C-H Functionalization of Heterocycles through Radical Process

Project Report

CH 800: Stage II

By

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CANDIDATE'S DECLARATION

I hereby certify that the work which is being presented in the thesis entitled **'C-H Functionalization of Heterocycles Through Radical Process'** in the partial fulfillment of the requirements for the award of the degree of **MASTER OF SCIENCE** and submitted in the **DEPARTMENT OF CHEMISTRY**, **Indian Institute of Technology Indore** is an authentic record of my own work carried out during the period from July 2020 to June 2021 under the supervision of Dr. Selvakumar Sermadurai. The matter presented in this thesis has not been submitted by me for the award of any other degree of this or any other institute.

Nkakde

Signature of the student (with date)

Neha Kakde

This is to certify that the above statement made by the candidate is correct to the best of my knowledge.

09.06.2021

Signature of the Supervisor (with date)

Dr. Selvakumar Sermadurai

Neha Kakde has successfully given her M.Sc. Oral Examination held on **09/06/2021.**

09.06.2021

Signature(s) of Supervisor(s) of MSc thesis

Convener, DPGC

Date**:**

Signature of PSPC Member

Dr. Tridib Kumar Sarma

Date:

Signature of PSPC Member

Dr. Abhinav Raghuvanshi

Date: 09/06/2021

ABSTRACT

Direct functionalization at the C3-site of Quinoxalin-2(1H)-one via oxidative addition of silyl radicals has been studied. Broad range of biological activities and pharmaceutical applications of C3-incorporated Quinoxalin-2(1H)-one has paved a way for the large advancement in the selective introduction of range of radicals for the new C-C, C-O, C-N, C-P, C-O and C-S linkage incorporations. In this work, a bond between silyl group andC3-carbon of Quinoxalin-2(1H)-one is entrenched under mild to tolerant oxidative reaction environment.

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List of Schemes

Acronyms

TBHP- tert-butyl hydrogen peroxide

DTBP- Di-tertbutylperoxide

TBPB- tert-Butylperoxybenzoate

DMF- N,N-Dimethylformamide

DCE- 1,2-Dichloroethane

CuI- Copper Iodide

$Cu(OAc)_2$- Copper (II) Acetate

TBAI- Tetrabutylammonium Iodide

1. INTRODUCTION

Heterocycles act as the building block for the development of various complex molecules that are essential for the proper functioning of the biological system. However, the activity of such complex molecules can be further enhanced by introducing variations in its construction. Recent advancement has been acknowledged by exploring nitrogen heterocycles. Over the years, Nitrogen heterocycles have been utilized for the composition of pharmaceutical compounds. Quinoxalin-2(1*H*)-one (Figure 1) is known to be one of the most relevant nitrogen heterocycles in the field of synthetic chemistry. It is proven to be quite promising candidate for its substantial pertinence in biological activities [1].

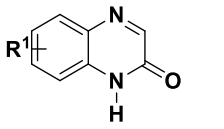


Figure 1. Structure of Quinoxalin-2(1*H*)-one

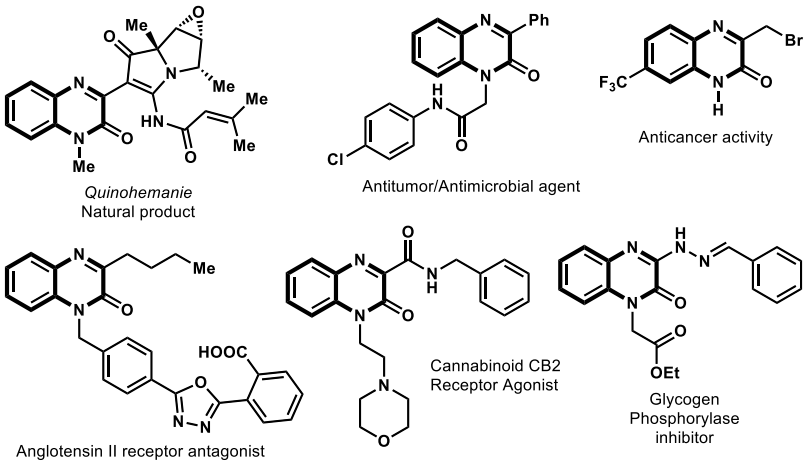
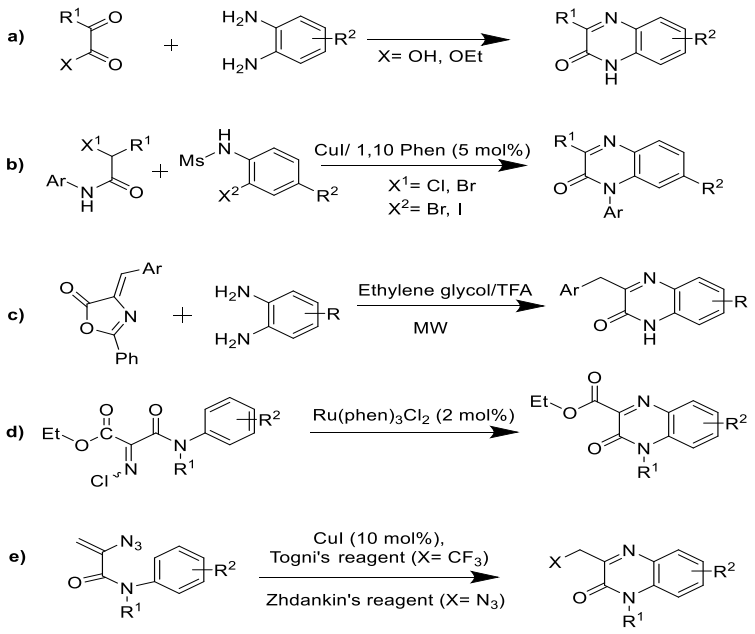


