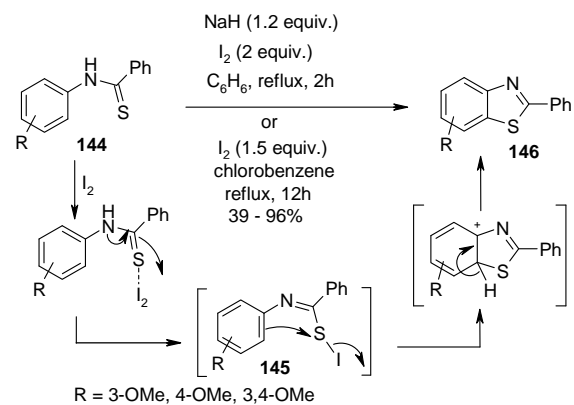
Shibahara and co-workers<sup>[61]</sup> prepared various 2-aza-indolizines **77** via an iodine-mediated, oxidative desulfurization<sup>[62, 63]</sup> promoted cyclizations of *N*-2-pyridylmethyl thioamides **140** (Scheme 40).



Scheme 40

Deprotonation of the *N*-2-pyridylmethyl thioamides **140** by pyridine, followed by double iodination at sulfur gave the intermediate **141**. Intramolecular substitution by the pyridine nitrogen of **141** and subsequent aromatization of the resultant intermediate **142** afforded the 2-aza-indolizines **143**.

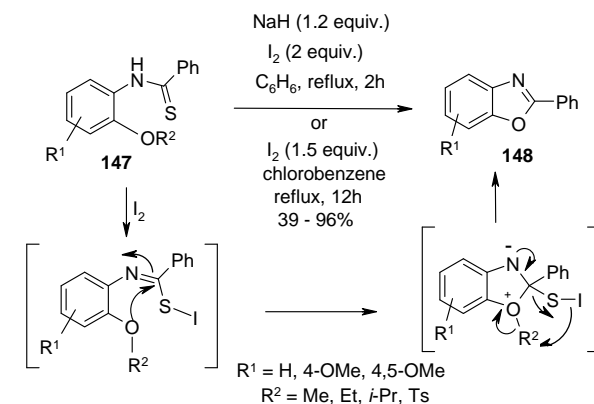
Downer-Riley and Jackson<sup>[64]</sup> described the formation of benzothiazoles and benzoxazoles from thiobenzamides (Scheme 41).



Scheme 41

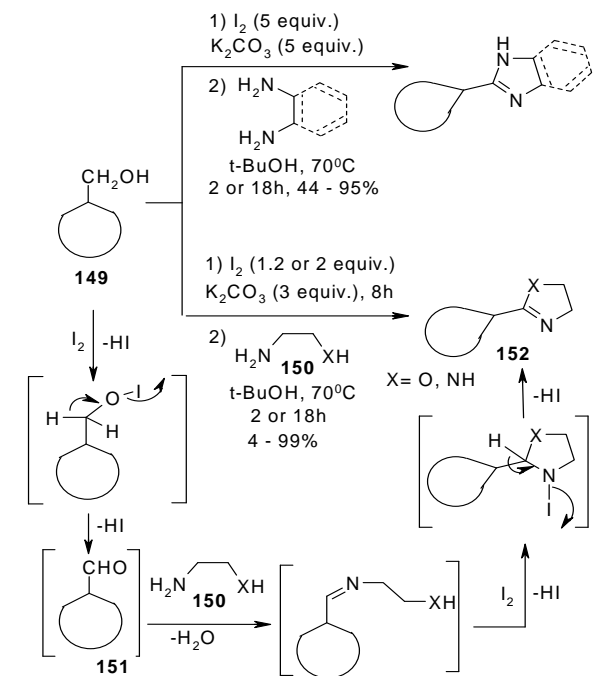
Thiobenzamides **144** reacts with iodine to give sulfenyl iodide **145** which, undergoes cyclization to furnish the corresponding benzothiazoles **146**. In all the examples reported, the benzene ring had an electron donating group.

When the same reaction of thiobenzamides **147** was carried out with an *ortho*-alkoxy or tosyloxy group, the corresponding benzoxazoles **148** were obtained (Scheme 42).



Scheme 42

The direct one-pot oxidative conversion of primary alcohols to the corresponding 2-imidazolines, 2-oxazolines and benzimidazoles<sup>[65, 66]</sup> has also been described (Scheme 43).



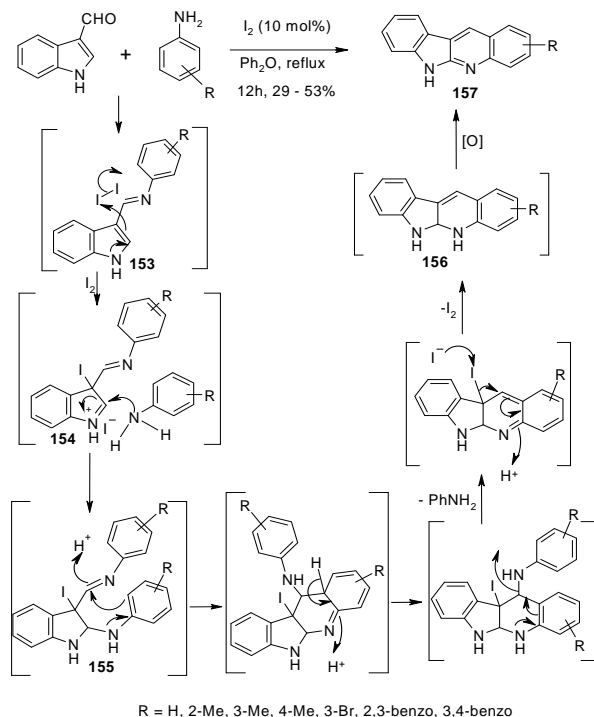
Scheme 43

Iodine initially oxidizes the alcohols **149** to aldehydes **151** which, then reacts with **150** to furnish the corresponding compounds **152** via iodine promoted cyclization reaction. The method is restricted

to benzyl alcohols only. Further, the benzyl alcohols bearing electron withdrawing groups gave poor yields of the products.

## ii) Six-membered heterocycles

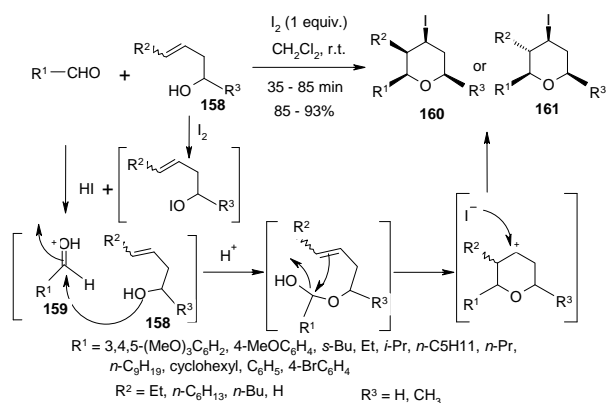
We have described<sup>[67]</sup> a one-pot method for the synthesis of various indoloquinolines *via* sequential imination, nucleophilic addition and annulation catalyzed by iodine (Scheme 44).



Scheme 44

Electrophilic attack of iodine on Schiff's base **153** formed *in situ* by the reaction of anilines with indole-3-carboxaldehyde formed 3-iodo-indolinium cation **154**. Nucleophilic attack by the amino group of another molecule of anilines on intermediates **154** resulted in the formation of 2-*N*-phenyl substituted indole **155**. Intramolecular electrophilic substitution followed by expulsion of anilines and subsequent departure of iodine afforded the dihydro-indoloquinoline intermediates **156**. Finally, the oxidation of **156** yielded the desired indoloquinolines **157**. The method is useful for aryl amines having electron donating groups and heterocyclic amines. However, it did not work with aryl amines having electron withdrawing groups.

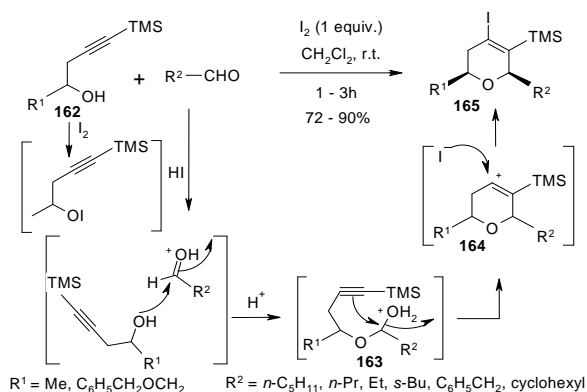
Yadav and co-workers<sup>[68]</sup> described the iodine-mediated Prins-cyclization for the preparation of 4-iodotetrahydropyran derivatives (Scheme 45).



Scheme 45

Treatment of homoallylic alcohols **158** with aldehydes in presence of iodine afforded the diastereomers **160** or **161** in excellent yields. The formation of the products may be explained by the formation of hemi-acetal **159** by HI generated *in situ* during the reaction and subsequent dehydration followed by Prins-cyclization. The use of *cis*-homoallylic alcohols yielded the products with all *cis*-configuration while *trans*-homoallylic alcohols gave the products with *trans-trans*-configuration. The reaction works very well with a wide range of aldehydes *viz.* aliphatic, cyclic and aromatic. Also unsubstituted homoallylic alcohols gave the corresponding products.

The same laboratory<sup>[69]</sup> reported a simple method for the synthesis of 4-iododihydropyrans **165** utilizing the silylalkyne-Prins cyclization<sup>[70-72]</sup> (Scheme 46).



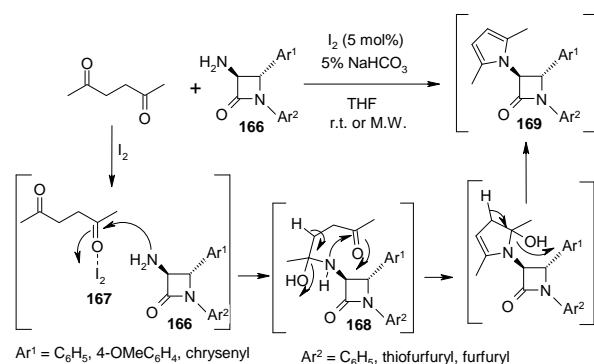
Scheme 46

The reaction was initiated *via* an acetal formation by HI generated *in situ* which was then attacked by homopropargylic alcohols **162** to form oxocarbenium ion intermediate **163**. The Prins-cyclization of **163** furnished  $\beta$ -carbocation **164** which is subsequently trapped by iodide ion to give the desired products **165**.

