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A New Protocol using Potassium Hydrogen Sulfate as the Promoter for An Efficient Synthesis of Functionalized Quinoxalines

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ABSTRACT

A simple, greener and highly efficient method for the synthesis of biologically important functionalized quinoxalines has beendeveloped employing KHSO4as a promoter in water. To the best of our knowledge this transformation isachieved for the first time using an organic catalyst. A small library of quinoxalineconjugates have been synthesized using this green chemistry oriented effective protocol.

Keywords: Green chemistry, KHSO4, medicinally important.

I. INTRODUCTION

Quinoxalines represent as important class of biologically active compounds that are known to have antimicrobial, [1, 2] as well as anticancer [3]. This scaffold is present in several anticancer agents such as XK469(**1**), chloroquinoxaline sulfonamide (**2**) and in some natural products like izumiphenazineC(**3)**and NCG555879-01 (**4)** (Fig. 1)[4,5] . It is also a part of various antibiotics such as actinoleutin,echinomycin andlevomycin which are known to inhibit the growth of Grampositive bacteria. Further, quinoxaline derivatives are also used in electroluminescent materials, organic semiconductors,dyes,cavitands, etc[6-12].

Owing to widespread applications of quinoxalines several synthetic methods for their preparation both in solution as well as in solid-phase have been developed. [13-17] Among them the condensation of 1,2-diamines with 2-hydroxy ketone and oxidative cyclization of a-hydroxy ketones with 1,2- diamines under various conditions are widely used.[18-24]

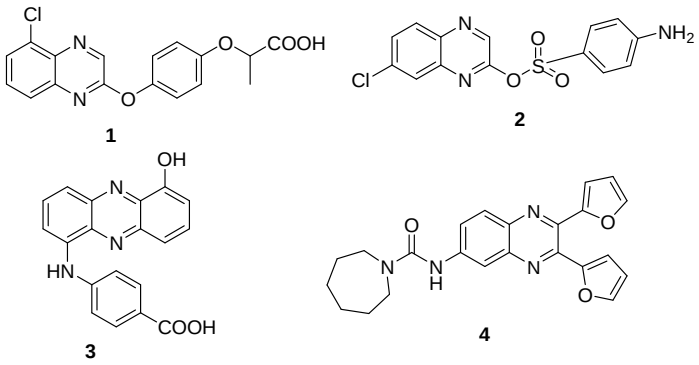
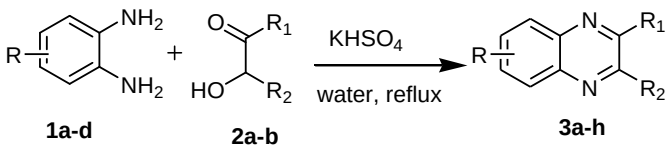


Figure 1. Biologically important quinoxalines.

Recent reports indicate the use of several catalysts such as Ru/C in the presence of b-Cyclodextin, manganese oxide octahedral molecular sieves (OMS-2), MnO_2, $RuCl_2(PPh3)_3$-TEMPO,KF/Al_2O_3, HgI_2 and Au-NPs for onepot synthesis of quinoxaline from a-hydroxy ketones.[25-31] However, they often suffer from one or more disadvantages such as long reaction time, use of costly and hazardous organic solvents, unsatisfactory product yields and harsh reaction conditions.On the other hand, organic catalysis is an emerging area of applied as well as core organic synthesis wherein small molecules are used to catalyze organic transformations. In continuation to our research towards the development of novel protocol for the organic transformations.[32,33] herein in this report we wish to introduce $KHSO_4$ as a mild and efficient catalyst [34] for the synthesis of substituted quinoxalines in high yields for the first time. The method is highly efficient and free from aforesaid drawbacks. The condensation reactionsofdiamine with

hydroxyketone proceeded smoothly at 60°C to afford the corresponding quinoxaline derivatives in high yields in shorter reaction times.



