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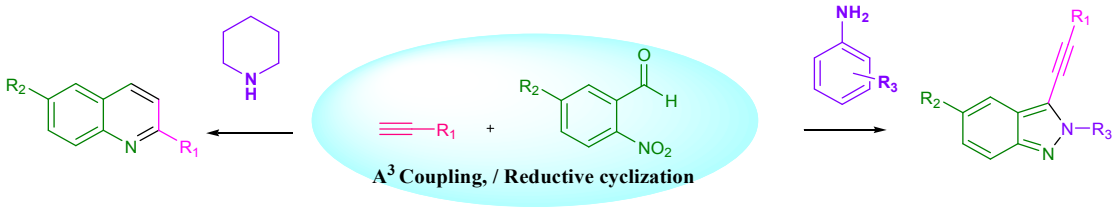

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Facile Synthesis of 2-Substituted Quinolines and 3-Alkynyl-2-Aryl-2*H*-Indazole *via* $SnCl_2$-Mediated Reductive Cyclization

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A rapid and efficient $SnCl_2.2H_2O$ mediated synthesis of quinolines and indazoles have been developed using A^3-coupling followed by reductive cyclization. The key highlights are the formation of quinoline in a one-pot fashion and indazole through N-N bond formation.

The synthesis of heterocyclic compounds embedded with nitrogen, are the subject of extensive research in organic chemistry as they are pivotal skeletons in many biologically active natural products as well as numerous pharmacologically interesting compounds.[1] Quinoline is one of the ubiquitous structural motifs and a variety of its derivatives have been used as antibacterial, antimalarial, anti-inflammatory, anticancer and antihypertensive.[2] They also have found utility as synthetic intermediates for the preparation of dyes, polymers and ligands for the preparation of OLED phosphorescence complexes.[3] Indazole ring system has also gained attention due to its efficacy as pharmacophores in drug discovery (Figure 1).[4]

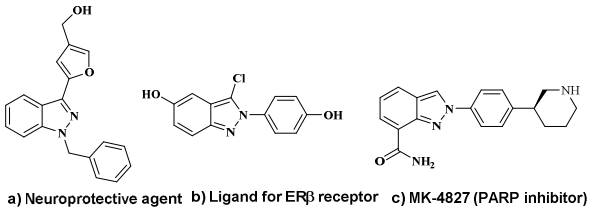
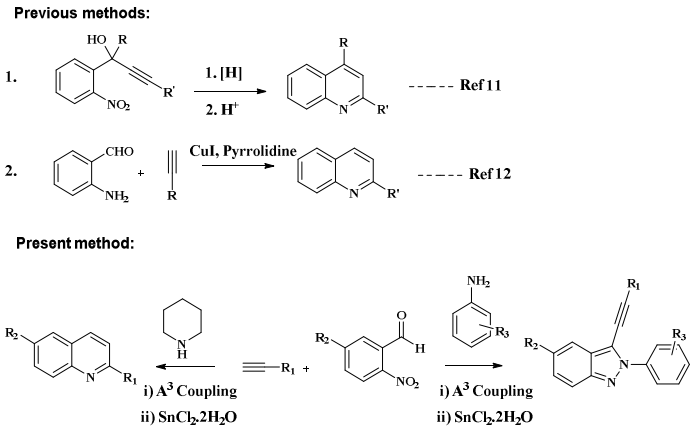


Figure 1. A few examples of biologically active indazoles

Synthesis of various quinoline derivatives have been radically studied since its discovery by Gerhardt in 1842.[5] Skraup reaction, Combes synthesis, Friedländer synthesis, Pfitzinger reaction and Doebner-Miller reaction[6] are some of the well-known synthetic methods for the synthesis of quinoline derivatives. Though many of these methods are effective they often require longer reaction time. Hence the reports dealing with simple and efficient synthesis of quinoline derivatives have drawn much attention in recent years.

