Molecular Iodine-Mediated Cyclization of Tethered Heteroatom-Containing Alkenyl or Alkynyl Systems

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Abstract: Molecular iodine has established itself as a readily available and easy-to-handle electrophilic and oxidizing reagent used in various organic transformations. In this review attention is focused on the use of molecular iodine in promoting cyclization (iodocyclization and cyclodehydroiodination) of tethered heteroatom-containing alkenyl or alkynyl systems.

Keywords: iodine; iodocyclization; cyclodehydroiodination

1. Introduction

In recent years, molecular iodine has received considerable attention as an inexpensive, non-toxic, readily available reagent to effect iodocyclization and cyclodehydroiodination reactions of tethered heteroatom-containing alkenyl or alkynyl systems to afford heterocyclic compounds with many synthetic and biological applications. For example, iodine-promoted cyclization of tethered heteroatom (oxygen-, nitrogen- or sulfur-)containing alkynes has proven to be an effective method for the synthesis of furans [1–3], pyroles [4,5], thiophenes [6,7] indoles [8,9], benzo[b]furans [10,11], and benzo[b]thiophenes [12–14]. The pyrrole moiety is widely distributed in a large number of naturally occurring compounds which display a variety of physiological properties [15] including antibacterial [16], antiviral [17], and antioxidant activities and also inhibit cytokine-mediated diseases [18,19]. On the other hand, the furan moiety is also found in naturally occurring compounds or synthetic derivatives such as naphtha[2,3-b]furan-4,9-diones 1 and naphtha[1,2-b]furan-4,5-diones 2 which have...
been found to exhibit *in vitro* cytotoxicity against KB cells [20]. Benzo[b]thiophene analogues 3a–c prepared through a combination of palladium–mediated coupling and iodine–promoted iodo cyclization were found to exhibit tubulin binding activities [6].

**Figure 1.** Structures of naphtha[2,3-\(b\)]furan-4,9-diones 1 and naphtha[1,2-\(b\)]furan-4,5-diones 2.

\[
\begin{align*}
1 & \quad R_1=\text{COMe, CHOHMe; } R_2=\text{H or OH} \\
2 & \quad R=\text{H, Me}
\end{align*}
\]

**Figure 2.** Structures of benzo[b]thiophene analogues 3a–c.

3a (\(R=\text{H}\)); 3b (\(R=\text{OH}\)) 3c

Although the popularity of molecular iodine–mediated cyclization reactions has been increasing over the years, to our knowledge, there is no comprehensive review in the literature on the use of iodine as an electrophile and/or oxidizing agent in the synthesis of heteroatom-containing compounds with potential synthetic and/or biological applications. Its applications in the oxidation of alcohols and aldehydes to esters, nitriles and amides as well as the introduction of protecting groups and deprotection have however been reviewed in detail before [21]. In another development, Banerjee et al. reviewed the application of molecular iodine in esterification, cycloaddition, allylation of aldehydes, acetalization of carbonyl compounds, acylation of alcohols, synthesis of cyclic ethers and aromatization of \(\alpha,\beta\)-unsaturated ketones [22]. In this review, particular attention is focused on methods that employ molecular iodine as an electrophile and/or oxidizing agent to promote cyclization of tethered alkenyl and alkynyl derivatives bearing a nucleophilic heteroatom-containing group.

**2. Iodine as an Electrophile in Cyclization Reactions**

Although halogen molecules on their own are nonpolar, they are easily polarized by the pi electrons of the C=C double bond to become electrophilic. The electrophilic properties of iodine have been exploited over the years to effect cyclization of heteroatom-containing alkenyl and alkynyl derivatives.
2.1. Iodine-promoted cyclization reactions

Halocyclization is a reaction whereby the intramolecular nucleophilic group attacks the carbon–carbon double or triple bond activated by electrophilic halogenating reagent to give cyclic compounds. The outcome of this cyclization strategy which has been exploited in recent years for the synthesis of furans, pyrroles and quinolinones and their analogues is rationalized in terms of the rules previously developed by Baldwin for predicting the relative ease of organic ring-forming reactions [23]. The physical bases for these three rules are the stereochemistry requirements of the transition states for various tetrahedral, trigonal, and digonal systems in nucleophilic, homolytic, and cationic ring closure processes [23]. Iodocyclization of tethered heteroatom-containing alkenyl or alkynyl derivatives as well as iodocyclization of 2-allyl-1,3-dicarbonyl derivatives take advantage of the electrophilic nature of iodine. We herein focus attention on iodine–mediated cyclization reactions involving O-, N- or S-containing group as an intramolecular nucleophile.

2.1.1. Iodocyclization of heteroatom-containing alkenyl derivatives

Iodocyclization of 4-penten-1-ol 4 using iodine in chloroform with 1 equivalent of pyridine is reported to afford mixture of products characterized as the tetrahydrofuran 5 and tetrahydropyran 6 (Scheme 1) [24]. Iodine (3 equiv.) in acetonitrile (CH₃CN) was found to promote iodocyclization of furyl-substituted pent-4-ene-1,2-diols 7a (XR₁=OH; R=H, alkyl) and their sulfonamide derivatives 7b (XR₁=NHTs; R=H) to afford iodotetrahydrofurans 8a (X=O; R=H, alkyl) and 5-furylpyrrolidine-2-methanol 8b (X=NTs, R=H), respectively (Scheme 2) [4].

