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ORGANO-Cu (II) CATALYST: AN EFFICIENT SYNTHESIS OF SUBSTITUTED *N*-HETEROCYCLES VIA DOUBLE CONDENSATION/ TANDEM OXIDATION-CYCLIZATION/ELIMINATION-CYCLIZATION REACTIONS FROM EASILY ACCESSIBLE PRECURSORS

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ABSTRACT

Several efficient, robust, versatile and straightforward strategies for the diversity-oriented convergent synthesis of a vast range of highly functionalized biologically active *N*-heterocycles such as quinoxaline, pyrazine, cyanopyrazine derivatives from different easily accessible, inexpensive starting motif has been reported by exploring the promising organo Cu (II) catalyst *via* double condensation/ tandem oxidation-cyclization/elimination-cyclization reactions. These methodologies have several advantages such as inexpensive, non-toxic starting materials as well as catalyst and easy reaction set-up. Avoid the use of hazardous materials has added another important advantage in these protocols.

Keywords: Pyrazine, Cyanopyrazine, Quinoxaline, Cu (II) catalyst, 1,2-dicarbonyl, phenacyl bromide.

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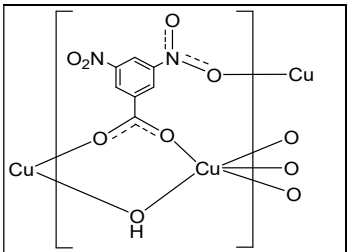
INTRODUCTION

Synthesis of *N*-heterocyclic compounds, which are discovered in a diverse array of bioactive motif, pharmaceuticals and synthetic drugs are the most profuse scaffold, has received much significance in recent years. These types of heterocycles are very imperative for industries due to their vast applicability in the field of coordination chemistry as ligands, in medicinal chemistry as an antibiotic, anticonvulsants, antihypertensive, antiallergic, anticancer, anti-HIV drugs, in catalysis technology, in materials science applications, in the field of photography and also in the field of agriculture as pesticides. As a consequence, establishment of a very simple protocol for such kind of heterocycle is always being a challenge for the researchers. Keeping this in mind as well as the reported potential of Cu (II) complexes as a catalyst in organic transformations we decided to put the newly synthesized copper catalyst[1] in use to explore its potential application for the synthesis of different types of fundamental heterocycles using easily accessible starting materials more simply.



Poly [(μ_3-3,5-dinitrobenzoatok^3 O^1:O$^{1'}$:O^3) (μ2-hydroxido-k^{2}O:O)-copper(II)]

Fig.-1: General Structure of the Catalyst

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In this article, we are very pleased to report that the above catalyst has a tremendous activity in synthesizing important heterocycles which have been elaborated herein in this manuscript. The catalyst was characterized by single-crystal XRD and SEM[1] analysis.

Several methodologies using various catalysts and precursors are available for the preparation of the above two classes of *N*-heterocycles.[2-11]However, most of them are associated with too many major drawbacks. Although the reported classical route for pyrazine and quinoxaline was used to afford quite a satisfactory yield, the long reaction time, use of strong acidic medium and high reaction temperature demands the necessity to find a milder, non-hazardous and greener protocol for their preparation.

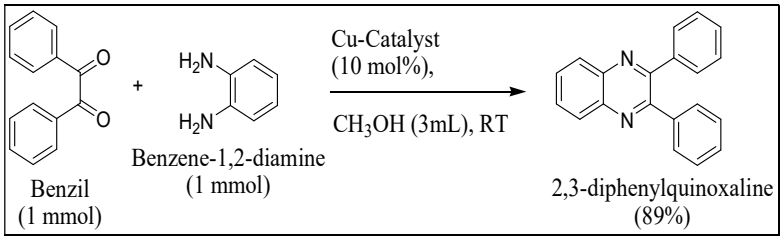


Fig.-2: Cu (II)-catalyzed double condensation of benzil and diamine

Using our lab made catalyst, we developed a very simple methodology for the synthesis of quinoxaline either from a diketone (Fig.-2) or from α-haloketones (Fig.-3) and a very facile and straightforward strategy for the synthesis of pyrazines by direct condensation of 1,2-diamine with either 1,2-diketones or with α-hydroxyketones (Fig.-4).

