March 2010 ISSN: 0974 - 7516 Volume 6 Issue 1

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 6(1), 2010 [139-143]

Efficient synthesis of quinoxaline with lead peroxide under mild conditions

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Received: 2nd February, 2010 ; Accepted: 12th February, 2010

ABSTRACT

Synthesis of Quinoxalines derivatives with excellent yields using a catalytic amount of lead peroxide (PbO_2) at room temperature. The advantages of this synthetic protocol are a wide substrate range, easy handling and commercially available inexpensive catalyst.

KEYWORDS

Amine;
Quinoxalines;
Lead peroxide;
Diketones.

INTRODUCTION

The development of simple, efficient, environmentally-benign and economically viable chemical processes or methodologies for widely used organic compounds is in great demand[1]. Quinoxaline derivatives are an important class of nitrogen containing heterocycles and they constitute useful intermediate in organic synthesis. Quinoxaline derivatives are well known in the pharmaceutical industry and have been shown to possess a broad spectrum of biological activities such as antibacterial, anti-inflammatory, antiviral and anticancer activity[2]. Besides these applications in dyes[3], efficient electroluminescent materials[4], organic semiconductors[5], building blocks for the synthesis of anion receptor[6], cavitands[7], dehydroannulenes[8] and DNA cleaving agents[9] have been reported. A number of synthetic strategies have been developed for the proportion of substituted quinoxalines.

Over the years, numerous synthetic methods for preparation of quinoxalines have been reported in the literature[10]. Among them, the condensation of 1,2-aryldiamine with 1,2-diketone in refluxing ethanol or acetic acid is a general approach[11]. Research efforts has been focused on finding new catalysts to improve the yield of this condensation reaction. In addition to common Lewis acids, many other catalysts including I_2[12a,12b], SA[12c], Montmorilinite K-10[12d], SSA[12e], $H_6P_2W_{18}O_{62}.24H_2O$[12f], $InCl_3$[12g], $MnCl_2$[12h], $CuSO_4.5H_2O$[12i], CAN[12j], p-TsOH[13], $Ga(OTF)_3$[14] and microwave[15] have been reported.

RESULTS AND DISCUSSION

Herein we report a simple, highly efficient process for the preparation of the biologically important quinoxaline derivatives through the reaction of 1,2-diamines and 1,2-diketones by using lead peroxide as a catalyst (Scheme 1).

The catalytic activity of lead peroxide for the synthesis of quinoxaline derivatives o-phenyldiamine (2 mmol), benzil (2 mmol), and lead peroxide(0.1 mmol) under room temperature was studied and it was found that the application of less than 0.1 mmol of lead peroxide in chloroform (2ml) gave a moderate yield of the corresponding quinoxaline (TABLE 1, entries 1, 2, 3), whereas the use of more than 0.1 mmol gave an excellent yield (TABLE 1, entries-4, 5, 6).

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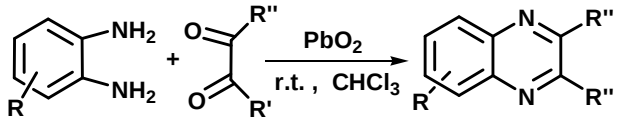


R', R'': Phenyl, Alkyl

Scheme 1

TABLE 2 : Quinoxilation of o-phenyldiamine(2mmol) and benzil(2mmol) in the presence of 0.1 mmol of PbO_2 in various solvents at room temperature

Entry	CuO mmol	Solvent	Time(min)	Yield[a](%)
1	1.0	THF	120	60
2	1.0	CH_2Cl_2	120	80
3	1.0	Et_2O	90	85
4	1.0	EtOAc	90	85
5	1.0	DMF	120	83
6	1.0	$CHCl_3$	30	93[b]
7	0.1	$CHCl_3$	30	93[b]

[a]Isolated Yield., [b] $CHCl_3$ solvent is more effective

In order to find out the most effective quinoxilation, o-phenyldiamine(2 mmol) was chosen as a model substrate. It was treated with 2 mmol of benzil in the presence of 0.1 mmol of PbO_2 in various solvents at room temperature (TABLE 2). The reaction in THF, CH_2Cl_2, H_2O, Et_2O, EtOAc, DMF (TABLE 2, entries 1-6) were found less effective. Since then, we have carried out the reaction in the presence of the $CHCI_3$ solvent to get an excellent yield (93%, entries 7, 8).

