CYCLIZATION OF ALKYNES UNDER METAL-FREE CONDITIONS: SYNTHESIS OF INDOLES

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Abstract. *The synthesis of indoles has attracted much attention because of their prevalence in numerous biologically active natural compounds, which have found widespread applications in medicinal chemistry, such as anticancer, anti-asthmatic, anti-HIV, anti-inflammatory, and antimalarial activities, among others. Transition metal-free cyclization of alkynes has become a powerful tool in the synthesis of indoles. Depending on the choice of alkyne structure and nitrogen source, a range of indoles having particular substitution patterns has been synthesized. This chapter describes the efforts in the synthesis of indole derivatives using alkynes and a nitrogen source under transition metal-free conditions.*

Contents

1. Introduction

The global need to increase the efficiency of chemical reactions by minimizing and preventing pollution has directed projects toward the development of methodologies that meet these prerequisites.[1] Cyclization reactions conducted under transition metal-free conditions have attracted many interest in the past decade because they meet the principles of green chemistry.[2] Various heterocycles that were only prepared by classical transition-metal catalyzed cyclization reactions can now be synthesized through the practice of green chemistry.[3] The base- or acid-catalyzed, radical, electrophilic cyclization reactions and electrochemical processes have recently emerged as efficient promoters of cyclization reactions, which use the principles of green chemistry. Indole derivatives are the core structures of numerous natural compounds and medicines, which have found widespread applications in medicinal chemistry, such as anticancer, anti-asthmatic, anti-HIV, anti-inflammatory and antimalarial activities, among others.[4] In this chapter, we combined the vast application of compounds containing the indole nucleus with the benefits to use a metal free-condition described in the literature in the past decade.

2. Synthesis of indoles *via* electrochemical-mediated cyclization of alkynes

Even though electrochemical-mediated reactions represent an efficient tool for organic transformation, the preparation of indoles using this methodology is rarely found in the literature, in the last ten years.[5] Following an electrochemical approach, 2-substituted indole derivatives **2** were prepared by cyclization reaction of *ortho*-alkynylanilines **1** with cyanomethyl anion (Scheme 1).[6] The cyclization was carried out by using the solvent-supporting electrolyte system [CH_3CN/0.1 M tetraethylammonium tetrafluoroborate (TEATFB)] with platinum electrodes in a divided cell under galvanostatic control (J=25 $mAcm^{-2}$) at 0 °C. The generation of the cyanomethyl anion occurred *via* a two-electron process becoming a catalytic reaction.

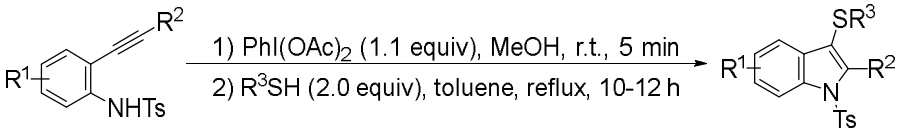
1 **2** 67-97%

R^1 = H, 2,4(Cl)$_2$, 3-F_3C, 3-Cl-5-O_2N; R^2 = H, EtO_2C; R^3 = H, aryl, alkyl, PhCH=CH_2.

Scheme 1

3. Synthesis of indoles *via* oxidative nucleophilic cyclization of alkynes

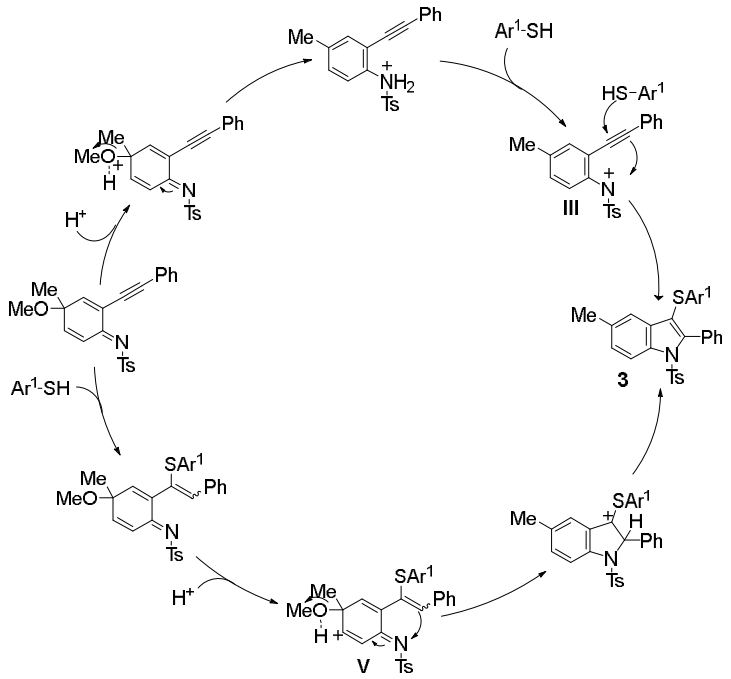
The oxidative nucleophilic cyclization of *ortho*-alkynylanilines **1** with thiophenols gave the 3-sulfenylindoles **3** *via* PhI(OAc)$_2$-mediated oxidative dearomatization and Brønsted acid-promoted nucleophilic cyclization (Scheme 2).[7] The authors carried out a series of control experiments and DFT calculations to further understand the reaction mechanism. They concluded that there are at least two possible reaction pathways, in which the structures of **III** and **V** were the key intermediates for the cyclization (Scheme 3).



1 **3** 51-76%

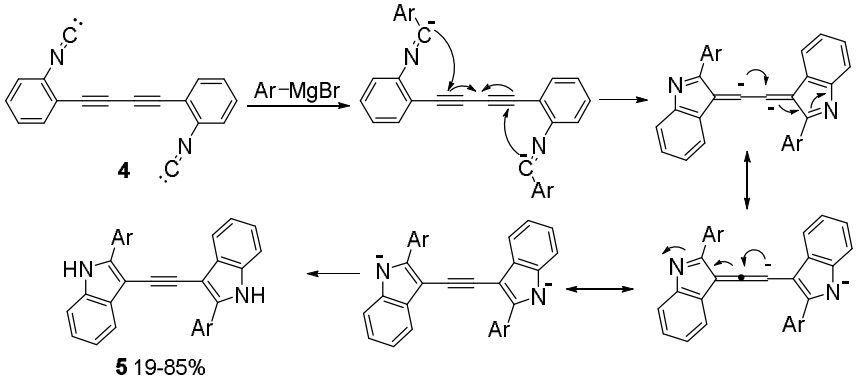
R^1 = H, alkyl, Br; R^2 = alkyl, aryl, heteroaryl, EtO_2C; R^3 = aryl.