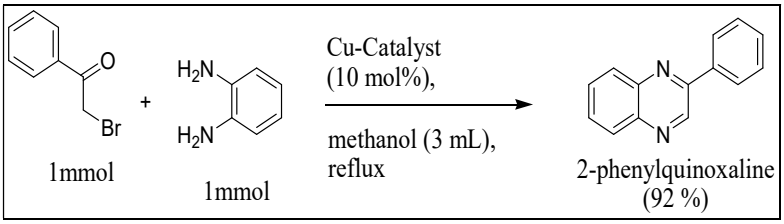


Fig.-3:Cu (II)-catalyzed synthesis of quinoxaline from α-haloketones

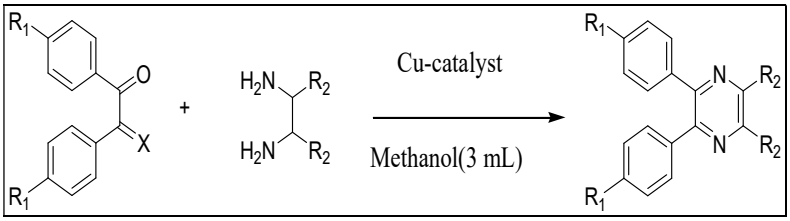


Fig.-4: Cu (II)-catalyzed preparation of pyrazine derivatives

EXPERIMENTAL

General Procedure

^{1}H NMR and ^{13}C NMR were recorded using 300 MHz Bruker Avance FT-NMR Spectrometer using TMS as internal standard and IR spectra were recorded on KBr disc in the range 4000-400 cm^{-1} on Shimadzu FT-IR 8300 Spectrometer. Splitting patterns of protons were described as s (singlet), d (doublet), t (triplet), br (broad) and m (multiplet).

General procedure for the preparation of Cu II-catalyst

A mixture of 3,5-dinitrobenzoic acid (0.1688 g), $Cu(NO_3)_2.3H_2O$ (0.1932 g) and melamine (0.1002 g) were taken and grind to dust in a mortar pistol. To the mixture, 1.5 mL of distilled water was added and stirred for 30 min until we got a suspension. Then the reaction mixture was sealed in a 10 mL Teflon-lined stainless-steel autoclave and heated for 45 h at 423 K. After that the autoclave was subjected to cooling (for 5 h) to room temperature. The reaction mixture was filtered and was subsequently washed

with distilled water. We got blue colored crystal of the product, which we take for further characterization by single-crystal X-ray diffraction, SEM.

General process for the preparation of substituted pyrazine

A mixture of substituted *vic*-diketone/α-hydroxy ketone (1 mmol), substituted ethane-1,2-diamine (1 mmol), catalyst (5 mol %) and methanol (3 mL) were added in a 50 mL round bottom flask and heated in an oil bath at 50 °C on a magnetic stirrer for a specified time (Table 2 and 3). The progress of the reaction was monitored by TLC. After the completion of the reaction, the product was extracted with ethyl acetate and further purified through column chromatography using silica gel 60-120 mesh. The solid product obtained from column chromatography was recrystallized using ethyl acetate and pet ether.

General process for the preparation of substituted cyano-pyrazine

A mixture of substituted diketone/α-hydroxy ketone (1 mmol), 2,3-diaminomaleonitrile (1 mmol), catalyst (5 mol%) and methanol (3 mL) were taken in a 50 mL round bottom flask and heated in an oil bath at 50°C on a magnetic stirrer with a magnetic bar for a specified time (Table 4). The progress of the reaction was monitored by TLC. After the completion of the reaction, the product was extracted with ethyl acetate and further purified by column chromatography using silica gel 60-120 mesh. The solid product obtained from column chromatography was recrystallized using ethyl acetate and pet ether.

General process for the preparation of 2, 3-disubstituted quinoxaline

A mixture of substituted benzil (1 mmol), *o*-phenylene diamine (1 mmol), copper catalyst (2.5 mol%) and methanol (3 mL) was taken in a 50 mL round bottom flask and heated in an oil bath at 40 °C with proper stirring on a magnetic stirrer for a specified time (Table 6). The progress of the reaction was monitored by TLC. After the completion of the reaction, the product was extracted with ethyl acetate and further purified by column chromatography using silica gel 60-120 mesh.