**Scheme 1.** Iodocyclization of 5-penten-1-ol in the presence of pyridine.

![Scheme 1](image)

**Scheme 2.** Iodocyclization of furyl-substituted pent-4-ene-1,2-diols.

![Scheme 2](image)

Tetrahydropyrans 10a and b were prepared in the ratio 2:1 from a diastereomeric mixture of 9a and b using iodine in dry acetonitrile (Scheme 3) [25].
Iodocyclization of γ-alkenyl-β-enaminoesters and α-alkenyl-β-enaminoesters with iodine-NaHCO₃ mixture in dichloromethane at room temperature, on the other hand, previously afforded novel 2-, and N-substituted 5-methylene-pyrrolidine benzamides and 2-, 3- and N-substituted 5-methylene-2-pyrroline benzamides, respectively [26]. Substituted proline derivatives 12 and 13 were prepared in excellent yields through 5-endo-iodocyclization of the corresponding α-alkenyl-α-amino esters 11 with iodine in the presence and absence of a base (Scheme 4) [27]. The analogous (E)-homoallylic sulfonamides have been found to undergo the normally disfavored 5-endo-trig iodocyclization in the presence of potassium carbonate or sodium carbonate in acetonitrile to afford trans-2,5-disubstituted-3-iodopyrrolidines in high yields [28]. The isomeric cis-2,5-disubstituted-3-iodopyrrolidine isomers were isolated as sole products in the absence of a base. It is believed that in the absence of a base, the initial kinetic trans products undergo rapid isomerization to afford the thermodynamic cis-2,5-disubstituted-3-iodopyrrolidine isomers by a ring opening-ring closure mechanism [28].

A general method for iodine–mediated cyclization reactions of unsaturated carbamates, ureas and amides which gives N-cyclized products as single regio-isomers was achieved in the presence of a strong base such as NaH or LiAl(Or-Bu)₄ [29]. The reaction of N-ethoxycarbonyl allylcarbamate 14 with iodine (3 equiv.) in tetrahydrofuran (THF) or toluene-THF mixture in the presence of NaH, nBuLi or LiAl(Or-Bu)₄ afforded the N-cyclized product 15 in 58 – 85% yield without traces of the O-cyclized derivative (Scheme 5).
Scheme 5. Base-promoted iodo cyclization of \( N \)-ethoxycarbonyl allylcarbamate.

\[
\begin{array}{c}
\text{O} \\
\text{NHO}_2\text{Et} \\
\text{O} \\
\text{CO}_2\text{Et} \\
\text{I} \\
\end{array}
\xrightarrow{\text{(i)}}
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{CO}_2\text{Et} \\
\text{I} \\
\end{array}
\]

| Base               | Solvent        | %Yield of 15 |
|--------------------|----------------|--------------|
| NaH                | THF            | 80           |
| \( n \)-BuLi       | THF            | 81           |
| LiAl(Ot-Bu)\(_4\)  | Toluene-THF    | 85           |

Reagents: (i) \( \text{I}_2 \), base, THF or THF-toluene.

Exclusive formation of the \( O \)-cyclized derivative 18 was observed when \( N \)-ethoxycarbonyl-\( N' \)-allylurea 16 was treated with iodine–NaHCO\(_3\) mixture in ether (Scheme 6) [29]. The \( N \)-cyclized derivatives of \( N \)-ethoxycarbonyl \( N' \)-allylurea 17 were isolated as sole products only when \( n \)-BuLi or LiAl(Ot-Bu)\(_4\) were used as bases. This reverse regioselectivity is presumably the result of the tendency for lithium ion to coordinate strongly with oxygen atoms in a six-membered cyclic transition state. Such interaction would render oxygen less nucleophilic and in turn favour nucleophilic attack by nitrogen to afford the \( N \)-cyclized products.

Scheme 6. Iodine-mediated cyclization of \( N \)-ethoxycarbonyl \( N' \)-allylurea.

\[
\begin{array}{c}
\text{O} \\
\text{NHCO}_2\text{Et} \\
\text{O} \\
\text{CO}_2\text{Et} \\
\text{I} \\
\end{array}
\xrightarrow{\text{(i)}}
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{EtO}_2\text{CN} \\
\text{I} \\
\end{array}
\]

| Base          | Solvent     | %Yield 17 | %Yield 18 |
|---------------|-------------|-----------|-----------|
| NaHCO\(_3\)   | Et\(_2\)O   | 0         | 77        |
| \( t \)-BuOK  | Toluene     | 0         | 18        |
| NaH           | THF         | 45        | 21        |
| \( n \)-BuLi  | THF         | 88        | Trace     |
| LiAl(Ot-Bu)\(_4\) | Toluene-THF | 88        | 0         |

Reagents: (i) \( \text{I}_2 \), base, solvent.

