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Iodine mediated cascade oxidative functionalization, cyclisation and annulation reactions

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Abstract

Molecular iodine has a huge application in the field of electrophilic cyclisation reactions, oxidation, oxidative cyclisation, multi-component reactions, ring opening, cyclisation, rearrangement, oxidative cross coupling, oxidative annulation, C-H functionalization reactions, synthesis of heterocycles and its derivatives. In this mini review I discuss the utilization of iodine mediated cascade reactions for oxidative annulation, functionalization and cyclisation of various organic compounds.

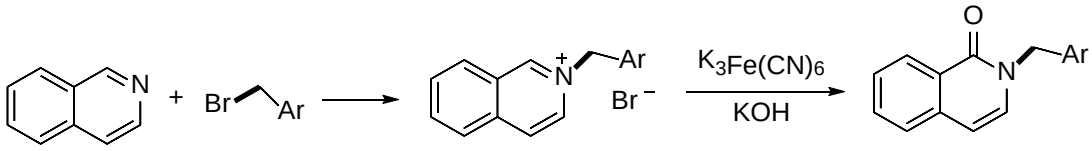
Keywords: Cascade process, coupling, cyclization.

Introduction

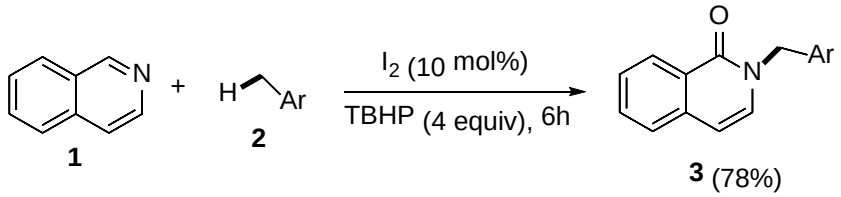
Molecular iodine is an efficient, inexpensive and readily available benign reagent for the synthesis of various heterocyclic compounds. Though the solubility of iodine is very less in water it may be easily increased with dissolved iodides, forming of tri-iodide ions (Svensson et al., 2003). Molecular iodine was recognized as a useful mediator and reagent (Togo et al., 2006), and is using as an efficient catalyst (Vaino et al., 2000) in organic synthesis. Due to the versatile characters of iodine it has been playing an important role in organic synthesis since its discovery. Because of the huge applications of iodine in the field of organic synthesis, the present review will therefore focus on recent applications of iodine mediated cascade reactions. Owing to the versatile characters of iodine, iodine mediated reactions are generally divided in three categories, iodine mediated domino reactions, iodine mediated tandem reactions and iodine mediated cascade reactions. This mini review presents on the iodine mediated cascade reactions.

Yang et al., (2016) established an *N*-alkylation and amidation cascade to provide isoquinolin-1(2H)-ones. The straight forward reaction between isoquinoline (**1**) and toluene (**2**) in presence of molecular iodine (10 mol%) and TBHP (4 equiv.) gave the corresponding isoquinolin-1(2H)-ones (**3**) in 78% yield (Scheme 1).

(a) Traditionally two-step synthetic route for *N*-substituted isoquinolin-1(2H)-ones

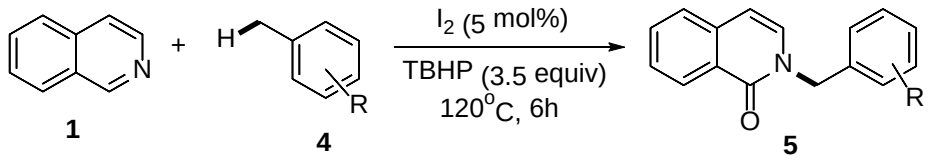


(b) Cascade oxidative functionalization of isoquinone with benzylic C(sp3)−H bond



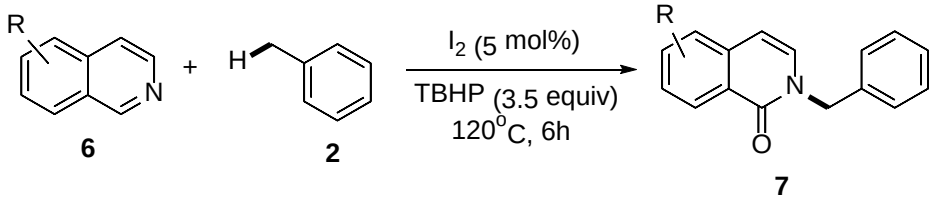
Scheme 1. Formation of *N*-Substituted Isoquinolin-1(2H)-ones.

