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PDTC Catalyzed Synthesis of Quinoxalines from Phenacyl Bromides and *Ortho* Phenylenediamine

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ABSTRACT

An alternative synthesis of quinoxaline derivatives have been synthesized by a simple, efficient, one-pot, two-component condensation of α,β-unsaturated ketones, *o*-phenylenediamine in the presence of a catalytic amount of Potassium dodecatungstocobaltate trihydrate ($K_5CoW_{12}O_{40}.3H_2O$: PDTC) in excellent yields. Environmental acceptability, low cost, high yields and recyclability of the PDTC are the important features of this protocol.

Key words: Quinoxaline, *o*-phenylenediamine, Potassium dodecatungstocobaltate trihydrate, heterogeneous catalyst.

Introduction

Quinoxaline derivatives are an important class of nitrogen-containing heterocycles in medicinal chemistry [1-5]. Quinoxaline synthesis and chemistry has attracted considerable attention in the past ten years [6,7]. For example, quinoxaline is a part of various antibiotics such as echinomycin, levomycin, and actinoleutin that are known to inhibit growth of gram positive bacteria, and are active against various transplantable tumors. Some of them exhibit biological activities including anti-viral, anti-bacterial, anti-inflammatory, anti-protozoal, anti-cancer (colon cancer therapies), anti-depressant, anti-HIV, and as kinase inhibitors [8-14]. They are also used in the agricultural field as fungicides, herbicides, and insecticides[1]. In addition, quinoxaline derivatives have also found applications in dyes, efficient electron luminescent materials, organic semiconductors, chemically controllable switches, building blocks for the synthesis of anion receptors, cavitands, and dehydoannulenes[15,16]. They also serve as useful rigid subunits in macrocyclic receptors in molecular recognition.

Several kinds of synthetic routes toward quinoxalines have been developed, which involve condensation of 1,2-diamines with α-diketones [17], Bi-catalyzed oxidative coupling of epoxides with ene-1,2-diamines [18], cyclization-oxidation of phenacyl bromides[19,20]. However, many of these processes suffer from one or more limitations such as drastic reaction conditions, low product yields, the use of toxic metal salts as catalysts, and relatively expensive reagents. Moreover, these reactions are often carried out in polar solvents such as DMSO leading to tedious work-up procedures. We were interested to examine the synthesis of quinoxalines by the condensation of*o*-phenylenediamine and substituted phenacylbromides in the presence of a catalytic amount of PDTC.

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Experimental

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 are 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 VG. Micromass 7070H and a Finnigan Mat 1020B mass spectrometers operating at 70eV.

General Procedure for synthesis of quinaxalines: To a solution of *o*-phenylene diamine (**1a,** 1.1 mmol), phenacyl bromide **(2a**, 1.0 mmol) was added PDTC (5 mg). The mixture was refluxed for 1-2 h in 10 mL of CH_3CN (progress of the reaction was monitored by TLC). After completion, the reaction mass was cooled to room temperature and the solid catalyst was filtered through a Buchner funnel, washed with CH_3CN (2 x 20 mL). The filtrate was removed under

reduced pressure, and the crude product was purified by column chromatograph. The recovered PDTC dried and reused for a number of cycles without significant loss of activity.

Data of Representative examples : **2-Phenyl quinoxaline (3a):** Solid; mp 77-78 °C; IR (KBr): ν_{max} 2914, 2840, 1916, 1710, 1620, 1521, 1401, 952, 821, 709 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.50-7.60 (s, 3H,Ar-H); 7.72-7.82 (m, 2H, Ar-H); 8.12-8.22 (m, 4H, Ar-H); 9.32 (s, 1H); MS(ESI)$^+$: m/z= 207 $[M+H]^+$.