Scheme 2



Scheme 3

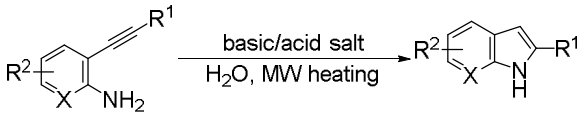
Recently, the double *ortho*-alkynyl isocyanides **4** cyclization was reported to the preparation of *bis*-(2-aryl-1*H*-indol-3-yl)ethynes **5** (Scheme 4).[8] The cyclization reaction initialized with the aryl Grignard reagent as the nucleophile, using THF as a solvent, for 10 min at room temperature. The authors investigated the structural and physicochemical features of the indole derivatives, by DFT calculations, and established that the π−electron systems and orbital energy levels can be tuned by various aromatic substituents at 2,2′-positions of the two indoles group.



Scheme 4

4. Synthesis of indoles *via* cyclization of alkynes promoted by microwave irradiation

The microwave irradiation application has been of high interest to researchers in diverse areas of chemistry. The rapid progress in microwave irradiation and its use in organic synthesis has become a consistent method for the synthesis of carbo- and heterocycles. Microwave-assisted synthesis of indole derivatives **7** was described through the intramolecular hydroamination process, followed by cycloisomerization of *ortho*-alkynylanilines **6** (Scheme 5).[9] The studies indicated that the addition of a catalytic amount of inorganic salts or bases, such as KCl, $NaHCO_3$, or pyrrolidine, proved to be very efficient to improve the yields. In addition, the authors compared the results with thermal heating conditions, finding that microwave irradiation is essential for product formation in a short reaction time and in good yields.



R^1 = H, aryl; R^2 = H, 4-MeO, 4-Cl, 4-MeOC; X = N, CH.

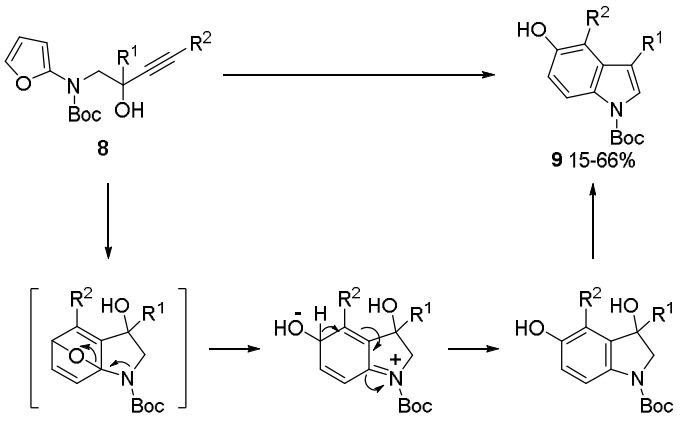
Scheme 5

The microwave-promoted the intramolecular [4+2]-cycloaddition of alkynols to furan derivatives **8**, followed by fragmentation, aromatization, and *N*-Boc deprotection cascade, gave 3,4-disubstituted 5-hydroxyindoles **9** in yields ranging from 15 to 66%.[10] When the trimethylsilyl group was directly bonded to terminal alkynes, a 1,3-silatropic rearrangement was observed, giving silyl- protected alcohol derivatives as the product (Scheme 6).

5. Synthesis of indoles *via* radical-promoted cyclization of alkynes

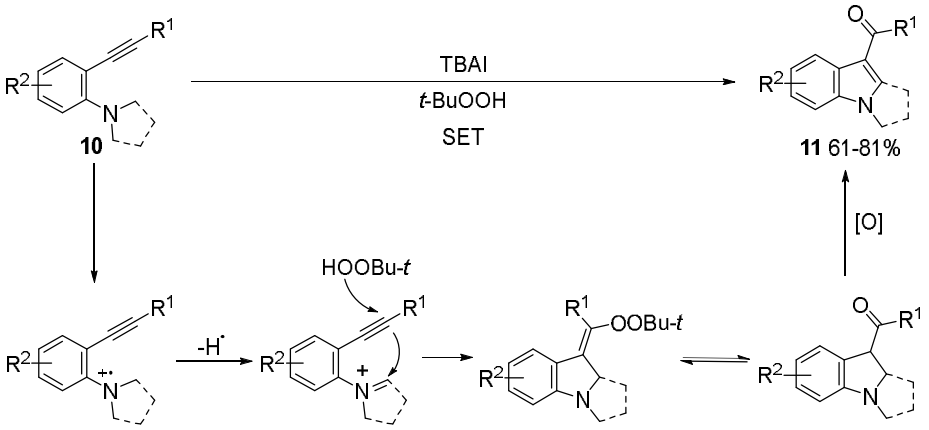
Radical cyclization reactions have found extensive use in organic synthesis, as they are well suited for the construction of both carbocyclic and heterocyclic rings. This process involves the selective radical generation, radical cyclization, and conversion of the cyclized radical to the carbo- and heterocycles. Radical

cyclization has gained prominence because of the mild reaction conditions associated with high regio- and stereochemistry and high functional group tolerance. Accordingly, 3-aroylindoles **11** were conveniently prepared by *ortho*-alkynylanilines **10** in an intramolecular oxidative coupling pathway using TBAI as a catalyst and TBHP as the oxidant. In this protocol, there was the simultaneous formation of carbon-carbon and carbon-oxygen bonds at the expense of two sp^3 carbon-hydrogen bonds (Scheme 7).[11] The mechanism proposed starts with the formation of an aminyl radical cation *via* a single electron transfer (SET) sequence, followed by the iminium intermediate formation *via* the abstraction of a hydrogen radical. The attack of water or TBHP at the triple bond gives the vinyl ether intermediate species, which after oxidation and aromatization processes afford the 3-aroylindoles (Scheme 7).



R^1 = alkyl, aryl, heteroaryl, $PhCH_2CH_2$; R^2 = alkyl, aryl.

Scheme 6

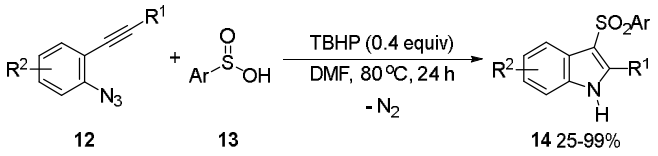


R^1 = aryl; R^2 = H, 4-Me, 4-Cl.

