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# SYNTHESIS OF POLYMER-SUPPORTED REAGENTS AND THEIR CATALYTIC PROPERTIES AND APPLICATIONS

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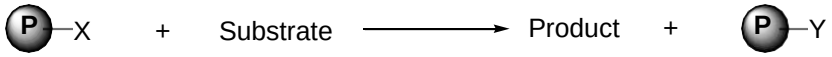
## INTRODUCTION

The polymer-supported reagents (also termed as functionalized polymers) are synthetic macromolecules having chemically bound functional groups, which may be utilized as reagents, catalysts or protecting groups in various chemical processes. The macromolecule can be linear, capable of forming a molecular solution in a suitable solvent or cross-linked, so called resin which though being readily solvated by a suitable solvent remains macroscopically insoluble. The concept of polymer-supported organic reactions has been of interest for more than 60 years. They began to be studied seriously in the 1940's and early 1950's following the commercial introduction of various organic ion-exchange resins. The later were usually sulfonated cross-linked polystyrene beads (strong acid cation-exchange resins), cross-linked beads prepared using acrylic or methacrylic acids (weak acid cation-exchange resins), or cross-linked beads containing quaternary ammonium salt residues (anion exchange-resins). Typical early studies involved using resin beads bearing sulfonic acid groups as catalysts for the reactions such as sucrose inversion, alcohol dehydration, ester hydrolysis, acetalization and acetal hydrolysis. Ion exchange resins were also used in appropriate form to achieve organic separations; for example, the bicarbonate form of an anion-exchange resin was used to separate carboxylic acid from aldehydes and ketones. Further, the use of ion-exchange materials to assist the purification of reaction products was a common task in organic reactions on polymer supports.

The study of polymer-supported reactions received an enormous boost in 1963 when Merrifield, reported the first example of solid phase peptide synthesis. Letsinger and Mahadevan also reported the synthesis of oligonucleotide which is employed extensively today in connection with genetic engineering. The result of an oligopeptide or oligonucleotide is attached to insoluble polymer beads and more appropriate residues are added one by one until the required oligomer has been assembled. The oligomer is than cleaved from the beads. These methods were first important examples of reaction involving the polymer-supported substrates. The major advantage of these is that at each stage the polymer-supported oligomer is always recovered by

simple filtration and washing the beads.

In early 1970's several research groups extended Merrifield and Letsinger's methods to other areas of organic synthesis. Hodge and Sherrington have recalled many of the developments at this time in the field of polymer-supported organic reactions. The supported species can be a substrate, a reagent or a catalyst. Many examples of organic reactions using polymer-supported substrates, reagents, catalysts or scavengers were investigated and by 1980 approximately a thousand relevant references were available. A wide variety of supports were also investigated. The importance of correct choice of reaction solvent, the ideas of site isolation, and examples of microenvironment effects were identified, studied and substantially understood. The pros and cons of using polymer-supported substrates, reagents and catalysts were clearly recognized and various types of separation processes were developed. It was evident that reactions using polymer-supported substrates were generally least attractive of these three types. A much better way was to use polymer-supported reagents and catalysts (Scheme 1.1.1).