General Process for the Preparation of 2-substitutedquinoxaline

A mixture of phenacyl bromide (1 mmol), *o*-phenylene diamine (1 mmol), copper catalyst (10 mol%), Na_2CO_3 (1 equiv.) and methanol (3 mL) was taken in a 50 mL round bottom flask and refluxed for a specified time (table 8). The progress of the reaction was monitored by TLC. After the completion of the reaction,the product was extracted with ethyl acetate and further purified by column chromatography using silica gel 60-120 mesh.

RESULTS AND DISCUSSION

In a model reaction, benzil (1 mmol), ethane-1,2-diamine (1 mmol) and Cu-catalyst (10 mol%) were taken in methanol (3 mL) and stirred at room temperature overnight. About 89% yield of the desired product (2,3-diphenylpyrazine) prompted us to investigate the protocol in detail. During the screening of the progress of reaction (monitored by TLC), using various solvents and varied reaction conditions (Table-1), dihydro pyrazine was also identified along with pyrazine (entry 2 and 3, Table-1), at the early stages of the reaction, This result indicates in situ aromatization of dihydro pyrazine to pyrazine without any additional step as was reported earlier. On further investigating of reaction condition, we reached our optimized reaction condition as, benzil (1 mmol), ethane-1,2-diamine (1 mmol), catalyst (5 mol%), methanol (3 mL) and the optimized temperature as 50 °C (entry 12, Table-1). Further decrease in the amount of catalyst caused a drastic fall in the yield of product formation (entry 14-18, Table-1).

Table-1: Optimization of Reaction Condition[a]

Entry	Catalyst (mol %)	Solvent (mL)	Temp (°C)	Time (h)	Yield (%)[b]
1[c]	10	Methanol	Room temperature (RT)	12	89
2[d]	10	Methanol	RT	3	57
3[d]	10	Methanol	RT	6	75
4[e]	10	Methanol	RT	9	89
5	5	Methanol	RT	12	89

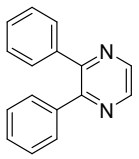
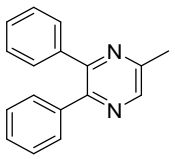
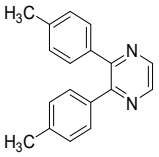
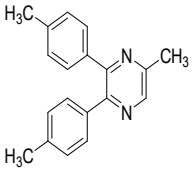
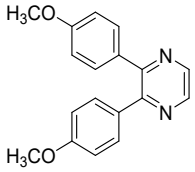
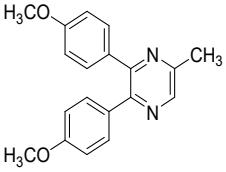
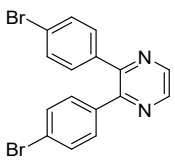
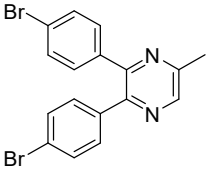
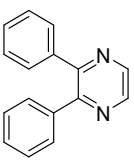
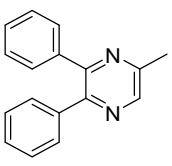
6	5	Acetonitrile	RT	16	< 30
7	5	Dichloromethane	RT	16	< 25
8	5	Chloroform	RT	16	Trace amount
9[f]	5	Water	RT	12	<40
10[g]	No catalyst	Methanol	RT	12	>10
11[g]	No catalyst	Methanol	Reflux	8	52 [h]
12[i]	5	Methanol	50	3	92
13	5	Methanol	Reflux	3	-
14	2.5	Methanol	50	4	72
15	2.5	Methanol	Reflux	4	75
16	1.5	Methanol	Reflux	6	69
17	1	Methanol	Reflux	8	64
18	0.5	Methanol	Reflux	6	60

[a]Reaction of benzil (1 mmol), ethane-1,2-diamine (1 mmol), 3ml solvent taking Cu-catalyst for every reaction; [b] Isolated yield after column chromatography; [c] primary effort for the synthesis of pyrazine; [d] formation of both pyrazine and dihydro pyrazine was observed; [e] no dihydro pyrazine was isolated; [f] used surfactant during the reaction; [g] reaction was performed without a catalyst; [h] no improvement in the yield after 8 hrs. and upto 12 hrs.; optimized reaction condition.

