

Synthesis of Quinoxaline Derivatives *via* Condensation of Aryl-1,2-diamines with 1,2-Diketones Using $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}\cdot 4\text{H}_2\text{O}$ as an Efficient, Mild and Reusable Catalyst

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Ammonium heptamolybdate tetrahydrate $[(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}\cdot 4\text{H}_2\text{O}]$ efficiently catalyzes the condensation of aryl-1,2-diamines with 1,2-diketones in EtOH/H₂O as a green media at room temperature to afford quinoxaline derivatives as biologically interesting compounds. Ease of recycling of the catalyst is one of the most advantages of the proposed method.

Keywords: Quinoxaline, Aryl-1,2-diamine, 1,2-Diketone, Ammonium heptamolybdate tetrahydrate, Green chemistry

INTRODUCTION

Quinoxaline derivatives are an important class of nitrogen-containing heterocycles in medicinal chemistry [1-3]. 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 [2], and are active against various transplantable tumors [3]. Several kinds of synthetic routes toward quinoxalines have been developed, including the condensation of aryl-1,2-diamines with a 1,2-diketones [4], Bi-catalyzed oxidative coupling of epoxides with ene-1,2-diamines [5], heteroannulation of nitroketene N,S-aryliminoacetals with POCl₃ [6], cyclization of α -arylimino oximes of α -dicarbonyl compounds [7], and formation of α -hydroxy ketones *via* a tandem oxidation process using Pd(OAc)₂ or RuCl₂-(PPh₃)₃-TEMPO [8] as well as MnO₂ [9]. It is worth noting that the methods that have been established for the preparation of quinoxaline derivatives are associated with one or more of the following drawbacks: (i) unsatisfactory yields, (ii) long reaction times, and (iii) harsh

reaction conditions. Thus, it seems highly desirable to find a more efficient and milder protocol for the synthesis of quinoxalines. We have found that ammonium heptamolybdate tetrahydrate can be easily used for this purpose [10].

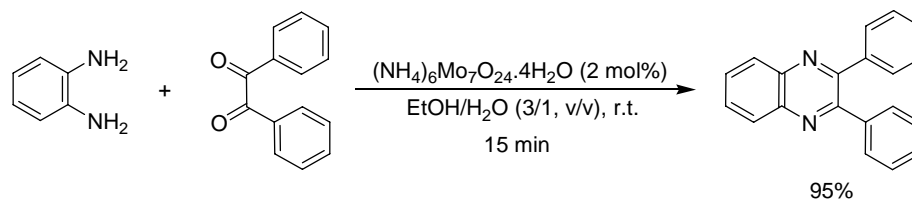
As a part of our research interest towards the development of efficient and environmentally benign synthetic methodologies using eco-friendly conditions [11], we report here the synthesis of quinoxalines from aryl 1,2-diamines and 1,2-diketones in the presence of ammonium heptamolybdate tetrahydrate in EtOH/H₂O (3/1) at room temperature (Scheme 1).

EXPERIMENTAL

General Procedure for the Preparation of Quinoxaline Derivatives

To a mixture of 1,2-diketone (1 mmol), $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}\cdot 4\text{H}_2\text{O}$ (0.025 g, 0.02 mmol) and EtOH/H₂O [3/1 (v/v), 20 ml] in a 50 ml round-bottomed flask was added aryl-1,2-diamine (1 mmol), and the resulting mixture was stirred at room temperature for the times reported in Table 3. Afterward, H₂O (20 ml) was added to the reaction mixture, and was allowed to stand at room temperature for 1 h. During

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Scheme 1

Table 1. Effect of Various Catalysts on the Condensation of Benzene-1,2-diamine (1 mmol) with Benzil (1 mmol) in EtOH/H₂O (3/1, v/v, 20 ml) at Room Temperature

Entry	Catalyst	Time (min)	Yield (%) ^a
1	(NH ₄) ₆ Mo ₇ O ₂₄ ·4H ₂ O (2 mol%)	15	95
2	ZnCl ₂ (4 mol%)	300	80
3	Zn(OAc) ₂ (4 mol%)	300	76
4	Mn(OAc) ₂ (4 mol%)	300	73
5	Cu(OAc) ₂ (4 mol%)	300	70
6	Co(OAc) ₂ (4 mol%)	300	69
7	Ni(OAc) ₂ (4 mol%)	480	64
8	CoCl ₂ (4 mol%)	300	59

^aYield refers to purified product.

this period, crystals of the crude product formed which were collected by filtration, and recrystallized from EtOH to give the pure product.

