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Pentafluorophenylammonium triflate: A highly efficient catalyst for the synthesis of quinoxaline derivatives in water

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ABSTRACT

A simple, inexpensive, environmentally friendly and efficient route for the rapid and efficient synthesis of quinoxaline derivatives using pentafluorophenylammonium triflate (PFPAT) as a catalyst is described. Various quinoxaline derivatives were synthesized in good to excellent yields. The preparation of PFPAT catalyst from simple and readily available starting materials makes this method more affordable.

1. Introduction

The use of water as a solvent for organic reactions has been important since the pioneering studies of Diels–Alder reactions by Breslow [1]. There has been increasing recognition that organic reactions can proceed well in aqueous media and offer advantages over those occurring in organic solvents [2]. Water has interesting physiochemical properties, which include high thermal capacity, hydrophobic association, high polarity, and hydrogen-bonding ability [3–7]. Due to these properties, the use of water as a reaction medium for clean catalytic transformations would have profound effects on reaction rates and product selectivity. Quinoxaline derivatives have attracted much attention owing to their biological activities. They display a broad range of biological, medicinal, and pharmacological properties and are constituents of antiviral, antibacterial, anti-inflammatory, and antiprotozoal drugs and as kinase inhibitors [8–12]. Their utility as dyes, electroluminescent materials, organic semiconductors, cavitands, chemically controllable switches, DNA cleaving agents and many other applications are well documented [13–18]. In particular, quinoxaline drugs, such as clofazimine, echinomycin, leromycin and actinomycin are some of the leading ones on the market with diverse functionalization around the quinoxaline motif [19–24]. In view of the great importance of quinoxaline derivatives, in recent years, efforts have been made in developing new methodologies for the synthesis of these compounds [25]. The condensation of aryl 1,2-diamines with 1,2-dicarbonyl compounds represents an important existing procedure for the synthesis of 2,3-disubstituted quinoxalines.

Generally, this condensation has been carried out under reflux conditions in ethanol or acetic acid [26]. In recent years, several new efficient methods have been developed, including the use of β-cyclodextrin (β-CD) [27], ionic liquids [28], molecular iodine [21], heteropolyacid [29], cellulose sulfuric acid [30], Zn[(L)proline] [31], hypervalent iodine(III) sulfonate in PEG [32], polyaniline-sulfate salt [33], DABCO [34], CAN [35], fluorinated alcohols [36] and $(NH_4)_6Mo_7O_{24}{\cdot}4\ H_2O$ [37]. These methods show varying degree of successes as well as limitations, such as harsh reaction conditions, expensive and detrimental metal reagents, tedious work-up, low product yields, long reaction times, and co-occurrence of several side products. Therefore, a simple, efficient method for quinoxaline synthesis remains an attractive goal. Recently Zhang

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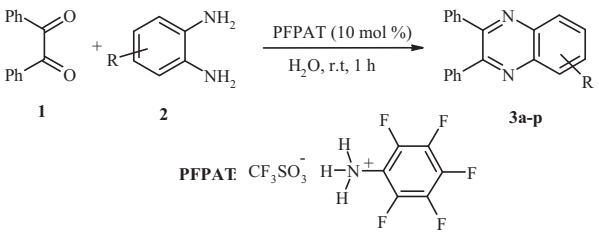
et al. have found that gallium(III) triflate can catalyze successfully the reactions of phenylene-1,2-diamines and 1,2-diketones under mild conditions [38]. This method was suitable for a wide range of substrates, and especially for functionalized phenylene-1,2-diamines. Yadav et al. have reported a one-pot synthesis of phenylene-1,2-diamine derivatives by cyclocondensation of arene-1,2-diamines with 1,2-dicarbonyls using a catalytic amount of bismuth(III) triflate [39]. The use of water as a solvent makes this procedure attractive and environmentally benign. However, realizing the fact that metal-free organocatalysis has drawn considerable interest from chemists, and that metal-free homogeneous catalysis is advantageous for designing suitable drugs devoid of any metal content, it would be desirable to develop this reaction using metal-free Lewis acid catalysts [40].

