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Electrophilic Iodination of Heterocyclic Compounds. Recent Advances 2008–2025: Part II

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ABSTRACT

The iodination of heterocyclic compounds has significant interest in synthetic organic chemistry, as it provides versatile and efficient pathways for the synthesis of a wide range of biologically active molecules. This review aims to highlight recent advances in the iodination of heterocyclic compounds using elemental iodine or iodide-based reagents, covering developments reported over the past 17 years.

1 | Introduction

The incorporation of iodine, inexpensive, readily available, and environmentally friendly element, for various organic transformations has gained significant attention due to its ability to generate versatile intermediates for synthetic organic chemistry. Iodine has been recognized as a versatile mediator and reagent in organic synthesis [1–3].

The design of safe and atom-efficient acid-catalyzed organic processes represents one of the major challenges in green chemistry [4]. The most attractive approach for the iodination of organic compounds involves the use of molecular iodine or iodide anions in combination with environmentally benign and atom-efficient oxidants. The application of green solvents or solvent-free conditions further improves the environmental compatibility and efficiency of these iodination methodologies [5]. A comprehensive overview of synthetic protocols for the electrophilic iodination of organic compounds using I_2 or iodide sources was reported in a review by Stavber and coworkers in 2008 [5]. However, the reports covered by this review mainly exhibited low green chemistry profiles, thereby highlighting the need for the development of more sustainable and environmentally friendly iodination protocols. In 2021, a further review reported the progress made in the iodination of organic compounds using elemental iodine or iodide reagents over the period from 2008 to 2021 [6]. This review covered a wide variety of substrates, including alkanes, alkenes, alkynes, and alkyl carbonyl compounds, illustrating the expanding scope and versatility of iodine-based iodination methodologies.

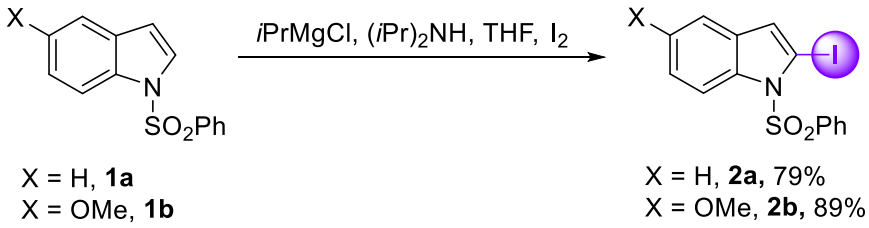
Heteroaryl iodides are widely used synthetic building blocks [7–13] and play a key role in numerous transformations, including cross-coupling and radical reactions. These compounds are present in numerous pharmaceutical agents and play an important role in medical imaging applications [14]. Thus, the present review elaborates relevant protocols to highlight recent advances in the iodination of heterocyclic compounds using elemental iodine or iodide-based reagents, covering the period from 2008 to 2025.

2 | Recent Advances

2.1 | Iodination of Heterocyclic Compounds Using Elemental Iodine

2.1.1 | Iodination of Five-Membered and Benzofused Heterocyclic Compounds

De Koning's group [15] described the treatment of 1-(phenylsulfonyl)indole **1a** and the methoxyindole derivative **1b** with the catalytic magnesiation conditions developed by Dinsmore, followed by reaction with iodine affording the



SCHEME 1 | Iodination of 1-(phenylsulfonyl)indole **1a** and the methoxyindole derivative **1b**.

corresponding iodinated intermediates **2a** and **2b** (Scheme 1). The observed C2 iodination results from the magnesiation step, which directs the reaction to the C2 position. These iodinated intermediates are key building blocks for further functionalization through Suzuki–Miyaura cross-coupling reactions.

Albrecht's group [16] reported a mild and efficient one-pot method for the selective iodination of aromatic heterocycles using an I_2/AgOAc system in dichloromethane. The protocol enables direct C—H iodination under neutral conditions, avoiding harsh oxidants, strongly acidic media, or prefunctionalized substrates. A broad range of *N*-heterocycles **3**, including imidazoles **3a** and **3d**, isoxazoles **3b**, and pyrazoles **3c**, were successfully iodinated into the corresponding products **4a–d**, in moderate to excellent yields, often providing better selectivity and efficiency than traditional I_2/KI methods (Scheme 2).

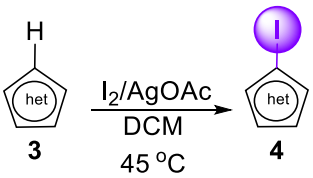
Related iodination strategies for the preparation of *ortho*-iodoaniline indazole derivatives from a dinitroindazole precursor have been illustrated by Anizon's group [17]. Initial N-1 protection with a tetrahydropyranyl group is followed by selective monoreduction of one nitro group using Pd/C and 1,4-cyclohexadiene. Subsequent iodination with iodine in DMSO affords the two regioisomeric o-iodoaniline derivatives, which are isolated in moderate yields and serve as key intermediates for further palladium-catalyzed reactions.

Yoshida and coworkers [18] reported the preparation of 2,5-disubstituted-3-iodopyrroles as an efficient method through an iodine-promoted electrophilic cyclization of propargylic aziridines **5**. The reaction proceeds under metal-free conditions using molecular iodine and sodium bicarbonate, affording a wide range of 3-iodopyrroles in good to excellent yields **8**.

A plausible mechanism involving iodonium ion formation **6** and intramolecular nucleophilic attack by the aziridine nitrogen affords intermediate **7**, which undergoes proton elimination to form **8** in good to excellent yields. A broad range of substituted 3-iodopyrroles was synthesized, and the synthetic utility of the iodo substituent was demonstrated by a successful Negishi coupling reaction (Scheme 3).

Scotney's group [19] described a reliable three-step synthetic route that has been successfully scaled to produce multi-kilogram amounts of 4-(4-Iodo-1H-pyrazol-1-yl)piperidine which serves as an important intermediate in the synthesis of Crizotinib. The sequence involves nucleophilic aromatic substitution of 4-chloropyridine with pyrazole, hydrogenation of the pyridine ring, and final iodination of the pyrazole.

Ortiz's group [20] reported that the degree of iodination in the 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY) core through I_2/HIO_3 can be controlled, enabling the preparation of mono-, di-, and polyiodinated derivatives. These compounds represent the first BODIPY dyes containing more than two halogen atoms in the core. In addition, the simple synthetic approach suggests that this method can be applied to other dyes in the same family with different degrees of substitution. Another important finding of this study is that polyhalogenated compounds can serve as useful synthetic building blocks for the



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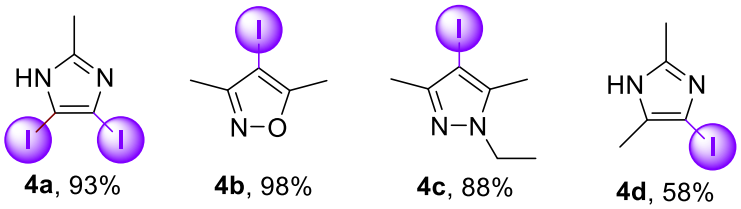
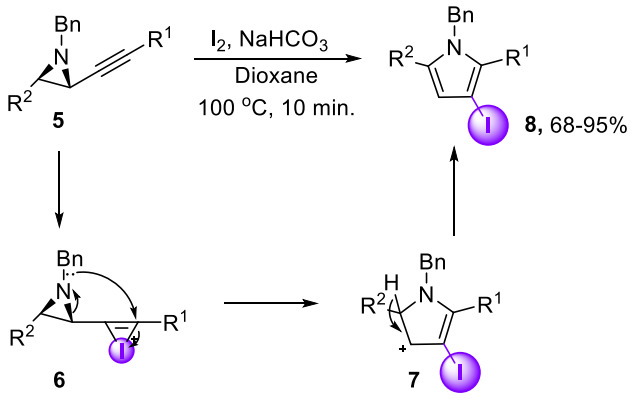


SCHEME 2 | Iodination of heterocycles **3** using I_2/AgOAc system.



SCHEME 3 | Proposed mechanistic pathway for the preparation of 2,5-disubstituted-3-iodopyrroles **8**.

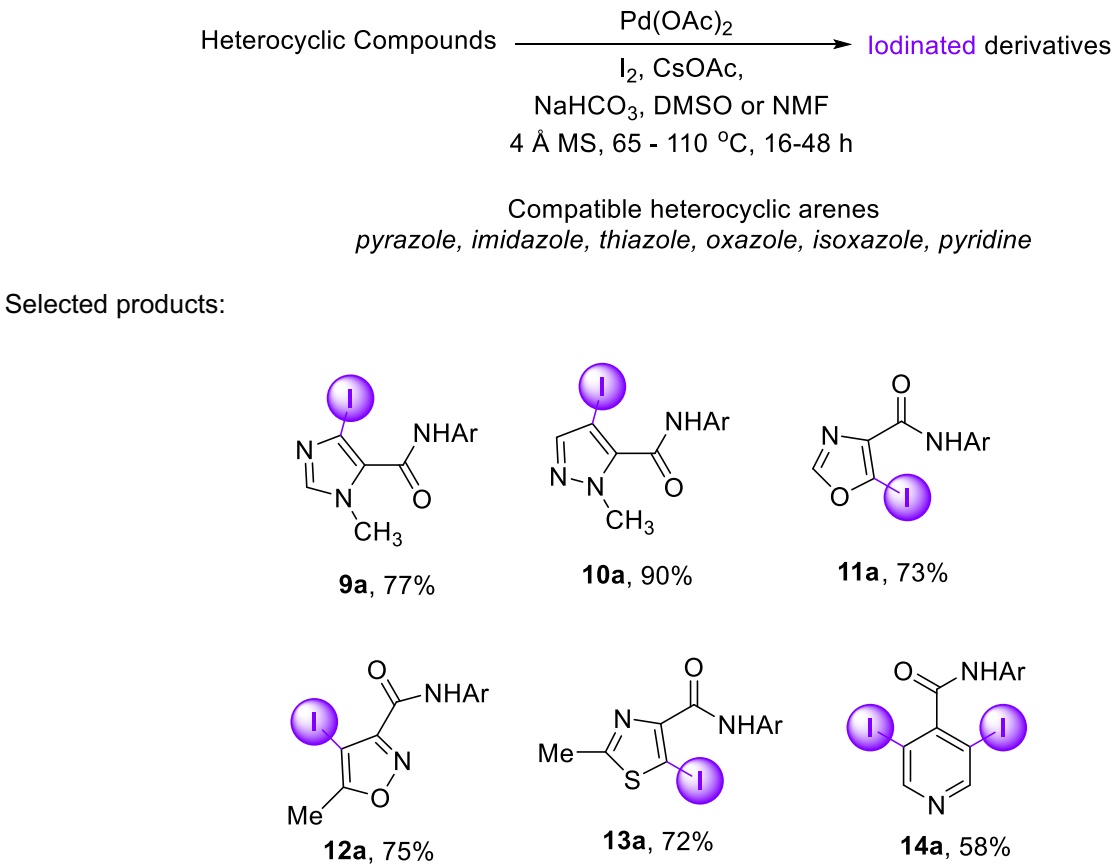
selective introduction of desired functional groups at specific positions on the BODIPY core.

