Recent applications of isatin in the synthesis of organic compounds

Razieh Moradi, a Ghodsi Mohammadi Ziarani, *a and Negar Lashgari b

a Department of Chemistry, Alzahra University, Tehran, Iran
b School of Chemistry, College of Science, University of Tehran, Tehran, Iran
E-mail: gmziarani@hotmail.com gmohammadi@alzahra.ac.ir

Abstract
Isatin has been used in design and synthesis of diverse types of heterocyclic and carbocyclic compounds and considered as a valuable building block in organic synthesis. There is a diversity of multicomponent reactions of this useful reagent. This article aims to review the advances in the use of isatin as starting material in the synthesis of various organic compounds and drugs up to June 2016.

Keywords: Isatin, organic compounds, heterocyclic compounds, carbocyclic compounds
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1. Introduction

Isatin was first obtained by Erdmann\(^1\) and Laurent\(^2\) in 1840 as a product of the oxidation of indigo dye by nitric acid and chromic acid. Isatin is one of the most important heterocyclic compounds. For example, Schiff bases of isatin are used for their pharmaceutical properties.\(^3\) Oxindole as an isatin derivative represents an important class of heterocyclic compounds endowed of interesting pharmacological\(^4,5\) and biological activities such as antimicrobial,\(^6\) antitumor,\(^7,8\) antitubercular,\(^9,10\) antimalaria,\(^11\) anti-HIV\(^12\) and antibacterial activities.\(^13\) On the other hand, the chiral 3,3-disubstituted oxindole framework is a privileged motif found in various natural products and pharmaceutically active compounds.\(^14\) As a class of important 3,3-disubstituted oxindoles, 3-substituted 3-hydroxyindolin-2-ones have attracted considerable attention because of their diverse biological activities.\(^15,16\)

During recent years several review articles were published on isatins. Singh and Desta reviewed isatin as a privileged molecule in design and synthesis of spiro-fused cyclic frameworks.\(^17\) Synthesis of spiro\(^18\) and multispirono\(^19\) heterocyclic compounds from isatin were studied by Borad et al. The enantioselective reactions of isatin were also the subject of several review articles.\(^20-22\) Herein, in continuation of our studies towards isatin,\(^23-25\) and since there is a wide range of reactions that include isatin in the synthesis of organic compounds, this review presents the recent applications of isatin in the synthesis of different types of organic compounds up to June 2016.

2. Reactions at the C-3 Position of Isatin

The direct asymmetric aldol reaction between isatin derivatives 1 and acetone 2 at -35 °C in EtOH using N-
arylprolinamides has been developed and the corresponding aldol products 3 were obtained (Scheme 1). The same authors used trans-4-hydroxy-L-prolinamide as a catalyst in this reaction. In a similar reaction, α-cross-coupling aldol addition of activated olefins 4 with isatins 1 has been described in the presence of ruthenium(III) chloride and tributyltin hydride (TBTH) at room temperature to afford 3-substituted-3-hydroxy-2-oxindoles 5 (Scheme 1).

![Scheme 1](image)

**Scheme 1**

The vinylation of isatins 1 by vinyl boronic acids 6 catalyzed by CoBr2 in the presence of DuanPhos was reported for the synthesis of the tertiary allylic alcohols 7 (Scheme 2).

![Scheme 2](image)

**Scheme 2**

The alkynylation reaction of isatins 1 and aryl-substituted alkynes 8 in the presence of bifunctional guanidine/CuI as catalyst was accomplished for the synthesis of 3-substituted 3-hydroxyoxindole scaffolds 9 (Scheme 3). In another study, zink dust was also used as catalyst in this reaction.
Scheme 3

1. **R**\(^1\) = H, 4-Cl, 5-F, 5-Br, 5-I, 5-MeO, 5-CF\(_3\)O, 7-F, 7-Br, 7-Cl, 7-I, 7-CF\(_3\), 7-CF\(_3\)O
2. **R**\(^2\) = 2-FC\(_6\)H\(_4\), 3-FC\(_6\)H\(_4\), 4-FC\(_6\)H\(_4\), 3-ClC\(_6\)H\(_4\), 3-MeC\(_6\)H\(_4\), 4-MeC\(_6\)H\(_4\), 3-MeOC\(_6\)H\(_4\), CH\(_2\)C\(_6\)H\(_4\), CH\(_2\)OAC, CH\(_2\)OCOPh, CH\(_2\)O\(_3\)Bu, CH\(_2\)NHBoc, \(^{1}\)Pr, cyclopropyl, \(^{1}\)C\(_5\)H\(_{11}\), \(^{1}\)C\(_{10}\)H\(_{21}\), cyclopentyl, cyclohexyl, propenyl, octynyl, 2-methylisonimidinyl-1,3-dione

**Scheme 4**
The diastereoselective total synthesis of leucolusine 16 was described by the coupling of enantioenriched (R)-1-benzyl-3-(2-bromoethyl)-3-((tert-butylimethylsilyl)oxy)indolin-2-one 13 with 14, which gave 15 in 57% yield (Scheme 4). Precursor 13 was prepared from 12 that obtained from 3-alkyl-3-hydroxyindolin-2-one 11 by the known organocatalytic cross-aldol reaction between acetaldehyde 10 and N-benzilisatin 1. Global deprotection of 15 using tBuLi/O2 in THF at -78 °C followed by treatment with TBAF led to the formation of natural leucolusine 16 with 68% isolated yield. In another study, the 3-allyl-3-hydroxyoxindoles 18 were obtained from allylation reaction of isatin derivatives 1 and allyltrimethylsilane 17 using the (S)-difluorophosphine derived chiral Hg(OTf)2 complex as a catalyst (Scheme 4).

The diastereoselective aldol addition of allenic esters 19 to isatins 1 in the presence of AuCl3 and chiral N,N'-dioxide has been reported for the synthesis of the carbinol allenoates 20 (Scheme 5). The decrease in yield and enantioselectivity was mainly due to the steric hindrance of vicinal 4-substituted bulky halogen atoms (4-Cl, 4-Br). 5,7-Dimethyl-substituted isatin provided the best enantioselectivity.

![Scheme 5]

A series of 3-hydroxy-7-aza-2-oxindoles 23 have been synthesized in good yields and moderate to high enantioselectivity via the enantioselective Morita–Baylis–Hillman (MBH) reaction of 7-azaisatins 21 with maleimides 22 in the presence of bifunctional tertiary amine, β-isocupreidine (β-ICD) as the catalyst (Scheme 6).

