Introduction and Review of the Previous Work: Synthesis of Heterocycles by Molecular Iodine-Mediated Cyclization Strategy

Review of Literature
Wide diversity of natural products possess heterocyclic scaffolds at appropriate position in their molecular framework. Literature contains a number of synthetic approaches to the heterocyclic ring structure, most of which has been compiled in comprehensive reviews devoted to this field. Five- and six-membered \( N \)- and \( O \)-heterocycles are probably one of the most common structural motifs spread across broad array of biologically active and medicinally significant molecules. They are important structural subunits in numerous natural products, such as polyacetylenic esters, phytane-type diterpenedilactones, cylindrine C, and lepadiformine. On the other hand Chalcogenophene heterocycles (S, Se, Te) and their derivatives have numerous uses in the fields of biochemistry, physical organic chemistry, materials chemistry, and organic synthesis. For example, selenophene oligomers are compounds of current interest because many of them show photoenhanced biological activities and crystalline polymerizations. The unusual growth of worldwide demand of heterocyclic compounds due to their pharmacological and biological activities have attracted the synthetic organic chemists to engage themselves towards the development of simple, novel and more effective synthetic strategies.

Since the last few years molecular iodine has established itself as a readily available and easy-to-handle electrophilic reagent as it is inexpensive and non-toxic reagent to generate compounds with synthetic and biological applications. It has allowed in the last few years a great advance in organic chemistry in the synthesis of heterocyclic compounds with many applications. The combined electrophilic and oxidative potential of iodine can be exploited to synthesize novel aromatic and heteroaromatic compounds that would be difficult to synthesize otherwise. Electrophilic cyclizations have been demonstrated as an efficient tool in the synthesis of highly functionalized indoles, furan, thiophene, selenophene, benzo[b]furan, benzo[b]thiophene, benzo[b]selenophene, and pyrroles, employing electrophiles like \( \text{I}_2 \), \( \text{ICl} \), or organochalcogen derivatives. Electrophilic cyclizations may be defined as those processes that involve addition of the electrophilic source to \( C(\text{sp}) \) or \( C(\text{sp}^2) \) bonds of alkenes, alkynes, allenes, conjugated dienes, and other carbon-carbon multiple bonds. The typical
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courses of this cyclization reaction involves (i) coordination of the electrophilic source to unsaturated carbon-carbon bond to generate intermediate B, which activates the carbon-carbon bond toward nucleophilic attack, (ii) nucleophilic anti attack of the heteroatom on the activated intermediate to produce the salt C; and (iii) facile removal of the group bonded to heteroatom Nu' present in the reaction mixture to generate the heterocyclic product.

These heterocyclic rings can be formed through endo or exo cyclization modes, depending on the chain length, the substitution pattern on the chain, and the electrophile employed. A series of guidelines that describe the propensity of various systems to participate in ring-forming reactions was reported by Baldwin. This set of guidelines, which describe the relative ease of ring formation, has become known as Baldwin's rules of ring closure and has been proved to be a useful tool in evaluating the feasibility of ring-forming reactions. Baldwin described his rules in terms of three features of the reaction: (1) the ring size being formed (indicated through a numerical prefix), (2) the hybridized state of the carbon atom undergoing the ring closing reaction (sp = diagonal ≈ dig, sp² = trigonal ≈ trig, and sp³ = tetrahedral ≈ tet), and (3) the nature of the breaking bond (exo, the breaking bond is external to the newly formed ring, and endo, the breaking bond is within newly formed ring). Examples of these formalizations are shown in Figure 2.
Due to the growing importance and utility of heterocycles in the field of organic synthesis and new remarkable findings and applications that have been published in the last few years, the purpose of this review is to show the importance of the electrophilic cyclization reactions in the field of heterocycle synthesis. This survey will focus mostly on reactions of alkenes, alkynes and allenes containing heteroatom with electrophilic sources followed by an intramolecular carbo- or heteroatom nucleophilic attack on the cationic intermediate via endo- or exo-dig cyclization.

We herein focus attention on the iodine-mediated cyclization reactions involving O-, N- chalcogens and carbon as an intramolecular nucleophile.

Most of the oxygen heterocycles like furan and pyran moieties appear as a versatile and useful class of heterocycles due to their prevalence in a great number of biologically active compounds as well as isolated natural products, including a wide variety of therapeutic applications, such as anti-HIV, anticancer, and anti-inflammatory. On the other hand nitrogen heterocycles are an important class of compounds due to their excellent biological effects, including antifungal, antiviral, and antiproliferative activities. In addition, these compounds are very useful synthetic intermediates and can function as suitable building blocks to synthesize some other biologically active compounds, such as natural products. Similarly, a wide variety of oligomers and related chalcogen compounds, including mixed thiophene-pyrrole oligomers, have been synthesized mainly with the expectation of obtaining excellent...
precursor compounds for molecular devices and electroconductive polymers.\textsuperscript{11} In addition, selenophenes are widely studied agents with a diverse array of biological effects, including antioxidant,\textsuperscript{12} antinociceptive,\textsuperscript{13} and anti-inflammatory properties,\textsuperscript{14} as well as efficacy as maturation-inducing agents.\textsuperscript{15} In this context, considerable effort has been made to the development of efficient strategies for the synthesis of furans pyrans, pyrroles and other heteroatom containing heterocycles.\textsuperscript{16}

