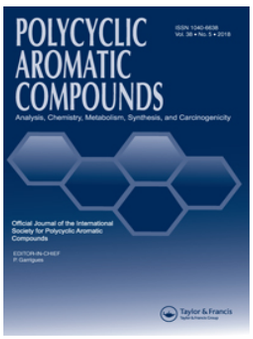

Polycyclic Aromatic Compounds

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$Cu(OAc)_2.H_2O$ Catalyzed C – H/C – N Bond Functionalization for the Synthesis of Isoquinoline Derivatives as Potential Antifungal Agent

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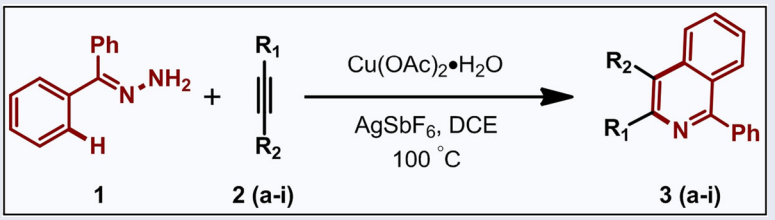
ABSTRACT

$Cu(OAc)_2.H_2O$ has shown good catalytic efficiency in the presence of $AgSbF_6$ as additive for the synthesis of isoquinoline from diphenylmethylene)hydrazine and 1,2-diphenylethyne under optimized reaction condition. Particular synthesized derivatives exhibited decent anti-fungal activity. The structure of all synthesized compounds was confirmed using spectroscopic techniques. Simple reaction process, easy work procedure, low cost and readily availability of catalyst are the some benefits of reported protocol.



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Diphenylmethylene)hydrazine; 12-diphenylethyne; isoquinoline; Cu(OAc)2.H2O; AgSbF6; cost efficient catalyst etc

Introduction

The isoquinoline moiety represent one of the ubiquitous structural motif found in various natural products and pharmaceutical compounds.[1,2] Derivatives of isoquinolines have effectively shown antimalarial, antibacterial, antifugal and anticancerous activities.[3] Thiosemicarbazone possess a good spectrum of pharmacological properties including antitumor, antifungal, antibacterial, antiviral and antimalarial activities.[4] Herein, Figure 1 (Compounds I-V) described the important isoquinoline drugs molecules in the market, which highlights our goal for the synthesis of isoquinoline.

In addition, isoquinoline derivatives play an important role in asymmetric catalysis and photochemistry; where they can be used as ligands[5–8] and their iridium complexes are used in organic light-emitting diodes.[9–11] Intended for these attractions, the efficient synthesis of isoquinoline scaffold remains to attract the interest of organic researcher.[12–15] Traditionally, isoquinoline has been synthesized from some conventional methods such as Bischer-Napieralski, Pictet-Spengler

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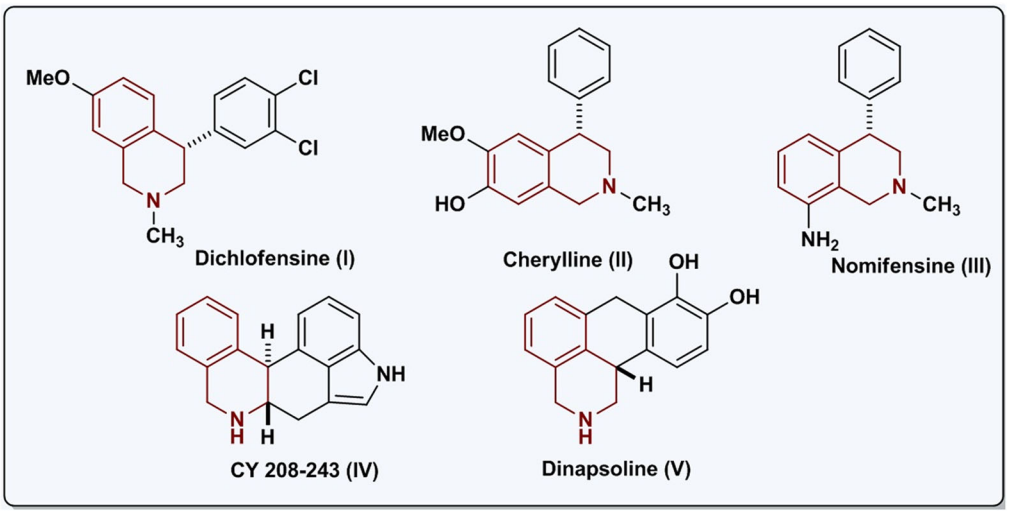