Scheme 7

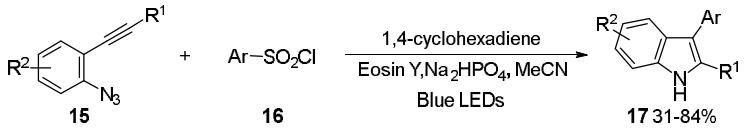
The *tert*-butyl hydroperoxide-promoted cascade sulfonation/cyclization of *ortho*-alkynylarylazides **12** was used to prepare 3-sulfonylindoles **14** (Scheme 8).[12] Based on the experimental evidence, the author concluded that in this annulation reaction, the TBHP is the sulfonyl radical initiator, whereas the sulfinic acid **13** is the sulfonating reagent. The cascade annulation involving *ortho*-alkynylarylazides **15** and arylsulfonyl chlorides **16** proceeded through the visible-light initiated cyclization reaction to give the

unsymmetrical 2,3-disubstituted indoles **17** (Scheme 9).[13] Recently, an alternative route to prepare unsymmetrical 2,3-diaryl-substituted indoles **20** was developed. The reaction involved the visible light and eosin Y to catalyze the cyclization reaction of *ortho*-alkynylarylazides **18** with aryl diazonium salts **19** *via* a photoredox process (Scheme 10).[14]



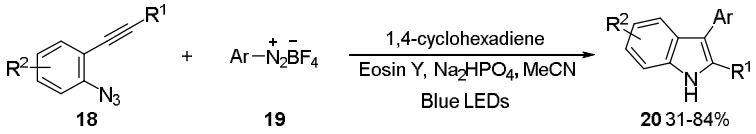
R^1 = aryl, heteroaryl, R^2 = H, 4-Me, 4-Br, 4-Cl, 4-F, 4-F_3C.

Scheme 8



R^1 = alkyl, aryl, heteroaryl; R^2 = H, 4-Cl, 3-F, 4-F, 3,4$(Cl)_2$, 4-MeO, 3-Me.

Scheme 9



R^1 = alkyl, aryl, heteroaryl; R^2 = H, 4-Cl, 3-F, 4-F, 3,4$(Cl)_2$, 4-MeO, 3-Me.

Scheme 10

In addition, several studies have shown that tryptophol derivatives **23** can be prepared by the reaction of *ortho*-alkynylanilines **21** with alkynes **22**. The reaction took place through the carbon-carbon hemolytic cleavage, followed by oxygen trapping with a subsequent intramolecular 1,5-hydrogen atom transfer and peroxide tryptophol reduction (Scheme 11).[15]

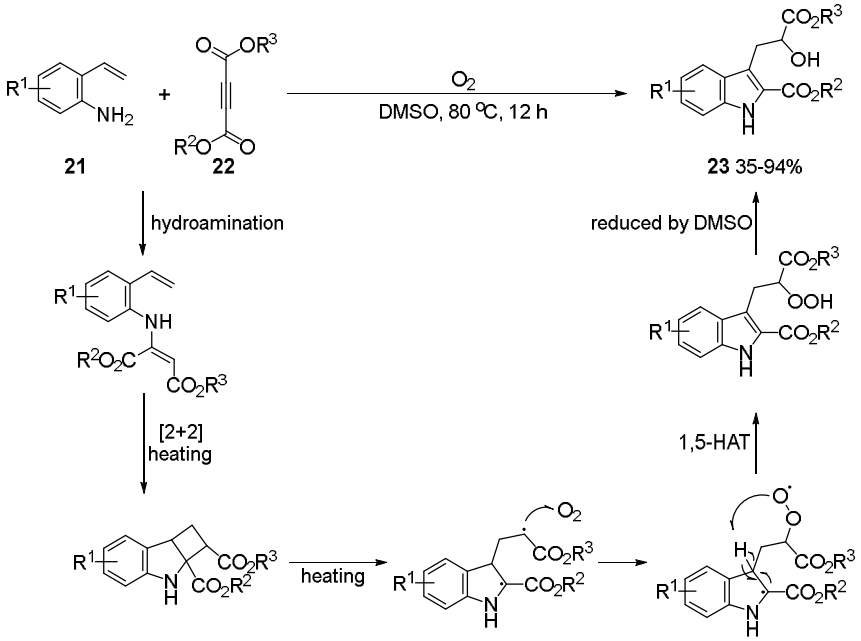
The oxidative cyclization of *ortho*-alkynylanilines **24** with diorganyl dichalcogenides **25** induced by visible-light irradiation, in the presence of H_2O_2, under transition metal- and photocatalyst free conditions, proceeds smoothly to form 3-organochalcogenylindoles **26** (Scheme 12).[16] The control experiments carried out by the authors indicated that the first reaction step consists of the cyclization of *ortho*-alkynylaniline promoted by hydroxyl radical, initiated by cleavage of H_2O_2 under blue LED irradiation. The reaction is finalized with dichalcogenides, which lead to the indole derivatives. The *tert*-butoxyl and *tert*-butylperoxy radicals and iodine can both promote the cascade radical annulation of *ortho*-alkynylanilines **27** with sulfonyl hydrazides **28**, introducing the sulfanyl functionalization at 3-carbon of the indoles **29** (Scheme 13).[9] When the reactions were carried out in the absence of TBHP the corresponding 3-arylsulfanylindoles were obtained, *via* classical electrophilic annulation reactions.

6. Synthesis of indoles *via* base-promoted cyclization of alkynes

Base-promoted annulation reaction of alkynes is one of the most convenient methods for the synthesis of heterocyclic compounds. In this context, o*rtho*-alkynylanilines **30** were transformed to the corresponding indoles **31** *via* reaction of KH at room temperature for 3 h (Scheme 14).[17] In a similar way, treatment of *ortho*-diyneanilines **32** under the same reaction conditions gave 2-alkynylindoles **33** in 73-83% yields (Scheme 15).[18]

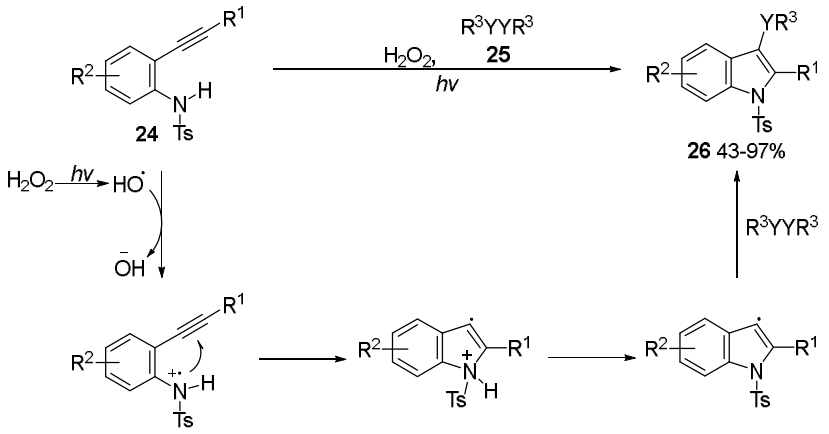
In another approach, 2-substituted indoles **36** were prepared using NaOH to induce a 5-*endo*-dig cyclization of *ortho*-alkynylanilines as the key step. A one-pot version of this cyclization, starting from

ortho-iodoanilines **34** and terminal alkynes **35**, was also efficient for the indoles formation; moreover, under these conditions, the use of palladium and copper(I) salts were required (Scheme 16).[19]



R^1 = H, 4-Me, 4-Et, 4-*n*-Bu, 4-*t*-Bu, 3-MeO, 4-MeO, 4-EtO, 4-MeO_2C, 4-EtO_2C, 4-Cl, 4-Br, 4-F, 4-Ph, 4-F_3CO, 2,4$(Me)_2$, 2-(Me)-3-(F); R^2 = R^3 = alkyl, vinyl; R^2 = Me, CN, Et and R^3 = alkyl, Ph.