Catalysis with small organic molecules, where an inorganic element is not part of the active principle, has become a highly dynamic area in chemical research [41]. Such catalysts have several important advantages, since they are usually robust, highly reactive, eco-friendly, inexpensive, readily available, and non-toxic [42–44]. As an inexpensive and commercially available organocatalyst, pentafluorophenylammonium triflate ($C_6F_5N^+H_3{}^*TfO^-$; PFPAT) has received increasing attention as a water-tolerant Brønsted acid catalyst for organic synthesis demonstrating highly chemo-, regio- and stereoselective results [45–47]. Due to the current challenges for developing environmentally benign synthetic processes and in continuation of our interest in the application of new organocatalysts for various organic transformations [48–53], we report an efficient route for the synthesis of quinoxaline derivatives using pentafluorophenylammonium triflate (PFPAT) as a catalyst (Scheme 1).

2. Results and discussion

In order to optimize the reaction conditions, we chose the condensation of the reaction of benzil (1 mmol) with *o*-phenylenediamine catalyzed by PFPAT under different conditions both in the absence and in the presence of PFPAT; the results are given in Table 1. It is noteworthy that in the absence of the catalyst, the reaction was rather sluggish in water and resulted in very low yields (20–35%) of quinoxalines, even after long reaction times (Table 1, entry 1). Then, the effects of temperature, the amount of catalyst, and the reaction time on the yield of the product were examined. Reaction at room temperature in water in the presence of 30 mg (10 mol%) PFPAT afforded the



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

Table 1
Effects of the amount of catalyst PFPAT used and of the solvent on the formation of **3**.

Entry	PFPAT amount (mol%)	Condition/ solvent	Time (h)/yield
1	0	rt/H_2O	6/30
2	5	rt/H_2O	5/80
3	10	rt/H_2O	1/95
4	10	rt/CH_2Cl_2	5/10
5	10	rt/THF	5/20
6	10	rt/ethanol	5/60
7	10	rt/toluene	5/10
8	10	rt/diethyl ether	10/10
9	20	rt/H_2O	1/95

product **3** in 95% yield (Table 1, entry 3). Increasing either the amount of catalyst and/or prolonging the reaction time did not improve the yield (Table 1, entry 9), while reducing these factors led to a reduction in the product yield (Table 1, entry 2). Further studies confirmed that 10 mol% of PFPAT was optimum for this reaction and gave a product in 95% yield in just 1 h (Table 1, entry 3). The reaction was also examined in solvents such as toluene, THF, CH_2Cl_2, ethanol, and diethyl ether. When the reaction was carried out in the presence of PFPAT in water, the expected product (**3a**) was obtained in high yield (95%) and with better reaction times compared with other organic solvents (Table 1, entries 3–8). With non-polar diethyl ether and toluene, the desired adduct was not produced. Moreover, when the reaction was carried out in water, the solid product was separated at the end of the reaction.

At the beginning of the reaction, the reagents itself were dissolved completely in the medium to form a homogeneous mixture (Fig. 1a), but near the completion of the reaction, the system became a suspension, and the product precipitated at the end of the reaction (Fig. 1b).

The products were obtained through simple filtering, and recrystallized from hot ethanol to afford pure products. The corresponding functionalized quinoxalines-scaffolds **3a**, shown in Table 1 and confirmed by NMR measurements, were obtained in good yield (95%).

Further experiments revealed that a similar procedure is applicable for the preparation of a wide range of

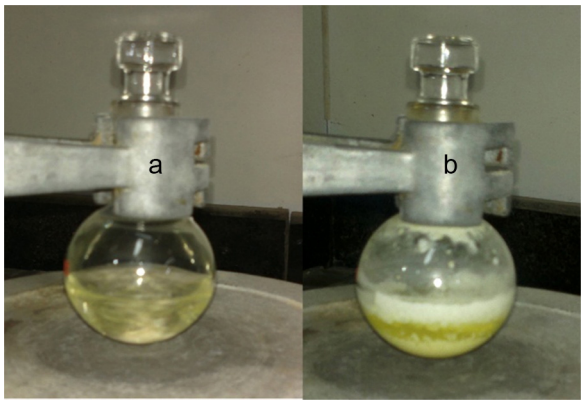


Fig. 1. (Color online.) (a) Homogeneous mixture during the reaction, and (b) at the end of the reaction; the product has precipitated.