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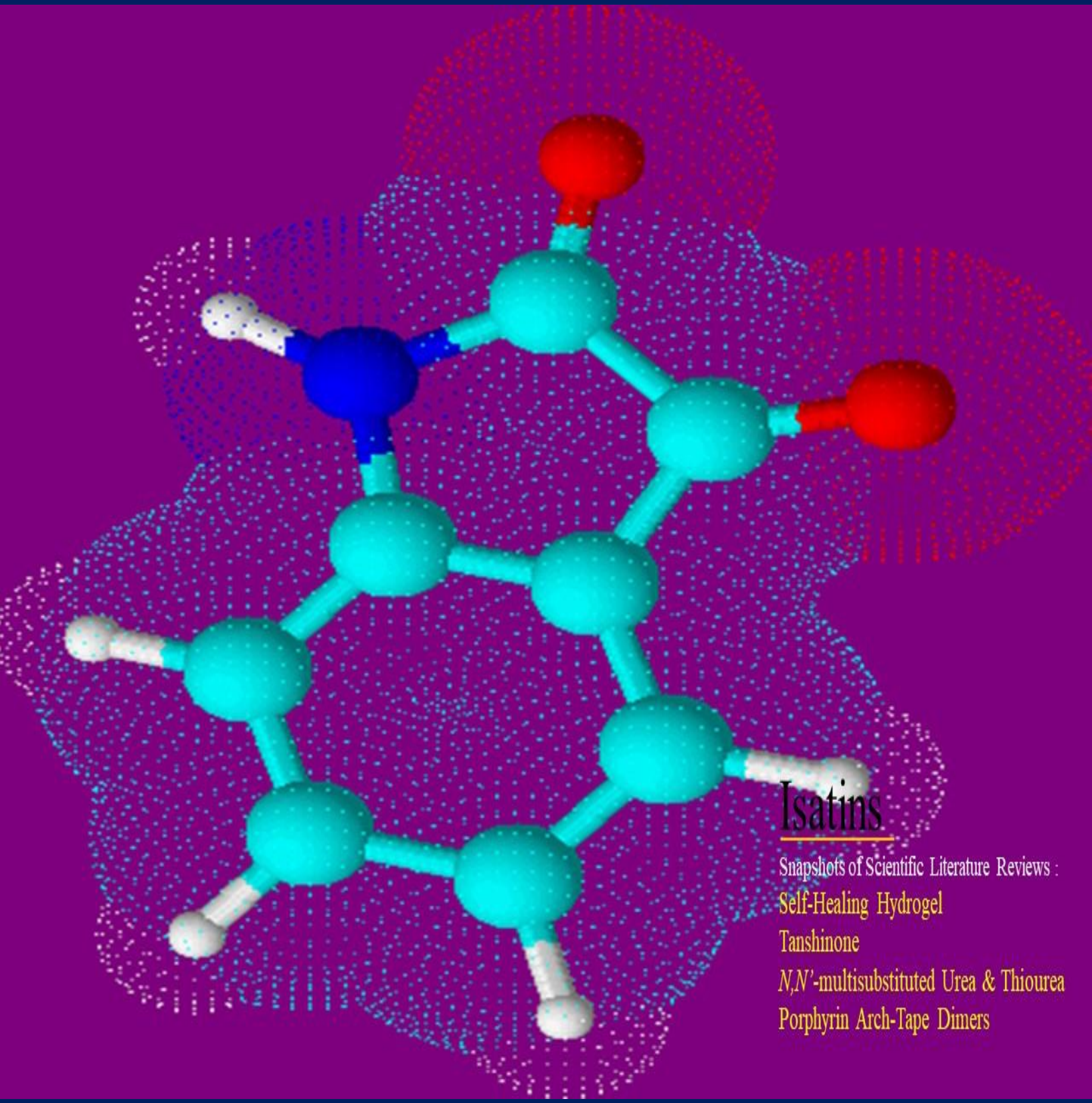
Insights

SCIENTIFIC LITERATURE REVIEW

ISSN 2590-0811

September 2018 | volume 1 | number 3



Isatins

Snapshots of Scientific Literature Reviews :

Self-Healing Hydrogel

Tanshinone

N,N'-multisubstituted Urea & Thiourea

Porphyrin Arch-Tape Dimers

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SCIENTIFIC LITERATURE REVIEW

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Recent Approaches of the Utility of Isatin as a Precursor for the Synthesis of Complex Polycyclic Compounds

Atef S. Iskander

Isatins are among the most important families of nitrogen-containing heterocycles which their structural framework constitute frequently the core unites of a wide variety of natural products, pharmaceuticals and other heterocycle molecules. The milestone advance in isatin is related to the reactivity of carbon-3 of the ring which enables to construct complex polycyclic compounds. Owing to the privileged nature of this structural motif and its focal role as progenitor to other classes of biologically active heterocycles, considerable attention has been devoted to exploiting the chemistry and bioactivity of this highly diversifiable molecule. This brief review covers the recent progress in the modification of carbon-3 of isatins.

Isatins have attracted considerable attention in organic synthesis for their potential applications in both the dye and pharmaceutical industries. Since their discovery in the year 1841 by Erdman and Laurent[1] as a product from the oxidation of indigo by nitric and chromic acids, a great number of studies have been undertaken to improve the synthetic pathways of isatins and their performance as well as to expand the range of isatin transformations in the synthesis of diverse complex heterocyclic compounds. The milestone feature of isatin consists in the α-keto amide that is present in its structural framework which allows the carbon on the 3-position of the ring to be susceptible to attack by nucleophiles producing oxindole derivatives. This structural framework constitutes the core unites of many natural products and pharmaceutically active compounds.

In order to create the diversity necessary to construct complex heterocyclic compounds based on isatins as building blocks, strategies have generally relied upon: (i) nucleophilic addition at position C-3 of isatin ring, which may provide an opportunity for further elaboration of the products by a cyclization

