Research Article

Synthesis of Isoquinolines Using Copper Nanoparticles Supported on Carbon Microsphere Cu-NP/C/PEG-400 as Heterogeneous Reusable Catalyst

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Abstract— A new, eco-friendly method for synthesizing 1-Phenyl Isoquinoline derivatives has been developed using Cu-NP/C/PEG-400 as a heterogeneous, reusable catalyst. This method involves the activation of C-H and N-N bonds in 1-(diphenylmethylene) hydrazine and substituted aryl acetylenes. The process utilizes Cu-NP/C as an oxidant and AgSbF6 as an additive, all within a biodegradable PEG-400 solvent. This approach offers several advantages, including a straightforward extraction procedure, high atom economy, a wide substrate scope, and high product yields, making it an efficient and sustainable protocol for producing isoquinoline derivatives.

Keywords— Green synthesis, Heterogeneous catalyst, Cu-NP/C, Biodegradable solvent.

1. Introduction

The substituted isoquinoline ring exhibits a wide array of biological and pharmacological activities, including anti-HIV, insect growth retardation, antitumor, antimicrobial, antileukemic, antibacterial, antimalarial properties, and activity against Parkinson's disease. It also serves as a scaffold for chiral ligands. Isoquinoline is a crucial source of leads for drug discovery and is a significant structural component in various natural products and pharmaceutical compounds. To explore this chemical space, several methods have been developed for the synthesis of substituted isoquinoline rings.

Traditional methods for synthesizing isoquinolines, such as the Bischer–Napieralski, Pictet–Spengler, and Pomeranz–Fritsch reactions, often encounter issues like low yields, limited substrate variety, and harsh reaction conditions. Some techniques involve preactivating halogen groups (like iodine or bromine) to facilitate the activation of the ortho-carbon in aromatic imines. The cyclization of o-halobenzimines with carbon-carbon π-components using palladium or nickel catalysis poses significant challenges for producing isoquinoline derivatives [1]. In contrast, C–H activation reactions [2] provide a more efficient pathway to isoquinoline scaffolds [3]. Recent advancements have emphasized the use of first-row transition metals for C–H functionalization [4]. Significant developments include Co(III) catalysts for C–H/N–O bond functionalization of oximes with alkynes [5], oxidative annulations of N–H imines with alkynes using external oxidants [6], C–H/N–H bond functionalization of amidines with diazo compounds [7], C–H/N–S bond functionalization of N-sulfinyl imines with alkynes [8], and the recent C–H/N–N bond functionalization of arylhydrazones for isoquinoline synthesis [9].

Jun, Cheng, and Ellman et al. reported the use of Rhodium(I)-catalyzed chelation-assisted C-H bond activation for aromatic imines or oximes with alkynes [10,11]. Similarly, Chiba's group described a Rh(III)-catalyzed cyclization of aryl ketone O-acyloximes with alkynes through C-H bond activation [12a-c]. Additionally, Rovis et al. and Li et al. demonstrated rhodium-catalyzed cyclization of aromatic ketoximes with alkynes via C-H bond activation [12d,f].

Recently, less expensive ruthenium catalysts have gained popularity over rhodium catalysts for cyclization reactions due to their remarkable regioselectivity and cost-effectiveness [13, 14]. Masilamani Jeganmohan and colleagues [15, 16] achieved complete regioselective synthesis of isoquinolines by cyclizing ketoximes with unsymmetrical alkynes using catalytic amounts of Ru(II) and NaOAc. They also reported a novel redox-free Ru(II) catalysis for benzimidates with alkenes in green ethanol solvent. More recently, Bhalchandra M. Bhanage et al. [17] demonstrated N-tosylhydrazone-directed annulation reactions with internal alkynes for isoquinoline synthesis using ruthenium in a homogeneous, recyclable catalytic system.

To the best of our knowledge, there have been no reports on simple, easily available hydrazine-directed annulation reactions with internal alkynes in a green protocol without the

need for a leaving group. In this work, we present an exceptional method using ruthenium catalysis in a homogeneous, recyclable catalytic system. This approach utilizes hydrazines with alkynes in PEG-400, a green and sustainable solvent, with Cu(OAc)$_2$ as the oxidant and AgSbF$_6$ as the additive, at ambient temperature for the synthesis of 1-Phenyl Isoquinoline derivatives. This methodology offers high atom economy, efficiency, and environmental benefits, while minimizing unnecessary prefunctionalization of the starting materials.