To generalize the developed protocol, several diversified 1,2-diketones and 1,2-diamines were used for the reaction to examine the scope of the new method (Table-2). Certainly, the catalyst helps to precede a tandem oxidation-cyclization of *α*-hydroxy ketone and directs alkyl *vic*-diamine to their respective pyrazines (entry 9, 10, Table-2) and thus found useful to produce methylated pyrazines. The equal effectiveness of the catalyst towards both the substituted (electron-donating or electron-withdrawing) and unsubstituted benzil and also for *α*-hydroxy ketone, instigate us to consider the effect of catalyst on other precursors for the double condensation-cyclization reactions to prepare the respective pyrazines. To check, we replaced one or both the aromatic rings of *vic*-diketones with aliphatic groups and run the reaction with our optimized condition by varying *vic*-diamines (Table-3). Once again, we discovered good results for the preparation of the corresponding pyrazines.).

To show the general applicability, we attempted the developed optimized protocol to naturally occurring big molecules, like pentacyclic triterpenoids of two different skeletons, lupane and friedelin. Very interestingly we observed, the same protocol gave excellent results (D/E//F, entry 11, table 2) when applied on their 1,2-diketo derivative (A, B, or C). Further, we observed similar efficiency of the catalyst during condensation reaction of 2,3-diaminomaleonitrile with *vic*-diketone/*α*-hydroxy ketone for cyano-pyrazine synthesis.

Table-2: Synthesis of pyrazine analog by optimized reaction condition[a]

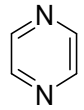
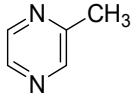
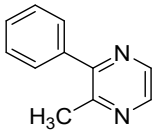
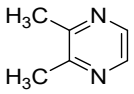
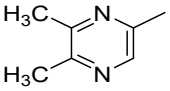
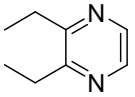
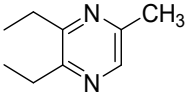
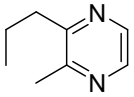
 3h, 92%	 3h, 92%	 3.5h, 90%	 3h, 91%	 4h, 86%
 4h, 89%	 4.5h, 85%	 3.5h, 90%	 3h, 91%	 3h, 92%

[a]Diketone/α-hydroxy ketone (1 mmol), diamine (1 mmol), catalyst (5 mol%), methanol (3 mL) at 50 ^{0}C. [b] Isolated yields.

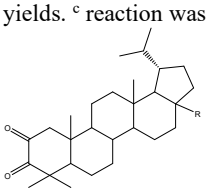
The catalytic activity of our prepared catalyst in the double condensation/tandem oxidation-cyclization process for the preparation of pyrazines encourages us to develop the synthetic scope of our catalyst and further herein we have tried to generate another protocol which involves the synthesis of 2, 3-diphenyl quinoxaline from *o*-phenylene diamine (1 mmol) and benzil (1 mmol), in methanol (3 mL) by using the

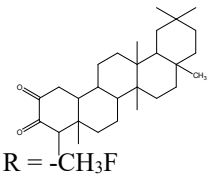
copper catalyst (10 mol%) at room temperature (Fig-4). Again, we were able to achieve an optimized reaction condition (entry 10, Table-5), which also performed well with other substituted *vic*-diketone/α-hydroxy ketone to provide their corresponding quinoxalines in good yield (Table-6).

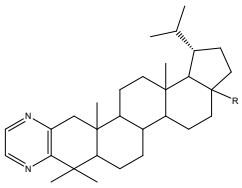
Table-3: Screening the efficacy of catalyst for pyrazine analog at optimized condition[a]

 3h, 90%	 3h, 92%	 4h, 89%	 4.5h, 90%
 4.5h, 87%	 3.5h, 89%	 3.5h, 90%	 4h, 84%

[a]Diketone/α-hydroxy ketone (1 mmol), diamine (1 mmol), catalyst (5 mol%), methanol (3 mL) at 50^0 C. [b] all yields are isolated yields. [c] reaction was done at room temperature.