Methylarenes (**4**) substituted by electron-donating or -with drawing groups on treatment with azaarene (**1**) in presence of molecular iodine (5 mol%) furnished the desired iso-quinolinone (**5**) via *N*-alkylation and amidation cascade in good yields (Scheme 2).



Scheme 2. Iodine-Catalyzed Oxidative Functionalization of Isoquinoline with Substituted Alkylarenes.

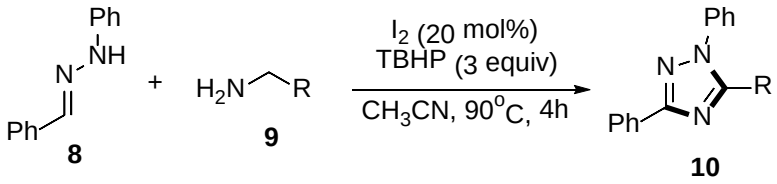
The excellent results of this iodine catalysed cascade reaction inspired to extend this reaction to substituted azaarenes. Substituted azaarenes (**6**) on treatment with methylarene formed the desired isoquinolone (**7**) in good yields (Scheme 3).



Scheme 3. Iodine-Catalyzed Oxidative *N*-Alkylation and amidation of substituted Isoquinolines.

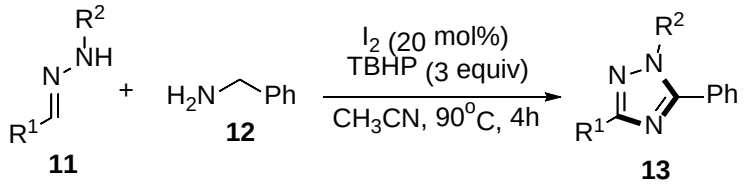
It was reported (Chen et al., 2016) the metal free iodine mediated synthesis of substituted 1,2,4-triazoles through acascade C−H functionalization, double C−N bonds formation, and oxidative aromatization under aerobic oxidative conditions.

The reaction between bisaryl hydrazone (**8**) and benzylamines (**9**) substituted by eletron-donating or withdrawing groups in the presence of 20 mol% I_2 and 3 equiv of TBHP in acetonitrile at 90^0C provided the corresponding triazoles (**10**) in high yield (Scheme 4).



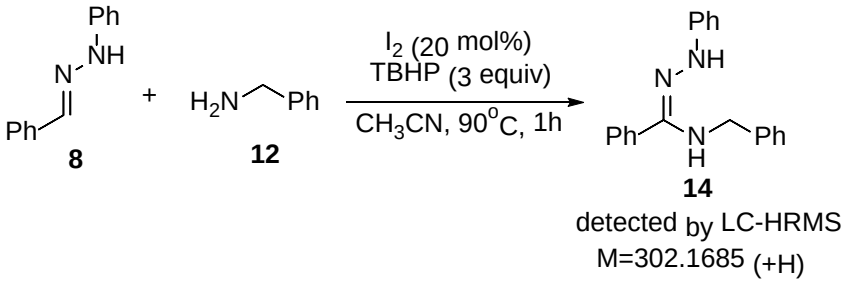
Scheme 4. Formation of 1,2,4-Triazoles from Diverse Amines.

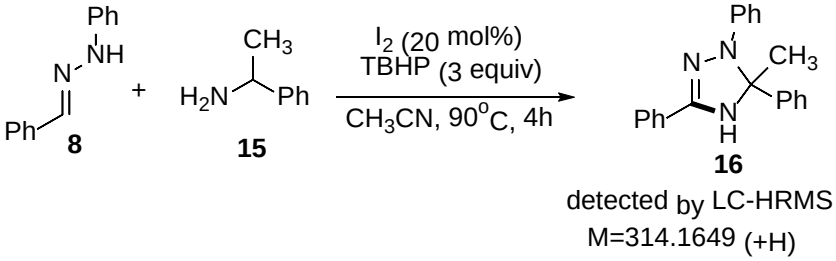
Inspired by the excellent results of this method it was extended to various substituted hydrazones (**11**) and also furnished the desired triazoles (**13**) in good yield (Scheme 5).