Multicomponent reactions (MCR) have been much utilized for the synthesis of functionalized heterocyclic molecules by one-pot strategy.[8] The remarkable advantage of these reactions are operational simplicity, convergence and facile automation. Chemists are fascinated by MCR's as they offer the synthesis of complex molecules using simple starting materials in a greener fashion. Stannous chloride is a mild and highly chemoselective reducing agent for various organic transformations and it is most commonly used for selective reduction of nitro to amine fuctionalities because of its high reactivity, affordability, eco-friendly nature and safety profile. $SnCl_2$ is also used for intramolecular cyclization of nitroaryl substrates.[9]



Scheme 1. Previous and present methods for the synthesis of quinolines

Quinolines are synthesized from propargylalcohol using $SnCl_2$ and $ZnCl_2$ by a one-pot two step reduction-condensation sequence.[10] The strategies employed by Shong *et al*.[11] and Patil *et al*.[12] have provided direct access to substituted quinolines. Nevertheless the former strategy suffers from the usage of dry reaction conditions for the preparation of propargylalcohol and drawback of latter one is the use of self condensing 2-aminobenzaldehyde as a starting material.[13] Thus the new routes are still desirable. The present method offers the efficient protocol for the preparation of quinoline derivatives from simple, safe starting materials and catalyst in a one-pot strategy.

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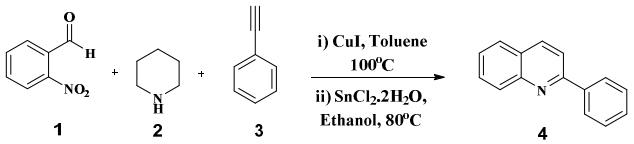
In recent years propargylamines are considered to be the most important starting materials for the synthesis of structurally diverged heterocyclic molecules.[14] Our research group have been working on the synthesis of various heterocyclic moieties from *N*-benzylpropargylamine derivatives using palladium catalyst.[15] As a continuation of our work to explore the synthetic utility of propargylamines, we herein report the simple and efficient synthesis of quinoline and 2*H*-indazole from 2-nitro-*N*-benzylpropargylamine *via* $SnCl_2.2H_2O$ mediated reductive cyclization. There have been many efforts taken by the chemists for the preparation of indazole derivatives.[16] Thus the current protocol yields simple and efficient procedure for the synthesis of 3-alkynyl-2-aryl-2*H*-indazole.

Results and Discussion:

In a preliminary study, *N*-benzyl propargylamines were prepared by A^3-coupling reaction using CuI as mentioned by the literature procedure.[15d] As an exploratory experiment 2-nitrobenzaldehyde **1**, piperidine **2** and phenylacetylene **3** were chosen as a model substrates to optimize the reaction conditions. After the completion of the reaction, solvent was removed and the product was purified by column chromatography. The reaction afforded propargylamine in 86% yield. To the ethanolic solution of propargylamine $SnCl_2.2H_2O$ was added and heated at 70°C for 2h. The reaction proceeded smoothly to afford a product quinoline **4** in 84% yield after work-up and purification by column chromatography (Scheme 2). The product was confirmed by NMR experiments. We have performed the similar reaction in one-pot fashion. To our delight the desired product was obtained without any significant change in the yield. To the best of our knowledge, there have been no reports for the synthesis of the quinoline derived from 2-nitrobenzaldehyde, piperidine and alkyne.



Scheme 2 .Preparation of quinoline by one-pot A^3- coupling followed by reductive cyclization

The optimization of reaction conditions including the reaction temperature, reductive reagent and its feed ratio to the reactant was then investigated (Table 1). In the beginning, we found that the usage of 2 equiv of $SnCl_2.2H_2O$ afforded 65% yield of **4** with incomplete conversion of propargylamine **5** even after heating at 70°C for 4 h (Table 1,entries 1 and 2). Eventually the increase in the feed ratio of $SnCl_2.2H_2O$ led to complete conversion with much improved 85% yield. Ultimately we found that better results and shorter reaction time could be achieved by the treatment of 4 equiv of $SnCl_2.2H_2O$. With this optimized ratio of catalyst, the increase in temperature and reaction time exhibited no apparent increase in yield (Table 1,entries 3 to 8). In addition it was observed that the usage of $SnCl_2.2H_2O$, HCl-EtOH as a reducing agent gave the lower yield of desired product (Table 1, entries 9 and 10). Thus the procedure reported in entry 5 has been chosen as our standard reaction conditions for our study of various derivatives.