1a-d **2a-b** **3a-h**

Scheme 1. $KHSO_4$ catalyzed synthesis of quinoxalines

II. RESULTS AND DISCUSSION

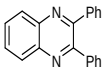
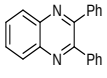
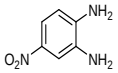
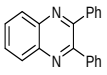
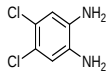
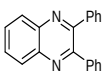
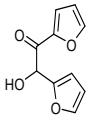
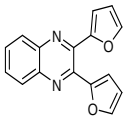
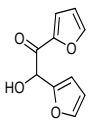
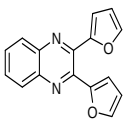
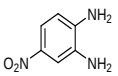
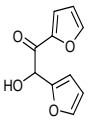
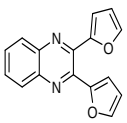
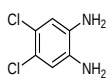
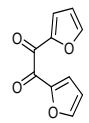
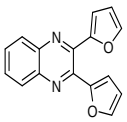
Chemistry In the beginning, a systematic study was carried out for the catalytic evaluation of Potassiumbisulfate ($KHSO_4$) towards the synthesis of quinoxalines. Initially a blank reaction was performed using benzoin and 1,2-diaminobenzene in water without any catalyst at room temperature and the completion of the reaction was monitored by TLC. It was observed that the reaction did not proceed even until 24 hours. Whereas the same reaction was executed in the presence of catalytic amounts of $KHSO_4$in water at room temperature and traces of the product were found (less than 5%). Later, this reaction was carried out under refuxing conditions and the desired transformation was observed furnishing the product in very good yield (Scheme 1). After obtaining the desired product, the amount of catalyst and the time required for the completion of reaction were evaluated. The reaction was performed using 5, 10, 20 and 30 mol% of the catalyst and was monitored for 2–8 hours. It was observed that 20 mol% of the catalyst loading provided maximum yield (87%) in 2 hours. While 5 and 10 mol% of the catalyst afforded 64% and 72% of the product even after refuxing the reaction for 8 hour and above. An additional increase of the catalyst loading to 30% did not improve the yield. On the contrary, the reaction slows down

Table 1. Condensation of benzoin and 1,2-diaminobenzene in waterat different catalyst ($KHSO_4$) concentrations.

Entry	catalyst (mole %)	Time (h)	yield (%) [a]
1	--	24	Nil
2	05	10	60
3	05	15	62
4	10	10	75
5	10	15	76
6	20	08	78
7	20	10	80
8	30	06	87
9	30	02	88

a = isolated yield

Table 2. $KHSO_4$ mediated synthesis of quinoxalines from hydroxy ketone with 1,2-diamines

Entry	Diamine	Hydoxyketone	Product	Time (h)	Yields[a] (%)
1				2	86
2				2	87
3				2.5	82
4				2	86
5				2	87
6				2	88
7				2	83
8				2	85

a = isolated yield

on adding more than 20 mol% of the catalyst (Table 1). With the optimized conditions in hand, the reaction was

performed with different set of substituents to explore the scope and generality of the present protocol. The quinoxaline derivatives were synthesized using two hydroxyl ketones namelybenzoin(**2a**) and furoin (**2b)** with varying 1,2-diamines(**1a-c**). Thediamines used possessed both ring activating as well as deactivatingsubstituents and the results of these observations aresummarized in Table 2. From the results it can be concludedthat the electronic factors of 1,2-diamine influences the progressof the reaction. Electron donating substituents such asmethyl (entry 2 and 6) provided excellent yields of the correspondingproducts.

In presence of weak ring deactivatinggroups such as dichloro (entry 4 and 8) thereaction progressed smoothly and the product was obtained ingood yields. This trend was also observed in the absence ofsubstituents on the diamine moiety. However, in case of ringdeactivating groups such as nitro (entry 3 and 7) the reactionwas slower and the yields were also comparable very lower.
In conclusion, we have successfully developed a simple, efficient and ecofriendlymethod for the synthesis of quinoxalines from 1,2-diamines and a hydoxyketones using cost-effective and readilyavailable catalyst $KHSO_4$. To the best of our knowledge thistransformation has not been reported with an inorganic catalyst.The advantages of this method over previous reports include itssimplicity of operation, cleaner reactions, higher yields, shorterreaction times and use of inexpensive catalyst. The mild reactioncondition makes this protocol an alternative procedureto the conventional acid or base-catalyzed processes for thesynthesis of quinoxalines and has practical applicability.Further, using this protocolsynthesis of library of quinoxaline–based conjugatesare under development for the medicinal chemistry driven drug synthesis.

III. CONCLUSION

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IV. EXPERIMENTAL

3.1 General remarks

Melting points were determined with an electrothermalmeltingpoint apparatus and are uncorrected. Infrared (IR) spectra wererecorded on Perkin-Elmer model 683 or 1310 spectrometerswith sodium chloride optics. 1H NMR spectra were recorded onanAvance 300 MHz spectrometer (Bruker, Fallanden, Switzerland)and^{13}CNMR spectra were recorded on a UNITY 300 MHz(Varian, Switzerland). Chemical shifts (d) are reported in ppm,downfield from internal TMS standard. Mass spectra wererecorded using a quadruple ion trap mass spectrometer (Thermo Finnign, San Jose, CA, USA) equipped with an electrospray source.

3.2 Representative experimental procedure for the synthesis quinoxalines (3a–h)

In a 50 mL round bottom flask 1,2-diamine (1 mmol) and hydoxyketone (1 mmol) were taken in water (5 mL). Catalyticamount (30 mol%) of potassium hydrofgen sulfate ($KHSO_4$) was added and the reactionmixture was refluxed for 2 hours. The progress of the reactionwas monitored by TLC. After completion of the reaction, themixture was cooled to room temperature. The precipitated solidwas collected by filtration, washed with water and recrystallizedusing methanol.