Thibonnet and co-workers\textsuperscript{17} recently reported halocyclization reactions of (2Z,4\texttextit{E})-dienamides using I\textsubscript{2} as electrophile and CH\textsubscript{2}Cl\textsubscript{2} as solvent to afford 5-alkylidenepyrrl-2(5\textsubscript{H})-ones establishing that the reaction proceeded via a N-attack pathway. However, Wang et al\textsuperscript{18} observed almost opposite behavior when compound 1 underwent iodocyclization reaction with molecular iodine in the presence of THF-H\textsubscript{2}O as solvent to give O-attack products 2 as the only products in excellent isolated yields. No N-attack products were obtained (Scheme 1).

\begin{center}
\begin{tikzpicture}
\node[align=center] (n1) at (-2,0) {\textbf{R\textsuperscript{1} = C\textsubscript{6}H\textsubscript{13}, PhCH\textsubscript{2}, 3-Cl-C\textsubscript{6}H\textsubscript{4}, 4-Me-C\textsubscript{6}H\textsubscript{4}, 3,5-Cl-C\textsubscript{6}H\textsubscript{3}}};
\node[align=center] (n2) at (0,0) {\textbf{R\textsuperscript{2} = H, Et, Pr; R\textsuperscript{3} = Et, Pr, Hex}};
\node[align=center] (n3) at (2,0) {\textbf{R\textsuperscript{4} = Et, Pr, Hex; R\textsuperscript{5} = H, Et, Pr}};
\node[align=center] (n4) at (4,0) {\textbf{R\textsuperscript{1}}};
\node[align=center] (n5) at (4,1.5) {\textbf{R\textsuperscript{2}}};
\node[align=center] (n6) at (4,3) {\textbf{R\textsuperscript{3}}};
\node[align=center] (n7) at (4,-1.5) {\textbf{R\textsuperscript{4}}};
\node[align=center] (n8) at (4,-3) {\textbf{R\textsuperscript{5}}};
\node[align=center] (n9) at (4,0) {\textbf{O}};
\node[align=center] (n10) at (2,0) {\textbf{I}};
\node[align=center] (n11) at (-2,0) {\textbf{I\textsubscript{2}, THF-H\textsubscript{2}O, rt}};
\end{tikzpicture}
\end{center}

In the multi step synthesis of natural products molecular iodine is frequently used in one of the most important steps. Recently, a set of unusual secondary metabolites of plakortin 1 have been isolated from Plakortis simplex and have shown a selective cytotoxic activity against the RAW 264-6 cell line.\textsuperscript{19} These compounds plakortethers A-G, possessed the parent plakortin carbon skeleton but featured additional functionality. When the intermediate 3 was subjected to iodolactonization using the standard conditions (I\textsubscript{2}-NaHCO\textsubscript{3}-CH\textsubscript{3}CN) slow formation of iodolactones 4 was observed, along with several unidentified by
products. It was found that the use of I$_2$ in THF-H$_2$O, followed by treatment with silica gel, provided a cleaner reaction and better yields (Scheme 2)\textsuperscript{20}

Iodocyclization reaction was also successfully utilized for the highly stereoselective total synthesis of (+)-varitriol 8, an antitumor natural product.\textsuperscript{21}

Chromatographically pure terminal allylic alcohol 6 afforded 4,5-\textit{cis} tetrasubstituted THF 7 with very high diastereoselectivity (>99:1) under the iodocyclization reaction condition (Scheme 3).\textsuperscript{22}

Recently an useful synthetic approach to (3S,5R,8S,9S)-3-butyl-5-propyl-8-hydroxyindolizidine 11, a species reported only in Borneo and collected in the sultanate of Brunei Darussalam and isolated from \textit{Myrmecia melanogaster}\textsuperscript{23} was reported by Lina \textit{et al}.\textsuperscript{24} Iodine-mediated heterocyclization of allylic urethane 9 was utilized to produce iodoazolidone 10 as the sole regio- and diastereomer in 70% yield (Scheme 4).

The first asymmetric syntheses of (+)-deoxyicetexone 14,\textsuperscript{25} icetexone 15,\textsuperscript{26} and 5-\textit{epi}-icetexone 16\textsuperscript{27} were reported by Majetich \textit{et al}.\textsuperscript{28} They efficiently utilized the molecular iodine-mediated heterocyclization strategy in its one of the
important steps to iodofuran 13 which on subsequent steps, afforded the desired natural products (Scheme 5).

Antonioletti et al. first reported the synthesis of 5-iodoalkyl-4,5-dihydrofurans 18 by the reaction of 2-alkenyl substituted 1,3-dicarbonyl compounds 17 with I₂-NaHCO₃ mixture in CH₂Cl₂ at room temperature via 5-exo-trig electrophilic cyclization (Scheme 6). Treatment of the 4,5-dihydrofuran derivatives 18 with DBU in refluxing benzene afforded 5-alkylidene-4,5-dihydrofurans 19 which were in turn isomerized to the corresponding 2,3,5-trisubstituted furans 20 in ether using an acid catalyst.