Scheme 11

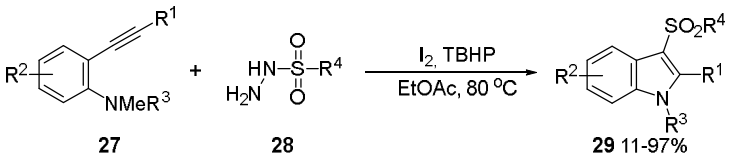


R^1 = aryl; R^2 = H, 4-Me, 4-MeO, 3-Cl, 4-Cl, 4-F, 4-NC, 4-Cl-2-F; R^3 = aryl, alkyl; Y = S, Se.

Scheme 12

The base-catalyzed cyclization of *ortho*-iodoanilines **37** having a sulfur substituent, afforded the 2-methylthio-indoles **38** in 54-89% yields (Scheme 17).[20] The presence of sulfur group was essential for the use of catalytic amounts of DBU. In this case, a propargyl-allenyl intermediate is easily formed by the

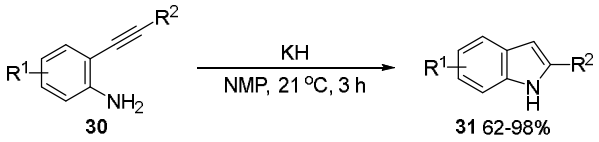
presence of base and the assistance of the sulfur atom, which activates the carbon-carbon triple bond towards the nitrogen nucleophilic attack.



27 **28** **29** 11-97%

R^1 = alkyl, aryl; R^2 = H, 4-Br, 3-Cl, 4-Cl, 4-F, 4-Me; R^3 = Et, $(CH_2)_3CH_2I$; R^4 = aryl.

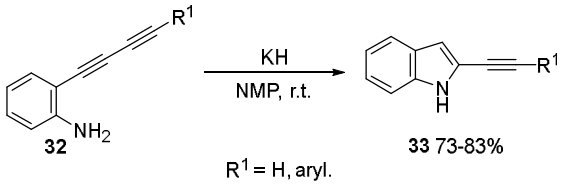
Scheme 13



30 **31** 62-98%

R^1 = Cl, EtO_2C, NC, Br, NC, EtO_2C, MeS, PhOC; R^2 = Aryl, Alkyl.

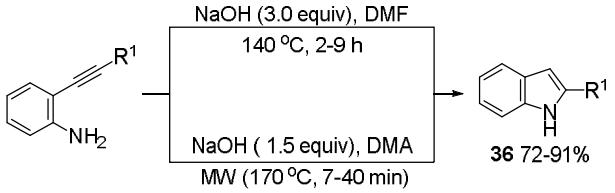
Scheme 14



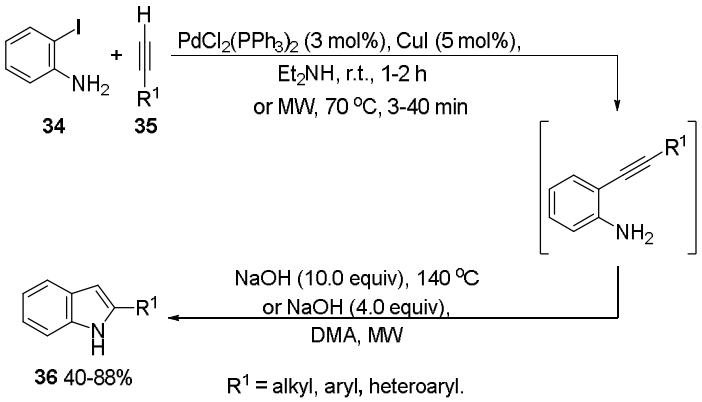
32 **33** 73-83%

R^1 = H, aryl.

Scheme 15



36 72-91%

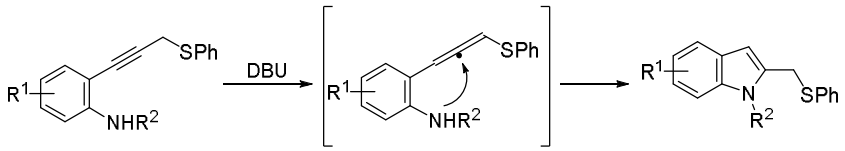


34 **35**

36 40-88%

R^1 = alkyl, aryl, heteroaryl.

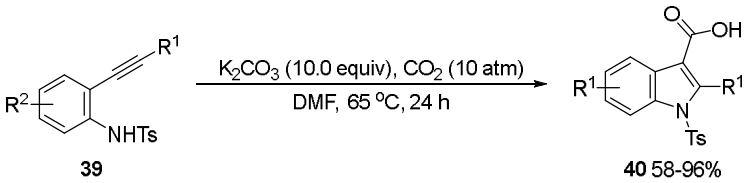
Scheme 16



R^1 = H, 4-Me; R^2 = H, alkyl, aryl, heteroaryl, Ms, Ac.

Scheme 17

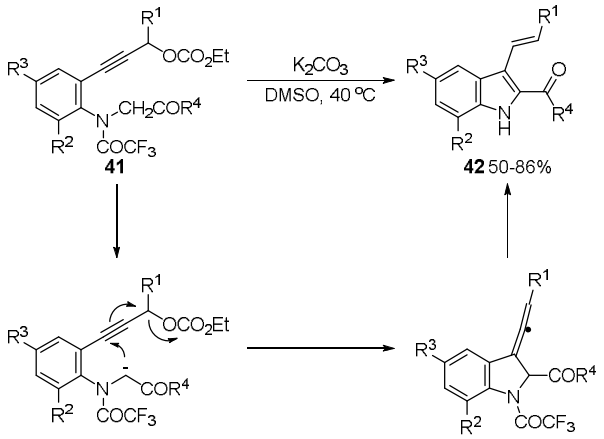
Tandem-type cyclization carboxylation reactions using *ortho*-alkynylaniline derivatives **39** provided 3-carboxylated indoles **40** (Scheme 18).[21] The complete optimization of the reaction conditions indicated that K_2CO_3 is the only reagent required to mediate the process. The reaction proceeds efficiently under 10 atm of CO_2 in the complete absence of any transition metal catalyst.



R^1 = alkyl, aryl; R^2 = H, 3-MeO, 4-MeO, 4-MeO_2C, 4-Br-, 3-Cl, 4-Cl, 4-F.

