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Polyethylene glycol (PEG-400) mediated synthesis of quinoxalines

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COMMUNICATION INFORMATION

KEYWORDS

ABSTRACT

A simple and highly efficient protocol for the synthesis of quinoxaline derivatives from various *ortho*-phenylenediamines with α-halo ketones under catalyst free conditions is reported by using polyethylene glycol (PEG-400) as an efficient recyclable medium without using any organic co-solvent or additive. This protocol gives wide range of quinoxaline derivatives with high yields.

1. Introduction

The quinoxaline moiety is an important structural motif in the preparation of substances with pronounced biological activities, such as antimycobacterial [1], antitumor [2], and antidepressant [3]. In the recent past, there has been an enhanced interest in the synthesis of quinoxaline derivatives due to their potential application in various antibiotics, such as Levomycin, Echinomycin and Actinoleutin that are known to inhibit growth of gram positive bacteria [4,5] and are active against various transplantable tumors [6]. In addition, these derivatives have been used as building blocks for the synthesis of organic semiconductors [7,8] and also applied for the extraction of metal cations [9].

The most common methods for the synthesis of the quinoxaline derivatives, which include condensation of 1,2-diamines and 1,2-dicarbonyl compounds [10-13], 1,4-addition of 1,2-diamines to diazenylbutenes [14], cyclization of phenacyl bromides with 1,2-diamines by using solid phase synthesis [15,16], oxidative coupling of α-hydroxy ketones with *ortho*-phenylenediamines (OPDA) *via* a tandem oxidation process by using various metal catalysts [17-22], cyclization of diketones with diamines in ethanol using Gallium triflate [23], cyclization-oxidation of phenacyl bromides with 1,2-diamines by HClO$_4$.SiO$_2$ [24], OPDA with an array of vicinal-diols in diglyme using ruthenium catalyst [25], polyethylene glycol (PEG-400) with other ketones in KOH [26], Copper catalyst with α-hydroxy ketones [27] and by using β-cyclodextrin with diamine and halo ketones [28].

However, most of the reported methodologies still have certain limitations such as expensive and air sensitive nature of catalysts, toxicity of solvents, restrictions for large scale applications, critical product isolation procedures, difficulty in recovery of high boiling solvents, excessive amounts of catalysts and generation of large amounts of toxic wastes in scaling up for industrial applications leading to environmental issues. Thus, the development of a simple and efficient method under catalyst free conditions for constructing these heterocyclic has been advocated.

In the recent years, PEG emerged as a powerful phase transfer catalyst and performs many useful organic transformations under mild reaction conditions. Moreover, PEG is inexpensive, easy to handle, thermally stable, non-toxic, and recyclable in various organic transformations, such as synthesis of β-amino sulfides, 2-substituted benzimidazoles, bis-benzimidazoles, 3,4-dihydropyrimidinones, β-keto sulfides and dibenz[*b,f*]-1,4-oxazapine [29-33]. This inspired us to focus on the aspect of synthesis of biologically active quinoxaline derivatives under catalyst free conditions by using PEG as an eco-friendly and recyclable media. In continuation of our program on the development of novel methodologies in organic synthesis [34-37], we have investigated the synthesis of quinoxaline derivatives by using PEG-400 as a recyclable medium without adding any organic solvent and catalyst. To the best of our knowledge there are no reports for the synthesis of quinoxaline derivatives by using PEG-400 as a reaction medium under catalyst free conditions (Scheme 1).
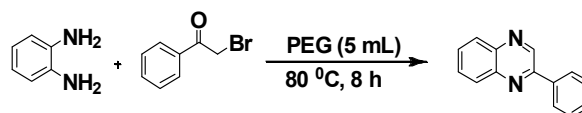
Scheme 1

2. Experimental

2.1. Material and methods

All the commercial reagents and solvents were used without further purification unless otherwise stated. Melting points were recorded on a Buchi 535 melting point apparatus and were uncorrected. All the reactions were monitored by thin layer chromatography performed on precoated silica gel $60F_{254}$ plates (Merck). Compounds were visualized with UV light at 254 nm and 365 nm, I_2 and heating plates after dipping in 2% phosphomolybdic acid in 15% aq. H_2SO_4 soln. IR spectra were recorded on a Perkin-Elmer 683 or a 1310 FT-IR spectrometers with KBr pellets. NMR spectra were recorded on a Varian Unity-400 MHz and BRUKER AMX 300 spectrometers using TMS as an internal standard. Mass spectra were recorded on a LCMSD-Trap mass spectrometer.

