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Lead Oxide (PbO) Mediated Synthesis of Quinoxaline

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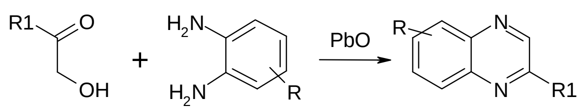
Lead oxide is used as an efficient oxidizing agent in the oxidation and condensation reaction of hydroxy ketone with diamine leading to form quinoxaline derivatives. The method is simple, cost effective and gives good yields in shorter reaction times.



Keywords: Lead oxide (PbO), Quinoxaline, Hydroxy ketones

INTRODUCTION

Among the various classes of heterocyclic compounds, quinoxalines form an important component of pharmacologically active compounds. Quinoxaline ring is a part of various antibiotics such as echinomycin, levomycin and actinomycin [1,2] that are known to inhibit the growth of Gram positive bacteria and are active against various transplantable tumors [3]. In addition, quinoxaline derivatives are also associated with a wide spectrum of biological effects including anathematic, anticancer [4], antimicrobial, antifungal, and antidepressant activities [5,6].

Recently, two substituted quinoxalines were prepared from hydroxy ketones by a one-pot manganese dioxide mediated tandem oxidation process (TOP) [7]. However, the requirement of an excess of activated manganese dioxide (usually 10 equivalents) was a detract the commercial use of this process. Further such reactions require longer reaction times and, in some cases, the yields are poor.

Lead oxide is a general term and can be lead monoxide or "litharge" (PbO), lead tetroxide or "red lead" (Pb_3O_4), or black or "gray" oxide, which is a mixture of 70 percent lead monoxide and 30 percent metallic lead. Litharge is used primarily in the manufacture of various ceramic products. Because of its electrical and electronic properties, litharge is also used in capacitors, Vidicon® tubes, and electrophotographic plates, as well as in ferromagnetic and ferroelectric materials. Additionally, it is used as an activator in rubber, a curing agent in elastomers, a sulfur removal agent in the production of thioles and in oil refining, and an oxidation catalyst in several organic chemical processes [8-10]. Moreover, lead oxide has important applications in the production of many lead chemicals, dry colors, soaps (i.e., lead stearate), and driers for paint. Another important use of litharge is the production of lead salts, particularly those used as stabilizers for plastics, notably polyvinylchloride materials

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[8-10].

Herein, we report a simple and efficient method for the preparation of substituted quinoxalines *via* oxidation and condensation using lead oxide.

EXPERIMENTAL

A mixture of hydroxyacetophenone (**1**) (10 mmol), diamine (**2**) (10 mmol) and lead oxide (4 mmol) in ethanol was heated at 60 ^{o}C for the appropriate time, as listed in Table 1. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into ice water and the precipitated solid was collected by filtration, washed with cold alcohol and purified by column chromatography (90:10 PE:EtOAc). All the synthesized compounds were characterized by ^{1}H NMR (Varian Gemini), ^{13}C NMR (Varian Gemini), mass spectrometry (ES-MS) (Water-Micromass Quattro II spectrometer), elemental analysis (Varian) and melting point (Tempo) and compared to those reported in the literature [7,11].

2,3-Diphenylquinoxaline (3a). ^{1}H NMR (DMSO-d_6): δ (ppm) = 7.24-7.38 (6H, m), 7.51-7.54 (4H, m), 7.72 (2H, m), 8.01 (2H, m); ^{13}C NMR (DMSO-d_6): δ (ppm) = 144, 144, 142, 142, 135.2, 135.2, 129, 129, 128, 128, 128, 128, 128, 128, 127.3, 127.3, 126, 126, 126, 126; mass (ES/MS): m/z 281 (M - H).

2-(2,4-Dichloro-phenyl)-quinoxaline (3i). ^{1}H NMR (DMSO-d_6): δ (ppm) = 7.20 (1H, s, H-5’), 7.32 (1H, d, H-2’), 7.34 (1H, d , H-3’), 7.6 (2H, m, H-6,7), 7.9 (2H, m, H-5,8), 8.68 (1H, s, H-3); ^{13}C NMR (DMSO-d_6): δ (ppm) = 144, 144, 142, 142.1, 134.1, 134, 132.2, 129, 129, 128.5, 125.2, 128, 128, 126.3; mass (ES/MS): m/z 273 (M - H).

2-(2,4-Difluoro-phenyl)-quinoxaline (3j). ^{1}H NMR (DMSO-d_6): δ (ppm) = 6.78 (1H, m, H-5’), 6.71 (1H, d, H-2’), 7.41 (1H, d, H-5’), 7.6 (2H, m, H-6,7), 7.9 (2H, m, H-5,8), 8.68 (1H, s, H-3); ^{13}C NMR (DMSO-d_6): δ (ppm) = 162.2, 161.1, 144, 144, 142, 142, 129.1, 129, 129, 128, 128, 117.8, 110.4, 102; mass (ES/MS): m/z 241 (M - H).