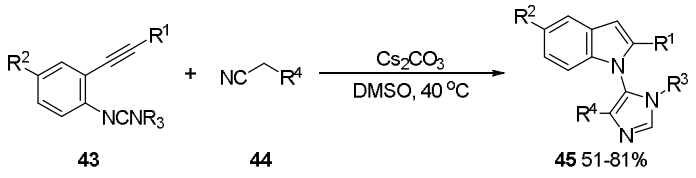
Scheme 18

The sequential alkylation/cyclization/isomerization of ethyl 3-(otrifluoroacetamidoaryl)-1-propargyl esters **41** was applied to the synthesis of 2-acyl and 2-ethoxycarbonyl-3-alkenyl indoles **42** (Scheme 19).[22] The reaction proceeded *via* the formation of an allenyl intermediate, which after isomerization and hydrolysis of the trifluoroacetamido group affords the free 1*H*-indole derivatives. Base-promoted sequential reaction has been also extended to *N*-[2-(1-alkynyl)phenyl]carbodiimides **43** with isocyanides **44**, which led to the preparation of *N*-imidazole indole derivatives **45** (Scheme 20).[23] The studies suggested that an initial [3+2]-cycloaddition of isocyanide to carbodiimide, followed by the intramolecular cyclization are involved in this process.



R^1 = H, phenyl; R^2 = H, Me, Cl, F; R^3 = H, Cl, Me; R^4 = Ph, EtO.

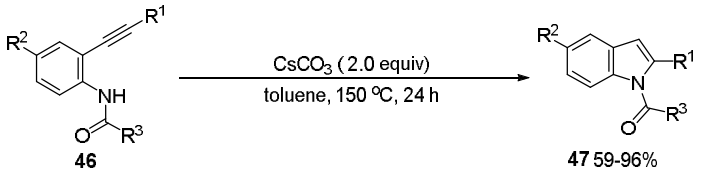
Scheme 19



R^1 = aryl, alkyl; R^2 = H, Me, Cl; R^3 = aryl, alkyl; R^4 = EtO_2C, *t*-BuO_2C, Ts.

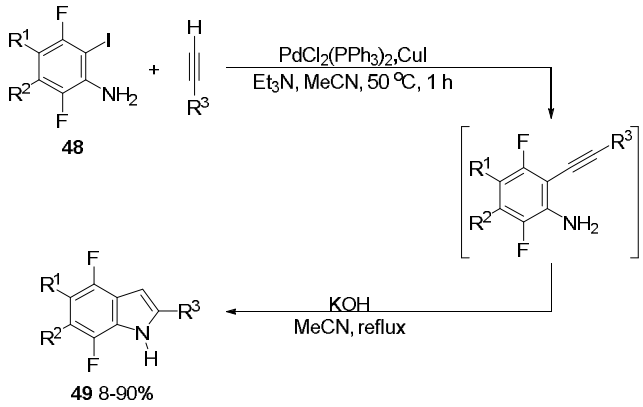
Scheme 20

The use of cesium carbonate to promote the cyclization of *ortho*-alkynylanilides **46** is another methodology available for the synthesis of *N*-substituted-indoles **47** (Scheme 21).[24] The reaction was carried out with Cs_2CO_3 in toluene at 150 °C for 24 h. KOH has been also found to be an efficient base for the conversion of polyfluorined *ortho*-alkynylanilines **48** to the corresponding indoles **49** (Scheme 22).[25] A one-pot version of this cyclization using a sequence of cross-coupling of polyfluorinated *ortho*-iodoanilines with terminal alkynes, followed by in situ cyclization of *ortho*-alkynylanilines, also afforded the corresponding indoles.



R^1 = H, Ph, *n*-Pr, $PhOCOCH_2CH_2$; R^2 = H, NC, MeO_2C; R^3 = Me, Ph.

Scheme 21



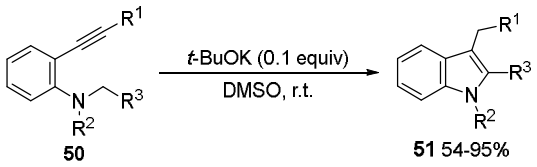
R^1 = H, F; R^2 = F_3C, F; R^3 = H, aryl, alkyl, $HO(CH_3)_2CH$, $THPOCH_2$.

Scheme 22

It was found that a catalytic amount of *t*-BuOK in DMSO at room temperature can be used to promote the intramolecular cyclization of *ortho*-alkynyl-*N*,*N*-dialkylarylanilines **50** leading to 2-aryl indoles **51** (Scheme 23).[26] The reaction mechanism involves the formation of α-aminoalkyl radical intermediates, in which the *t*-BuOK/DMSO system probably works as the crucial initiator.

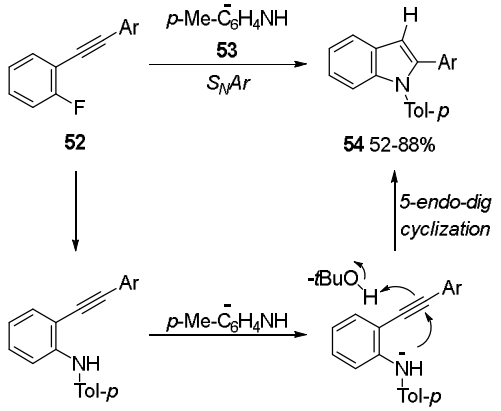
Nucleophilic aromatic substitution, followed by a 5-*endo*-dig cyclization reaction between *ortho*-fluoro-arylalkynes **52** and a nucleophile, such as *p*-toluidine **53**, under *t*-BuOK conditions was an efficient methodology to prepare 2-substituted-indoles **54** (Scheme 24).[27] It was mentioned that

carbon-carbon from alkynes has a dual role acting as an electron-withdrawing group to activate the substrate for S_NAr, and to deliver the carbon-carbon group for the formation of the indole ring.



R^1 = alkyl, naphthyl, aryl; R^2 = alkyl; R^3 = H, aryl, naphthyl.

Scheme 23



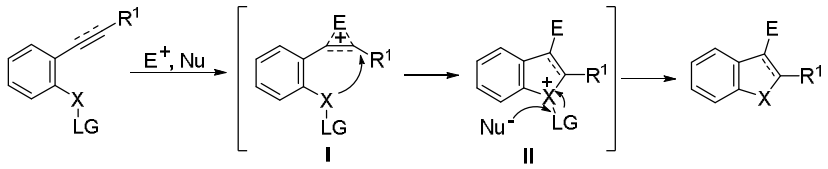
Scheme 24

7. Synthesis of indoles *via* nucleophilic cyclization of alkynes promoted by electrophiles

The necessity to develop most environmentally, cost effective, green and mild methodologies for the preparation of *N*-heterocycles is a global trend adopted by all laboratories in the last decades. Many *N*-heterocycles that were previously prepared only by classical transition-metal catalyzed cyclization reactions can now be prepared using metal-free conditions, without losing the advantages that other methods offered. The benefits to use a metal free-condition are the reduction of chemical wastes generation, the reaction time, solvent, and energy, resulting in clear economic impacts and environmental benefits. From the synthetic point of view, the use of ionic liquids as solvents and microwave-irradiated reactions were the main tools used to achieve these benefits. There are many methodologies described in the scientific literature that use conditions which can led to efficient, cheaper and more sustainable reactions. Among them, base- or acid-catalyzed, radical, electrophilic cyclization reactions and electrochemical processes have recently emerged as efficient promoters of cyclization reactions. In the next sections, we will report the methodologies published in the last ten years, which used metal-free conditions to prepare indoles starting from alkynes and nitrogen compounds.