Figure 2. Representative biologically active molecules containing 3-substituted Quinoxaline-2(1*H*)-one framework

Apart from its applications in pharmaceutical chemistry, Quinoxalin-2(1*H*)-one enacts as a substratum in multiple biologically active molecules. In particular, C-3 substituted quinoxaline-2(1*H*)-one derivatives unveiled an extensive purview of biological activities. To give an instance, a natural product Quinohemanine that was isolated from *Streptomyces sp*. CPCC 200497 shows mild cytotoxicity against cancer cell line HepG2. Other C-3 incorporated quinoxaline-2(1*H*)-one derivatives have displayed diverse activities such as antitumor agents, angiotensin II receptor antagonist, antimicrobial agent, aldolase reductase inhibitor, histamine-4-receptor, cannabinoid CB2 receptor agonist and others (Figure 2) [2].

Initially, C3-substituted Quinoxalin-2(1*H*)-one was formed by direct condensation between 1, 2-diaminobenzene derivatives and α-keto acids or α-keto esters (Scheme 1). However, this method witnessed a few limitations such as multi-step synthesis and limited substrate scope [3].



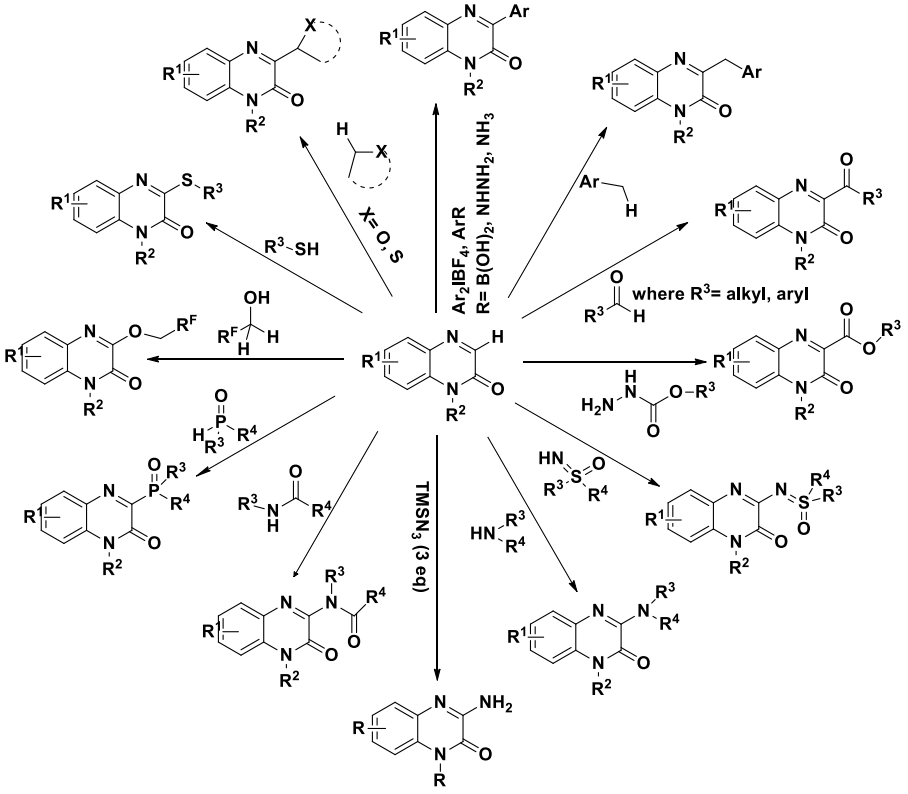
Scheme 1: Synthesis of C3-substituted Quinoxalin-2(1*H*)-one derivative

Due to the above limitations, several synthetic route for direct substitution on the C3 site of Quinoxalin-2(1*H*)-one was reported [4].In particular, radical based direct substitution on the C3 site of quinoxalin-2(1*H*)-one received much attention [5, 6].

2. LITERATURE REVIEW

2.1. C-H Functionalization by various radical sources:

With respect to C3-substitution onQuinoxalin-2(1*H*)-one, there were multiple previous reports published. However, it showcased a few drawbacks like prefunctionalization of substrates and multi-step synthesis. Hence, an approach of direct functionalization on Quinoxalin-2(1*H*)-one using various ionic and radical precursors was studied extensively. Recent reports on reaction involving several radicals with Quinoxalin-2(1*H*)-one have been recorded for the numerous substitution reactions.



Scheme 2. Reaction involving Quinoxalin-2(1*H*)-one and various radical sources

2.2. C-H silylation of Quinoxalin-2(1*H*)-one:

Remodeling of numerous complex molecules has witnessed enhanced activity by optimizing competent groups. For years, the influence of competent groups like Organosilanes has been the area of interest among researchers. According to the previous reports, silicon bioisostere has played a huge role in biochemistry as well as synthetic chemistry. Silicon bioisostere in complex molecules has shown enhanced selectivity and increased lipophilic nature. Such variations are carried out by introducing organosilyl motifs to study its overall effect on the molecule. Organosilanes possess properties that can enhance the biological activity of the molecule by reducing the level of toxicity. Organosilanes have known to improve the lipophilicity of the molecules that helps membrane crossing thus increasing bioavailability. Silicon is used as a bio isostere in amino acids to improve its physiochemical properties by increasing stability and reactivity. Discovery of silicon containing drug molecules has termed to be profitable due to its unique properties (Figure 3) [7].