## 2) Activation of carbonyl and/or imine

### i) Five-membered heterocycles

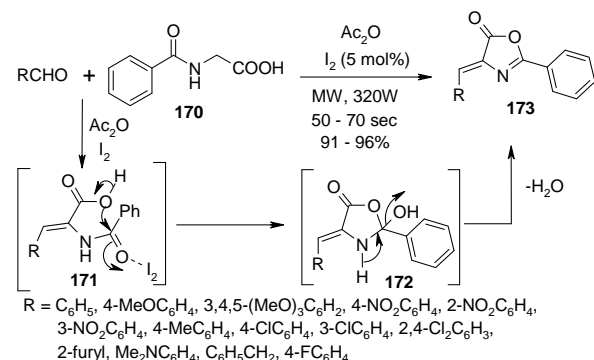
Paal-Knorr approach which uses 1,4-diketones is very popular for the synthesis of pyrroles. Bandyopadhyay and others<sup>[73, 74]</sup> prepared various pyrroles from 2,5-dimethoxytetrahydrofurans using 5% iodine as catalyst under microwave conditions. Also  $\beta$ -lactam fused pyrroles starting from 3-amino- $\beta$ -lactams and 1,4-diketo compound were prepared (Scheme 47).



Scheme 47

Amino group of compound **166** attacks the iodine-activated carbonyl compound **167** to give the compound **168** which, readily eliminates H<sub>2</sub>O and subsequently undergoes cyclization and loss of one more molecule of H<sub>2</sub>O to afford the respective pyrroles **169**.

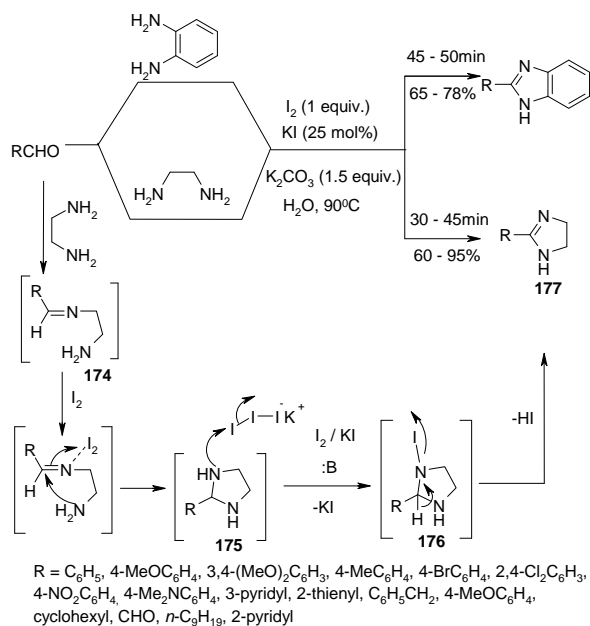
Madhusudana Reddy and Pasha<sup>[75]</sup> demonstrated microwave-assisted one-pot synthesis of azalactones under solvent-free conditions (Scheme 48).



Scheme 48

The reaction of hippuric acid **170**, acetic anhydride and aldehydes in presence of iodine under microwave irradiation forms the intermediate **171** via Perkin reaction. Intramolecular cyclization of **171** and subsequent loss of water of the resultant intermediate **172** afforded the 5-arylmethylidene-2-phenyloxazol-4-ones (azalactones) **173** in excellent yield.

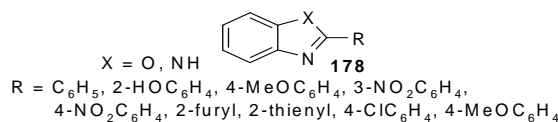
Gogoi and Konwar<sup>[76]</sup> reported the synthesis of imidazolines and benzimidazoles via an oxidation process with iodine and potassium iodide in water (Scheme 49).



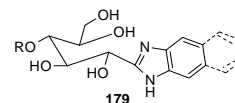
Scheme 49

Iodine-activated Schiff's base **174** formed *in situ* by the reaction of amine with aldehydes undergoes intramolecular cyclization to form the cyclized intermediate **175** which, reacts with KI<sub>3</sub><sup>[77]</sup> (generated *in situ* from I<sub>2</sub> and KI) to give an *N*-iodo intermediate **176**. Finally, the elimination of HI produces the required products **177**. Electron rich and electron deficient-aryl aldehydes, aliphatic and heterocyclic aldehydes, all gave good yields of imidazolines.

In a similar way Ponnala and Sahu<sup>[30]</sup> have synthesized 2-arylbenzoxazoles and 2-arylbenzimidazoles by the reaction of aldehydes with 2-aminophenol and *o*-phenylenediamines in presence of iodine under solvent-free condition (Fig. **178**).



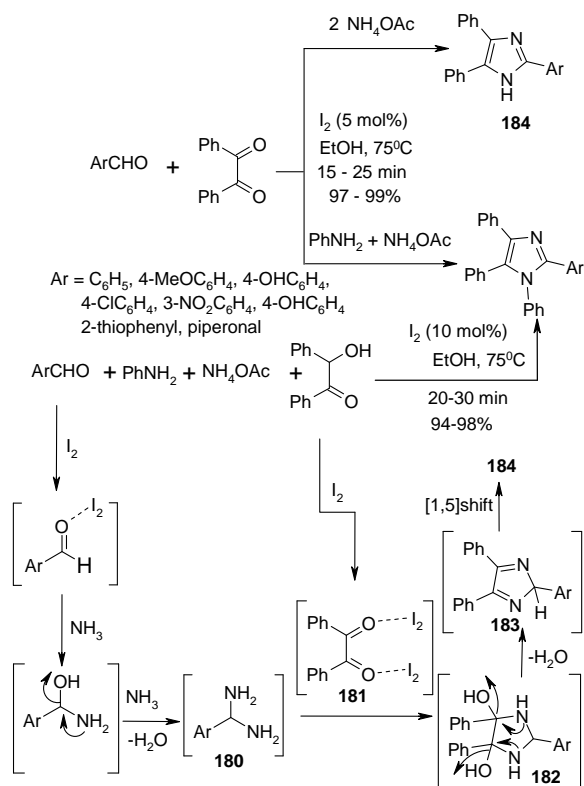
Lin *et al.*<sup>[78]</sup> achieved a convenient method for the synthesis of aldo-benzimidazoles from *o*-phenylenediamine and aldo-naphthimidazoles from *o*-naphthenediamine using catalytic amount of iodine as an oxidant and promoter from different aldoses i.e. mono-, di- and tri-saccharides (Fig. **179**)



Ishihara and Togo<sup>[65]</sup> have also prepared a variety of 2-imidazolines and 2-oxazolines from aldehydes and ethylenediamine or aminoethanol. In both the cases, the yields of enolizable aldehydes were found to be low.

Kidwai and Mothsra<sup>[79]</sup> reported a one-pot three component method for the synthesis of 2,4,5-trisubstituted imidazoles using 5 mol% iodine from benzil, aryl aldehyde and ammonium acetate and 1,2,4,5-tetrasubstituted imidazoles from benzil, aryl aldehyde,

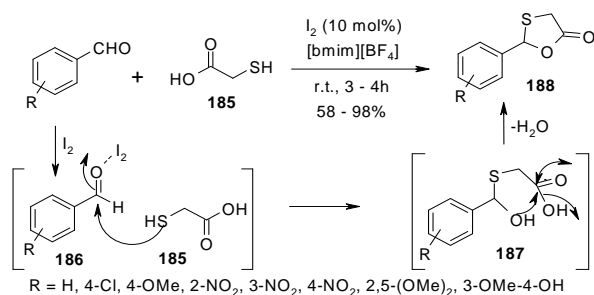
aniline and ammonium acetate. The same group<sup>[80]</sup> also reported a second generation synthesis of 1,2,3,5-tetraaryl imidazoles which includes *in situ* oxidation of benzoin to benzil (Scheme 50).



Scheme 50

Iodine catalyzes the reaction by bonding with the carbonyl oxygen which, facilitate the formation of a diamine intermediate **180** and then condenses with the iodine-activated carbonyl carbon of 1,2-diketone **181** to form the cyclized intermediate **182**. Dehydration of **182** followed by [1,5] sigmatropic shift of the intermediate **183** afforded the respective imidazoles **184**. Similarly benzil, ammonium acetate, aryl aldehyde and aniline yielded 1,2,4,5-tetra-substituted imidazoles.

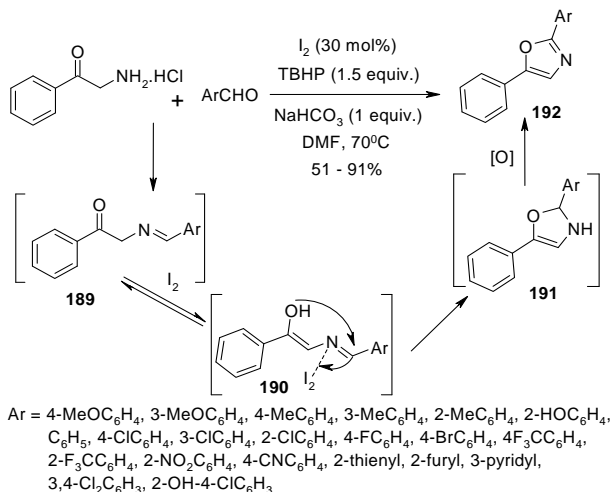
Mozumdar and others<sup>[81]</sup> developed a simple method for the synthesis of 1,3-oxathiolane-5-ones in ionic liquid from mercaptoacetic acid and aryl aldehydes (Scheme 51).



Scheme 51

Thiol group of mercaptoacetic acid **185** attacks the iodine-activated carbonyl carbon of **186** to give the intermediate **187** which undergoes intramolecular cyclization to form the products **188**.

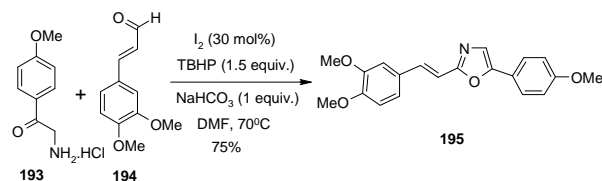
Wan *et al.*<sup>[82]</sup> demonstrated the synthesis of 2,5-disubstituted oxazoles *via* tandem oxidation cyclization protocol catalyzed by iodine (Scheme 52).



Scheme 52

The *in situ* generated Schiff's base **189** is in equilibrium with its enol form **190**. Intramolecular nucleophilic attack of oxygen atom on iodine activated Schiff's base **190** followed by oxidation of the resultant cyclized intermediate **191** provided the respective products **192**. A wide range of aromatic aldehydes with electron donating and electron withdrawing groups can be used as substrates. Heterocyclic aldehydes were also found to be good substrates.

Using the above methodology, annuloline **195** – the first isolated natural product containing an oxazole sub-structure was prepared by reacting **193** with **194** in 75% yield (Scheme 53).