Shankaraiah's group designed the synthesis of new (Z)-3-(3’-methoxy-4’-(2-amino-2-oxoethoxy)benzylidene)indolin-2-one derivatives 25 from the Knoevenagel condensation reaction of isatin derivatives 1 and 3-methoxy-4-(2-amino-2-oxoethoxy)benzaldehydes 24 (Scheme 7). The products were evaluated for their cytotoxic activity against selected human cancer cell lines of prostate (PC-3 and DU-145), breast (BT-549 and MDA-MB-231) and non-tumorigenic prostate epithelial cells (RWPE-1).
Shaker and Marzouk investigated the condensation of isatin 1 with acetohydrazide 26 to yield the oxindolinyldene 27 (Scheme 8). The newly prepared compound was tested in vitro against a panel of four human tumor cell lines, namely hepatocellular carcinoma (liver) HePG-2, colon cancer HCT-116, human prostate cancer PC3, and mammary gland breast MCF-7. It was also tested as an antioxidant.
Terada’s group developed a methodology based on the two-step sequence strategy for the synthesis of 3-aryl isatin derivatives 30 from the isatin derivatives 1 and aryl boron salts 29. The methodology involves the formation of an oxindole having a phosphate moiety 28 at the C-3 position via the [1,2]-phospha-Brook rearrangement under Brønsted base catalysis and the subsequent palladium-catalyzed cross-coupling reaction with aryl boron 29 reagents (Scheme 9).  

Scheme 9

Bajaj and co-workers reported the use of macrocyclic Ti(IV)-salen complexes as catalysts for enantioselective hydrophosphonylation (EHP) reaction of isatin derived ketimines 31 with diphenyl phosphate 32 as nucleophile. The corresponding phosphorylated products 33 were obtained in high enantioselectivity (ee up to 99%) (Scheme 10). 

Scheme 10
In another study, Su and Xu developed the synthesis of optically pure 2-oxoindolinyl-β\textsubscript{3,3}-amino esters 36 in good yields via the diastereoselective asymmetric Reformatsky-type reaction of isatin-derived chiral N-sulfinyl ketimines 34 with ethyl bromoacetate 35 (Scheme 11).

\[
\begin{align*}
\text{R} &= \text{H, 5-F, 5-Cl, 5-Br, 5-I, 5-Me, 5-MeO, 5-Pr, 6-Cl, 6-Br, 7-F, 4,6-F_2, 5-F-6-MeO} \\
\end{align*}
\]

Scheme 11

Kureshy’s group synthesized the β-nitro amines 38 from the asymmetric aza-Henry reaction of various isatin derived N-Boc ketimines 31 with nitromethanes 37 in the presence of the chiral Cu(II) dimeric macrocyclic salen complex as catalyst (ee, up to 99%). This protocol was also used for the synthesis of enantiomerically pure (S)-β-diamines 39 via asymmetric aza-Henry reaction of N-Boc ketimine 31 in two steps in good yield and high enantioselectivity (Scheme 12).

\[
\begin{align*}
\text{R}^1 &= \text{H, Cl} \\
\text{R}^2 &= \text{H, Br} \\
\text{R}^3 &= \text{Me, }^7\text{Bu, Me}_2 \\
\end{align*}
\]
Pedro’s group reported the enantioselective addition of 4-substituted pyrazolones 40 to isatin-derived ketimines 31. In this study, the authors used a bifunctional organocatalyst (a quinine-derived thiourea) to provide a variety of chiral heterocyclic compounds containing both amino oxindole and pyrazolone moieties bearing vicinal quaternary stereocenters 41 (Scheme 13).42,43

### Scheme 13

- **R**
  - **R1** = Me, Ph, Allyl, Bn, CH2OMe, CO2Et
  - **R2** = H, 5- Me, 5-MeO, 5-Cl, 5-NO2, 6-Cl, 5,7- Me2
  - **R3** = Me, Et, Bn
  - **R4** = Me, Ph
  - **R5** = Me, Ph

### Scheme 14

- **R1** = Bn, Ph3C, 4-MeOC6H4CH2, Me
- **R2** = H, 6-Br, 7-F
- **R3** = H, Me, n-C6H13, Me2C=CH(CH2)2
- **R4** = H, Me, n-C6H13, Me2C=CH(CH2)2, Ph
- **Ar** = C6H15, 4-MeC6H4, 4-i-PrC6H4, 4-MeOC6H4, 4-FC6H4, 4-ClC6H4, 4-BrC6H4, 4-IC6H4, 4-F3CC6H4, 3,5-Me2C6H3, 2,4-F2C6H3
Various α-allylated 3-amino-2-oxindoles 43a were achieved by the Barbier-type alkylation of isatin imines 31 with allylic compounds 42a using metallic barium as the promoter (Scheme 14). In a similar study, Chen and Cai described the In(OTf)3-catalyzed alkylation of ketimines derived from isatins 31 in the presence of an imidazolylpyridine ligand, L (Scheme 14).

The 2-oxindoles bearing chiral α-tertiary amines at the 3-position 46 were prepared in good yields and with high enantioselectivities via a Pd(II)/Pyrox-catalyzed addition of arylboronic acids 45 to 3-ketimine isatins 44 (Scheme 15). The absolute configuration of one of the products (R\(^2\)= H) was determined to be R and the absolute configuration of the C=N bond of the 3-ketimine isatin was determined to be E by X-ray crystallographic analysis.

**Scheme 15**

A simple and efficient way for the synthesis of a series of chiral α-trifluoromethylamines 49 with excellent yields and stereoselectivities was reported by Li and co-workers. The reaction was performed between N-2,2,2-trifluoroethylisatin ketimines 47 and MBH type carbonates 48 using β-isocupreidine (β-ICD) as catalyst. A possible mechanism of this reaction was proposed, as shown in scheme 16, β-ICD attacks the MBH carbonate 48 via an \( S_N 2' \) process (intermediate B). It behaves as a Lewis base chiral catalyst. This is followed by another \( S_N 2' \)-type process, with the isatinketimine 47 acting as an active nucleophile (intermediate A) (Scheme 16).

Elghamry and Al-Faiyz developed a new method for the synthesis of quinoline-4-carboxylic acids 51 using isatin 1 and enaminones 50 as a substitute for 1,3-dicarbonyl compounds in the Pfitzinger reaction (Scheme 17).