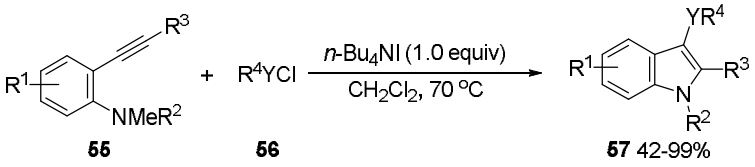
The electrophilic heteroatom cyclization, in particular halocyclization reactions of alkynes, has emerged as powerful methods to construct carbocycles and heterocycles. The main advantages to use this methodology are that the electrophilic source has dual role, by acting as a *cyclizing* agent and to incorporate the electrophile, which is suitable to suffer further transformations. The electrophilic cyclization has been demonstrated as an efficient tool in the syntheses of highly functionalized indoles, employing electrophiles like I_2, ICl, or organochalcogen derivatives. This process involves the activation of carbon-carbon triple bond of alkyne by the addition of the electrophilic source, affording an intermediate **I**. The anti-nucleophilic attack of the nitrogen atom on the activated intermediate gives the salt **II**. The removal of the group bonded

to nitrogen, *via* nucleophilic substitution by the nucleophile present in the reaction mixture, generates the indole product (Scheme 25).



Scheme 25

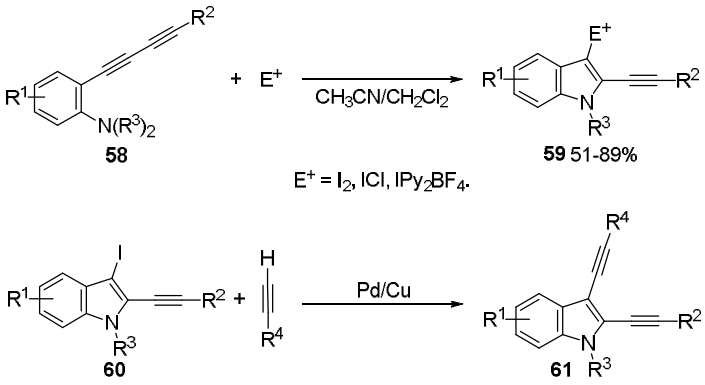
3-Sulfenyl and 3-selenylindoles **57** were prepared by *n*-Bu_4NI-induced electrophilic cyclization of *N*,*N*-dialkyl-2-(1-alkynyl)anilines **55** using arylsulfenyl or arylselenyl chlorides **56** as electrophilic sources (Scheme 26).[28] These reaction conditions permitted the construction of the indole and the installation of a sulfenyl or selenyl group in the 3-position of the indole ring. The presence of *n*-Bu_4NI was a critical factor to the success of the cyclization, which acted either to remove the methyl group from nitrogen *via* nucleophilic substitution or to the in situ preparation of arylchalcogenyl iodide, *via* halogen exchange reaction from arylchalcogenyl chlorides.



R^1 = aryl; R^2 = alkyl; aryl; R^3 = H, Me, Br, CO_2Me; R^4 = aryl; Y = S, Se.

Scheme 26

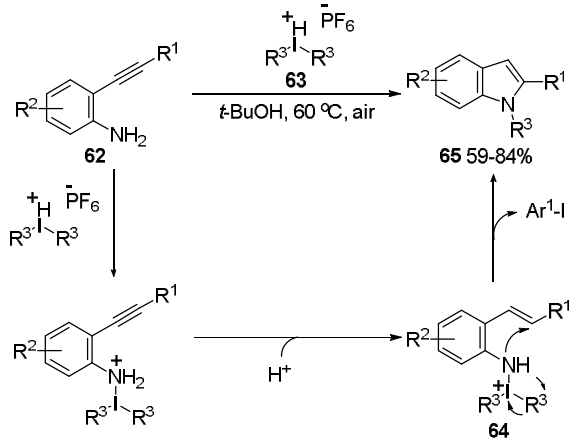
The iodocyclization of *ortho*-2,3-diyneanilines **58** allowed the preparation, in a single step, of 2-alkynyl indoles **59** having an iodine functionality at the 2-position (Scheme 27).[29] The authors found that the effect of solvent polarity and the nucleophilicity of nitrogen group were parameters that influence the yields of the indole derivatives. In addition, the 2-alkynyl indoles **60** were used as starting material for the Sonogashira cross-coupling leading to the preparation of enediynes fused to indoles **61**. It was also found that *N*-arylindoles **65** could be prepared from *ortho*-alkynylanilines **62** and diphenyliodonium hexafluorophosphate **63** in *t*-BuOH under air at 60 °C.[30]



R^1 = H, 4-EtO_2C, 4-MeO_2C; R^2 = alkyl, Ph, $HO(CH_2)_4$, $TBDMSO(CH_2)_4$; R^3 = alkyl; R^4 = alkyl, $HOCH_2CH_2CH_2$, TMS, aryl.

Scheme 27

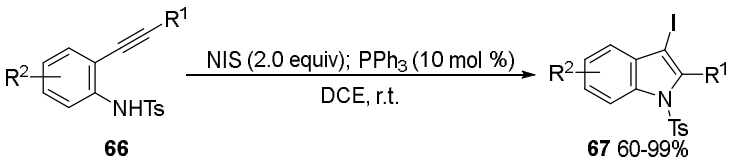
The authors carried out some control experiments, which indicated that the structure **64** is the key intermediate of the cyclization and that the aryl transfer to the nitrogen atom occurred during the cyclization process rather than as an arylation of 1*H*-indole (Scheme 28).



R^1 = aryl; R^2 = H, 4-Me, 4-Cl, 4-F; R^3 = aryl.

Scheme 28

The utility of triphenylphosphine as activating of iodine atom from NIS was tested in the electrophilic cyclization reaction of *ortho*-alkynylanilines **66** giving 3-iodoindole derivatives **67** as products (Scheme 29).[31] The authors studied the effects of various reaction parameters, such as the use of different phosphines, solvents, temperature, and *N*-protecting groups on *ortho*-alkynylanilines, which could affect the yields. The results indicated that the reaction rate depends on the triphenylphosphine as a catalyst and the presence of sulfonamides as an *N*-protecting group.