Ferraz and coworkers previously reported the synthesis of \( N \)-substituted pyrrole derivatives from alkenyl 1,3-dicarbonyl compounds via the formation of iodo-1,3-enamino esters followed by dehydroiodination [30,31]. Iodine-promoted cyclization of 19 to afford mixture of \( \text{cis} \) and \( \text{trans} \) isomers of 4,5-dihydro-5-iodomethyl-4-phenyl-2(3\(_H\))-furanones 20 and 21 has been described before (Scheme 7) [32]. A detailed review describing examples of iodine–mediated cyclization of nonconjugated unsaturated acids, diallyl-hydroxyacetic acids, benzyl carbamates, norbornene derivatives, aryl-allenoic acids, olefinic amides and \( \gamma \)-methallyl malonic acids to afford iodolactones and lactones was published recently [33].
Scheme 7. Iodine-promoted cyclization of nonconjugated unsaturated acids.

\[
\begin{align*}
\text{Reagents: (i) I}_2, \text{NaHCO}_3, \text{CHCl}_3.
\end{align*}
\]

Variously substituted \((E)-(\text{pyridin-2-yl})\text{allyl acetates} \text{22 were previously subjected to iodine in triethyl amine to afford the corresponding indolizines} \text{23 via 5-endo-trig iodocyclization (Scheme 8) [34]. In this one-pot reaction sequence, pyridinyl nitrogen was involved as an internal nucleophile of iodocyclization.}

Scheme 8. Iodocyclization of \((E)-(\text{pyridin-2-yl})\text{allyl acetates.}

\[
\begin{align*}
\text{Reagents: (i) I}_2, \text{NEt}_3, \text{r.t.}
\end{align*}
\]

Stereoselective formation of \(Z\)-4-(1-iodo-2-alkyl)ethylene-2-trichloromethyl-4,5-dihydro-1,3-oxazoles \text{25 was previously achieved via iodocyclization of the trichloroacetimidate derivatives of primary }\alpha\text{-allenic alcohol} \text{24 using iodine and potassium carbonate mixture in ether (Scheme 9) [35]. The Z-vinyl iodides} \text{25 (R=alkyl) were isolated in high yields (58 – 80%) as major isomers.}

Scheme 9. Iodocyclization of the trichloroacetimidate derivatives of primary \(\alpha\text{-allenic alcohol.}

\[
\begin{align*}
\text{Reagents: (i) I}_2, \text{K}_2\text{CO}_3, \text{ether, r.t.}
\end{align*}
\]

2.1.2. Iodocyclization of heteroatom-containing alkynyl and ynone derivatives

Iodine and sodium bicarbonate mixture in dichloromethane at 0 °C was found to promote a one-pot 5-endo-dig cyclization of 3-alkynyl-1,2-diols and subsequent dehydration to afford \(\beta\)-iodofurans in high yield [1,3]. In a follow up investigation, Knight and coworkers treated a series of 3-alkyne-1,2-
diols 27 with iodine (3.3 equiv.) and NaHCO₃ (3.3 equiv.) mixture in MeCN at room temperature and isolated the corresponding β-iodofurans 28 (Scheme 10) [36].

**Scheme 10. Iodocyclization of 3-alkyne-1,2-diols.**

| R₁ | R₂ | % Yield |
|----|----|---------|
| 28a | Ph | Ph | 60 |
| 28b | Ph | Bu | 71 |
| 28c | Bu | Ph | 77 |
| 28d | Me | Ph | 88 |
| 28e | Me | Bu | 65 |
| 28f | CO₂Me | Ph | 47 |

Reagents: (i) I₂, NaHCO₃, CH₃CN, r.t., 1h.

A representative series of homopropargylic sulfonamides have been found to undergo 5-endo-dig cyclization upon exposure to excess iodine in acetonitrile in the presence of potassium carbonate to afford 4-iodo-2,3-dihydropyrroles and β-iodopyrroles substituted with ester group at the 2-position [4]. A range of 3-hydroxy-2-sulfonylamino-4-alkynes 29 was also treated with iodine–K₂CO₃ mixture in dichloromethane to afford systems 30, which were in turn dehydrated using methanesulfonyl chloride in dichloromethane in the presence of triethylamine to yield iodopyrroles 31 (Scheme 11) [37].

**Scheme 11. Iodocyclization of homopropargylic sulfonamides.**

Reagents: (i) I₂, K₂CO₃, CH₂Cl₂, r.t, 16h; (ii) CH₃SO₂Cl, NEt₃, CH₂Cl₂, r.t., 16 h.

A pyridinyl nitrogen was involved as an internal nucleophile during iodine-mediated 5-endo-dig cyclization of series of propargylic acid esters 32 in dichloromethane at room temperature to afford the corresponding highly functionalized indolizines 33 (R₂=alkyl, aromatic or heteroaromatic) in high yields (Scheme 12) [38]. Under similar reaction conditions, the analogues 2-pyridin-2-yl-pent-4-ynoic acid ethyl esters 34 afforded the corresponding 3-acylated indolizines 35 (R=alkyl or aryl) via iodine-mediated hydrative cyclization (Scheme 13) [39]. Improved yields were observed when acetonitrile-water mixture (10:1, v/v) was used as solvent. The mechanism of this transformation is believed to
involve 5-\textit{exo-dig} iodoncyclization, deprotonation, incorporation of another iodo group, deprotonation and subsequent replacement of the diiodo group by water.