2,3-Diphenylquinoxaline (3a)

Whitish solid; Mp: 125–126^{o}C; ^{1}HNMR (300 MHz $CDCl_3$): d 7.30–7.41 (m, 6H), 7.51–7.56 (m, 4H), 7.77–7.83 (m, 2H), 8.15–8.23 (m,2H); ^{13}C NMR (75 MHz $CDCl_3$): d 127.49, 128.10, 128.41, 129.00,129.31, 138.0, 140.34, 152.57; ESI-MS: m/z = 283 (M + H)+.

6-Methyl-2,3-diphenylquinoxaline (3b)

Brown white solid; Mp: 120–121^{o}C; ^{1}HNMR (300 MHz $CDCl_3$): d 2.6(s, 3H), 7.3 (d, J =6.8 Hz, 6H), 7.5 (d, J = 6.79 Hz, 4H), 7.6(dd, J = 1.51, 8.7 Hz, 1H), 7.9 (s, 1H), 8.0 (d, J = 8.49 Hz, 1H);^{13}C NMR (75 MHz $CDCl_3$): d 20.8,

126.8, 127.0, 127.5,127.6, 128.8, 131.1, 138.0, 138.4, 139.3, 140.0, 151.2,151.9; ESI-MS: m/z = 297 (M + H)+.

6-Nitro-2,3-diphenylquinoxaline (3c)

solid; Mp: 139–140°C; ^{1}HNMR (300 MHz $CDCl_3$): d 7.34–7.46 (m, 6H), 7.53–7.57 (m, 4H), 8.3 (d, J = 9.25 Hz, 1H), 8.5(dd, J = 2.45 & 9.25 Hz, 1H), 9.1 (d, J = 2.45 Hz, 1H); ^{13}C NMR(75 MHz $CDCl_3$): d 123.3, 125.6, 128.4, 129.6, 129.7,129.8, 129.8, 130.7, 138.0, 138.1, 139.9, 143.5, 147.8,155.6, 156.2; ESI-MS: m/z = 328 (M + H)+.

6,7-Dichloro-2,3-diphenylquinoxaline (3d)

Solid; Mp: 141–143 °C; ^{1}H NMR (300 MHz $CDCl_3$): d 7.3–7.4 (m, 6H), 7.50–7.54 (m, 4H), 8.3 (s, 2H); ^{13}C NMR (75 MHz$CDCl_3$): d 127.6, 128.6, 129.0, 133.4, 137.6, 139.1, 153.7;ESI-MS: m/z = 351 (M + H)+.

2,3-Di(furan-2-yl)quinoxaline (3e)

Solid; Mp: 134–135°C; ^{1}HNMR (300 MHz $CDCl_3$): d 6.5–6.6 (m, 2H), 6.6 (dd, J =0.56 & 3.58 Hz, 2H), 7.6 (dd, J = 0.56& 1.70 Hz, 2H), 7.7–7.8 (m, 2H), 8.11–8.17 (m, 2H); ^{13}C NMR(75 MHz $CDCl_3$): d 111.8, 112.9, 129.0, 130.3, 138.4,140.5, 142.5, 144.1; m/z = 263 (M + H)+.

2,3-Di(furan-2-yl)-6-methylquinoxaline (3f)

Solid; Mp: 123–124 °C; ^{1}H NMR (300 MHz $CDCl_3$): d 6.6 (d, J =16.42 Hz, 4H), 7.6 (t, J =8.87 Hz, 3H), 7.9 (s, 1H), 8.0 (d, J = 8.49 Hz, 1H); ^{13}C NMR (75 MHz $CDCl_3$): d 21.2, 111.3, 111.9, 112.2, 127.2, 127.8, 132.1, 138.3, 140.0, 140.4, 141.0, 141.8, 143.3, 143.4, 150.2; ESI-MS: m/z = 277 (M +H)+.

2,3-Di(furan-2-yl)-6-nitroquinoxaline (3g)

Solid; Mp: 152–154 °C; ^{1}H NMR (300 MHz $CDCl_3$): d 6.6–6.6 (m, 2H), 6.87 (dd, J = 3.58 & 16.80 Hz, 2H), 7.65 (dd, J = 0.94& 5.09 Hz, 2H), 8.2 (d, J = 9.253 Hz, 1H), 8.5 (dd, J = 2.45 & 9.253 Hz, 1H), 9.0 (d, J = 2.45 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): d 111.3, 111.4, 113.4, 114.3, 122.4, 123.9, 129.4,137.92, 141.8, 142.9, 143.4, 143.9, 144.4, 146.6, 148.9,150.0; ESI-MS: m/z = 308 (M + H)+.

6,7-Dichloro-2,3-di(furan-2-yl)quinoxaline (3h)

Solid; Mp: 135–137 °C; ^{1}H NMR (300 MHz $CDCl_3$): d 6.6–6.7 (m, 2H), 6.7 (d, J = 3.50 Hz, 2H), 7.6 (d, J = 1.06 Hz, 2H),8.2 (s, 2H); ^{13}C NMR (75 MHz $CDCl_3$): d 111.5, 113.2, 128.7,133.7, 138.4, 142.5, 143.9, 149.5; ESI-MS: m/z = 330 (M +H)+.

V. ACKNOWLEDGEMENT

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