2-(4-Methoxyphenyl) quinoxaline (3c): Solid; mp 94-98 °C; IR (KBr): ν_{max} 2925, 1604, 1535, 1485, 1458, 1425, 1175, 953, 845,756 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.88 (s, 3H, OCH_3); 7.00-7.10 (d, *J*=9 Hz, 2H, Ar-H); 7.6-7.6 (m, 2H, Ar-H); 8.03-8.10 (m, 3H, Ar-H); 8.15-8.20 (d, *J*=8.5Hz, 2H, Ar-H); 9.25 (s, 1H,=CH); MS(ESI)$^+$: m/z= 237 $[M+H]^+$.

2-(4-Flourophenyl)quinoxaline (3d): Solid; mp 112-113 °C; IR: ν_{max}.2925, 2855, 1596, 1540, 1417, 1311, 1227, 1118, 956, 835, 753 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.20-7.25 (m, 2H, Ar-H); 7.6-7.7 (m,2H, Ar-H); 8.06-8.10 (m, 2H, Ar-H); 8.20-8.25 (m, 2H, Ar-H); 9.28 (s, 1H, =CH).

2-(4-Chlorophenyl) quinoxaline (3e): Solid; mp-129-130 °C; IR: ν_{max} 2925, 1590, 1536, 1485, 1310, 1120, 1045, 955, 830, 755 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.40-7.53 (d, *J*= 7.6Hz, 2H, Ar-H); 7.70-7.77 (m, 2H, Ar-H); 8.09-8.10 (t, *J*= 6.35 Hz, 2H, Ar-H); 8.15-8.18 (d, *J*= 7.86Hz, 2H, Ar-H); 9.30 (s, 1H, =CH); MS(ESI)$^+$: m/z= 241 $[M+H]^+$.

2-(4-Bromophenyl) quinoxaline (3f): Solid; mp 129-130°C; IR: ν_{max} 2925, 1635, 1583, 1535, 1480, 1420, 1305, 1120, 1070, 953, 827, 710 cm^1. ^1H NMR (300 MHz, $CDCl_3$): δ 7.66-7.70 (d, *J*=8.5 Hz, 2H, Ar-H); 7.73-7.80 (t, *J*= 7.8 Hz, 2H, Ar-H); 8.04-8.14 (d, *J*= 8.5 Hz, 4H, Ar-H); 9.26 (s, 1H, =CH);. MS(ESI)$^+$: m/z= 287 $[M+H]^+$.

7-Bromo-3-(4-methylphenyl)pyrido[2,3-*b*]pyrazine (3j): Solid; mp 118-120°C; IR: ν_{max} 2926, 2855, 1785, 1585, 1430, 1365, 1124, 984, 874, 822, 753 cm^{-1}.; ^1H NMR (300 MHz, $CDCl_3$): δ 2.46 (s, 3H, CH_3); 7.35-7.36 (d, *J*= 8.4Hz,4H, Ar-H); 7.51-7.70 (m, 1H, Ar-H); 8.17-8.27 (d, J=8.4 Hz, 2H, Ar-H); 8.59-8.58 (d, *J*=2.24 Hz, 1H, Ar-H); 9.13-9.15 (d, *J*= 2.3Hz, 1H, Ar-H).

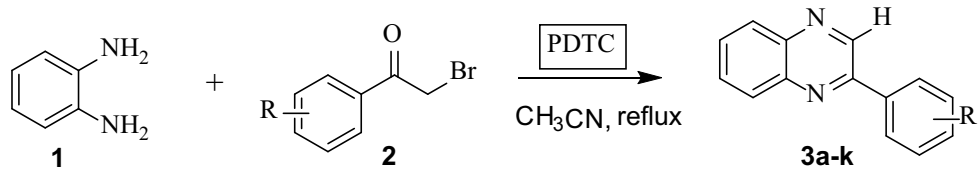
2-(Biphenyl-4-yl) quinoxaline (3k): Solid; mp 117-118 °C; IR: ν_{max} 2925, 1720, 1675, 1532,1417, 1300, 1125, 953, 915, 844, 720 cm^{-1}.^1H NMR (300 MHz, $CDCl_3$): δ 7.35-7.36 (d, *J*=7.2Hz, 1H, Ar-H); 7.40-7.47 (t, *J*= 7.2 Hz, 2H, Ar-H); 7.63-7.66 (d, *J*=7.2 Hz, 2H, Ar-H); 7.62-7.77 (m,4H, Ar-H); 8.00-8.18 (t, *J*=10.6 Hz, 2H, Ar-H); 8.26 -8.30 (d, *J*=8.4 Hz, 2H, Ar-H); 9.34 (s, 1H, =CH).