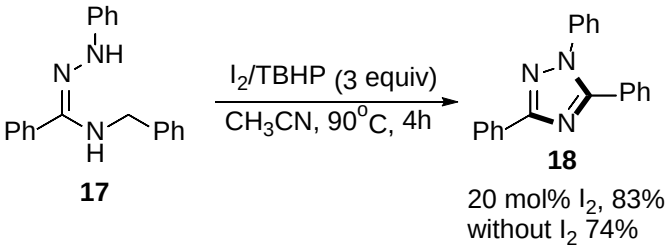


Scheme 5. Formation of 1,2,4-Triazoles from Diverse Hydrazones.

It was assumed by the mechanistic investigations that the reaction proceeded through a radical process. Following controlled experiments (Scheme 6) were done to explore the reaction mechanism.



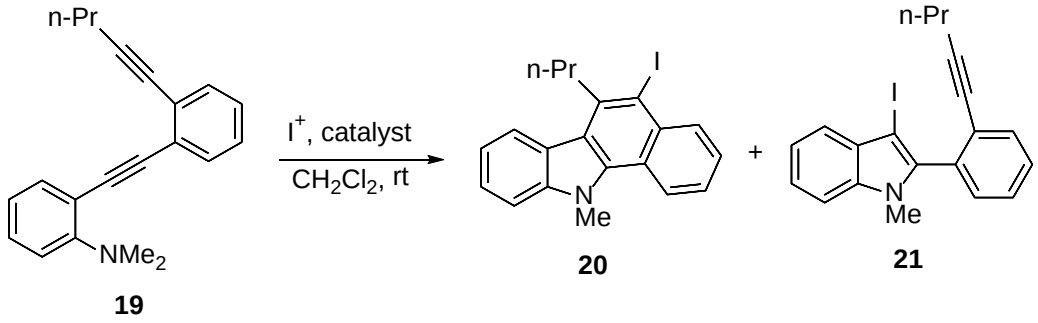




Scheme 6. Control Experiments.

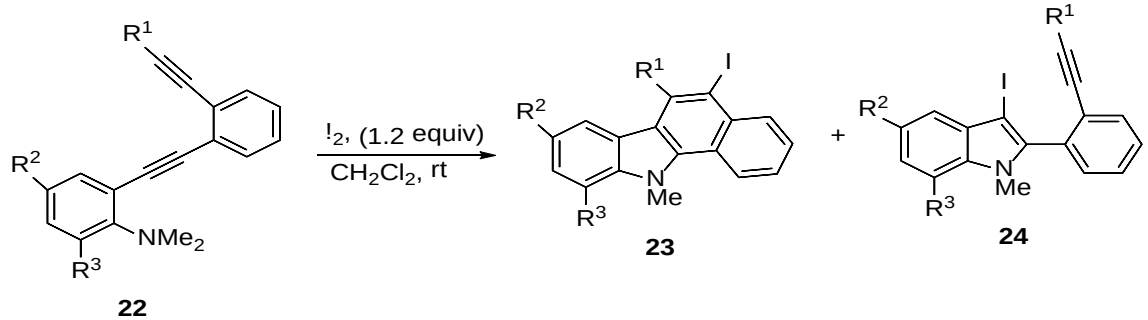
Chen et al., (2011) subjected *N, N*-dimethyl-2-[2-(2-pentynylphenyl) ethynyl] aniline (**19**) with 2 equivalent of iodine (I_2) in dichloromethane for 1h at room temperature and obtained the iodinated carbazole (**20**) directly in 96% yield. A wide range of experiments revealed that this reaction goes through the haloindole (**21**) which is cyclized to give the desired benzo [*a*] carbazoles (**20**) by iodonium ion catalysed reaction.

On reduction the amount of iodine to 1.2 equivalent the reaction conditions were optimised to obtain the carbazole derivatives (**20**) in a competitive yield. It was also reported that replacement of iodine by NIS (*N*-iodo-succinimide) provided an indole adduct (**21**) in 90% yield (Scheme 7).



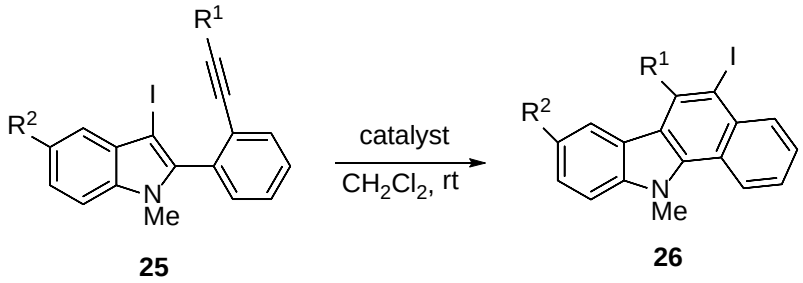
Scheme 7. Cascade Iodocyclization of *N, N*-dimethyl-2-[2-(2-pentynylphenyl) ethynyl]aniline.