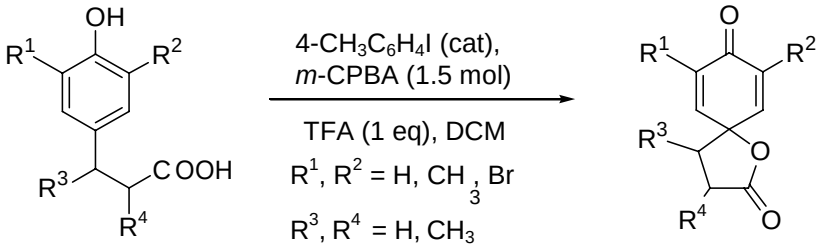



PS-reagent/catalyst Spent polymer byproduct

Scheme 1.1.1 Reaction on a polymer support

## CATALYTIC PROPERTIES OF POLYMER-SUPPORTED REAGENTS

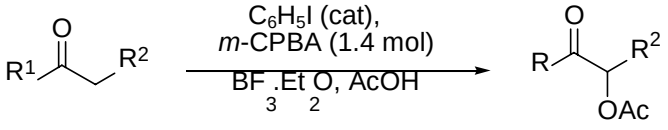
There is a growing interest in the chemistry of hypervalent iodine compounds as reflected in the vast majority of chemical transformations induced by them. Hypervalent iodine compounds containing two heteroatom ligands are generally synthesized by the oxidation of corresponding iodoarenes using various oxidizing agents e.g. peracetic acid generated *in situ* from acetic anhydride and hydrogen peroxide, sodium perborate, *m*-chloroperbenzoic acid etc. During chemical transformations, the heteroatom ligands serves as leaving group in both the ligand exchange step of iodine (III) reagent to monovalent iodine. Facile conversion of iodine (III) to monovalent iodine in reductive elimination step constitutes a driving force for chemical transformation. In general, stoichiometric amount of iodine (III) reagents are required for these chemical transformations and thus, after completion of the reaction, equimolar amount of iodoarene as waste is produced which was initially employed for the synthesis of iodine (III) reagent. If the iodoarene is reoxidized to a hypervalent iodine species *in situ*, than the transformation may need only a catalytic amount of the expensive iodoarene. Kita et al. recently introduced *m*-chloroperbenzoic acid (*m*-CPBA) as oxidant in the synthesis of novel and recyclable adamantane based hypervalent iodine reagents. This result forms the basis for the development of catalytic reactions with hypervalent iodine reagents. The same research group then reported the use of catalytic amounts of hypervalent iodine (III) reagents in the spirocyclization of various phenol derivatives (**49**). Using 5 mol% of 4-iodotoluene in combination with 1.5 equivalents of *m*-CPBA as terminal oxidant resulted in spirocyclization to lactone (**50**) (Scheme 1.2.1).




**49** **50**

Scheme 1.2.1

Ochiai et al. then successfully described α-acetoxylation of ketones with catalytic amount of iodobenzene with *m*-CPBA. Exposure of various ketones (**43**) to dried *m*-CPBA (1.4 g/eq) in acetic acid in presence of a catalytic amount of iodobenzene and $BF_3.Et_2O$ afforded corresponding α-acetoxy ketones (**51**) (Scheme 1.2.2).

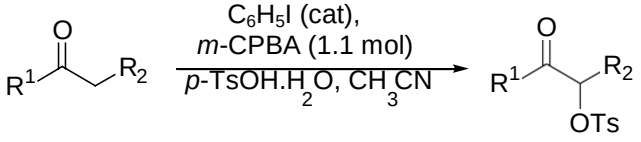



**43** **51**

$R^1$ = alkyl, allyl, aryl; $R^2$ = H, $CH_3$

Scheme 1.2.2

An extension of catalytic use of hypervalent iodine reagents in the α-oxygenation of ketones has been reported by Togo et al.[5] Various ketones (**43**) were converted to the corresponding α-tosyloxy ketones (**45**) with *m*-CPBA and *p*-toluenesulfonic acid with varying amounts of iodobenzene (Scheme 1.2.3).



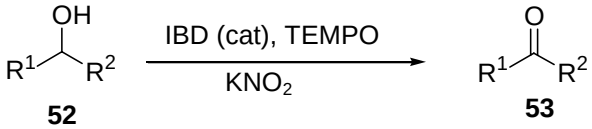

**43** **45**

$R^1$ = alkyl, cycloalkyl,aryl; $R^2$ = H, alkyl, COOR

Scheme 1.2.3

The catalytic α-tosyloxylation of ketones has also been accomplished by an ionic liquid-supported HTIB in presence of *p*-toluenesulfonic acid.

Instead of an iodoarene, a catalytic amount of hypervalent iodine reagent can also be used. Liu et al. used a catalytic amount of IBD in the presence of TEMPO (1 mol %) and potassium nitrite for the oxidation of alcohols (**52**) to carbonyl compounds (**53**) (Scheme 1.2.4).

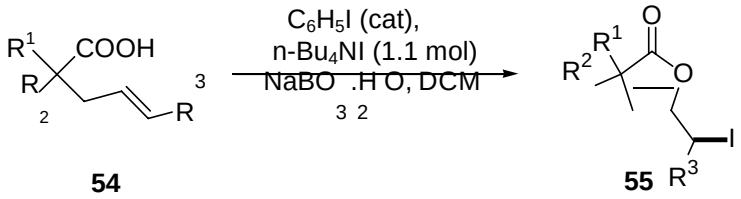



**52** **53**

$R^1$ = alkyl, allyl, aryl; $R^2$ = H, $CH_3$

Scheme 1.2.4

Likewise, a suitable terminal oxidant instead of *m*-CPBA, sodium perborate monohydrate as the stoichiometric oxidant with tetra-n-butyl ammonium iodide has also been used in iodolactonization of a variety of olefinic acids (**54**) to lactones (**55**). The species effective for iodolactonization was generated using catalytic amount iodobenzene and sodium perborate (Scheme 1.2.5).




**54** **55**

$R^1$ = H, $CH_3$, $C_2H_5$, Bn; $R^2$ = H, $CH_3$

$R^3$ = H, $CH_3$, $C_2H_5$

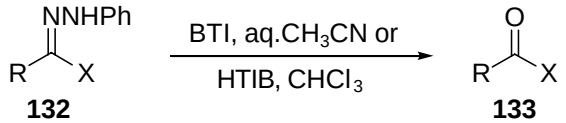
Scheme 1.2.5

Keeping in view of the importance of catalytic properties, it was thought to utilize PS-HTIB (**36**) and PS-I (**33**) in catalytic amount for the α-tosyloxylation of enolizable ketones (**43**) and to study their catalytic properties.