Having established the optimal reaction conditions we then examined a variety of alkyne and aldehyde substrates to explore the generality of this new method (Table 2). Initially a variety

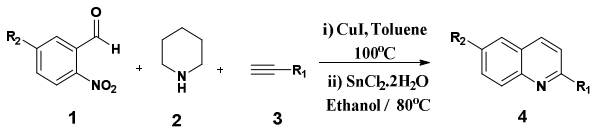
Table 1. Optimization of reaction conditions:

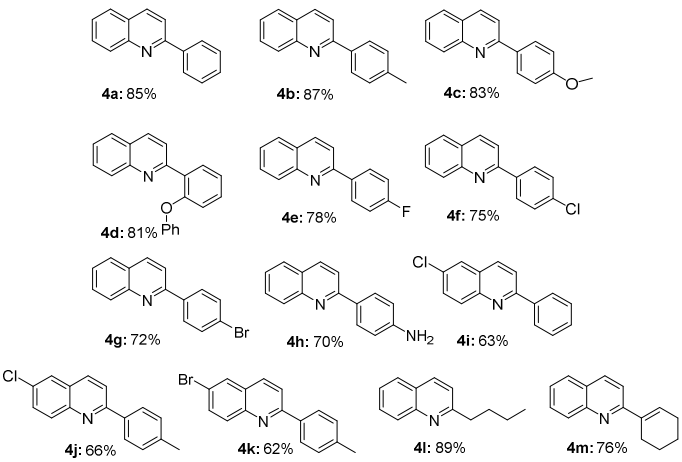
Entry	Reducing agent	Ratio[a]	Time(h)	Yield[b] (%)
1	$SnCl_2.2H_2O$, EtOH	1:2	2	65
2	$SnCl_2.2H_2O$, EtOH	1:2	4	68
3	$SnCl_2.2H_2O$, EtOH	1:3	2	70
4	$SnCl_2.2H_2O$, EtOH	1:3	2	69[c]
5	$SnCl_2.2H_2O$, EtOH	1:4	2	85
6	$SnCl_2.2H_2O$, EtOH	1:4	3	84
7	$SnCl_2.2H_2O$, EtOH	1:4	2	70[c]
8	$SnCl_2.2H_2O$, EtOH	1:5	2	81
9	$SnCl_2.2H_2O$,HCl-EtOH	1:2	2	59
10	$SnCl_2.2H_2O$, HCl-EtOH	1:4	2	62

[a] Ratio between the reactant and reducing agent. [b] Isolated yield.
[c] Reactions carried out at 80°C.

ofsubstituents that were attached to the alkyne moiety were studied. To our delight, arylalkynes that contain electron-donating groups such as -Me, -OMe and -OPh (Table 2, compounds **4b-d**) persisted under the reaction conditions to give the desired products efficiently in very good yields when compared to the unsubstituted arylalkyne (Table 2, compound **4a**). Another advantage of this method is that

Table 2. The synthesis of variety of quinoline derivatives through one-pot A^3- coupling /reductive cyclization





even electron-withdrawing substituents, such as -F, -Cl, -Br and -NO_2 in the arylalkyne were tolerated, although the yield of desired quinoline is low (Table 2, compounds **4e-h**). In addition the aliphatic alkynes (1-hexyne and 1-ethynylcyclohex-1-ene) were also used to extend the scope of our protocol (Table 2, compounds **4l and m**). To our surprise the aliphatic alkyne such as 1-hexyne gave corresponding quinoline in excellent yield. The presence of electron-

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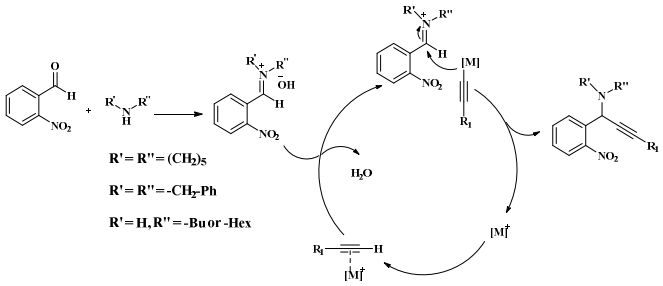
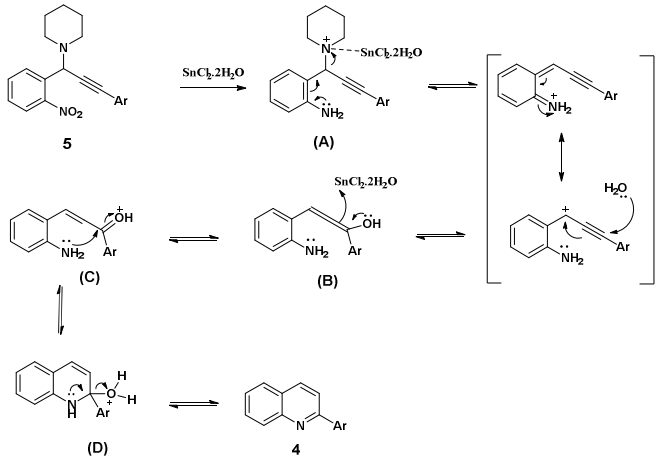
withdrawing group on the 2-nitrobenzaldehyde appeared to give moderate yield of the desired products (Table 2, compounds **4i-k**).