2.2. General procedure for the synthesis of 2-phenyl quinoxaline

A mixture of *o*-phenylenediamine (1.1 mmol) and phenacyl bromide (1.0 mmol) was stirred in PEG-400 (5 mL) at 80 ^{0}C temperature for 8 h. The progress of the reaction was monitored by TLC and then allowed to cool to room temperature**.** After completion, the mixture was poured onto water and extracted with ethyl acetate (3 x 10 mL). The extracts were concentrated and the residue was subjected to column chromatography (silica gel, ethyl acetate–hexane 2:8) to obtain the pure quinoxaline. The PEG was recovered from the water and recycled without affecting the yields of the products. Representative examples of synthesized compounds:

2-Phenylquinoxaline (Table 2, Entry 1): Bright yellow solid. Yield: 0.185 g, (90%). M.p.: 75–78 °C. R_f (20% EtOAc/*n*-hexane) 0.5. ^{1}H NMR (200 MHz, CDCl$_3$) *δ:* 7.52–7.61 (m, 3H, ArH), 7.73–7.83 (m, 2H, ArH), 8.13–8.22 (m, 4H, ArH), 9.33 (s, 1H, C$_3$–H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 127.3, 129.0, 129.1, 129.5, 129.6, 130.1, 130.2, 136.7, 141.5, 142.2, 143.3, 151.7. MS (ESI): m/z 207 (M+H)$^+$.

2-(4-Nitrophenyl)quinoxaline (Table 2, Entry 4): Pale yellow solid. Yield: 35%. M.p.: 185–190 °C. R_f (20% EtOAc/*n*-hexane) 0.2. ^{1}H NMR (200 MHz, CDCl$_3$) δ: 7.82–7.86 (m, 2H, ArH), 8.16–8.21 (m, 2H, ArH), 8.4 (s, 4H, ArH), 9.4 (s, 1H, C$_3$–H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 113.3, 128.0, 128.2, 130.3, 130.9, 140.0, 152.3, 160.0. MS (ESI): m/z 252 (M+H)$^+$.

4-(Quinoxalin-2-yl)benzonitrile (Table 2, Entry 7): Pale yellow solid. Yield: 90%. M.p.: 193–195 °C. R_f (20% EtOAc/*n*-hexane) 0.28. ^{1}H NMR (200 MHz, CDCl$_3$) δ: 7.82–7.88 (m, 4H, ArH), 8.13–8.20 (m, 2H, ArH), 8.33–8.36 (d, *J* = 8.309, 2H, ArH), 9.35 (s, 1H, C$_3$–H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 113.8, 118.4, 127.5, 128.0, 129.0, 129.8, 130.7, 130.9, 132.9, 140.6, 141.6, 142.3, 142.3, 149.6. MS (ESI): m/z 232 (M+H)$^+$.

N,N-Diethyl-4-(quinoxalin-2-yl)benzenamine (Table 2, Entry 9): Dark yellow solid. Yield: 89%.M.p.: 82–85 °C. R_f (20% EtOAc/*n*-hexane) 0.45. ^{1}H NMR (200 MHz, CDCl$_3$) δ: 1.17–1.22 (m, 6H, CH$_3$), 3.34–3.44 (m, 4H, CH$_2$), 6.4–6.8 (m, 2H, ArH), 7.6–7.8 (m, 2H, ArH), 7.99–8.10 (m, 4H, ArH), 9.28 (s, 1H, C$_3$–H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 12.0, 12.0, 43.8, 44.3, 110, 111.3, 111.6, 111.7, 128.2, 128.8, 128.9, 129.0, 129.05, 129.8, 130.8, 140.7, 142.5, 143. MS (ESI): m/z 278 (M+H)$^+$.

2-(Furan-2-yl)quinoxaline (Table 2, Entry 13): Solid. Yield: 83%. M.p.: 95–98 °C. R_f (20% EtOAc/*n*-hexane) 0.45. ^{1}H NMR (200 MHz, CDCl$_3$) δ: 6.58–6.59 (m, 1H, ArH), 7.28 (d, *J* = 3.5 Hz, 1H, Furan H), 7.65–7.7 (m, 3H, ArH), 8.0–8.08 (m, 2H, Furan H), 9.5 (s, 1H, C$_3$–H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 112.2, 112.8, 129.5, 129.6, 130.8, 141.6, 142.4, 142.4, 144.2, 145.4, 151.3. MS (ESI): m/z 197 (M+H)$^+$.