Microwave assisted synthesis of 4-phenyl-1,3-thiazole derivatives 54 from the reaction of isatin 1, 2-bromoethanones 52 and thiosemicarbazide 53 has been accomplished (Scheme 18). The synthesized compounds were tested for their antimicrobial activities.
R^1 = H, 4-Cl, 4-Br, 5-Me, 5-Br
R^2 = Me, Et, OMe, OEt, O'Bu
R^3 = C_6H_5, 2-ClC_6H_4, 2-MeC_6H_4, 2-MeOC_6H_4,
3-ClC_6H_4, 3-MeC_6H_4, 3-MeOC_6H_4, 4-ClC_6H_4,
4-FC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4, 4-MeOC_6H_4,
thienyl, α-naphthyl, β-naphthyl

Scheme 16

Ar= C_6H_6, 4-MeC_6H_4, 4-MeOC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4

Scheme 17

R= H, Br, F

Scheme 18
2,4-Dinitrophenol (DNP) facilitated the three component reaction of isatins 1, cyclic-amines 55 and alkynes 8 to prepare the mono-functionalized α-alkynyl-3-amino-2-oxindole derivatives 56 (Scheme 19).

\[
\begin{align*}
&\text{R}^1= \text{Me, Pr, Bu, Bn, Propargyl, Allyl} \\
&\text{R}^2= H, F, Cl, Br, I, NO_2, Me, OMe, OCF_3 \\
&\text{R}^3= H, Me
\end{align*}
\]

Scheme 19

The new indole derivative 5,5”-difluoro-1H,1’”H-[3,3’;3’,3”-terindol]-2’(1’H)-one 58 has been synthesized from the reaction of isatin 1 and 2 eq. 5-fluoroindole 57 in the presence of sulfamic acid as an efficient organocatalyst (Scheme 20). Crystal structure of the product was determined by X-ray structure analysis. In other studies, the reactions of various isatin derivatives 1 and indoles 57 were also investigated in the presence of nano SiO\(_2\) and Fe\(_3\)O\(_4\)@SiO\(_2\)@SO\(_3\)H as catalysts.

\[
\begin{align*}
&\text{NH}_2\text{SO}_3\text{H} (20 \text{ mol } \%) \\
&\text{EtOH} : \text{H}_2\text{O}
\end{align*}
\]

Scheme 20

A tunable copper-catalyzed azide-alkyne cycloaddition (CuAAC)-initiated multicomponent reaction strategy for the construction of 3-functionalized indolin-2-ones have been reported. In this regard, the reaction of isatins 1, tosyl azides 59, and terminal alkynes 8 the presence of Cul and Et\(_4\)NI was developed. This tandem process can be manipulated to proceed in three-component and four-component fashion respectively, yielding a range of (Z)-3-alkenyloxindole 60 or 3-substituted 3-hydroxyoxindole 61 compounds (Scheme 21).

Meshram and co-workers reported a one-pot four component protocol for the synthesis of a novel class of functionalized (Z)-5-(3-hydroxy-2-oxindolin-3-yl)-2-iminothiazolidin-4-ones 63 by the reaction of substituted isatins 1, amines 55, phenylisothiocyanate 62 and ethyl bromoacetate 35 in the presence of DABCO as catalyst in aqueous medium (Scheme 22). The 5-halo isatins reacted under standard condition and resulted in moderate yields of products while other 5-substituted isatins reacted smoothly to furnish the desired products in high yields. As like monosubstituted isatins, disubstituted isatins reacted in the same way and afforded comparatively less yield of desired products under standard reaction conditions.
The heterocyclic spirooxindole ring system is a widely distributed structural framework in a number of pharmaceuticals and natural products,\textsuperscript{56} including cytostatic alkaloids such as spirotryprostatins A, B, and strychnophylline.\textsuperscript{57} The unique structural array and the highly pronounced pharmacological activity displayed by the class of spirooxindole compounds have made them attractive synthetic targets (Figure 1).\textsuperscript{58-60}

3. Synthesis of Isatin-based Spiro-fused Heterocyclic Frameworks

The heterocyclic spirooxindole ring system is a widely distributed structural framework in a number of pharmaceuticals and natural products,\textsuperscript{56} including cytostatic alkaloids such as spirotryprostatins A, B, and strychnophylline.\textsuperscript{57} The unique structural array and the highly pronounced pharmacological activity displayed by the class of spirooxindole compounds have made them attractive synthetic targets (Figure 1).\textsuperscript{58-60}
3.1 Synthesis involving two-component reactions of isatins

3.1.1. Three-membered heterocycles. Hajra et al. carried out the asymmetric synthesis of spiroaziridine oxindoles 67a, 67b via the aza Corey-Chaykovsky reaction of isatin-derived tert-butanesulfynyl ketimines 64 with in situ generated sulfur ylide from trimethylsulfonium iodide 65 (or the reaction of benzyl sulfur ylides generated from S-benzyl tetrahydrothiophenium bromide 66 with chiral tertbutanesulfynyl ketimines 64) and NaH (Scheme 23).

An efficient chemoselective access to rare spiro-epoxyoxindoles 70 has been developed through the addition of the carbenoidic chloromethyllithium 69 to various N-functionalized isatins 1 followed by the ring closure (Scheme 24).
Scheme 24

3.1.2. Five-membered heterocycles. Wang et al. developed an α-regioselective asymmetric [3 + 2] annulation reaction of isatins 71 and 1-azadienes 72 for the synthesis of bulky 1,2-benzoisothiazole 1,1-dioxide motifs 73 (Scheme 25).  

\[
\text{Scheme 25}
\]

\[
\begin{align*}
\text{R}^1 &= 5-\text{Me}, 5-\text{MeO}, 5,7-\text{Me}_{2}, 5-\text{F}, 5-\text{Cl}, 5-\text{Br}, 5-\text{I}, 5-\text{CF}_3\text{O}, 7-\text{F} \\
\text{R}^2 &= \text{C}_6\text{H}_5, 3-\text{MeC}_6\text{H}_4, 4-\text{MeC}_6\text{H}_4, 2-\text{MeOC}_6\text{H}_4, 4-\text{MeOC}_6\text{H}_4, \text{4-FC}_6\text{H}_4, 2-\text{CiC}_6\text{H}_4, 4-\text{CF}_3\text{C}_6\text{H}_4, 3,4-\text{Cl}_2\text{C}_6\text{H}_3, 1-\text{naphthyl}, \text{2-naphthyl}, 2-\text{furyl}, 2-\text{styryl}, 2-\text{thienyl}, 5-\text{methylbenzo}[1,3]\text{dioxole} \\
\text{R}^3 &= \text{H}, 6-\text{Br}, 7-\text{F}, 5,7-\text{Me}_2 \\
\text{X} &= \text{SO}_2, \text{OSO}_2 \\
\text{EWG} &= \text{CO}_2\text{Me}, \text{CN}
\end{align*}
\]

Zhao and Du developed an efficient cascade Michael/Michael reaction catalyzed by a bifunctional tertiary amine–squaramide catalyst for the asymmetric synthesis of five-membered spirooxindoles containing five contiguous stereocenters 76 from the reaction of isatin derived enoates 74 and α-alkylidene succinimides 75. The products were obtained with excellent diastereoselectivities and enantioselectivities (Scheme 26).
The functionalized 3,3′-pyrrolidinyldispirooxindole derivatives 78 with three stereogenic centers, including two contiguous spiro-stereocenters were achieved from the stereoselective organocatalytic Mannich/Boc-deprotection/aza-Michael sequence reaction of isatin imines 31 and the 3-substituted oxindoles 77 employing the commercially available (DHQD)$_2$PHAL as the catalyst (Scheme 27).  