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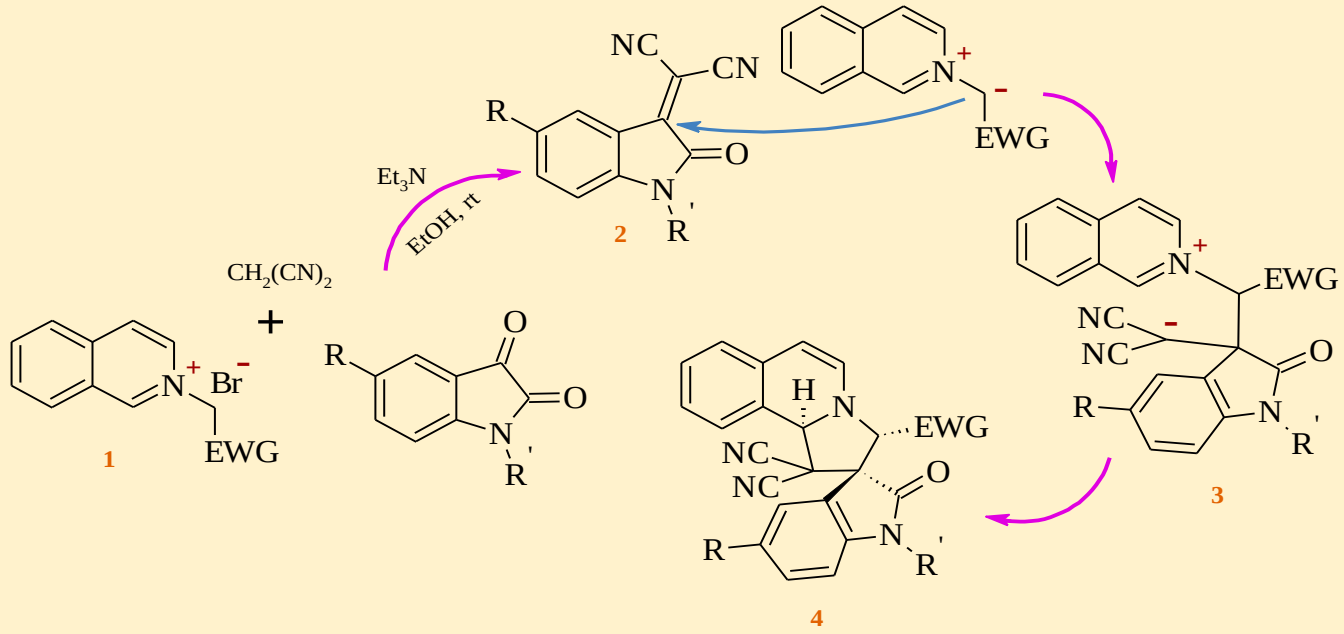
process; or by a spiro-annelation at position C-3 to produce spiro-oxindole; or (ii) oxidation of the heterocyclic ring to form isatoic anhydride followed by further transformations; or (iii) reduction of the heterocyclic ring to yield indole derivatives; or (iv) opening the heterocyclic ring by nucleophilic substitution at position C-2 which may be followed by intramolecular or intermolecular *exo-tris* cyclization.

This review highlights recent modifications of C-3 of isatins in a number of miscellaneous reactions based on the key transformation step involved.

Reactions Based on 1,3-Dipolar Cycloaddition

Azomethine ylides have widespread utility not only in 1,3-dipolar cycloaddition reactions to construct 5-membered heterocycles[2], but also in the formation of other heterocyclic compounds, such as formation of 7-membered ring and [1,7]-electrocyclizations.[3-7] The cyclic nitrogen *N*-ylides, such as pyridinium, thiazolium, quinolinium, isoquinolinium methylides are a group of reactive azomethine ylides, which can be generated from the deprotonation of their corresponding iminiums salts and benzo-fused analogs with *N*-methyl group connecting with powerful electron-withdrawing groups. On the other hand, spiro-oxindoles compounds display interesting biological properties and have attracted considerable attention owing to their unusual cage-like structures. Yan and co-workers reported an interesting three-component reaction of isoquinolinium salts **1** with isatin and malononitrile (Scheme 1).[8] The reaction proceeded in ethanol in the presence of trimethylamine as base at room temperature to afford functionalized spiro[indoline-3,2′-pyrrolo[2,1-*a*]isoquinolines] **4** via the intramolecular coupling of cyclic iminium ion with the carbanion of intermediate **3** which was generated through Michael addition of the isoquinolinium ylide to isatylidene malononitrile **2**. In this reaction, trimethylamine promoted the condensation of isatin with malononitrile to form intermediate **2**, while isoquinolinium ylide was produced *in situ* from basic deprotonation of its corresponding salt.



Scheme 1: Three-component synthesis of spiro[indoline-3,2′-pyrrolo[2,1-*a*]isoquinolines].

Generally, multicomponent reactions are characterized by their high degree of atom economy. They have several advantages, for example, the simplicity of a one-pot procedure, a wide variety of possible structural variations, easy synthesis of complicated products, and a large number of accessible compounds.[9]

Most of spirocyclic compounds contain one or more chiral centers which are important as such structures are involved in many biological activities against a variety of targets. For instance, chiral 3-amino-3-phosphonyl-substituted oxindole derivatives that bearing a quaternary stereogenic center at the C3-position have become important synthetic targets. Kim and co-workers reported an enantioselective addition of diphenyl phosphonate to ketimines derived from isatins **5** catalyzed by binaphthyl-modified squaramide-tertiary amine **6** in ethyl acetate at 0 °C (Scheme 2).[10] Chiral 3-amino-3-phosphonyl-substituted oxindole derivatives **8** were obtained in high yields (70-94 %) and excellent enantioselectivities (up to 99% ee). The reaction proceeded by the activation of isatin by squaramide moiety through hydrogen bonding, whereas diphenyl phosphonate is activated by the basic nitrogen atom in tertiary amine of the catalyst. Then, diphenyl phosphonate attacks the *re*-face of C-3 of isatin **7**.

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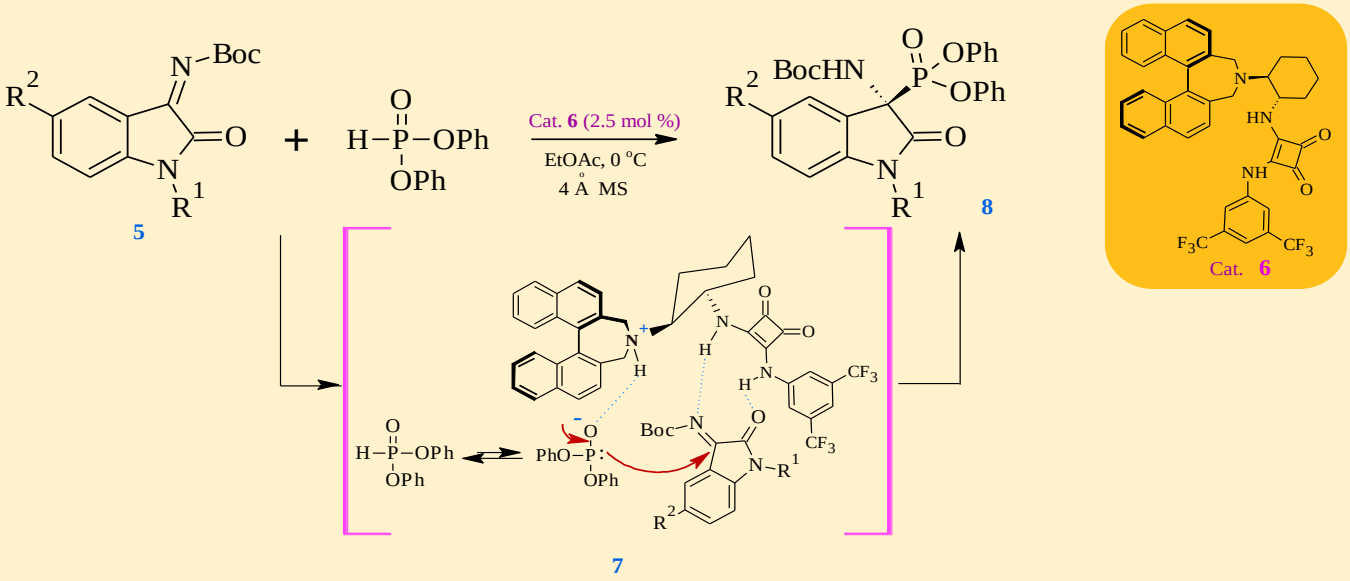
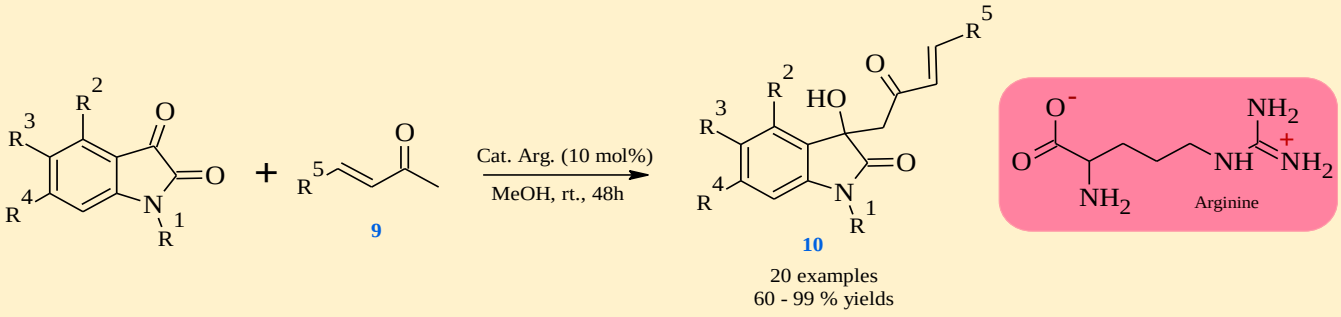