In order to find out the most effective catalyst for quinoxilation, we employed various metal oxides during the quinoxilation of o-phenyldiamine with benzil (1:1 equimolar) at room temperature (TABLE 3). According to the results obtained, lead peroxide was found to be the most efficient catalyst. However, other metal oxides such as ZnO, MgO, Cu_2O_3, SiO_2, CaO exhibit less significant catalytic properties in the quinoxilation of o-phenyldiamine with benzyl.

We used a wide variety of compounds to which were applied optimal reaction conditions to prepare a wide range of quinoxalines. The results are summarized in TABLE 4.

In order to expand the scope of this new protocol to synthesize quinoxaline from o-phenylenediamine and diketones, we investigated the reaction in the presence of lead peroxide (TABLE 4, entries 1-16). Results in TABLE-4 show that electron-donating groups at the phenyl ring of 1, 2-diamine favored the product with

TABLE 1 : Catalytic effect of PbO_2 in the synthesis of quinoxaline derivatives at room temperature

Entry	PbO_2 mmol(mg)	Time(min)	Yield(%)[a]
1	0.005(1.2)	240	50
2	0.01 (2.3)	120	65
3	0.05 (12)	90	75
4	0.10 (24)	30	93
5	0.15 (36)	30	93
6	0.20 (48)	30	93

[a]Isolated yield of the corresponding quinoxaline product

TABLE 3 : Quinoxilation of o-phenyldiamine with benzil in the presence of different metal oxides with $CHCl_3$ solvent

Entry	Metal oxide	mmol(mg)	Time (min)	Yield[a] (%)
1	CuO	0.1(8)	120	20
2	ZnO	0.1(8.1)	120	25
3	MgO	0.2(8)	120	25
4	Cu_2O_3	0.1(17.6)	120	20
5	SiO_2	0.1(6.0)	120	30
6	CaO	0.1(5.6)	120	30
7	PbO_2	0.1(24)	30	93
8	PbO_2	0.01(2.3)	30	93