Yu and coworkers [21] reported the first palladium-catalyzed C—H iodination that uses molecular iodine as the sole oxidant (Scheme 4). The palladium loading can be lowered to 0.5 mol% on a gram scale. The method also exhibits a broad substrate scope, enabling the iodination of diverse heterocycles that were previously unsuitable for directed C—H activation.

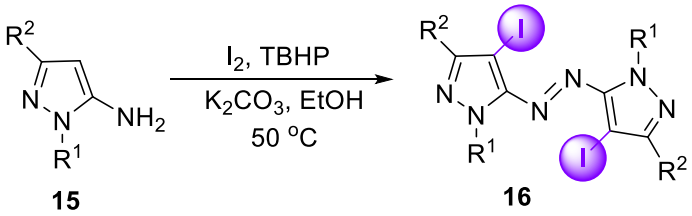
Variation of the nitrogen-linked substituents on pyrazole **15**, including methyl, cyclopropyl, ethyl, and tert-butyl groups, led to the formation of heteroaryl azo compounds **16** in moderate to good yields [22]. This transformation proceeds via oxidative dehydrogenative coupling followed by iodination using TBHP as the oxidant (Scheme 5). Notably, iodination of heteroaromatic systems proceeds through an electrophilic substitution pathway and has significant synthetic and industrial importance.

Zhao's group [23] developed a mild and efficient method for the direct C—H iodination of 1,3-azoles **17** in the presence of $CuBr_2$ as the catalyst, using the weak base Li*O*t*Bu in the presence of 1,10-phenanthroline. The method was applied to five classes of 1,3-azoles, including benzoxazole, benzothiazole, 5-phenyloxazole, *N*-methylbenzimidazole, and 2-phenyl-1,3,4-oxadiazole, providing the corresponding iodinated compounds **18**. Coordination of the copper salt to benzoxazole, followed by deprotonation with Li*O*t*Bu in the presence of 1,10-phenanthroline, forms a benzoxazole–copper intermediate. This intermediate then reacts with iodine to provide the iodinated product (Scheme 6).

Lokhande and coworkers [24] reported a simple and efficient one-pot method for the direct iodination of tetrahydrocarbazoles using molecular iodine in DMSO at 110°C. The reaction shows good regioselectivity and tolerates both electron-rich and electron-poor groups, providing moderate to excellent yields. This approach was successfully applied to the total synthesis of several natural products including glycozoline, 3-formyl-6-methoxy-carbazole, and 6-methoxy-carbazole-3-methylcarboxylate.



SCHEME 4 | *Ortho*-iodination of heterocyclic compounds catalyzed by palladium.



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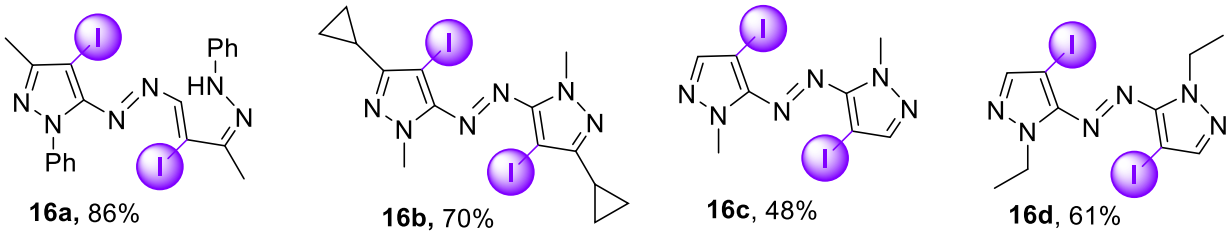
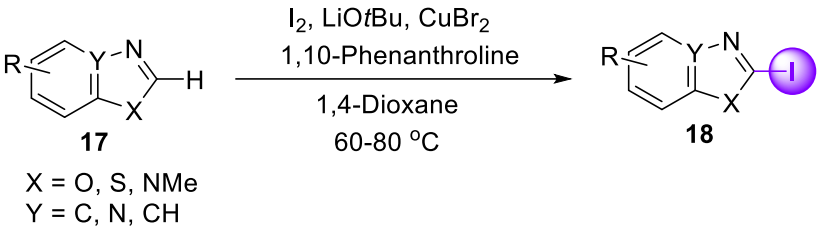


SCHEME 5 | Synthesis of azopyrrole derivatives **15**.



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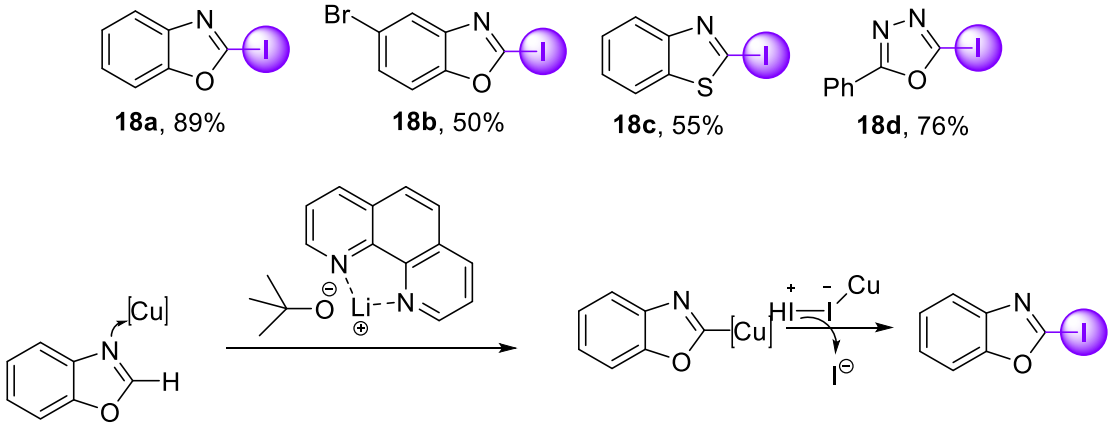


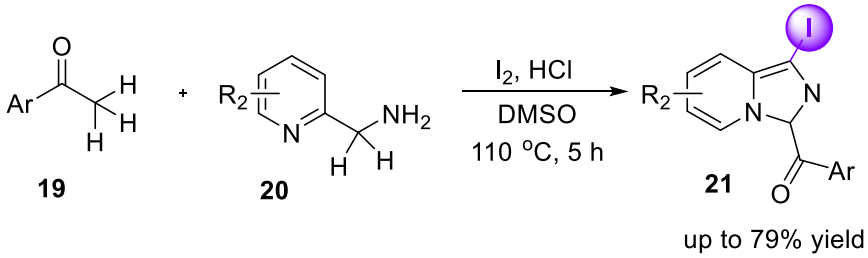
SCHEME 6 | Direct C—H iodination of 1,3-azoles **17**.

Iodination of carbohydrate-derived 3,6-dihydro-2*H*-1,2-oxazines using iodine and pyridine in DMF efficiently afforded the corresponding 5-iodo-1,2-oxazine derivatives in high yields [25].

Hajra and coworkers [26] developed an environmentally friendly method for the iodination of imidazoheterocycles via sp^2 C—H bond functionalization using molecular iodine in water catalyzed by an imidazole-based zwitterionic molten salt at room temperature for 2 h. This protocol is applicable to imidazo[2,1-*b*]thiazole and imidazole frameworks.

Gorjizadeh and coworkers [27] reported a practical, efficient, and low-cost method for the synthesis of iodopyrazoles through the direct reaction of pyrazoles with iodine at room temperature. The reaction utilizes *n*-butyltriphenylphosphonium peroxodisulfate as an effective and mild oxidant.

Wu and coworkers [28] developed direct $C_{sp}{}^3$—H iodination of pyridin-2-ylmethylamines **20** promoted by iodine providing a simple and efficient route to 1-iodoimidazo[1,5-a]pyridines **21** in moderate to good yields (Scheme 7).