Selected Physical and Spectroscopic Data of Isolated the Products

2,3-Diphenylquinoxaline (1). White solid; m.p.: 130-131 °C (Lit. [4a] 128-129 °C); ¹H NMR (CDCl₃): δ 7.31-7.43 (m, 6H), 7.51-7.58 (m, 4H), 7.82 (m, 2H), 8.17 (m, 2H); ¹³C NMR (CDCl₃): δ 128.5, 129.0, 129.4, 129.8, 130.3, 138.7, 141.1, 153.2.

6-Chloro-2,3-bis(4-methoxyphenyl)quinoxaline (8). Pale yellow solid; m.p.: 149-151 °C (Lit. [4d] 151 °C); ¹H NMR (CDCl₃): δ 3.90 (s, 6H), 6.79 (m, 4H), 7.48-7.57 (m, 4H), 7.72 (m, 1H), 8.10-8.16 (m, 2H); ¹³C NMR (CDCl₃): δ 54.6, 112.9, 128.2, 130.1, 130.4, 131.3, 131.5, 135.7, 140.0, 141.6, 153.1, 153.7, 160.5, 160.6.

RESULTS AND DISCUSSION

In order to find a suitable catalyst for the preparation of quinoxalines from aryl-1,2-diamines and 1,2-diketones, the condensation of benzene-1,2-diamine with benzil was chosen as a model reaction, and its behavior was studied in the presence of different catalysts in EtOH/H₂O at room temperature. The results are summarized in Table 1. As Table 1 indicates, ZnCl₂, Zn(OAc)₂, Mn(OAc)₂, Cu(OAc)₂, Co(OAc)₂, Ni(OAc)₂ and CoCl₂ gave relatively good yields of the product in long reaction times; however, by using (NH₄)₆Mo₇O₂₄·4H₂O, the product was produced in excellent yield in very shorter reaction time. Thus, (NH₄)₆Mo₇O₂₄·4H₂O was the catalyst of choice for all reactions.

In another study, the effect of different solvents upon the reaction was investigated (Table 2). The results showed that the examined solvents were not suitable separately. The

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satisfactory results were obtained when a mixture of EtOH and H₂O was used as solvent. The best ratio of EtOH/H₂O (v/v) was found to be 3/1.

To establish the generality and scope of our method, various aryl-1,2-diamines were reacted with some 1,2-diketones. The results are displayed in Table 3. As seen, the reactions proceeded efficiently and the respective quinoxalines

were obtained in good to excellent yields and short reaction times.

The effect of electron-releasing and electron-withdrawing substituents on the aromatic ring of aryl-1,2-diamines on the reaction was investigated. As Table 3 demonstrates, electron-releasing groups did not affected significantly on the yields and the reaction times (Table 3, entries 2, 3, 6 and 9). Using

Table 2. The Influence of Different Solvents (20 ml) on the Reaction of Benzene-1,2-diamine (1 mmol) with Benzil (1 mmol) in the Presence of (NH₄)₆Mo₇O₂₄·4H₂O (0.02 mmol) at Room Temperature

Entry	Solvent	Time (min)	Yield (%) ^a
1	EtOH	120	83
2	H ₂ O	120	77
3	THF	240	74
4	CHCl ₃	240	68
5	MeCN	240	72
6	DMSO	240	61
7	EtOH/H ₂ O (3/1)	15	95

^aYield refers to purified product.