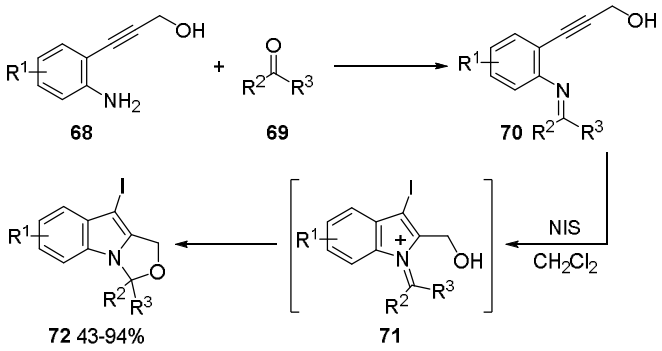
R^1 = aryl, alkyl; R^2 = H, 4-Me, 5-Me, 4-MeO, 4-Br, 4-Cl, EtO_2C.

Scheme 29

The application of a Schiff's base, easily prepared by condensation of *ortho*-alkynylanilines **68** with carbonyls compounds **69**, in a tandem electrophilic cyclization, followed by nucleophilic addition, was a useful way to the preparation of indoles **72** in a one-pot procedure (Scheme 30).[32] This methodology was further successfully applied to the synthesis quinoline and quinolone derivatives using the same starting material just by a simple modification in the reaction conditions. The authors proposed a very clear reaction mechanism, in which an iminium ion **71** could be one of the key intermediates for the second cyclization step. The same group successfully applied the iodocyclization of *ortho*-alkynylbenzimidate **73** for the preparation of thieno-fused indoles **74** (Scheme 31).[33] The authors demonstrated the applicability of thieno-fused indoles to substrates in cross-coupling reactions.

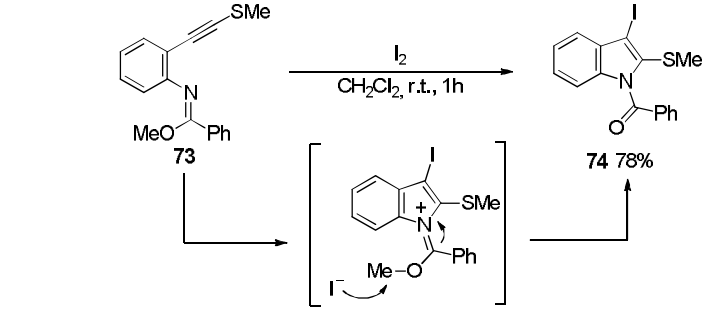
The cyclization of 1-(2-aminoaryl)propynols **75** to 1*H*-indole-2-carbaldehydes **76** has been achieved with NIS as the electrophilic source and a mixture of H_2O/acetone (25:1) as solvent (Scheme 32).[34] The mechanism proposed by the authors involves the nucleophilic addition of nitrogen to the alkyne associated with the capture of the iodine from NIS, giving the vinyl iodide intermediate **77**. Activation of the hydroxyl

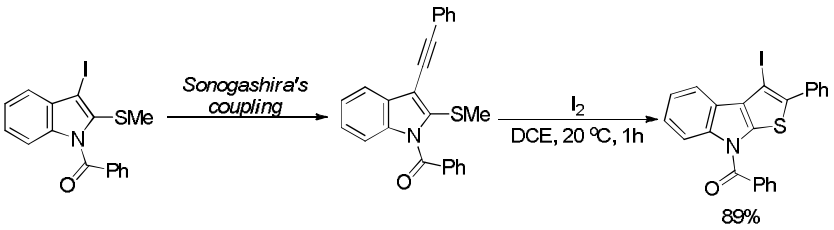
group by another molecule of NIS, followed by nucleophilic substitution by H_2O, affords the indole after the elimination of HI and nitrogen deprotection (Scheme 33).



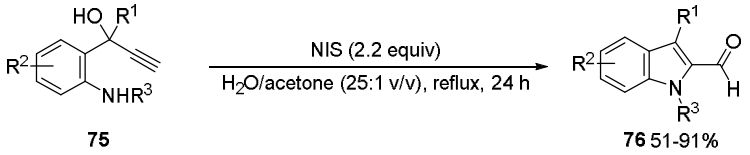
R^1 = H, 4-Me; R^2 = aryl, EtO; R^3 = H, aryl, OEt.

Scheme 30





Scheme 31

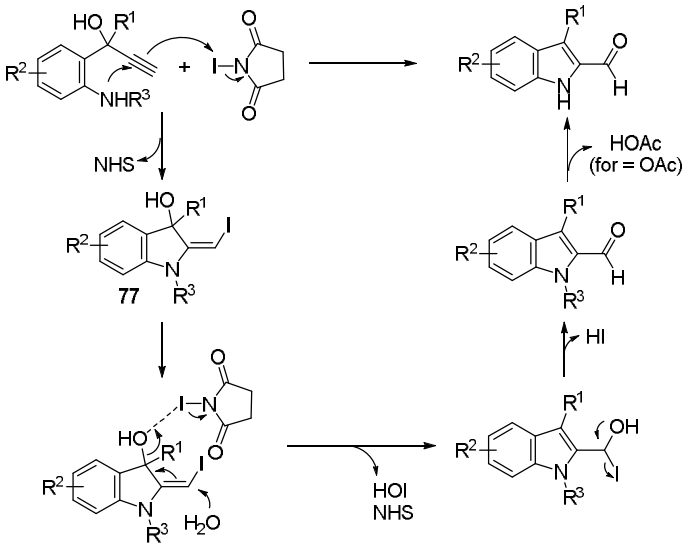


R^1 = H, alkyl, aryl; R^2 = H, 4-Me, 4-MeO, 4-Br, 4-Cl, 2,4-$(Me)_2$; R^3 = H, Ts, Ac.

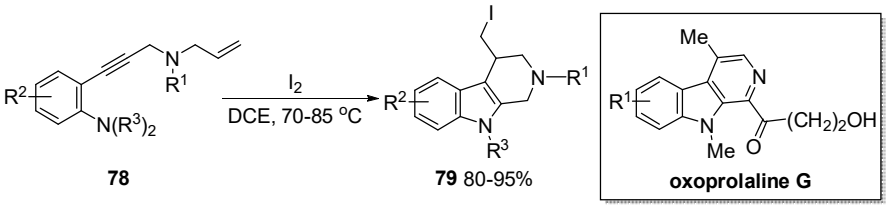
Scheme 32

The comparison of reactivity between alkynes and alkenes, in the electrophilic cyclization of *ortho*-alkynylanilines **78** having an alkene chain in the terminus position, has been reported to the preparation of 4-iodomethyl substituted tetrahydro-β-carboline indoles **79** (Scheme 34).[35] The results

indicated that this methodology involved two electrophilic iodocyclization reactions, in which the carbon-carbon from alkynes was cyclized first then alkenes. In addition, the authors also used this approach to the formal synthesis of the natural product oxopropaline G.