A, R= -CH_3 C


D, R = -CH_3F


B, R= -$COOCH_3$E, R = -$COOCH_3$

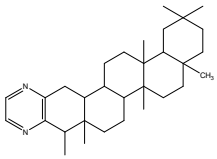
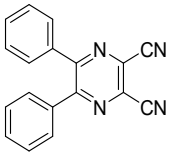
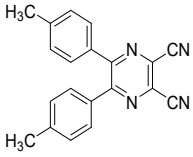
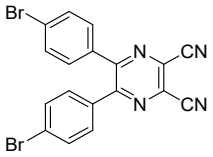
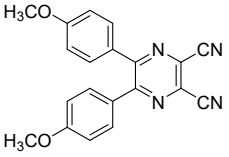
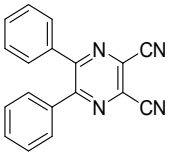
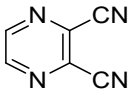
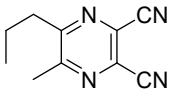
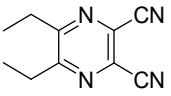
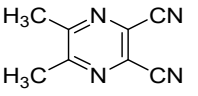
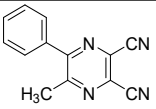


Table-4: Synthesis of cyano-pyrazine at our optimized reaction condition[a]

 4h, 91%	 4.5h, 90%	 5h, 79%	 4h, 85%	 4.5h, 89%
 3h, 88%	 3.5h, 89%	 3h, 90%	 4h, 79%	 4h, 84%

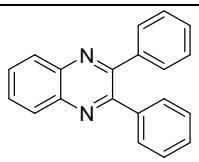
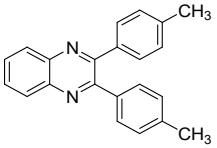
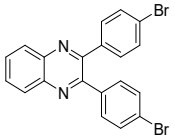
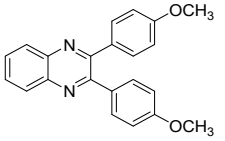
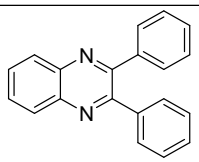
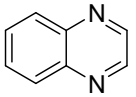
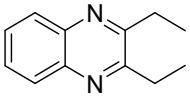
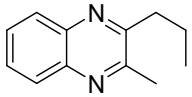
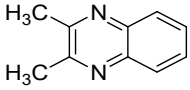
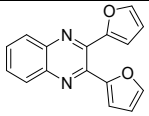
[a]diketone/α-hydroxy ketone (1 mmol), 2,3-diaminomaleonitrile (1 mmol), catalyst (5 mol%), methanol (3 mL) at 50^0 C.

Table-5: optimization of reaction condition for the preparation of 2,3-diphenyl quinoxaline[a]

Entry	Solvent (3 mL)	Catalyst (mol %)	Temp (^{0}C)	Time (h)	Yield(%)[a]
1	Methanol	10	Room temp	1	-
2	Methanol	10	Room temp	3	45
3	Methanol	10	Room temp	6	65
4[b]	Methanol	10	Room temp	9	89
5	Acetonitrile	10	Room temp	16	35
6	Dichloromethane	10	Room temp	16	46
7	Chloroform	10	Room temp	16	38
8	Water	10	Room temp	12	20
9	Methanol	5	Room temp	12	89
10[c, d]	-	2.5	40	3	90
11	-	1.5	reflux	6	85
12	-	0.5	Reflux	6	72

[a]Yields are isolated yields, [b] yield of the product remains unchanged after 12h, [c]product yield remains unchanged after 6h[d] optimized reaction condition: benzil (1 mmol), *o*-phenylene diamine (1 mmol), copper catalyst (2.5 mol%) and methanol (3 mL)

Table-6: Generality of optimized condition for 2, 3-disubstituted quinoxaline[a]

 3h, 90%	 3h, 87%	 3.5h, 89%	 4h, 85%	 3.5h, 90%
 3h, 89%	 4h, 91%	 3.5h, 82%	 3h, 84%	 4h, 86%

[a]1,2-di ketone (1 mmol), o-phenylene diamine (1 mmol), copper catalyst (2.5 mol%) and methanol (3 mL) at 40 °C.

