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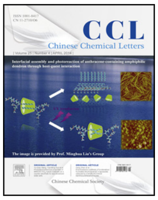

Original article

A highly efficient procedure for the synthesis of quinoxaline derivatives using polyvinylpolypyrrolidone supported triflic acid catalyst (PVPP·OTf)

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ABSTRACT

A polyvinylpolypyrrolidone supported triflic acid was shown to be useful as a recyclable heterogeneous catalyst for the rapid and efficient synthesis of quinoxaline derivatives in good-to-excellent yields. The catalyst is easily prepared, air-stable, reusable, and easily removed from the reaction mixtures.

1. Introduction

Quinoxaline derivatives are significant for their pharmacological activities. In particular, they exhibit potential antiviral, antibacterial, anti-inflammatory, antiprotozoal, and kinase inhibitory properties [1–5]. They are also utilized as dyes, electroluminescent materials, organic semiconductors, cavitands, chemically controllable switches, and DNA cleaving agents [6–11]. Furthermore, the quinoxaline ring is the core moiety in several drug molecules, such as clofazimine, echinomycin, leromycin, and actinomycin [12–17]. In light of the great importance of quinoxaline derivatives, in recent years efforts have been made in developing new methodologies for the synthesis of these compounds [18]. Among them, the condensation of aryl 1,2-diamines with 1,2-dicarbonyl compounds in refluxing ethanol or acetic acid is a general approach [12]. In recent years, several new efficient methods have been developed including the use of β-cyclodextrin (β-CD) [19], ionic liquids [20], citric acid [21], heteropolyacid [22], cellulose sulfuric acid [23], PEG-400 [24], hypervalent iodine(III) sulfonate in PEG [25], polyaniline-sulfate salt [26], DABCO [27], CAN [28], $HClO_4$–SiO_2 [29], MnO_2 [30], fluorinated alcohols [31], and $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ [32]. However, the reported methods still have drawbacks such as such as tedious workup procedures, harsh reaction conditions, low yields, long reaction times, and the requirement for an inert atmosphere. Therefore, the development of simple, efficient, high-yielding, and eco-friendly methods for quinoxaline synthesis remains an attractive goal. Recently, the use of triflic acid immobilized inorganic materials has also attracted attention, but they are all subject to leaching [33,34]. Recent applications of polyvinylpolypyrrolidone as a reagent support [35–38] have been extensively investigated. We have recently demonstrated that polyvinylpolypyrrolidonium triflate efficiently catalyzed reaction between indole and aldehydes for the preparation of bis-indolyl methane derivatives [39]. In continuing our studies on the application of new reagents or systems for organic functional group transformations [40–42], we report a new application of polyvinylpolypyrrolidonium triflate as an efficient, mild, noncorrosive, and recyclable catalyst in an alternative method for the synthesis of quinoxaline derivatives (Scheme 1).

2. Experimental

2.1. Preparation of the polyvinylpolypyrrolidone supported triflic acid (PVPP·OTf)

To a suspension of polyvinylpolypyrrolidone (3.0 g) in toluene (35 mL), TfOH (2.0 g, 13 mmol) was added. The mixture was stirred

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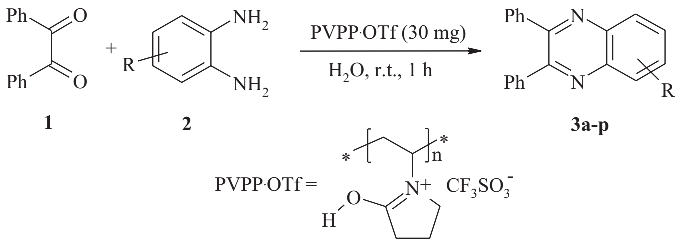

Scheme 1. Synthesis of 2,3-disubstituted quinoxalines derivatives in water.

magnetically for 60 min at r.t. The toluene was removed under reduced pressure and the residue was dried at 110 °C for 2 h to afford PVPP·OTf as a white powder. The number of H^+ sites in PVPP·OTf as determined by acid–base titration was 10 mmol g^{-1}.

2.2. *Typical experimental procedure*

A mixture of 1,2-dicarbonyl compounds (1 mmol), aryl 1,2-diamines (1 mmol) dissolved in 4 mL water, and PVPP·OTf (30 mg) was stirred for 1 h. The reaction was monitored by TLC. After completion of the reaction, the mixture was washed with chloroform and filtered to recover the catalyst. The filtrate was evaporated and purified by recrystallization from hot ethanol to afford pure products. Products were characterized by comparison of their physical and spectral data with those of authentic samples. Spectroscopic data for selected examples as follows:

2,3-Diphenylquinoxaline (Table 1, entry 1): White solid; mp 126–127 °C; IR (KBr, cm^{-1}): ν 3051, 1630, 1528, 1348, 772; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33–7.41 (m, 6H), 7.53–7.57 (m, 4H), 7.76–7.83 (m, 2H), 8.20–8.23 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 128.2, 128.9, 129.2, 129.8, 129.9, 139.1, 141.2, 153.4.