**Scheme 12.** Iodoncyclization of (\textit{E})-(pyridin-2-yl)alkynyl acetates.

\[
\begin{align*}
N & \text{O} \\
A & \text{c} \\
R_2 & \text{OAc} \\
\text{(i)} & \\
32 & \rightarrow & 33 (89–100\%) \\
\text{Reagents: } & I_2, \text{ CH}_2\text{Cl}_2, \text{ r.t.} \\
\end{align*}
\]

**Scheme 13.** Iodoncyclization of 2-pyridin-2-yl-pent-4-ynoic acid ethyl esters.

\[
\begin{align*}
& \text{CO}_2\text{Et} \\
\text{(i)} & \\
34 & \rightarrow & 35 \\
\text{Reagents: } & (i) I_2, \text{ CH}_2\text{Cl}_2 \text{ or } \text{CH}_3\text{CN-H}_2\text{O} (10:1), \text{ r.t.} \\
\end{align*}
\]

Iodine–promoted cyclization of 2-alkynylaniline 36 (X=CH; R_1, R_3=H; R_2=2-HO-C_6H_4, 2-MeO-C_6H_4) afforded iodoindoles 37 (X=CH; R_1, R_3=H; R_2=2-HO-C_6H_4, 2-MeO-C_6H_4) in low yields (10–20\%) presumably due to the presence of free hydroxyl or amino groups on the substrate (Scheme 14) [40]. Treatment of the analogous \textit{N}-tosyl-2-alkynylaniline derivatives 36 (X=CH; R_1=Ts; R_2=Ph, Bu, Si(CH_3)_3; R_3=5-NO_2) and 2-(\textit{N}-tosyl)-3-alkynylpyridines (X=N; R_1=Ts; R_2=Ph, Si(CH_3)_3; R_3=H) with iodine (3 equiv.) and K_2CO_3 (3 equiv) in acetonitrile at 0–20 °C afforded the corresponding iodoindoles (82–95\%) and azaindoles (75–89\%), respectively [9]. Iodoncyclization of 2-alkynyldimethylaniline derivatives (R_1=Me; R_2=alkyl) previously afforded 3-iodoindole (R_2=Me) [41]. Electrophilic cyclization of \textit{N},\textit{N}-dialkyl-o-(alkynyl)anilines with iodine in dichloromethane, on the other hand, led to the isolation of \textit{N}-alkyl-3-iodoindoles in excellent yields [8].

**Scheme 14.** Iodine-promoted cyclization of 2-alkynylanilines, \textit{N}-tosyl-2-alkynylanilines and 2-(\textit{N}-tosyl)-3-alkynylpyridine derivatives.

\[
\begin{align*}
& \text{X} \\
& \text{NHR}_1 \\
36 & \rightarrow & 37 \\
& \text{(X=CH; R}_1, R_3=H; R_2=2-HO-C_6H_4, 2-MeO-C_6H_4) \\
& \text{(X=CH; R}_1=Ts; R_3=5-NO_2; R_2=Ph, Bu, Si(CH_3)_3) \\
& \text{(X=N; R}_1=Ts; R_2=Ph, Si(Me)_3; R_3=H) \\
\text{Reagents: } & (i) I_2, K_2CO_3, \text{ CH}_3\text{CN, r.t.} \\
\end{align*}
\]
The 5-endo-dig-iodocyclization of 2-alkynylphenols with iodine in the presence of NaHCO₃ at room temperature produced 2-substituted 3-iodobenzo[b]furans, which are useful synthetic intermediates for the preparation of 2,3-disubstituted benzo[b]furans via Pd-catalyzed reactions [13,14,42]. Iodocyclization of 2-alkynylanisole derivatives 38a and the alkyl(2-alkynylphenyl) sulfides 38b afforded the corresponding iodo furan 39a [40] and 3-iodobenzo[b]thiophenes 39b [41], respectively (Scheme 15). o-(Phenylethynyl)thioanisole and o-(1-alkynyl)thioanisoles have also been treated with iodine (1.5 equiv.) in dichloromethane at room temperature to afford 3-iodo-2-(alkyl/aryl)benzo[b]thiophenes in more than 95% yield [13]. Flynn and coworkers previously employed this strategy in the synthesis of novel tubulin polymerization inhibitors 3 from the corresponding 3-iodobenzo[b]thiophene prepared, in turn, via 5-endo-dig iodocyclization of benzyl o-ethynylphenyl sulfides with iodine in dichloromethane [12].

Scheme 15. Iodine-promoted cyclization of 2-alkynylanisoles and alkyl(2-alkynylphenyl) sulfides.

\[
\begin{align*}
38a \quad & (X=O; R_1=\text{Me}; R_2=4-\text{BnO}-C_6H_4; R_3=\text{OTs}) \\
39a \quad & (X=O; R_2=4-\text{BnO}-C_6H_4; R_3=\text{OTs}) \\
38b \quad & (X=\text{S}; R_1=\text{alkyl}; R_2=\text{aryl}) \\
39b \quad & (X=\text{S}; R_2=\text{aryl})
\end{align*}
\]

Reagents: (i) I₂, CH₂Cl₂, r.t.