Results and Discussion

We report in this communication an efficient and an alternative synthesis of quinoxalines derivatives using PDTC as solid acid catalyst. To the best of our knowledge, in the literature there appears no reports for the synthesis of quinoxalines derivatives using PDTC. This fact has prompted us to investigate in depth the utility of PDTC for the synthesis of quinoxalines.

In order to optimize the reaction conditions, including solvents and temperature, and a suitable catalyst for the preparation of quinoxalines from *o*-phenylene diamine and α-halo-ketones, the condensation of *o*-phenylenediamine, with phenacyl bromide was chosen as a model reaction, and its behavior was studied in the presence of different catalysts and without catalyst in CH_3CN at reflux temperature: however by using PDTC the product was produced in excellent yield in very short reaction time. Thus, PDTC was the catalyst of choice for all the reactions.

Subsequently, we investigated on the use of different solvents for the purpose. In chlorinated solvents such as dichloromethane and chloroform the reaction was very slow and resulted in lower product yield. Similar results were obtained in coordinating solvents such as THF, diethyl and dimethyl ether. On the other hand, conducting the reaction in inert solvents such as CH_3CN improved the reaction rates as well as product yields. After screening different solvents, CH_3CN came out as the solvent of choice, which not only afforded the products in good yield, but also with higher reaction rates (91.5% yield in 1.5 h). It is also noticed that the condensation using PDTC proceeds rapidly and is superior to the different reagents with respect to reaction time, temperature and yield. This claim is justified through the representative examples, in which the efficiency of PDTC has been compared with those of different Lewis/protic acid catalysts.

