*Journal of the Korean Chemical Society*
**2009**, *Vol. 53, No. 6*
Printed in the Republic of Korea

# 인 몰립덴산을 촉매로 이용한 효과적이고 간단한 퀸옥살린의 One-Pot합성

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(접수 2009. 7. 7; 수정 2009. 10. 8; 게재확정 2009. 12. 1)

# Phosphomolybdic Acid-Catalyzed Highly Efficient and Simple One-Pot Synthesis of Quinoxaline

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(Received July 7, 2009; Revised October 8, 2009; Accepted December 1, 2009)

**요약.** 촉매로서 인 몰립덴산을 이용하여 일련의 퀸옥살린의 유도체를 높은 수율로 합성하였다. 이 방법의 장점은 실내 온도에서 간단한 조작, HPA 촉매의 재사용, 반응단계의 친환경적인 면이다.

**주제어:** 퀸옥살린, 실내온도, 인 몰립덴사, 1,2-Benzenediamines, 1,2-Diketones

**ABSTRACT.** A series of quinoxaline derivatives were efficiently synthesized in excellent yield using phosphomolybdic acid as a catalyst. The advantages of present methods are ambient reaction temperature, simplicity of operation, high atom economy, recyclability of HPA catalyst and ecofriendly nature of reaction medium.

**Keywords:** Quinoxaline, Room temperature, Phosphomolybdic acid, 1,2-Benzenediamines, 1,2-Diketones

## INTRODUCTION

Functionalized quinoxaline represents an important class of nitrogen-containing heterocycles and they constitute useful intermediates in organic synthesis. Quinoxaline derivatives are well known in pharmaceutical industries and have been shown to possess a broad spectrum of biological activities.[1-3] They exhibit anticancer, antibacterial, antifungal, anti-inflammatory and antiviral activities.[3-5] They also have been used as building blocks for synthesis of organic semiconductors,[6] electroluminescent materials,[7] and DNA cleaving agents.[8]

A number of synthetic strategies has been developed for the preparation of substituted quinoxaline from 1,2-benzenediamines and 1,2-dicarbonyl compounds by refluxing it in ethanol or acetic acid for 2 ~ 12 hours in 34 ~ 85% yield.[9] Numerous methods are available in the literature for synthesis of quinoxaline derivatives including Bi-catalyzed oxidative coupling of epoxides and 1,2-diamines,[10] cyclization of aryl amino oximes and α-dicarbonyl compounds under reflux in acetic anhydride,[11] condensation of *ortho* phenylenediamine and 1,2-dicarbonyl compounds in MeOH/AcOH under microwave irradiation.[12] solid phase synthesis.[13] molecular io-

dine as a catalyst,[14] ionic liquid.[15] CAN-catalyzed cyclocondensation reaction between 1,2-dicarbonyl compounds and 1,2-diamine,[16] and tandem oxidation of α-hydroxyl ketones using lead acetate[17] or $MnO_2$[18] as well as by grinding method.[19] However, most of the existing methodologies suffer from one or more drawbacks such as unsatisfactory product yield, critical product isolation procedure, expensive and inaccessible starting material, drastic conditions, and use of volatile organic solvents and expensive reagents which limits their use under the aspect of environmentally benign processes.

In order to overcome these difficulties of reported methods for synthesis of quinoxaline derivatives and as a part of our ongoing research[20] on phosphomolybdic acid-catalyzed reactions, we report herein a simple, highly efficient process for synthesis of biologically important quinoxaline derivatives by reacting 1,2-diamines with 1,2-diketones in presence of phosphomolybdic acid.

In recent decades, use of heteropoly acids (HPAs) as catalyst have become important in industries related with fine chemicals.[21a] HPAs are more active catalyst than conventional inorganic and organic acids for various reactions in solution.[21b,c] Solid HPAs have gained importance due to easy work-up procedures and minimization of waste generation. They are non-corrosive and environmentally benign, as they can be recycled and reused.[21d] Phosphomolybdic acid, one of the HPAs, is attractive catalyst not only for oxidation but also for acid-catalyzed reactions. It has very strong brönsted acidity and therefore is widely used for several types of reactions such as hydration of propylene and polymerization of hydro-furans.[21e-k] Acidities of heteropolyacids in solution have been studied by conductivity,[22] Hammett acidity constants,[23] and the $^{13}C$ shift of mesityl oxide.[24]

In the beginning, a systematic comparative study was carried out to find the catalytic activity of phosphomolybdic acid (PMA) compared with the other acid catalysts on the reaction rate as well as on the product formation. The results are summarized in *Table* 1.