Table 3. Synthesis of Quinoxaline Derivatives *via* the Condensation of Aryl-1,2-diamines with 1,2-Diketones Using (NH₄)₆Mo₇O₂₄·4H₂O at Room Temperature

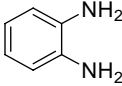
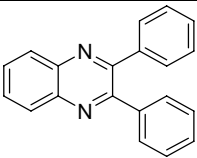
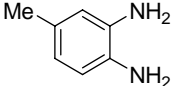
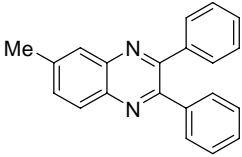
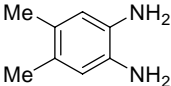
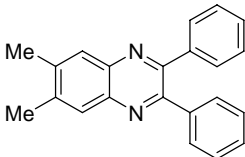
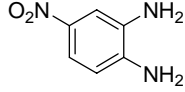
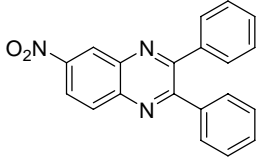
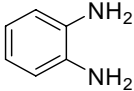
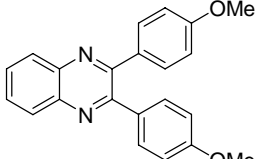
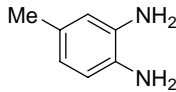
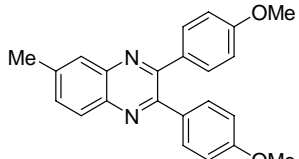
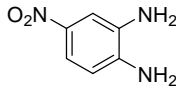
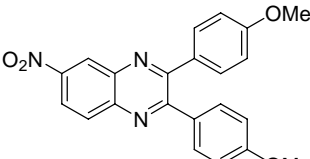
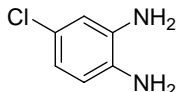
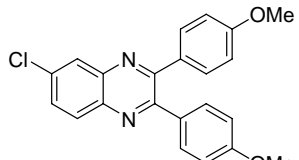
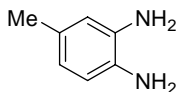
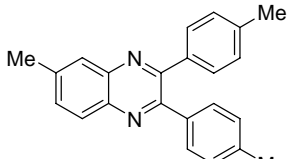
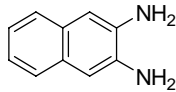
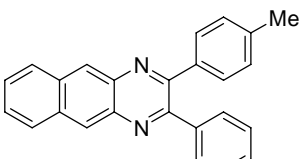
Entry	Diamine	Product	Time (min)	Yield (%) ^a	M.p. °C (Lit)
1			15	95	130-131 (128-129) [4a]
2			20	94	116-118 (117-118) [4a]
3			20	92	176-178 (172) [4b]

Table 3. Continued

4			30	75	189-191 (193-194) [4a]
5			15	91	146-147 (151-152) [4c]
6			15	92	130-132 (125-127) [4c]
7			30	73	189-191 (192-194) [4c]
8			20	90	149-151 (151) [4d]
9			15	93	139-140 (137) [4d]
10			20	91	196-198 (198) [4d]

^aYield refers to purified product.

Table 4. The Results of the Condensation of Benzene-1,2-diamine with Benzil in the Presence of Recycled $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}\cdot 4\text{H}_2\text{O}$

Entry	Cycle	Time (min)	Yield (%) ^a
1	-	15	95
2	1	15	94
3	2	15	91
4	3	15	92
5	4	15	90

^aYield refers to purified product.

aryl-1,2-diamines possessing electron-withdrawing substituents needed longer reaction times and the yields were lower (Table 3, entries 4 and 7). The presence of a halogen (Cl) on the aromatic ring of aryl-1,2-diamines had no significant influence on the reaction results (Table 3, entry 8). Moreover, it has been observed that the electronic properties of the aromatic ring of 1,2-diketones had negligible effect on the yields and the reaction times. When naphthalene-2,3-diamine was applied in the reaction, the excellent results were obtained (Table 3, entry 10).

Ease of recycling of the catalyst is one of the most advantages of our method. For the reaction of benzene-1,2-diamine with benzil no significant loss of the product yield was observed when $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}\cdot 4\text{H}_2\text{O}$ was used after four times recycling (Table 4).

CONCLUSIONS

In summary, this present procedure provides a new methodology for the preparation of quinoxalines from aryl-1,2-diamines and 1,2-diketones. The advantages of this method are extremely mild reaction conditions, short reaction times, high yields, simple experimental and isolation procedures, and compliance with the green chemistry protocols.

ACKNOWLEDGEMENTS

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