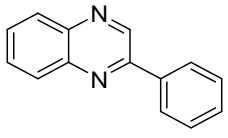
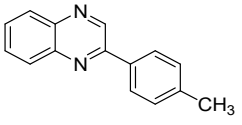
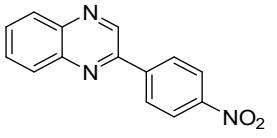
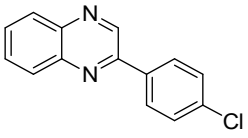
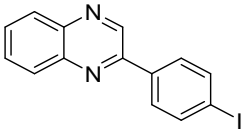
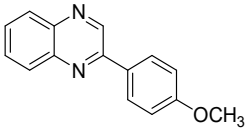
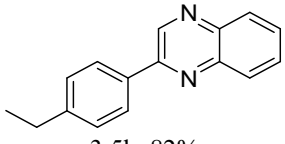
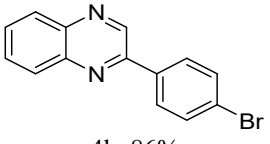
Further, we also tested the ability of the catalyst in providing very simple alternative protocols for the synthesis of quinoxaline by the reaction of phenacyl bromide/substituted phenacyl bromide and *vic*-diamine. For this, we choose phenacyl bromide (1 mmol), *o*-phenylene diamine (1 mmol), copper catalyst (10 mol%) and Na_2CO_3 (1 equiv.) using methanol (3 mL) as a solvent under reflux condition (Fig-3) and get satisfactory yield (92 %) for the expected quinoxaline (2-Phenyl quinoxaline). This result encourages us to further investigate to establish a suitable reaction condition. Finally, we were able to reach an optimized condition for the reaction (entry 1, Table-7). Moreover, the wide applicability of the protocol taking other substituted reactants (both in phenacyl bromide part and *vic*-diamine part) proves the generality of our optimized reaction condition (Table-8).

Table-7: Screening of optimized condition for preparation of 2-phenylquinoxaline

Entry	Solvent	Catalyst (mol %)	Base[a]	Temp (^{0}C)	Time (h)	Yield[b](%)
1[c, d]	Methanol	10	Na_2CO_3	reflux	3	92
2	Methanol	10	Na_2CO_3	-	6	-
3[e]	Methanol	10	Na_2CO_3	50	6	75
4	Methanol	5	Na_2CO_3	reflux	12	42
5	Acetonitrile	10	Na_2CO_3	reflux	16	50
6	Dichloromethane	10	Na_2CO_3	reflux	16	42
7	Chloroform	10	Na_2CO_3	reflux	16	29
8	Water	10	Na_2CO_3	reflux	12	nr

[a]Base was taken in 1 equivalent, [b]isolated yields, [c] reaction was also checked using bases like KOH, $NaHCO_3$ and K_2CO_3 in 1 equiv. amount but the yield was not satisfactory, [d]our optimized reaction condition (i.e. phenacyl bromide (1mmol), *o*-phenylene diamine (1 mmol), copper catalyst (10 mol%), Na_2CO_3 (1equiv.) and methanol (3 mL), [e]no change of yield was observed upto 12 h.

Table-8: Synthesis of 2-substituted quinoxaline[a]

 3h, 92%	 3h, 90%	 3.5h, 85%	 4h, 83%
 4h, 85%	 4.5h, 90%	 3.5h, 82%	 4h, 86%

[a]Phenacyl bromide (1 mmol), *o*-phenylene diamine (1 mmol), copper catalyst (10 mol%), Na_2CO_3 (1 equiv.) and methanol (3 mL) under reflux condition.

CONCLUSION

In conclusion, we have designed several straightforward and facile methodologies for the preparation of quinoxaline and pyrazine using organo Cu (II) catalyst. The use of inexpensive starting materials and catalysts, functional group tolerance, less reaction time, easy reaction set-up is the significance of these protocols. This protocol is anticipated to accomplish wide applicability in natural product synthesis and in the pharmaceutical industry.

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