2,3-Diphenylpyrido[2,3-b]pyrazine (Table 1, entry 6): Yellow crystals; mp 135–137 °C; IR (KBr, cm^{-1}): ν 3055, 1640, 1530, 1340; ^1H NMR (400 MHz, $CDCl_3$): δ 7.34–7.45 (m, 5H), 7.59–7.66 (m, 4H), 7.73–7.76 (m, 2H), 8.54–8.56 (m, 1H), 9.20 (d, 1H, J = 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 125.6, 128.5, 128.8, 129.7, 129.8, 130.2, 130.6, 136.6,138.5, 138.9, 150.2, 154.4, 155.1, 156.7.

Acenaphtho[1,2-b]quinoxaline (Table 1, entry 11): White solid; mp 242–245 °C. IR (KBr, cm^{-1}): ν 3443, 3047, 2922, 2361, 1614, 1481. ^1H NMR (400 MHz, $CDCl_3$): δ 7.70–7.75 (m, 2H), 7.98 (t, 2H, J = 7.7 Hz), 8.15 (d, 2H, J = 7.7 Hz), 8.18–8.22 (m, 2H), 8.42 (d, 2H, J = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 125.7, 126.8, 127.2, 128.2, 128.9, 129.6, 130.1, 133.2, 142.5, 145.3.

3. Results and discussion

To initiate our study, the reaction of benzil (1 mmol) with *o*-phenylenediamine was chosen as a model reaction in water at room temperature. The corresponding 2,3-disubstituted quinoxalines **3a** was obtained in high yield (90%) after 60 min (Table 1, entry 1). The new methodology allowed us to prepare the 2,3-disubstituted quinoxalines shown in Table 1.

In order to evaluate the efficiency of this methodology, various arene-1,2-diamines, such as mono- and disubstituted amines, reacted efficiently with 1,2-dicarbonyl compounds to give the corresponding 2,3-disubstituted quinoxalines (Table 1). Results in Table 1 show that electron-donating groups at the phenyl ring of 1,2-diamine favoured the formation of product (Table 1, entries 1 and 2) In contrast, electron-withdrawing groups such as chloro and bromo gave slightly lower yields (85%–88%) (Table 1, entries 4 and 5). Interestingly, 2,3-diaminopyridine underwent smooth coupling with benzil to afford the corresponding pyrido[2,3-b]pyrazine **3f** in 85% yield (Table 1, entry 6). Similarly, several 1,2-dicarbonyl compounds, such as furil, 1,2-di(4-chlorophenyl)ethanedione, phenylglyoxal, ninhydrin, and acenaphthene-1,2-quinone also reacted rapidly with 1,2-diamines to produce a variety of quinoxaline derivatives (Table 1, entries 8–19). In all cases, the reactions proceeded rapidly at room temperature with high efficiency. The products were characterized by ^1H and ^{13}C NMR, IR spectroscopic data, and also by comparison with authentic samples. This method not only affords the products in excellent yields but also avoids the problems associated with catalyst cost, handling, safety, and pollution. One of the major advantages of this protocol is the isolation and purification of the products, which have been achieved by simple filtration and crystallization of the crude products. The characterization of the Brønsted acid sites present in the polymer was performed by recording the FT-IR spectrum of PVPP-OTf, which shows a strong broad absorption at 3400 cm^{-1} for the O–H bond and a moderate absorption at 1648 cm^{-1} that corresponds to the internal imine groups present in the pendant rings of the polymer (Fig. 1). Respectively, the bands at 1225 cm^{-1} and 1174 cm^{-1} were assigned to the S=O asymmetric and symmetric stretching vibrations of $-SO_3^-$ group [37]. Loading capacity of the reagent was determined by