The synthesis of 3,2′-dihydropyrrolyl spirooxindoles 80 with excellent enantioselectivities (up to >99%) was accomplished by asymmetric [3 + 2] annulation of isatin imines 31 with zwitterions generated from allenyl esters as well as allenyl ketones 79 catalyzed by L-isoleucine derived bifunctional $N$-acylaminophosphine (Scheme 28).
Scheme 28

The enantioenriched spirooxindole based 4-thiazolidinones 82 were accessed through the catalytic asymmetric [3 + 2] annulation of isatin ketimines 31 with the 1,4-dithiane-2,5-diol 81 using a bifunctional catalyst followed by simple oxidation with high enantioselectivity (up to 98% ee) (Scheme 29).  

Scheme 29

3.1.3. Six-membered heterocycles. The hetero-Diels–Alder (hDA) reaction of isatins 1 with enones 83 that was catalyzed by an amine-based catalyst system composed of three molecules (an amine, an acid and a thiourea) was accomplished for synthesis of the functionalized spirooxindole tetrahydropyran derivatives 84 according to intermediates A-C (Scheme 30).
Scheme 30

The enantioselective [4 + 2] assembly of spirolactones 85 through a chiral \(N\)-heterocyclic carbene (NHC)-catalyzed remote \(\gamma\)-carbon addition of enals 83 with isatins 1 was reported by Zhou and co-workers (Scheme 31).\(^{70}\) Yao and co-workers studied this reaction using the same catalyst and base.\(^{71}\)

Scheme 31

The vinylogous aldol-cyclization cascade reaction of 3-alkylidene oxindoles 86 to isatins 1 has been achieved by using bifunctional organocatalysts in \(\text{CH}_2\text{Cl}_2\) at room temperature. According to the proposed
mechanism, first oxindole 87 was deprotonated by catalyst and generated s-cis enolate A, which then was added through the Si face to isatin 1 to give alkoxide intermediate B. After cyclization and protonation of the intermediate B, the desired product 87 was delivered and catalyst was regenerated (Scheme 32).

Scheme 32

The biologically active dihydropyrones 89 with a high level of enantioselectivities were synthesized from the hetero-Diels–Alder reaction of isatins 1 and glyoxal 88 in the presence of chiral copper catalyst (Scheme 33).

Scheme 33

The synthesis of 1-H-spiro[isoindoline-1,2’-quinazoline]-3,4’(3’H)-diones 91 has been expediently accomplished by a reaction of isatins 1 and anthranilamide 90 in the presence of sulfamic acid as an efficient
catalyst (Scheme 34). The products were found to be fluorescent with absorption in UV region (302, 362 nm) and emission in visible region (413-436 nm) with Stokes shift of 44-72 nm.

Scheme 34

Kumarswamyreddy and Kesavan used the bifunctional squaramide organocatalyst derived from L-proline in the reaction between isatylidine β,γ-unsaturated α-ketoesters 92 and pyrazolones 40 for the synthesis of dihydrospiro[indoline-3,4'-pyrano[2,3-c]pyrazole] derivatives 93 (Scheme 35).

Scheme 35

An enantioselective Michael–Michael cascade reaction for the synthesis of chiral spirotetrahydrothiopyrans 95 was studied by Wang et al. In this reaction, highly functionalized scaffolds were assembled via the reaction of chiral spiro-tetrahydrothiopyranoxindoles 94 with trans-enones 83 using the organocatalyst in excellent diastereo- and enantio-selectivities (>30:1 dr, ≥99% ee) with the creation of four consecutive stereogenic centers. The novel spiro-oxindole scaffolds were validated as a new class of p53-MDM2 protein-protein interaction inhibitors with good antitumor activity (Scheme 36).
Moradi, R. et al. reported the synthesis of 1,3-dihydro-3-ureidoformimido-2H-indol-2-ones 97 and spiro[3H-indole-3,2'('1'H)-(1,3,5)triazine]-2,4',6'(1H,3'H,5'H)-triones 98 from the reaction of isatins 1 and biuret 96 (Scheme 37). The reactions were carried out in two different methods; method A under slightly acidic conditions and method B in the presence of glacial acetic acid as reaction medium. It was observed that under both conditions compound 97 was obtained as the main product, however method B also resulted in the formation of compound 98 as a minor product.

Scheme 37

3.1.4. Seven-membered heterocycles. The quaternary aza-spirocycloheptane oxindole scaffolds 100 have been synthesized via the [4 + 3] cycloaddition reaction of MBH carbonates derived from isatin 71 and N-(o-chloromethyl)aryl amides 99 catalyzed by Lewis base and Brønsted base (Scheme 38). According to the proposed mechanism, the nucleophilic reaction of Bu₃P with MBH carbonate affords intermediate A with the concurrent release of CO₂. The in situ generated tert-butoxide anion then deprotonates intermediate A to yield the allylic phosphonium ylids B. Intermediate D is obtained by a γ-regioselective Michael type addition between allylic phosphonium ylide B and aza-α-quinonone methide C generated in situ through the Cs₂CO₃-mediated elimination of 99. Finally, intermediate D undergoes an intramolecular cyclization process to afford the desired product 100 with the regeneration of Bu₃P (Scheme 38).
Reactions involving more than two components are usually referred to as multicomponent reactions (MCRs). Multicomponent reactions have emerged as powerful synthetic strategies because of their efficiency, atom economy, high selectivity and convenient construction of multiple new bonds.79-81 These characteristics give rapid access to combinatorial libraries of complex organic molecules for efficient lead structure identification and optimization in drug discovery.82-84 This section reviews three-, four and five-component reactions of isatins that have been employed in the synthesis of three- to seven membered spiro-heterocycles bearing one or more heteroatoms.