2. Experimental Method

2.1. General details

All chemicals and solvents were utilized in their commercial anhydrous grade without additional purification. PEGs were dried prior to use according to established literature methods. For thin layer chromatography, 20 x 20 cm aluminum sheets and Merck-grade silica gel 60 F254 were employed to monitor the reaction progress. Melting points were measured using open capillary tubes and are uncorrected. IR, ^{1}H, and ^{13}C NMR spectra were recorded using a Bruker AV-400 MHz and 100 MHz spectrometer in CDCl$_3$ and DMSO. Mass spectra were obtained with a Polaris-Q Thermo Scientific MS.

2.2. Experimental Procedure:

A screw-capped vial was charged with a spinevane triangular-shaped Teflon stirrer bar, aryl hydrazone (1 mmol), diphenylacetate (1.5 mmol), Cu-NP/C (10 mol%), silver hexafluoroantimonate (AgSbF$_6$) (10 mol%), and Cu-NP/C (1 mmol), along with PEG 400 (0.5 mL). The reaction mixture was stirred under an air atmosphere at 112 °C in an oil bath for 10 hours. Upon completion, the mixture was allowed to cool to room temperature and then extracted with 7–8 mL of diethyl ether, repeating the extraction three to four times. The collected diethyl ether was concentrated under reduced pressure to yield a crude residue, which was subsequently purified by silica gel column chromatography using a pet ether/ethyl acetate eluent to obtain the desired pure isoquinoline product.

Spectral data:

2.2.1. 1,3,4-triphenylisoquinoline (3a): White solid, M.P. (188-191°C) : ^{1}H NMR (300 MHz, CHCl$_3$): δ 7.15-7.17 (m, 3H), 7.31-7.32 (d, 2H), 7.30-7.51 (m, 5H), 7.51-7.56(m,5H), 7.70-7.80(d,1H), 7.82-7.83(d,1H), 8.14-8.18(d,1H). ^{13}C-NMR (300 MHz, CDCl$_3$):δ154.86, 148.44, 140.28, 140.09, 136.11, 136.86, 132.13, 130.03, 129.11, 129.98, 129.63, 128.28, 127.88, 127.17, 127.08, 127.04, 126.86, 126.36, 125.76, 125.12.

2.2.2. 3,4-bis(4-fluorophenyl)-1-phenylisoquinoline (3b): White solid, M.P. (182-184°C) ^{1}H NMR (300 MHz, CHCl$_3$): δ 7.13-7.16 (dd, 2H), 7.345-7.36 (dd, 2H), 7.46-7.50 (m,2H),7.62-7.76(m,2H),7.78-7.80(m,4H),7.82-7.88(m,1H),7.93-8.14(d,1H),8.05-8.05(d,2H),8.43-8.46 (d,1H).^{13}C-NMR (300MHz, CDCl$_3$): δ162.85, 162.21, 160.72,160.66,160.15,147.90, 133.11, 132.45, 131.95,

131.76,130.48,129.88,128.68,128.16,127.44,124.94,115.78,115.18,114.78,114.57,114.17,77.28,77.09,76.62.

2.2.3.3,4-bis(4-(trifluoromethyl)phenyl)-1-phenylisoquinoline (3c): White solid, M.P. (209-210°C) ^{1}H NMR (300 MHz, CHCl$_3$):** δ 7.43-7.78 (m, 10H), 7.80-7.88 (m, 4H), 7.96-8.10 (d, 2H), 8.40-8.42(d,1H).^{13}C-NMR (300MHz, CDCl$_3$): δ161.12, 147.96, 144.86, 140.84, 138.80, 135.52,131.70,130.77,130.32,129.63,129.26,129.04,128.93,128.90,128.54,127.74,127.19,125.65,125.50,124.67,123.14,123.06,77.15,77.00,76.77.

2.2.4. Diethyl 4,4-(1-Phenylisoquinoline-3,4-diyl)dibenzoate (3d): White solid, M.P. (174-176°C) ^{1}H NMR (300 MHz, CHCl$_3$): δ 1.54-1.66 (t, 6H), 4.50-4.65 (q, 4H), 7.57-7.50 (d, 2H), 7.60-7.84(m,6H),8.00-8.06(m,4H),8.17-8.30(q,2H),8.41-8.42(d,1H).^{13}C-NMR (300 MHz,CDCl$_3$):δ166.48,166.33,160.55,148.45,144.80,142.17,139.21,136.50,131.36,130.53,130.41,131.20,129.73,129.70,129.44,129.18,129.00,128.86,128.42,127.78,127.24,125.70,125.65,77.33,77.02,76.70,61.17,60.93,14.36,14.30.

