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Green Protocol for the Synthesis of PEG-SO3H Catalyzed Quinoxaline Derivatives at Room Temperature

Yogesh M. Patel*, Rajendra R. Patel, Umesh P. Tarpada, Vivek N. Dave

Government Science College, Gandhinagar, Gujarat-382016, India

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For Correspondence:
Yogesh M. Patel
Government Science College, Gandhinagar, Gujarat-382016, India

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ABSTRACT:

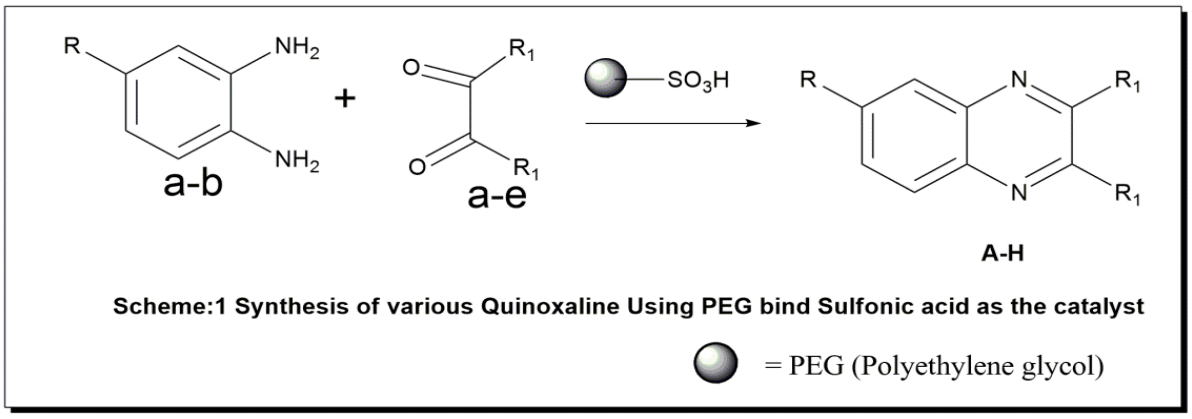
PEG-SO_3H was found to be an effective heterogeneous catalyst for the one pot synthesis of various quinoxaline derivatives from condensation reaction between 1,2-diamines with 1,2-dicarbonyl compounds in ethanol to affords excellent yields. Synthesis was attempted at room temperature using ethanol as the solvent. Heterogeneity of the catalyst allowed its recycling for five times with almost retention in catalytic activity. Reaction carried out at room temperature shows special advantageous because it has contribution in the green chemistry aspect.

KEY WORDS: Quinoxaline; antioxidant activity; heterogeneous catalyst; o-phenylenediamine; 1, 2- diarylketone.

1. INTRODUCTION:

Quinoxaline derivatives are of significant interest from both academic and industrial perspectives because they are noteworthy intermediates for the manufacturing of pharmaceuticals and advanced materials [1]. A number of on nitrogen-containing heterocycles show antimicrobial activity and have been synthesized for medical use. Among various classes of heterocyclic units, quinoxaline ring has frequently been used as a component of various antibiotic molecules, such as levomycin and hinomycin, which inhibit the growth of Gram-positive bacteria and are active against various transplantable tumors [2]. Quinoxalines are very important compounds due to their wide spectrum of biological activities such as anticancer [3-4] and activity as kinase inhibitors [5]. They are well known for their application in rigid subunits in macrocyclic receptors [6] electroluminescent materials [7], organic semiconductors [8] and DNA cleaving agents [9]. Considering the significant applications in the fields of medicinal, industrial and synthetic organic chemistry, there has been tremendous interest in developing efficient methods for the synthesis of quinoxalines. Improved methods have been reported by using different catalyst such as Pd $(OAc)_2$, MnO_2, CAN, manganese octahedral molecular sieves, task-specific ionic liquid and bismuth (III). Although great success has been obtained, many of these methodologies suffer one or more drawbacks such as drastic reaction conditions, low yields, and tedious work-up procedures, using toxic metal salts as catalysts, long reaction time and relatively expensive reagents. A number of synthetic strategies have been developed for the preparation of substituted quinoxalines [10-26], The most common method involve the condensation of an aryl-1,2-diamine with a 1,2-dicarbonyl compound in refluxing ethanol or acetic acid for 2–12 h,