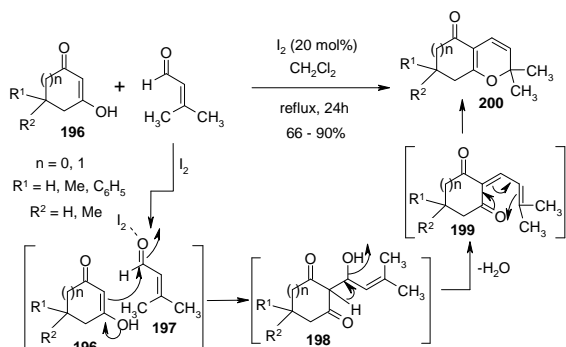


Scheme 53

## ii) Six-membered heterocycles

Jung *et al.*<sup>[83]</sup> developed a one-pot method for the synthesis of 2H-pyrans *via* iodine-mediated domino Knoevenagel - 6π-electrocyclization reactions from 1,3-dicarbonyl and 3-methyl-2-butenol or 1-cyclohexen-1-carboxyaldehyde (Scheme 54 and 55).

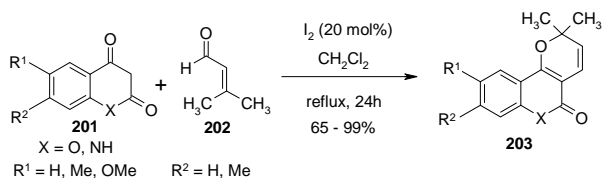




Scheme 54

The dimesone **196** attacks the iodine activated aldehydes **197** to generate intermediate **198** which readily eliminates water on heating to give **199**. Electrocyclization of **199** furnished the required cycloadduct **200** (Scheme 54).

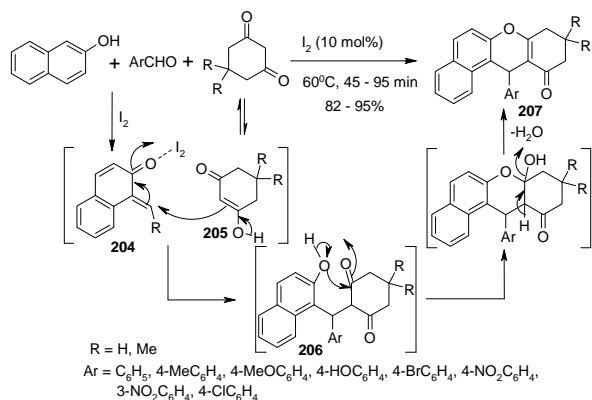
When the reactions were carried out by treating compounds **201** with **202**, the angular products **203** were obtained in good to excellent yield (Scheme 55).



Scheme 55

The methodology was applied to synthesis of pyranoquinoline alkaloids flindersine, *N*-methylflindersine, hapalamine and *N*-methylhapalamine.

Wang and co-workers<sup>[84]</sup> developed the solventless one-pot, three-component approach for the formation of 12-aryl-8,9,10,12-tetrahydro-benzo[*a*]xanthen-11-one derivatives (Scheme 56).

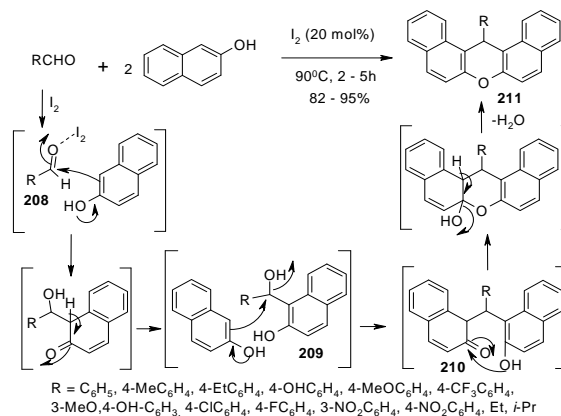


Scheme 56

2-Naphthol reacts with aldehydes in presence of iodine to give the intermediate **204** which reacts with the enolic form of dimesone **205** to furnish the key intermediate **206**. Intramolecular

cyclization of **206** and subsequent loss of water afforded the products **207**. Aromatic aldehydes with both electron donating and electron deficient groups gave products in good to excellent yields with electron rich aldehydes taking longer time for the completion of reaction.

Das and co-workers<sup>[85]</sup> described a convenient method for the formation of 14-aryl or alkyl-14*H*-dibenzo[*a,j*]xanthenes **173** by one-pot condensation of 2-naphthol with aromatic or aliphatic aldehydes in presence of 20 mol% iodine under solvent-free condition (Scheme 57).

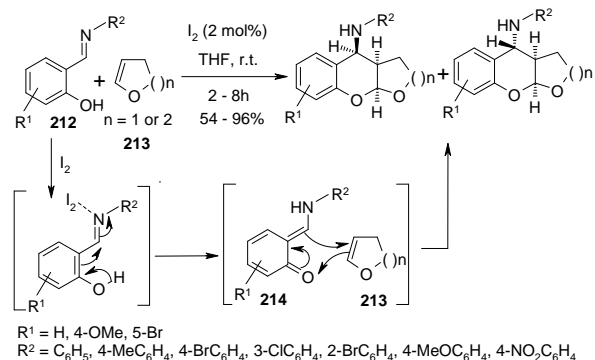


Scheme 57

Friedel-Crafts alkylation of  $\beta$ -naphthol with iodine activated aldehydes **208** followed by another Friedel-Crafts alkylation of other molecule of  $\beta$ -naphthol with intermediate **209** generates the intermediate **210**. Intramolecular cyclization and subsequent loss of water gave the aromatized products **211**. However, the reaction failed to yield product with phenol.

Pasha and Jayashankara<sup>[86]</sup> demonstrated that the above sequence (Scheme 57) can be carried out using still lesser amount of iodine (2.5 mol%) as a catalyst.

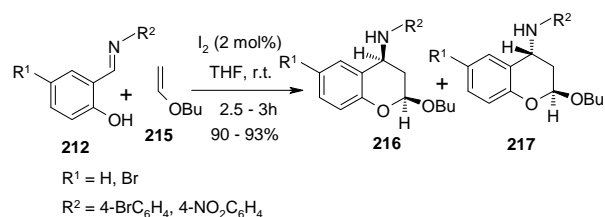
Wang and co-workers<sup>[87]</sup> prepared several cis-fused pyranobenzopyrans and furanobenzopyrans by reacting *o*-hydroxybenzaldimines **212** with 3,4-dihydro-2*H*-pyran (DHP) or 2,3-dihydrofuran (DHF) **213** at ambient temperature (Scheme 58).



Scheme 58

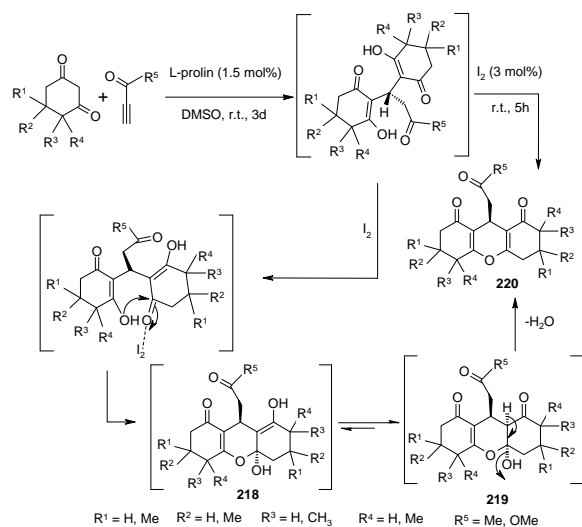
Enolic carbon of DHF or THF attacks the activated imine to generate oxadiene **214** which undergoes [4+2] cycloaddition with **213** to furnish the corresponding pyranobenzopyrans or furanobenzopyrans as a mixture of diastereomers in 54 – 96 % yields.

Similarly, the reaction of **212** with acyclic vinyl ether **215** gave the respective 2-butoxy-4-*N*-arylamino benzopyrans as a mixture of diastereoisomers **216** and **217** in excellent yields (Scheme 59).



Scheme 59

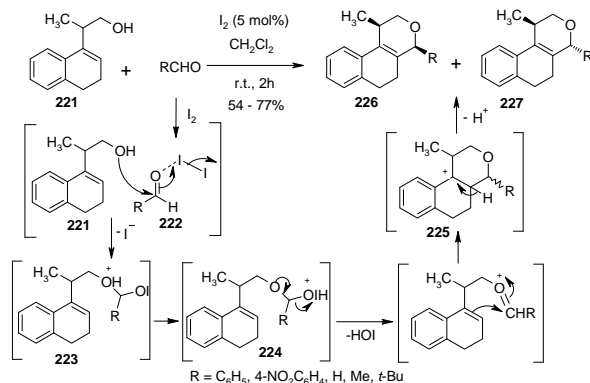
Luna *et al.*<sup>[88]</sup> described the synthesis of 9-substituted-1,8-dioxooctahydroxanthenes *via* sequential, tandem Michael-iodine-catalyzed cyclization approach (Scheme 60).



Scheme 60

Activation of carbonyl group by  $\text{I}_2$  followed by intramolecular nucleophilic attack of the other enol moiety resulted in the formation of hemiketal intermediate **218** which exist in its keto form **219**. Elimination of a water molecule afforded the corresponding octahydroxanthene **220**.

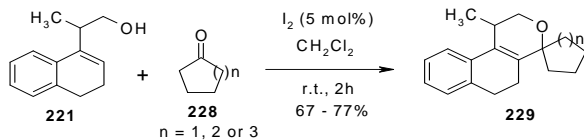
Silva Jr. and Quintiliano<sup>[89]</sup> described the iodine-induced Prins cyclization for the preparation of hexahydrobenzo[*f*]isochromenes (Scheme 61).



Scheme 61

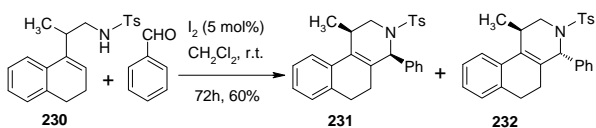
Homobenzylic alcohol **221** attacks the iodine-activated aldehydes **222** to form intermediate **223**. Elimination of HOI from **224** and subsequent intramolecular cyclization afforded the six-membered cyclic intermediate **225**. Loss of proton gave the respective products **226** or **227**. When R = Ph, mixture of diastereomers (*cis/trans*) were obtained in 77% yield while a single diastereomer was formed when R =  $\text{NO}_2\text{C}_6\text{H}_4$  or Me in 68% and 78% yield, respectively.

Under similar conditions, the Prins cyclization of **221** with the cyclic ketones **228** provided the spiro compounds **229** in good yields (Scheme 62).