Antonioletti's group also subjected a series of 2-allyl-1,3-dicarbonyl derivatives 17 bearing one substituent (R = Me, Ph, 2-furyl etc.) at the allylic position to iodocyclization reactions with I₂-Na₂CO₃ mixture in CH₂Cl₂ at room temperature to afford a diastereomeric mixtures of 5-iodomethyl-4,5-dihydrofuran derivatives 18 (Scheme 7). Alkyl substituents at the allyl chain (R = alkyl) were found to favor the trans 5-iodomethyl-4,5-dihydrofuran isomers, whereas aromatic substituents led to cis isomers.
Lee and Oh subjected the α-allyl substituted β-keto sulfones 21 to I₂-NaHCO₃ mixture in acetonitrile at room temperature to afford the corresponding 5-iodomethyl-4,5-dihydrofurans 22 (Scheme 8). Dehydroiodination with DBU (1.2 equiv) in benzene at room temperature afforded 5-methylene-4,5-dihydrofurans 23. Direct one-pot dehydroiodination-isomerization to furan derivatives 24 were achieved by the use of excess DBU (3.0-5.0 equiv) in benzene at room temperature or under reflux.

Highly chemo- and stereoselective cyclization of (S)-allylalanine derivatives 25 was reported by Pattarozzi et al. (diastereomeric ratios up to 96:4) where the reaction course can be completely controlled by switching from γ-lactones to cyclic carbamates simply with the proper choice of the amino acid protecting groups. Both processes are stereoconvergent and afford the (S,S)-products in high yields in short reaction times under mild reaction conditions (Scheme 9).

Lee et al. interested in electrophilic halocyclization to examine the ionic reactions in detail. Electrophilic iodo cyclization of unsaturated amides with an
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Internal vinylic halogen (Cl, Br, or I) substitution afforded exclusively the corresponding cyclic iminoketones 29 via iodolactamization. On the other hand, amides having a terminal vinylic halogen substituent underwent iodolactonization only. The above results provided a convenient and efficient method for the iodocyclization of unsaturated amides under acidic conditions rather than the usual basic conditions. More importantly, the results clearly revealed the unique effect of halogen atom substitution in directing the iodocyclization to proceed via exclusive N-attack or O-attack. Theoretical calculations revealed that the iodocyclization proceeds via the intramolecular iodonium ion transfer from the amide nitrogen to the C=C bond (Scheme 10).34

Another important reaction with a remarkable effect in controlling the regioselectivity of the cyclization was observed by Lu et al.35 The photolysis of N-(4-halo-4-pentenyl)sulfonamides 31 with diacetoxy iodobenzene (DIB) and iodine at room temperature afforded exclusively the corresponding piperidines 33 in 73-98% yield via a 6-endo radical cyclization. On the other hand, the reaction of sulfonamide 31 under typical iodocyclization condition (I2/NaHCO3, Et2O-H2O, rt) afforded only the 5-exo cyclization product 32. These results clearly indicate the different reactivities and selectivity patterns between the radical cyclization and the ionic cyclization. While the electrophilic halocyclization occurs exclusively in a 5-exo mode, the internal vinylic substitution in 31 strongly encourages the radical cyclization in a 6-endo mode (Scheme 11).
Iodocyclization of sulfinimine-derived enantiopure homoallylic sulfonamides 34 affords *trans*-2,5-disubstituted 3-iodopyrrolidines 35 and represents valuable methodology for the asymmetric synthesis of this important heterocyclic ring system (Scheme 12)\(^{36}\).

![Scheme 12](image)

Utilizing molecular iodine-mediated heterocyclization Caupe'ne *et al*\(^ {37} \) reported an efficient stereoselective synthesis of 3,4-dihydroxy-α-Tfm-proline 39, as well as enantiopure α-Tfm-prolines 38,\(^ {38} \) potential azasugar analogues in peptide synthesis. When the reaction was carried out with compound 36 in refluxing CH\(_2\)Cl\(_2\) or refluxing toluene, the expected five-membered ring product 37 were selectively obtained in 87% yield which after several steps yielded 3,4-dihydroxy-α-Tfm-proline and enantiopure α-Tfm-proline (Scheme 13).

![Scheme 13](image)

Recently, Campbell *et al*\(^ {39} \) developed an efficient enantioselective synthesis of benzyl (1S,2R,4R)-4-(tert-butoxycarbonylamino)-2-(hydroxymethyl)cyclohexylcarbamate 42, an essential intermediate for a series of potent CCR2 antagonists.\(^ {40} \) The key step in the sequence is an iodolactamization of 40 to yield the highly functionalized (1R,2S,4S,5S)-tert-butyl 2-(benzyloxy carbonylamino)- 4-iodo-7-oxo-6-azabicyclo[3.2.1]octane-6-carboxylate 41 (Scheme 14).

![Scheme 14](image)
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Iodine-mediated synthesis of 3H-indoles 46 were reported via intramolecular cyclization of enamines 43 through oxidative iodination followed by Friedel-Craft alkylation steps (Scheme 15).

Majumdar et al. recently reported an efficient approach for the synthesis of 3,4-dihydro-2H-1,4-benzoxazine derivatives 48 utilizing molecular iodine-mediated cyclization. The reaction condition is very simple, offers easy isolation, and affords good to excellent yields of the products (Scheme 16).