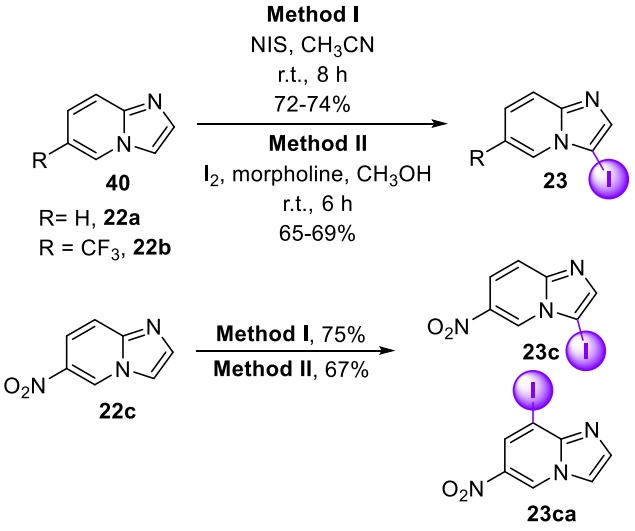


SCHEME 7 | Iodination of pyridin-2-ylmethylamines **20** promoted by iodine.

Koley and coworkers [29] reported a simple and efficient Ni-catalyzed C—H iodination protocol using molecular iodine as the sole oxidant. The method shows high selectivity, affording mono-iodinated products from a broad range of heteroarene substrates. Notably, the addition of ammonium thiocyanate completely suppresses iodination at the quinoline ring.

In a related approach, Chai and coworkers [30] developed a simple method for the iodination of imidazo[1,2-*a*]pyridines **22**, in which iodination occurs selectively at the C-3 position **23**. *N*-Iodosuccinimide (NIS) and an I_2–morpholine system were employed as effective iodinating reagents. When a nitro group was present as the substituent, iodination occurred at both the C-3 and C-8 positions **23c** and **23ca** (Scheme 8).

Kotagiri and coworkers [31] developed a one-pot oxidative coupling and iodination protocol in which oxindoles react with alcohols under a $PhI(OCOCF_3)_2/I_2$ system providing 5-iodo-3-monoalkoxy and 5-iodo-3,3-dialkoxy oxindoles in moderate to good yields.



SCHEME 8 | Iodination of imidazo[1,2-α]pyridines **22** using NIS or I_2.

Reaction of 3,3a,4,5-tetrahydro-3-aryl-2-phenyl-2H-benzo[g]indazoles **24** with I_2/DMSO caused oxidation of the five-membered ring to form **25** and simultaneously promoted iodination of the N-phenyl group together with ring oxidation **26** (Scheme 9) [32].

2.1.2 | Iodination of Six-Membered and Benzofused Heterocyclic Compounds

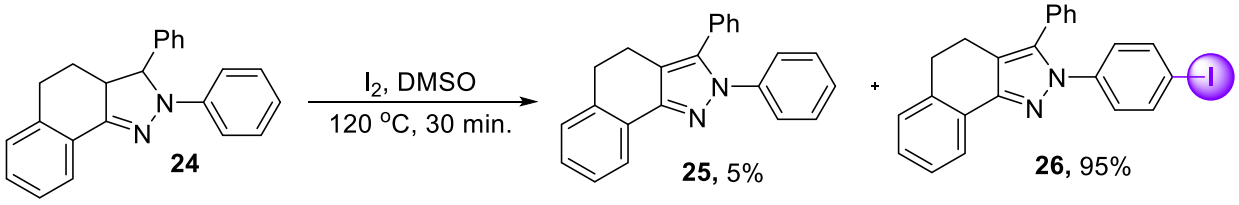
Yamamoto's group [33] reported a general strategy for the synthesis approach of pyrrolopyridines **28** through iodine-mediated electrophilic cyclization of 2-alkynyl-1-methylene azide aromatics **27** (Scheme 10).

Using an alternative one-pot strategy, Boto and coworkers [34] described a methodology for converting readily available proline derivatives into β-iodinated iminosugar-based nucleosides under mild conditions. The process combines radical decarboxylation, oxidation, and β-iodination using hypervalent iodine reagents and molecular iodine, followed by reaction of the resulting acyliminium intermediate with nitrogen bases. The iodine atom is selectively introduced at a previously unfunctionalized 3-position.

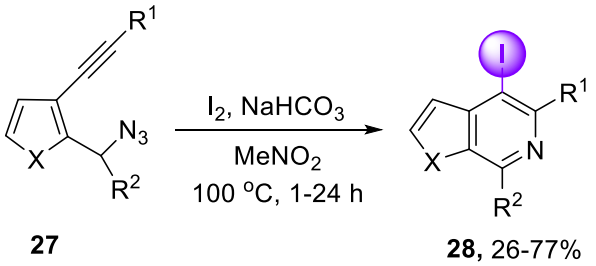
Yamamoto's group [33] reported a general strategy for the synthesis of highly substituted isoquinolines starting from *o*-alkynyl benzyl azides. Iodine interacts with the carbon–carbon triple bond of substrates **29**, proceeding through iodonium ion formation **30**, followed by intramolecular cyclization by the azide group **31**. Subsequent loss of proton and nitrogen gas leads to the formation of isoquinolines **32** (Scheme 11). This new methodology was successfully employed for the synthesis of norchelerythrine.

Treatment of pyrazolo[1,5-*a*]pyridine dicarboxylates **33** in THF with commercially available $(TMP)_2Zn{\cdot}2MgCl_2 \cdot 2LiCl$, followed by quenching with iodine in THF, afforded the target methyl carboxylate **34** along with the corresponding demethylated carboxylic acid **35** (Scheme 12) [35].

Along similar lines, Jain and coworkers [36] reported a direct, regioselective, and metal-free method for the synthesis of fused *N*-heterocyclic iodides **37**. The transformation proceeds through regioselective C—H functionalization mediated by tert-butyl hydroperoxide (TBHP), which enables dual activation of



SCHEME 9 | Aromatization and iodination of **24** using I_2/DMSO.



27 **28,** 26-77%

SCHEME 10 | Synthesis of **27** mediated by iodine.

molecular iodine and the heterocyclic substrate **36** (Scheme 13). This process generates electrophilic iodine species (I^+) in situ along with tert-butoxy or tert-butylperoxy radicals, thereby promoting efficient iodination.

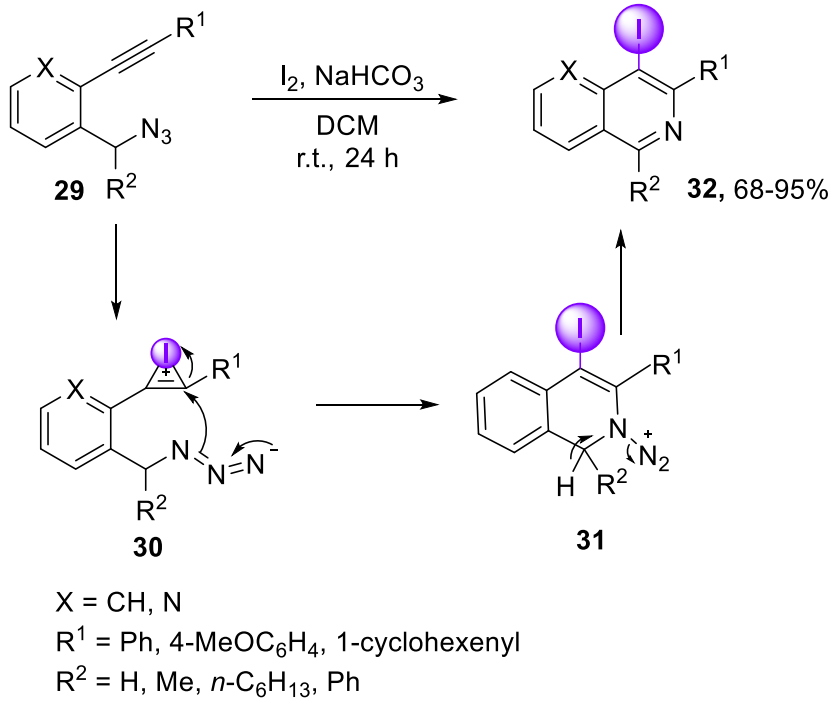
Su and coworkers [37] developed an efficient and practical copper-catalyzed protocol for C—H iodination of 8-aminoquinoline-based aromatic carboxamides **38**. The method exhibits a broad substrate scope and affords moderate to high yields (Scheme 14).

Kakiuchi's group [38] achieved ortho-selective C—H iodination of N-(8-quinolinyl)benzamide derivatives using I_2 in the presence of palladium as the catalyst under both electrochemical and non-electrochemical conditions. C—H iodination carried out at 90°C under base-free conditions afforded the iodinated products in high yields. Moreover, anodic oxidation significantly enhanced the efficiency of iodination at sterically hindered positions.

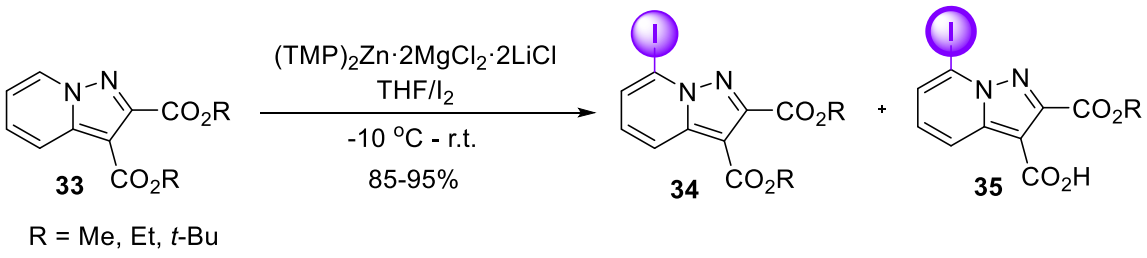
In contrast to this metal-catalyzed approach, Wang and coworkers [39] developed a simple and efficient method for the regioselective C3 iodination of quinolines using molecular iodine and TBHP. The reaction tolerates various functional groups and works on a gram scale, and the product can be further functionalized by Buchwald–Hartwig amination. Preliminary mechanistic studies indicate that the reaction proceeds through a radical intermediate.