and this typically gives yields of 34–70 %. Hence, the search for the better method, especially the readily available and green catalysts, is still being actively pursued, therefore we have plane reported green protocol for one-pot synthesis of quinoxaline derivatives from readily available *o*-phenylenediamines and 1, 2-diaryl ketones under conditions are mild and a wide range of functional groups can be tolerated in the building blocks.



Scheme:1 Synthesis of various Quinoxaline Using PEG bind Sulfonic acid as the catalyst

= PEG (Polyethylene glycol)

2. EXPERIMENTAL

2.1. Chemicals and reagents

All chemicals used were of laboratory reagent grade and used without further purification**.** PEG, were obtained from S.D. Fine Chem. Pvt. Ltd., Mumbai, India *o-phenylenediamines*, sodiumhydroxide and sulphanilic acid were obtained from Samir Tech Chem. Pvt. Ltd., Vadodara, India. Various 1, 2- diketone were used as received from Merck, Mumbai, India. All the solvents were supplied by Sisco Chem. Pvt. Ltd., Mumbai, India.

2.2. Analytical methods

Melting points were determined by open capillary method and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded as solutions in DMSO-*d6* on a Bruker Avance 400 spectrometer operating at 400 MHz for ^{1}H NMR, and 100 MHz for ^{13}C NMR. Chemical shifts (δ) are expressed in parts per million (ppm) and referenced to the residual protic solvent. FT-IR spectra were recorded on ABB Bomem Inc. FT-IR 3000 spectrophotometer and are expressed in wave numbers (cm^{-1}). The mass spectra (ESI-MS) were recorded on Shimadzu LCMS-2010 spectrometer and Carbon, Hydrogen and Nitrogen were estimated on a PerkinElmer 2400 Series II CHNS/O Elemental Analyzer. All the reactions were monitored by TLC using aluminum sheet precoated with silica gel 60 f_{254} (Merck).

2.3. General experimental procedure for synthesis of quinoxalines A-H.

To a mixture of an *o*-phenylenediamine (1 mmol) and benzil (1 mmol) in ethanol (5mL), 5% w/w PEG-SO_3H with respect to benzil was added and the mixture was stirred at room temperature. The progress of the reaction was monitored by TLC using aluminum sheet precoated with silica gel 60 f_{254} (Merck). After completion of the reaction, ethyl acetate was added to the solidified mixture and the insoluble catalyst was separated by filtration. The filtrate was dried over anhydrous Na_2SO_4. The solvent was evaporated with care and the pure product was obtained. The product obtained had been characterized by FT-IR, ^{1}HNMR, ^{13}CNMR and GC-MS analysis. A variety of substituted 1, 2-phenylenediamines were condensed with benzil. The recovered catalyst was washed with ethanol, chloroform, diethyl ether and subsequently dried at 80°C to recycle in the subsequent model reaction. Compounds A-H were synthesized by taking properly substituted 1, 2-dicarbonyl component in the reaction mixture.