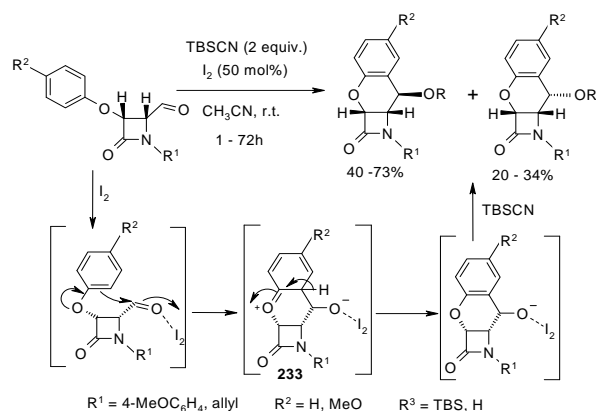
Scheme 62

The aza-Prins cyclization of **230** with benzaldehyde using 20 mol% of iodine to afford the mixture of diastereomers **231** and **232** in 60% yield which has a structure similar to Populene D<sup>[90]</sup> (Scheme 63).



Scheme 63

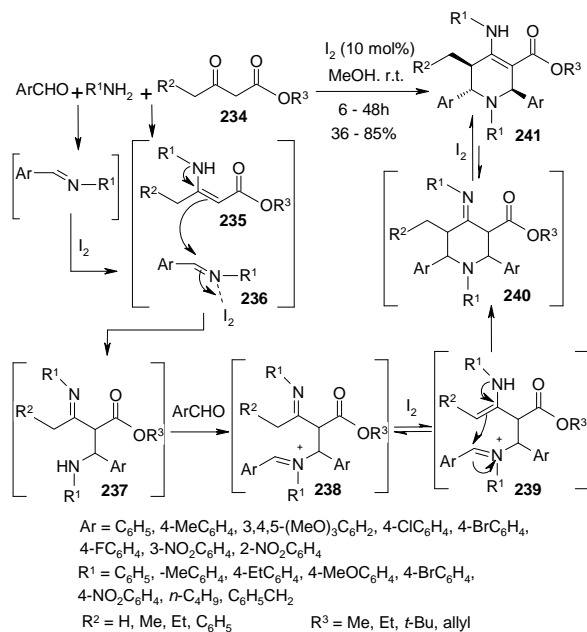
Alcaide and co-workers<sup>[91]</sup> demonstrated the iodine-mediated reaction of 3-aryloxy- $\beta$ -lactams to give the cyclized product  $\beta$ -lactam-fused chromenes as a mixture of *cis*- and *trans*-isomers (Scheme 64).



Scheme 64

Iodine promotes the reaction by coordinating with the oxygen of aldehydic carbonyl group which, undergoes intramolecular Friedel-Crafts cyclization to form six-membered Wheland-type intermediate **233**. Deprotonation followed by iodine-silicon exchange generates the desired products.

Khan and co-workers<sup>[92]</sup> described an iodine-catalyzed one-pot five component approach for the preparation of highly functionalized piperidine derivatives (Scheme 65).

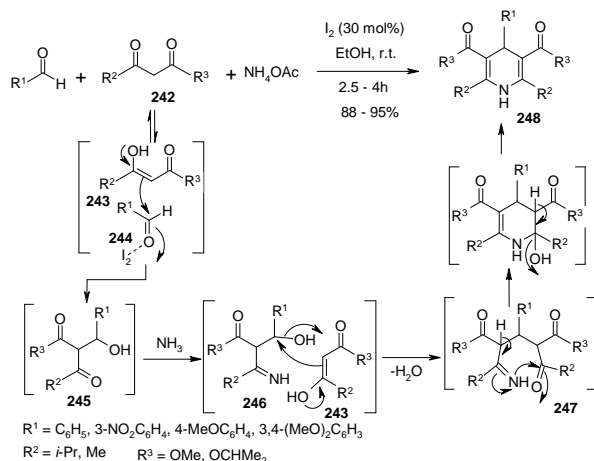


Scheme 65

Enamine **235** generated *in situ* by the reaction of  $\beta$ -keto esters **234** with amines underwent Mannich-type reaction with iodine-activated Schiff's base **236** to give the intermediate **237**. The intermediate **237** then reacts with aldehydes to form **238** which, in presence of iodine tautomerizes to give the **239**. Intramolecular Mannich-type reaction of **239** resulted in the formation of **240** which, tautomerizes to furnish the corresponding products **241**.

Akbari *et al.*<sup>[93]</sup> reported the synthesis of 1,4-dihydropyridines *via* multicomponent reactions of aldehydes, 1,3-dicarbonyl

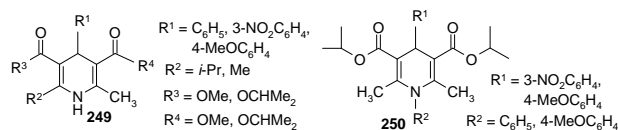
compounds and ammonium acetate using 30 mol% of iodine (Scheme 66).



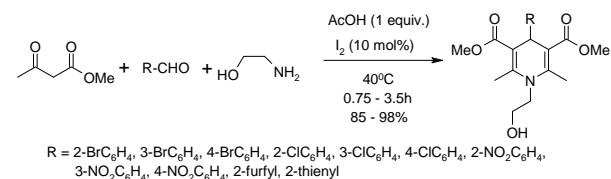
Scheme 66

1,3-Dicarbonyl compounds **242** are in equilibrium with its enol form **243** which, attacks the iodine-activated carbonyl carbon of **244** to generate intermediate **245**. Intermediate **246** formed by condensation of  $\text{NH}_3$  with **245** were then attacked by another molecule of **243** to give **247**. Intramolecular cyclization followed by elimination of water afforded the cyclized products **248**.

In a similar fashion, various unsymmetrically substituted 1,4-dihydropyridines (Fig. **249**) were prepared from aldehydes, 1,3-dicarbonyl compounds, methyl acetoacetate and ammonium acetate in 88 – 94% yield. Interestingly, no mixture of symmetrical and unsymmetrical products were observed. Also *N*-substituted 1,4-dihydropyridines (Fig. **250**) have been prepared from aldehydes, isopropyl acetoacetate and aryl amines.

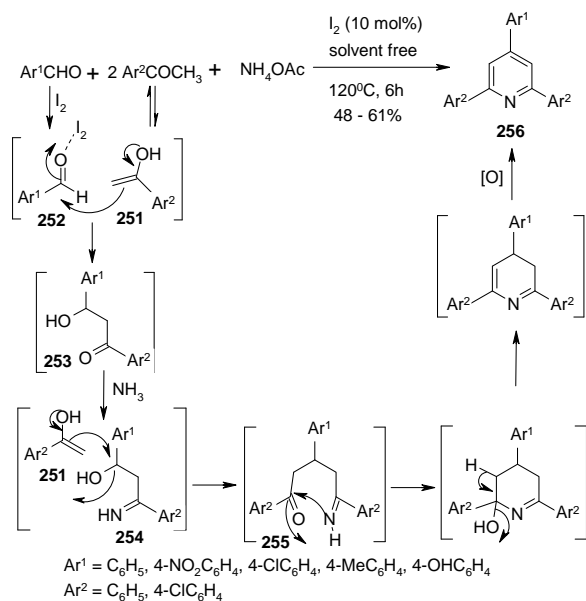


Zolfigol *et al.*<sup>[94]</sup> have reported the synthesis of Hantzsch *N*-hydroxyethyl-1,4-dihydropyridines under mild reaction conditions (Scheme 67).



Scheme 67

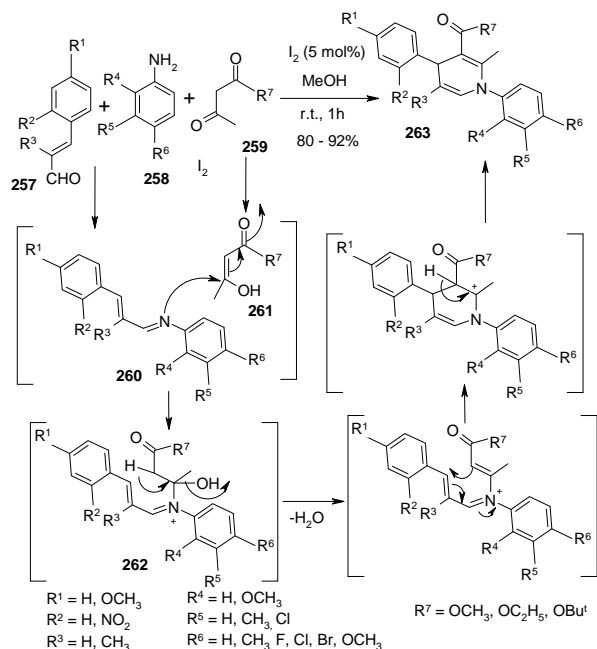
Ren and Cai<sup>[95]</sup> prepared 2,4,6-triarylpyridines **256** *via* Hantzsch reaction in one-pot under solvent-free conditions (Scheme 68).



Scheme 68

Enol **251** attacks the iodine-activated aldehydes **252** to give the  $\beta$ -hydroxy keto intermediate **253** which reacts with ammonia to form **254**. Nucleophilic attack of another molecule of enol **251** on **254** resulted in the formation of imino-keto intermediate **255**. Intramolecular cyclization of **255** followed by loss of  $\text{H}_2\text{O}$  and subsequent oxidation resulted in the formation of the products **256**.

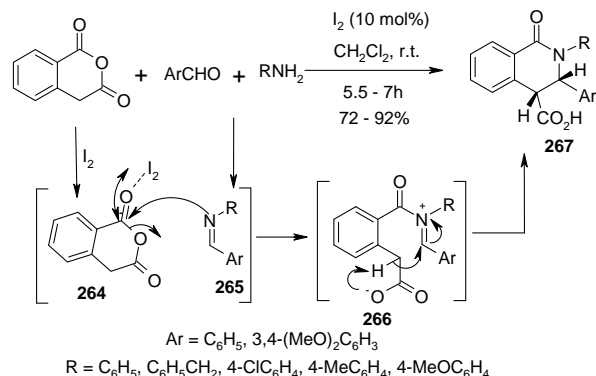
Kumar *et al.*<sup>[96]</sup> described the formation of *N*-aryl-1,4-dihydropyridines **263** via iodine-catalyzed three component reaction of substituted cinnamaldehydes **257**, anilines **258** and 2-keto esters **259** in methanol (Scheme 69). All the synthesized 1,4-dihydropyridines were screened for their antidiabetic and antioxidant activity *in vivo* and *in vitro*.



Scheme 69

Schiff's base **260** formed by treating **257** and **258** underwent 1,4-addition with the enol **261** to generate the intermediate **262**. Elimination of water followed by intramolecular cyclization and subsequent loss of proton afforded the corresponding compounds **263**.