Iodine–cerium(IV) ammonium nitrate (CAN) mixture in acetonitrile at room temperature previously induced cyclization of (2-methoxyaryl)-substituted yrones 40 to produce 3-iodochromenones (3-iodo-4H-1-benzopyran-4-ones) 41 in excellent yields (Scheme 16) [43]. In another development, the phenyl derivative 40 (R=Ph) was transformed to 41a using iodine in dichloromethane at room temperature [40]. 1-(2-Alkylthiophenyl)alk-2-yn-1-ones 42 and their 1-(2-alkylthiophenyl)alk-2-yn-1-ol derivatives exhibited strong bias toward the 5-exo-dig pathway to give 43 instead of the 6-endo-dig pathway leading to 3-iodothioflavones 44 (Scheme 17) [14,41].

Scheme 16. Iodine-CAN mediated cyclizations of (2-methoxyaryl) alk-2-yn-1-ones.

\[
\begin{align*}
40 & \quad \text{I₂, CAN MeCN, r.t.} \\
41 & \\
R & \quad \%Yield \\
41a & \quad \text{Ph} \quad 97 \\
41b & \quad 4-\text{Me-C}_6\text{H}_4 \quad 95 \\
41c & \quad \text{Hexyl} \quad 91 \\
41d & \quad 4-\text{MeO-C}_6\text{H}_4 \quad 98
\end{align*}
\]
Scheme 17. Iodine-mediated cyclization of 2-(N,N-dimethylaminophenyl)alk-2-yn-1-ones.



Highly selective 5-exo- and 6-endo-dig iodocyclization protocols that give direct access to a variety of indoles and quinolines have been described in literature [41]. Iodocyclization of the dimethylamino systems 45 using iodine in dichloromethane or acetonitrile proved highly selective for the 6-endo-digonal pathway to afford 2-substituted 3-iodo-1-methylquinolin-4(1H)-ones in high yield 46 (Scheme 18) [41].

Scheme 18. Iodine-mediated cyclization of 2-(N,N-dimethylamino) substituted ynones.

When secondary and tertiary alcohols 47 were subjected to iodine in acetonitrile or dichloromethane, the endo product 48 was produced exclusively and then transformed to quinolium salt 50 by direct heating of the reaction mixture (Scheme 19) [41]. The 5-exo-dig products 49 which were isolated as 2-acylindoles 51 were found to form exclusively in protic solvents such as methanol or ethanol. This strategy was previously applied for the synthesis of novel tubulin polymerization inhibitors 3a-c from the corresponding 3-iodobenzo[b]thiophene prepared, in turn, via 5-endo-dig iodocyclization of benzyl o-ethynylphenyl sulfides with iodine in dichloromethane [6,14].

The reaction of β-(2-aminophenyl)-α,β-ynone 52 with I₂ and NaHCO₃ in CH₃CN afforded the 3,4-diiodo-2-(4-methoxyphenyl)quinoline 53 in 34% yield (Scheme 20) [44]. This observation was found to be remarkably different from the regio-controlled iodoaminocyclization reaction of related derivatives.

Molecular iodine in acetonitrile effected regioselective iodocyclization of o-(1-alkynyl)benzenesulfonamides 54 to yield a variety of 4-iodo-2H-benzo[e][1,2]thiazene-1,1-dioxides 55 (Scheme 21) [45]. The iodocyclization step was found to tolerate a variety of functional groups such as hydroxyl, chloro, cyano, and methoxy substituent to produce a six-membered ring exclusively.
Scheme 19. Iodine-mediated cyclization of 2-\((N,N\)-dimethylaminophenyl\)alk-2-yn-1-ols in polar aprotic (\(\text{CH}_3\text{CN}\)) and polar protic (methanol or ethanol) solvents.

\[
\begin{align*}
\text{Scheme 20. Iodine-\(\text{NaHCO}_3\) promoted cyclization of \(\beta\)-(2-aminophenyl)-\(\alpha\),\(\beta\)-ynone.} \\
52 & \xrightarrow{(i)} 53 \text{ (34\%)} \\
\text{Reagents: (i) } & \text{I}_2, \text{NaHCO}_3, \text{CH}_3\text{CN}
\end{align*}
\]

Scheme 21. Iodine-\(\text{K}_2\text{CO}_3\) mediated cyclization of \(o\)-(1-alkynyl)benzenesulfonamides.

\[
\begin{align*}
\text{Reagents: (i) } & \text{I}_2, \text{K}_2\text{CO}_3, \text{CH}_3\text{CN, r.t.}
\end{align*}
\]
A series of \( o \)-(1-alkynyl)benzamides 56 were previously treated with iodine in dichloromethane at room temperature to afford the corresponding isoindolin-1-ones 57 and isoquinolin-1(2\( H \))-ones 58 as a mixture (Scheme 22) [46]. Better regioselectivity was observed for iodine compared to other electrophiles (ICl, NBS, PhSeCl and \( p \)-NO\(_2\)C\(_6\)H\(_4\)SCI) and this improved in acetonitrile or methanol in the presence of a base.