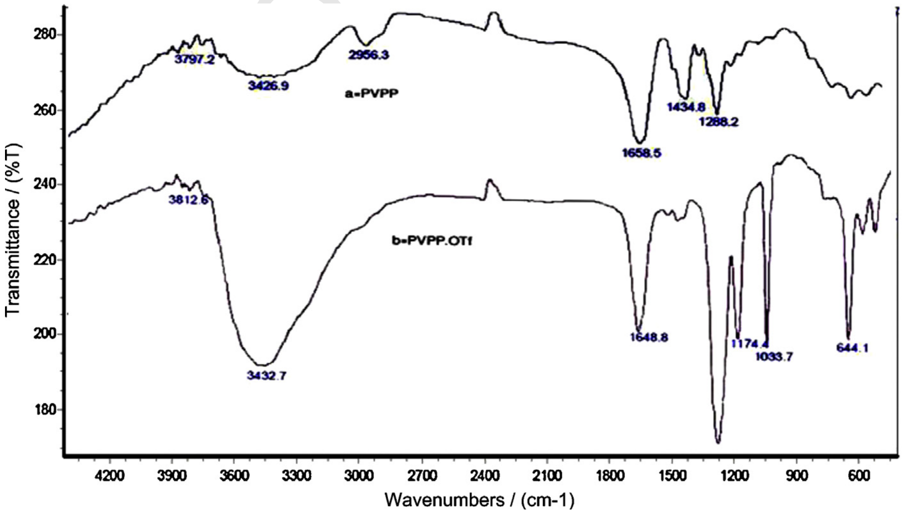

Fig. 1. The FT-IR spectrum of polyvinylpolypyrrolidone (PVPP) and (PVPP·OTf) catalyst.

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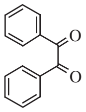
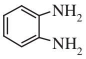
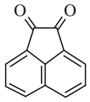
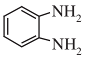
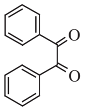
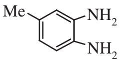
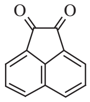
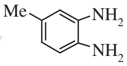
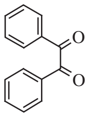
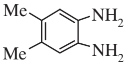
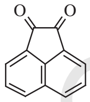
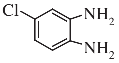
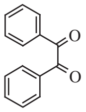
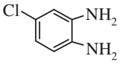
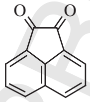
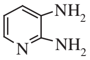
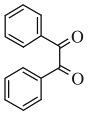
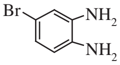
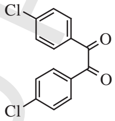
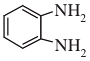
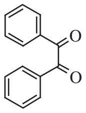
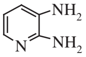
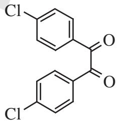
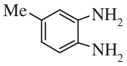
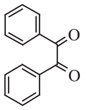
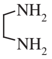
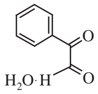
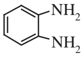
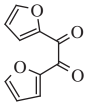
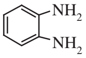
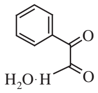
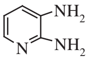
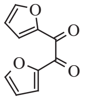
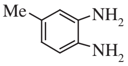
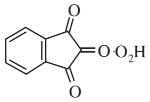
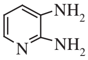
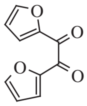
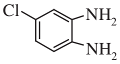
Table 1
Quinoxaline derivatives from the reaction of 1,2-diamines and 1,2-diketones catalyzed by PVPP·OTf.

Entry	Dicarbonyls	Diamines	Product	Yield %	Entry	Dicarbonyls	Diamines	Product	Yield %
1			**3a**	90	11			**3k**	90
2			**3b**	95	12			**3l**	95
3			**3c**	95	13			**3m**	85
4			**3d**	85	14			**3n**	82
5			**3e**	88	15			**3o**	92
6			**3f**	85	16			**3p**	95
7			**3g**	80	17			**3q**	90
8			**3h**	95	18			**3r**	80
9			**3i**	95	19			**3s**	80
10			**3j**	85					

titration and found to be 10 mmol g^{-1}, whereas its silica supported analogue has a loading capacity of less than 1 mmol g^{-1}.

As PVPP·OTf is not soluble in acetonitrile, no PVPP·OTf leaching as well as no contribution of homogeneous catalysis in the course of reaction was expected. To prove this, after 1 h, the catalyst was removed from acetonitrile by filtration and the supernatant was tested for activity. No activity was observed, indicating that there was no contribution of homogeneous catalysis in this reaction. After reaction, the catalyst can be easily separated (by filtration) and reused without decrease in its activity. For example, the reaction of benzil and *o*-phenylenediamine afforded the corresponding 2,3-diphenylquinoxaline derivatives in 90%, 90%, 88%, 88%, and 85% isolated yields over five cycles. We believe that the procedure is simple and convenient, and it does not require any aqueous work-up, thereby avoiding the generation of waste, and so it may contribute to the area of green chemistry.

4. Conclusion

In conclusion, we have developed a simple and highly efficient method for the synthesis of quinoxaline derivatives through the reaction of aryl 1,2-diamines with 1,2-dicarbonyl compounds at room temperature catalyzed by polyvinylpolypyrrolidoniume

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triflate in water. The advantages of this procedure are operational simplicity, wide substrate scope, and high yields.

Acknowledgment

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