2-(Naphthalen-2-yl)quinoxaline (Table 2, Entry 16): Dark yellow solid. Yield: 90%. M.p.: 135 °C. R_f (20% EtOAc/*n*-hexane) 0.45. ^{1}H NMR (200 MHz, CDCl$_3$) δ: 7.51–7.56 (m, 2H, ArH), 7.69–8.19 (m, 7H, ArH), 8.36–8.41 (m, 1H, ArH), 8.65 (s, 1H, ArH), 9.50 (s, 1H, C$_3$–H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 127.1, 127.8, 127.9, 128.8, 128.9, 129.5, 129.7, 130.5, 135.3, 140.1, 140.2, 140.8, 141.0, 142.3, 142.7, 143.0, 151.0. MS (ESI): m/z 257 (M+H)$^+$.

3. Results and Discussion

In our model reaction, *ortho*-phenylenediamine (1.1 mmol) was treated with phenacyl bromide (1.0 mmol) in PEG (5 mL) for 8 h; the corresponding quinoxaline was obtained in 90% yield (Scheme 1). The reaction of *ortho*-phenylenediamine with phenacyl bromide was also examined in different solvents such as toluene, acetonitrile, dimethyl sulphoxide, methanol water and PEG for the sake of comparisons and the results were shown in Table 1. Among these, PEG was found to be the best solvent for the reaction (Table 1).

Table 1. The solvent effect for synthesis of quinoxalines[a].

Entry	Solvent (5 mL)	Yield[b] (%)
1	Toluene	25
2	MeCN	50
3	MeOH	54
4	DMSO	51
5	Water	45
6	PEG	90

[a] *O*-Phenylenediamine (1.1 mmol), α-Bromoketone (1.0 mmol), 80 ºC, 8 h.
[b] Isolated yields.

To explore the scope of this novel transformation, reaction of various *o*-phenylenediamines with various α-halo ketones was evaluated (Table 2). Phenacyl Bromides bearing electron-donating groups and electron-withdrawing groups at the para position of the substrates gave the desired products in quantitative yields in 8 h. Results have shown that the substitution groups played a less significant role in governing the reactivity of the substrates. Furthermore, this protocol is proved to be effective for the condensation of aliphatic phenacyl bromide with *o*-phenylene diamine, as the desired product was obtained in moderate yield (Table 2, entry 17). Also we have examined generality of the reaction with phenacyl tosylate to react with *o*-phenylene diamine in 5 mL PEG for 8 h. The reaction proceeded in similar passion to yield corresponding product in 90% yield (Scheme 2).
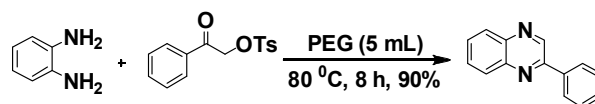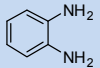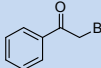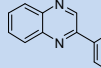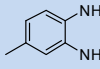

Scheme 2
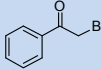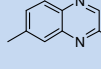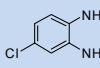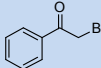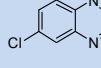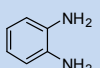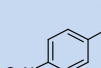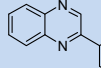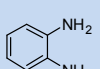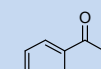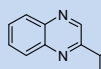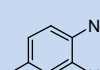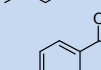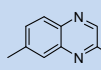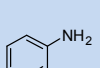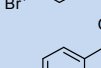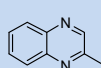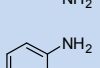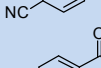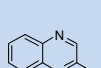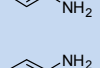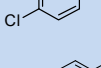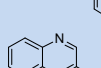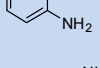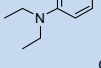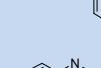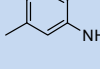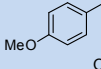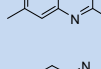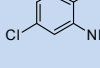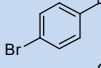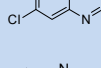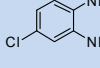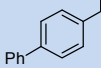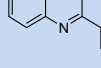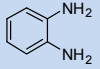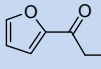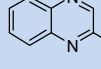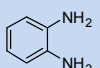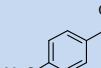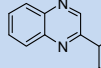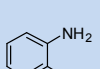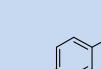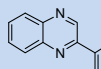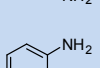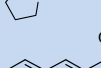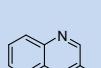
In general, all the reactions were very clean, and the quinoxaline derivatives were obtained in high yields. The compounds were isolated by just passing through a small silica gel column. The reaction with phenyl tosylates was relatively faster than the bromides which gave the corresponding quinoxaline derivatives in high yield. All the products were isolated and characterized by ^{1}H NMR, ^{13}C NMR, mass and by comparison with the authentic samples.