2.2.5 3,4-bis(4-methoxyphenyl)-1-phenylisoquinoline (3e): White solid, M.P. (175-176°C) ^{1}H NMR (300 MHz, CHCl$_3$):** δ3.99 (t, 3H), 4.10 (t, 3H), 6.96-6.99 (d, 2H), 7.17-7.20(m, 2H),7.44-7.47(m,2H),7.48-7.62(d,2H), 7.65-7.96(m,5H), 7.99-8.03(d,1H),8.04-8.07(t,2H) 8.38-8.40 (d, 2H). ^{13}C-NMR (300MHz, CDCl$_3$): δ 159.79, 159.62, 158.86, 149.20, 142.10, 139.78, 138.98, 136.93, 130.24, 128.60, 128.53, 128.28, 121.00, 116.76, 115.35, 113.62, 113.17, 77.44, 77.03, 76.60, 55.27, 55.11.

2.2.6 3,4-bis(4-chlorophenyl)-1-phenylisoquinoline (3f): White solid, M.P. (189-191°C) ^{1}H NMR (300 MHz, CHCl$_3$):δ7.98-8.80 (q, 1H), 8.09-8.16 (q, 3H), 8.23-8.48 (q, 3H), 8.49-8.55(q, 5H),8.58-8.61(q,2H),8.71-8.74(d,2H), 9.10-9.13(d,1H). ^{13}C-NMR (300MHz, CDCl$_3$): δ 160.48,148.16,142.25,139.39,139.07,136.60,134.38, 133.75, 131.14,130.50,130.43,130.14, 129.81,129.53,128.78, 128.64, 128.48,128.39,127.85,127.68,127.43,127.11,125.68,125.58,77.27,77.02,76.77.

2.2.7 1-phenyl-3,4-dim-tolylisoquinoline (3g): White solid, M.P. (224-226°C) ^{1}H NMR (300 MHz, CHCl$_3$): δ2.57 (s, 3H), 2.66 (s, 3H), 7.28-7.41 (q, 1H), 7.46(s, 1H), (q,2H),7.49-7.92(m,5H), 8.03-8.06(d,1H), 8.13-8.16 (d, 2H), 8.47-8.50(d,1H).^{13}C-NMR (300MHz, CDCl$_3$): δ 159.57, 149.61, 140.73, 139.88, 137.73, 137.51, 137.06, 136.97, 131.93, 131.17, 130.24, 129.86, 129.77, 128.44, 128.38, 128.26, 128.12, 127.91, 127.71, 127.48, 127.40, 127.18, 126.42, 126.13,125.35,77.43,77.04,76.60, 21.43.

**2.2.8 1-phenyl-3,4-dip-tolylisoquinoline (3h): White solid, M.P. (218-220°C)** ^{1}H NMR (300 MHz, CHCl$_3$):** δ3.79(s, 3H), 3.90 (s, 3H), 6.90-7.12 (q, 1H), 7.18(s, 1H), 7.28-7.42 (t,2H),7.67-7.47(q,1H), 7.69-7.80(m,5H), 7.93-7.96 (d, 1H), 7.98-8.01(d,2H),8.34-8.37(d,1H).^{13}C-NMR(300MHz, CDCl$_3$):δ156.27,156.11,155.33,145.73,138.63,136.26,135.48,133.41,126.72,125.08,125.03,124.77,119.48,113.26,111.85,110.11,109.66,73.93,73.51,73.09,51.77,51.58.

2.2.9 3,4-bis(3-methoxyphenyl)-1-phenylisoquinoline (3i): White solid, M.P. (194-196°C) ^{1}H NMR (300 MHz, CHCl$_3$): δ 4.95(s, 3H), 5.06 (s, 3H), 8.06-8.26 (m, 1H), 8.28 (s, 1H), 8.34-8.60(m,1H),8.68(s,2H), 8.83-8.85(m,1H), 8.86-8.87(m,1H),8.87-8.96(m,5H),9.14(d,1H),9.16-9.17(d,2H),9.50-9.53(d,1H).^{13}C-NMR(300MHz,CDCl$_3$): δ160.48, 160.32, 159.55, 149.93, 142.86,140.48,139.70,137.62, 130.93, 130.06, 129.28, 129.25, 129.00, 123.70, 117.45, 116.05, 114.33,113.87,78.15,77.71,77.30,55.97,55.80.