Along similar lines, Raminelli and coworkers [40] developed an efficient method for the iodination of quinoline derivatives using molecular iodine and hydrogen peroxide in water at 50°C for 24 h, affording the products in good to excellent yields.

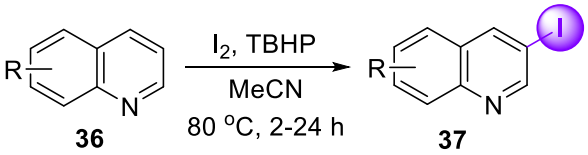
Sekar's group [41] reported an efficient and environmentally benign protocol for the iodination of isoquinolone derivatives **42** using I_2/TBHP system in water, affording the corresponding products **43** in moderate to quantitative yields (Scheme 15).



SCHEME 11 | Cyclization of *o*-alkynyl benzyl azides mediated by iodine.



SCHEME 12 | Iodination of pyrazolo[1,5-*a*]pyridine dicarboxylates **33**.



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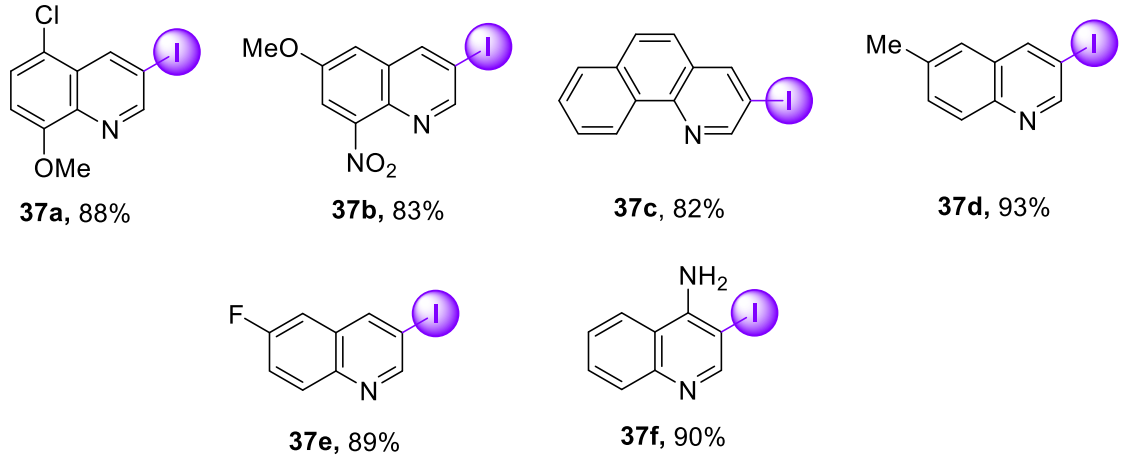
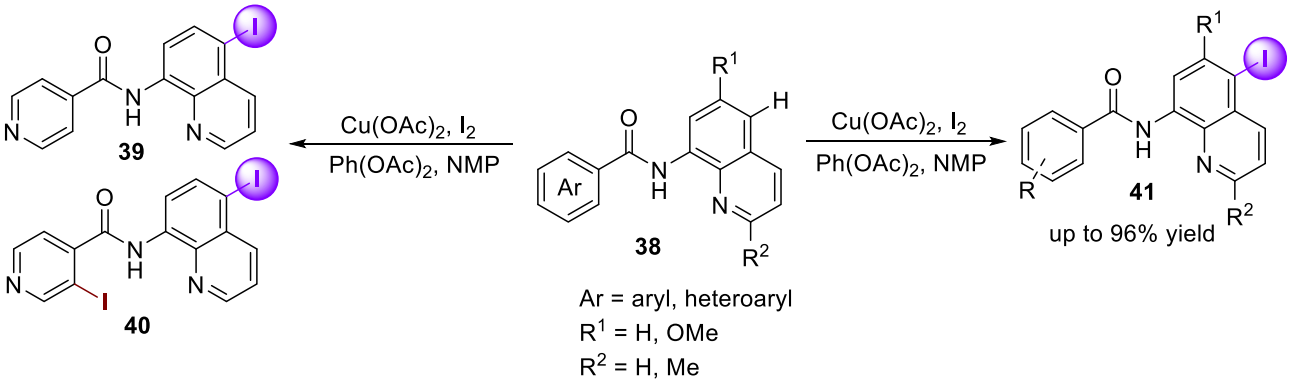
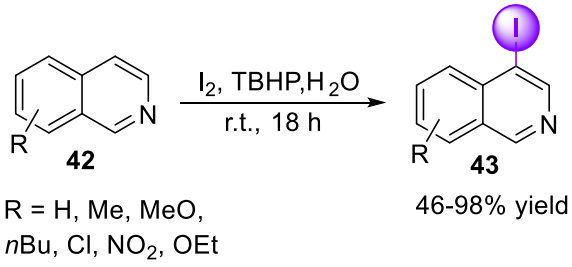


SCHEME 13 | Synthesis of fused *N*-heterocyclic iodides **37** mediated by TBHP.



SCHEME 14 | Copper-catalyzed C—H iodination of 8-aminoquinoline-based aromatic carboxamides **38**.



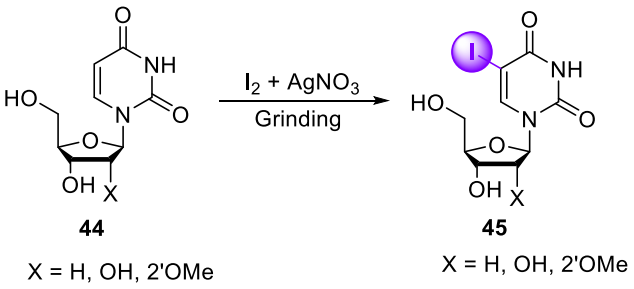
SCHEME 15 | Iodination of isoquinoline derivatives **42** using I_2/TBHP system.

Lee and coworkers [42] presented a green and solvent-free method for the iodination of pyrimidine derivatives **44** using the grinding method. Solid iodine and silver nitrate enable selective C5 iodination of pyrimidines and nucleoside derivatives at room temperature, giving high yields in short reaction times **45**. The protocol avoids toxic reagents and solvents, shows broad substrate applicability, and offers an environmentally friendly approach to accessing iodinated pyrimidines relevant for nucleobase-related drug design (Scheme 16).

2.2 | Iodination of Heterocyclic Compounds Using Iodide Sources

2.2.1 | Iodination of Five-Membered and Benzofused Heterocyclic Compounds

Petrosyan's group [43] reported the development of an electrochemical method for the selective iodination of pyrazoles to afford 4-iodopyrazole derivatives. Iodination is carried out via galvanostatic electrolysis of pyrazoles in aqueous KI using Pt-anode, avoiding the need for molecular iodine or strong



SCHEME 16 | Iodination of pyrimidine derivatives **44** by mechanical grinding.

chemical oxidants. The reaction efficiency strongly depends on the electronic nature and position of substituents on the pyrazole ring. Electron-donating groups at carbon positions enhance iodination yields, while electron-withdrawing substituents significantly reduce reactivity. Alkyl groups attached to the nitrogen atom of the pyrazole ring slow down the electroiodination process.

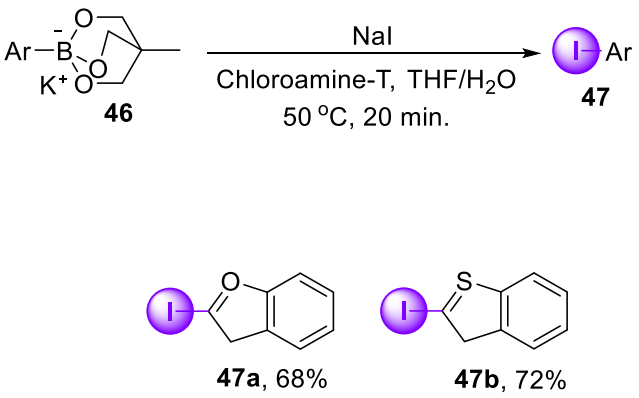
In a further application, iodination of triolborate **46** was achieved using NaI and chloramine-T in a THF/H_2O solvent system providing the corresponding iodoheteroarene **47** (Scheme 17) [44].

One-pot synthetic protocol for the preparation of 5-halo-1,4-disubstituted-1,2,3-triazoles by combining Cu^I-catalyzed azide–alkyne cycloaddition with oxidative halogenation was presented [45]. The developed CuI–NCS system enables efficient formation of 5-iodotriazoles, under mild reaction conditions. The protocol shows high functional group tolerance and provides an effective route to halogenated triazoles.

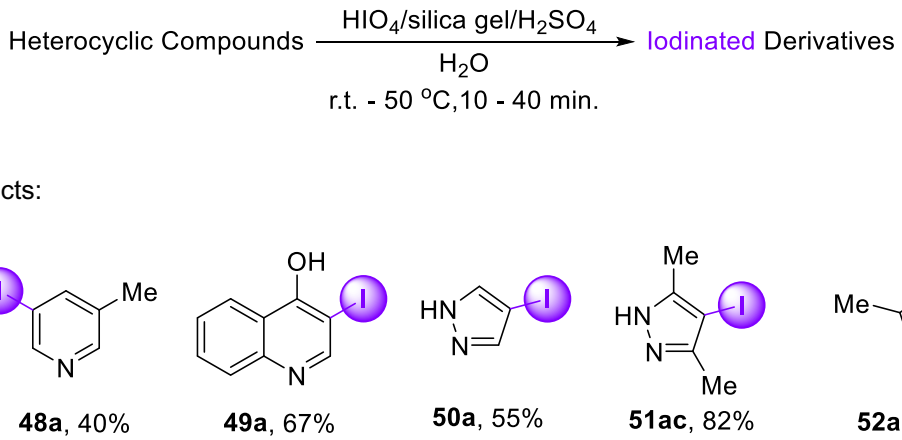
A fast and simple method for iodinating heterocyclic compounds using a HIO_4 /NaCl/silica gel/H_2SO_4 system in water at mild temperatures was reported [46]. The method is environmentally friendly, avoids harsh conditions and toxic metals, and provides moderate to excellent yields for a wide range of heterocycles, including pyridines, quinolines, pyrazoles, and imidazoles, **48a–52a** (Scheme 18). A key advantage is the direct iodination of pyridines with good selectivity and efficiency, making the protocol valuable for natural products and pharmaceutically important compounds.