4.1. Three-membered heterocycles
The three-component reaction of isatins 1, N-substituted aziridine 101 and 2-(trimethylsilyl)aryl triflate 102 was carried out for the synthesis of trisubstituted N-aryl α-amino epoxides 103 (Scheme 39).85
4.2. Five-membered heterocycles

Kumar and co-workers reported the microwave-assisted three-component 1,3-dipolar cycloaddition reaction of isatin 1, 1-allyl-3,5-bis(4-methoxyphenylmethylidene)piperidin-4-one 104 and thioproline 105 for the regioselective synthesis of dispiro oxindole-pyrrolothiazole-piperidones 106 (Scheme 40).86

Scheme 40

Liu et al. developed a method for the synthesis of isoxazole-fused spiropyrrrolidine oxindoles 110-112 via a 1,3-dipolar cycloaddition reaction of azomethine ylides (thermally generated in situ from isatin 1 derivatives and proline 107/ thioproline 105/ sarcosine 108) with 3-methyl-4-nitro-5-alkenyl-isoxazoles 109 (Scheme 41).87 The products showed considerable cytotoxicities against human prostate cancer cells PC-3, human lung cancer cells A549 and human leukemia cells K562.

The multicomponent 1,3-dipolar cycloaddition reaction of azomethine ylides (generated in situ from isatin derivatives 1 and sarcosine 108) with dienones 113 was carried out and novel turmerone motif fused spiropyrrrolidine oxindoles 114 were obtained in high yields and good diastereoselectivity (up to >20:1) (Scheme 42).88 The biological activity test results demonstrated that most of the compounds showed considerable cytotoxicities to cell lines of K562 and A549, showed comparably potent or even more potent than the positive control of cisplatin (up to 5.1 times).
Scheme 41

Scheme 42

Novel spiro-tethered pyrazolo[3,4-b]quinoline hybrids 117-119 from the reaction of isatin 1, α-amino acids (108, 105, 116) and 6-arylidene-pyrazolo[3,4-b]quinolin-5-ones 115, have been synthesized (Scheme 43).
A series of novel functionalized dispirooxindoles \( \text{121, 122} \) have been synthesized through 1,3-dipolar cycloaddition of an azomethine ylide formed from isatins \( \text{1} \) and various amino acids such as sarcosine \( \text{108} \) and proline \( \text{107} \) with 4-arylmethylene-2-pyrrolin-5-one \( \text{120} \) under microwave irradiation conditions (Scheme 44).\(^\text{90}\)

**Scheme 43**

![Scheme 43 Diagram](image)

\( \text{R}^1 = \text{H, Cl, Me, CN} \)
\( \text{R}^2 = \text{4-Me, 4-MeO, 4-F, 4-Cl, 2-Cl, 3-Br, 2,4-Cl}_2 \)

**Scheme 44**

![Scheme 44 Diagram](image)

\( \text{R}^1 = \text{H, Bn} \)
\( \text{R}^2 = \text{H, Cl, I, Me} \)
\( \text{R}^3 = \text{Bu, Bn} \)
\( \text{R}^4 = \text{H, Me} \)
\( \text{R}^5 = \text{H, Cl, Br, OMe} \)
The spirooxindole-pyrrolidine/piperidine fused nitrochromanes 124 were synthesized via cycloaddition reaction of isatin 1, proline 107 and nitrochromene 123 (Scheme 45). The regio- and stereo-chemical results were ascertained by X-ray crystallographic study. 

![Scheme 45](image)

The indole-based compounds 126 were obtained through the multi-component reaction of azomethine ylides (generated through condensation of isatins 1 with sarcosine 108) with 1-alkyl-3,5-bis(arylidene)-4-piperidones 125 (Scheme 46). X-ray studies of products provided good support for the regio- and stereoselectivity of the reaction. Many of the synthesized spiro-indoles exhibit antitumor properties against HeLa (cervical cancer) cell line. 

![Scheme 46](image)

The regio- and stereoselective fashion three-component 1,3-dipolar cycloaddition of azomethine ylides generated in situ from the condensation of isatins 1 and secondary amino acids (sarcosine 108/L-thioproline 105) with 3-arylideneithiocroman-4-ones 127 resulted in the formation of a series of novel dispiro compounds containing oxindole pyrrolidine/oxindolopyrrolothiazole-thiochroman-4-one hybrid frameworks 128, 129 (Scheme 47).
Mohan’s group described the synthesis of new and highly functionalized regio- and stereoselective bisoxindole-containing dispiropyrrolidinyl/thiapyrrolizidinyl hybrid molecules 131, 132 obtained through 1,3-dipolar cycloaddition reactions of azomethines (generated in situ from isatin 1 and sarcosine 108 or thioproline 105) with \((E)-3-((2\text{-methoxyquinolin}-3\text{-yl})\text{-methylene})\text{indolin-2-one dipolarophiles} 130 (Scheme 48)\). All synthesized compounds were evaluated for their in vitro antioxidant activities.

Hamama et al. described the azomethine cycloaddition reactions to the synthesis of dispiro[indoline-3,2’-pyrrolidine-3’,3’-quino] 134 using isatin 1, sarcosine 108, and \(\alpha,\beta\)-unsaturated ketone 133 (Scheme 49). From the calculations using frontier orbital theory, the authors found that the endo cycloaddition intermediate has a binding energy with 42.9 Kcal/mol more negative value than the exo cycloaddition intermediate.
Because the benzene ring of arylide and the benzene ring of azomethine ylid are parallel to each other, the endo cycloaddition intermediate is more stable than the exo cycloaddition intermediate, and the dispiro endo-cycloaddition is formed while the dispiro exo-cycloaddition product is not formed by exocycloaddition (Scheme 49).  

Scheme 49

The reaction of (2E,4E)-ethyl 5-(phenylsulfonyl)penta-2,4-dienoate 135 as a dipolarophile with in situ generated azomethine ylides from isatin 1 and sarcosine 108 derivatives in refluxing 1,4-dioxane furnished the cycloadducts 136 in good yields (Scheme 50).  

Scheme 50

Through the reaction of isatin derivatives 1, benzyl amines 55 and (Z)-3-(2-oxo-2-phenylethylidene)indolin-2-one 137 using ceric ammonium nitrate (CAN), the functionalized spirooxindole-pyrrolidines 138 were synthesized (Scheme 51). All the synthesized products showed good antimicrobial activity.
Spiro[indoline-3,2'-pyrrole] derivatives were obtained from the reaction of isatins 1, α-amino acids 108 and phenylpropionic acid esters 139 in refluxing isopropanol in high regioselectivity and yields. A plausible mechanism for this multicomponent reaction was proposed (Scheme 52).\(^{98}\) First, the condensation of isatin 1 with sarcosine 108 afforded the corresponding azomethine ylide A. Subsequently, the protic solvent of isopropanol would promote the decarboxylation of azomethine ylide A to form the 1,3-dipole B. Then, the 1,3-dipolar cycloaddition of intermediate B with methyl 3-phenylpropionate 139 results in the final product spiro[indoline-3,2'-pyrrole] 140.