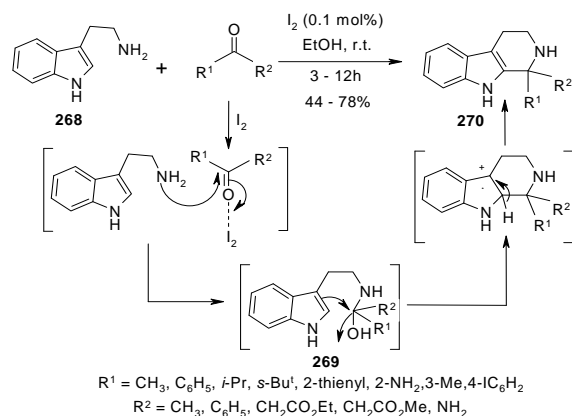
Yadav and co-workers<sup>[97]</sup> described the iodine-promoted one-pot approach for the synthesis of *cis*-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid by three component reaction of aldehydes, amines and homophthalic anhydride under mild reaction conditions (Scheme 70).



Scheme 70

*In situ* generated Schiff's base **265** attacks the iodine-activated carbonyl carbon of compound **264** to form intermediate **266** which gets converted to the desired products **267**.

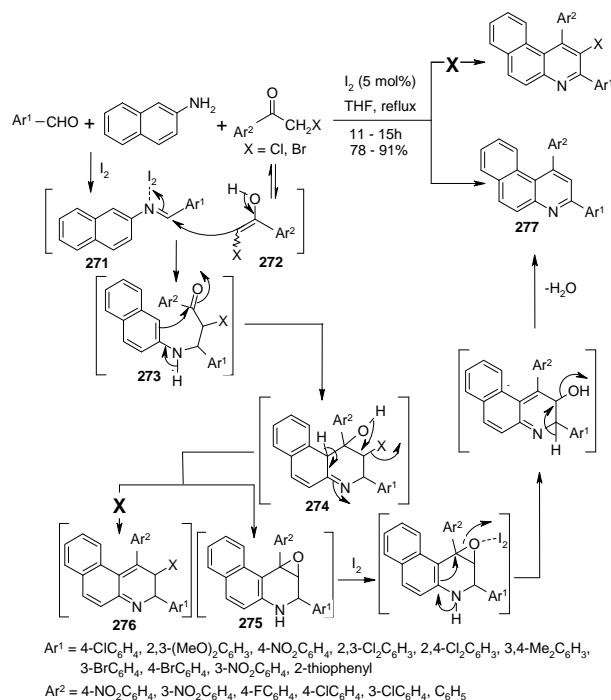
Lingam and co-workers<sup>[98]</sup> prepared various 1,1-disubstituted tetrahydro- $\beta$ -carbolines via an iodine-induced Pictet-Spengler reaction<sup>[99]</sup> (Scheme 71).



Scheme 71

Iodine catalyzes the reaction by coordinating with the carbonyl oxygen of ketones which was then attacked by the amino group of tryptamine **268** to generate the intermediate **269**. Intramolecular Friedel-Crafts cyclization of **269** followed by loss of proton yielded the desired products **270**.

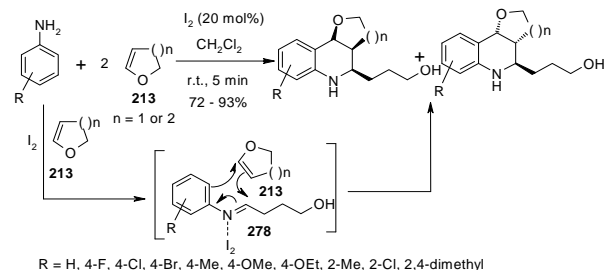
Wang and co-workers<sup>[100]</sup> accomplished an efficient method for the synthesis of 1,3-diarylbenzo[*f*]quinolines *via* three-component reaction of aromatic aldehydes, naphthalene-2-amine and 2-halogenated acetophenone using 5 mol% I<sub>2</sub> as a catalyst (Scheme 72).



Scheme 72

Enol **272** attacks the iodine-activated Schiff's base **271** to give compound **273** which undergoes Friedel-Crafts cyclization to afford the intermediate **274**. The intermediate **274** then eliminates HX instead of H<sub>2</sub>O to form the compound **275** rather than **276**. Opening of oxirane ring induced by iodine and subsequent loss of water afforded the 1,3-diaryl benzoquinoline **277**.

Lin *et al.*<sup>[101]</sup> demonstrated an efficient method for the preparation of 1,2,3,4-tetrahydroquinolines *via* an iodine-mediated domino reaction of anilines with cyclic enol ethers under mild reaction conditions (Scheme 73).

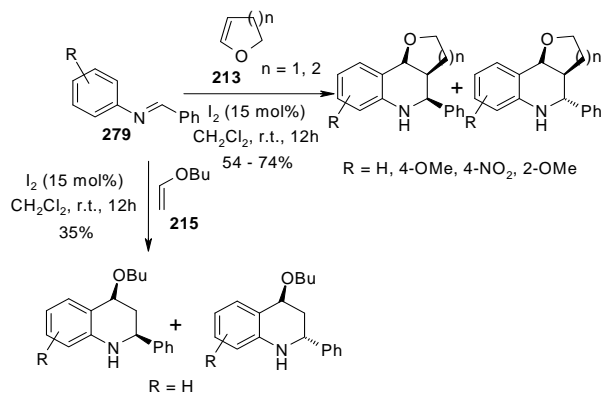


Scheme 73

2-Azadienes **278** formed *in situ* by reacting cyclic enol ethers **213** with anilines underwent aza-Diels-Alder reaction with another molecule of cyclic enol ethers **213** in presence of iodine which acts as a mild Lewis acid to form the corresponding

tetrahydroquinolines as a mixture of *endo/exo* isomers. The method is applied to anilines having alkoxy, alkyl and halo functionalities.

Yan and co-workers<sup>[102]</sup> reported the preparation of tetrahydroquinolines *via* iodine-mediated aza-Diels-Alder reaction (Scheme 74).

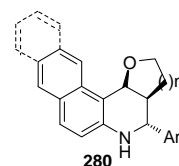


Scheme 74

The reaction of imine **279** with cyclic ethers **213** or acyclic ether **215** afforded the respective tetrahydroquinoline derivatives as a mixture of *cis*- and *trans*-isomers. The method works well with aryl amines having electron donating as well as electron withdrawing groups.

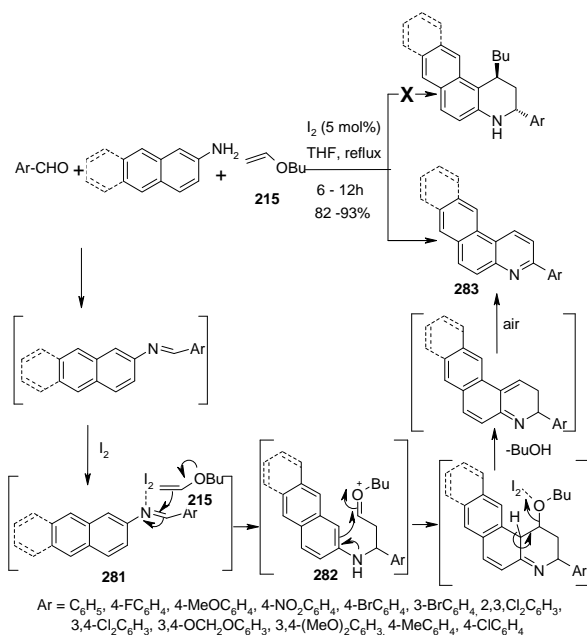
Jin *et al.*<sup>[103]</sup> extended this method recently for the synthesis of 2-perfluorophenyl tetrahydroquinolines in trifluoroethanol. The authors were also able to synthesize the pyrano-tetrahydroquinolines in a one pot method as reported earlier by Rai *et al.*<sup>[104]</sup>

Interestingly, Wang and co-workers<sup>[102]</sup> obtained exclusively *exo*-pyranoquinoline and *exo*-furoquinoline (Fig. **280**) derivatives *via* three component reactions of aromatic aldehydes, naphthalen-2-amine or anthracen-2-amine and 2,3-dihydrofuran or 3,4-dihydro-2*H*-pyran in THF in presence of 5 mol % I<sub>2</sub>.



Ar = C<sub>6</sub>H<sub>5</sub>, 4-FC<sub>6</sub>H<sub>4</sub>, 4-MeOC<sub>6</sub>H<sub>4</sub>, 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, 4-BrC<sub>6</sub>H<sub>4</sub>, 3-BrC<sub>6</sub>H<sub>4</sub>, 3-FC<sub>6</sub>H<sub>4</sub>, 3-ClC<sub>6</sub>H<sub>4</sub>, 3,4-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, 2-MeOC<sub>6</sub>H<sub>4</sub>, 3,4-(MeO)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>, 3-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, 2-thienyl

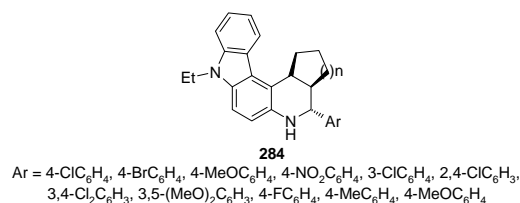
When the acyclic vinyl ether *viz.* *n*-butylvinyl ether **215** was used, the aromatized compounds **283** were obtained in high yields (Scheme 75) instead of corresponding tetrahydroquinoline as obtained in case of aniline in scheme 74.



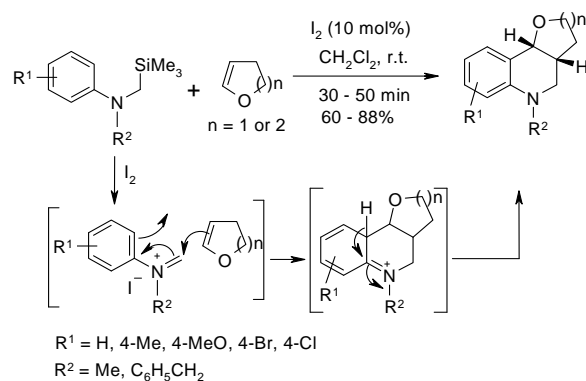
Scheme 75

The vinyl ether **215** attacks the iodine-activated Schiff's base **281** to generate intermediate **282**. Intramolecular Friedel-Crafts cyclization followed by expulsion of BuOH induced by iodine and subsequent air oxidation resulted in the formation of aromatized 3-arylbenzo[*f*]quinolines **283**.

Wang and co-workers<sup>[106]</sup> also extended this method for the synthesis of *exo*-hexahydro-2*H*-furo- and *exo*-hexahydro-pyrano[3,2-*c*]indolo[3,2-*f*]quinoline derivatives from aryl aldehydes, 3-amino-9-ethylcarbazole and 2,3-dihydrofuran or 3,4-dihydro-2*H*-pyran (Fig. **284**).