Scheme 2: Synthesis of chiral 3-amino-3-phosphonyl-substituted oxindole derivatives. MS = molecular sieves.

Reactions Based on the Aldol reaction

Insertion a hydroxyl group into substituted C-3 of oxindoles with an additional enone moiety can pave the way for further elaboration of the products. Xie *et al* reported the synthesis of 3-substituted-3-hydroxy-2-oxindoles **10** via nucleophilic addition of *α,β*-unsaturated ketones **9** to isatins using arginine as an organocatalyst (Scheme 3).[11]



Scheme 3: The aldol reaction of isatins and *α,β*-unsaturated ketones.

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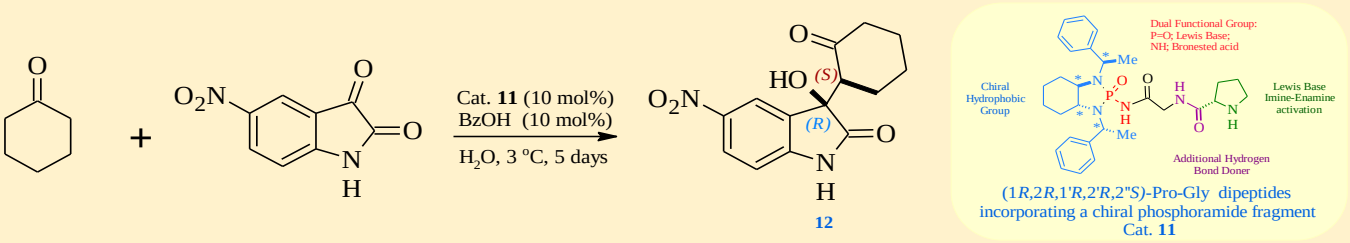
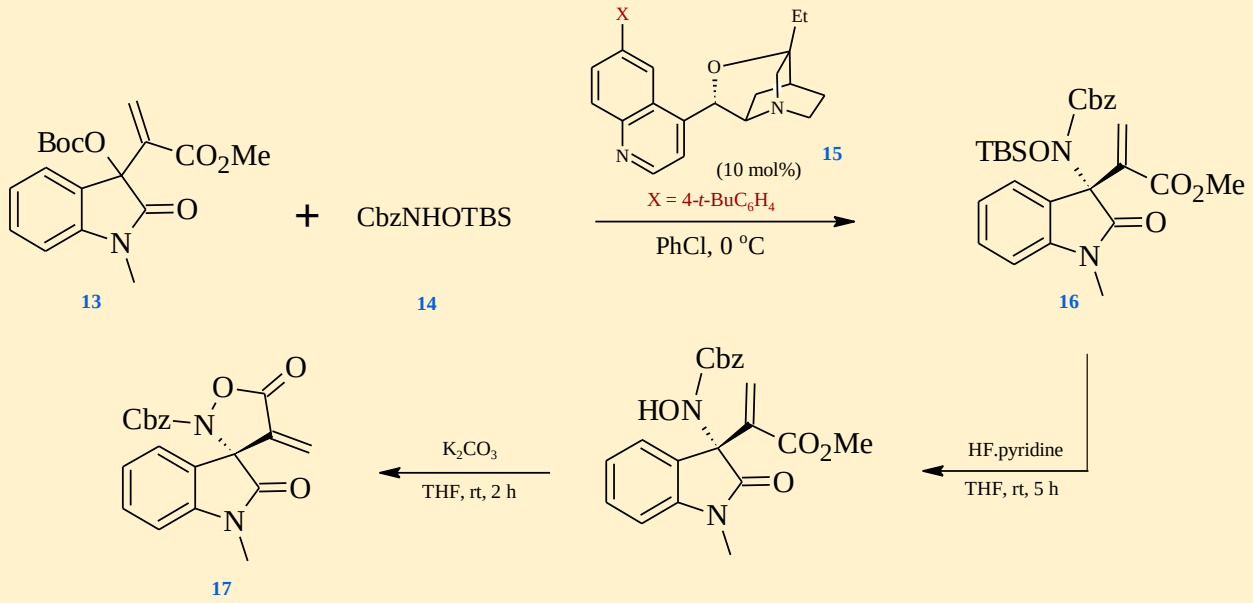
A multifunctional chiral organocatalyst system was also demonstrated to be effective for the diastereo- and enantioselective aldol addition of cyclohexanone to isatin in the presence of benzoic acid (BzOH) as additive and water to deliver spirocyclic products **12** in good yield and stereoselectivity. This chiral catalyst system **11** incorporates a dipeptidic (*R*)- or (*S*)-proline-glycine moiety in combination with chiral phosphoramide segment (Scheme 4).[12] In this regard, the organocatalyst is characterized by the following advantages: (i) incorporates large hydrophobic groups that brings the substrates closer together leading to more robust transition states; (ii) forms the catalytically active core (through (*R)* or (*S*) – Pro-Gly fragment); performs enamine activation (pyrrolidine fragment); and activates the electrophilies (by two acidic NH hydrogens); (iii) creates a large cavity for the fixation and activation of electrophilies (via glycine spacer); and (iv) develops group-assisted purification (GAP) chemistry and technology (through *N*-phosphonylimine segment).