In conclusion, this paper describes a convenient and efficient process for the synthesis of quinoxaline derivatives by use of PEG as a recyclable medium without the addition of any additive or organic co-solvent. Present methodology offers very attractive features such as simple experimental procedure, reduced reaction times, higher yields and economic viability, when compared with conventional method as well as with other catalysts, and will have wide scope in organic synthesis.

Acknowledgement

Table 2. Synthesis of quinoxaline derivatives in PEG[a].

Entry	Diamine	Haloketone	Product	Yield [b] (%)
1	benzene-1,2-diamine	2-bromo-1-phenylethanone	2-phenylquinoxaline	90
2	4-methylbenzene-1,2-diamine	2-bromo-1-phenylethanone	6-methyl-2-phenylquinoxaline	85
3	4-chlorobenzene-1,2-diamine	2-bromo-1-phenylethanone	6-chloro-2-phenylquinoxaline	81
4	benzene-1,2-diamine	2-bromo-1-(4-nitrophenyl)ethanone	2-(4-nitrophenyl)quinoxaline	35
5	benzene-1,2-diamine	2-bromo-1-(4-methylphenyl)ethanone	2-(4-methylphenyl)quinoxaline	85
6	4-methylbenzene-1,2-diamine	2-bromo-1-(4-bromophenyl)ethanone	2-(4-bromophenyl)-6-methylquinoxaline	83
7	benzene-1,2-diamine	2-bromo-1-(4-cyanophenyl)ethanone	4-(quinoxalin-2-yl)benzonitrile	90
8	benzene-1,2-diamine	2-bromo-1-(4-chlorophenyl)ethanone	2-(4-chlorophenyl)quinoxaline	90
9	benzene-1,2-diamine	2-bromo-1-(4-diethylaminophenyl)ethanone	N,N-diethyl-4-(quinoxalin-2-yl)aniline	89
10	4-methylbenzene-1,2-diamine	2-bromo-1-(4-methoxyphenyl)ethanone	2-(4-methoxyphenyl)-6-methylquinoxaline	87
11	4-chlorobenzene-1,2-diamine	2-bromo-1-(4-bromophenyl)ethanone	2-(4-bromophenyl)-6-chloroquinoxaline	79
12	4-chlorobenzene-1,2-diamine	2-bromo-1-(biphenyl-4-yl)ethanone	2-(biphenyl-4-yl)-6-chloroquinoxaline	82
13	benzene-1,2-diamine	2-bromo-1-(furan-2-yl)ethanone	2-(furan-2-yl)quinoxaline	83
14	benzene-1,2-diamine	2-bromo-1-(4-methoxyphenyl)ethanone	2-(4-methoxyphenyl)quinoxaline	87
15	benzene-1,2-diamine	2-bromo-1-(4-pyrrolidin-1-ylphenyl)ethanone	2-(4-pyrrolidin-1-ylphenyl)quinoxaline	86
16	benzene-1,2-diamine	2-bromo-1-(naphthalen-2-yl)ethanone	2-(naphthalen-2-yl)quinoxaline	90
17	benzene-1,2-diamine	1-bromo-3,3-dimethylbutan-2-one	2-tert-butylquinoxaline	57

[a] Diamine (1.1 mmol), Halo ketone (1.0 mmol), PEG (5 mL), 80 ºC, 8 h.

[b] Isolated yields.

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