A new $Cu(OAc)_2$-catalyzed method for the direct oxidative C—H acetoxylation and iodination of indoles **53** using $PhI(OAc)_2$ as the terminal oxidant is presented [47]. Using this approach, both indol-3-yl acetates **54** and 3-iodoindoles **55** were formed in an approximately 1:1 yield ratio (Scheme 19).

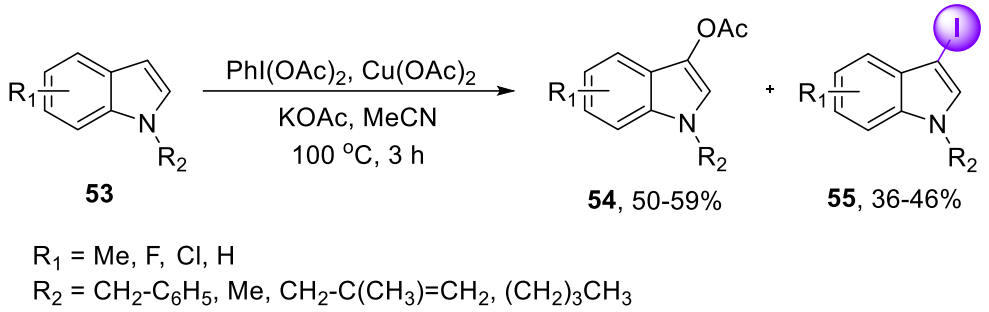
A copper-mediated method for the regioselective cyanation of indoles and 2-phenylpyridines was developed using ammonium iodide and DMF as a combined source of the cyano group under "palladium-free" *conditions*. Mechanistic studies show that the



SCHEME 17 | Synthesis of aryl iodides **47** from triolborates **46**.



SCHEME 18 | Iodination of heterocyclic compounds using HIO_4/NaCl/silica gel/H_2SO_4 system.



SCHEME 19 | Direct 3-acetoxylation and iodination of indoles **53** catalyzed by $Cu(OAc)_2$.

transformation of indoles occurs via an electrophilic initial iodination step, followed by cyanation [48].

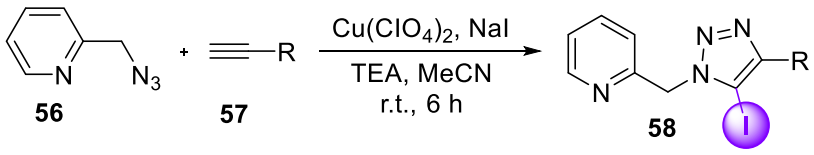
The combination of copper(II) perchlorate and sodium iodide solutions produces copper(I) species along with electrophilic triiodide ions that all mediate the cycloaddition reaction between organic azides **56** and terminal alkynes **57**, forming 5-iodo-1,4-disubstituted-1,2,3-triazoles **58a–d** (Scheme 20) [49]. Under the reaction conditions, copper(II) reacts with sodium iodide to form copper(I) species, I_2, and triiodide ions. A base such as DBU or TEA deprotonates the alkyne after it binds to copper(I), forming a copper acetylide **I**. This step is the rate-determining step of the reaction. The coordination of the azide leads to the formation of a dinuclear intermediate **III**, which then rearranges to give a copper(I) triazolide **IV.** Reaction of the triazolide with triiodide produces the desired 5-iodotriazole **V.** When an excess amount of TEA is present, it forms triethylammonium, which competes with triiodide for copper(I) triazolide and results in the formation of the byproduct 5-prototriazole **V'** (Scheme 21).

Pujol and coworkers [50] developed a protocol for the direct iodination of indoles and related derivatives using iodine monochloride (ICl) in the presence of Celite. The scope of this method is demonstrated by the iodination of melatonin, which proceeds in 98% yield.

Another transformation is achieved by treating imidazole with iodine in the presence of potassium iodide under basic aqueous conditions, leading to efficient and high-yield introduction of iodine atoms at the 2, 4, and 5 positions of the imidazole ring [51].

Il'inykh's group [52] described the synthesis of new S-alkenyl derivatives of 5-(trifluoromethyl)-4*H*-1,2,4-triazole-3-thiol through alkenylation reactions with various alkenyl halides. Reaction between iodine and S-alkenylated products proceeds in a regiospecific manner, affording novel fused fluorine- and iodine-containing [1,2,4]triazolo[3,4-*b*] [1,3] thiazine heterocyclic systems.

A method for the synthesis of 4-iodo-substituted pyrazoles was developed by Lyalin and Petrosyan [53], based on the iodination of pyrazole and its derivatives in a heterophase medium (H_2O/$CHCl_3$ or CCl_4) system using KI–KIO_3 in the presence of H_2SO_4. The protocol was effective for a wide range of pyrazole substrates, affording 4-iodinated products in high yields of 80%–97%. A notable exception was 3-nitropyrazole-5-carboxylic acid, which provided a significantly lower yield of 32%.



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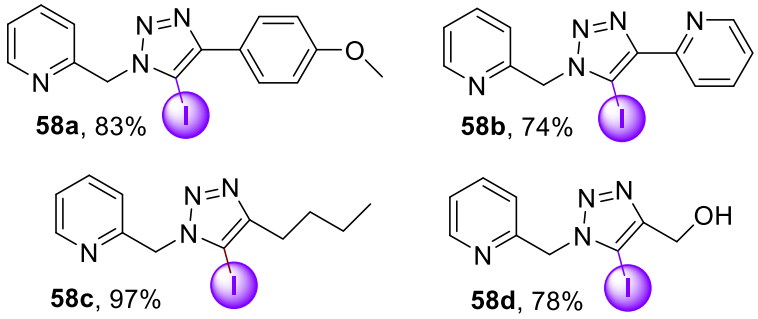
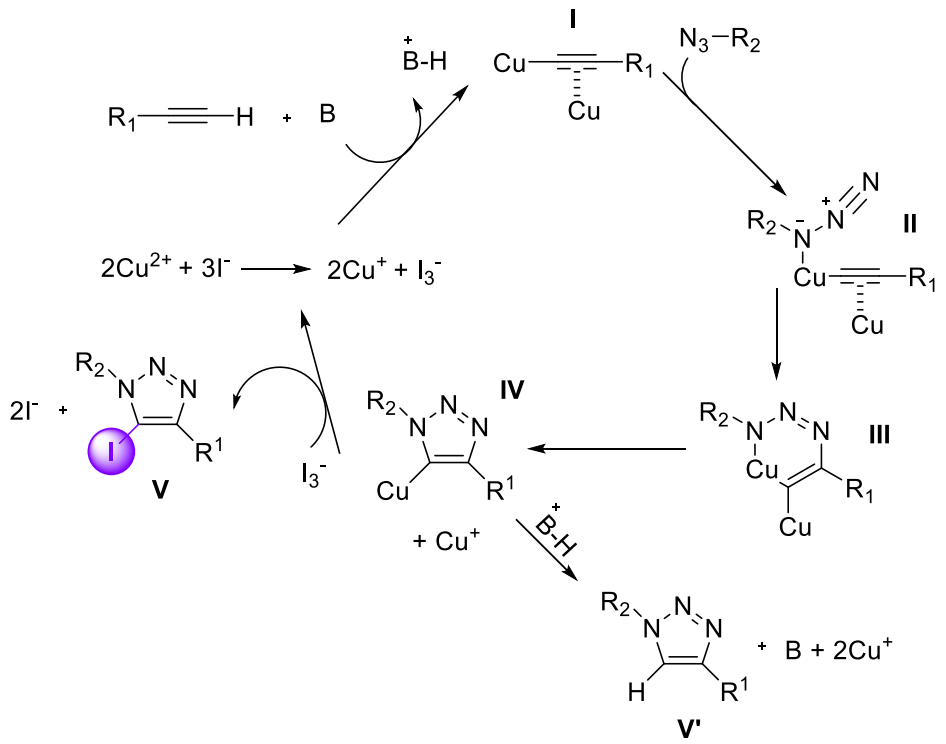


SCHEME 20 | Synthesis of 5-iodotriazole **58** with different terminal alkyne molecules **57** using NaI.

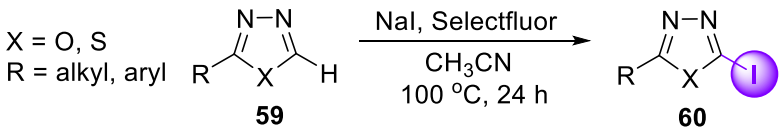


SCHEME 21 | Plausible mechanistic pathway.

An alternative approach for iodinating aromatic heterocycles employs an NH_4I/H_2O_2 system in acetic acid, with the reaction proceeding over 20 h [54].

A new protocol for direct aryl iodination of isoindolines and isoindoline nitroxides is described using periodic acid and potassium iodide in sulfuric acid [55]. This method enables the synthesis of diiodinated tetramethyl and tetraethyl isoindolines, as well as a di-tetramethyl isoindoline nitroxide, in high yields of 70%–82%. In contrast, the corresponding monoiodinated products are obtained in moderate yields of 34%–48%. Iodinated nitrones were also formed from a tetraethyl isoindoline nitroxide.