Encouraged by the excellent yields of this cascade cyclisation process it was extended to various substituted *N, N*-dimethyl-2-[2-(2-alkynylphenyl)- ethynyl] anilines (Scheme 8).



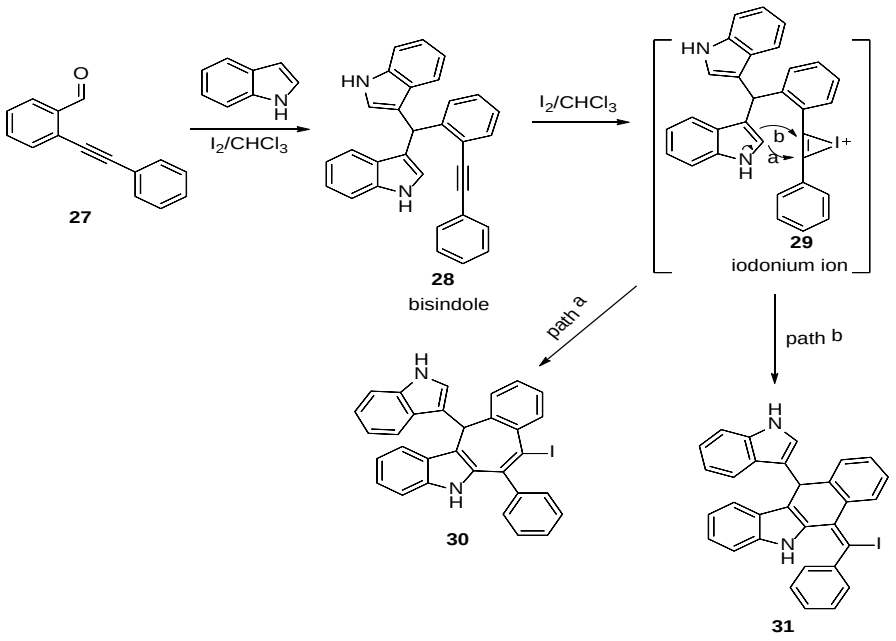
Scheme 8. Cascade Iodocyclization to Form Benzo [*a*] carbazoles.

Study of the formation of the iodinated indole derivatives (**25**) which was found by using NIS instead of iodine illustrated the mechanism of this reaction. Treatment of the iodinated indole derivatives (**25**) with a catalytic amount (5 mol %) of iodine in dichloromethane at room temperature for 2 h, gave the iodinated carbazole derivatives (**26**) in 90% yield (Scheme 9).



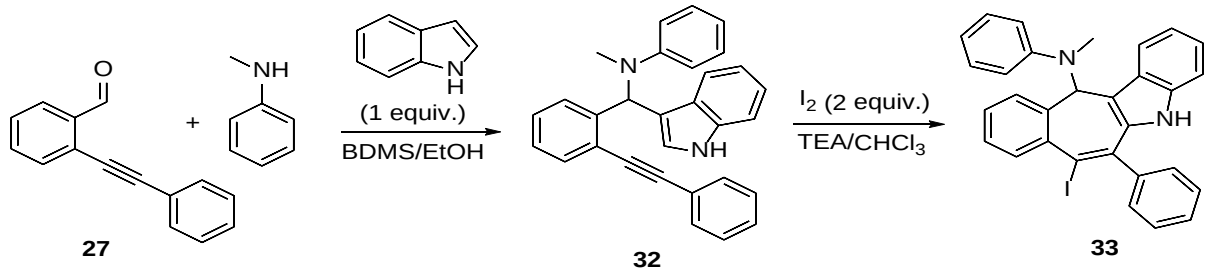
Scheme 9. Study of the Formation of Iodinated Indole to Carbazole.

