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$MnCl_2$-Promoted Synthesis of Quinoxaline Derivatives at Room Temperature

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ABSTRACT: *$MnCl_2$ efficiently catalyzes the condensation of o-phenylenediamine derivatives with 1,2-diketones at room temperature to afford the corresponding quinoxaline derivatives in high yields.* Heteroatom Chem 19:218–220, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20401

INTRODUCTION

Quinoxaline and their derivatives are an important class of bioactive molecules and are widely used as anticancer and anthelmintic agents [1], antiviral, antibacterial [2], anti-inflammatory, and as kinase inhibitors [3]. They have been reported for their applications in dyes [4], pharmaceuticals [5], and have been used as building blocks for the synthesis of organic semiconductors [6], and they also serve as useful rigid subunits in macrocyclic receptors or molecular recognition [7] and chemically controllable switches [8]. By far, the most common method used for the synthesis of quinoxaline is based on the condensation of an aryl 1,2-diamine with a 1,2-dicarbonyl compound in refluxing ethanol or acetic acid for 2–12 h giving 34%–85% yields [9]. Nevertheless, most of these methods suffer from unsatisfactory product isolation procedures, expensive detrimental metal precursors, and harsh reaction conditions. However, many improved methods have been reported for the synthesis of quinoxalines using catalytic amount of variety of metal precursors, acids, zeolites, and molecular iodine [10–12]. These methods have their own merits and drawbacks.

Very recently, we have developed convenient and efficient procedures for the synthesis of quinoxaline derivatives using cupric sulfate pentahydrate, IBX, and Zn [l-proline] as catalysts [13].

As part of our ongoing interest in synthesis of heterocyclic compounds containing nitrogen [14], in this communication, we report a facile method for the synthesis of quinoxaline derivatives by the condensation of 1,2-phenylenediamines with 4,4′-disubstituted benzils catalyzed by $MnCl_2$ at room temperature.

RESULTS AND DISCUSSION

A mixture of benzil (1 mmol), *o*-phenylenediamine (1 mmol), and a catalytic amount of $MnCl_2$(0.01 g, 10 mol%) was stirred in EtOH at ambient temperature and after 17 min the mixture was solidified. At this stage, TLC analysis showed that both reactants have been completely consumed and the corresponding quinoxaline **3** was formed. After that, the reaction was heated, the product was dissolved in ethanol, and the catalyst was separated easily from the reaction mixture without any further recrystallization; the pure product was obtained in 94% yield. To establish the generality of the procedure, in a similar manner, other 4-substituted 1,2-phenylenediamines also reacted smoothly with

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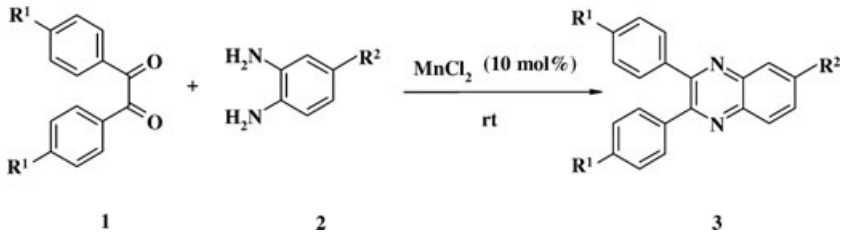

SCHEME 1

4,4′-disubstituted benzils to afford the corresponding quinoxalines in excellent yields (Scheme 1; Table 1).

The results listed in Table 1 show that different kinds of quinoxaline are prepared with ease in excellent yields. The reaction proceeds very cleanly at room temperature and no undesirable side products are observed. In the absence of $MnCl_2$, the reaction did not proceed even after prolonged reflux condition.

In summary, we describe a simple, efficient, straightforward, and one-pot method for the synthesis of quinoxalines via $MnCl_2$-catalyzed condensation ofa variety of 1,2-diamines and α-diketone derivatives. The ambient conditions, high reaction rates, excellent product yields, and easy work-up procedure which avoids the use of corrosive solvents, not only make this methodology an alternative platform to the conventional acid/base catalyzed thermal processes, but also make it significant under the umbrella of environmentally greener and safer processes.

EXPERIMENTAL

Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. ^{1}H NMR spectra were recorded on a Bruker AQS AVANCE-300 MHz spectrometer using TMS as an internal standard ($CDCl_3$ solution). IR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27. All products were characterized by spectra and physical data.

General Procedure for the Preparation of Quinoxalines

A mixture of 1,2-diketone **1** (1 mmol), 1,2-diaminoarene **2** (1 mmol), and $MnCl_2$(10 mol%) in EtOH (3 mL) was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was heated, the product dissolves in ethanol, and the catalyst is separated easily from the mixture. The pure product **3** was crystallized from ethanol. The products were characterized by spectra and physical data.

Physical and Spectroscopic Data for Selected Compounds

2,3-Diphenylquinoxaline (**1**): mp = 128°C–129°C; ^{1}H NMR ($CDC1_3$, 300 MHz) δ (ppm): 8.2 (dd, $J = 3.43$, 6.30 Hz, 2H), 7.79 (dd, $J = 3.43$, 6.30 Hz, 2H), 7.55 (m, 4H), 7.39 (m, 6H); IR (KBr) ν_{max} (cm^{-1}): 3055, 1541, 1345, 768, 729.

6-Nitro-2,3-diphenylquinoxaline (**3**): mp = 193°C–194°C;^{1}H NMR ($CDC1_3$, 300 MHz) δ (ppm): 9.2 (d, $J = 2.38$ Hz, 1H), 8.53 (dd, $J = 2.50$, 9.10 Hz, 1H,), 8.39 (d, $J = 9.17$ Hz, 1H), 7.6 (m, 4H), 7.42 (m, 6H); IR (KBr) ν_{max} (cm^{-1}): 3057, 2935, 1621, 1341, 1135, 699.

6-Methyl-2,3-diphenylquinoxaline (**5**): mp = 117°C–118°C; ^{1}H NMR ($CDC1_3$, 300 MHz) δ (ppm): 8.1 (d, $J = 8.55$ Hz, 1H), 7.96 (s, 1H), 7.63 (dd, $J = 1.72$, 8.56 Hz, 1H), 7.5 (m, 4H), 7.35 (m, 6H), 2.6 (s, 3H); IR (KBr) ν_{max} (cm^{-1}): 3063, 1660, 1592, 1210, 874, 719, 640.

TABLE 1 Synthesis of Quinoxaline Derivatives Catalyzed by $MnCl_2$

Entry	*R^1*	*R^2*	*Product*[a]	*Time (min)*	*Yield (%)*[b]	*MP (°C)*
1	H	H	2,3-Diphenylquinoxaline	17	94	128–129
2	MeO	H	2,3-Bis(4-methoxyphenyl) quinoxaline	15	93	151–152.5
3	H	NO_2	6-Nitro-2,3-diphenylquinoxaline	17	92	193–194
4	MeO	NO_2	2,3-Bis(4-methoxyphenyl)-6-nitro quinoxaline	15	90	192–194
5	H	CH_3	6-Methyl-2,3-diphenylquinoxaline	15	92	117–118
6	MeO	CH_3	2,3-Bis(4-methoxyphenyl)-6-methyl quinoxaline	10	91	125–127

[a]All products were well characterized using ^{1}H NMR and IR spectra.
[b]Yields refer to isolated pure products.

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