[a]Isolated yield

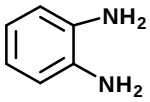
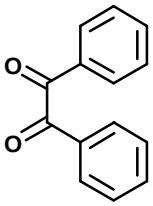
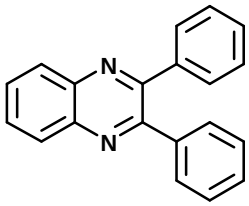
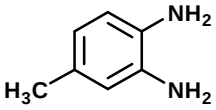
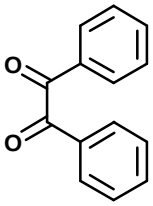
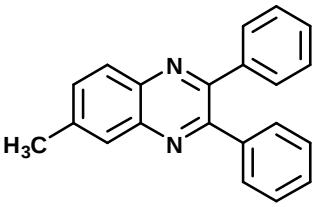
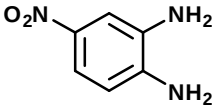
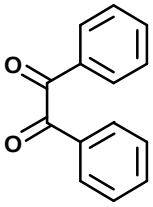
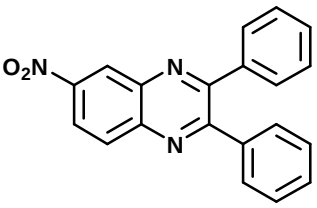
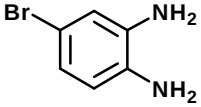
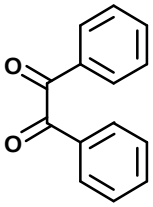
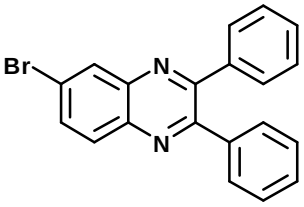
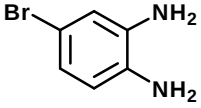
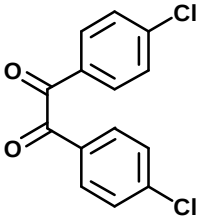
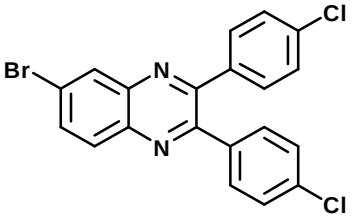
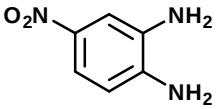
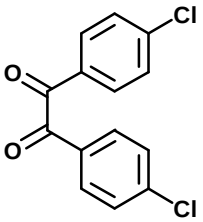
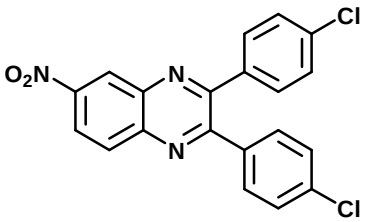
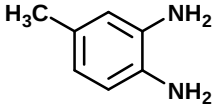
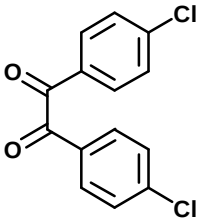
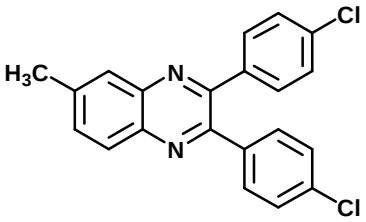
quantitative yields (TABLE 4, entries 2, 7 and 10). In contrast, electron-withdrowing groups such as nitro, Chloro and bromo groups afforded slightly lower yields. Ethylene-1,2-diamine which was also reacted under similar conditions gave considerable yields (TABLE 4, entries 13-15). Different 1,2-diketones were gave excellent yields of quinoxaline derivatives, while 1,2-dialkylketones afforded the reaction (TABLE 4, entries 16).

In conclusion, this manuscript describes a method in which PbO_2 is a highly efficient catalyst for the synthesis of quinoxaline derivatives. The advantages include low cost, ease of catalyst handling, mild reaction conditions and reactions carried out at room temperature with excellent yields.

EXPERIMENTAL

General Experimental Procedure: A mixture of o-phenyldiamine (2 mmol), benzil (2 mmol), $CHCl_3$ (1ml) and lead peroxide(0.1 mmol) was stirred magnetically at room temperature and the progress of the reaction was monitored by thin-layer chromatography (TLC). The reaction mixture was filtered and extracted with

TABLE 4 : Synthesis of quinoxaline in presence of PbO_2 at room temperature

Entry	1, 2-Diamine[a]	1, 2-Diketone	Product[b]	Time (min)	Yield[c] (%)
1				30	93
2				30	92
3				30	91
4				30	85
5				30	90
6				30	92
7				20	93