The expeditious synthesis of highly substituted furan, pyrrole and thiophenes, selenophenes and benzo[b]thiophenes have been individually achieved by a two-step approach involving the Sonogashira coupling of 2-iodoanisoles, 2-iodo-N-alkylanilines, 2-iodoselenoanisoles and 2-iodothioanisoles with terminal alkynes followed by electrophilic cyclization using iodine in DCM at rt (Scheme 17).
2,5-Disubstituted 3-iodofurans 52 are readily prepared under very mild reaction conditions by the palladium/copper-catalyzed cross-coupling of (Z)-β-bromoenoacetates and terminal alkynes, followed by iodocyclization reaction. It was observed that aryl- and alkyl-substituted alkynes undergo iodocyclization in good to excellent yields. 2,3,5-Trisubstituted furans can be readily synthesized from the resulting iodine-containing furans (Scheme 18).46

\[ \text{Scheme 17} \]

\[
\begin{array}{c}
\text{R} = \text{n-C}_8\text{H}_{17}, \text{n-C}_6\text{H}_{13}, \text{c-C}_9\text{H}_{19}, \text{C}_3\text{H}_6\text{CN}, \text{C}_6\text{H}_6\text{CO}_2\text{Me}, \text{C(\text{CH}_3)_2\text{OH},}
\end{array}
\]

\[
\begin{array}{c}
\text{X} = \text{OMe}, \text{NHMe}, \text{NHEt}, \text{SMe}, \text{SeMe}
\end{array}
\]

Scheme 17

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\[ \text{Scheme 18} \]

\[ R^1 = \text{OCONEt}_2 \]

\[ X = \text{OMe, NHMe, NHEt, SMe, SeMe} \]

\[ \text{Scheme 17} \]

\[ \text{I}_2, \text{NaHCO}_3, \text{DCM, rt} \]

\[ 51 \quad R_1 = R^1 = \text{alkyl, aryl} \]

\[ \text{Scheme 18} \]

\[ \text{N-Methyl-4-alkoxy-3-alkynylpyridin-2(1H)-ones 53 readily undergo iodine-promoted 5-endo-heteroannulation under mild conditions to 3-iodofuropyridine salts 55 in moderate to good yields. The beauty of the reaction is that by refluxing with NaI in the presence of acetonitrile as solvent dealkylation occurs in situ to afford the corresponding 3-iodofuro[2,3-b]pyridin-4(1H)-ones 54 (Scheme 19).}^{47} \]

\[ \text{Scheme 19} \]

\[ \text{R}^1 = \text{Me, CH}_2\text{Ph} \]

\[ \text{R}^2 = \text{n-Pr, TMS, Ph, 4-CO}_2\text{Me-Ph} \]

A variety of substituted isocoumarins 57 were prepared in excellent yields (90-93%) under very mild reaction condition by the reaction of \( o-(1- \)
alkynyl)benzoates 56 with molecular iodine in CH$_2$Cl$_2$ at room temperature via 6-endo-dig electrophilic cyclization (Scheme 20).\textsuperscript{48}

\[ \text{Scheme 20} \]

Chemoselective behavior of iodine in different solvents in the electrophilic iodo cyclization of o-alkynyl aldehydes is described by Verma \textit{et al}.\textsuperscript{49} o-Alkynyl aldehydes 61 on reaction with I$_2$ in CH$_2$Cl$_2$ in the presence of K$_2$CO$_3$ with appropriate nucleophiles provides pyrano[4,3-b]quinolines 62 via the formation of cyclic iodonium intermediate. However, using alcohol as a solvent as well as nucleophile, o-alkynyl esters 63 were obtained selectively in good to excellent yields. Subsequently, o-alkynyl esters were converted into pyranoquinolinones 64 and isocoumarins (X = CH) by electrophilic iodo cyclization (Scheme 21).

\[ \text{Scheme 21} \]

On the basis of above observations a mechanism was proposed which is summarized in Scheme 22. Intermediate 65 was generated from the reaction of electrophile I$_2$ and 2-alkynyl aldehydes 61. Electrophilic attack of the carbonyl
oxygen on the electron deficient alkyne and subsequent attack of the nucleophile ROH, afforded the products 62. When alcohols were used as the solvent as well as the nucleophile, hemiacetal 66 was obtained by the preferential attack of the alcohols on the carbonyl carbon rather than attacking iodine on the alkynyl carbon. Compound 62 can also be obtained via the formation of intermediate 67. Ester 63 may be formed from the hemiacetal 66, via formation of hypoiodide intermediate 68, with the elimination of HI.

A novel iodine-catalyzed tandem cyclization-cycloaddition reaction of ortho-alkynyl-substituted benzaldehydes 69 leading to polyoxacyclic ring systems 70 has been developed by Xie et al. It represents a useful approach towards the synthesis of the oxabicyclo-[3.2.1]octane ring skeleton found in a variety of natural products (Scheme 23).
The tandem iodocyclization reaction is proposed to follow the following steps: 
(i) coordination of the carbon–carbon triple bond and I₂ to generate an iodonium 
intermediates 71, and intramolecular nucleophilic attack of the oxygen of the 
carbonyl group on the activated iodonium intermediate to produce 
iodinesubstituted carbonyl ylides 72; (ii) successive tandem [3 + 2] 
cycloaddition with alkene leads to oxabicyclic skeleton intermediates 73; (iii) in 
the presence NaHCO₃, the intermediates 73 is immediately trapped by the 
nucleophilic OH⁻ present in the reaction, to form hydroxyl-substituted 
intermediates 74; and (iv) simple removal of HI to generate the desired 
oxabicyclic products 70 (Scheme 24).