## IBD/PS-IBD MEDIATED SYNTHESIS OF 1,2,3-BENZOTRIAZINES, 1,3,4-OXADIAZOLES AND 2-NITROBENZYLACETATE FROM 2-NITROBEZALDEHYDE HYDRAZONES

Among the various applications of these reagents, one area of recent interest is the oxidation studies of nitrogen containing compounds such as hydrazones, acid hydrazides and related compounds. Iodine (III) oxidation reactions of these compounds results in the formation of some interesting products. In particular, aryl and aroyl hydrazones results in the formation of products depending upon the nature as well as substituent on carbonyl moiety. Some of earlier research work involving the hydrazones oxidation is described here.

Phenyl hydrazones (**132**) of keto ester or ketones on reaction with hypervalent iodine reagent bistrifluoroacetoxy iodobenzene (BTI) (**26**) or [hydroxy(tosyloxy)]iodobenzene (HTIB) (**27**) resulted in oxidative cleavage of hydrazones to regenerate the parent keto ester or ketones (**133**). The reaction involves the intermediacy of hydroxy azo compound which was further hydrolyzed to the parent carbonyl compound (Scheme 3.1).

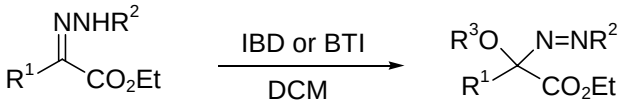



**132** **133**

R = $CH_3$, Ph; X = $CO_2Et$, Ph

Scheme 3.1

On the other hand, α-acetoxy, hydroxy, methoxy azo compounds (**135**) were readily synthesized from phenyl and methyl hydrazones (**134**) using **26** or **27** in dichloromethane or methanol (Scheme 3.2). **135** can either be hydrolyzed to the corresponding α-hydroxy phenyl azo compounds or can be transformed into important compounds, such as indazoles and pyrazoles.

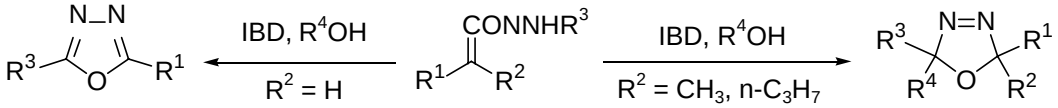



**134** **135**

$R^1$ = $CH_3$, $C_6H_5$; $R^2$ = $CH_3$, $C_6H_5$, t-Bu;
$R^3$ = H, $CH_3CO$,$CF_3CO$

Scheme 3.2

Oxidation of ketone N-acyl hydrazones (**136**) with IBD methanol or ethanol resulted in the oxidative cyclization yielding 2-methoxy-$\Delta^3$-1,3,4-oxadiazolines (**137**). However, the oxidative cyclization of aldehydes N-acyl hydrazones resulted in formation of 1,3,4-oxadiazole (**138**) in methanol or dichloromethane (Scheme 3.3).

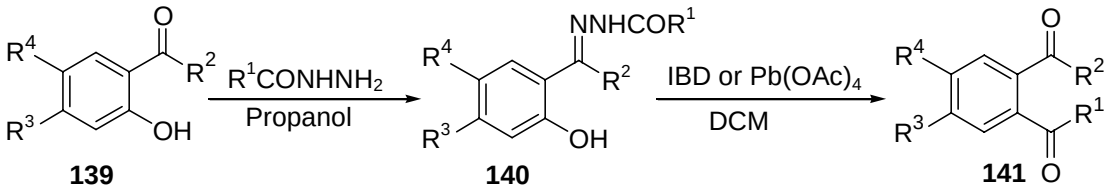



**138** **136** **137**

$R^1$ = $CH_3$, $(CH_2)_5$, n-$C_3H_7$; $R^2$ = $CH_3$, n-$C_3H_7$;
$R^3$ = $C_6H_5$, Bn; $R^4$ = $CH_3$, $C_2H_5$

Scheme 3.3

The important extension of N-acyl hydrazones oxidation was with substrates bearing a suitable substituent present *ortho* to aryl ketones that provided important products. *o*-Hydroxyarylketone-N-acylhydrazones (**140**) underwent an oxidative rearrangement resulting in an unusual replacement of the phenolic hydroxyl group with the acyl substituent to give 1,2-diacylbenzenes (**141**) using IBD as well as lead (IV) acetate (LTA) (Scheme 3.5). The rearrangement has also been found to be equally effective when PS-IBD was employed as an oxidant .