2.4. Characterization of selected compounds

2.4.1. 2, 3-di (furan-2-yl)-6-nitroquinoxaline D

IR (KBr): 1566,1520, 1474, 1342, 1011, 910, 887 cm^{-1}; ^{1}H NMR (DMSO-*d6*, δ ppm): 8.77 (d, 1H, *J*= 2.4 Hz, Ar-H), 8.464 (dd, 1H, *J*= 2.8 Hz, *J*= 9.2 Hz, Ar-H), 8.23 (d, 1H, *J*=9.2 Hz, Ar-H), 7.97 (dd, 2H, *J*=0.8 Hz, *J*= 6.4 Hz, Ar-H), 6.89-6.75 (m, 4H, Ar-H); ^{13}C NMR (DMSO-*d6*, δ ppm):150.17, 150.07, 148.01, 146.78, 146.24, 146.00, 144.54, 144.00, 142.84, 138.91, 130.89, 130.76, 124.93,

124.22, 113.04, 112.82; ESI-MS: m/z 308.10 $(M+H)^+$; Anal. Calcd. for $C_{16}H_9N_3O_4$: C, 62.54; H, 2.95; N, 13.68, O, 20.83 ; Found: C, 62.63; H, 2.35; N, 20.94.

2.4.2. 6-chloro-2, 3-di p-tolylquinoxaline *G*

IR (KBr): 1605,1466, 1335, 1242, 1180, 1065, 980, 818, 725, 602 cm^{-1}; ^1H NMR (DMSO-*d6*, δ ppm): 8.19-8.13 (m, 2H, Ar-H), 7.86 (dd, 1H, *J*= 2.4 Hz, *J*= 8.8 Hz, Ar-H), 7.37 (d, 4H, *J*=8 Hz, Ar-H), 7.177 (d, 4H, *J*=7.6 Hz, Ar-H), 2.329 (s, 6H); ^{13}C NMR (DMSO-*d6*, δ ppm): 154.42, 153.84, 141.17, 139.51, 139.13, 139.03, 136.18, 136.12, 134.85, 131.27, 131.12, 130.10, 129.65, 129.42, 129.23, 129.15, 128.92, 127.96, 127.80; ESI-MS: m/z 345.2 $(M+H)^+$; Anal. Calcd. for $C_{22}H_{17}ClN_2$: C, 76.63; H, 4.97; N, 8.12; Found: C, 76.93; H, 5.31; N, 8.25.

3. RESULT AND DISCUSSION

3.1. Optimization of reaction condition

Table 1 Effect of different catalyst on the condensation of benzil and benzene-1,2-diamine in ethanol as the solvent at room temperature

Entry	Catalyst	At room temperature Time (min.)	Yields[b] (%)
1	1mmol % HCl	100	80
2	1mmol % CH_3COOH	100	82
3	1mmol % H_2SO_4	100	83
4	1mmol % $ZnCl_2$	110	78
5	1mmol % $CoCl_2$	110	80
6	1mmol % $NiCl_2$	110	80
7	**5 % w/w PEG-SO_3H**	**85**	**90**

[a] Reaction was monitored by TLC.

[b] Isolated yields

The condensation reaction of benzene-1, 2-diamine with benzil under ethanol as the solvent at room temperature was employed as the model reaction to screen the suitable reaction conditions (Table 1). Among different catalysts and PEG-SO_3H (Table 1, entries 1–7), 5 % w/w PEG-SO_3H was best suited for the reaction It was observed that 5 % w/w amount of catalyst is suitable to complete the reaction in moderate time with high yield of product. Higher amount of the catalyst did not increase the yield noticeably. Thus, it was found that the condensation reaction carried out in the presence 5 % w/w PEG-SO_3H at room temperature showed the highest conversion and this was chosen as the optimized condition.

3.2. Effect of different catalyst at room temperature and at reflux temperature

Model reaction was carried out by using different catalyst such as HCl, CH_3COOH, H_2SO_4, $ZnCl_2$, $CoCl_2$, $NiCl_2$ and **5 % w/w PEG-SO_3H.** It was found that by using HCl, CH_3COOH and H_2SO_4 as the catalyst, reaction was completed in 100 minute with 75 % yield at room

Table 2 Synthesis of quinoxalines **A-H** by using ENPFSA as heterogeneous catalyst in ethanol at room temperature.