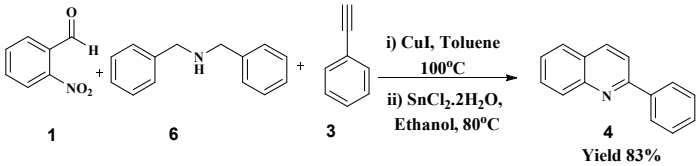
Scheme 3: A mechanism for the formation of *N*-propargylamine.

The mechanism for the formation of different propargylamines were depicted in Scheme 3.[17] The plausible mechanism for the conversion of propargylamine to quinoline is outlined in Scheme 4.[11] The propargyamine **5** formed from the A^3 -coupling reaction undergoes reduction in the presence of $SnCl_2.2H_2O$ and the reduced primary amine on further treatment with $SnCl_2.2H_2O$ undergoes Meyer-Schuster type of rearrangement to furnish quinoline.



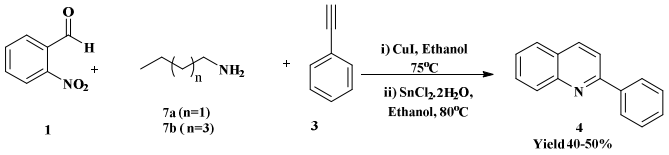
Scheme 4: A plausible mechanism for the $SnCl_2.2H_2O$ mediated reductive cyclization

To further explore the applicability of this developed method, we examined the scope of amine substrates. Dibenzylamine substrates **6** reacted in a similar fashion as that of piperidine **2** in one-pot fashion to afford quinoline **4** in the yield of 83% (Scheme 5).



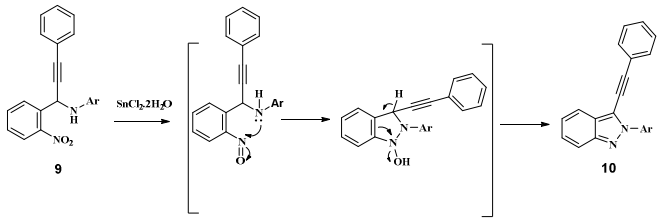
Scheme 5: Preparation of quinoline from dibenzylamine substrate

The aliphatic primary amines such as n-butylamine **7a** and n-hexylamine **7b** were also used to prepare propargylamine.[18] It is on further treatment with 4 equiv of $SnCl_2.2H_2O$ afforded quinoline in 40-50% yield.



Scheme 6: Preparation of quinoline from alkylamine substrates

In addition we have used arylamine **9** to perform the reductive cyclization. At first aniline was used as substrate, to prepare N-arylpropargylamines **10** as per literature procedure.[19] These propargylamines on further treatment with $SnCl_2.2H_2O$ for 2h afforded the new spot on TLC plate. After the completion of the reaction it was purified by column chromatography. The absence of two protons in ^1H NMR and presence of two characteristic peaks at δ 78.2 and 100.4 corresponds to the alkynyl carbons in ^{13}C NMR excludes the formation of six membered quinoline ring. We found that the alkyne is not involving in the cyclization. Based on the literature report[120] and NMR experiments we confirmed the formation of indazole through reductive cyclization. Then we proposed the possible mechanism which shows the reaction occurs through the nucleophilic attack of amine to the reduced nitroso group. The mechanistic pathway for the formation of indazole is described in Scheme 7. The optimized conditions for the quinoline synthesis were exactly applicable for the synthesis of indazole. The product was confirmed by NMR and HRMS mass spectroscopy techniques.



Scheme 7: Possible mechanism for the formation of indazole

Having defined an effective catalyst and reaction conditions for the synthesis of 2*H*-indazole, we next explored substrate scope for aromatic amines **8**, 2-nitrobenzaldehyde **1** and alkyne **3**. Aniline led to the indazole product **10a** in 72% yield (Table 3, **10a**). As expected, electron-donating substituents on aromatic amine such as –Me and –OMe gave improved yield of 79% and 81% (Table 3, **10b** and **10c**) respectively. The electron-withdrawing substituents on 2-nitrobenzaldehyde gave lower yield of corresponding indazoles (Table 3, **10d-f**). 4-Methyl substituted aromatic alkyne increases the yield of indazole than that of the 4-bromo substituted aromatic alkyne (Table 3, **10e** and **f**).