Figure 1. The important isoquinoline drugs molecules.

and Pomeranz-Fritsch. Most of these approaches often suffer from a few drawbacks such as low yields, narrow substrate scope and harsh reaction conditions.[16–19]

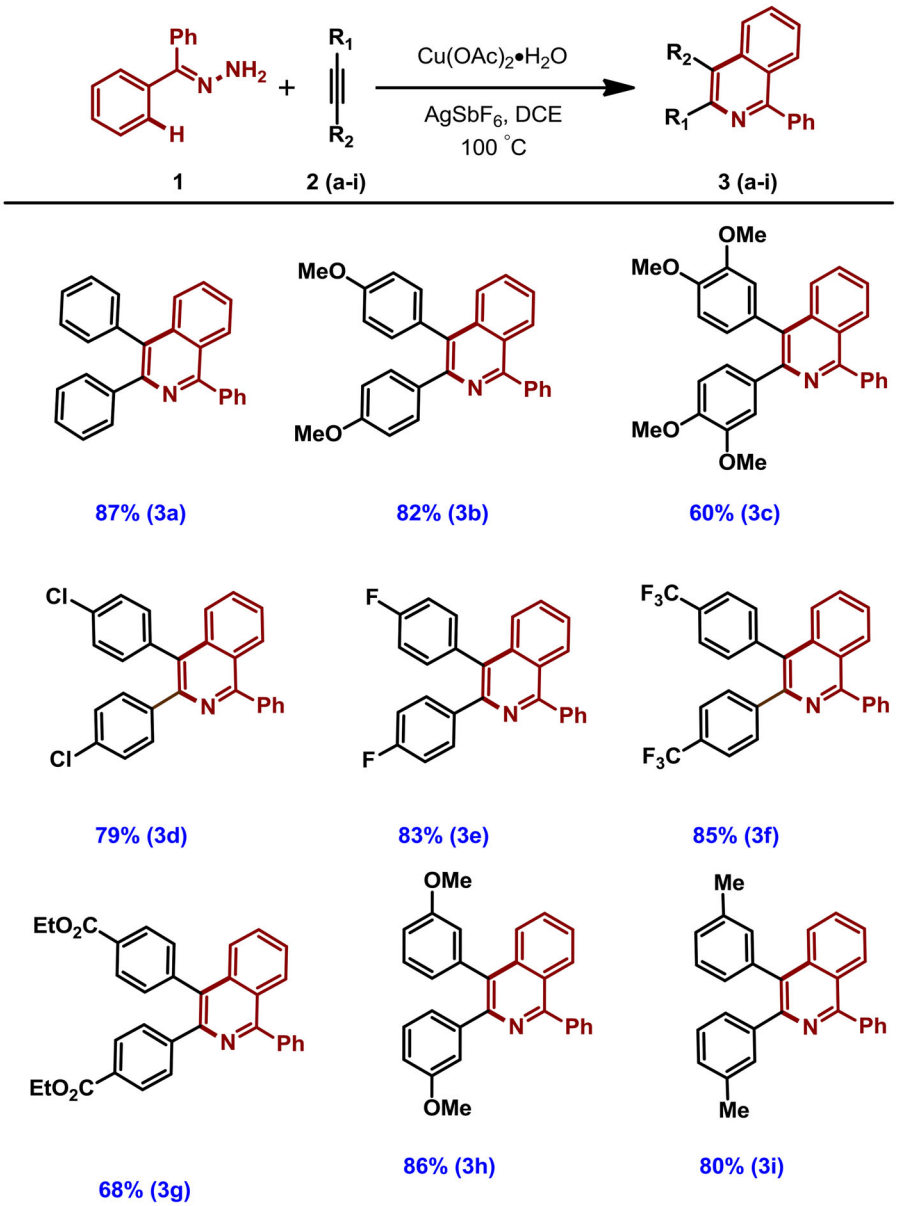
In recent years, C – H activation reactions have provided an alternate route to access isoquinoline scaffolds with large diversity in a concise manner.[20–24] Although, these methods provide straightforward access to isoquinolines; they often require the use of precious transition metals such as Pd,[25] Rh,[26] Ru,[27] Ni,[28] Cu,[29] Zr,[30] Ag.[31] Therefore, there is need to use cheap metals and protocol should be more ecofriendly for the synthesis of isoquinoline.