Jiang and coworkers [56] reported a cost-effective copper-mediated aerobic domino C—H iodination and nitration of indoles. The one-step process proceeds under mild conditions



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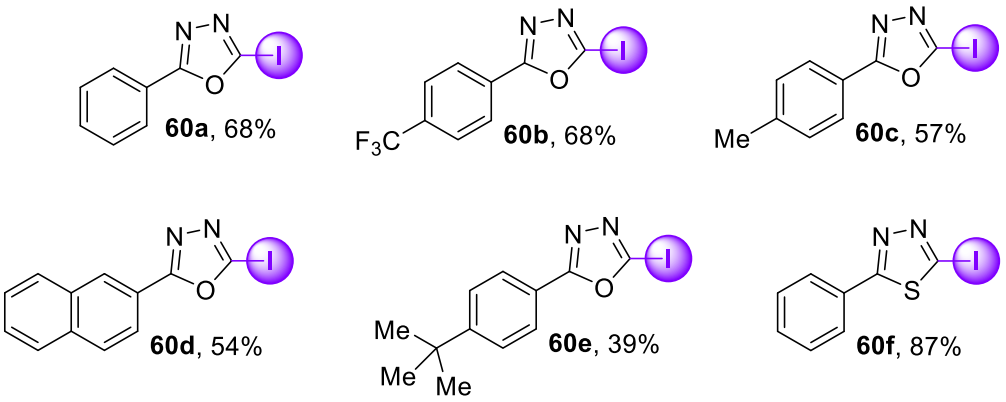


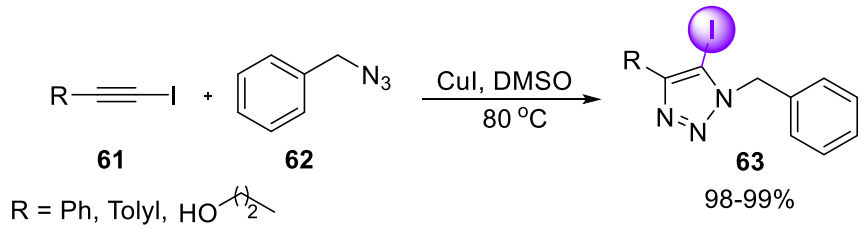
SCHEME 22 | Oxidative iodination of 1,3,4-oxadiazoles and 1,3,4-thiadiazoles **60** using NaI.

to afford 3-iodo-2-nitroindoles with high regioselectivity and a broad substrate scope. The iodination step is proposed to occur through a Cu(III)–iodide intermediate that undergoes electrophilic addition at the C3 position of the indole ring. The subsequent nitration proceeds via C—H activation, followed by oxidative addition of a nitro radical and reductive elimination.

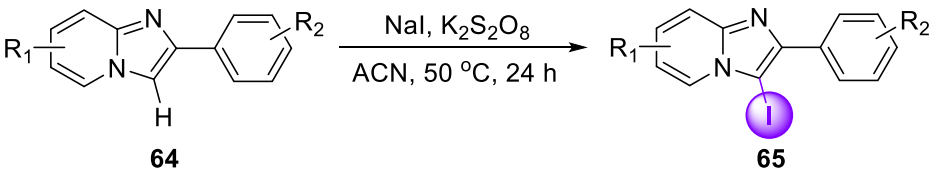
Transition-metal-free oxidative iodination of 1,3,4-oxadiazoles **59** was efficiently carried out with sodium iodide as the iodine source and Selectfluor as the oxidizing agent. A variety of substituted iodinated derivatives **60** were obtained in moderate to good yields, and the applicability of this protocol to 1,3,4-thiadiazoles **59** was also demonstrated (Scheme 22) [57].

A two-step electrochemical method was used to prepare 4-iodo-substituted pyrazole compounds [58]. In the first step, potassium iodate (KIO_3) was produced at a Ni anode by electrolysis of an alkaline water solution of KI or iodine under constant current conditions. In the second step, pyrazole and its derivatives were iodinated in a two-phase H_2O–$CHCl_3$ or CCl_4 system. This reaction used the KIO_3–KI or KIO_3–I_2 system with sulfuric acid. The yields of iodopyrazoles were between 74% and 92%. Electrochemical iodination was also applied to anisole, 2-methylpyrazole, and thiophene. This gave 4-iodoanisole with 88% yield, 4,5-diiodo-2-methylimidazole with 54% yield, a mixture of 2-iodothiophene with 60% yield, and 2,5-diiodothiophene with 4% yield.

Jiao's group [59] reported an efficient and practical method for low-cost iodination of heteroarenes including indole, pyrazole, azaindole, thiophene, and benzothiophene using DMSO and



SCHEME 23 | Synthesis of 5-iodo-1,4-disubstituted-1,2,3-triazoles **63** using CuI.



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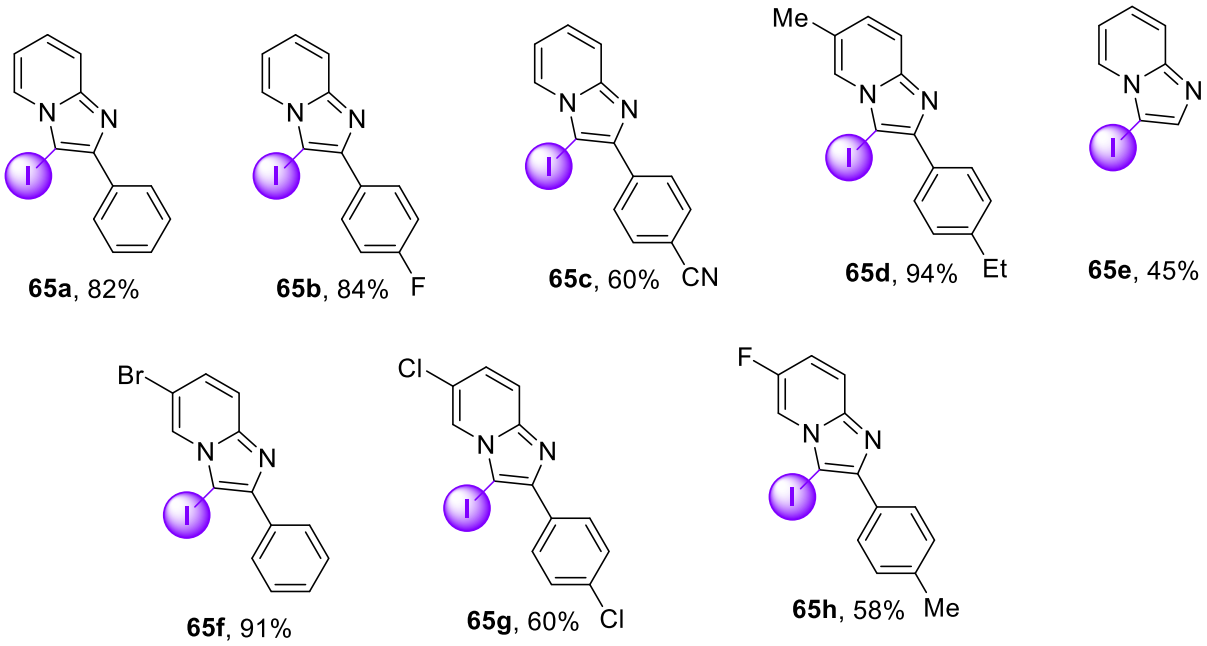
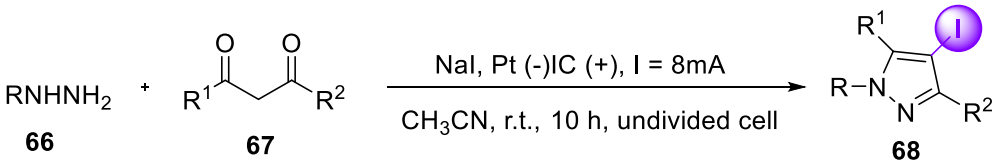
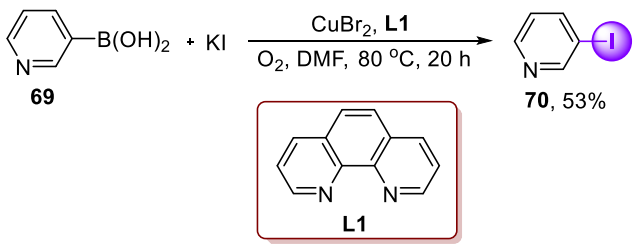


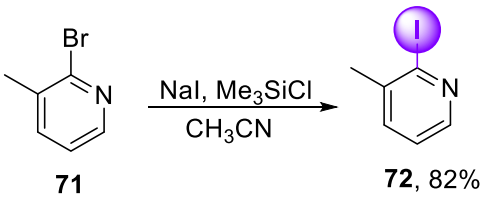
SCHEME 24 | Iodination of Imidazo[1,2-*a*]pyridines **64**.



SCHEME 25 | Multicomponent synthesis of 4-iodopyrazoles **68** using NaI.



SCHEME 26 | $CuBr_2$-catalyzed iodination of heteroaromatic boronic acid **69** by KI.



SCHEME 27 | Iodination of 2-bromo-3-methylpyridine **71** with NaI/Me_3SiCl.

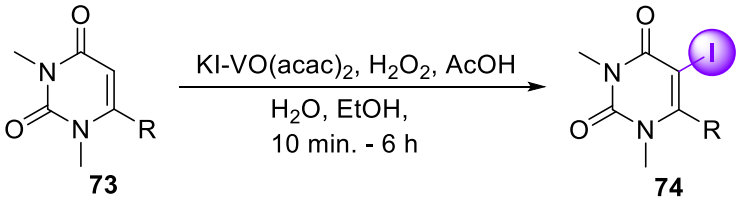
HI as reagents in EtOAc, at 60°C, providing the corresponding products in 72%–98% yield.