Another efficient strategy for the synthesis of substituted quinolines via 
electrophilic cyclization is developed by Huo et. al²⁵ The intramolecular 
cyclization of 1-azido-2-(2-propynyl)benzene 75 proceeds smoothly in the 
presence of I₂ in CH₃NO₂ and NaHCO₃ at room temperature to afford the 
corresponding quinolines 78 in good to excellent yields via the formation of 
intermediates 76 and 77. Elimination of N₂ from the intermediate 77 is the 
driving force of the reaction (Scheme 25)
Yamamoto et al.\textsuperscript{52} reported the synthesis of isoquinolines 82 in moderate to good yields (58-72\%) from a series of 2-alkylbenzyl azides 79 by iodocyclization with molecular iodine via 6-endo-dig electrophilic cyclization (Scheme 26). The substituents $R^1$-$R^4$ could be chosen without restrictions. But the substituents $R$ and $R_5$ would have some restrictions on the reaction time and yield of the product. For example, when $R = p$-CF$_3$-Ph ($\sigma$-electron withdrawing group), the reaction time required for the full conversion of the starting material was 72 h. In case of $R = p$-CO$_2$Et-Ph ($\pi$-electron-withdrawing group), the yield of the quinoline derivative dropped to only 11\%. On the other hand, when $R_5 = \text{OMe}$ or $\text{CH}=$CH-CH=CH-\text{-}, iodocyclization did not occur.

Highly substituted 3-iodoquinolines 84 bearing different alkyl and aryl moieties can be synthesized in moderate to excellent yields by 6-endo-dig iodocyclization of 2-tosylaminophenylprop-1-yne-3-ols 83 with molecular iodine under mild conditions. The cyclization is highly regioselective and the resulting 3-iodoquinolines can be further functionalized by various coupling reactions (Scheme 27).\textsuperscript{53}
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\[ R^1 = \text{H, 5-Cl, 5-Br} \]
\[ R^2 = \text{Me, Et, Ph, 4-Me-C}_6\text{H}_4, 4-\text{Br-C}_6\text{H}_4 \]
\[ R^3 = \text{n-propyl, Ph, 4-Me-C}_6\text{H}_4, 4-\text{Br-C}_6\text{H}_4, 4-\text{OMe-C}_6\text{H}_4, 4-\text{Cl-C}_6\text{H}_4, 3-\text{Me-C}_6\text{H}_4, 3-\text{OMe-C}_6\text{H}_4, 2-\text{Me-C}_6\text{H}_4, 2-\text{Cl-C}_6\text{H}_4 \text{ etc} \]

Scheme 27

The electrophilic cyclization of alkynes containing neighboring arenes provides a very valuable approach to a wide range of heterocycles. Depending on the reaction conditions and the substrates, this process may result in the formation of spirocycles via ipso-cyclization. A simple and convenient example of an iodonium ion-induced intramolecular ipso-cyclization of an alkyne onto an arene under extremely mild reaction conditions to form a wide variety of 3-halospirotrienones has been developed by Zhang et al.\(^5\) The reaction of 85 with 2 equiv of I\(_2\) in CH\(_2\)C\(_2\) at -78 °C produced the spirotrienones 86 in excellent yield. Surprisingly when the cyclization of 85 was performed at room temperature, the spirotrienones 86 was obtained together with 6-endo product 87 suggesting that ipso-cyclization is a kinetically favored process (Scheme 28).\(^5\)

\[ R^1 = 2,4-\text{Me, 2-Cl-4-Me, 2-Br-4-Me, 2,4,6-Me, 4-Me, 4-C}_4\text{H}_9, 4-\text{OMe} \]
\[ X = \text{O, NHMe, Y = CH}_2\text{O} \]

Scheme 28

Angular-pyridoquinolone and pyridocoumarin derivatives 89 have been efficiently synthesized in good yields by molecular iodine-mediated cyclization of easily available starting materials, 6-(N-propargyl) amino quinolone and coumarin derivatives 88, in the presence of NaHCO\(_3\) (Scheme 29).\(^5\)
A series of 4-substituted-3-iodoquinolines 91 were prepared from $N$-(2-alkynyl)anilines 90 by iodocyclization with $I_2$-$NaHCO_3$ mixture in acetonitrile at room temperature in good to excellent yields via regioselective 6-endo-dig electrophilic cyclization followed by oxidation with excess iodine (Scheme 30)\textsuperscript{57}

![Scheme 29](image)

Scheme 29

$X = O, NMe, NEt$
$R = Me, Ph, 4-Ch$_2$C$_6$H$_4, 4$-Me-C$_6$H$_4, 4$-OMe-C$_6$H$_4$

A simple and efficient method for the synthesis of some hitherto unreported pyrimidine-annelated spiro-heterocycles via 5-endo mode of iodocyclization has been described by Majumdar et al\textsuperscript{58} The reaction is an example of iodocyclization of 1,5-enynes which proceeds in the absence of a base and affords the products in excellent yields (Scheme 31). The yields of the spiroproduct may also be rationalized by the nature of the group present on the alkyne terminal; more electron donating group which stabilized the iodonium intermediate 94 gives better yield compared to that of the electron withdrawing substituent (-COCH$_3$)

![Scheme 30](image)

Scheme 30

$R^1 = alkyl$, $aryl$
$R^2 = H, Me, R^3 = H, CO$_2$Et, NO$_2$

![Scheme 31](image)

Scheme 31

$R = Me, Et$
$R^1 = H, Me, Cl, COCH$_3$
The reaction may proceed through the formation of iodonium intermediate 94. Intramolecular nucleophilic attack of the double bond of the pyrimidine ring to the activated triple bond by a 5-endo dig mode of cyclization leads to the formation of the intermediate 95. Then H$_2$O may attack the carbocation from the opposite side of the substituent -R to avoid steric crowding to form the intermediate 96. The intermediate 96 finally may afford the spiro-product. Thus diastereoselectivity of the reaction is controlled by steric factor (Scheme 32).