2.2.10 3,4-bis(3-chlorophenyl)-1-phenylisoquinoline (3j): White solid, M.P. (213-215°C) ^{1}H NMR (300 MHz, CHCl$_3$): δ 7.46-7.51(t, 1H), 7.55-7.58 (q, 3H), 7.59-7.73 (q, 3H), 7.75-7.95 (m, 5H), 7.97-8.08(q,2H),8.18-8.21(d,2H),8.57-8.80(d,2H).^{13}C-NMR(300MHz,CDCl$_3$):δ158.08, 145.75,139.85,136.98,134.20,131.98,131.34, 128.73, 128.05, 127.73,127.40,127.10, 26.36,126.22,126.08, 125.98,125.44, 125.28,125.00,124.70,123.28,123.17,74.86,74.87,74.60,74.35

3. Results and Discussion

Scheme 1:
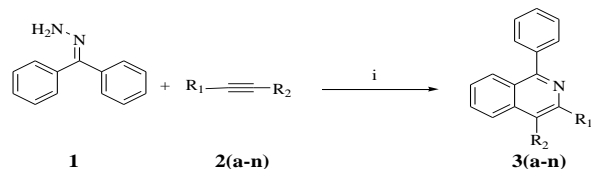
Scheme 1: Reagent and conditions: i) Cu-NP/C, AgSbF6, PEG-400, 110°C, air atm,9-10 hrs,85-95%.

Table 1: Optimization of reaction parameters:

Entry	Catalyst	Solvent	Oxidant & Additives	Additives	Time (hrs)	Yield (in %)
1	-	EtOH	Cu(OAc)$_2$	AgSbF$_6$	20	56
2	-	EtOH	NaOAc	AgSbF$_6$	23	45
3	SnCl$_2$	EtOH	NaOAc	AgSbF$_6$	20	60
4	SnCl$_2$	Toluene	Cu(OAc)$_2$	AgSbF$_6$	18	62
5	L- Proline	EtOH	Cu(OAc)$_2$	AgSbF$_6$	19	65
6	L-Proline	DCM	Cu(OAc)$_2$	AgSbF$_6$	21	63
7	InCl$_3$	EtOH	Cu(OAc)$_2$	AgSbF$_6$	25	70
8	InCl$_3$	DCM	Cu(OAc)$_2$	AgSbF$_6$	24	50
9	DMAP	EtOH	Cu(OAc)$_2$	AgSbF$_6$	16	68
10	DMAP	PEG-400	Cu(OAc)$_2$	AgSbF$_6$	15	75
11	[Ru (p-cymene)Cl$_2$]$_2$	DCM	Cu(OAc)$_2$	AgSbF$_6$	14	60
12	[Ru (p-cymene)Cl$_2$]$_2$	PEG-400	Cu(OAc)$_2$	AgSbF$_6$	11.30	80
13	Cu-NP/C	EtOH	Cu(OAc)$_2$	AgSbF$_6$	10	82
14	**[Ru (p-cymene)Cl$_2$]$_2$**	**PEG-400**	**Cu(OAc)$_2$**	**AgSbF$_6$**	**10**	**90**

For optimization of the isoquinoline synthesis, initially various catalysts were tested for the model reaction of benzophenone hydrazone 1a as a starting substrate and diphenylacetylene 2a as a coupling partner. A summary of the experiment optimization is provided in Table 1. It was found that, Cu-NP/C was the most efficient catalyst compared with SnCl$_4$, InCl$_3$, DMAP and L-Proline which exhibited from moderate to poor catalytic properties. When benzophenone

