Mercuric Iodide (HgI_2) as an Oxidizing Agent for the Synthesis of Quinoxaline

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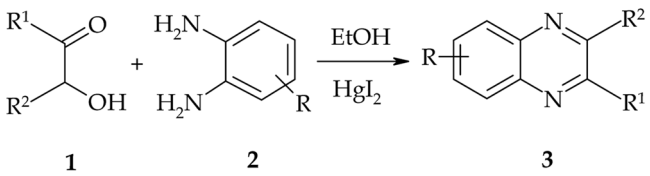
Nitrogen-containing heterocyclic compounds are indispensable structural units for both the chemist and the biochemist. Among the various classes of heterocyclic compounds, quinoxalines form an important component of pharmacologically active compounds. Quinoxaline ring is a part of various antibiotics such as Hinomycin, Levomycin and Actinoleutin[1,2] that are known to inhibit 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 activities ranging from anthelmintic and anticancer to antimicrobial, antifungal, antidepressant, antibacterial and anti-inflammatory activities.[4-9]

Recently, 2-substituted quinoxaline can be prepared by one-pot process commencing from hydroxy ketone using manganese dioxide-mediated tandem oxidation process (TOP).[10] However, the requirement of excess of activated manganese dioxide (usually 10 equivalents) detracts the commercial attraction and green credential of this process. Furthermore, such reactions require longer reaction times and in some cases the yields are poor.

Mercuric iodide has been used as a mild and efficient catalyst for the synthesis of oligosaccharide[11] and for the addition of silyl ketene acetals to acrylate esters or other electrophiles.[12,13]

The condensation of *C,O,O*-tris(trimethylsilyl)ketene acetal with aldehydes in the presence of catalytic amounts of mercuric iodide at room temperature affords *syn* and *anti* β-trimethylsiloxy α-trimethylsilyl alkanoic acid silyl esters.[14] Mercuric chloride is used as an oxidizing agent for 2-amino-3-(2,3-dihydroxypropylideneamino)malenonitrile to give 5-methyl-2,3-pyrazinedicrbonitrile.[15] Mercuric chloride-mediated cyclization of tethered alkynedithioacetals has been established as a general route to five- and six-membered carbocycles and heterocycles.[16] However, there are no examples of the use of HgI_2 as an oxidizing agent for the synthesis of quinoxaline derivatives.

Herein, we report a general and practical route for the synthesis of quinoxaline using HgI_2 as a catalyst. In the presence of mercuric iodide (HgI_2), the reaction of hydroxy ketone and aromatic diamine was carried out in one-pot condition at 60 °C and resulted in the formation of quinoxaline in 60-85% yield (Table 1). Many pharmacologically relevant substituents on the aromatic ring could be introduced with high efficiency in moderate to excellent yields with high purities.



1 **2** **3**

Scheme 1

In conclusion, a simple and general method for the synthesis of substituted quinoxaline using mercuric iodide as an oxidizing agent is developed. The compatibility with various functional groups, mild reaction conditions, high yields and application of inexpensive, mild, readily and easily available mercuric iodide are the main advantages of the present procedure.

Experimental Section

Melting points are uncorrected. ^{1}H NMR and ^{13}C-NMR spectra were recorded on Varian Gemini 200 MHz spectrometer. Chemical shifts are reported in δ units (ppm) relative to TMS as an internal standard. Electron spray ionization mass spectra (ESI-MS) were recorded on Water-Micromass Quattro II spectrometer. All the reagents used were of AR grade and were used without further purification. Column chromatography employed silica gel of 60-120 mesh.

General procedure: A mixture of hydroxyacetophenone (**1**) (10 mmol), diamine (**2**) (10 mmol) and mercuric iodide (2 mmol) in ethanol was heated at 60 °C for 45-55 minutes. The reaction was monitored by TLC. After completion of reaction, the reaction mixture was poured into ice water and the precipitated solid was collected by filtration, washed with cold alcohol and the product was purified by column chromatography (PE/EtOAc, 9 : 1) to afford pure compound.

2-(2,4-Dichlorophenyl)-quinoxaline (3i): ^{1}H NMR (DMSO-d_6) δ 7.20 (s, 1H, H-5'), 7.32 (d, 1H, H-2'), 7.34 (d, 1H, H-3'), 7.60 (m, 2H, H-6,7), 7.90 (m, 2H, H-5,8), 8.68 (s, 1H, H-3); ^{13}C NMR (50 MHz, DMSO-d_6) δ 146.2, 144.5, 136.1, 136.0, 134.2, 131.0, 130.6, 130.0, 128.4; Mass (ESI-MS) *m/z* 273 (M^--H).