Scheme 4: the asymmetric Aldol reaction between cyclohexanone and 5-nitroisatin catalyzed by chiral phosphoramide of (1*R*,2*R*,1'*R*,2'*R*,2"*S)*-Pro-Gly dipeptides.

Reactions Based on C3 Amination

The formation of 3-amino-2-oxindoles with a C3 quaternary chiral center constitute useful units for the synthesis of natural products and therapeutic agents. Chen *et al.* reported a highly enantioselective allylic amination of Morita–Baylis–Hillman (MBH) carbonates derived from isatins **13** with protected hydroxylamine **14** by the catalysis of a modified β-Isocupreidine (β-ICD) derivative **15** in chlorobenzene at 0 °C, which provided an electrophilic process to 3-amino-2-oxindoles with a C3-quaternary chiral center **16** (Scheme 5).[13] Further elaborations of intermediate **16** by the removal of *O*-TBS unit by hydrofluoric acid then an intramolecular transesterification process afforded a spirocyclic oxindole **17** without loss of enantiopurity.

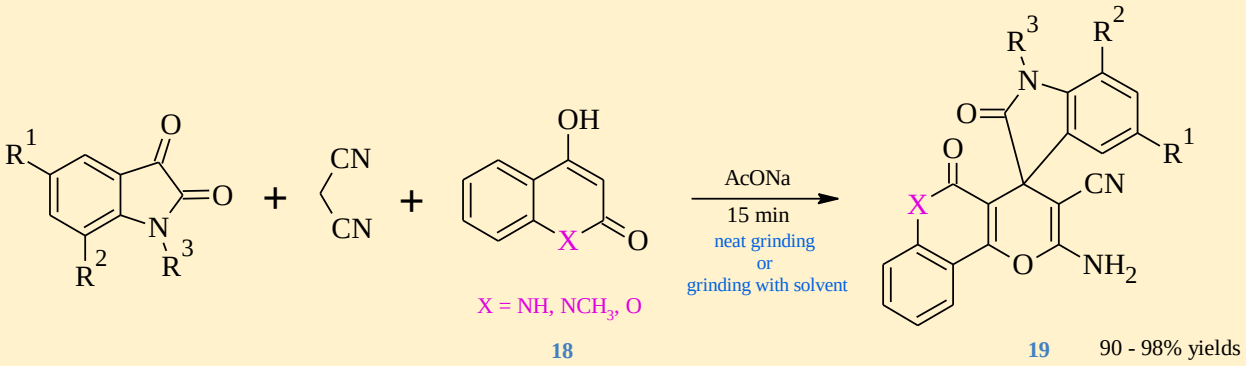


Scheme 5: Synthetic transformations of multifunctional product of asymmetric allylic amination of MBH carbonate of isatin.

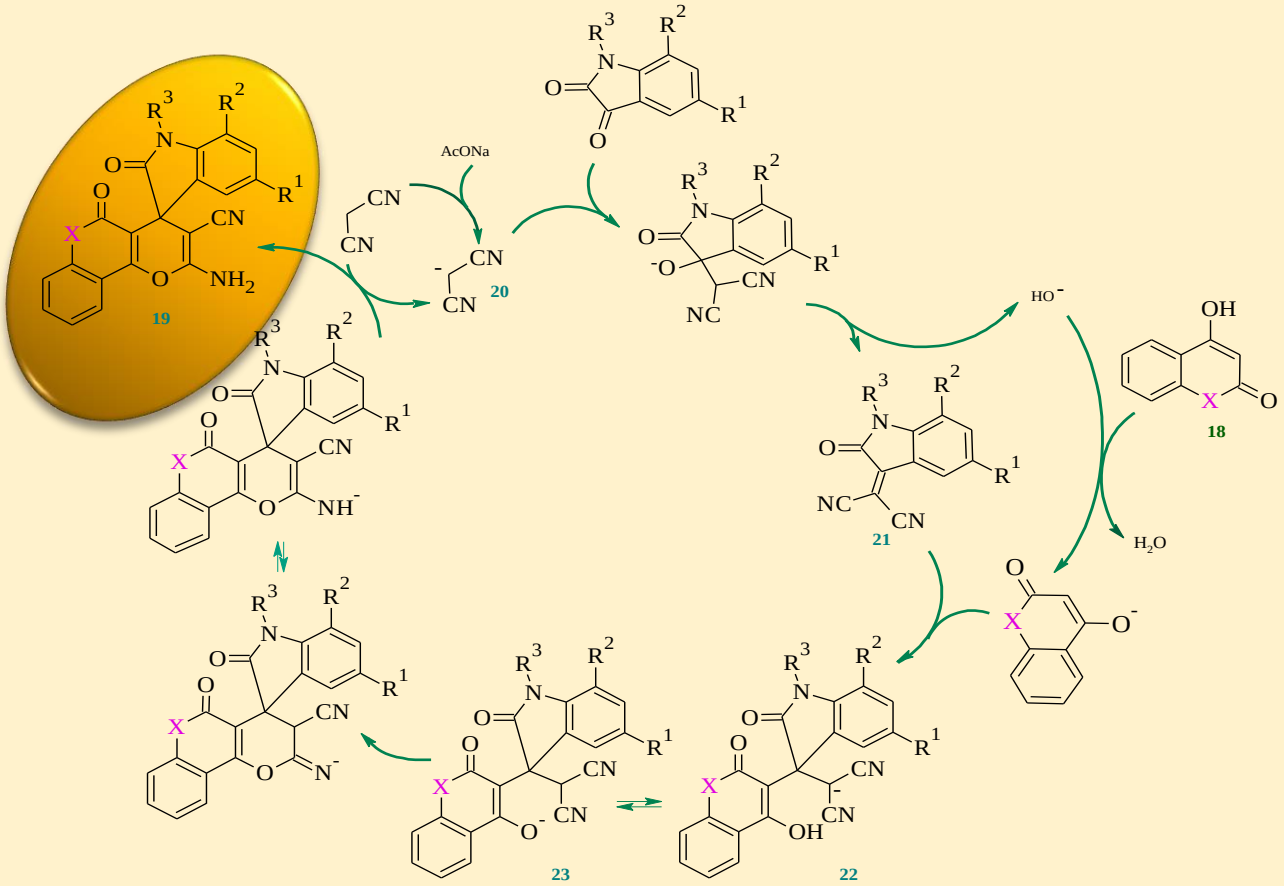
Reactions Based on the Knoevenagel Reaction

The reactivity of the C-3 carbonyl group of isatin facilitates Knoevenagel condensation in which the addition of nucleophilic methylene substrate takes place at C-3 followed by dehydration reaction. The electron-deficient Knoevenagel products can further initiate domino reactions in the presence of a third component to produce complex and diverse heterocyclic compounds.