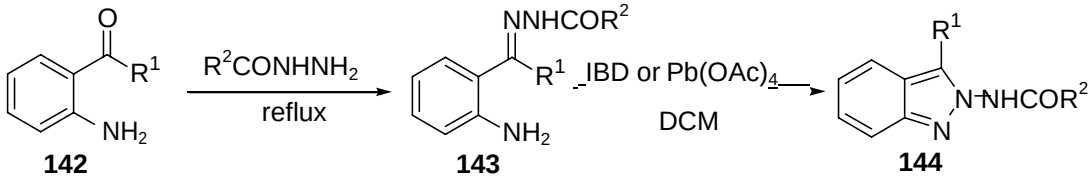



**139** **140** **141**

$R^1$ = $CH_3$, $C_6H_5$, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 2-thienyl, 2-furyl;
$R^2$ = $CH_3$, H; $R^3$ = H, $OCH_3$; $R^4$ = H, $CH_3$

Scheme 3.5

In another report, Kotali and Harris described oxidative cyclization of 2-aminoarylketone N-acylhydrazones (**143**) to 2-acylaminoindazoles (**144**) using IBD or lead (IV) acetate in dichloromethane on stirring (Scheme 3.6).

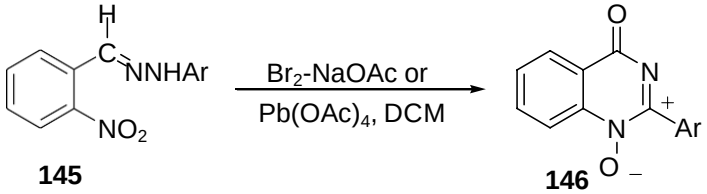



**142** **143** **144**

$R^1 = CH_3, C_6H_5$; $R^2 = CH_3, C_6H_5, 2\text{-}OHC_6H_4, OBn, OC_2H_5$

Scheme 3.6

Mild oxidation of 2-nitrobenzaldehyde arylhydrazones (**145**) with either bromine-sodium acetate or lead (IV) acetate in dichloromethane resulted in overall loss of two hydrogen atoms and production of 2-aryl-1,2,3-benzotriazine-1,4-dioxides (**146**) (Scheme 3.7).

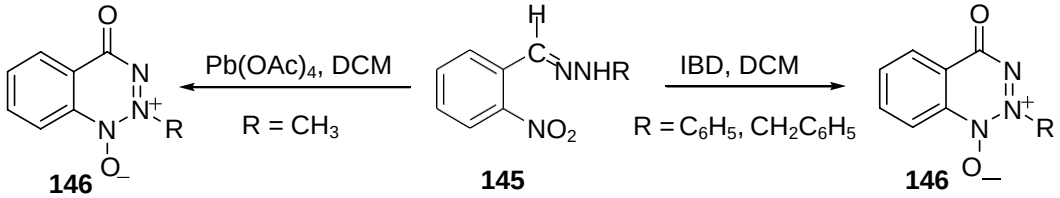



**145** **146**

Ar = $CH_3, C_6H_5, 4\text{-}BrC_6H_4, 4\text{-}CH_3C_6H_4, 4\text{-}OCH_3C_6H_4$

Scheme 3.7

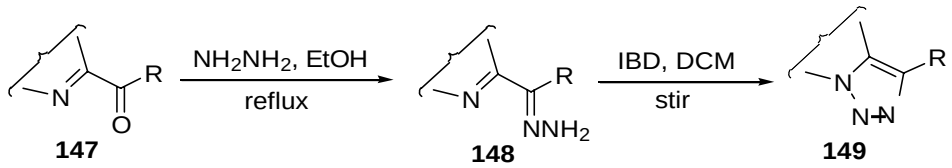
2-Nitrobenzaldehyde phenyl and benzyl hydrazones (**145**) have been oxidized using IBD or BTI to the corresponding 2-phenyl/benzyl-1,2,3-benzotriazine-1,4-dioxides (**146**) in dichloromethane. However the cyclization was not effective in case of 2-nitrobenzaldehyde methyl hydrazone with iodine (III) reagents. Here, lead (IV) acetate was effective in inducing the cyclization (Scheme 3.8).




**146** **145** **146**

Scheme 3.8

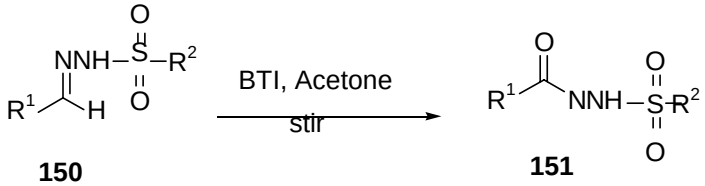
Hydrazone of nitrogen heterocyclic ketones and aldehydes have been found to afford fused 1,2,3-triazolo compounds by intramolecular cyclization of hydrazone using IBD in dichloromethane. A number of hetercocyclic ketones and aldehydes hydrazone of 2-acetylpyridine, 2-benzoylpyridine, pyridine 2-carbaldehyde and benzothiazole 2-carbaldehyde (**148**) underwent smooth cyclization to the corresponding triazolo compounds (**149**) (Scheme 3.9).




R = H, $CH_3$, $C_6H_5$

Scheme 3.9

However, aromatic N-sulfonylhydrazones (**150**) reacted smoothly with BTI (**27**) in acetone at room temperature to afford N-aroyl-N'-sulfonylhydrazines (**151**) (Scheme 3.10).