Gawande et al., (2013) synthesized the iodo-substituted tetracyclic indole fused azulene derivatives. They treated 2-(substituted phenylethynyl)-benzaldehydes (**27**) with a variety of indoles in the presence of molecular iodine to obtain the corresponding iodo-substituted tetra-cyclic indole fused azulene derivatives. At first a bisindole derivative (**28**) is formed from the reaction between 2-(substituted phenylethynyl) benzaldehyde and indole which on iodocyclization in a one-pot cascade process gave the desired iodo-substituted tetracyclic indole fused azulene derivatives. A variety of 2-(substituted phenylethynyl)-benzaldehydes and different indoles were treated in this process to form a variety of iodo-substituted tetracyclic indole fused azulene derivatives (Scheme 10).



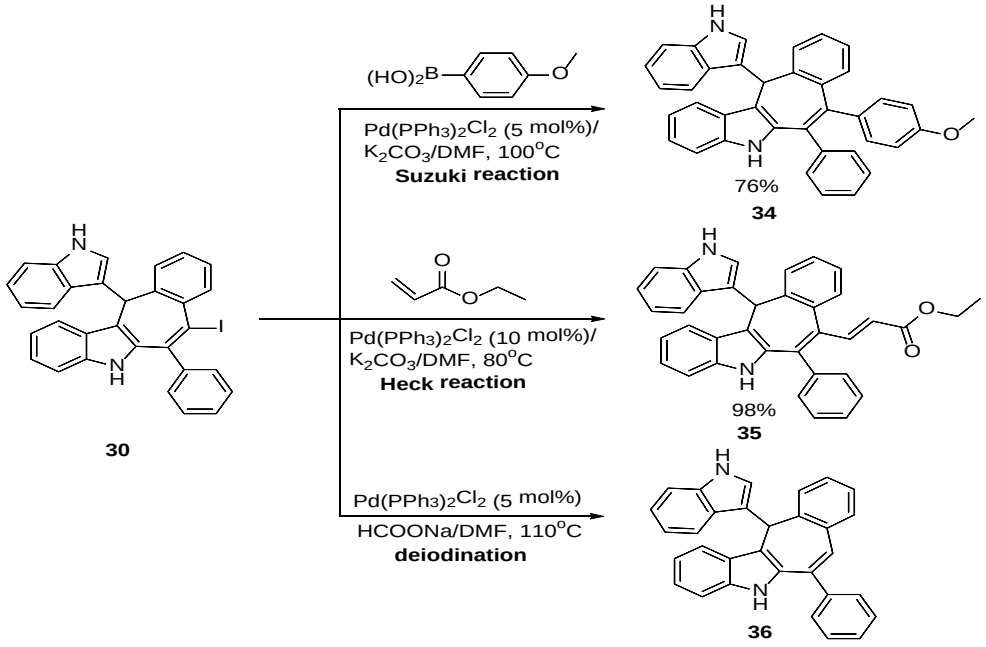
Scheme 10. Formation of products from plausible common intermediate.

Inspired by this process it was extended this protocol to form *N*-{(1H-indol-3-yl) [2(phenylethynyl) phenyl] methyl} -*N*-methylaniline (**32**). Treatment of *N*-methyl-aniline, 2-(phenylethynyl) benzaldehyde and indole derivative in presence of bromo dimethyl sulfonium bromide (BDMS, 10 mol%) in ethanol gave the crude compound (**32)**. The crude compound (**32**) was then subjected with iodine in presence of tri-ethylamine to produce the desired compound (**33**) in 65% yield (Scheme 11).