2-(2,4-Difluorophenyl)-quinoxaline (3j): ^{1}H NMR (DMSO-d_6) δ 6.78 (m, 1H, H-5'), 6.71 (d, 1H, H-2'), 7.41 (d, 1H, H-5'), 7.6 (m, 2H, H-6,7), 7.9 (m, 2H, H-5,8), 8.68 (s, 1H, H-3); ^{13}C NMR (50 MHz, DMSO-d_6) δ 146.2, 144.6,

Table 1. Mercuric iodide-mediated synthesis of quinoxaline derivatives

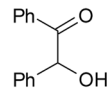
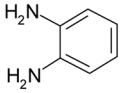
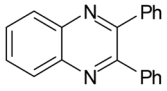
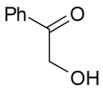
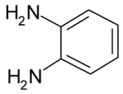
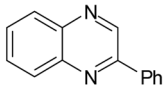
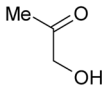
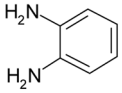
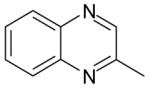
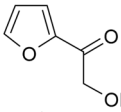
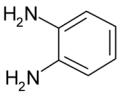
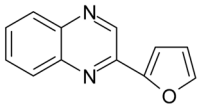
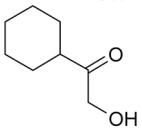
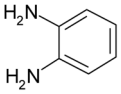
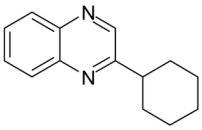
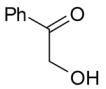
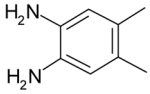
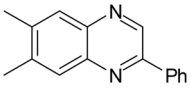
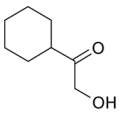
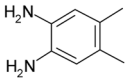
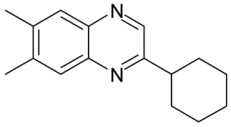
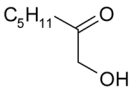
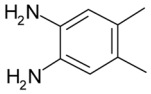
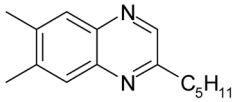
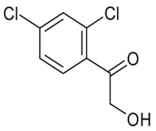
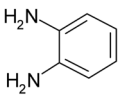
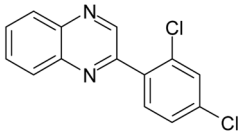
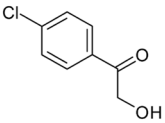
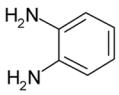
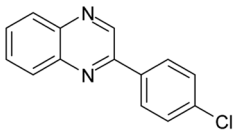
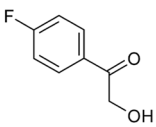
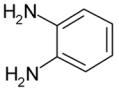
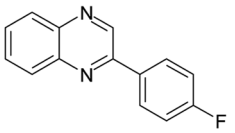
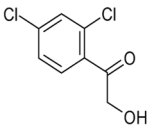
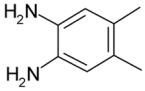
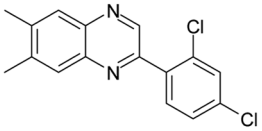
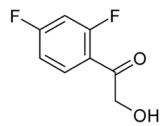
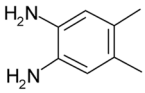
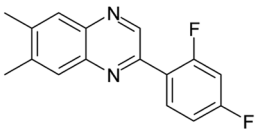
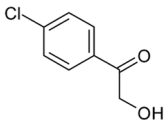
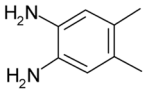
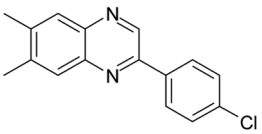
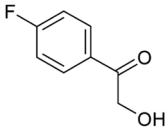
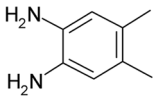
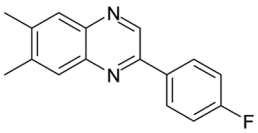
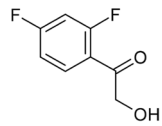
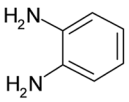
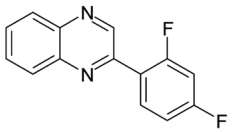
Entry	Hydroxy Compound	Diamine	Product	Yield (%)	M.P. °C	Elemental analysis %		
				Found (Reported)[10]	Found (Reported)[10]	C Calc. Found	H Calc. Found	N Calc. Found
a				85 (66)	126-128 (128)	85.08 85.16	5.00 5.08	9.92 8.85
b				80 (79)	82 (81)	81.53 81.45	4.89 4.81	13.58 13.51
c				80 (79)	Orange Oil (Orange Oil)	74.98 74.88	5.59 5.51	19.43 19.35
d				80 (89)	103 (101)	73.46 73.39	4.11 4.05	14.28 14.22
e				85 (78)	44-46 (46)	79.21 79.15	7.60 7.52	13.20 13.25
f				75 (66)	121 (120)	82.02 82.10	6.02 5.95	11.96 11.89
g				80 (89)	67 (66)	79.96 79.91	8.39 8.47	11.66 11.62
h				60 (62)	Orange Oil (Orange Oil)	76.71 76.65	7.02 7.10	16.26 16.21
i				75 (–)	125 (–)	61.12 61.20	2.93 2.90	10.18 10.15
j				80 (–)	130 (–)	69.86 69.81	3.77 3.71	11.64 11.71
k				82 (–)	120 (–)	74.99 74.91	4.05 4.12	12.49 12.58
l				83 (–)	126-128 (–)	63.38 63.45	3.99 3.91	9.24 9.35