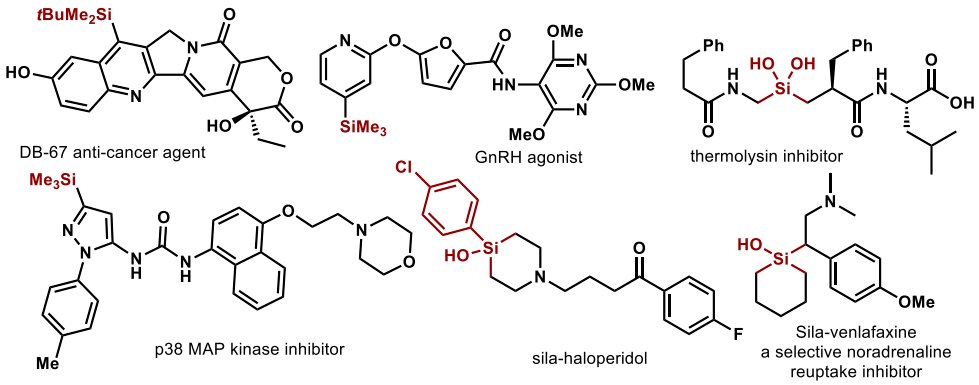
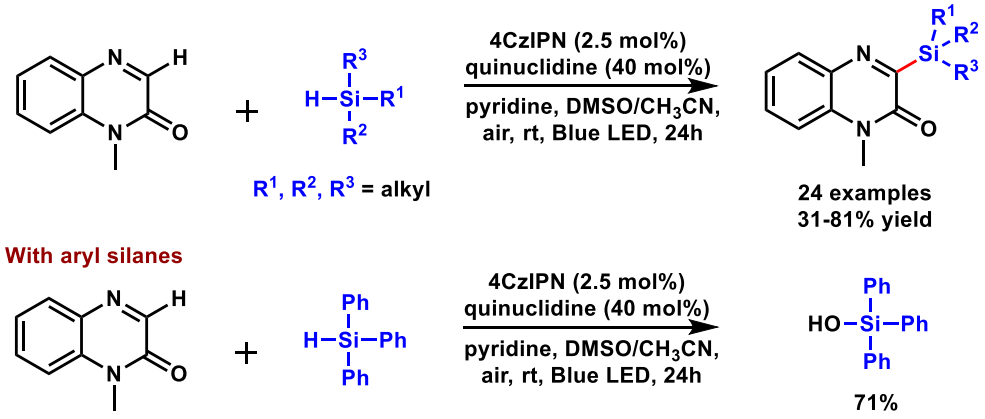


Figure 3. Representative examples of silicon containing drugs

Hence, the introduction of Organosilanes in heteroarene system is under a lot of interest. Numerous strategies for the incorporation of Organosilanes in heteroarene systems have been designed successfully [8].The strategies include cross coupling reaction between aryl halides or

aryl esters along with hydrosilanes or disilanes under the influence of transition metal. However, the direct C-H silylation of heteroarenes were analyzed using triflates like Me_3SiOTf along with Lewis acid or Brønsted acid, typically known as Friedel Crafts Silylation [9]. Another study involves application of hydrosilanes on heteroarenes in the presence of strong base like KO^tBu [10]. Considering the advantages on introduction of silyl substituents on heterocycles and the impact of substituents on the biological properties of Quinoxaline-2(1*H*)-one derivatives, the instigation of innovative and coherent prospects for the preparation of C3-silylated Quinoxaline-2(1H)-one derivatives by direct C–H substitution will be of great value in the screening of aberrant complex active molecules. Very recently, Sun and Liu reported visible light photoredox catalytic approach towards the C-H silylation of quinoxalinones. However, this method suffers from the oxidation of aryl silanes, so it was limited to the application of trialkyl silanes (Scheme 3) [11].Hence, we attempted to develop an efficient method to incorporate alkyl and aryl silane at the C-3 position of quinoxalin-2(1*H*)-one.



Scheme 3. Photocatalytic direct C-H Silylation of Quinoxalin-2(1H)-one

Considering the advantages on introduction of silyl substituents on heterocycles and the impact of substituents on the biological properties of Quinoxaline-2(1*H*)-one derivatives, the instigation of innovative and

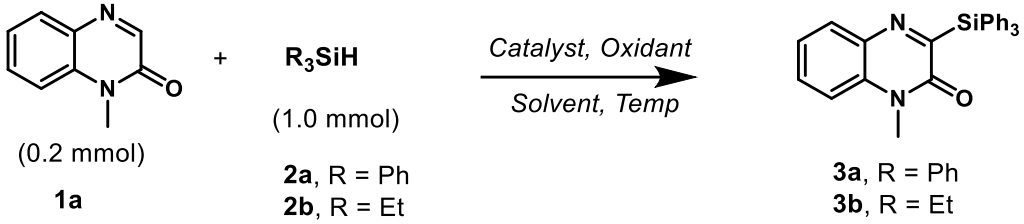
coherent prospects for the preparation of C3-silylated Quinoxaline-2(1H)-one derivatives by direct C–H substitution will be of great value in the screening of aberrant complex active molecules. Very recently, Sun and Liu reported visible light photoredox catalytic approach towards the C-H silylation of quinoxalinones. However, this method suffers from the oxidation of aryl silanes, so it was limited to the application of trialkyl silanes (Scheme 3) [11].Hence, we attempted to develop an efficient method to incorporate alkyl and aryl silane at the C-3 position of quinoxalin-2(1*H*)-one.