**Scheme 22.** Iodine-NaHCO\(_3\) mediated cyclization of \( o \)-(1-alkynyl)benzamides.

![Scheme 22](image)

**Reagents:** (i) I\(_2\), NaHCO\(_3\), CH\(_3\)CN or MeOH, r.t.

2.1.3. Iodocyclization of \textit{ortho}-allylphenols

Iodoenolcyclization of \textit{ortho}-allylphenol 59 using either I\(_2\)-SnCl\(_4\) mixture in dichloromethane [47] or I\(_2\) and Ethopropazine, EPZ-10 (a clay-supported ZnCl\(_2\) catalyst) mixture or ZnCl\(_2\) in methanol is reported to afford the 2-iodomethyl-2,3-dihydrobenzofuran 60 (Scheme 23) [48]. Iodoenolcyclization of 2-(2-butenyl)phenol 61 with I\(_2\)-SnCl\(_4\) mixture in dichloromethane at room temperature, on the other hand, previously afforded 3-iodo-2-methylbenzopyran 62 in excellent yield (Scheme 24) [47]. Muzart \textit{et al.} [49], reported the reaction of a variety of 2-allylphenols with iodine in water which led to the corresponding 2-iodomethyl-2,3-dihydrobenzofurans in the absence of any additives or organic solvents.

**Scheme 23.** Iodine-SnCl\(_4\) mediated cyclization of 2-allylphenol.

![Scheme 23](image)

**Reagents:** (i) I\(_2\)/ SnCl\(_4\), CH\(_2\)Cl\(_2\) for 24 h.

**Scheme 24.** Iodine-SnCl\(_4\) mediated cyclization of 2-(2-butenyl)phenol.

![Scheme 24](image)

**Reagents:** (i) (i) I\(_2\)/ SnCl\(_4\), CH\(_2\)Cl\(_2\) for 24 h.

2.1.4. Iodocyclization of 2-allyl-1,3-dicarbonyl derivatives

A convenient approach to furan derivatives by iodine-induced cyclization of 2-alkenyl substituted 1,3-dicarbonyl compounds was first reported by Antonioletti and coworkers [50]. These authors
subjected a series of 2-alkenyl substituted 1,3-dicarbonyl compounds 63 to I$_2$–NaHCO$_3$ mixture in dichloromethane at room temperature to afford 5-iodoalkyl-4,5-dihydrofurans 64 (Scheme 25). Treatment of the latter with 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) in refluxing benzene afforded 5-alkylidene-4,5-di hydrofurans 65, which were in turn isomerized to the corresponding 2,3,5-trisubstituted furans 66 in ether using an acid catalyst. The generality of this reaction was demonstrated in a follow up study involving treatment of 2-alkenyl-1,3-dicarbonyl derivatives under similar reaction conditions to yield series of 2,3,4,5-tetrasubstituted furans [51].

**Scheme 25.** I$_2$–NaHCO$_3$ mediated iodoenolcyclization of 2-alkenyl-1,3-dicarbonyl compounds.

Antonioletti’s group also showed that I$_2$–Na$_2$CO$_3$ mixture promotes iodoenolcyclization of 2-allyl-1,3-dicarbonyl derivatives 67 bearing mono and disubstituted double bonds in dichloromethane at room temperature to afford diastereomeric mixtures of 5-iodomethyl-4,5-dihydrofuran derivatives 68 which can be dehydroiodinated using DBU to afford 69 (Scheme 26) [52,53]. Alkyl substituents were found to favour trans 5-iodomethyl-4,5-dihydrofuran isomers, whereas aromatic substituents led to cis isomers.

**Scheme 26.** I$_2$–Na$_2$CO$_3$ mediated iodoenolcyclization of 2-allyl-1,3-dicarbonyl derivatives.
The 2-iodomethyl-3,5,6,7-tetrahydrobenzofuran-4-ones have also been recently prepared by polymer-supported selenium-induced electrophilic cyclization of allyl substituted 1,3-dicarbonyl compounds followed by cleavage of the selenium linkers using CH$_3$I/NaI in DMF [24]. In another development, Ferraz and coworkers applied I$_2$–NaHCO$_3$ mixture in dichloromethane at room temperature to series of α-alkenyl β-keto esters and γ-alkenyl β-keto esters bearing mono or disubstituted double bond to afford variously substituted iodocyclic ethers [54]. Among the systems employed as substrates were the 2-allyl-1,3-cyclohexanedione derivatives 70, which afforded 2-iodomethyl-3,5,6,7-tetrahydrobenzofuran-4-ones 71 in high yield (Scheme 27) [54].

**Scheme 27.** Iodine-mediated cyclization of 2-allylcyclohexane-1,3-diones.

![Scheme 27](image)

**Reagents:** (i) I$_2$, NaHCO$_3$, CH$_2$Cl$_2$, r.t.

Ferraz and coworkers also subjected 2-allyl-β-benzylaminodimedone 72 to I$_2$–NEt$_3$ mixture to afford 2-iodomethyl-6,6-dimethyl-1-(phenylmethyl)indol-4-one 73 followed by its dehydrohalogenation with 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) to form 4-oxo-6,7-dihydroindole 74 in 87% yield (Scheme 28) [30]. However, these authors did not provide the corresponding analytical data and the yield for compound 73, which is implicated in the reaction and the generality of this reaction has not been demonstrated.