Scheme 52

Shi and co-workers developed an asymmetric chemoselective 1,3-dipolar cycloaddition of azomethine ylide with imines via the three component reaction of isatin-derived imines 31, aldehydes 11 and amino-ester
in the presence of chiral phosphoric acid. In this reaction, spiro[imidazolidine-2,3'-oxindole] frameworks were obtained with high diastereo and enantioselectivities (97 : 3 er, all >95:5 dr) (Scheme 53).99

Scheme 53

Safaei-Ghomi and Zahedi reported application of Fe₃O₄-L-proline NPs as a chiral catalyst to achieve high diastereoselectivities in the asymmetric 1,3-dipolar cycloaddition reaction of isatins 1, N-arylhydroxylamines 143 and enones 83 for the synthesis of spiroisoxazolidines 144 (Scheme 54).100

Scheme 54

DBSA (p-dodecylbenzenesulfonic acid) as an efficient Brønsted acid surfactant combined catalyst facilitated the reaction of isatin derivatives 1 with primary amines 55 and thioglycolic acid 145 for the synthesis of a series of pharmacologically important spiro[indoline-3,2'-thiazolidinones] 146, 147. First, a reaction of isatin 1 and amines 55 was carried out to generate the corresponding Schiff base intermediate A and B which after the addition of thioglycolic acid in the same flask afforded the desired product (Scheme 55).101
Rajeswari et al. employed a one-pot four-component [3 + 2] cycloaddition process using N-propargylated isatin 1, coumarin-3-carboxylic acid 147, L-proline 107/sarcosine 108 and aryl azides 148 with Cu as a catalyst to prepare the selective spirooxindole pyrrolizine linked 1,2,3-triazole conjugates 149, 150 (Scheme 56).\textsuperscript{102}

Meshram’s group have demonstrated an efficient and regioselective synthesis of spirooxindoles 153 from the reaction of isatins 1, β-nitrostyrenes 151 and benzylamine 55/α-amino acids 152 under microwave irradiation (Scheme 57).\textsuperscript{103} All products were screened for antimicrobial activity and the majority of compounds showed significant activities.
Khurana's group reported the synthesis of novel heterocyclic triazolyl spirocyclic oxindoles 155 via the one-pot five component reaction of isatin 1, 1,3-dicarbonyl 154, aryl azides 148, aromatic aldehydes 11, and L-proline 107 using DBU as a catalyst in PEG-400 (Scheme 58).

Ar=Ar'= 4-NO\textsubscript{2}C\textsubscript{6}H\textsubscript{4}, 4-MeC\textsubscript{6}H\textsubscript{4}, 4-BrC\textsubscript{6}H\textsubscript{4}

Scheme 58

4.3. Six-membered heterocycles

The spiro-dihydropyridine derivatives 158 were synthesized via a one-pot multicomponent condensation of isatin derivatives 1 and malononitrile 156 with ketene aminals 157 under catalyst-free conditions in PEG-400 as a highly efficient and green biodegradable polymeric medium (Scheme 59). All compounds showed moderate to high level activity against acetyl and butyrylcholinesterase.

Scheme 59
Spirooxindoles incorporating a "medicinally privileged" indenopyridine moiety 161 have been synthesized regioselectively via multicomponent reaction of isatins 1, 1,1-dicyanomethylene-3-indanone 159 and malononitrile 156 in the presence of amines 160 (Scheme 60). The product is a spirooxindole-fused indenopyridine salt that was successfully neutralized by dilute hydrochloric acid.

Scheme 60

Treatment of isatin derivatives 1 and barbituric acids 162 with 6-amino-1,3-dimethyl uracil 163 using SBA-15-Pr-SO$_3$H as a heterogeneous nano catalyst in one pot reaction, resulted in the formation of the spirooxindole dipyrimidine derivatives 164 in high yields (Scheme 61).

Scheme 61

In another study, Mohammadi Ziarani and co-workers reported a method for the synthesis of spiro indeno[1,2-b]pyrido[2,3-d]pyrimidine-5,3'-indolines 166 through the condensation reaction of isatins 1, 6-aminouracil 163 and 1,3-indanedione 165 in the presence of SBA-15-Pr-SO$_3$H as a heterogeneous nano catalyst (Scheme 62). The same authors also reported microwave irradiation condition for this reaction.
Scheme 62

Siddiqui’s group prepared the pyrazolo-pyridopyrimidines 169 by the four-component reaction of isatins 1, 6-amino-1-methyluracil 163, β-ketoester 167 and hydrazines 168 in the presence of a catalytic amount of iodine (Scheme 63).\(^{110}\)

Scheme 63

An efficient methodology for the synthesis of substituted spiro[indolo-3,10′-inden[1,2-b]quinoline]-2,4,11′-triones 170 by the reaction of isatins 1, 1,3-indanedione 165, and enamiones 50 using La(OTf)\(_3\) as catalyst in PEG-400 under conventional heating and or ultrasonic irradiation was reported by Kumari et al. (Scheme 64).\(^{111}\)

Scheme 64

Thanikachalam and co-workers prepared a spirooxindole compound namely 2′-amino-6′-(1H-indol-3-yl)-2-oxospiro[indole-3,4′-pyran]-3′,5′-dicarbonitrile 172, from the reaction of isatin 1, 2-cyanoacetyllindole 171 and malononitrile 156 (Scheme 65).\(^{112}\)
Scheme 65

The one-pot three-component condensation of isatins 1, α or β-naphthols 173, 174, and cyclic 1,3-dicarbonyl compounds 154 in the presence of Fe₃O₄@MCM-41-SO₃H@[HMIm][HSO₄] as catalyst was successfully established for the synthesis of new derivatives of spiro[benzoxanthene-indoline]diones 175 (Scheme 66).113

Scheme 66

Shi and Yan reported a method for the synthesis of functionalized spiro[indoline-3,4'-pyrano[3,2-h]quinolines] 178 via the three-component condensation of isatins 1, 8-hydroxyquinoline 176 and malononitrile 156 or ethyl cyanoacetate 177 (Scheme 67).114

Scheme 67

A dicationic ionic liquid (IL) and K₂CO₃ were used as an efficient catalytic system for the synthesis of 4H-pyrans 179 via the three-component condensation reaction of isatin derivatives 1, malononitrile 156, and 1,3-dicarbonyl compounds 154 in water (Scheme 68).115 This reaction has been widely studied and different
catalysts such as [Amb] L-proline,\textsuperscript{116} tetrabutylammonium bromide (TBAB),\textsuperscript{117} boron nitride supported iron oxide (BN@Fe₃O₄),\textsuperscript{118} Al-ITQ-HB,\textsuperscript{119} [bmim]OH,\textsuperscript{120} Fe₃O₄,\textsuperscript{121} carbon nanotube (CNT),\textsuperscript{122} NaOAc,\textsuperscript{123} CuFe₂O₄ nanoparticles\textsuperscript{124} and trisodium citrate dihydrate\textsuperscript{125} were used in this reaction.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme68.png}
\caption{Scheme 68}
\end{figure}