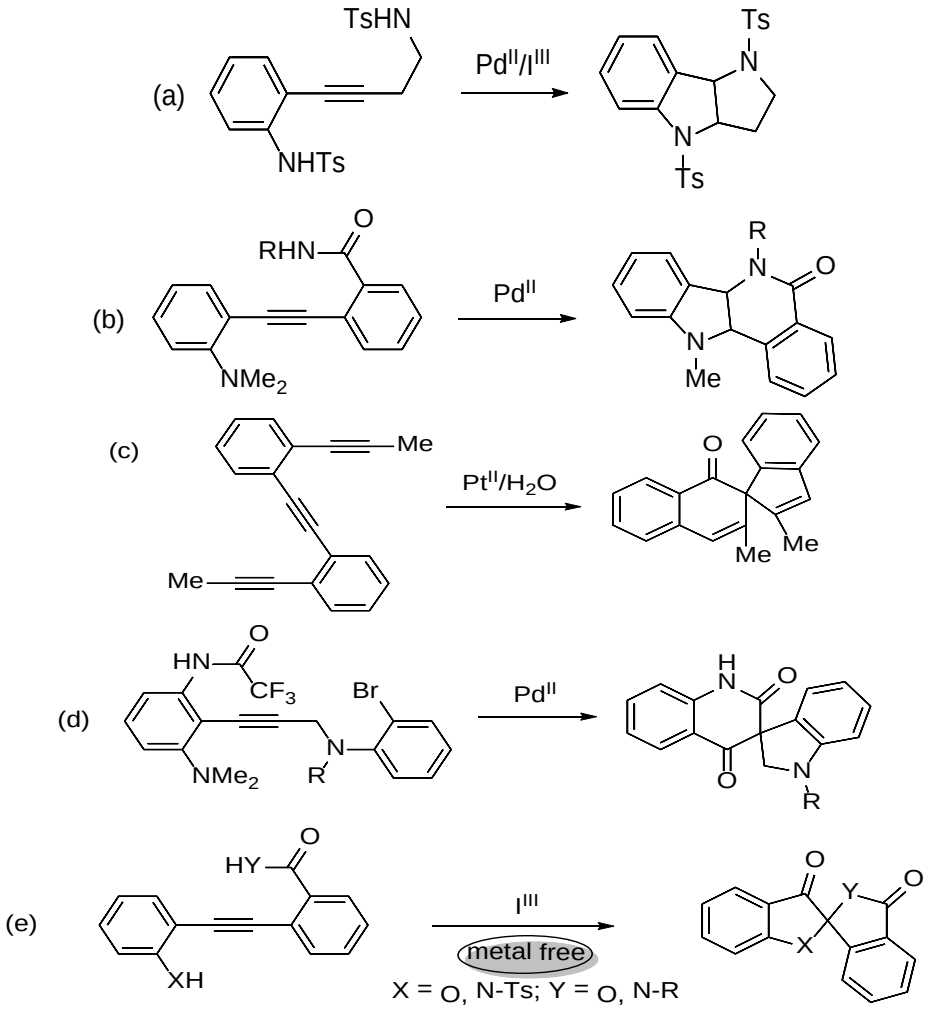
Scheme 11. Synthesis of tetracyclic indole fused azulene derivatives.

A variety of palladium catalyzed coupling reactions of the iodo-tetracyclic compounds produced different functionalized tetracyclic azulene derivatives (Scheme 12). Compound **30** was subjected under Suzuki reaction conditions with 4-methoxy-phenylboronic acid to produce the desired product **34** in 76% yield. Then, the Heck-type product **35** was obtained in excellent yield (98%) on treatment of compound **30** with ethyl acrylate and bis (triphenyl phosphine) palladium (II) dichloride in the presence of K_2CO_3 as a base in DMF. Finally, deiodination of the compound **30** by tetrakis (triphenyl phosphine) palladium (0) and sodium formate produced the deiodinated product **36** in 74% yield.



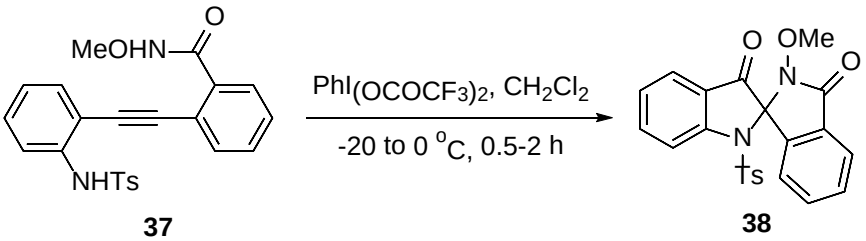
Scheme 12. Functionalization of indolotetracyclic azulene.

Zhang et al., (2015) reported the formation of spiro heterocycles through the cascade annulation of internal alkynes with a hyper valentiodine. The reaction proceeds through a sequential C–N/ C–O bond formations and insertion of a carbonyl oxygen.



Scheme 13. Cascade annulation of internal alkynes.