3. RESULTS AND DISCUSSION

3.1. Optimization:

Reaction optimization was initiated by using Quinoxalin-2(1*H*)-one **1a** as substrates along with triphenylsilane **2a** as silyl radical precursor. To begin with thermal reaction conditions, Studer's electron catalysis [12] condition was adopted with catalytic amount of TBAI (5 mol%)and TBHP (3 equiv) in the role of oxidant in benzene at 90℃ for 24h. Under this condition desired product was obtained in 12% yield along with a side product as an inseparable mixture (Table 1, entry 1). Structure of desired product **3a** was tentatively assigned with help of ^{1}H NMR. Reaction did not take place when 70% TBHP in H_2O was used as an oxidant (Table 1, entry 2). Triethylsilane **2b** as silyl radical precursor afforded the desired product in trace amount (Table 1, entry 3). Reaction did not take place when the oxidant was replaced with DTBP (Table 1, entry 4). Replacing TBAI with CuI as catalyst along with TBHP as oxidant gave 6% of desired product **3a** for triphenyl silane using *tert*-BuOH as solvent at 110℃ (Table 1, entry 5).

Table 1. Screening of reaction condition[a]



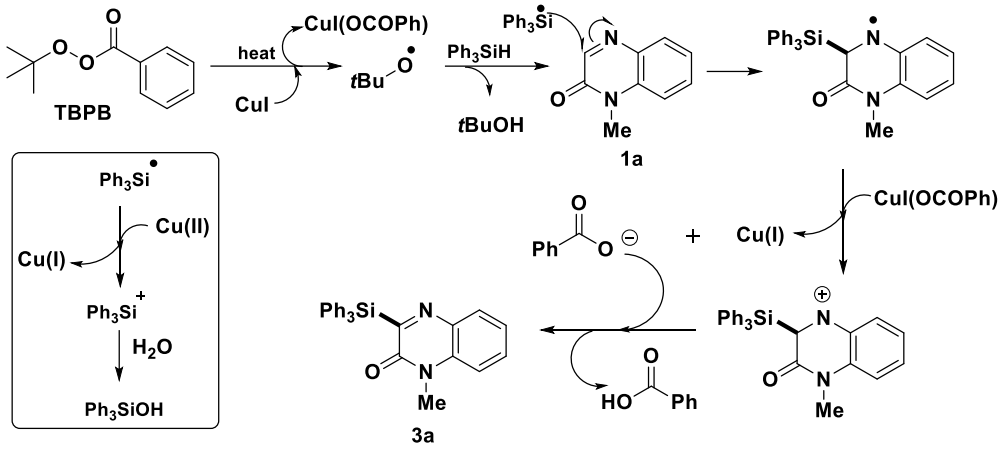
Entry	Catalyst (mol%)	Silane	Oxidant (equiv.)	Solvent	Temp (°C)	Time	Yield (%)[b]
1[c]	TBAI (5)	**2a**	TBHP (3)	Benzene	90	24 h	12
2[d]	TBAI (5)	**2a**	TBHP (3)	Benzene	90	24 h	NR
3[c]	TBAI (5)	**2b**	TBHP (3)	Benzene	90	24 h	trace
4[c]	TBAI (5)	**2a**	DTBP (3)	Benzene	90	24 h	NR
5[c]	CuI (5)	**2a**	TBHP (3)	*tert*-BuOH	110	24 h	06[e]
6	CuI (5)	2a	TBPB (3)	C_6H_5-CF_3	120	20 h	24[e]
7	$Cu(OAc)_2$(5)	**2a**	TBPB (3)	*tert*-BuOH	110	20 h	trace

[a]Reaction conditions: **1** (0.2 mmol), **2** (1.0 mmol), catalyst (0.01 mmol%) and oxidant (0.6 mmol) in2 mL solvent under N_2 atmosphere for 20 h in a sealed tube. [b]Yield of isolated products. [c]Using (5.0 – 6.0 M) TBHP in decane.[d]Using 70% TBHP in water.[e]Large amount of Triphenylsilanol formation was observed. NR = no reaction.

In order to improve the conversion, further screening of oxidants revealed that TBPB was found to be more efficient than TBHP in affording the expected product **3a** in 24% yield using α,α,α-trifluorotoluene at 120 °C (Table 1, entry 6).Replacing CuI with $Cu(OAc)_2$ as catalyst, the yield of the reaction decreased drastically to trace amount of **3a** with the formation of large amount of triphenyl silanol(Table 1, entry 7). It was concluded that TBPB oxidant worked successfully along with CuI catalyst in *tert*-

BuOH at 110℃ and has been identified as an optimized condition at this stage.

3.2. Reaction Pathway



Scheme 4. Probable reaction pathway

On the basis of previous literature reports, a probable reaction course is suggested (Scheme 4). The reaction pathway begins with the single electron transfer from Cu(I) to TBPB giving rise to *tert*-butoxy radical and benzoate anion. The resultant *tert*-butoxy radical then abstracts hydrogen atom from triphenylsilane to form *tert*-butanol and triphenylsilyl radical. Further, the latter reacts with quinoxalin-2(1*H*)-one**1a** on the C3 site by homolysis and results into a nitrogen centered radical intermediate. This intermediate then undergoes a single electron transfer with Cu(II) to give nitrogen centered cation intermediate and Cu(I) by eliminating the benzoate anion. Lastly, the benzoate anion abstracts proton from the C3 position, and the intermediate regains its aromaticity to give the desired product **3a**.