Flynn group showed that $N$-(o-alkynylphenyl) imines 97 subjected to electrophilic cyclization delivered either ring-fused indoles 98 or quinolines 99, depending on the electrophilic source used (Scheme 33).\(^5\)

The syn-aminonitrile 100 when subjected to a carbamate annulation \textit{via} treatment with NaHCO$_3$ and I$_2$ surprisingly, in contrast to the usual high selectivity of this reaction,\(^6\) two diastereomeric carbamates 101a and 101b (dr = 4:1) were formed. Here, the major carbamate was the 4,5-cis-isomer 101a, as confirmed by X-ray analysis which after few steps afforded the D-galacto derived azasugar 102 (Scheme 34).\(^6\)
Ding et. al described an easy route to prepare isoquinoline derivatives via 6-endo-dig electrophilic cyclization reaction of hydrazides. The reaction was studied with N-(2-alkynylbenzylidene)hydrazides with I$_2$ as electrophilic source in dichloromethane at room temperature. In general, when the electrophilic source was changed from I$_2$ to Br$_2$ or ICl, no difference in the yields was found. The reaction was tolerant to several different functional groups in the alkyne, such as aryl, butyl, and cyclopropyl groups. The cyclization also worked well for a benzoyl or benzenesulfonyl group on the nitrogen atom (Scheme 35). The advantages of this method are the easy availability of the halo-containing H-pyrazolo[5,1-a]isoquinoline compounds which are the precursors for the palladium-catalyzed cross-coupling reaction.

2-Ethynylbenzaldehyde 61, an intriguing substrate, has been used in the one pot synthesis of diverse polycyclic compounds. Ouyang et. al reported an efficient protocol for the synthesis of iodoisoquinoline-fused benzimidazoles 108 by copper-promoted tandem iodocyclization of 61 with o-benzenediamines 106 via the intermediates 105 and 107 (Scheme 36).
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Another approach of electrophilic cyclizations of $\alpha,\beta$-alkynic hydrazones 110 by molecular iodine was developed for the synthesis of 4-iodopyrazoles 111 by the treatment of the substrates 110 with molecular iodine in the presence of sodium bicarbonate (Scheme 37).

A series of 2,3-disubstituted benzo[b]thiophenes 113a,b were synthesized in good to excellent yields from the benzyl o-ethynylphenylsulfides 112a and o-(1-alkynyl)thioanisole derivatives 112b respectively via molecular iodine-mediated 5-endo-dig electrophilic cyclization reactions (Scheme 38).

Solid-phase synthesis of 2,3-disubstituted benzo[b]thiophenes 115 were reported by Bui et al. from the resin-bound substrates 114 via molecular iodine-mediated cyclizations (Scheme 39).
When propynols 116a (R² = n-Pr, P = benzyl or alkyl) with a 2-thioxyphenyl substituent were subjected to iodocyclizations with I₂ in CH₂Cl₂ at 18 °C (method A) or with I₂ in EtOH at 18 °C (method B), selectively 2-(1-iodoalkenyl)-benzo[b]thiophenes 117 or exclusively 2-acyl-benzo[b]thiophenes 118 (R² = n-Pr), respectively were obtained in good to excellent yields via 5-exo-dig electrophilic cyclization (Scheme 40). But the propynols 116b (R² = aryl; P = benzyl or alkyl) gave 2-acyl-benzo[b]thiophenes 118 (R² = aryl) exclusively under iodocyclization with molecular iodine in CH₂Cl₂ at 18 °C (method A).

The formation of the above compounds was rationalized by the following mechanism (Scheme 41).
4-Iodophosphaisocoumarins 125 can be prepared in good yield and with high regioselectivity by the reaction of \( o-\text{(1-alkynyl)} \) phenylphosphonates 124 with \( I_2 \). The reaction represents the first example of a phosphonate iodocyclization onto a C-C triple bond (Scheme 42).\(^7^2\)

\[
\begin{align*}
\text{Scheme 42} \\
\end{align*}
\]

Iodocyclization of \( \text{gem-difluorohomoallenyl alcohol 126} \) to give 2,2-difluoro-3-iodo-2,5-dihydrofuran 127 at low temperature was reported by Arimitsu \( et \ al.\) (Scheme 43).\(^7^3\)

\[
\begin{align*}
\text{Scheme 43} \\
\end{align*}
\]

Lu \( et \ al.\)\(^7^4\) have developed an efficient way to synthesize 2-(1'(Z)-iodoalkenyl)tetrahydrofurans by the reaction of 4,5-allenols and \( I_2 \). It was observed that the reaction of the 4,5-allenols 128 with a substituent in the 3-position afforded the \( \text{trans-2,3-disubstituted tetrahydrofurans 130} \) with very high diastereoselectivity. However, when the axially optically active 4,5-allenol
was treated with I$_2$ in n-hexane, the efficiency of chirality transfer was low. This problem was overcome by conducting the reaction in CH$_2$Cl$_2$ at room temperature and using N-iodosuccinimide as the electrophilic reagent (Scheme 44).