A selective oxidative iodination of porphyrin C—H bonds using iodide and hydrogen peroxide in acetic acid is reported [60]. Iodination occurs specifically at the β-position of the porphyrin framework and proceeds efficiently under mild reaction conditions.

An efficient and highly regioselective iron(III)-catalyzed iodination of activated arenes and heteroarenes has been developed by Sutherland group [61], which can be further accelerated using a triflimide-based ionic liquid.

Cai's group [62] reported a copper-mediated iodination of heteroaromatic carboxylic acids, including indoles, benzofurans, and benzothiofurans, carried out in DMSO at 160°C for 20–30 h. The transformation was also achieved using $Pd(OAc)_2$, affording the desired iodinated products in moderate to quantitative yields.

Reddy and coworkers [63] reported the synthetic utility of 1-iodoalkynes **61** through a 1,3-dipolar cycloaddition with benzyl azide **62**, affording 5-iodo-1,4-disubstituted-1,2,3-triazoles **63** in quantitative yields (Scheme 23).



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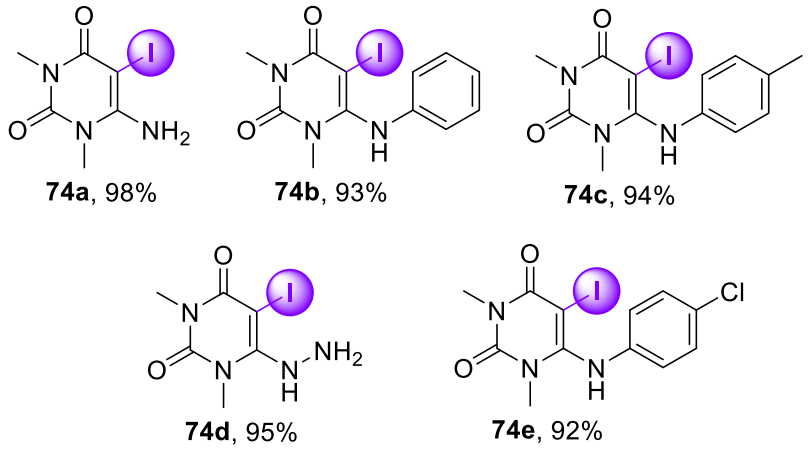


SCHEME 28 | Iodination of pyrimidinediones **73** employing KI–$VO(acac)_2$–H_2O_2.

Expanding iodination strategies to more complex heterocyclic frameworks, Adimurthy's group [64] described an efficient iodination strategy for imidazo-fused heterocycles **64** using NaI as halogen sources and $K_2S_2O_8$ or Oxone as the promoter. The method enables selective C-3 iodination of imidazo[1,2-*a*]pyridines and benzo[d]imidazo[2,1-*b*]thiazoles **65** in good to excellent yields (Scheme 24). In addition, this protocol is applicable to other heterocycles, including 2-aminopyridines, 2-aminopyrimidines, indole, and isoquinoline, affording the corresponding halogenated products in moderate to excellent yields.

In 2024, Huang and coworkers [65] introduced indolyl ketosulfoxonium ylides as a novel class of monoaryl atropisomers. Using NIS and a chiral phosphoric acid (CPA) catalyst, they achieved the iodoaminocyclization of o-aminophenylethynyl ketosulfoxonium ylides. The resulting atropisomers could be readily transformed into other chiral frameworks without loss of optical purity.

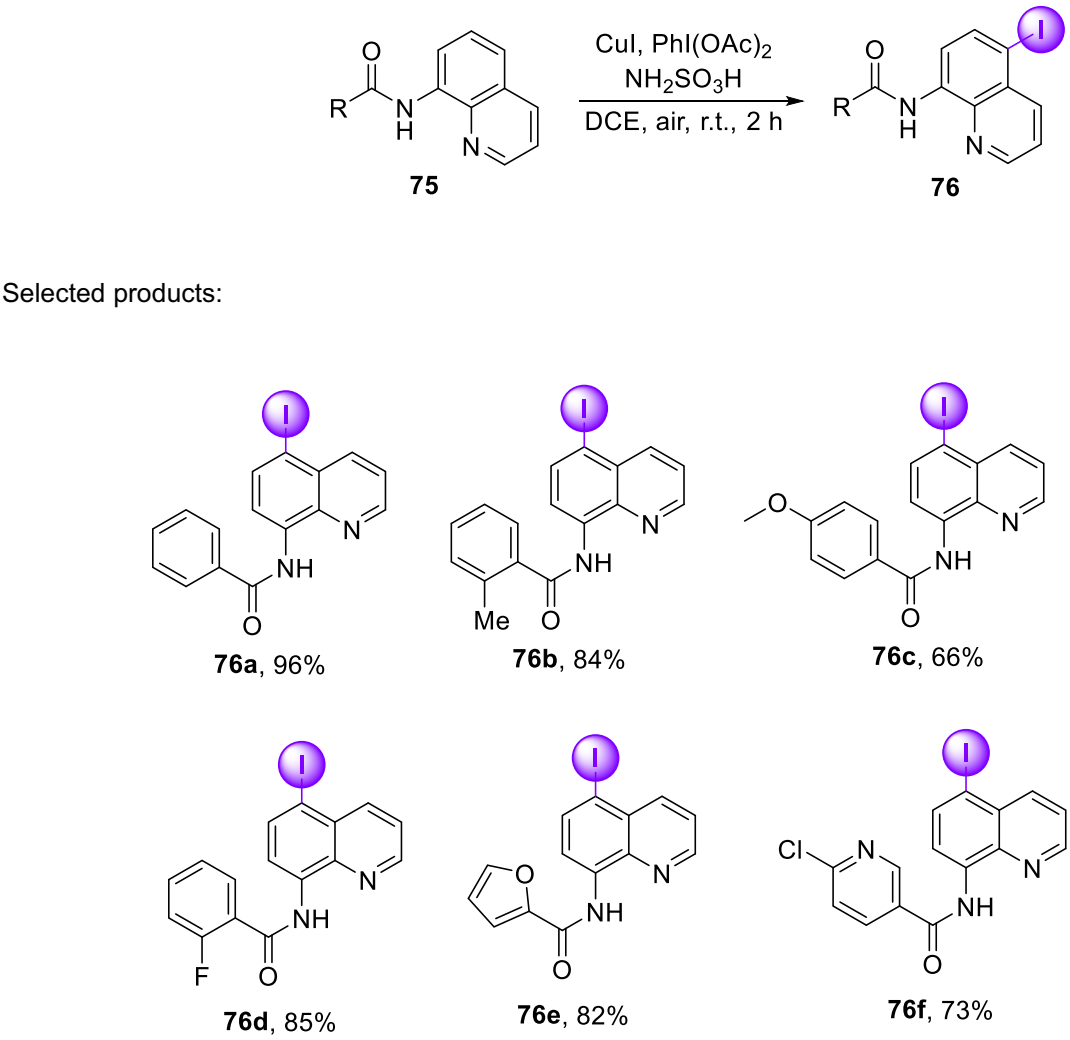
In the same year, Liu and coworkers [66] reported a site selective method for C3 alkenylation of indoles using an in situ C—H iodination strategy followed by a Heck-type coupling. The method shows broad substrate scope and tolerates a wide range of alkenes including unactivated alkenes, acryclic acid, acrylates, and vinyl sulfone as well.

He and coworkers [67] reported an electrocatalytic three-component strategy for the synthesis of 4-iodopyrazoles **68** from hydrazines **66**, acetylacetones **67**, and sodium halides. The reaction proceeds under oxidant- and additive-free conditions, with sodium iodide serving both as the halogen source and the supporting electrolyte. The method shows broad substrate scope, good functional group tolerance, and scalability, providing an environmentally friendly and practical approach to valuable iodopyrazole building blocks **68** (Scheme 25).

2.2.2 | Iodination of Six-Membered and Benzofused Heterocyclic Compounds

Pinna and coworkers [68] synthesized a series of tetraiodinated benzimidazoles as highly potent inhibitors of protein kinase CK2. Using an iodine–periodic acid system in sulfuric acid, the authors successfully prepared 4,5,6,7-tetraiodobenzimidazole (TIBI) and several 2-substituted- and *N*-1-carboxymethyl-substituted derivatives of TIBI.

In a related medicinal chemistry context, the synthesis of 5-iodopyrimidine derivatives and their evaluation for antimicrobial activity was reported [69]. Iodination of 2-benzylthiopyrimidine under basic conditions gives a key 5-iodo intermediate, which is further modified to produce a range of amino and Schiff base



SCHEME 29 | Iodination of **75** using CuI.

derivatives. Several of the iodinated compounds show good antibacterial and antifungal activity, indicating that iodine substitution at the 5-position of the pyrimidine ring plays an important role in biological activity.

Alternatively, heteroaromatic boronic acids, including pyridin-3-ylboronic acid **69**, were found to react efficiently, providing the corresponding heteroaryl iodide **70** [70] (Scheme 26).