2-(4-Chloro-phenyl)-quinoxaline(3k). ^{1}H NMR (DMSO-d_6): δ (ppm) = 7.31 (2H, d, H-3’,5’), 7.41 (2H, d, H-2’,6’), 7.6 (2H, m, H-6,7), 7.9 (2H, m, H-5,8), 8.68 (1H, s, H-3); ^{13}C NMR (DMSO-d_6): δ (ppm) = 144, 144, 142, 142, 133.2, 132.4, 129, 129, 128.2, 128.2, 128, 128, 127.2, 127.2; mass (ES/MS): m/z 239 (M - H).

2-(4-Fluoro-phenyl)-quinoxaline (3l). ^{1}H NMR (DMSO-d_6): δ (ppm) = 7.01 (2H, d, H-3’,5’), 7.41 (2H, d, H-2’,6’), 7.3 (2H, m, H-6,7), 8.0 (2H, m, H-5,8), 8.68 (1H, s , H-3); ^{13}C NMR (DMSO-d_6): δ (ppm) = 161.1, 144, 144, 142, 142, 142, 131.1, 129, 129, 128, 128, 127.4, 127.4, 115.1, 115.1; mass (ES/MS): m/z 223 (M - H).

2-(2,4-Dichloro-phenyl)-6,7-dimethyl-quinoxaline (3m). ^{1}H NMR (DMSO-d_6): δ (ppm) = 2.31 (6H, s, $2CH_3$), 7.20 (1H, d, H-5’), 7.32 (1H, d, H-3’), 7.34 (1H, d, H-6’), 7.6 (2H, m, H-5,8), 8.68 (1H, s, H-3); ^{13}C NMR (DMSO-d_6): δ (ppm) = 143, 143, 140, 140, 140, 140, 134.1, 134, 132.5, 128.7, 128.7, 127, 127, 126.2, 14.2, 14.2; mass (ES/MS): m/z 301 (M - H).

2-(2,4-Difluoro-phenyl)-6,7-dimethyl-quinoxaline (3n). ^{1}H NMR (DMSO-d_6): δ (ppm) = 2.31 (6H, s, $2CH_3$), 6.78 (1H, d, H-5’), 6.71 (1H, d, H-3’), 7.41 (1H, d , H-6’), 7.6 (2H, m, H-5,8), 8.68 (1H, s, H-3); ^{13}C NMR (DMSO-d_6): δ (ppm) = 162.2, 161.1, 143,143, 140, 140, 140, 140, 129, 127, 127, 118.1, 110.2, 102, 14.1,14.1; mass (ES/MS): m/z 269 (M - H).

2-(4-Chloro-phenyl)-6,7-dimethyl-quinoxaline(3o). ^{1}H NMR (DMSO-d_6): δ (ppm) = 2.31 (6H, s, $2CH_3$), 7.31 (2H, d, H-3’,5’), 7.41 (2H, d, H-2’,6’), 7.6 (2H, m, H-5,8), 8.68 (1H, s, H-3); ^{13}C NMR (DMSO-d_6): δ (ppm) = 143, 143, 140, 140, 140, 140, 133.6, 133.2, 128.2, 128.2, 127.1, 127.1, 127, 127, 14.1 14.1; mass (ES/MS): m/z 267 (M - H).

2-(4-Fluoro-phenyl)-6,7-dimethyl-quinoxaline (3p). ^{1}H NMR (DMSO-d_6): δ (ppm) = 2.31 (6H, s, $2CH_3$), 7.01 (2H, d, H-3’,5’), 7.41 (2H, d, H-2’,6’), 8.0 (2H, m, H-5,8), 8.68 (1H, s, H-3); ^{13}C NMR (DMSO-d_6): δ (ppm) = 161, 143, 143, 140, 140, 140, 140, 131.1, 127.4, 127.4, 127, 127, 115, 115, 14.1, 14.1; mass (ES/MS): m/z 251 (M - H).

RESULTS AND DISCUSSION

In the presence of lead monoxide (PbO), the reaction of hydroxy ketone and diamine carried out in a one-pot method at 60-90 °C results in the formation of quinoxaline with an 85-95% yield. To extend the scope of this reaction and to generalize the procedure, we investigated the reaction of a series of substituted hydroxy ketones with various substituted diamines to obtain the corresponding quinoxalines (Table 1).