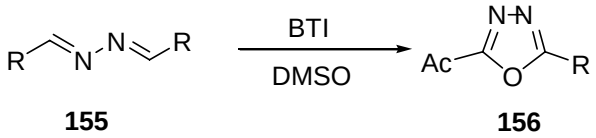



$R^1$ = $C_6H_5$, 4-$CH_3C_6H_4$, 4-$BrC_6H_4$, 4-$OCH_3C_6H_4$, 2-furyl; $R^2$ = $C_6H_5$, 4-$CH_3C_6H_4$, 4-$ClC_6H_4$

Scheme 3.10

A closely related transformation has been described to involve oxidative dimerization of acid hydrazides (**152**) with IBD. Further, diacylhydrazine (**153**) so obtained can be dehydrated in presence of thionyl chloride to 1,3,4-oxadiazoles) (**154**) (Scheme 3.11).

Recently, aldazines (**155**) have been efficiently converted to 2,5-disubstituted-1,3,4-oxadiazoles (**156**) by oxidative cyclization using BTI in dimethylsulfoxide (Scheme 3.12).




R = aryl, heteroaryl

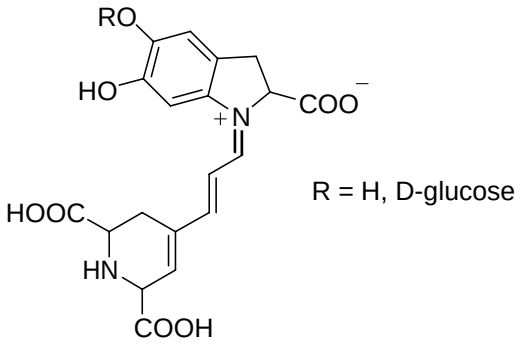
Scheme 3.12

## RING CONTRACTION OF 2-ARYL-1,2,3,4-TETRAHYDRO-4-QUINOLONES: SYNTHESIS OF *TRANS* METHYL 2-ARYL-2,3-DIHYDROINDOL-3-CARBOXYLATES

The indole ring appears in tryptophan, an essential amino acid and metabolites of tryptophan that are important in the biological chemistry of both plants and animals. In plants, indole alkaloids, including indole-3-acetic acid and its secondary metabolites are known as plant growth hormones. In animals, serotonin (5-hydroxytryptamine) is a crucial neurotransmitter in the central nervous system. The potent physiological properties of indole derivatives led to vast research for their use as medicine in the field of pharmaceutical chemistry. Indomethacin, a non-steroidal anti-inflammatory agent and pindolol, a β-adrenergic blocks, are clinically proven indole compounds. Several naturally occurring indoles are also of clinical relevance, vincristine,

a dimerize indole alkaloid and related compounds were the first of antimitotic class of chemotheraptic agent for cancer.

Dihydroindole derivatives, also called indolines, are likewise of great pharmacological interest as herbicides, precursor for the preparation of dyes, amino acids, photosensitive and thermosensitive materials and as antioxidant for cosmetics and oral hygiene products. Heterocyclic carboxamides containing 2,3-dihydroindole moiety have been found as potential antipsychotic agents. 2,3-Dihydroindoles containing 2-aminoalkyl/aryl moiety behave as selective monoamine oxidase (MAO) inhibitors and topical anti-inflammatory agents for treatment of various skin disorders including exogenous as well as endogenous dermatitis, dermatitis of unknown etiology and other cutaneous disorders with an inflammatory component respectively. Some of the other important physiological activity associated with 2,3-dihydroindole compounds are non-peptide angiotensin II receptor antagonists and potent aldose inhibitors. 2,3-Dihydroindoles are also found in nature. Betanin (**176**) a member of coloring pigments called betalains occurring naturally in plants have been found to contain 2,3-dihydroindole ring (Figure 4.1.1).

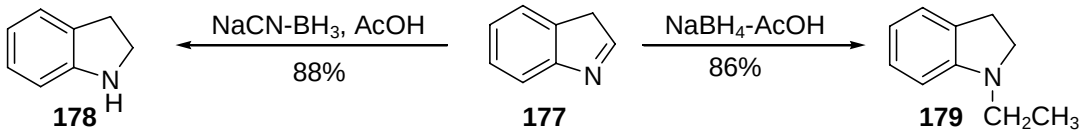



**176**

Figure 4.1.1

Further, various substituted 2,3-dihydroindole derivatives serve as potential starting building blocks for synthesis of biologically interesting indole alkaloids since they can be easily dehydrogenated. The presence of 2,3-dihydroindole moiety in a variety of natural products and potential physiological activity associated with them resulted in the development of several strategies for their synthesis.