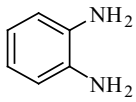
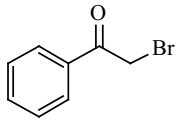
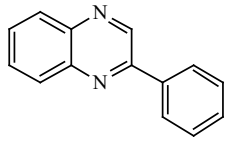
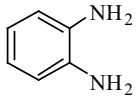
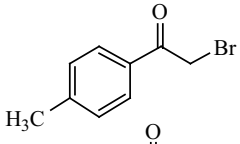
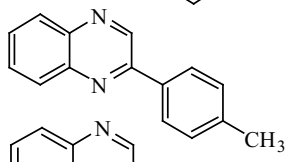
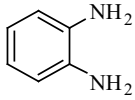
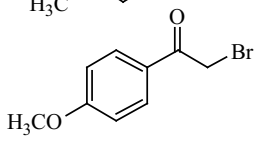
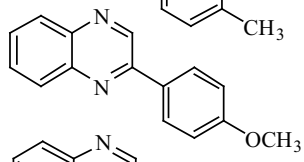
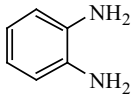
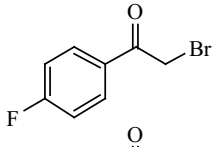
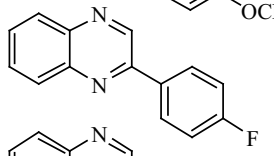
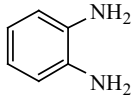
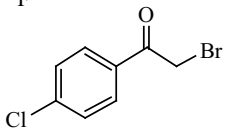
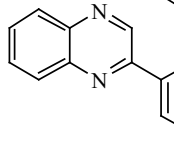
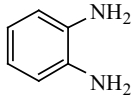
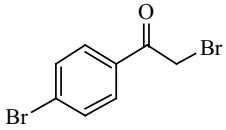
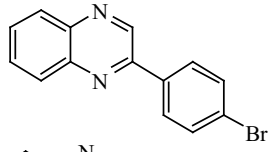
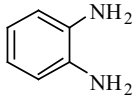
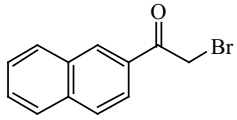
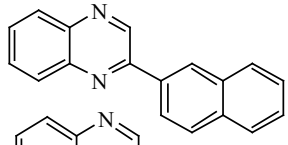
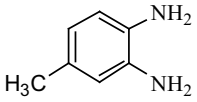
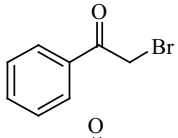
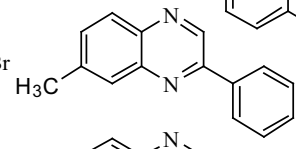
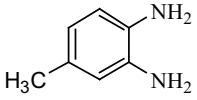
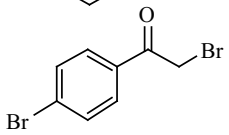
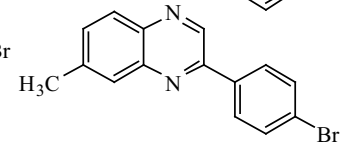
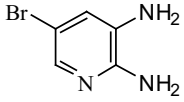
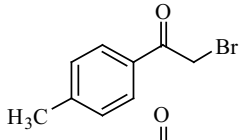
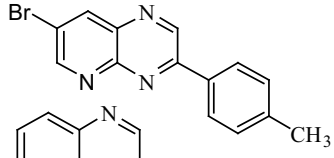
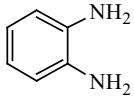
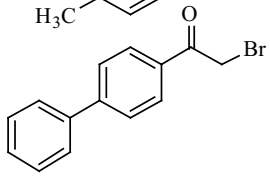
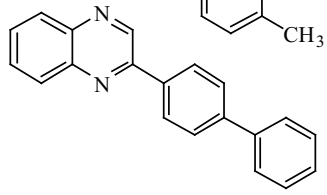


Scheme 1

To establish the generality and scope of our method, various phenacyl bromides have been reacted with *o*-phenylenediamine. The results are displayed in Table 2. As seen, the reaction proceeds efficiently and the respective quinoxalines were obtained in good to excellent yields and shorter reaction times.

Table 2: Synthesis of quinoxaline derivatives using PDTC

Table 2: Synthesis of quinoxaline derivatives using PDTC

Entry	Diamine	Haloketone	Product (3a-3k)	Time h	Yield %[a]
1				1.0	88.5
2				1.5	86.0
3				1.0	90.0
4				2.0	86.5
5				1.0	89.5
6				2.0	84.5
7				2.0	82.0
8				1.5	91.5
9				1.5	79.8
10				2.0	80.5
11				2.0	78.8

[a]Isolated yields

The effect of electron releasing and electron with drawing substituent on the aromatic ring of phenacyl bromides on the reaction was investigated. As Table 1 demonstrates, electron releasing groups and electron withdrawing groups did not affect significantly on the yields and the reaction times. Using 1,2-diamines possessing electron-withdrawing substituent needed longer reaction times and the yields were lower.

Ease of recycling of the catalyst is one of the most advantages of our method. For the reaction of *o*-phenylenediamine,with phenacyl bromide no significant loss of the product yield was observed when PDTC was used after four times recycling.

Conclusion

In conclusion, we have successfully synthesized and characterized derivatives of substituted quinoxalines using a catalytic amount of PDTC. This simple procedure is efficient and can be applied to a wide variety of phenacyl bromides. Shorter reaction times and excellent product yields make this catalytic system an alternative method for the synthesis of substituted quinoxaline derivatives. The remarkable catalytic activity of PDTC exhibited is convincingly superior to the recently reported other catalytic methods with respect to reaction time, amount of catalyst used. Easy workup and ready availability of the catalyst makes the procedure superior over the existing methods.

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