Experimental Section

Typical experimental procedure for the preparation of quinoline (4a-m): N-alkylpropargylamines were prepared according to the similar procedure as reported.[15d] A mixture of copper iodide (15 mol %), 2-nitrobezaldehyde **1** (1.0mmol), piperidine **2** (1.2 mmol) and alkyne **3** (1.2 mmol) in toluene was heated at 100°C for 3h. Then the reaction mixture was cooled to rt and the solvent was removed then used directly without further purification. The reaction mixture of N-alkylpropargylamine **5** was dissolved in 5 ml of ethanol and added $SnCl_2.2H_2O$ (4.0 mmol) then heated at 70°C for 2h. After the

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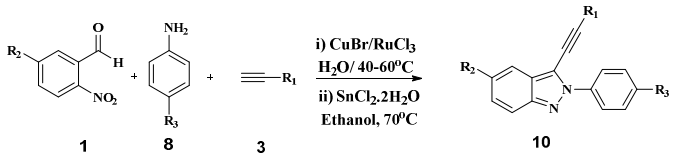
completion of reaction it was filtered through celite by washing with ethylacetate and added water (50ml) extracted with same solvent

Table 3: Reductive cyclization for the preparation of 2H-indazole derivatives:



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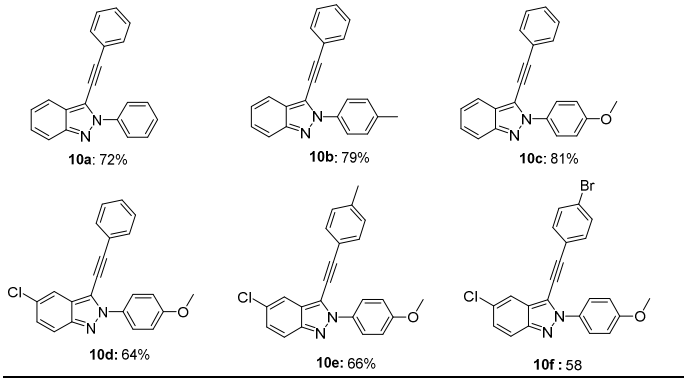

(2x20ml). The combined organic layer washed with saturated NaOH and brine solution and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel using petroleum ether/ ethyl acetate (5-20%) to afford quinoline derivatives **4a-m** in 62-89% yield. All the prepared compounds were characterized by NMR and Mass spectroscopy techniques.

General Procedure for the preparation of 3-alkynyl-2-aryl-2*H*-indazole (10a-f): A mixture of the aldehyde **1** (1.0 mmol) and aniline **8** (1.2 mmol) was heated at 60°C for about 2h. Then $RuCl_3$ (3 mol %), CuBr (30 mol%), alkyne **3** (1.2 mmol), and water (flashed with nitrogen) (2ml) were added into the reaction mixture under nitrogen. The mixture was stirred at rt for 10 min and then at 40°C overnight. After the completion of the reaction it was extracted with ethylacetate and then purified by column chromatography. Then the pure N-arylpropargylamine **9** was dissolved in 5 ml of ethanol and added $SnCl_2.2H_2O$ (4.0 mmol) then heated at 70°C for 2h. After the completion of reaction it was concentrated to remove the solvent and extracted.with ethylacetate. The organic layer washed with saturated NaOH and brine solution and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel using petroleum ether/ ethyl acetate (5-20%) to afford indazole derivatives **10a-f** in 58-81% yield. All the prepared compounds were characterized by NMR and Mass spectroscopy techniques

Conclusions

In summary we have reported first efficient example of one-pot reductive cyclization which yields to two different heterocycles by varying the substrates. This technique has several advantages such as ordinary reaction conditions, use of cheap and stable starting materials, mild and efficient eco-friendly catalyst. A broad range of alkynes, aldehyde and amines participate in the reaction provide access to the large variety of substituted quinolines. The present strategy offers the simple route for the synthesis of 2-substituted quinolines in excellent yields. This methodology is also applicable for the synthesis of 3-alkynyl-2-aryl-2*H*-indazoles. Further studies to extend the scope of this methodology are underway.

Acknowledgements

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Notes

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