Another approach of iodine-induced trifluoromethylated oxaphospholene formation was reported by Li et al. For this purpose trifluoromethallylenic phosphonates 131 was used as the starting material. When iodocyclization reaction was carried out with 131 and 3 equiv of iodine in CH$_3$CN or CH$_2$Cl$_2$ the substituted oxaphospholenes 132 were formed in good to excellent yields (Scheme 45).

A facile, efficient, and general synthetic method for the construction of 3,4-diiododihydrothiophenes has been developed via the electrophilic iodocyclization of various S-hydroxy-2-butynyl ethanethioates. Presumably, initial activation of the propargyl hydroxyl group of 133 with a Lewis acidic iodine leads to the propargyl carbocation intermediate 134 or allene cation 135 along with an unstable hypoiodous acid (HOI) and an iodine anion. Attack of the iodine anion onto 134 or the cation in 135 affords iodoallene 136 which reacts with hypoiodous acid to form an iodonium intermediate 137. Subsequent intramolecular nucleophilic addition of sulfur to the activated allene...
followed by deprotection of acetyl group produces 139 and acetic acid (Scheme 46).

![Diagram of iodocyclization reaction](image)

A convenient approach to synthesize novel 3-selena-1-dethiacephems 145 and selenazepines 143, was accomplished via the regioselective iodocyclization reaction of compounds 140 using iodine-mediated heterocyclization strategy. The reaction of compounds 140 with iodine gave iodonium 141 and released an iodide ion at the same time. With the assistance of the iodine anion, intramolecular nucleophilic attack of selenium in the seleno urea group on the center carbon of allene (when R1 = H) favored exo mode to afford the corresponding cyclization products 145, whereas attack of selenium in the seleno urea group on the terminal carbon of allene (when R1 = CH3, C2H5, or n-C3H7) in the unfavored endo mode may afford the corresponding cyclization products 143 accompanied by the simultaneous elimination of HI (Scheme 47).

![Diagram of iodocyclization reaction](image)

Recently, solvent-free organic reactions which offers environmentally friendly protocols and sometimes remarkable reaction acceleration and more convenient product purification, have drawn the public’s concerns. Dihydrofuran products
148 were effectively synthesized from substituted benzaldehydes 147 and dimeredone 146 utilizing combined iodocyclization reaction and the mechanical milling technique, a powerful tool to promote solvent-free reactions (Scheme 48).52

\[
\text{Scheme 48} \quad \begin{array}{ccc}
\text{O} & \overset{\text{R}}{\text{C}} & \text{O} \\
& & \\
\text{146} & + & \text{147} \\
\end{array} \quad \overset{\text{I}_2, \text{DMAP}, \text{rt}}{\xrightarrow{\text{ball milling (30Hz)}}} \quad \begin{array}{cc}
\text{O} & \overset{\text{R}}{\text{C}} & \text{O} \\
& & \\
\text{148} & \overset{\text{O}}{\text{C}} & \text{O} \\
\end{array}
\]

\[ \text{R} = 3-\text{NO}_2-C_6H_4, 4-\text{NO}_2-C_6H_4, 4-\text{CN}-C_6H_4, 3,4-\text{Cl}_2-C_6H_4, 4-\text{CHO}-C_6H_4, 4-\text{OCH}_3-C_6H_4, 3,4-(\text{CH}_3)_2-C_6H_4, 3,4-(\text{OCH}_3)_2-C_6H_4 \text{ etc}
\]

A possible reaction mechanism has been proposed based on the above observation. It was reported that the reaction of a 1,3-dicarbonyl compound with iodine gave the R-iodinated product.83 Similarly, the reaction of compound 151 with iodine gave iodide 153 as the key intermediate. An intramolecular nucleophilic O-attack via 154 with elimination of HI afforded the dihydrofurans 148 (Scheme 49).

\[
\text{Scheme 49} \quad \begin{array}{ccc}
\text{O} & \overset{\text{R}}{\text{C}} & \text{O} \\
& & \\
\text{146} & + & \text{147} \\
\end{array} \quad \overset{\text{base, R, I2}}{\xrightarrow{\text{}} \text{149}} \quad \begin{array}{cc}
\text{O} & \overset{\text{R}}{\text{C}} & \text{O} \\
& & \\
\text{148} & \overset{\text{O}}{\text{C}} & \text{O} \\
\end{array} \quad \overset{\text{O-attack, I2}}{\xrightarrow{\text{}} \text{154}} \quad \begin{array}{cc}
\text{O} & \overset{\text{R}}{\text{C}} & \text{O} \\
& & \\
\text{153} & \overset{\text{O}}{\text{C}} & \text{O} \\
\end{array}
\]

Raffa et al.84 reported a facile, efficient, and general synthetic method for 3,4-diiodofurans 156 via the electrophilic iodocyclization of various 4-hydroxy-2-but-2-yn-1-ones 155. The use of MeOH as a solvent is crucial for the chemoselective synthesis of the 3,4-diiodofurans (Scheme 50).