Moreover, there have been significant research devoted to the catalytic activity of copper in synthesizing isoquinolines. The chemists were interested in catalytic application of Cu for the synthesis of isoquinoline, due to the accessibility of copper and it has been well known for its catalytic activity and it is the cheapest metal among 1st row d-block elements.[14] Copper catalyzed isoquinoline derivative synthesis has been described here.

In the present work, $Cu(OAc)_2.H_2O$ catalyzed C – H/C – N bond functionalization for arylhydrazones with alkynes has been developed for the synthesis of isoquinoline derivatives. The arylhydrazones are easy to prepare and require inexpensive and commercially available hydrazine hydrate. The reaction works well with a variety of internal alkynes and arylhydrazones and offers broad scope, good functional group tolerance and high yields under good catalytic conditions in presence of air. The present protocol has contributed in the synthesis of isoquinoline derivatives, which have been playing a very important role in the drug discovery; the formation variety of substituted isoquinolines will play a leading role in the new drug discovery.

Experimental

All commercial reagents and solvents were used without additional purification. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F_{254} plates. Visualization on TLC was achieved by the use of UV light (254 nm). Column chromatography was undertaken on silica gel (100–200 mesh) using a proper eluent system. NMR spectra were recorded in chloroform-*d* and DMSO-d_6 at 400 MHz for ^{1}H NMR spectra and 100 MHz for ^{13}C NMR spectra. Chemical shifts were quoted in parts per million (ppm) referenced to the appropriate solvent peak or 0.0 ppm for tetramethylsilane.

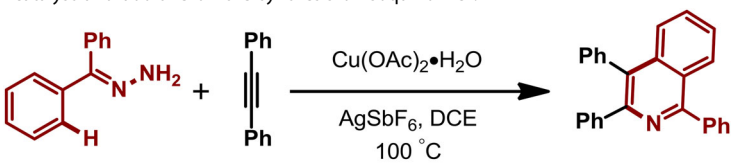


Scheme 1. Synthesis of isoquinolines under optimized reaction condition.

General procedure for preparation of isoquinolines

In an oven dried round bottom flask charged aryl hydrazone **1a** (1 mmol) under nitrogen atmosphere was added in 10 mL 1, 2-dichloroethane (DCE), resulting compound was soluble, then alkyne **2** (1.5 mmol.) was added, followed by 20 mol. % $Cu(OAc)_2.H_2O$ incorporated with 10 mol. % $AgSbF_6$, resulting mixture was stirred at 100 °C. The completion of the reaction was monitored by TLC. After completion it was cool down to room temperature and quenched by sat. NH_4Cl and extracted with ethyl acetate, organic layer was evaporated and purified by using column chromatography. (All the compounds confirmed by NMR, Mass analysis). Some of the derivatives were recrystallized to get clean NMR (Scheme 1).

Table 1. Influence of catalyst and additive on the synthesis of isoquinoline[a].