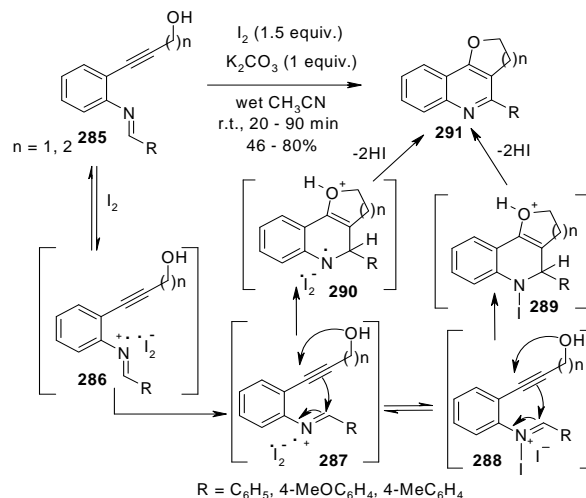
Subba Reddy and Grewal<sup>[107]</sup> accomplished a facile method for the synthesis of hexahydropyrano- and tetrahydrofuro-[3,2-*c*]quinoline derivatives *via* aza-Diels-Alder reaction using 10 mol% of iodine *N*-(methyl-*N*-trimethylsilyl)methylaniline and DHF or DHP (Scheme 76).



Scheme 76

*In situ* generated aza-diene from *N*-(methyl-*N*-trimethylsilyl)methylaniline in presence of a catalytic amount of molecular iodine undergoes [4+2] cycloaddition with electron rich ethers - DHF and DHP to yield the desired products with *cis*-selectivity. The catalytic activity of iodine was found to be superior to other Lewis acids like SnCl<sub>3</sub>, BiCl<sub>3</sub>, ZnCl<sub>2</sub> and FeCl<sub>3</sub>. A large number of angularly fused quinolines were prepared by this method.

Halim *et al.*<sup>[108]</sup> prepared a series of angular dihydrofuro- and tetrahydropyrano-quinolines *via* iodine-induced tandem cyclization of *N*-(*o*-alkynylphenyl)imines (Scheme 77).

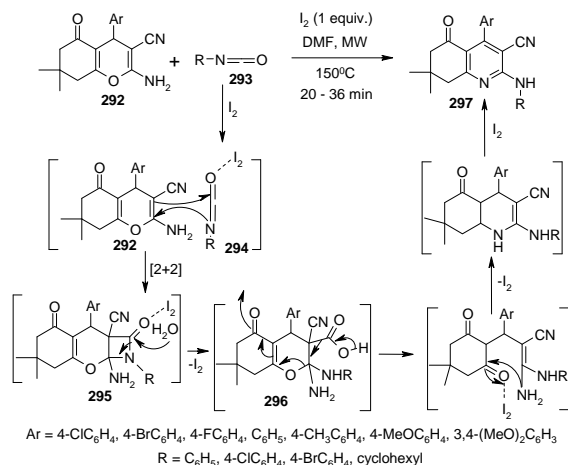


Scheme 77

Intermediate **286** formed by rapid and reversible single electron extraction from imine **285** by I<sub>2</sub> may convert to its rotomer **287** which, then undergoes concerted cocyclization reaction to give **290**. Alternately, **287** may first converted to *N*-iodoiminium ion **288** and then cocyclize to give **289**. Intermediate **289** / **290** then eliminate two equivalents of HI to afford the respective products **291**.

Jiang *et al.*<sup>[109]</sup> described the iodine-mediated domino reactions of 2-aminochromene-3-carbonitrile **292** with various isocyanates **293** under microwave irradiation to give the *N*-

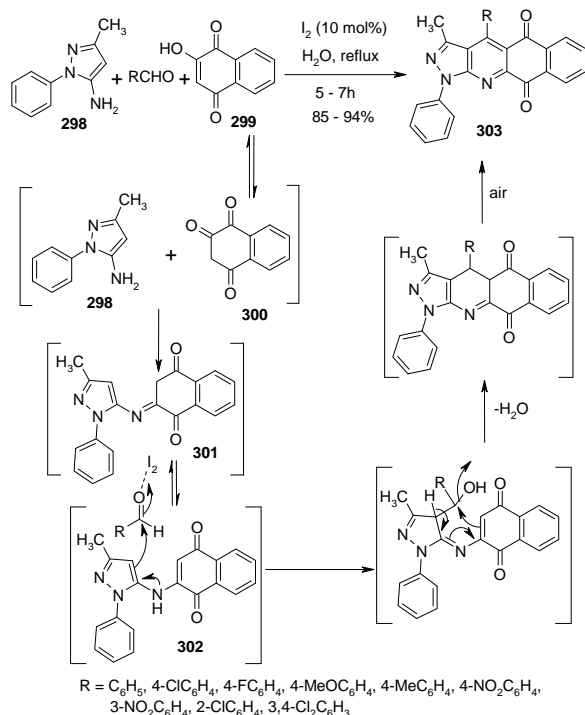
substituted 2-aminoquinoline-3-carbonitriles **297** in 62 – 85% yield (Scheme 78).



Scheme 78

[2+2] cycloaddition of **292** with iodine activated isocyanate **294** resulted in the formation of  $\beta$ -lactam **295**, which then hydrolyzed to give the ring opened intermediate **296**. Decarboxylation of **296** followed by intramolecular cyclization and subsequent dehydrogenation provided the aromatized compounds **297**. The reaction showed broad scope of substrates with a wide range of 2-aminochromene-3-carbonate and isocyanate.

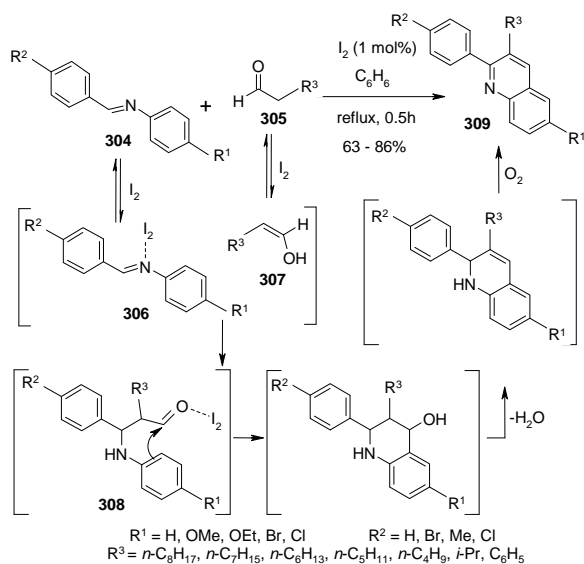
Wu and co-workers<sup>[110]</sup> developed an efficient one-pot method for the preparation of 4-aryl-3-methyl-1*H*-benzo[*h*]pyrazolo[3-*b*]quinoline-5,10-diones via three component condensation reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine, aldehydes and 2-hydroxynaphthalene-1,4-dione using 10 mol% of iodine in water (Scheme 79).



Scheme 79

Dione **299** is in equilibrium with its keto form **300** which, reacts with **298** to form intermediate **301** and then tautomerizes to give intermediate **302**. Nucleophilic attack of **302** on iodine-activated carbonyl carbon of aldehydes followed by intramolecular cyclization and subsequent oxidation yielded the desired products **303**.

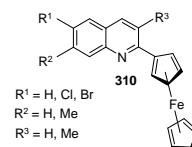
Lin *et al.*<sup>[111]</sup> prepared a series of substituted quinolines **309** via iodine-mediated one-pot domino reaction of imines **304** with enolizable aldehydes **305** (Scheme 80).



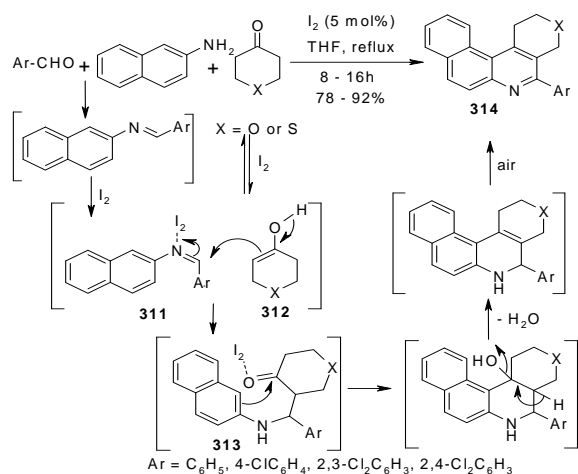
Scheme 80

The *in situ* generated enol **307** reacts with the iodine-activated imine **306** to form intermediate **308** which, underwent intramolecular Friedel-Crafts cyclization and subsequent dehydration and then oxidation to yield the aromatized products **309**.

Zora and Velioglu<sup>[112]</sup> described a one-pot synthesis of ferrocenyl-substituted quinolines (Fig. **310**) by reacting ferrocenylimines with enolizable aldehydes.



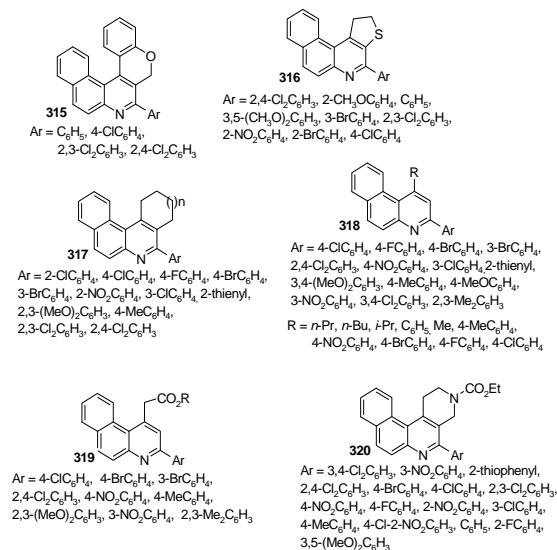
Wang and co-workers<sup>[113]</sup> described the preparation of pyranoquinoline, thiopyranoquinoline, thienoquinoline and naphtho[2,7]naphthyridine derivatives (Scheme 81).



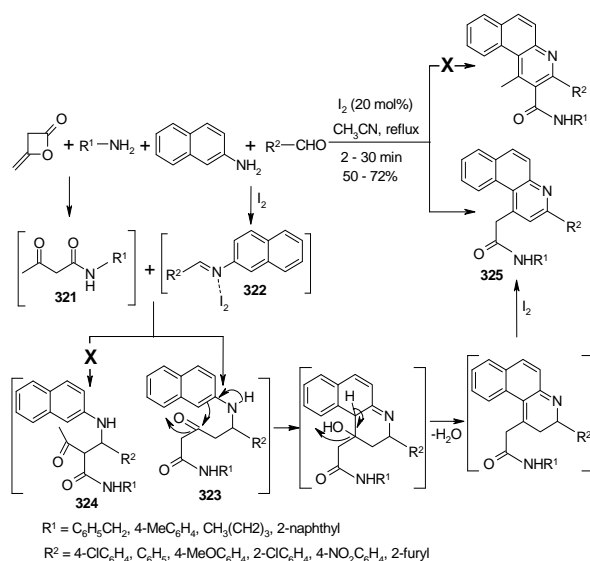
Scheme 81

In presence of iodine, the ketone is in equilibrium with the enol form **312** which, immediately attacks the *in situ* formed Schiff's base **311** to form intermediate **313**. Intramolecular Friedel-Crafts cyclization followed by dehydration and oxidation provided the desired aromatized compounds **314**.

