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AN EFFICIENT SYNTHESIS OF QUINOXALINE DERIVATIVES USING ZEOLITE Y AS A CATALYST

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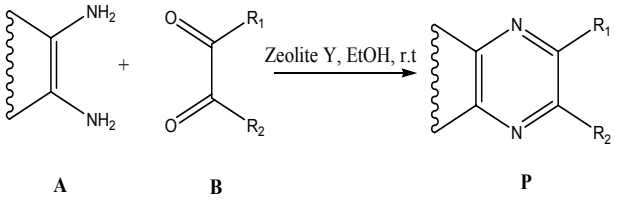
A convenient and simple procedure for the synthesis of some quinoxaline derivatives was developed via a reaction of o-aryldiamines and 1,2-dicarbonyl compounds in the presence of Zeolite NaY as an efficient catalyst. The reactions were carried out at room temperature in ethanol and catalyst reused for several times. This method has many appealing attributes, such as good yields, short reaction times, and simple work-up procedures. Also the synthesis of quinoxaline derivatives was carried out in the presence of HY Zeolite under the same conditions and the results were discussed.



INTRODUCTION

Quinoxaline derivatives are important class of nitrogen-containing heterocycles, having interesting therapeutic properties such as antiviral, antibacterial, antibiotic, anti-inflammatory and kinase inhibition.[1] They have also been evaluated as an anticancer, antimycobacterial, and antihelmintic agents.[2] Besides this, they are potential building blocks for the synthesis of anion receptors,[3] cavitands,[4] dehydroannulenes,[5] organic semiconductors[6] and dyes.[7] All these interesting properties and nitrogen sites enable them to act as therapeutic agents that are capable of binding and cleaving DNA under the physiological condition.[8] In addition, organometallic complexes of these ligands show interesting optical, electrochemical and electroluminescent properties.[9]

A number of methods have been developed for the synthesis of substituted quinoxaline derivatives and the most common method is the condensation of an aryl 1,2-diamine with 1,2-dicarbonylcompounds.[10] Apart from this, other methods such as solid phase synthesis,[11] oxidative cyclisation of α-hydroxy ketones with 1,2–diamines,[12] cyclisation-oxidation of phenacyl bromides with 1,2-diamines by $HClO_4$-SiO_2,[13] cyclisation of 1,2-phenylenediamine with propiophenone by using KOH,[14] and oxidative coupling of epoxides with ene-1,2-diamines[15], have also been reported. Nevertheless, most of these methods suffer from several drawbacks such as use of volatile organic solvents, critical product isolation, expensive metal catalyst, harsh reaction conditions, and use of strong oxidizing agents, long reaction time and low yields. Due to these disadvantages, the search for new catalysts which are green and cheaper remains an existing challenge.

In recent years, Zeolite has received considerable attention as an inexpensive, reusable without any loss of activity, nontoxic, readily available catalyst for various organic transformations under mild and convenient conditions to afford the corresponding products in excellent yields with high selectivity.[16]

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As a part of our research interest towards the development of efficient and environmentally benign synthetic methodologies using eco-friendly conditions,[17] we have reported the synthesis of quinoxaline derivatives in good yields (30-98%) from aryl-1,2-diamines and 1,2-diketones in the presence of Y-Zeolite as a catalyst in Ethanol and at room temperature (Scheme 1).

EXPERIMENTAL

1. Materials and methods

All the commercial reagents and solvents were used without further purification unless otherwise stated. All chemicals were purchased from Merck or Fluka chemical companies. All known compounds were identified by comparison of their melting points and NMR data with the authentic samples. ^{1}HNMR and ^{13}CNMR spectra were recorded on a Bruker Avance 300 MHz spectrometer using TMS as an internal standard. NMR spectra were recorded in $CDCl_3$, DMSO-d_6 (δ in ppm). IR spectra were recorded on Perkin FT-IR spectrometer (ν in cm^{-1}) using KBr pellets. Microanalyses were performed by the Elemental Analyzer (Elemental, Vario EL III) at the Arak University. All the reactions were monitored by thin layer chromatography performed on precoated silicagel $60F_{254}$ plates (Merck) in EtOAc/n-Hexane (1:3) as an eluent.