1 2 a 3 a

Entry	Catalyst	Amount of Catalyst	Additive (10 mol. %)	Reaction time[b] (h)	Yield[c] (%)
1	—	——	——	24	22
2	$Cu(OAc)_2.H_2O$	20 mol. %	——	24	45
3	$Cu(OAc)_2.H_2O$	20 mol. %	$AgSbF_6$	8	87
4	$Cu(OAc)_2.H_2O$	20 mol. %	CH_3COOH	12	57
5	$Cu(OAc)_2.H_2O$	20 mol. %	CF_3COOH	12	75
6	$Cu(OAc)_2.H_2O$	20 mol. %	$ClCH_2COOH$	16	64
7	$Cu(OAc)_2.H_2O$	25 mol. %	$AgSbF_6$	8	88
8	$Cu(OAc)_2.H_2O$	15 mol. %	$AgSbF_6$	20	63
9	$Cu(OAc)_2.H_2O$	10 mol. %	$AgSbF_6$	24	54
10	$Cu(OAc)_2.H_2O$	20 mol. %	$AgSbF_6$ (7.5 mol. %)	12	66
11	$Cu(OAc)_2.H_2O$	20 mol. %	$AgSbF_6$ (5 mol. %)	18	58
12	$Cu(OAc)_2.H_2O$	20 mol. %	$AgSbF_6$ (15 mol. %)	12	80
13	$Cu(OAc)_2.H_2O$	20 mol. %	$AgSbF_6$ (20 mol. %)	20	69

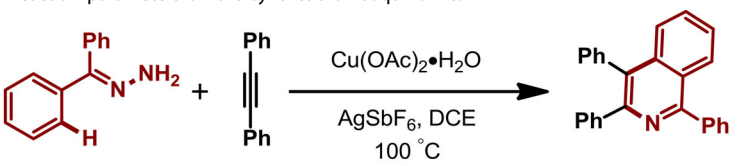
[a]Reaction condition: (diphenylmethylene)hydrazine **1** with 1,2-diphenylethyne **2 a**, stirred in 10 mL DCE solvent at 100 °C under nitrogen atmosphere.
[b]Monitored by TLC.
[c]Isolated yield.

Result and discussion

In our ongoing efforts to design novel and proficient approaches for the synthesis of heterocyclic compounds promoted by heterogeneous and metal catalysts,[32–36] herein we wish to report that $Cu(OAc)_2.H_2O$ catalyzed cyclization of aryl hydrazone with alkyne can produce good to satisfactory yield of isoquinolines. In order to framework optimized reaction conditions for the present transformation, initially we conducted neat reaction of (diphenylmethylene)hydrazine **1** with 1,2-diphenylethyne **2 a**, stirred in 10 mL DCE solvent at 100 °C, under nitrogen atmosphere, this resulted in very poor yield of product (Table 1, Entry 1). Afterword, we checked catalytic activity of 20 mol. % $Cu(OAc)_2.H_2O$ for present transformation, it improved yield of product but still not up to mark. This result indicated that, alone catalyst does not work efficiently for the synthesis of isoquinolines and it seem to need of additive for further development in yield. To our delight, same reaction carried out in the presence of 20 mol. % $Cu(OAc)_2.H_2O$ and 10 mol. % of $AgSbF_6$ as additive. The addition of $AgSbF_6$ reported surprising 87% yield of targeted moiety after stirring of reactants in 10 mL DCE solvent at 100 °C for 8 h (Table 1, Entry 3). Inspiring from this result, we carried out same reaction in attendance of $Cu(OAc)_2.H_2O$ catalyst along with some additive (10 mol. %) such as CH_3COOH, CF_3COOH and $ClCH_2COOH$. Results showed that these additives were not much effective as compare with $AgSbF_6$ and gave 57%, 75% and 64% yield of respective derivatives (Table 1, Entries 4-6).

Moreover, to study the effect of concentration of catalyst as well as additive on out puts of reaction was also necessary to get more promising reaction conditions. At first, we conducted reaction with increasing concentration of catalyst, 25 mol. % $Cu(OAc)_2.H_2O$ does not improved yield of isoquinoline and gave parallel result as obtained with 20 mol. % $Cu(OAc)_2.H_2O$ catalyst (Table 1, Entry 7). While loading of lower amount (15 mol. % and 10 mol. %) of catalyst with 10 mol. % of AgSbF6 unable to produce satisfactory results (Table 1, Entries 8 & 9). Additionally, we have examine several reactions with varying amount of $AgSbF_6$ additive, the obtained results expressed that the 10 mol. % $AgSbF_6$ sufficient and appropriate amount to get standard results (Table 1, Entries 10-13). From the entries 12 and 13 (Table 1), we have concluded as the loading of higher amount of additive does not showed any positive sign on reaction production. Excess

Table 2. Influence of reaction parameters on the synthesis of isoquinoline.[a]