The preparation of spiropyran derivatives \textbf{180} using silica-bonded 1,4-diazabicyclo[2.2.2]octane-sulfonic acid chloride (SBDBSAC) as a catalyst in multicomponent reaction of isatin derivatives \textbf{1}, barbituric acids \textbf{162}, and 1,3-dicarbonyl compounds \textbf{154} was reported by Moosavi-Zare and co-workers (Scheme 69).\textsuperscript{126}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme69.png}
\caption{Scheme 69}
\end{figure}

The synthesis of chiral, enantioenriched spiro(indoline-pyrimidine)-dione derivatives \textbf{182} from the asymmetric, Biginelli-like reaction of \textit{N}-substituted isatins \textbf{1}, urea \textbf{181} and \textit{β}-ketoesters \textbf{167} using BINOL-derived phosphoric acid as a catalyst has been studied by Stucchi \textit{et al.} (Scheme 70).\textsuperscript{127}
Scheme 70

A variety of spirooxindole derivatives 184 were synthesized by a facile one pot, three-component protocol using isatin 1, isatoic anhydride 183 and amines 55 in the presence of CuO–Pd nanoparticles as catalyst. The nucleophilic addition of aniline 55 to isatoic anhydride 183, in the presence of the CuO–Pd NPs, followed by decarboxylation, produced 2-aminobenzamide A. The condensation of A with isatin 1, in the presence of CuO–Pd NPs, gave imine B, which on intramolecular cyclization gave the final product 184 (Scheme 71). 

Scheme 71
Pardasani and co-workers studied a novel three-component reaction for the synthesis of spirobenzimidazoquinazolinones 186 via the reaction of isatins 1, dimedone 154 and 2-aminobenzimidazole 185 under microwave irradiation (Scheme 72). This one-pot process involves the formation of one C–C and two C–N bonds during the synthesis of the spiro-compounds as confirmed by X-ray analysis.

Scheme 72

Alizadeh and Moafi developed a three-component domino reaction of isatin derivatives 1, 2-aryl-2-oxoethyl thiocyanates 187 and hydrazonoyl chlorides 188 that provides a convenient method for the synthesis of 4′H-spiro[indole-3,5′-[1,3,4]thiadiazin]-2(1H)-ones 189 (Scheme 73).

Scheme 73

Novel steroidal dihydropyridinyl spirooxindoles 192 were synthesized by the multicomponent reaction of isatins 1, pregnenolone (PREG) 190, malononitrile 156 and ammonium acetate 191 (Scheme 74). MTT assay indicated that some of these compounds exhibited moderate to excellent cytotoxic activity against the tested cancer cell lines. The cytotoxic activities varied greatly depending on the position and electronic nature of substituents on the isatin nucleus and N-benzyl moieties.
Rajanarendar et al. used p-toluene sulfonic acid (p-TSA) as an efficient catalyst in the reaction of isatin derivatives 1, 1,3-indanedione 165 and 4-amino-3-methyl-5-styrilisoxazole 193 for the synthesis of isoxazolylspiro[diindeno[1,2-b;2',1'-e]pyridine-11,3'-indoline]-2',10,12-triones 194 (Scheme 75).\textsuperscript{132}

**Scheme 74**

Oxalic acid dihydrate: proline (LTTM) promoted the synthesis of spiro[diindeno[1,2-b:2',1'-e]pyridine-11,3'-indoline]-triones 195 in the reaction of isatins 1, 1,3-indanedione 165 and anilines 55 as starting materials (Scheme 76).\textsuperscript{133}

Shaabani et al. studied the synthesis of fully substituted naphthyridines 199 through the domino reaction of isatin derivatives 1, diamines 196, 1,1-bis(methylthio)-2-nitroethylene 197 and 2-aminoprop-1-ene-1,1,3-tricarbonitrile 198 using a deep eutectic solvent (DES) (Scheme 77).\textsuperscript{134}
Shrestha et al. reported a one-pot synthesis of biologically spiro[indoline-3,4′-pyrano[2,3-c]pyrazole] derivatives 200 using CeO$_2$ nanoparticle-catalyzed four-component reaction of isatins 1, β-ketoesters 167, phenylhydrazines 168 and malononitrile 156 in water (Scheme 78).$^{135}$ In another study, Fe$_3$O$_4$@SiO$_2$ was used as the catalyst of this reaction.$^{136}$
The synthesis of 2-hydroxy-3-[(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)(phenyl)methyl]-naphthalene-1,4-dione derivatives 202 has been developed through a one-pot, four-component reaction of isatin 1, 2-hydroxy-1,4-naphthoquinone 201, hydrazine 168 and β-ketoester 167 catalyzed by MgCl$_2$ in ethylene glycol (Scheme 79).

Scheme 79

4.4. Seven-membered heterocycles
Condensation of isatin 1 with a C,N-1,6-binucleophile generated in situ from o-aminobenzaldehyde 11 and 2-methylindole 57 through a Mannich-type reaction was established for the synthesis of a quinoline-fused 1-benzazepine derivative 203 (Scheme 80).

Scheme 80

5. Synthesis of Isatin-based Spiro-fused Carbocyclic Frameworks
Zhan et al. investigated the asymmetric annulation reactions of Morita–Baylis–Hillman carbonates, derived from isatins 71 and 2-alkyldene-1H-indene-1,3(2H)-diones 165, catalyzed by various chiral Lewis bases, which resulted in a switch in chemo- and diastereoselectivity. While [2 + 1] reactions catalyzed by chiral tertiary amines, derived from cinchona alkaloids, produced densely substituted cyclopropanes 204, diastereodivergent
[3 + 2] annulations generated bis(spirocycl)ic oxindoles 205 by employing either a chiral phosphine or a DMAP-type catalyst (Scheme 81).

Scheme 81

Pepsin was used as a biocatalyst in the domino Knoevenagel/Michael/Michael reaction for the synthesis of spirooxindole derivatives in methanol. A wide range of isatins 1 and enones 83 in reaction with malononitrile 156 provided spirocyclic oxindoles 206 in yields of up to 99% and oxindoles 207 in trace yields with diastereoselectivity up to >99:1 dr (Scheme 82). Reactions with isatins bearing an electron-donating group in the 5-position gave better yields than those bearing a strong electron-withdrawing group in the 5-position. The position of substituents also had effects on the reaction yield. The isatins with a substituent in the 5-position gave higher yields than those with a substituent in the 1- or 7-position.