In order to create new compounds in an optimal synthetic method, domino reaction strategy is extremely versatile option in the sustainability sense since domino procedures engage with PASE (Pot, Atom, Step Economic)- strategy. In this context, Elinson and co-workers[14] reported a fast and facile PASE solvent-assisted methodology for multicomponent assembling of isatins, bicyclic CH-acids **18**, and malononitrile in the presence of sodium acetate as a catalyst at room temperature to effectively provide substituted spiro-oxindoles **19** in 90-98% yields in 15 minutes (Scheme 6). The reaction was achieved under solvent-free as well as on-solvent (limited quantity of ethanol) conditions.



Scheme 6. Multicomponent reaction of isatins, malononitrile, bicyclic CH-acids.



Scheme 7: The proposed mechanism of the preparation of spiro-oxindole **19**.

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Mechanistically, the reaction begins with the deprotonation of a malononitrile molecule induced by sodium acetate to generate malononitrile anion **20** (Scheme 7). Then, Knoevenagel condensation of anion **20** with isatin takes place to form Knoevenagel adduct **21** and eliminated hydroxyl anion which subsequently promotes Michael addition of bicyclic CH-acid **18** to the electron-deficient Knoevenagel adduct **21** yielding the anions **22** and **23**. Further cyclization of anion **23** and protonation with the participation of the next malononitrile molecule produces spiro-oxindole **19** with the regeneration of malononitrile anion at the last step of the catalytic cycle.

Conclusion

Isatins have been used as building blocks in a wide variety of organic synthesis, especially in terms of complex polycyclic compounds. Many useful reactions have been developed, including high degree of atom-economy process, spirocyclic compounds, formation of quaternary stereogenic center which constitutes useful unites for the synthesis of natural products, and knoevenagel reaction. Moreover, the privileged nature of these scaffolds inspired researchers to develop multifunctional chiral organocatalyst. With the tremendous growth in the field of natural products as well as the biologically active heterocycles, especially in complex and diverse polycyclic compounds, further activities towards the development of new types of cascade cyclization are anticipated in the near future.

References

1. a) O. L. Erdmann, *Journal für Praktische Chemie*, **1840**, *19*, 321–362; b) A. Laurent, **1840**, *3*, 393-434.
2. I. Coldham, R. Hufton, *Chem. Rev.*, **2005**, *105* (7), 2765–2810.
3. L. Yun Liu, J.W. Sun, *J. Org. Chem.*, **2012,** *77*, 1191–1197.
4. V. A. Osyanin, D. V. Osipov, Y. N. Klimochkin, *J. Org. Chem.*,**2013**, *78*, 5505–5520.
5. A. M. D'Souza , N. Spiccia, J. Basutto, P. Jokisz, L. S.-M. Wong, A. G. Meyer, A. B. Holmes, J. M. White, J. H. Ryan, *Org. Lett.*, **2011**, *13* (3), 486–489.
6. J. H. Ryan, *Organic Letters.*, **2011**, *13 (3)*, 486–489.
7. N. A. *Nedolya, B. A. Trofimov, Chemistry of Heterocyclic Compounds, 2013, 49 (1), 152–176.*
8. J. Sun, G. l. Shen, Y. Huang, C. G. Yan, *Sci. Rep.*, **2017**, *7*, 41024.
9. a) A. Dömling, I. Ugi, *Angew. Chem.*, **2000**, *112*, 3300-3344; b) A. Dömling, I. Ugi, *Angew. Chem. Int. ED.*, **2000**, *39*, 3168-3210.

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10. H. S. Jang, Y. K. and D. Y. Kim, *Beilstein J. Org. Chem.*, **2016,** *12*, 1551–1556.
11. T. Yan, X. Wang, H. Sun, J. Liu, Y. Xie, *Molecules*, **2013**, *18*, 14505-14518.
12. C. Cruz-Hernándeza, P. E. Hernández-Gonzáleza, E. Juaristi, *Synthesis*, **2018**, *50*, 3445–3459.
13. H. Zhang, S.-J. Zhang, Q.-Q. Zhou, L. Dong, Y.-C. Chen, *Beilstein J. Org. Chem.*, **2012,** *8*, 1241–1245.
14. M. N. Elinson, A. N. Vereshchagin, F. V. Ryzhkov, Y. E. Anisina, *Arkivoc*, **2018**, *part iv*, 0-0.

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Snapshots of some topics of interest of recent notable advances in chemistry

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New Bioinspired Self-Healing Hydrogel for Diverse Potential Bioapplications

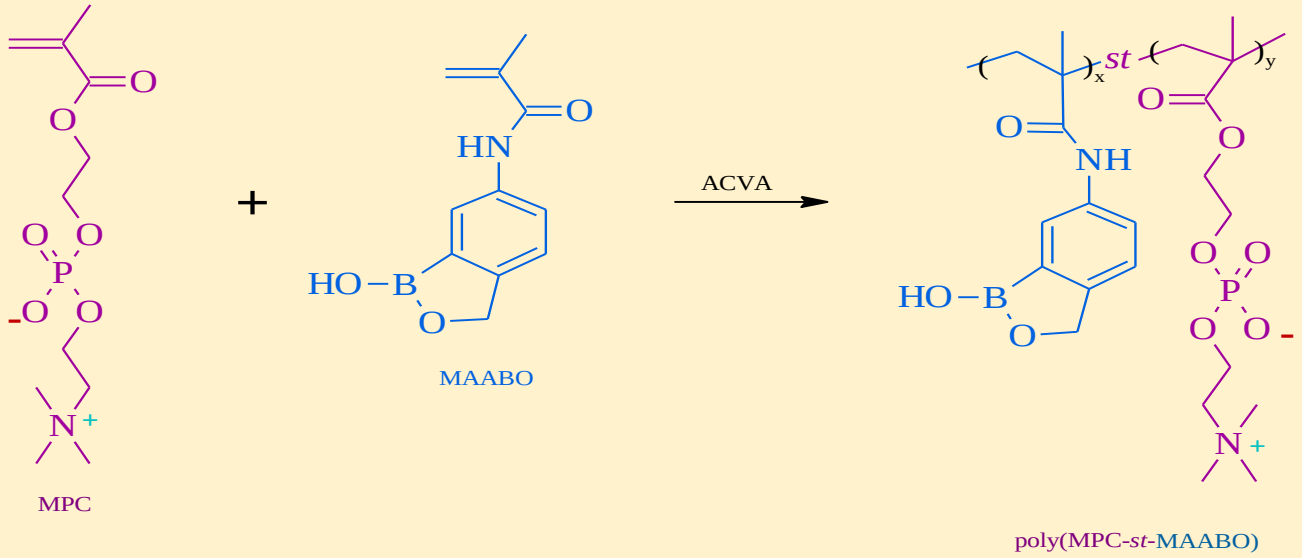
A new strategy to design self-healing and dual-responsive hydrogels based on crosslinking between two kinds of zwitterionic copolymers with benzoxaborole and catechol pendant groups is highlighted. The resulting hydrogels can be applied for diverse potential bioapplications like drug delivery and tissue engineering.

Hydrogels are cross-linked polymeric materials that retain large amounts of water in their structures. They are characterized by their ability to absorb water due to the hydrophilic groups attached to the polymeric backbone, as well as by their resistance to dissolution owing to their cross-linked networks.