hydrazone 1a was treated with diphenylacetylene 2a without presence of any catalyst only using Cu(OAc)$_2$, NaOAc as a oxidants and AgSbF$_6$ (10 mol %) as additive in EtOH, it was found that only Cu(OAc)$_2$ gives the better yield than NaOAc as oxidant (entry 1and 2), using this result we further used Cu(OAc)2 as oxidant for different catalysts as well as solvents. When the reaction was performed using Cu-NP/C (5mole %) as catalyst, Cu(OAC)$_2$ as oxidant and AgSbF6 as additive in PEG-400 as green solvent gives the isoquinoline with good yield (90%) within 10 hrs at 110oC in an air atm pressure. Before this when reaction was performed using SnCl$_4$ as catalyst, Cu(OAc)$_2$ and NaOAc as oxidants and AgSbF$_6$ as additive in EtOH and toluene, it furnished desired isoquinoline 3a in low yield but better in case of Cu(OAc)$_2$ than NaOAc (Table 1, entry 3.4). Therefore, from results (entry 1,2,3,4), it was concluded that Cu(OAc)$_2$ acts as better oxidizing agent than NaOAc. Gratifyingly, introduction of catalyst such as InCl3, DMAP, and L-Proline was found to promote the reaction (Table 1, entries 5−9) in solvent such as EtOH, DCM, Toluene and PEG-400. More pleasingly, when solvents were tested (Table 1, entries 5−7), it was found that use of PEG-400 furnished the required isoquinoline in almost quantitative yield (Table 1, entry 10).
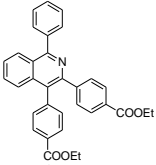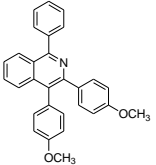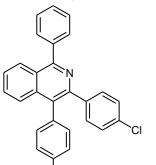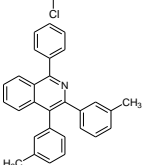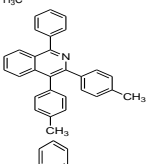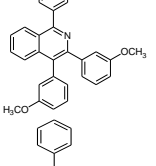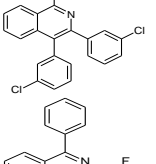
Table 2: Effect of catalyst concentration Cu-NP/C in solvent PEG-400.

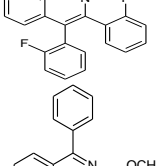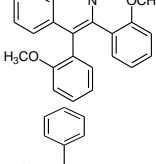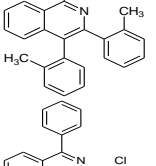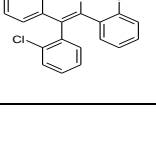| Entry	Catalyst (mole %)	Time (hrs)	Tempt °C	Yield^a (%)
1	5	12.30	110	85
2	**10**	**10**	**110**	**90**
4	15	10	110	86
5	20	11	110	80
6	10	13	100	70
7	10	10	120	75

After optimization effect of concentration of the catalyst have been studied (Table 2). It was found that loading of 10mol % of catalyst gives 90% of the yield in stipulated time (Table 2, entry2). Increase and decrease of catalytic concentration decreases the percentage of yield. With this optimization in our hand we also studied effect of decrease and increase of the reaction temperature resulted in a diminished yield of the product (Table 2, entry 6, 7).

Table 3: Exploration of the substrate scope for the synthesis of isoquinoline derivatives.

Entry	Substituted Phenyl acetylene	Time (hrs)	Product	M.P. °C	Yield^a %
3a	H	10		187-191[18a]	90
3b	4-F	11		183-185[18a]	88
3c	4-CF$_3$	12		208-210[9]	85

3d	4-COOEt	11		173-175[9]	86
3e	4-OMe	10		175-177[18b]	91
3f	4-Cl	10.5		189-191[18a]	90
3g	3-CH₃	10		224-226[18a]	88
3h	4-CH₃	10		218-220	92
3i	3-OCH₃	11.5		194-196[19]	95
3j	3-Cl	12		213-215[9]	87
3k	2-F	11		203-206	88
3l	2-OCH₃	10.5		208-210[19]	90
3m	2-CH₃	10		194-196	87
3n	2-Cl	11		233-235	89

ᵃ Isolated yield

4. Conclusion and Future Scope

In this study, we present an innovative approach using ruthenium-catalyzed heterogeneous recyclable catalytic systems for the reaction of hydrazines with alkynes. This method leverages PEG-400 as a green and sustainable solvent, with Cu-NP/C as the oxidant and AgSbF₆ as the additive, all at ambient temperature, for synthesizing 1-Phenyl Isoquinoline derivatives. The methodology is notable for its high atom economy, efficiency, and minimal environmental impact, offering an elegant solution that eliminates the need for unnecessary prefunctionalization of starting materials

Data Availability
None

Conflict of Interest
We declare that we do not have any conflict of interest.

Funding Source
None

Authors' Contributions
Author-1 researched literature and conceived the study. Author-2 involved in protocol development, gaining ethical approval, patient recruitment, and data analysis. Author-3 wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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