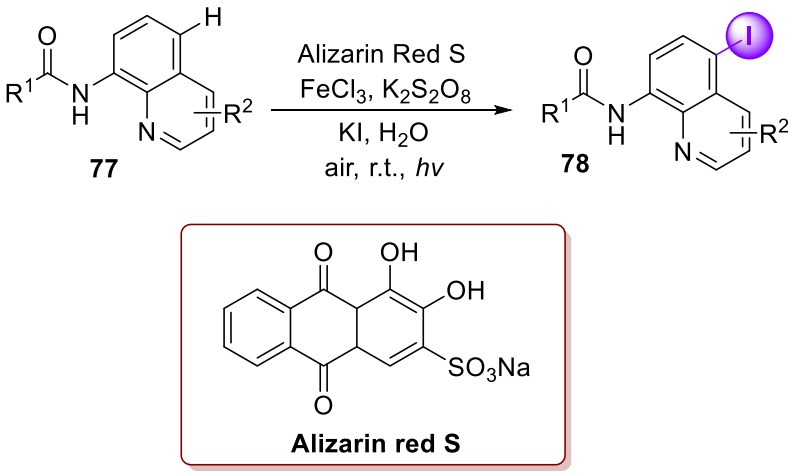
Albrecht's group [16] reported a mild and efficient one-pot method for the selective iodination of aromatic heterocycles using I_2/AgOAc system in dichloromethane. However, direct iodination of 3-methylpyridine using either the I_2/KI or I_2/AgOAc method was unsuccessful. Instead, 2-iodo-3-methylpyridine **72** was successfully prepared by reacting 2-bromo-3-methylpyridine **71** with sodium iodide and trimethylsilyl chloride in acetonitrile (Scheme 27). This transformation required reaction times longer than 7 days and elevated temperatures to achieve high yields of the corresponding product.

2,4,6-Trifluoropyridine underwent diiodination using a combination of KI, H_5IO_6 in H_2SO_4, at 55°C for 2 h affording product 2,4,6-trifluoro-3,5-diiodopyridine in 85% yield [71].

During efforts to synthesize functionalized 5-iodopyridine derivatives, the unexpected formation of iodo [1, 3]dioxolo[4,5-*c*]pyridines was observed [72]. Under basic conditions, 3-alkoxypyridin-4-ols were converted to the corresponding 5-iodo derivatives using one equivalent of iodine or tetramethylammonium dichloroiodate under basic conditions. When three equivalents of iodine were employed in chlorinated solvents, initial 5-iodination was followed by transformation of the 3-alkoxy group, leading to cyclization with the 4-hydroxyl group and formation of a 1,3-dioxolane ring. The resulting iodo [1,3]dioxolo[4,5-*c*]pyridines are proposed to arise through a radical mechanism related to the Hofmann–Löffler–Freytag reaction.

The KI–$VO(acac)_2$–H_2O_2 system in an aqueous ethanol medium, with AcOH as an additive, has been shown to effectively iodinate pyrimidinediones **73** and aromatic amines [73] under mild conditions and offers an efficient and environmentally friendly iodination method (Scheme 28).

Huang's group [74] reported a general and efficient $PhI(OAc)_2$-mediated oxidative strategy for highly regioselective C—H halogenation of quinolines **75** at the C-5 position. The method



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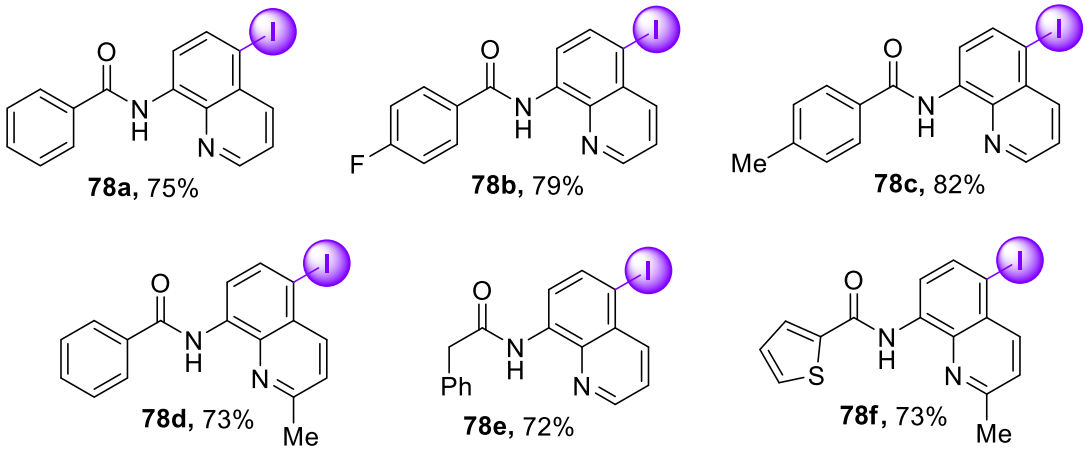
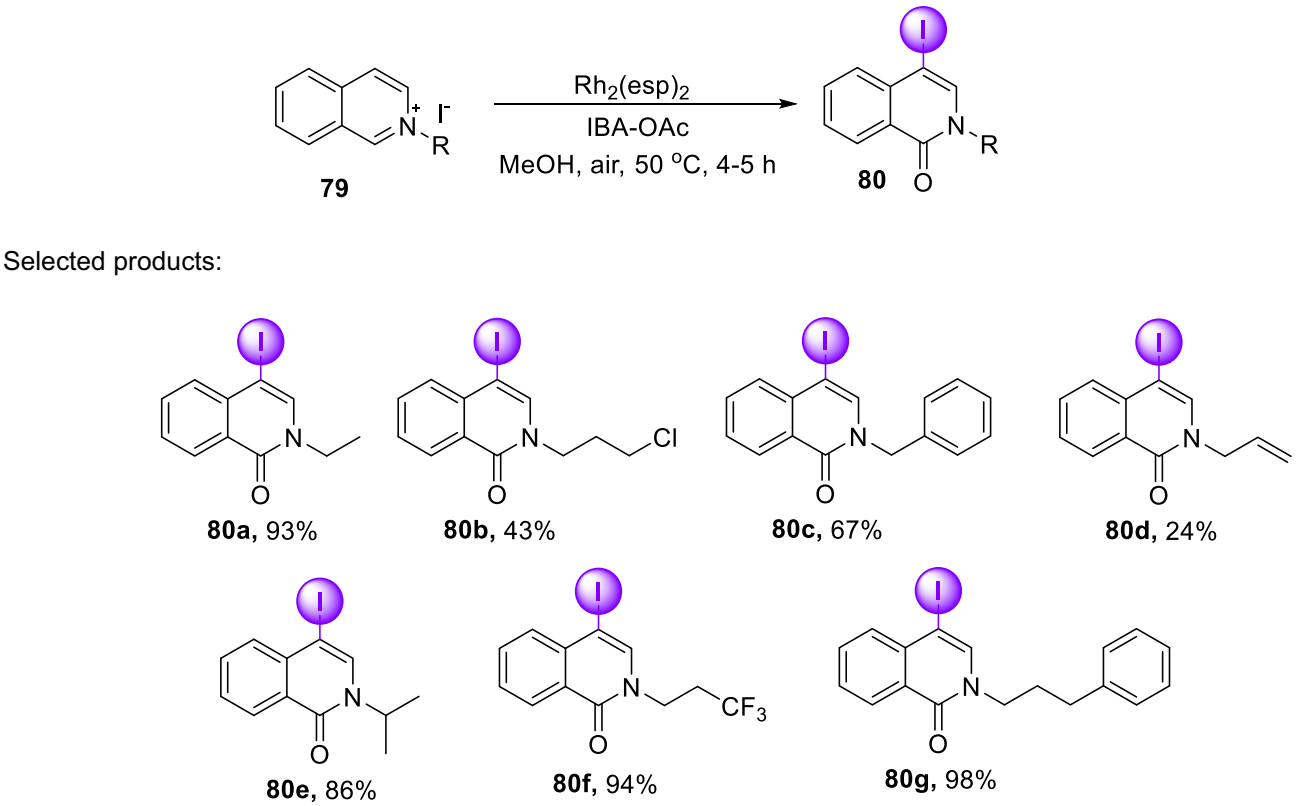


SCHEME 30 | Iodination of 8-aminoquinoline **77** catalyzed by Iron(III).



SCHEME 31 | Oxidation and iodination of *N*-alkylisoquinolinium salts **79** catalyzed by Rh_2(II, II).

employs readily available CuI as halogen sources and demonstrates high efficiency, broad substrate scope, and good functional group tolerance (Scheme 29).

Wu's group [75] reported simple, efficient, and environmentally friendly method for C5 iodination of 8-aminoquinoline **77** catalyzed by iron(III) using potassium iodide under photoredox conditions providing the corresponding products **78** in good to excellent yields. Additionally, a quinoline substrate bearing a methyl substituent was also successfully converted to the corresponding product (Scheme 30).

Wang and coworkers [76] described an iodination–oxidation strategy of isoquinolinium iodide salts **79** catalyzed by Rh_2(II, II) that efficiently provides 4-iodoisoquinolin-1(2H)-ones **80** in good to excellent yields. The practical utility of the method was confirmed by gram-scale synthesis and its application to the preparation of a key intermediate for the CRTH2 antagonist CRA-680 (Scheme 31).

Liu and coworkers [77, 78] developed a simple electrochemical method that enables the synthesis of 3-halochromones and haloarenes using NaI without external oxidants. The reaction proceeds under mild, room-temperature conditions and offers an environmentally friendly approach with broad substrate scope.

3 | Summary and Outlook

This review has summarized recent advances in the iodination of heterocyclic compounds using molecular iodine or iodide-based sources. A wide range of catalytic and non-catalytic strategies has been discussed, highlighting their scope and efficiency. The developed methods offer good selectivity and yield through different pathways, while enabling the preparation of the iodinated intermediates for further synthetic transformations. Iodine-mediated iodination continues to be a powerful and practical tool in modern heterocyclic synthesis. Despite these significant developments, further efforts toward the design of environmentally benign iodination protocols remain highly desirable. In particular, the development of reactions conducted in aqueous media or under solvent-free conditions represents a promising and attractive direction for future research.

Overall, this review is intended to provide a useful resource for both researchers and students, helping to support the development of more efficient and selective iodination methods and encouraging further work in this field. By bringing together recent advances, it offers a clearer overview of current progress. It may also help guide future studies and inspire new ideas in halogenation chemistry.

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Conflicts of Interest

The authors declare no conflicts of interest.

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