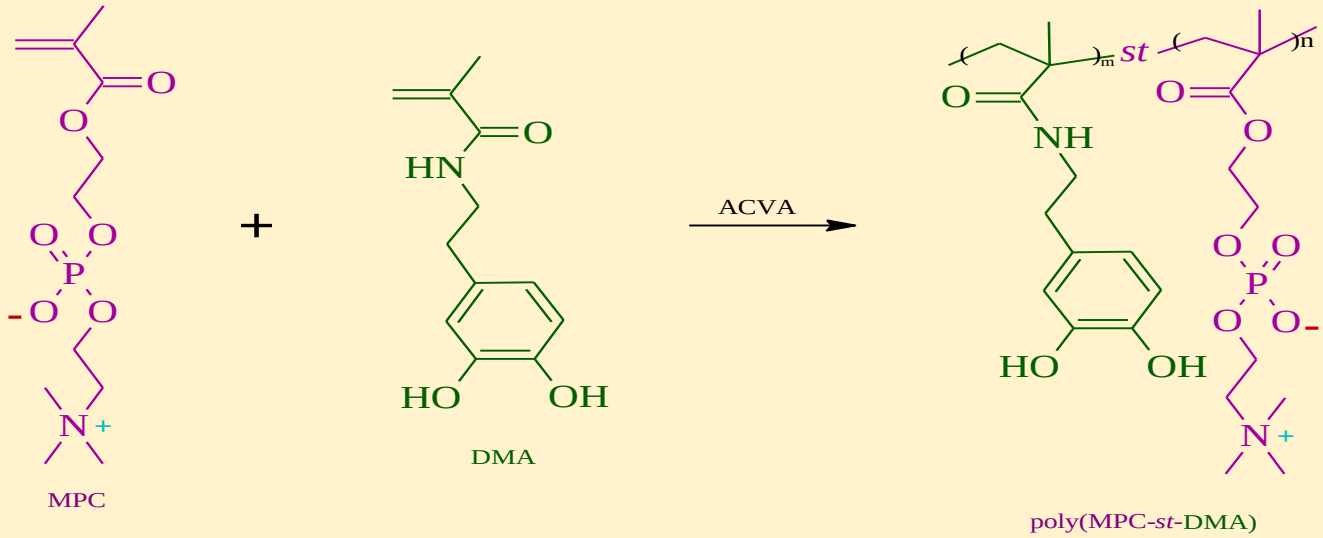
Recently, self-healing and stimuli-responsive hydrogels have received considerable attention owing to their good performance. The responsiveness to the physical and chemical stimuli enables hydrogels to control the release of loaded therapeutic agents. Self-healing hydrogels can be classified into two types based on the nature of crosslinking: (a) physical hydrogels depend upon non-covalent bonds, such as metal-ligand interactions or hydrogen bonds to form a reversible network; and (b) dynamic covalent chemistry which are linked by reversible covalent bonding, such as Schiff base, hydrazone, disulfide, boronic ester, and Diels-Alder reaction, forming a permanent network. In this regard, chemical hydrogels are more convenient to achieve the simultaneous stimuli-responsiveness via dissociation of the covalent bonds.

Narain and co-workers adapted a new strategy to design self-healing and dual-responsive hydrogels based on crosslinking between two kinds of zwitterionic copolymers with benzoxaborole and catechol pendant groups, respectively, via free-radical polymerization. They took advantage of zwitterionic polymers that have superior antifouling ability and excellent biocompatibility which fit the most significant criterion in their biological utility. The selectivity of 2-methacryloxyethyl phosphoryl-choline (MPC) as a mature zwitterionic molecule with cell-membrane mimicking structure can be ideal copolymer for biomedical utility such as three-dimensional (3D) cell encapsulation. On the other hand, benzoxaborole has a pK_a value (~ 7.2) lower than physiological pH which allows their use in the

biomedical fields. Moreover, it exhibits high binding affinity with *cis*-1,2-diol of monosaccharides to produce stable five-membered boronate rings.



Scheme 1: Synthetic route of benzoxaborole-containing copolymer poly(MPC-*st*-MAABO).



Scheme 2: Synthetic route of catechol-containing copolymer poly(MPC-*st*-DMA).

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The polymerization of MPC with both benzoxaborole-containing monomer 5-methacrylamido-1,2-benzoxaborole (MAABO) and catechol-containing monomer dopamine methacrylamide (DMA), in the presence of 4,4′-azobis(4-cyanovaleric acid) (ACVA) produced zwitterionic copolymers poly(MPC-st-MAABO) (Scheme 1)and poly(MPC-st-DMA) (Scheme 2), respectively.

The resulting hydrogels showed fast self-healing ability and can be dissociated by lowering the pH or adding competitive saccharides. Moreover, benefiting from the cell membrane bioinspired MPC- based polymeric matrix showed excellent biocompatibility when used for 3D cell encapsulation. This type of benzoxaborole-catechol complexation can be applied for many wide-ranging biomedical applications.

Review:

Y. Chen, D. Diaz-Dussan, D. Wu, W. Wang, Y.Y. Peng, A. B. Asha, D. G. Hall, K. Ishihara, R. Narain, *ACS Macro Lett.*, **2018**, *7*, 904−908.

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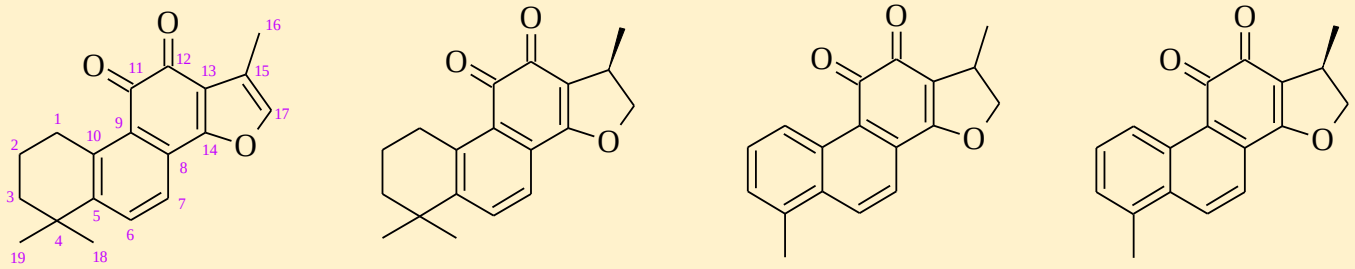
Synthesis of Novel Tanshinone Derivatives

Simple routes are described for synthesis of oxazole, imidazole, and pyrazine attached to Tanshinones between C-11/C-12.

Tanshinones are a class of abietane diterpene compounds, isolated from *Salvia miltiorrhiza*,a well-known herb in Traditional Chinese Medicine as preventive or therapeutic remedies for heart diseases. Recent studies have shown that tanshinones exhibit anti-cancer activities.[1,2] Tanshinones are a class of lipophilic constituents, including tanshinone IIA **1**, cryptotanshinone **2**, tanshinone I **3**, and dihydrotanshinone I **4** (Figure). They are characterized by their 11,12-orthoquinone skeleton, which have attracted researchers to modify these compounds and improve their anti-cancer efficacy.