2. General procedure for the synthesis of quinoxalines in the presence of Zeolite NaY

A mixture of 1,2-dicarbonyl (1 mmol) and aromatic 1,2-diamine (1 mmol) in ethanol (5 ml) was stirred at room temperature in presence of Zeolite NaY as a catalyst (5 wt. %). The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered to recover the catalyst. The further purified products were obtained by recrystalization from ethanol/water (3:1).

3. Preparation of Zeolite HY

A mixture of zeolite NaY (1g) and Ammonium chloride solution (100 mL, 0/01 M) was stirred for 24 hours at room temperature. Then flatten it and put in the oven for 3 h at 400 °C. 0.8g of clean white precipitate zeolite HY with a yield over 80% is obtained and carefully separated.

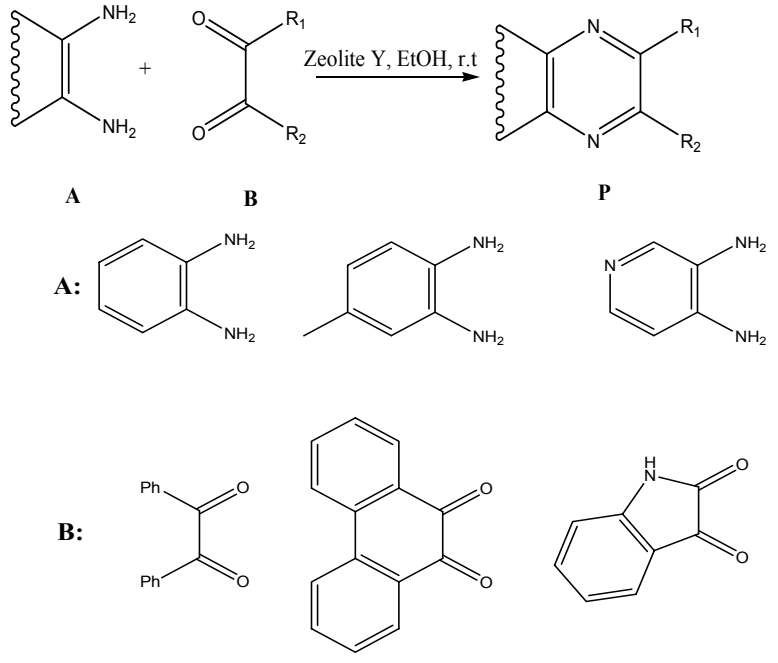
3.1. General procedure for the synthesis of quinoxalines in the presence of Zeolite HY

A mixture of 1,2-dicarbonyl (1 mmol) and aromatic 1,2-diamine (1 mmol) in ethanol (5 ml) was stirred at room temperature in presence of Zeolite HY as a catalyst (5 wt. %). The reaction was monitored by TLC. The reaction mixture was filtered to recover the catalyst. The further purified products were obtained by recrystalization from ethanol/water (3:1).

4. Spectral Data of the synthesized compounds (a-f)

Dibenzo [a, c] phenazine (a): FT-IR (ν_{max}, KBr): 3054, 1604, 1500, 1357, 1022, 767, 725 cm^{-1}. ^{1}HNMR (δ, $CDCl_3$): δ= 7.73 -7.89 (m, 6H), 8.34 (dd, J=7.5, 3 Hz, 2H), 8.57 (d, J=7.5Hz, 2H), 9.41(d, J=8.1Hz, 2H) ppm. ^{13}CNMR (δ, $CDCl_3$): δ= 122.9, 126.2, 127.9, 129.4, 129.7, 130.2, 132.0, 142.2, 142.4 ppm. Anal Calcd for $C_{20}H_{12}N_2$: C, 85.69; H, 4.31; N, 9.99. Found: C, 86.02; H, 4.52; N, 10.11.