4. EXPERIMENTAL SECTION

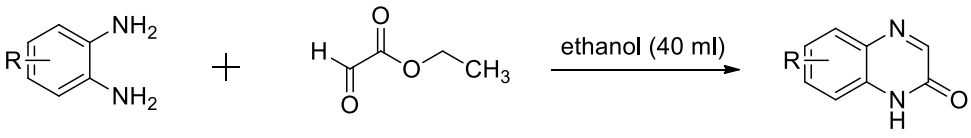
4.1. General Information:

All the reagents and solvents were attained from commercial authorities. The substrates were synthesized as enlisted in the conventional protocol mentioned below. The reagents and solvents were used without any purification. Ethyl acetate and hexane were distilled before use. All of the reactions were performed in inert medium and supervised by thin-layer chromatography (TLC) using Merck 60 F254 precoated silica gel plates, and the products were observed by UV detection. Purification of the synthesized products was executed by Column Chromatography filled with silica gel (100-200 mesh).

4.2. Instrumentation:

The purified products were authenticated through NMR Spectra recorded on a Bruker Advance 400 Spectrometer 400 MHz (^{1}H) in $CDCl_3$ and DMSO-d_6 using tetramethylsilane as an internal standard. All chemical shift values are mentioned in δ scale in parts per million (ppm). The residual solvent peaks of $CDCl_3$ and DMSO-d_6 were recorded at 7.26 and 2.50 ppm respectively. The multiplicities of desired peaks were denoted as given s= singlet, d= doublet, dd= doublet of doublet, t= triplet, q= quartet, m= multiplet.

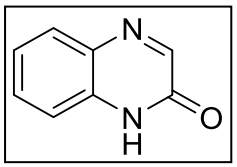
4.3. Conventional protocol for the synthesis of Quinoxalin-2(1H)-one:



To a 100 ml RB flask, o-arylenediamine (1 equiv) in 40 ml ethanol (1 mol/L) was added. To this compound, ethyl glyoxalate (1.1 equiv) was transferred in the presence of nitrogen medium. The resultant mixture was

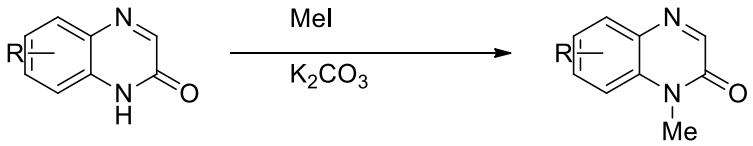
agitated for 3 hours under reflux condition at 65℃ in an oil bath. After completion of 3 hours, the mixture was stirred overnight at room temperature on magnetic stirrer. As the mixture was stirred overnight, precipitation occurred that further underwent extraction through filtration. The filtration and washing of precipitate was carried out with cold ethanol under vacuum pump and air dried.

Quinoxalin-2(1*H*)-one:



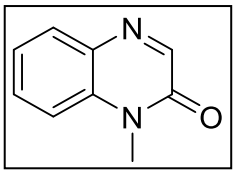
R_f value in Hexane: Ethyl acetate (10:1) is 0.2; White solid (0.757g,57%). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.66 (1H, s), 8.34 (1H, s), 7.90 (1H, d, J = 6.4 Hz), 7.55 (1H, m), 7.25 (2H, m).

4.4 Conventional protocol for N-Methylation of Quinoxalin-2(1H)-one:



Under nitrogen atmosphere, Quinoxalin-2(1*H*)-one (3 mmol, 435 mg) in DMF (6 ml) was added in a 25 ml RB Flask. To this solution, potassium carbonate (1.2 equiv) and Methyl Iodide (1.6 equiv) was transferred. The resultant mixture was agitated overnight on magnetic stirrer at ambient condition under nitrogen atmosphere. After monitoring the reaction through TLC, Ethyl acetate (10 ml) was used for the dilution of reaction mixture. The desired product was extracted in the organic layer after separating it from the aqueous layer (10 ml). The organic layer was then washed with aqueous layer (10 ml) twice. The organic component underwent evaporation for the purification of reaction mixture through Column Chromatography.

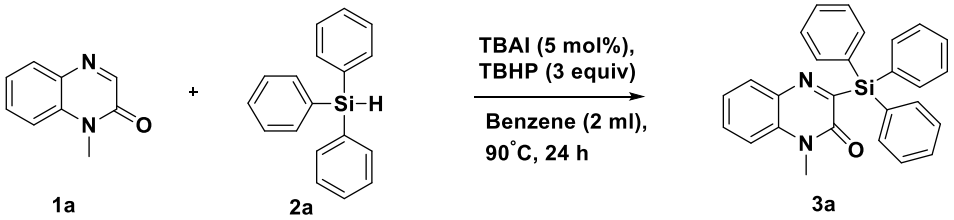
1-Methylquinoxalin-2(1H)-one



R_f value= 0.2 in Hexane: Ethyl acetate (10:1 v/v). White solid (0.438 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm)8.31 (s, 1H), 7.90-7.88 (m, 1H), 7.63-7.59 (m, 1H), 7.39-7.26 (m, 2H), 3.70 (s, 3H).