1 2 a 3 a

Entry	Catalyst (20 mol. %)	Additive (10 mol. %)	Solvent (10 mL)	Temperature (°C)	Reaction time[b] (h)	Yield[c] (%)
1	$Cu(OAc)_2.H_2O$	$AgSbF_6$	CH_3CN	100	18	12
2			Ethanol	100	18	10
3			Benzene	100	14	18
4			Toluene	100	16	22
5			DCE	120	14	60
6			DCE	140	14	38
7			DCE	80	18	54
8			DCE	60	20	36
9			DCE	rt	24	00

[a]Reaction condition: (diphenylmethylene)hydrazine **1** with 1,2-diphenylethyne **2 a**, stirred in under nitrogen atmosphere in presence of catalyst and additive.
[b]Monitored by TLC.
[c]Isolated yield.

addition of $AgSbF_6$ (15 mol. % and 20 mol. %) significantly suppresses the formation of isoquinolines, reported only 80% and 69% yield correspondingly. It probably may be due to excess amount of additive affects the catalytic activity of $Cu(OAc)_2.H_2O$.

Herein, from the above dissertation, the amount of catalyst and additive were finalized but the influence of solvent and reaction temperature still need to elaborate for proper optimization of reaction parameters. For this, we accompanied several reactions of (diphenylmethylene)hydrazine **1** with 1,2-diphenylethyne **2 a** in presence of 20 mol.% $Cu(OAc)_2.H_2O$ and 10 mol. % $AgSbF_6$ under nitrogen atmosphere. We checked applicability of solvents like CH_3CN, EtOH, benzene and toluene for the production of isoquinolines. The obtained results revealed that these solvents were not suitable for the present reaction and they furnished with minute yield of product (Table 2, Entries 1-4). This may be due to, these solvents have a greater coordination ability with transition metals than DCE solvent. Therefore, these solvents may be produce complex with metal catalyst or additive via coordination and which decreases catalytic activity of $Cu(OAc)_2.H_2O$.[37,38] Such solvent-metal coordination affected the output of current transformation and resulted in lower yield of product.

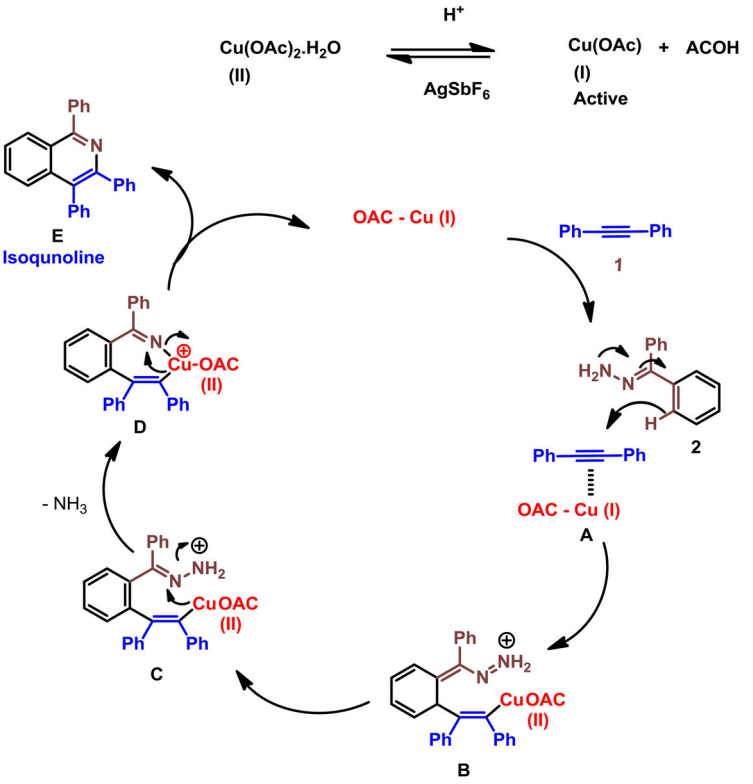
Furthermore, temperature also is a key factor in such catalytic reactions. The studies exhibited that the favored temperature for the reaction was 100 °C. When the reaction was conducted in 1, 2-dichloroethane (DCE) at higher temperature to 120 °C and 140 °C, it decreases the yild and obtained only 60% & 38% product respectively, even though the reaction was conducted prolonged to 14 h (Table 2, entries 5 & 6). While, with lowering of temperature to 80 °C, 60 °C and room temperature, present preparation was not proceeds smoothly and ends with unsatisfactory to negligible yield (Table 2, entries 7-9).