Recently, Qin and Xu and their co-workers[2] reported synthesis of three types of heteroatom containing derivatives of tanshinones. Tanshinones 1-4 were treated with methyl- or ethylamine in ethanol to form salviamine A and isosalviamine A in 50-76% yields (Scheme – route a), while refluxing with ammonium acetate and aldehyde in ethanol produced their imidazole derivatives in 55-80% yields (Scheme – route b). Pyrazine derivatives were obtained in 40-60% yields by treatment of tanshinones with diamine in ethanol (Scheme – route c).

Modification of C11-C12 quinone have shown some antitumor activity, especially, introduction of imidazole ring at C11-C12.



tanshinone IIA **1** | cryptotanshinone IIA **2** | tanshinone I **3** | dihydrotanshinone I **4**

Figure: Structures of tanshinones.

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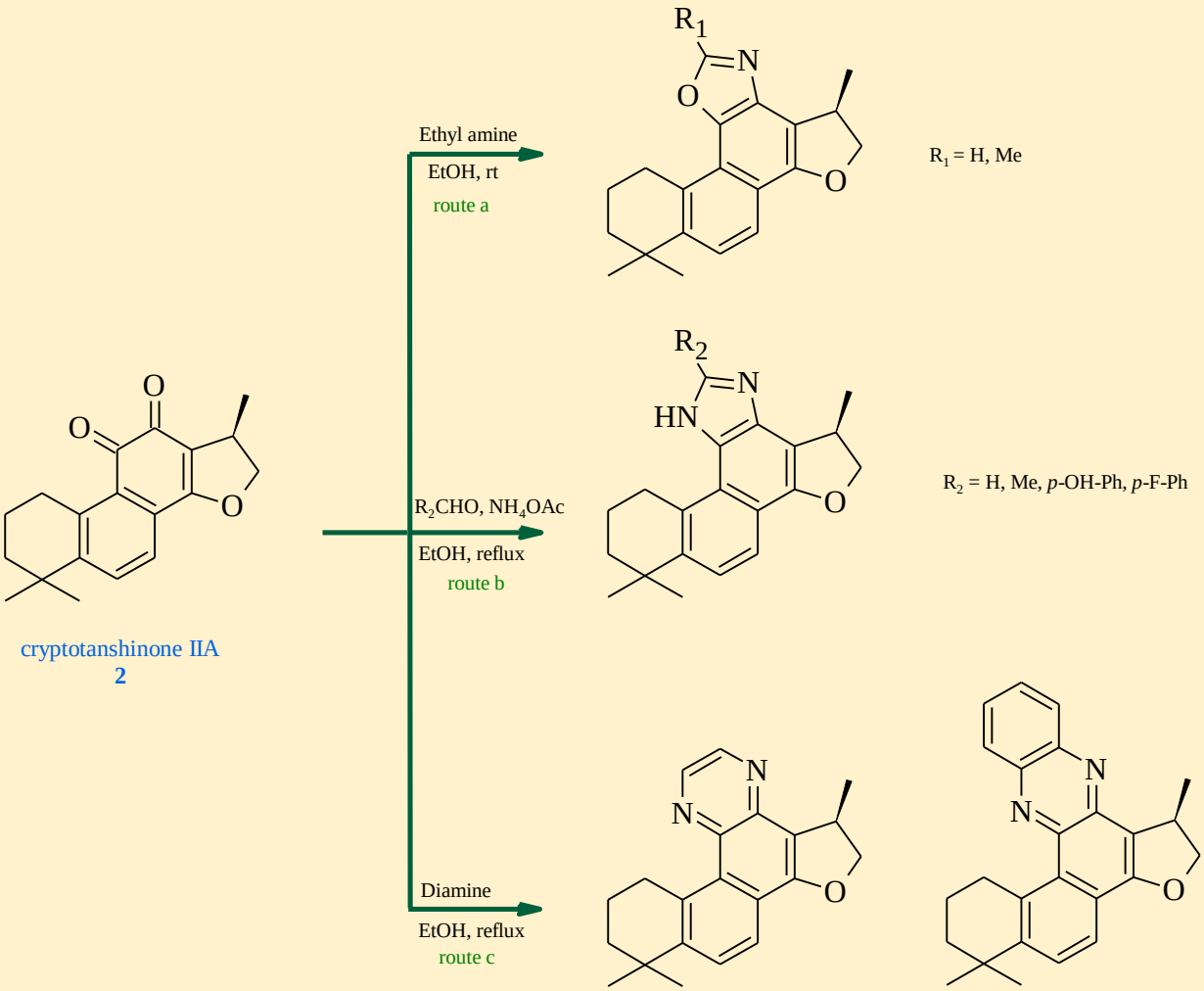

Scheme: synthetic routes to introduction of oxazoline, imidazole and pyrazine at C11-C12 of tanshinones.

Review:

1. Y. Dong, S.L. Morris-Natschke, K.H. Lee, *Nat. Prod. Rep.*,**2011**, *28*, 539-542.
2. M.M. Li, F. Xia, C.J. Li, G. Xu, H.B. Qin, *Tetrahedron Lett.* **2018**, *59*, 46–48.

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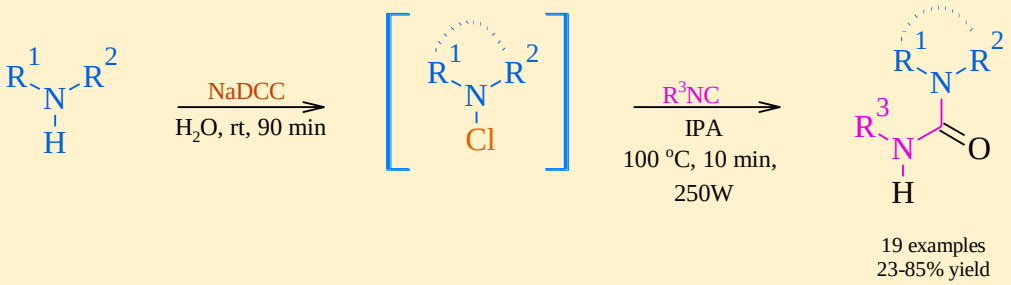
A Green One-pot Synthesis of *N*-*N*′-multisubstituted Urea and Thiourea

Simple and green one-pot three-component procedure is described for the synthesis of *N*-*N*′-multisubstituted urea and thiourea based on the reaction of *in situ* generated secondary *N*-chloro-amines with isocyanides in water or sodium sulfide under dry conditions.