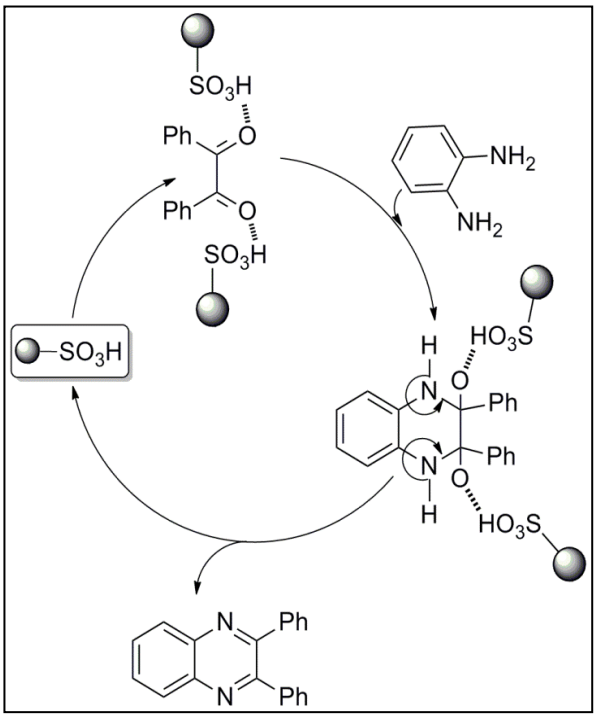
Entry	Product	R	R_1	Time (min.)[a]	Yield[b] (%)
1	A	NO_2	C_6H_5	38	88
2	B	NO_2	*p*-$CH_3C_6H_4$	41	86
3	C	NO_2	Phenanthrene-9,10-dione[c]	41	86
4	D	NO_2	2-furyl	45	85
5	E	NO_2	2-thenyl	45	85
6	F	Cl	C_6H_5	42	84
7	G	Cl	*p*-$CH_3C_6H_4$	45	84
8	H	Cl	Phenanthrene-9,10-dione[c]	45	85

[a] Reaction was monitored by TLC.

[b] Isolated yields

temperature (Table 1, entries 1- 3). By using $ZnCl_2$, $CoCl_2$, $NiCl_2$ as the catalyst, reaction got completed in 110 minutes with 75 % yield (Table 1, entry 4-6). Thus the reaction was completed in shorter time with high yield by using acid catalyst as compared to metal chloride catalysts. Using **5 % w/w PEG-SO_3H** as the catalyst, reaction was completed in 85 minute with 90 % yield at room temperature (Table 1, entry 7). Model reaction was performed by using 5 % PEG-SO_3H as the catalyst, reaction was completed in 40 minutes with 88% yield at room temperature (Table 1, entry 7). By using these optimized conditions, various quinoxaline derivatives **A-H** were synthesized in shorter time as well as in high yields. It was observed that diketone having phenyl ring as the substituent underwent the conversion smoothly in short time as compared to diketone having furyl and thenyl ring as the substituent.

3.3. Mechanism for formation of quinoxaline



Scheme : 2 Reaction mechanism for synthesis of quinoxalines

The formation of quinoxaline derivatives is outlined in the following mechanism (**Scheme 2**). 1, 2-Diketone stabilized in the interlayer of PEG-SO_3H via interaction with H^+ by partial polarization of carbonyl group reacts readily with o-phenylenediamine. The resultant amino-1, 2-diol undergoes dehydration to give quinoxaline as the end product.

4. CONCLUSION

We have reported green protocol for one-pot synthesis of quinoxaline derivatives from readily available *o*-phenylenediamines and 1, 2- diaryl ketones, by a simple and convenient protocol. The conditions are mild and a wide range of functional groups can be tolerated in the building blocks for synthesized quinoxalines. PEG-SO_3H as catalyst offers advantages including simplicity of operation, easy workup, time savy, recyclability to give high yields and excellent purity of products.

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