11-Methyl dibenzo [a, c] phenazine (b): FT-IR (ν_{max}, KBr): 3057, 2906, 1624, 1500, 1448, 1357, 1022, 765, 725 cm^{-1}. ^{1}HNMR (δ, $CDCl_3$): δ= 2.68 (s, 3H), 7.66 -7.81 (m, 5H), 8.08 (s, 1H), 8.20 (d, J= 6.0Hz, 1H), 8.55 (d, J=6.0Hz, 2H), 9.38 (d, J=7.2 Hz, 2H) ppm. ^{13}CNMR (δ, $CDCl_3$): 22.0, 122.9, 126.0, 126.1, 127.7, 127.8, 128.0, 128.9, 129.9, 130.0, 130.3, 130.4, 131.8, 131.9, 132.3, 140.2, 140.7, 141.6, 142.2 ppm. Anal Calcd for $C_{21}H_{14}N_2$: C, 85.69; H, 4.79; N, 9.52. Found: C, 85.91; H, 4.59; N, 9.61.



Scheme 1 – Efficient synthesis of quinoxalines using Zeolite Y.

2, 3-Diphenylquinoxaline (c): FT-IR (ν_{max}, KBr): 3057, 1479, 1348, 1022, 771, 698 cm^{-1}. ^{1}HNMR (DMSO-d_6): δ= 7.36-7.42 (m, 6H, H4, H5), 7.47-7.49 (m, 4H, H3), 7.89 (d, J=3.0Hz, 1H, H_2'), 8.15 (d, J=3.0Hz, 1H, H_1'), 8.17 (d, J=3.0Hz, 1H, H_1) ppm. ^{13}CNMR (DMSO-d_6): δ= 128.4, 129.1, 129.2, 130.1, 130.8, 139.2, 140.9, 153.4 ppm. Anal Calcd for $C_{20}H_{14}N_2$: C, 85.08; H, 5.00; N, 9.92. Found: C, 85.33; H, 5.11; N, 10.09.

2,3-Diphenylpyrido [4, 3-b] pyrazine (d): FT-IR (ν_{max}, KBr): 3045, 1593, 1543, 1446, 1388, 1028, 696 cm^{-1}. ^{1}HNMR (DMSO-d_6): δ= 7.37-7.42 (m, 6H, H_5, H_6), 7.54 -7.58 (m, 4H, H_4), 8.01(dd, J= 5.8 Hz, J= 0.6 Hz, 1H, H_3), 8.85(d, J=5.8 Hz, 1H, H_2), 9.62(d, J=0.6 Hz, 1H, H_1) ppm. ^{13}CNMR (DMSO-d_6): δ= 121.4, 129.4, 129.5, 129.7, 129.8, 129.9, 138.2, 143.5, 147.4, 154.5 ppm. Anal Calcd for $C_{19}H_{15}N_3$: C, 79.98; H, 5.30; N, 14.73. Found: C, 80.14; H, 5.38; N, 14.91.

6-Methyl 2, 3-diphenylquinoxaline (e): FT-IR (ν_{max}, KBr): 3055, 2943, 1620, 1487 1444, 1344, 1022, 702 cm^{-1}. ^{1}HNMR (DMSO-d_6): δ= 7.35-7.37 (m, 6H, H_5, H_6), 7.44-7.45 (m, 4H, H_4), 7.47 (d, J= 1.5 Hz, 1H, H_2), 7.84 (s, 1H, H_1), 8.10 (d, J=1.5 Hz, 1H, H_3) ppm. ^{13}CNMR (DMSO-d_6): δ= 127.9, 128.4, 128.7, 129.0, 129.1, 130.1, 132.9, 139.3, 139.4, 140.9, 152.5, 153.2 ppm. Anal Calcd for $C_{21}H_{16}N_2$: C, 85.11; H, 5.44; N, 9.45. Found: C, 85.27; H, 5.53; N, 9.63.