After the screening of all reaction parameters, we concluded as the 20 mol. % $Cu(OAc)_2.H_2O$ catalyst displayed high efficiency with 10 mole. % $AgSbF_6$ in 10 mL DCE solvent at 100 °C temperature for the synthesis of isoquinolines under nitrogen atmosphere. With the optimized condition in hand, we generalized the present protocol and investigated scope of this reaction. The obtained results expressed that substituted 1,2-diphenylethyne with electron donating as well as withdrawing groups readily reacted with (diphenylmethylene)hydrazine under prescribed reaction condition.

Herein, we synthesized nine novel derivatives of isoquinolines under optimized reaction condition, all reactants produced satisfactory to outstanding (60-87%) yield of targeted scaffold. Additionally, mono substituted ethynes showed superior yield of products than disubstituted ethynes.

Table 3. Anti-fungal activity of synthesized isoquinolines.

		MIC (μM)	
Entry	Compound	*A. niger*	*C. albicans*
1	3a	84.8	84.8
2	3b	**4**	**4**
3	3c	22.3	34.8
4	3d	55.6	66.4
5	3e	40.2	48.5
6	3f	42.8	36.2
7	3g	**12.5**	**16.7**
8	3h	80.2	85.6
9	3i	72.6	72.6
10	*Fluconazole*	1	1



Scheme 2. Probable mechanism for the synthesis of isoquinolines catalyzed with $Cu(OAc)_2.H_2O$.

3,4-dimethoxyphenylethyne and diethyl 4,4′-(ethyne-1,2-diyl)dibenzoate reported lowest 60% and 68% yield respectively under sketched protocol and here this was due to steric factor of four methoxy groups and two ethyl groups of benzoate moiety in respective reactions. Meanwhile, all the functionalities were stable and preserved throughout the course of reaction. After the successfully synthesis and purification of isoquinolines, the structure of all prepared derivatives is confirmed through different spectroscopic techniques. Subsequently, all synthesized samples tested for anti-fungal activity.

Anti-fungal activity

Finally, these synthesized isoquinoline derivatives were tested for biological activity. For these purpose it was screened for strain such as A. niger and C. albicans, using fluconazole as standard

antifungal. The results were summarized in table 3. Results exhibited that some of the synthesized isoquinoline derivatives found to be exhibit moderate to good anti-fungal activity. Compound **3 b** showed good activity against *A. niger* and *C. albicans* while **3 g** derivative showed moderate activity. Synthesized isoquinoline derivatives displayed good activity against *A. niger* than *C. albicans* strain. Its good starting point to start further development for drug discovery programme. As per demand for anti-fungal drugs, it can be contributed.

Probable mechanism

The possible mechanism for the synthesis of isoquinolines can be explained based on obtained results and literature data.[38–41] The first step was dissociation of Cu (II) in to Cu (I) in the presence of $AgSbF_6$. The Cu (I) activates the alkyne **1** to yield **A** intermediate. The coordination of hydrazone **2** via ortho C-H bond activation forms **B**. Followed by remove of $-NH_3$, the coordination of **B** via the imine nitrogen to Cu (I) gives a seven-membered intermediate **D.** The formation of isoquinoline **E** from **D** can be obtained via reductive elimination of Cu (I) (Scheme 2).

Conclusion

In summary, an efficient protocol developed for the synthesis of substituted isoquinolines. Many functional groups tolerated and resulted in good yields. The synthesized compounds have shown good anti-fungal activity and their tractable points for further drug discovery programme. $Cu(OAc)_2.H_2O$ exhibited remarkable catalytic activity for the synthesis of isoquinolines under prescribed condition. Readily arability and cost proficiency of the catalyst, respectable yield, and manageable reaction time is the some compensations of reported protocol.

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