Scheme 82
Hegade and co-workers developed an organocatalyzed pseudo four-component reaction of isatin derivatives 1, cyclohexanone 208, and malononitrile 156 in the presence of a catalytic amount of DABCO for the synthesis of functionalized spirooxindoles 209 (Scheme 83).\(^{141}\)

![Scheme 83](image)

### 6. Miscellaneous Reactions

From the reaction of isatin 1 and thiosemicarbazide 53 through multiple steps (involving the intermediates A-E) a series of semicarbazones containing 1,3,4-thiadiazino and indole rings 210 were synthesized (Scheme 84).\(^{142}\) All the newly synthesized compounds were investigated for anticonvulsant activity.

![Scheme 84](image)

A unique two-carbon ring expansion of isatins 1 has been achieved to conveniently construct the functionalized dibenzo[b,d]azepin-6-one scaffolds 212 while one carbon atom is from the N-substituent of...
pyridinium bromide \(211\) and the other is from indene-1,3-dione \(165\). The possible reaction mechanism for two-carbon ring expansion has been shown in scheme 85. Pyridinium bromide \(211\) was first deprotonated to a pyridinium ylide under the basic conditions. The Michael addition of pyridinium ylide to the condensation product \(A\) resulted in the formation of zwitterion \(B\) without other regio-isomers, and this might have resulted from the more electron-deficient 3-position on the isatin \(1\) than the 2-position of indan-1,3-dione \(165\). The following proton transfer gave a new zwitterion \(C\), and the intramolecular nucleophilic addition of the carbon anion to the 2-carbonyl group of the isatinyl moiety afforded a cyclopropyl intermediate \(D\). The less strong electron-withdrawing nature of \(R^2\) groups such as \(p\)-nitrobenzyl makes this transfer hard to occur, and this multi-component reaction stops at this stage. The re-opening of cyclopropane oxide \(D\) leads to the attack of the newly generated carbon anion on the carbonyl group in the indene-1,3-dione \(165\). The resulting cyclopropyl oxide \(E\) further re-opened and the removal of pyridine afforded cyclopropane \(F\). The following cyclopropane reorganized to the ring-expanded product \(212\) (Scheme 85).\(^{143}\)

![Scheme 85](image-url)
The spiro[pyrrolo-4,10'-indenol[1,2-b]quinolin]-3-carboxylate compounds 213 were obtained from the reaction of isatin derivatives 1, amines 55, β-ketoesters 167 and indane-1,3-dione 165 with activated alumina balls (3–5 mm diameter) as a catalyst under neat reaction conditions (Scheme 86). Except for n-butylamine (which resulted in lower yields), the products were obtained in good to excellent yields (72–92%) whether there is an electron-donating or –withdrawing substituent on the aromatic ring. The substituted isatin derivatives with Cl and Br at the 5-position also reacted efficiently to give high yields.

![Scheme 86](image)

**R¹ = H, Allyl, Bn, Me, CO₂Me, CO₂Et, ÑBu**

**R² = H, Cl, Br**

**R³ = H, 4-MeC₆H₄, 4-MeOC₆H₄, 4-BrC₆H₄, 4-ClC₆H₄, 3,4-Me₂C₆H₃, 3-CO₂HC₆H₄, 4-CO₂HC₆H₄, 3-MeC₆H₄, 2,2-PrC₆H₄, iPr, ÑBu**

**R⁴ = CO₂Et, CO₂Me**

### 7. Conclusions

Isatin is one of the important heterocyclic structures with special significance for the synthesis of organic compounds. Schiff bases of isatin, 3,3-disubstituted oxindoles and spirooxindoles are some important structures that can be synthesized using isatin as an starting material. More importantly, most of these compounds exhibit biological and pharmaceutical activities. In recent years, isatin has been widely used in the synthesis of a variety of organic compounds. Due to the widespread use of isatin in organic reactions and pursuant to our previous studies, herein we have an overview of recent applications of isatin in the synthesis of organic compounds up to June 2016.

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### Abbreviations

- DABCO: diazabicyclooctane
- DBU: diazabicycloundecene
- DCE: dichloroethane
- DCM: dichloromethane
- DMF: dimethylformamide
- EG: ethylene glycol
- MTBE: methyl tertiary-butyl ether
PEG: polyethylene glycol
TBAF: tetrabutylammonium fluoride
TBSOTf: tert-butyldimethylsilyl trifluoromethanesulfonate
TFA: trifluoroacetic acid
THF: tetrahydrofuran

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**Authors Biographies**

**Ghodsi Mohammadi Ziarani** was born in Iran, in 1964. She received her B.Sc. degree in Chemistry from Teacher Training University, Tehran, Iran, in 1987, her M.Sc. degree in Organic Chemistry from the Teacher Training University, Tehran, Iran, under the supervision of Professor Jafar Asgarin and Professor Mohammad Ali Bigdeli in 1991 and her Ph.D. degree in asymmetric synthesis (Biotransformation) from Laval University, Quebec, Canada under the supervision of Professor Chenevert, in 2000. She is Full Professor in the Science faculty of Alzahra University. Her research interests include organic synthesis, heterocyclic synthesis, asymmetric synthesis, natural products synthesis, synthetic methodology and applications of nano-heterogeneous catalysts in multicomponent reactions.
Razieh Moradi was born in 1990 in Lorestan, Iran. She obtained her B.Sc. degree in Chemistry from the University of Lorestan (2012) and her M.Sc. degree in Organic Chemistry at Alzahra University under the supervision of Dr Ghodsi Mohammadi Ziarani. She is currently Ph.D. student in Organic Chemistry at Alzahra University under the supervision of Dr Ghodsi Mohammadi Ziarani. Her research field is on the synthesis of heterocyclic compounds based on isatin and application of nano-heterogeneous catalysts in organic synthesis and multicomponent reactions.

Negar Lashgari was born in 1985 in Tehran, Iran. She received her B.Sc. degree in Applied Chemistry from Teacher Training University, Tehran, Iran (2008) and her M.Sc. degree in Organic Chemistry at Alzahra University, Tehran, Iran (2011) under the supervision of Dr Ghodsi Mohammadi Ziarani. She is currently working towards her Ph.D. in Nano-Chemistry at University of Tehran under the supervision of Dr Alireza Badiei and Dr Ghodsi Mohammadi Ziarani. Her research field is synthesis and application of nano-heterogeneous catalysts in multicomponent reactions.