Scheme 33



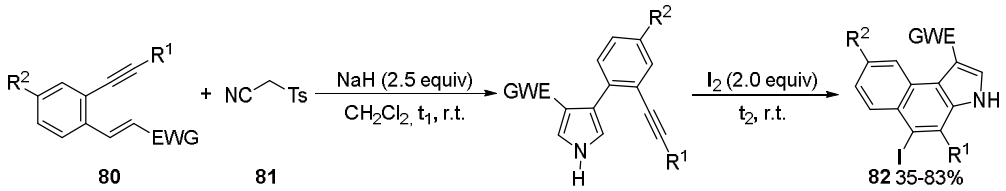
R^1 = Ts, Ms, Bn; R^2 = H, 4-Me, 3-MeO, 4-Cl, 4-O_2N; R^3 = alkyl.

Scheme 34

The halogen functionalization of the 3-position of indoles, *via* the electrophilic cyclization reaction of *ortho*-alkynylanilines is extensively used, whereas the functionalization of the 6-position is quite rare. An efficient regioselective [3+2]-cycloaddition/iodocyclization cascade reaction involving *ortho*-alkynylchalcones/cinnamates **80** and toluenesulfonylmethyl isocyanide **81** has been described to the preparation of 6-iodoindole derivatives **82** (Scheme 35).[36] The key steps for this cyclization are the formation of a pyrrole ring *via* a [3+2]-cycloaddition of cinnamates with toluenesulfonylmethyl isocyanide, followed by an intramolecular 6-*endo*-dig halo cyclization.

8. Miscellaneous strategies

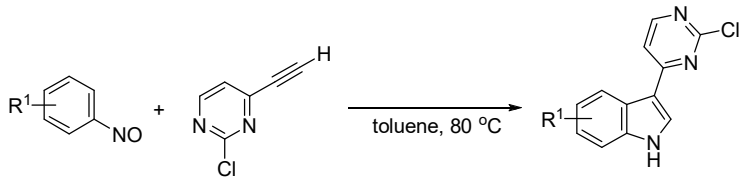
The indolization of nitrosoarenes **83** was carried out by using terminal alkynes **84** in toluene at 80 °C for the preparation of 3-(2-chloropyrimidinyl)-indoles **85** in moderate to good yields (Scheme 36).[37] The scale-up procedure for one reaction starting from 2 g of starting material gave the products in very similar yields, indicating that this methodology is robust without the necessity of adaptation in the reaction conditions for gram-scale preparation. The methodology was applied in the syntheses of meridianins and meridianin analogues, which are marine alkaloids known as kinase inhibitors.



80 **81** **82** 35-83%

R^1 = aryl, heteroaryl, vinyl; R^2 = H, halogen.

Scheme 35

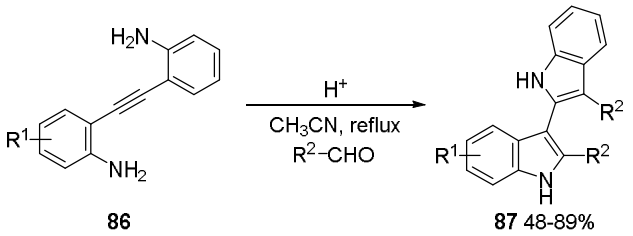


83 **84** **85** 19-71%

R^1 = H, 2-CH_3, 3-Br, 4-Br, 2-F_3C, 2-O_2N, 4-O_2N, 4-NC, 4-HO_2C, 4-MeO.

Scheme 36

When the condensation of *ortho*-alkynylanilines **86** with aldehydes was carried out under Brønsted acid catalysis, 2,2′-disubstituted 1*H*,1′*H*-3,3′-biindoles **87** was formed from 48 to 89% yields (Scheme 37).[38] The procedure required only a catalytic amount of HCl in acetonitrile to form four new chemical bonds and two indole rings in a one step reaction.



86 **87** 48-89%

R^1 = H, 2-Cl, 2-F, 3-F_3C; R^2 = aryl.

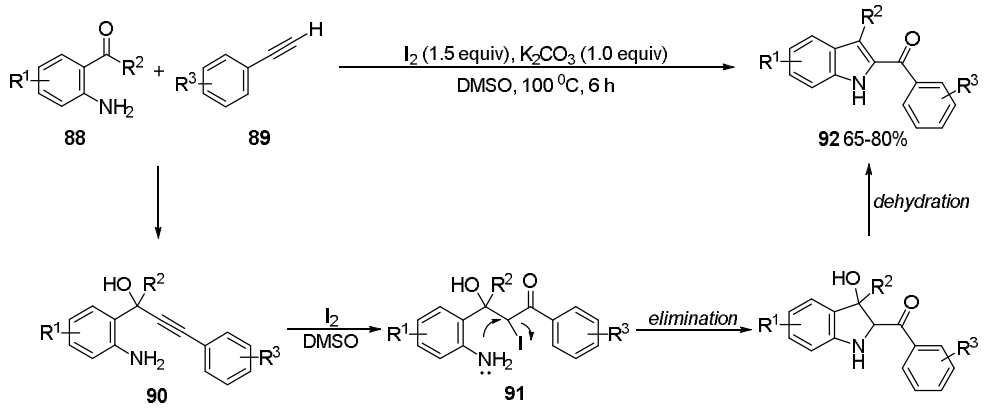
Scheme 37

By continuing on the subject of carbonyl compound and alkyne uses in a metal-free conditions to prepare indoles, the condensation reaction of 2-amino acetophenones **88** and alkynes **89** in the presence of I_2 (1.5 equiv), K_2CO_3 (1.0 equiv) in DMSO at 100 °C was employed to prepare 2-acylindoles **92** (Scheme 38).[39] The authors have performed a series of experiments and concluded that this cyclization afforded the indoles *via* an initial attack of the terminal alkyne on keto group on 2-amino acetophenone, giving the aminopropargyl alcohol derivative **90**. The iodine/DMSO activates the alkyne group and forms the carbonyl intermediate **91**, which affords the product *via* cyclization, elimination and dehydratation sequence.

9. Conclusion

The presence of indole nucleus in numerous biologically active natural compounds, which have found widespread applications in medicinal chemistry, such as anticancer, anti-asthmatic, anti-HIV, anti-inflammatory and antimalarial activities, among others, has attracted much attention from chemists for several decades to the synthesis and applications of these *N*-heterocycle compounds. The reaction of alkynes with a nitrogen source, under transition-metal free conditions, is one of the most efficient strategy for the

synthesis of higher substituted indoles. To demonstrate the potential of this methodology, the chapter mostly focused on recent approaches involving the cyclization of alkynes with amino compounds *via* electrochemical conditions, oxidative nucleophilic cyclization of alkynes, microwave irradiation, radical-promoted cyclization, base-and electrophile-promoted the cyclization reactions.



Scheme 38

Acknowledgements

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