**Scheme 28.** Iodocyclization of 2-allyl-3-benzylamino-5,5-dimethyl-2-cyclohexen-1-one.

![Scheme 28](image)

**Reagents:** (i) I$_2$, NEt$_3$, r.t.; (ii) DBU, Benzene, heat.

A series of 2-allyl-3-benzylamino-2-cyclohexenones 75 were recently subjected to iodine–methanol mixture under reflux to afford products characterized by combination of NMR (1H- and 13C-), IR and mass spectroscopic techniques as the conjugated iodolium betaine derivatives of 2-iodomethyltetrahydroindolones 77 (Scheme 29) [55]. The zwitterionic nature of the products in solution and in the solid state was also confirmed by their chemical behavior and the experimental data were corroborated by information from quantum chemical calculations. Several attempts to dehydrohalogenate systems 77 in analogy with strategy previously employed by Ferraz and coworkers [31] on product 73 above led to complicated mixtures of products. Compounds 79a, b and d, however,
aromatized on attempted purification on silica gel column to afford the corresponding 4-hydroxy-2-
iodomethylidihydroindole derivatives 80 in low yields due to decomposition. The observed stability of
these conjugated iodolium betaine derivatives is attributed to the increased propensity of nitrogen for
electron pair delocalization resulting in a strong C2P–N2P pi bond interaction.

Scheme 29. Iodine-methanol promoted cyclization of 2-allyl-3-benzylamine-2-cyclohexen-1-ones.

![Scheme 29](image)

| R  | R’ | R” | %Yield 77 | %Yield 79 | %Yield 80 |
|----|----|----|-----------|-----------|-----------|
| a  | H  | H  | 99        | 40        | 77        |
| b  | H  | Me | 97        | 35        | 60        |
| c  | Me | Me | 95        | -         | -         |
| d  | H  | Me | 98        | 30        | -         |

Lee and Oh previously subjected α-allyl substituted β-keto sulfones 81 to I2–NaHCO3 mixture in
acetonitrile and isolated the corresponding 4,5-dihydro-5-iodomethylfurans 82 (Scheme 30) [56].
Dehydroiodination with DBU (1.2 equiv.) in benzene at room temperature afforded 4,5-dihydro-5-
methylenefururan 83. Direct one-pot dehydroiodination–isomerization to furan derivatives 84 was
achieved through the use of excess DBU (3–5 equiv.) in benzene at room temperature or under reflux.

In another development involving iodine–mediated cyclization, a series of δ-alkynyl-β-ketoesters
85 were reacted with iodine in dichloromethane at room temperature for several hours (Scheme 31)
[57]. This 5-endo-dig mode of carbocyclization of active methylene compounds 85 onto terminal and
internal alkynes led to novel iodocyclopentenes 86 in 20–80% yield.
3. Combined Electrophilic and Oxidative Properties of Iodine in Cyclization Reactions

Although the combined electrophilic and oxidizing properties of iodine have been exploited in the synthesis of heteroatom-containing cyclic compounds, such reactions do not feature at all in the recent reviews on the application of molecular iodine in organic transformation [21,22].

3.1. Iodine-mediated oxidative cyclization reactions

Iodine in refluxing triethylene glycol previously promoted oxidative cyclization of 1,3-diphenyl-prop-2-en-1-ones 87 to afford the A- and B-ring substituted flavones 88 (Scheme 32) [58]. The mechanism of this reaction is believed to involve initial electrophilic addition of iodine to the double bond followed by β-elimination of HI. Conjugate addition of the hydroxyl group then affords the 3-iodo flavanone derivative which in turn undergoes β-elimination of HI to afford the flavone. A one-pot iodine-mediated cyclization and oxidative dehydrogenation of 2-hydroxy-3-(4'-methylsulfonyl-phenyl)prop-2-en-1-ones in refluxing dimethylsulfoxide (DMSO) previously afforded 2-{4'-(methyl-sulfonyl)phenyl}benzopyran-4-one as a precursor for the synthesis of 2,3-diarylbenzopyran derivatives with potential to serve as cyclooxygenase-2 (COX-2) inhibitors [60]. Use of iodine in triethylene glycol
or DMSO has been found to be superior to cyclodehydrogenation of 2-hydroxychalcones with 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) in refluxing dioxane, which leads to mixtures of flavanones (3–13%), flavones (28–42%) and aurones (3–17%) [60].

**Scheme 32.** One-pot iodo cyclization and oxidative dehydrogenation of 2-hydroxy-3-phenylprop-2-en-1-ones.

![Scheme 32](image)

| Comp | R₁ | R₂ | R₃ | %Yield |
|------|----|----|----|--------|
| 88a  | H  | H  | H  | 83     |
| 88b  | H  | H  | Me | 72     |
| 88c  | H  | OMe| OMe| 71     |
| 88d  | H  | H  | Cl | 75     |
| 88e  | H  | H  | OH | 50     |
| 88f  | OH | H  | H  | 41     |

Reagents: (i) I₂, triethylene glycol, 140–150 °C, 1–4 h.