The conventional method for the preparation of *N,N*′-multisubstituted (thio)ureas can be accomplished through the treatment of the corresponding amines with iso(thio)cyanates or (thio)phosgene. These transformations are associated with high toxicity of the reagents. In 2001, Katritzky *et al*. reported the reaction of benzotriazole-1-carboximidoyl chlorides as *N*-chlorinated reactants with isocyanides. Inspired by this approach and to overcome these synthetic drawbacks, Kanizsai and co-workers reported their development of such a strategy to synthesize diverse *N,N*′-multisubstituted ureas and thioureas via a simple and green one-pot three-component procedure. The approach based on the chlorination *in situ* of secondary amines with sodium dichloroioscyanurate (NaDCC) at room temperature, then mixing the solvent with 2-propanol (IPA) followed by addition of the ioscyanide to afford the desired urea compounds with up to 85% yields under microwave-assisted conditions (Scheme 1). In the case of thiourea synthesis, the reaction proceeded under dry conditions using sodium sulfide as the third reactant to furnish *N,N*′-multisubstituted thioureas with up to 68% yields (Scheme 2).



Scheme 1: synthesis of multisubstituted urea

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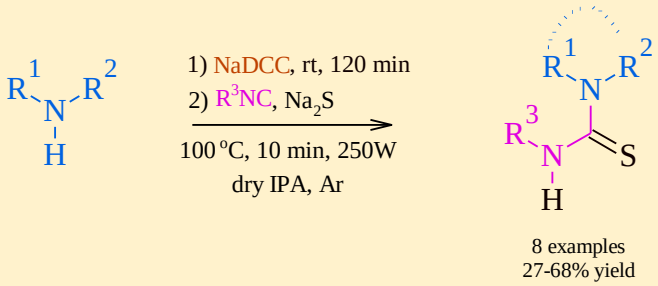

Scheme 2: Synthesis of multisubstituted thiourea.

Review:

1. A. Angyal, A. Demjén, J. Wölfling, L. G. Puskás, I. Kanizsai, *Tetrahedron Lett.*, **2018**, *59*, 54–57.

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Synthesis of Doubly Heteroatoms-embedded Porphyrin Arch-Tape Dimers

A novel design of doubly sulfone-inserted porphyrin arch-tape dimer possessing two neighboring seven-membered rings is described.

Porphyrin tapes are *meso-meso β-β β-β* triply linked porphyrin arrays that exhibit outstanding properties due to their fully conjugated characteristic π-electronic networks. Incorporation of heteroatoms onto the porphyrin periphery extended further the conjugated involvement of π-electronic networks. Such arch-tape displays a narrow electrochemical HOMO-LUMO gap, which influences positively the electronic and structural properties of this porphyrin tape. Recently, Fukui and Osuka reported a novel design of doubly sulfone-inserted porphyrin arch-tape dimer having two neighboring seven-membered rings.

The synthetic pathway involved palladium-catalyzed cross-coupling reaction of 2,18-diiodoporphyrin **1** with bis(tributylstannyl)sulfide to furnish *β-to-β β-to-β* doubly sulfer-bridged porphyrin dimer **2** in 17% yield (Scheme). Then, tungsten-catalyzed oxidation of **2** with hydrogen peroxide afforded *β-to-β β-to-β* doubly sulfone-bridged porphyrin dimer **3** in 64% yield. The doubly sulfone-inserted arch-tape dimer **4** was obtained in 64% yield by the oxidative fusion reaction of **3** with $AuCl_3$ and AgOTf.

Dimer **4** displays a contorted structure as a result of the presence of two neighboring seven-membered rings. The degree of molecular contortion plays a dominant role in controlling the HOMO-LUMO energy gap of porphyrin arch-tape dimers.

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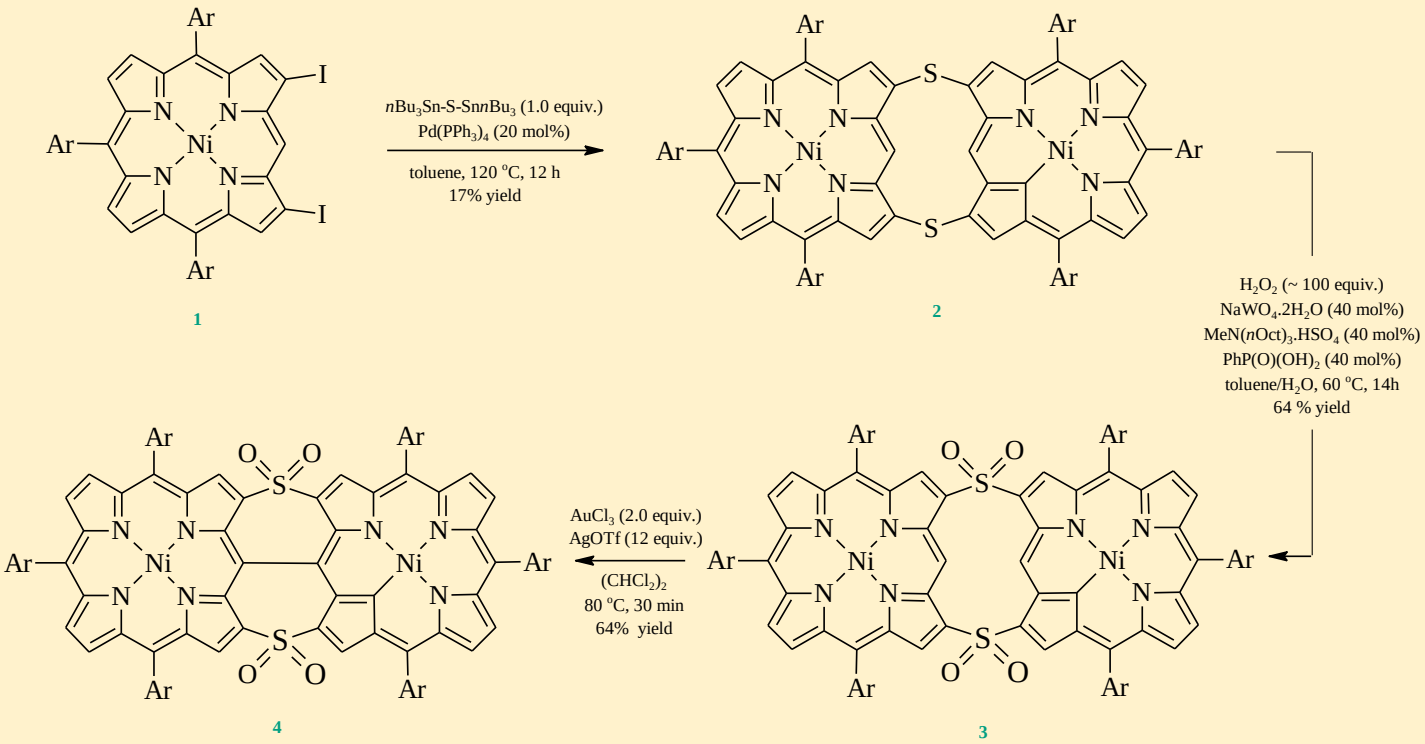

Scheme: Synthesis of doubly sulfone-inserted arch-tape dimer. Ar = 3,5-di-*tert*-butylphenyl.

Review:

N. Fukui, A. Osuka, *Bull. Chem. Soc. Jpn.*, **2018**, 91, 1131-1137.