Analogously, the naphtho[2,7]naphthyridines<sup>[113]</sup> (Fig. **315**), thienoquinolines<sup>[113]</sup> (Fig. **316**), bezof[*f*]quinolines<sup>[114]</sup> and benzo[*a*]phenanthridines<sup>[114]</sup> (Fig. **317**), 3-aryl-1-substituted benzo[*f*]quinolines<sup>[115, 116]</sup> (Fig. **318** & **319**) and 1,2-dihydro-5-arylnaphtho[2,1-*c*][2,7]naphthyridines<sup>[117]</sup> (Fig. **320**) were prepared.



Zeng and Cai<sup>[118]</sup> presented an interesting domino approach for the synthesis of benzo[*f*]quinolinyl and benzo[*h*]quinolinyl acetamides (Scheme 82).

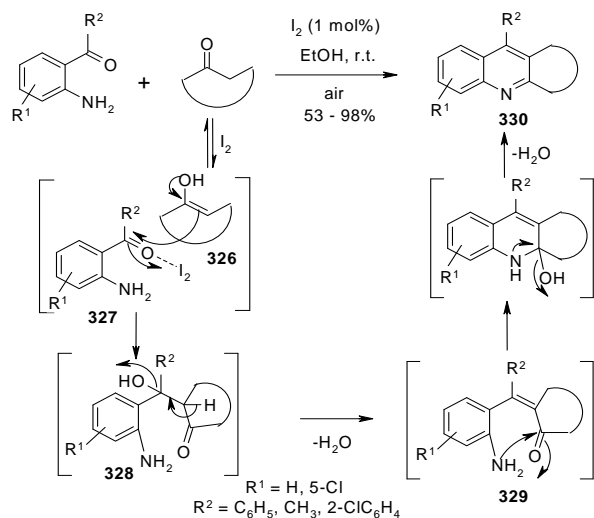


Scheme 82

*In situ* generated intermediate **321** reacts with iodine-activated Schiff's base **322** to form intermediate **323** rather than more favorable intermediate **324**. Intramolecular cyclization of **323** followed by elimination of H<sub>2</sub>O and subsequent aromatization provided the benzo[*f*]quinolinyl acetamides **325** in good yields.

Under similar reaction conditions, benzo[*h*]quinolinyl acetamides were prepared by using 1-naphthylamine instead of 2-naphthylamine as one of the starting material.

Wu and co-workers<sup>[119]</sup> reported the synthesis of quinolines via Friedlander annulation<sup>[120, 121]</sup> (Scheme 83).

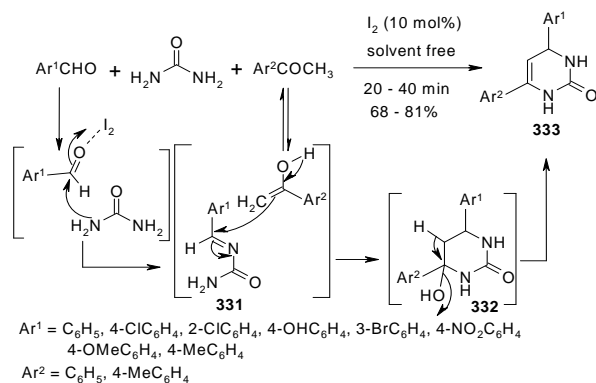


Scheme 83

*In situ* formed enols **326** undergoes Aldol condensation with iodine-activated 2-aminobenzophenones **327** to give intermediate **328** which readily loses water to form  $\alpha,\beta$ -unsaturated ketone intermediate **329**. Final ring closure by the attack of amino group on the carbonyl carbon generates the required compounds **330**.



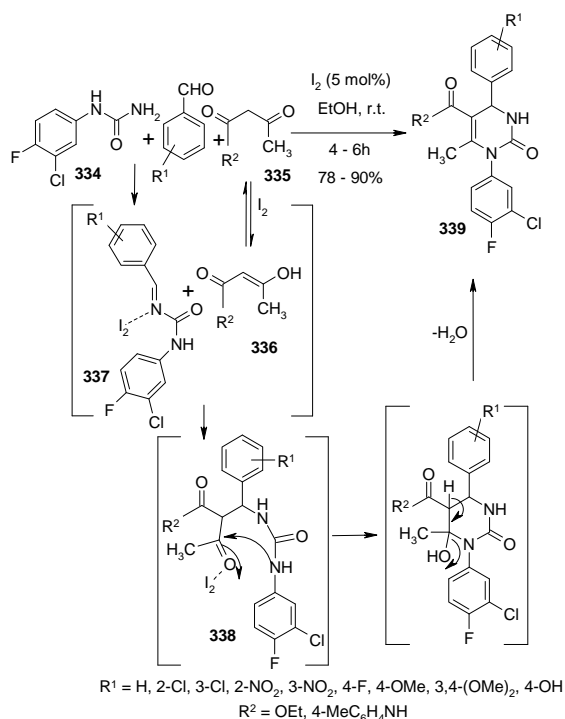
Ren and Cai<sup>[195]</sup> reported one-pot, three-components method for the synthesis of 3,4-dihydro-4,6-diphenylpyrimidin-2(1H)-one *via* Beiginelli-like reaction (Scheme 84).



Scheme 84

Urea attacks the iodine-activated aldehydes to give the intermediate **331**. Condensation of **331** with the enolizable ketones resulted in the formation of intermediate **332** which, underwent intramolecular cyclization and subsequently eliminates molecule of water to furnish the products **333**.

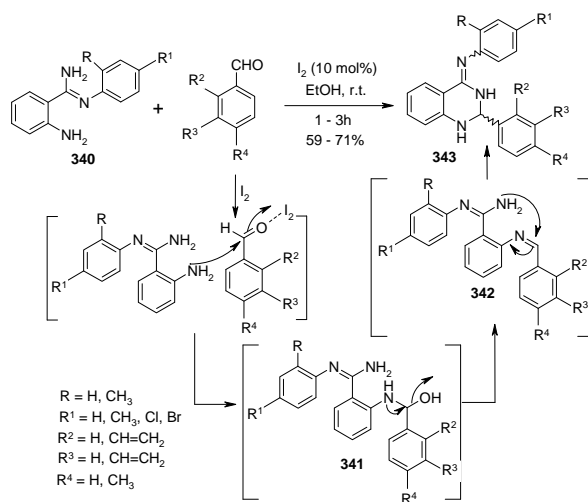
Zalavadiya *et al.*<sup>[122]</sup> demonstrated the three component domino approach for the synthesis of dihydropyrimidines (DHPMs) from aromatic aldehydes, 1,3-dicarbonyl compounds and *N*-(3-chloro-4-fluorophenyl)urea using 5 mol% of iodine (Scheme 85) and these were screened for their *in vitro* antimycobacterial activity.



Scheme 85

In presence of iodine, 1,3-diketone **335** is in equilibrium with its enol form **336** which, attacks the iodine activated *N*-acylium ion intermediate **337** formed *in situ* by the condensation of **334** with aldehydes to give intermediate **338**. Intramolecular cyclization of **338** followed by dehydration resulted in the formation of DHPMs **339**.

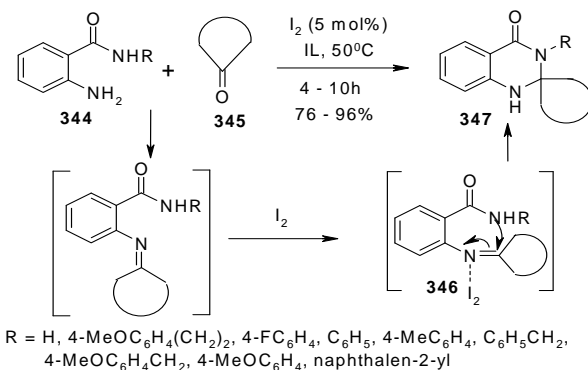
El-Shaieb and co-workers<sup>[123]</sup> described a facile one-pot method for the synthesis of 2,3-dihydroquinazolines (Scheme 86).



Scheme 86

Amino group of compound **340** attacks the iodine activated aldehydes to form the intermediate **341** which eliminates the molecule of H<sub>2</sub>O to furnish the imine **342**. The intramolecular cyclization of **342** gave the desired products **343**.

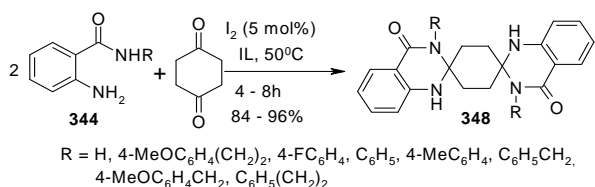
Wang and co-workers<sup>[124]</sup> reported the synthesis of quinazoline-4-(1H)-one derivatives in high yields catalyzed by iodine in ionic liquid (Scheme 87).



Scheme 87

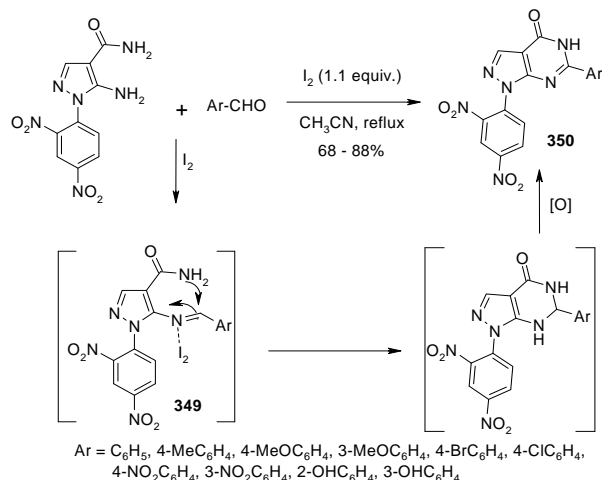
Intramolecular nucleophilic attack of the nitrogen of the amide group on iodine-activated Schiff's base **346** formed by reacting **344** with **35** gave the cyclized product **347**.

Analogously, dispirocyclic compounds containing quinazolin-4-(1H)-one derivatives **348** were prepared by reacting cyclohexane-1,4-dione with two molecules of **344** (Scheme 88).