Table 1. Continued

Entry	Hydroxy Compound	Diamine	Product	Yield (%)	M.P. °C	Elemental analysis %		
				Found (Reported)[10]	Found (Reported)[10]	C Calc. Found	H Calc. Found	N Calc. Found
m				80 (–)	140 (–)	71.10 71.18	4.48 4.55	10.36 10.45
n				82 (–)	160 (–)	71.51 71.42	4.88 4.75	10.42 10.32
o				82 (–)	146 (–)	76.17 76.11	5.19 5.09	11.10 11.18
p				83 (–)	148-150 (–)	69.42 68.35	3.33 3.25	11.56 11.45

135.2, 134.2, 131.0, 130.2, 130.0, 129.4; Mass (ESI-MS): *m/z* 241 (M^--H).

2-(4-Chlorophenyl)-quinoxaline (3k): ^{1}H NMR (DMSO-d_6) δ 7.31 (d, 2H,H-3',5'), 7.41 (d, 2H, H-2',6'), 7.6 (m, 2H, H-6,7), 7.9 (m, 2H, H-5,8), 8.68 (s, 1H, H-3); ^{13}C NMR (50 MHz, DMSO-d_6) δ 161.3, 146.2, 131.4, 142.0, 131.0, 130.0, 129.5, 117.2; Mass (ESI-MS): *m/z* 239 (M^--H).

2-(4-Fluorophenyl)-quinoxaline (3l): ^{1}H NMR (DMSO-d_6) δ 7.01 (d, 2H, H-3',5'), 7.41 (d, 2H, H-2',6'), 7.3 (m, 2H, H-6,7), 8.0 (m, 2H, H-5,8), 8.68 (s, 1H, H-3); ^{13}C NMR (50 MHz, DMSO-d_6) δ 145.2, 142, 129.1, 136.2, 136.4, 134.3, 130.5, 129.2, 128.9, 13.8; Mass (ESI-MS) : *m/z* 223 (M^--H).

2-(2,4-Dichlorophenyl)-6,7-dimethyl-quinoxaline (3m): ^{1}H NMR (DMSO-d_6) δ 2.31 (s, 6H, 2 x CH_3), 7.20 (d, 1H, H-5'), 7.32 (d, 1H, H-3'), 7.34 (d, 1H, H-6'), 7.6 (m, 2H, H-5,8), 8.68 (s, 1H, H-3); ^{13}C NMR (50 MHz, DMSO-d_6) δ 162.5, 161.4, 145.0, 142.0, 131.4, 104.3, 120.4, 129.4, 15.4; Mass (ESI-MS): *m/z* 301 (M^--H).

2-(2,4-Difluorophenyl)-6,7-dimethyl-quinoxaline (3n): ^{1}H NMR (DMSO-d_6) δ 2.31 (s, 6 H, 2 x CH_3), 6.78 (d, 1H, H-5'), 6.71 (d, 1H, H-3'), 7.41 (d, 1H, H-6'), 7.6 (m, 2H, H-5,8), 8.68 (s, 1H, H-3); ^{13}C NMR (50 MHz, DMSO-d_6) δ 145.2, 142.0, 135.8, 134.5, 130.8, 129.8, 129.0, 14.8; Mass (ESI-MS) : *m/z* 269 (M^--H).

2-(4-Chlorophenyl)-6,7-dimethyl-quinoxaline (3o): ^{1}H NMR (DMSO-d_6) δ 2.31 (s, 6H, 2 x CH_3), 7.31 (d, 2H, H-3',5'), 7.41 (d, 2H, H-2',6'), 7.6 (m, 2H, H-5,8), 8.68 (s, 1H, H-3); ^{13}C NMR (50 MHz, DMSO-d_6) δ 163.2, 145.2, 142.1, 133.2, 129.6, 129.1, 117.2, 14.8; Mass (ESI-MS) : *m/z* 267 (M^--H).

2-(4-Fluorophenyl)-6,7-dimethyl-quinoxaline (3p): ^{1}H NMR (DMSO-d_6) δ 2.31(s, 6H, 2 x CH_3), 7.01 (d, 2H, H-3',5'), 7.41 (d, 2H, H-2',6'), 8.0 (m, 2H, H-5,8), 8.68 (s, 1H, H-3); ^{13}C NMR (50 MHz, DMSO-d_6) δ 164.4, 163.5, 146.2, 144.3, 130.8 130.6, 129.8 112.1; Mass (ESI-MS) : *m/z* 251 (M^--H).

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