Iodine-pyridine mixture in THF previously effected one-pot oxidative desulfurization and cyclization of \(N\)-2-pyridylmethyl thioamides 89 to afford 2-azaindolizines (imidazo[1,5-a]pyridines 90 (59 – 95%) and sulfur-bridged 2-azaindolizine dimer 91 (ca. 7%) (Scheme 33) [61]. Prolonged reaction time (21 hours) in THF or DMF however led to mixtures of 90 and 91 in comparable yields depending on the nature of substituent on the R group.

**Scheme 33.** Iodine-mediated oxidative desulfurization promoted cyclization of thioamides.

![Scheme 33](image)

| Comp | R      | %Yield | Comp | R      | %Yield |
|------|--------|--------|------|--------|--------|
| 90a  | 2-Py-  | 89     | 90f  | 4-FC₆H₄| 89     |
| 90b  | Ph     | 84     | 90g  | 4-MeC₆H₄| 87     |
| 90c  | 4-MeOC₆H₄| 89    | 90h  | 4-Me₂NC₆H₄| 83    |
| 90d  | 4-F₂CC₆H₄| 95     | 90i  | 2-thienyl| 81     |
| 90e  | 4-BrC₆H₄| 89     | 90j  | iPr    | 59     |

Reagents: (i) I₂ (3 equiv.), pyridine (3 equiv.), THF, 0 °C then rt, 15 min.
3.2. Iodine-mediated cyclization and oxidative aromatization reactions

Progress in modern synthesis is dependent on development of novel methodologies and the combined electrophilic and oxidative properties of iodine were exploited further to synthesize novel iodo-functionalized heterocyclic compounds in a one-pot operation. The strategy involved treatment of 2-allylcyclohexenone derivatives 92 with iodine in refluxing methanol to afford a mixture of 2-iodomethyl-3,5,6,7-tetrahydrobenzofurans 93 (minor) and 2-iodomethyl-4-methoxy-2,3-dihydrobenzo-furans 94 (major) (Scheme 34) [62]. Products 93 are the result of the exo-trig type of cyclization which is more favoured than endo-trig type of cyclization according to Baldwin’s rule [23]. On the other hand, the formation of products 94 was interpreted as a consequence of an initial 1,2-addition of methanol to 93 followed by dehydration and oxidative aromatization. The use of iodine-methanol mixture as an oxidant to effect aromatization of cyclohexenones to anisole derivatives was first reported in 1980 by Tamura and Yoshimoto [63]. The generality of this aromatization reaction was later demonstrated by several researchers who employed this mixture on cyclohexenone derivatives [64–72] and their heterocyclic analogues [73] to prepare novel aromatic compounds that would be difficult to synthesize otherwise.

Scheme 34. One-pot iodocyclization and oxidative aromatization of 2-allylcyclohexenones.

Under similar reaction conditions applied to systems 92, diethyl [[2-(2-propenyl)cyclohexenone]methyl]phosphonates 95 afforded the corresponding 4-[[diethoxyphosphonyl]methyl]-2-
iodomethyl-2,3-dihydrobenzofuran derivatives 96a and b as sole products (Scheme 35) [62]. The observed result was interpreted as a consequence of initial formation of hemiacetal A from 95 followed by cyclization and the loss of methanol to form B. Iodine-assisted dehydrogenation of B would then result in the formation of 96.

Scheme 35. Iodocyclization and oxidative aromatization of diethyl {[2-(2-propenyl)cyclohexenone]methyl}phosphonates.

Iodine-methanol reaction mixture has established itself to be more effective than metal–catalyzed aromatization of substituted cyclohexenones to the corresponding phenols or phenol ethers [74–78]. This reagent mixture was also found to be superior to the use of DDQ in dioxane, which was previously employed to dehydrogenate 5-acetyl-4-oxo-4,5,6,7-tetrahydrobenzofuran and methyl-4-oxo-4,5,6,7-tetrahydrobenzofuran-5-carboxylate [78].

4. Conclusions

Iodine has established itself as an efficient, readily available and easy-to-handle electrophilic reagent to effect halocyclization reactions to afford novel iodofunctionalized heterocyclic molecules that serve as versatile intermediates in synthetic organic chemistry [79]. Carbon-heteroatom bond-forming reactions constitute the central theme of organic synthesis, and progress in modern synthesis is dependent on development of novel methodologies for the same. Series of 3-iodoindoles prepared via iodocyclization of the corresponding N,N-dialkyl-o-(1-alkynyl)anilines, for example, were recently subjected to palladium–catalyzed Sonogashira and Suzuki cross coupling reactions in solution and on a solid support to afford a 42-member library of 1,2,3,5-tetrasubstituted indoles after cleavage from the support [80]. In summary, molecular iodine has allowed in the last years a great advance in organic chemistry in the synthesis of heterocyclic compounds with many 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.
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