Many pharmacologically relevant substitution patterns on the aromatic ring were introduced with high efficiency and

Table 1. Lead Oxide (PbO) Catalyzed Synthesis of Quinoxaline (**3a**-**3p**)

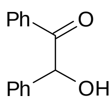
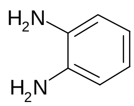
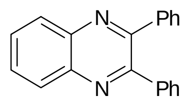
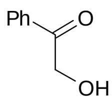
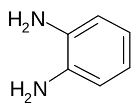
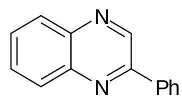
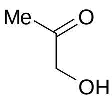
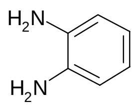
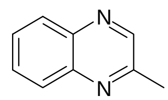
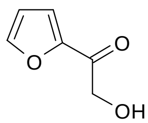
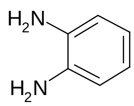
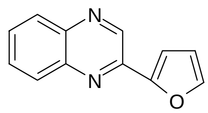
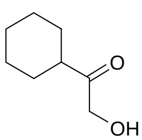
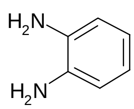
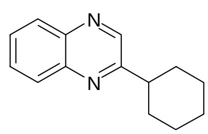
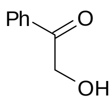
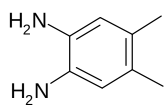
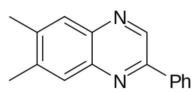
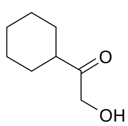
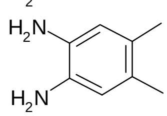
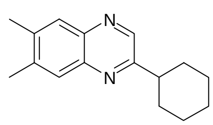
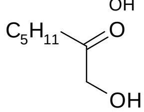
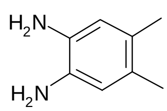
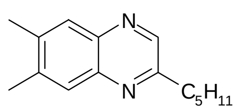
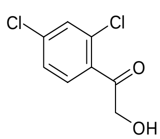
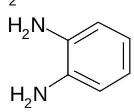
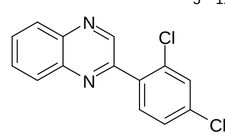
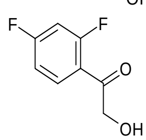
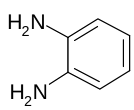
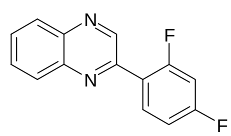
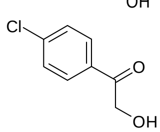
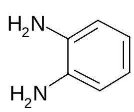
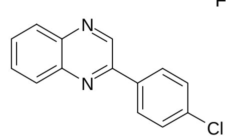
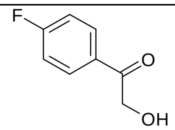
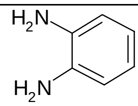
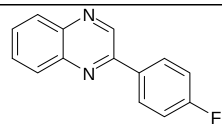
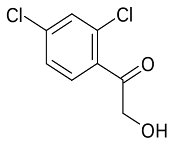
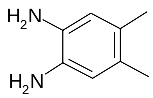
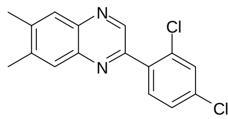
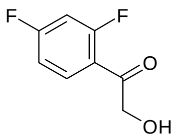
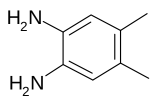
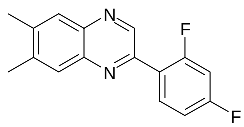
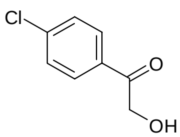
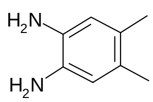
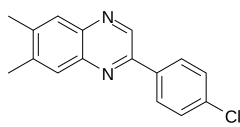
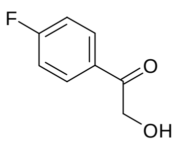
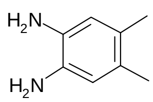
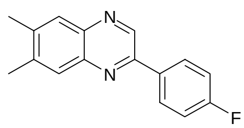
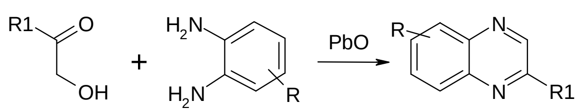
Sr. No.	Hydroxy compound	Diamine	Product	Time (min)	Yield (%)[a]			M.P. (°C)	
					Reported [7,11]	Without catalyst	PbO	Found	Reported [7,11]
3a				55	66	10	95	127	128
3b				50	79	10	93	80-82	81
3c				45	79	05	85	Orange oil	Orange oil
3d				50	89	05	90	102-104	101
3e				50	78	05	85	44-46	46
3f				50	66	10	90	121	120
3g				50	89	05	90	67	66
3h				50	62	05	88	Orange oil	Orange oil
3i				45	--	15	95	125-127	--
3j				45	--	15	95	130-133	--
3k				45	--	15	95	120-122	--

Table 1. Continued

3l				45	--	15	95	126-129	--
3m				45	--	15	93	140-142	--
3n				45	--	15	93	158-160	--
3o				45	--	15	93	146-148	--
3p				45	--	15	93	150	--

[a]Isolated yield after column chromatography.



1 2 3

Scheme 1

most importantly, hydroxyl ketones carrying either electron-donating or electron withdrawing substituents all reacted very well, giving moderate to excellent yields with high purities. In general we observed that the reactions proceeded faster than conventional ones and the yields were comparable.

In conclusion, we have demonstrated an efficient and simple alternative for the preparation of substituted quinoxalines using lead oxide (PbO) as a catalyst. Prominent among the advantages of this new method are operational simplicity, good yields, shorter reaction times, low cost, availability of the catalyst and the easy workup procedure employed.

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