6H-Indolo [2, 3-b] quinoxaline (f): FT-IR (ν_{max}, KBr): 3464, 3198, 3059, 1740, 1618, 1462, 1332, 1022 cm^{-1}. ^{1}HNMR (DMSO, d_6): δ= 6.93 (d, J= 7.8 Hz, 2H, H_2), 7.06 (t, J=7.5, 2H, H_4, H_5), 7.49 (d, J=7.3 Hz, 2H, H_1), 7.56(d, J=9.0 Hz, 1H, H_6), 7.59 (d, J=6.0 Hz, 1H, H_3), 11.02 (s, 1H, NH) ppm. ^{13}CNMR (DMSO-d_6): δ= 112.7, 118.2, 123.3, 125.1, 151.2, 159.8, 184.8 ppm. Anal Calcd for $C_{14}H_9N_3$: C, 76.70; H, 4.14; N, 19.17. Found: C, 76.89; H, 4.21; N, 19.13.

RESULTS AND DISCUSSION

Choosing an appropriate solvent has crucial importance for the successful organic synthesis. Different solvents with various polarities were screened (Table 1). Among all these solvents Ethanol (Table 1, entry 5) was found to be the best solvent. Also the use of 5% zeolite NaY was effective for the reaction. After optimization, to explore the scope of this novel transformation, reaction of some 1,2-aryldiamines with various α-diketones were evaluated. Generally, the cyclocondensation reactions proceeded well and afforded the desired products in moderate to good yields (Table 2).

Table 1

Effect of solvents for the synthesis of quinoxaline derivatives[a]

Entry	Solvent	Time(h)	Yield(%)[b]
1	H_2O	8	20
2	CH_3CN	8	15
3	CH_3OH	8	54
4	Toluene	8	25
5	C_2H_5OH	8	94, 91, 90

[a] 1,2-Phenylenediamine (1 mmol), Benzil (1 mmol), Zeolite NaY (5 wt.%), solvent (5 mL), Room temperature.
[b] Isolated yields.

Table 2

Synthesis of Quinoxalines in the presence of zeolite NaY and HY[a]

Entry	Product	Zeolite NaY		Zeolite HY	
		Time (h)	Yield (%)[b]	Time (h)	Yield (%)[b]
a	Dibenzo [a, c] phenazine	6	96	4	98
b	11-Methyl dibenzo [a, c] phenazine	6	54	4	78
c	2,3-Diphenylquinoxaline	2	67	2	76
d	2, 3-Diphenylpyrido [4, 3-b] pyrazine	12	30	10	43
e	6-Methyl 2, 3-diphenylquinoxaline	10	58	8	67
f	6H-Indolo [2, 3-b] quinoxaline	6	33	4	38

[a] 1,2-Aryldiamine (1 mmol), 1,2-dicarbonyl compound (1 mmol), Zeolite y (5 wt.%), EtOH (5 mL), Room temperature.
[b] Isolated yields.

The acid strength of zeolite by a simple process raised and synthesis of quinoxaline derivatives was carried out in the presence of HY Zeolite under the same conditions. Results clearly indicated that the acid strength of zeolites, in addition to the relative increase of the reaction rate, effectively improved product yields (Table 2). The absence of the absorption band corresponding to amino stretching frequency of the 1,2-diamine moiety in the IR spectra of compounds (a-f) clearly confirm the products formation.

The effect of electron-releasing and electron-withdrawing substituents on the aromatic ring of aryl-1,2-diamines on the reaction was investigated. Electron-releasing groups did not affect significantly the yields and the reaction times (Table 2, entries b and e). Moreover, it has been observed that the electronic properties of the aromatic ring of 1,2-diketones had negligible effect on the yields and the reaction times.

After completion of the reaction, the catalyst was separated by simple filtration and washed several times with ethanol. The reusability of the catalyst was found to be effective up to several cycles without any loss in the activity (Table 1, entry 5). Products were characterized by FT-IR, ^{1}H NMR, and ^{13}CNMR analysis.

CONCLUSIONS

In summary, we have demonstrated a practical method for the synthesis of some quinoxaline derivatives in good yields (30-98 %) by employing Y-Zeolite as an efficient catalyst in ethanol as more suitable solvent. This new strategy has several advantages, such as good yield, short reaction time, low cost, simple experimental as well as isolation procedures, and it is in agreement with the green chemistry protocols. Moreover, Zeolite catalysts are non-toxic, inexpensive and reusable.

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