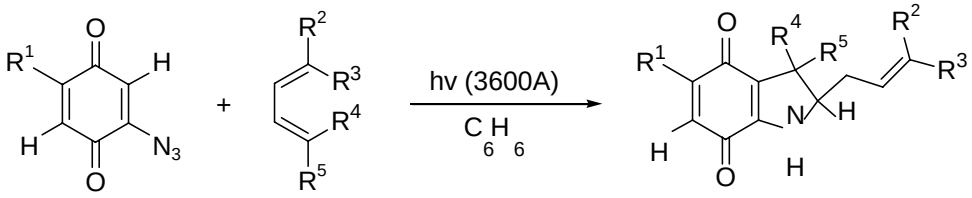
Reduction of indoles to indoline i.e. 2,3-dihydroindole has been one of the most common route employed for its synthesis. $NaBH_4$ in neat carboxylic acid reduced the indole double bond but simultaneously alkylate the nitrogen atom to afford N-alkyl-2,3-dihydroindoles (**179**). However, the use of $NaCN\text{-}BH_3$ under similar conditions avoids N-alkylation thereby permitting selective reduction of indoles to 2,3-dihydroindoles (**178**) (Scheme 4.1.1).




Scheme 4.1.1

The reduction of N-protected i.e. (N-phenylsulfonyl)indoles to corresponding (N-phenylsulfonyl)-2,3-dihydroindoles is also accomplished using $NaCN-BH_3$ in trifluoroacetic acid with good to excellent yield.

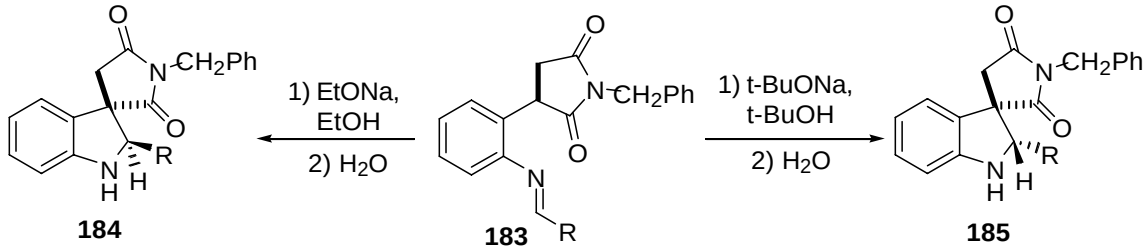
Photolysis of 2-azido-1,4-quinones (**180**) in the presence of various 1,3-dienes (**181**) resulted in the formation of 2-alkenyl-2,3-dihydroindole-4,7-diones (**182**). The reaction is regiospecific giving only that isomer having the alkenyl substituent at position-2 (Scheme 4.1.2).




$R^1$ = H, $CH_3$, $C(CH_3)_3$; $R^2$ = H, $CH_3$; $R^3$ = H, $CH_3$; $R^4$ = H, $CH_3$; $R^5$ = H, $CH_3$

Scheme 4.1.2

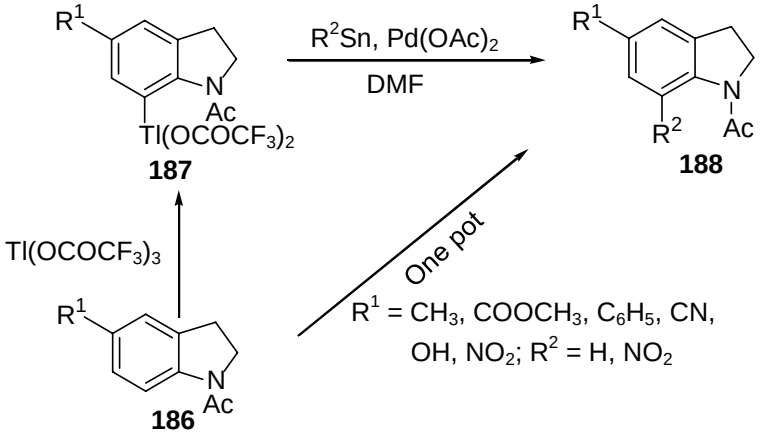
1,5-Electrocyclization of imines (**183**) underwent spirocyclization to *trans*-2,3-dihydroindoles (**184**) or *cis*-2,3-dihydroindoles (**185**) by stirring in a polar solvent at ambient temperature in the presence of a catalytic amount of a base. Treatment with EtOH/EtONa gave **184** while in case of t-BuOH/t-BuONa the corresponding **185** was obtained, thereby indicating that the stereochemistry of the spirocyclization is highly governed by the type of solvent used (Scheme 4.1.3).