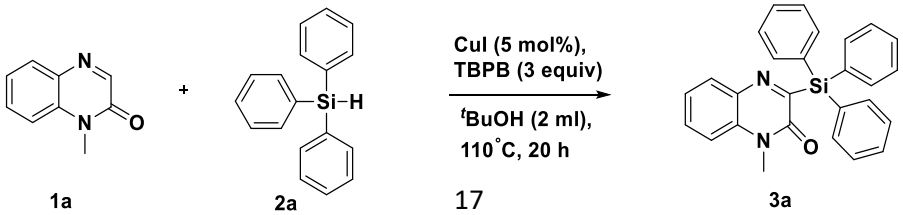
4.5 General Procedure for C3-silylation of Quinoxalin-2(1H)-one:

Procedure A

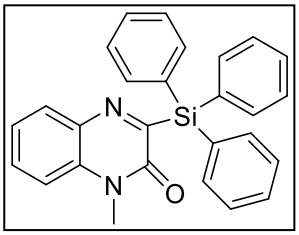


In a sealed tube, 1-Methylquinoxalin-2(1H)-one **1a** (1 equiv, 32 mg) in Benzene (2 ml) was added. To this solution, TBAI initiator (5 mol%) was added along with Triphenylsilane **2a** (5 equiv, 260.41 mg). Lastly, the oxidant TBHP (3 equiv) was transferred slowly under Nitrogen atmosphere. The reaction mixture was stirred over magnetic stirrer at 90℃ for 24 hours under Nitrogen atmosphere. After monitoring the reaction through TLC, Ethyl acetate (10 ml) was used for the dilution of the reaction mixture. The diluted solution was further separated into organic and aqueous layers. The residue of interest was extracted in the organic component and washed in water (10 ml) twice. Following the evaporation of solvent, the mixture was run through silica gel column chromatography for purification and the product **3a**.

Procedure B



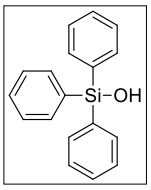
In a sealed tube, 1-Methylquinoxalin-2(1H)-one (1 equiv, 32 mg) in tert-BuOH(2 ml) was added. CuI salt (5 mol%) along with Triphenylsilane (5 equiv, 260.41 mg) was added into the mixture. Lastly the oxidant TBPB (3.5 equiv) was transferred further the subsequent compound underwent agitation at 110℃ for 20 hours. Further, the mixture was monitored using TLC and Ethyl acetate (10 ml) was used for the dilution of reaction mixture. The diluted solution was further separated into organic and aqueous layers. The residue of interest was extracted in the organic component and washed in water (10 ml) twice. Following the evaporation of solvent in vacuum, the mixture was run through silica gel column chromatography for purification and the product **3a**was obtained in 24% yield (0.052 g).



3-(Triphenylsilyl)-1-methylquinoxalin-2(1H)-one

R_f value= 0.3. Hexane: Ethyl acetate (1:0.06 v/v). White solid (0.052 g, 24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.88 (d, *J* = 7.5 Hz, 1H), 7.68−7.48 (m, 6H), 7.34−7.19 (m, 12H), 3.54 (s, 3H)

Triphenylsilanol

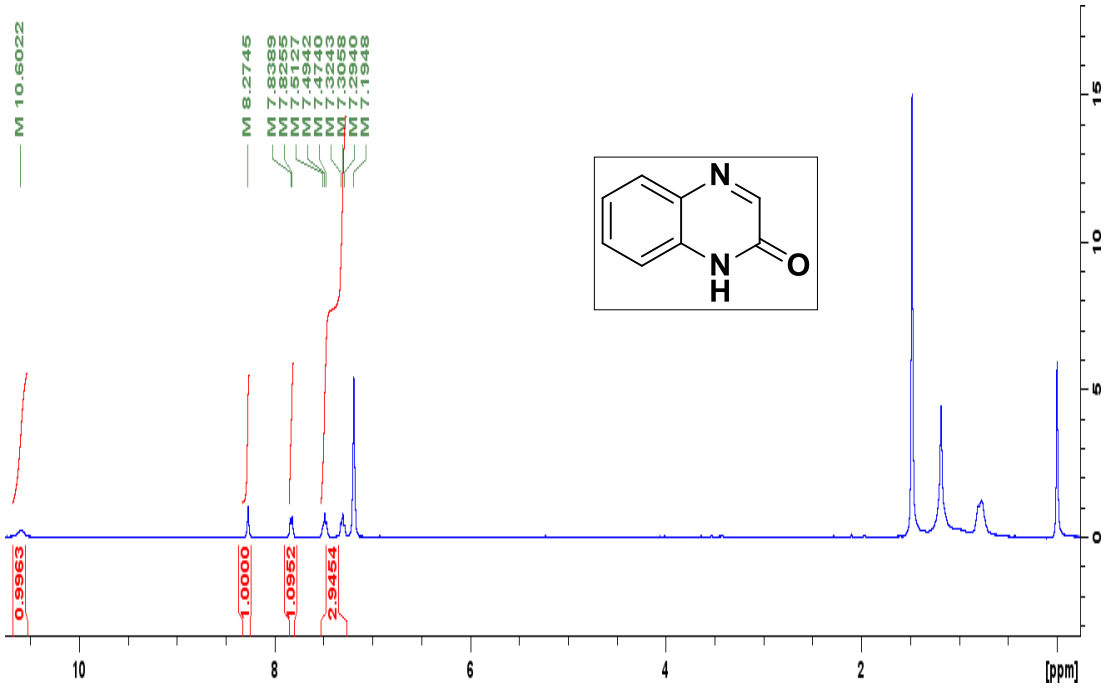


R_f value= 0.4. Hexane: Ethyl acetate (1:0.06 v/v). White solid^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.56−7.54 (m, 6H), 7.38−7.29 (m, 9H), 2.50 (s, 1H)