\[
\text{Scheme 50} \quad \begin{array}{ccc}
\text{HO} & \overset{\text{R}^1}{\text{C}} & \text{O} \\
& & \\
\text{155} & + & \text{156} \\
\end{array} \quad \overset{\text{I2, MeOH, rt}}{\xrightarrow{\text{}} \text{157}} \quad \begin{array}{cc}
\text{I} & \overset{\text{R}^1}{\text{C}} & \text{I} \\
& & \\
\text{157} & \overset{\text{I}}{\text{C}} & \text{I} \\
\end{array}
\]

\[ \text{R}^1 = \text{H, n-C}_3\text{H}_{11}, \text{Ph} \\
\text{R}^2 = \text{H, n-C}_3\text{H}_{11}, \text{Ph, 4-Cl-C}_6\text{H}_4, 4-\text{OMe-C}_6\text{H}_4, 1-\text{naphthyl}
\]

Iodocyclization reaction was efficiently employed as one of the key steps in the multistep synthesis of a new genus of calcareous sponges Leucascandra
Introduction and review of the previous work Synthesis of heterocycles by molecular iodine-mediated cyclization strategy
caveolata obtained from the northeastern coast of New Calendonia Coral Sea, which resulted in the discovery of a highly complex natural product designated as leucascandrolide A (1) (Scheme 51).\textsuperscript{86}

Iodine-catalyzed synthesis of quinolines 162 was reported via two-component reaction of imines 160 and aldehydes 161 (Scheme 52). Wu \textit{et al.}\textsuperscript{87} also described the synthesis of quinolines 162 via molecular iodine-catalyzed two-component reaction of substituted 2-aminoaryl ketones 163 and \( \alpha \)-methylene ketones 161 in the presence of air.

\[
\begin{array}{c}
R^1 = \text{H, Me, OMe, OEt, Br} \\
R^2 = \text{aryl} \\
R^3 = \text{H, R}^4 = \text{alkyl, benzyl} \\
R^1 = \text{H, Cl, R}^2 = \text{Me, aryl} \\
R^3 = \text{CH}_2R, R^4 = \text{CO}_2\text{Et, COMe}
\end{array}
\]

Scheme 52

Molecular iodine-catalyzed and air-mediated tandem synthesis of quinolines 162 have recently been reported by three-component reaction of readily available amines 164, aldehydes 147 and alkynes 165 in 61-82% yields (Scheme 53).\textsuperscript{88} On the other hand, Wang \textit{et al.}\textsuperscript{89} reported the synthesis of quinolines 162 via molecular iodine-catalyzed one-pot reaction of amines 164, aldehydes 147 and ketones 161 in good to excellent yields (82-96%).
The iodine-mediated, oxidative desulfurization promoted cyclization process was explored by Shibahara et al.\(^{90}\) For this purpose different N-2-pyridylmethyl-2-pyridinecarbothioamides 166 were synthesized and it reacted with iodine in the presence of pyridine in THF for 15 min to give the 2-azaindolizines 167 in excellent yields along with a rare compound, the sulfur-bridged 2-azaindolizine dimer 168\(^{80}\) in very minor amount (Scheme 54).

A plausible mechanism for the novel cyclization reaction leading to 2-azaindolizines is given in Scheme 55. In this pathway, deprotonation of the N-2-pyridylmethyl thioamide 166 by pyridine is followed by iodination at sulfur afforded the intermediate 169. Subsequent iodination, again at sulfur, takes place to form the electrophilic intermediate 170, which undergoes intramolecular substitution by the pyridine nitrogen at the imino carbon to form 171. Finally, aromatization of 171 by deprotonation gives 2-azaindolizines 167.\(^{91}\) It is interesting to note that in this mechanistic route, the sulfur atom of the starting thioamides is formally oxidized to form a sulfur (+II) species (presumably sulfur diiodide).\(^{91b}\) Electrophilic substitution reaction by sulfur diiodide on the initially formed 2-azaindolizine 167 yields intermediate 172, which serves as a precursor to the sulfur-bridged dimer 168.\(^{92}\)
Seven-membered oxacycles are frequently found in wide diversity of natural products at appropriate position in their molecular architecture. Moreover, these units serve as target molecules in numerous synthetic studies. However, there are only few examples of medium-ring oxygen heterocycles construction utilizing iodine-induced heterocyclization strategy. Zhu et al. reported the synthesis of different benzoxepine derivatives by electrophilic carbocyclization of aryl propargylic alcohols in moderate to good yields under mild conditions (Scheme 56).

In this review, we have presented numerous very useful processes for the synthesis of heterocycles that involve electrophilic cyclization reactions via addition of the electrophilic source to the C(sp) bond of alkynes. The resulting functionalized heterocycles often undergo a variety of useful transformations to give highly substituted heterocycles as well as biologically important products. These cyclization reactions proceed under relatively mild reaction conditions and tolerate a wide variety of functional groups, thus avoiding protection group chemistry. Most electrophilic cyclization-based methodologies proceed stereo- and regioselectively in excellent yields. In summary, molecular iodine has allowed in the last few years a great advance in organic chemistry in the synthesis of heterocyclic compounds with varied applications. Moreover, the combined electrophilic and oxidative potential of iodine can be exploited to synthesize novel aromatic and heteroaromatic compounds that would be difficult to synthesize otherwise.