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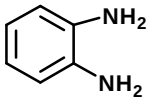
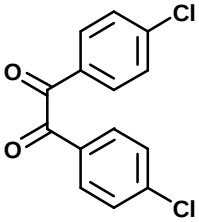
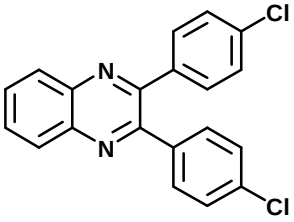
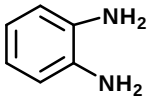
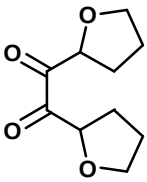
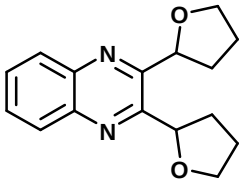
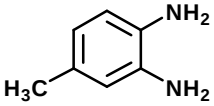
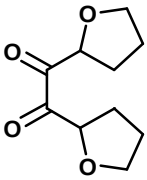
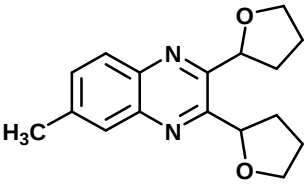
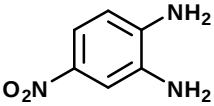
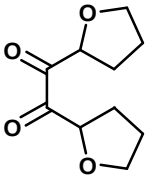
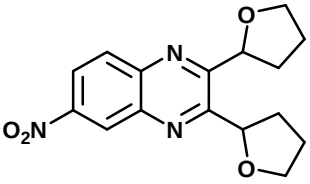
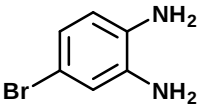
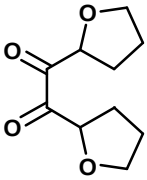
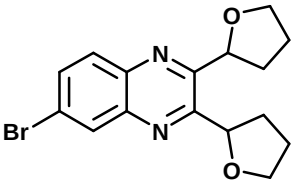
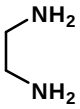
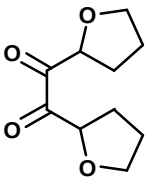
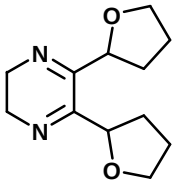
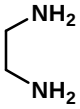
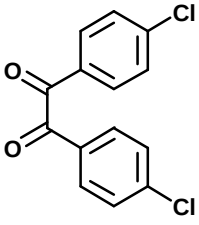
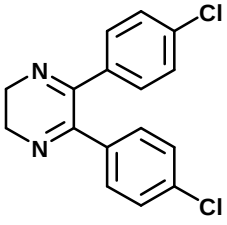
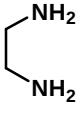
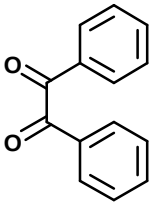
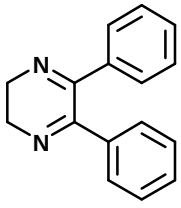
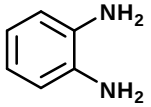
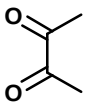
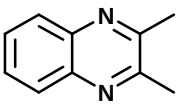
8				30	92
9				30	91
10				30	95
11				30	90
12				30	91
13				50	90
14				50	87
15				60	89
16				60	30

ethyl acetates (3 × 30ml). The combined ethyl acetates extracts were dried with Na_2SO_4 and concentrated under reduced pressure. In all the cases, the product obtained after the usual work up gave satisfactory spectral data.

SPECTRAL ANALYSIS

2,3- Diphenylquinoxaline (1b) M.P. 119°C

IR (KBr): 697, 770, 1211, 1346, 1578, 1659, 1675, 3058 cm^{-1};H^1 NMR (300MHz, $CDCl_2$): δ = 7.55 (m, 5H), 7.35 (m,5H) ; 8.0 (d, 2H, J = 8 Hz); 8.2(m,2H, J = 8 Hz); Anal. Calcd. for $C_{20}H_{14}N_2$: C, 85.08; H, 5.00, N, 9.92, Found: C, 85.09; H, 5.00, N, 9.93.

2,3-Diphenyl-6-Nitro quinoxaline (3b) M.P. 148°C

IR (KBr): 690, 772, 1215, 1351, 1576, 1672, 1658, 3053 cm^{-1}; H^1 NMR (300MHz, $CDCl_2$): δ = 7.50-7.85 (m, 10H), 8.05 (d, 2H, J = 7.4 Hz); 8.29(s,1H, J = 7.4 Hz); Anal. Calcd. for $C_{20}H_{13}N_3O$: C, 73.38; H, 4.00, N, 12.84, Found: C, 73.35; H, 4.02, N, 12.85.

ACKNOWLEDGEMENTS

The authors acknowledge the partial support of this work by Dr.G.A.Meshram, Reader, University of Mumbai, Maharashtra, India.

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