R = n-$C_3H_7$, $C(CH_3)_3$, $C_6H_5$, 4-$CH_3C_6H_4$, 2-pyrrolo, *E*-CH=CH-$COOCH_3$

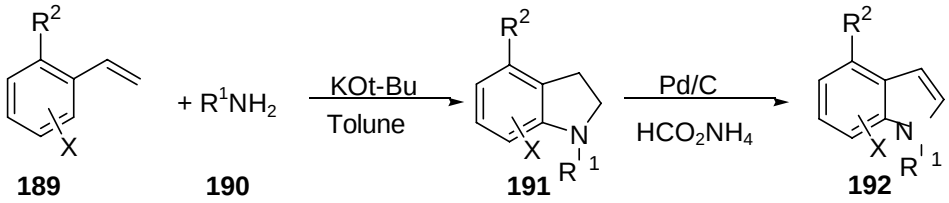
Scheme 4.1.3

Somei et al. described a simple route for obtaining 7-substituted 1-acetyl-2,3-dihydroindoles (**188**) which are suitable building blocks for synthesis of biologically interesting indole alkaloid bearing a substituent at position-7 utilizing (N-acetyl-2,3-dihydroindol-7-yl)thallium bis(trifluoroacetate) (**187**) readily available from 1-acetyl-2,3-dihydroindole (**186**) (Scheme 4.1.4).




Scheme 4.1.4

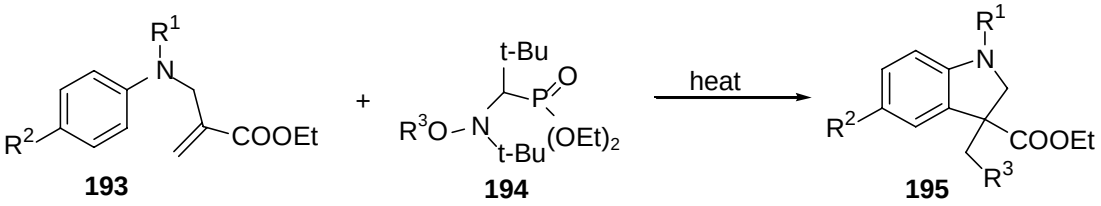
Aliphatic and aromatic amines (**190**) react with 2 and 3-chlorostyrene (**189**) in presence of potassium tert-butoxide to give N-substituted-2,3-dihydroindoles (**191**) which were easily dehydrogenated with Pd/C in $HCO_2NH_4$ to produce the corresponding indoles (**192**) (Scheme 4.1.5).




$R^1$ = $C_6H_5$, 2-$CH_3C_6H_4$, 4-$FC_6H_4$, 2-$CF_3C_6H_4$, 4-biphenyl, 1-anthracenyl; $R^2$= H, Cl; X = 2-Cl, 3-Cl

Scheme 4.1.5

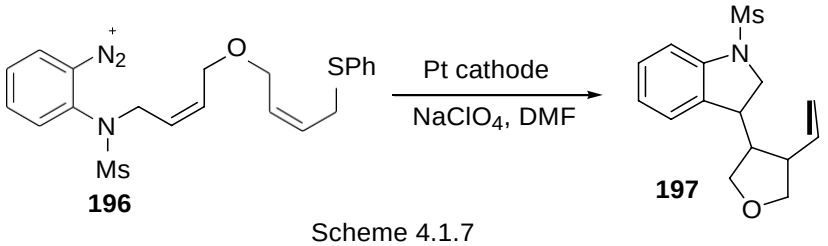
In another report, synthesis of 2,3-dihydroindoles (**195**) was accomplished through alkoxy amine-mediated radical synthesis in which radical reaction of N-alkylaniline (**193**) with alkoxyamine afforded **195** (Scheme 4.1.6).




$R^1$ = $CH_3$, Bs, BOC; $R^2$ = H, $OCH_3$, $NO_2$; t-Bu, $CH_2COOCH_3$

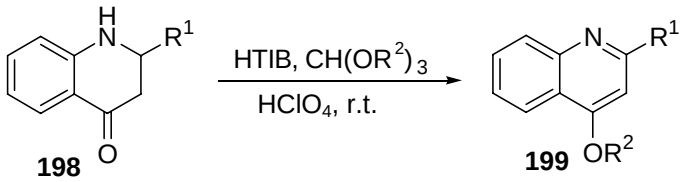
Scheme 4.1.6

Lestrat et al. described the controlled potential electrochemistry for the synthesis of N-mesyloxy-2,3-dihydroindoles (**197**) by direct electrochemical reduction of arenediazonium salts (**196**) (Scheme 4.1.7).




Scheme 4.1.7

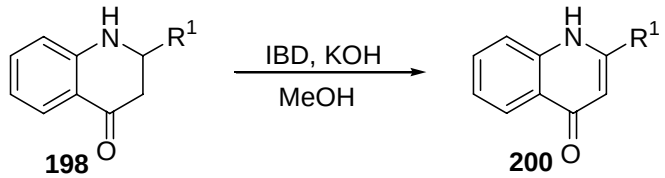
Further, oxidation of quinolones derivatives using hypervalent iodine reagents has been studied extensively and reported to afford quinoline alkaloids and other useful products depending upon the reaction conditions employed and nature of the hypervalent iodine reagent. 2-Aryl-1,2,3,4-tetrahydro-4-quinolones were (**198**) efficiently oxidized to the biologically active 4-alkoxy-2-arylquinoline (**199**) using HTIB in trialkylorthoformate in presence of catalytic amount of perchloric acid (Scheme 4.1.8).[30] Similar oxidation is also accomplished using ferric chloride hexahydrate in methanol as well as molecular iodine in methanol.