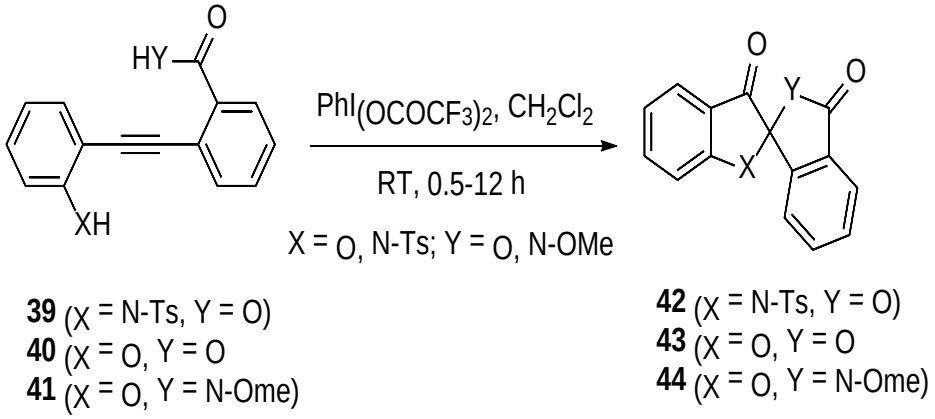
It was investigated the scope of this cascade annulation reactions of internal alkynes with a variety of diarylacetylene derivatives **37** to obtain different spiro heterocycles (Scheme 14).



37 **38**

Scheme 14. Synthesis of spirocycles containing an *N*, *N*-ketal.

Inspired by this reaction, it was extended to three more series: 39 (X=N-Ts, Y=O), 40 (X=O, Y=O), and 41 (X=O, Y=N-OMe) (Scheme 15).

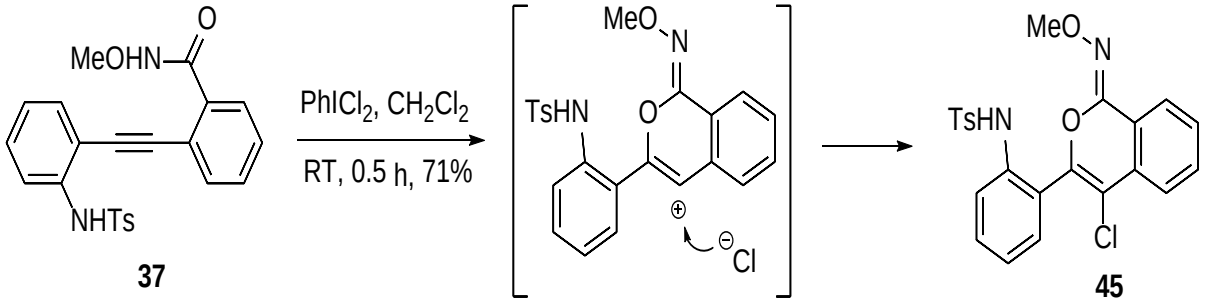


39 (X = N-Ts, Y = O)
40 (X = O, Y = O
41 (X = O, Y = N-Ome)

42 (X = N-Ts, Y = O)
43 (X = O, Y = O
44 (X = O, Y = N-Ome)

Scheme 15. Synthesis of spirocycles containing an N, O- or O, O-ketal.

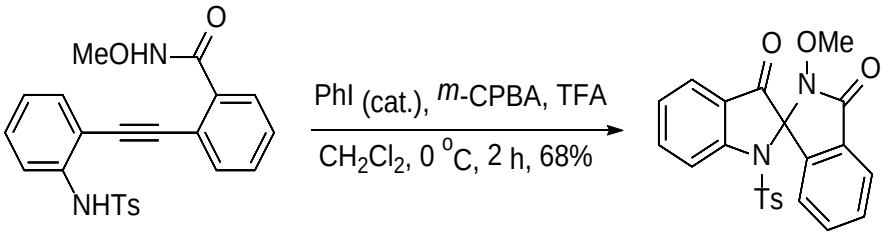
Treatment of the alkyne derivative **37** with $PhICl_2$ furnished the isochromen-1-one derivative **45** in 71% yield (Scheme 16).



37 **45**

Scheme 16. Synthesis of isochromen-1-one.

It was also noted that the spiro product **46** could be achieved through an organo catalytic oxidation of the compound **37** with the catalyst PhI and the terminal oxidant *m*-chloroper benzoic acid (*m*-CPBA) (Scheme 17).



37 **46**

Scheme 17. Synthesis of the spiro product 46.

Conclusion

It is concluded that iodine mediated cascade reactions are very useful for the preparation of a variety of isoquinolinone derivatives from azaarenes and alkylarenes, triazole derivatives from different hydrazones and diverse amines, tetracyclic indoloazulene derivatives from 2 (phenylethynyl) benzaldehyde and indole and a variety of spiro compounds from di-ortho-substituted diarylacetylenes. This procedure may be applicable for the construction of various biologically and medicinally active compounds.

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