Scheme 88

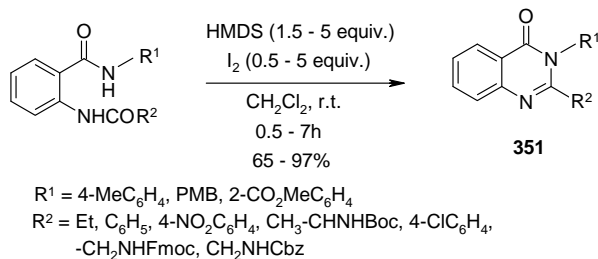
Bakavoli and co-workers<sup>[125]</sup> accomplished the one-pot iodocyclization reaction to prepare a series of pyrazolo[3,4-*d*]pyrimidine derivatives (Scheme 89) and evaluated their antibacterial activity.



Scheme 89

*In situ* generated Schiff's base **349** underwent intramolecular cyclization and subsequent oxidation to give the corresponding products **350** in good to excellent yields.

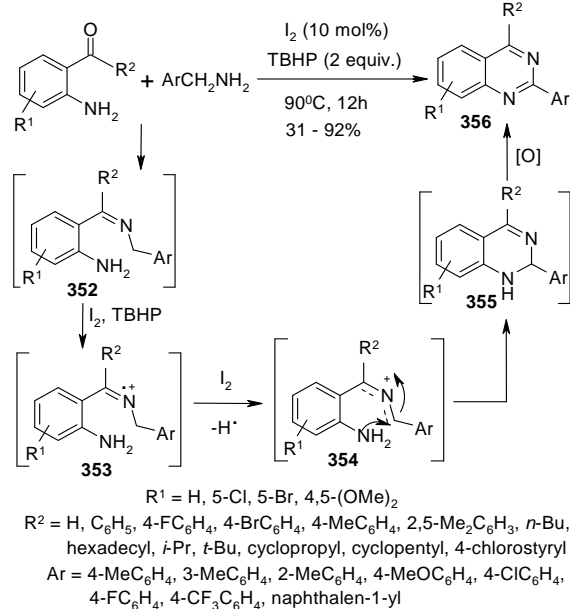
Argade and others<sup>[126]</sup> presented a general approach to prepare a various quinazolines *via* HMDS / I<sub>2</sub> induced intramolecular dehydrative cyclization (Scheme 90).



Scheme 90

The formation of the products were not observed in the absence of either HMDS or I<sub>2</sub> and the presence of a catalytic amount of iodine was necessary to induce the first silylation of the more reactive amide carbonyl group which, then undergoes intramolecular cyclization (ring closure with deoxysilylation) to yield the respective quinazolines **351**.

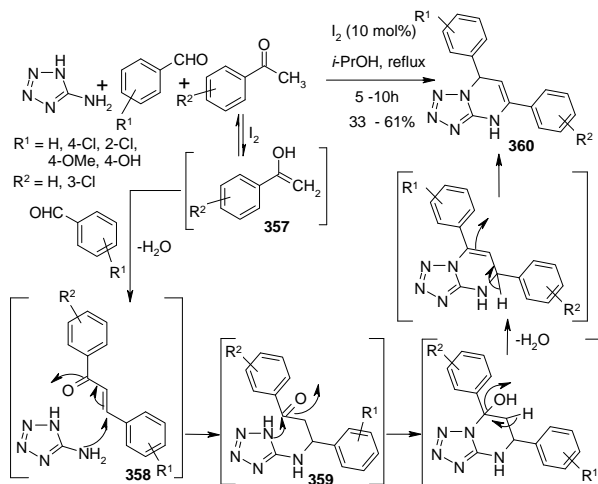
Zhang *et al.*<sup>[127]</sup> developed a novel tandem approach for the synthesis of various 2-phenylquinazolines (Scheme 91).



Scheme 91

Oxidation of *in situ* generated Schiff's base **352** resulted in the formation of intermediate **353** *via* sp<sup>3</sup> C-H functionalization.<sup>[128, 129]</sup> Intramolecular cyclization of **354** and subsequent oxidation of the resultant intermediate **355** provided the respective 2-phenylquinazoline derivatives **356**. A wide variety of 2-amino-4-substituted ketones and benzylamines were successfully employed.

Zeng and Cai<sup>[130]</sup> accomplished a convenient multicomponent approach for the construction of diverse tetrazolopyrimidines and tetrazoloquinazolines (Scheme 92).

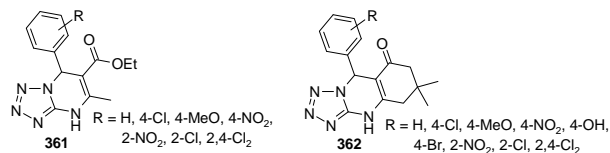


Scheme 92

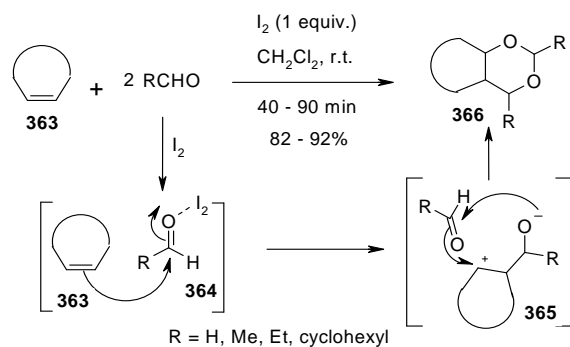
According to authors, *in situ* formed enols **357** reacts with aldehydes to form chalcones. 1,4-Addition of free amino group of

5-aminotetrazole with **358** followed by intramolecular cyclization gave intermediate **359**. Elimination of water and subsequent isomerization of double bond furnishes the corresponding tetrazolopyrimidines **360**.

Similarly, tetrazolopyrimidines (Fig. **361**) and tetrazoloquinazolines (Fig. **362**) were prepared.



Yadav and co-workers<sup>[131]</sup> developed a simple method for the synthesis of 1,3-dioxane derivatives *via* an iodine-mediated Prins cyclization in excellent yield (Scheme 93).

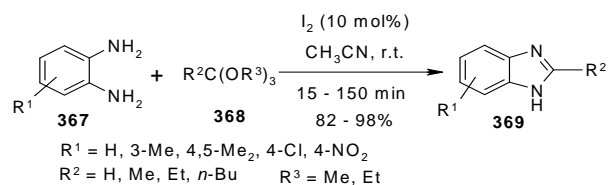


Scheme 93

Treatment of olefin **363** with activated aldehyde **364** gave the key intermediate **365**. *O*-alkylation of **365** with another molecule of aldehydes followed by attack of oxygen anion on carbocation provided the corresponding 1,3-dioxane derivatives **366**. The method is not only applicable to styrene derivatives but also to aliphatic olefins. However, aromatic aldehydes failed to give the products.

## 5) Activation of orthoformate

Zhang *et al.*<sup>[132]</sup> developed an efficient route for the synthesis of 2-substituted benzimidazoles (Scheme 94).

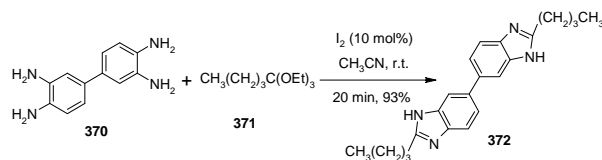


Scheme 94

Condensation of 1,2-phenylene diamines **367** with orthoesters **368** in presence of 10 mol% of iodine afforded the respective 2-substituted benzimidazoles **369** in high yield.

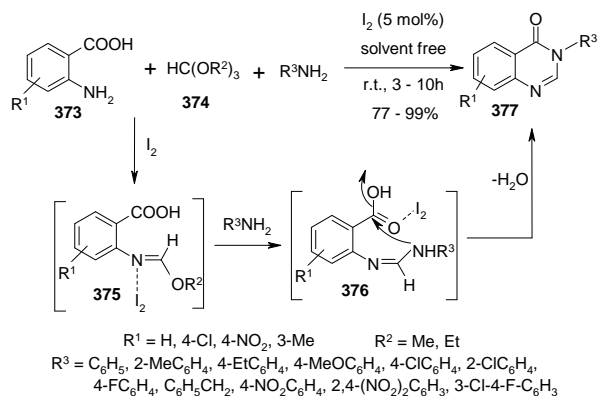
Under similar reaction conditions, bis-benzimidazole **372** was prepared by reacting 3,3'-diaminobenzidine **370** with two

equivalents of triethyl orthovalerate **371** in excellent yield (Scheme 95).



Scheme 95

Wang and co-workers<sup>[133]</sup> accomplished the one-pot synthesis of 3,4-dihydroquinazolin-4-ones *via* three component reaction of anthranilic acids, ortho esters and amines using 5 mol% of iodine under solvent-free conditions (Scheme 96).



Scheme 96

Iodine facilitates the formation of imidic ester intermediate **375** by reacting anthranilic acids **373** with ortho esters **374** which, react rapidly with amines to generate amidine intermediate **376**. Intramolecular attack of the amino group at iodine activated carbonyl carbon afforded the cyclized products **377**. A wide variety of aryl amines with electron donating and electron withdrawing groups were successfully used.

## Summary and Outlook

This review has presented the recent progress in the synthesis of heterocyclic compounds based on the iodine-mediated domino or multicomponent reactions of various alkynes, alkenes, imines, enamines and carbonyl or analogous compounds. Carbon-heteroatom bond-forming reactions constitutes the central theme of organic synthesis and iodine has established itself as a versatile catalyst or reagent for the construction of various heterocycles ranging from mono-cyclic compounds to complex polycyclic systems. As amply demonstrated above, the iodine-mediated heterocyclization reactions were mostly carried out in one-pot and without the need of any additional toxic reagents and thus helps in the context of green chemistry. It will not be surprising of more and more applications of this benign reagent in organic synthesis appear in near future.

## Acknowledgements

We thank DST and CSIR, New Delhi for the financial support and one of us (P. T. P) is thankful to CSIR for awarding Senior Research Fellowship.

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Received: ((will be filled in by the editorial staff))  
Revised: ((will be filled in by the editorial staff))  
Published online: ((will be filled in by the editorial staff))

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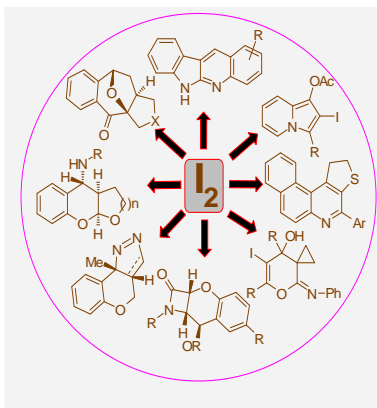
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## Eco-friendly Iodine

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*P. T. Parvatkar, P. S. Parameswaran\*, S. G. Tilve\**  
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### Recent Developments in the Synthesis of Five- and Six-Membered Heterocycles Using Molecular Iodine



Heterocyclic scaffolds represent the key structural subunits of many biologically active compounds. Over the last few years, iodine-mediated reactions have been extensively studied due to its low cost and eco-friendliness. This review covers the advances in the field of iodine-mediated synthesis of heterocyclic compounds since 2006, especially with emphasis on mechanism of ring formation.