Ar = $C_6H_5$, 4-$ClC_6H_4$, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, 3,4-$(OCH_2O)C_6H_3$; $R^2$ = $CH_3$, $C_2H_5$

Scheme 4.1.8

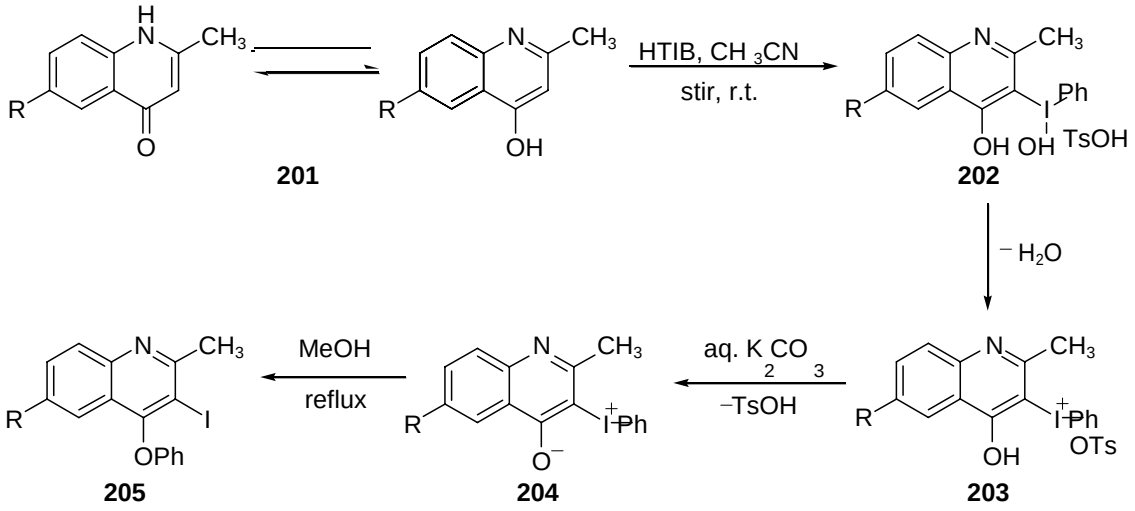
However, oxidation of **198** with IBD in methanolic potassium hydroxide resulted in dehydrogenation providing a convenient route to 2-phenyl-4-quinolone (**200**) which are otherwise available through a difficult route (Scheme 4.1.9).




$R^1$ = $C_6H_5$, 4-$CH_3C_6H_4$, 4-$ClC_6H_4$, 4-$CH_3OC_6H_4$, 3,4-$(OCH_2O)C_6H_3$

Scheme 4.1.9

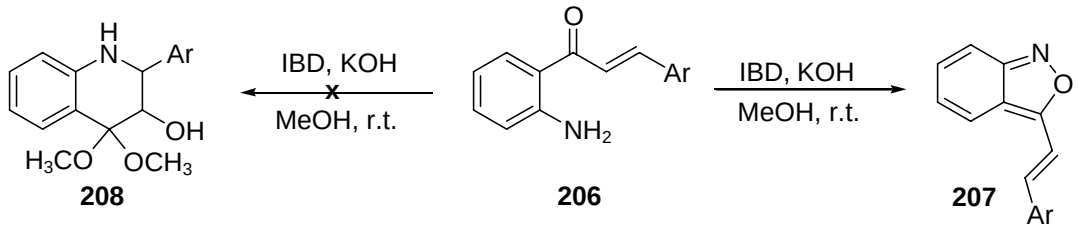
Treatment of 2-methylquinoline derivatives (**201**) with HTIB (**36**) at room temperature resulted in the formation of α-phenyliodiniumtosylate (**203**) which on basification with aqueous potassium carbonate furnished stable monocarbonyl ylides (**204**). **204** underwent intramolecular rearrangement on refluxing in methanol to afford 2-methyl-3-iodo-4-phenoxyquinoline (**205**) (Scheme 4.1.10).




R = H, $CH_3$, $OCH_3$, Cl

Scheme 4.1.10

Oxidation of 2-aminochalcones (**206**) with IBD (**26**) in methanolic potassium hydroxide afforded 3-(β-styryl)-2,1-benzisoxazole (**207**) instead of expected *cis*-3-hydroxyflavanone dimethylacetals (**208**) (Scheme 4.1.11).




Ar = $C_6H_5$, 4-$CH_3OC_6H_4$, 3,4-$(CH_2O)C_6H_3$, 4-$CH_3C_6H_4$, 4-$ClC_6H_4$, 4-$BrC_6H_4$

Scheme 4.1.11

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