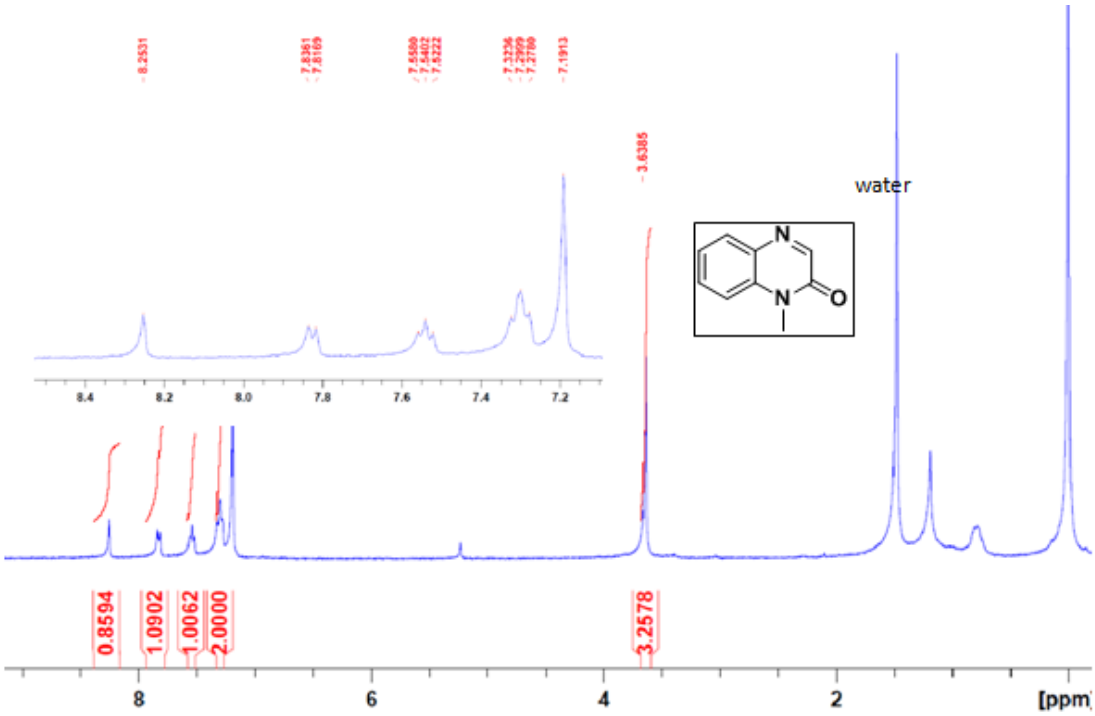
5. CHARACTERIZATION

5.1. ^{1}H NMR Spectra of compounds:

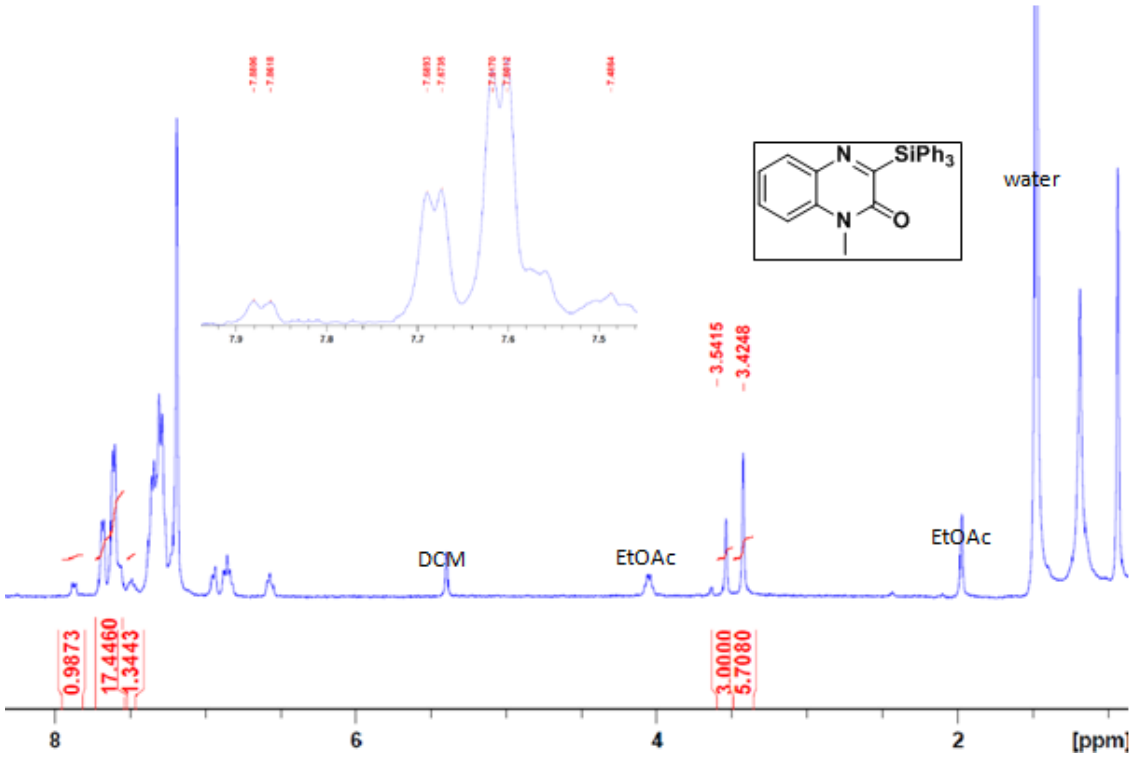
1) Quinoxalin-2(1H)-one in $CDCl_3$:



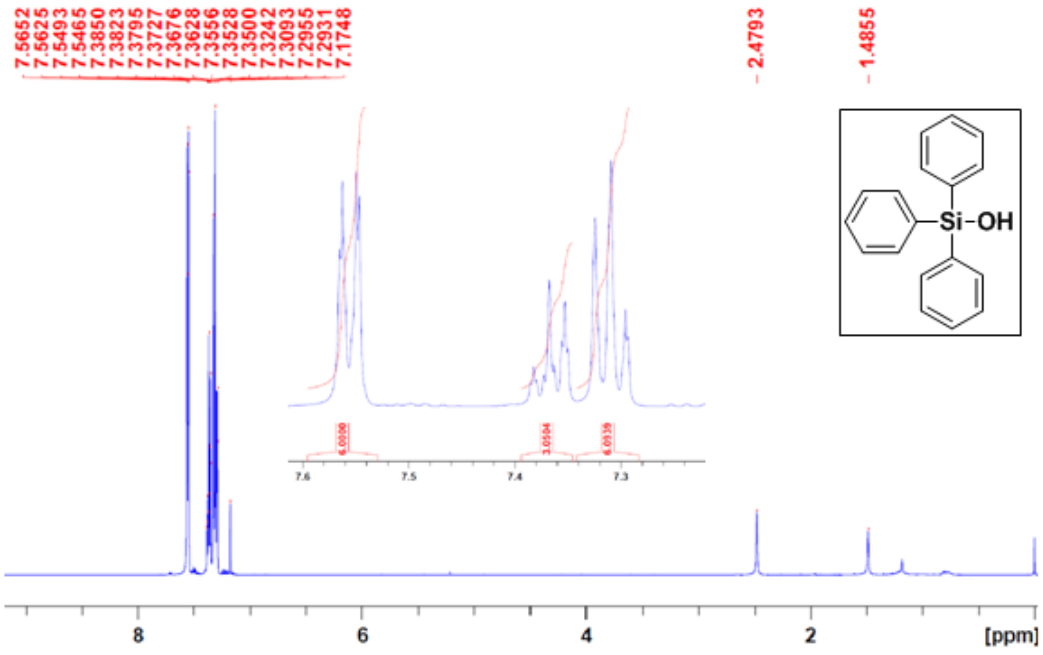
2) 1-Methylquinoxalin-2(1H)-one in $CDCl_3$:



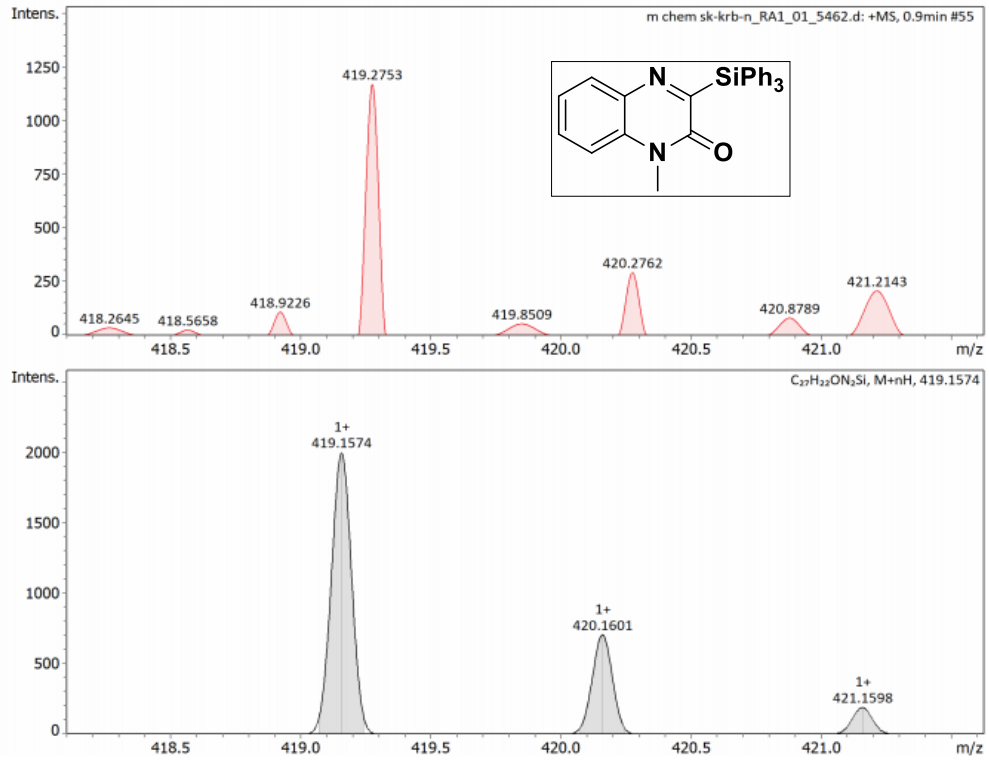
3) 1-Methyl-3-triphenylquinoxalinone in $CDCl_3$:



4) Triphenylsilanol in $CDCl_3$:



5. LCMS of 1-Methyl-3-triphenylquinoxalinone in acetonitrile:



6. CONCLUSION

An attempt to formulate C3-silylated Quinoxalin-2(1H)-one is termed to be efficacious. The desired product was successfully acquired using minimal proportion of CuI (I) salt under thermal condition. Furthermore, substrate scope of the reaction strategy needs to be investigated. As a result, new advances can be expected in the field of heterocyclic chemistry.

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