From this study it was found that phosphomolybdic acid was superior to all other catalysts examined and gave good atom economy. Due to the keggin structure of phosphomolybdic acid the first and second protons dissociates completely and accelerate the rate of reaction. Keeping all these results in view, we decided to generalize the protocol by treating various 1,2-diketones with 1,2-benzenediamines in presence of phosphomolybdic acid. Quinoxaline synthesis of all the substrate was observed in 72 to 89% yield. This process is applicable for both aliphatic as well as aromatic 1,2-dicarbonyl compounds (*Table* 2).

*Table* 1. Catalyst effect on quinoxaline synthesis. Reaction of benzil and *ortho*-phenylenediamine in presences of various catalysts.

| Entry | Catalyst[a] | Time (Min) | Yield (%)[b] |
|---|---|---|---|
| 1 | $CaCl_2$ | 55 | 29 |
| 2 | $CoCl_2 \cdot 6H_2O$ | 75 | 22 |
| 3 | $FeCl_3$ | 60 | 37 |
| 4 | $SnCl_2 \cdot 5H_2O$ | 43 | 32 |
| 5 | $AlCl_3$ | 47 | 32 |
| 6 | $SnCl_2 \cdot 2H_2O$ | 50 | 70 |
| 7 | PMA | 10 | 89 |

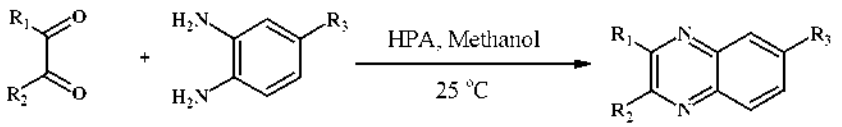
[a]Benzil = 0.01 mol, *ortho*-phenylenediamine, 0.01 mol. Catalyst 0.0002 mol, solvent-Methanol, temp. 25 °C. [b]Isolated Yield in %.

Recovery and reusability of catalyst are the demanding feature for the ecofriendly catalytic process. In this protocol we used heteropoly acid as recyclable catalyst. After completion of reaction, the heteropoly acid was recovered and reused. Even after three runs, we observed negligible change in the catalytic activity of phosphomolybdic acid (*Table* 3).

## EXPERIMENTAL SECTION

All commercial reagents are used as received without purification and all solvents were reagent grade. The reaction was monitored by TLC using on 0.25 mm E-Merck silica gel 60 $F_{254}$ precoated plates, which were visualized with UV light. Melting points were taken in open capillaries. The IR spectra were recorded on a Perkin-Elmer 257 spectrometer using KBr discs. $^1H$ NMR and $^{13}C$ NMR spectra

*Table* 2. Synthesis of substituted quinoxaline derivatives using HPA




1 2 3

| Entry | Diketone[1] | Diamine[2] | Quinoxalines[3] | Time[a] | Yield[b] |
|---|---|---|---|---|---|
| a | $R_1$, $R_2$ = Ph | $R_3$ = H | $R_1$, $R_2$ = Ph, $R_3$ = H | 10 | 89 |
| b | $R_1$, $R_2$ = Ph | $R_3$ = COPh | $R_1$, $R_2$ = Ph, $R_3$ = COPh | 11 | 87 |
| c | $R_1$, $R_2$ = Ph | $R_3$ = $NO_2$ | $R_1$, $R_2$ = Ph, $R_3$ = $NO_2$ | 14 | 73 |
| d | $R_1$, $R_2$ = Ph-*p*-Me | $R_3$ = H | $R_1$, $R_2$ = Ph-*p*-Me, $R_3$ = H | 12 | 84 |
| e | $R_1$, $R_2$ = Ph-*p*-OMe | $R_3$ = $CH_3$ | $R_1$, $R_2$ = Ph-*p*-OMe, $R_3$ = $CH_3$ | 10 | 87 |
| f | $R_1$, $R_2$ = Ph-*p*-Br | $R_3$ = H | $R_1$, $R_2$ = Ph-*p*-Br, $R_3$ = H | 16 | 85 |
| g | $R_1$, $R_2$ = Ph-*p*-Br | $R_3$ = $CH_3$ | $R_1$, $R_2$ = Ph-*p*-Br, $R_3$ = $CH_3$ | 13 | 88 |
| h | $R_1$, $R_2$ = Ph-*p*-Br | $R_3$ = $NO_2$ | $R_1$, $R_2$ = Ph-*p*-Br, $R_3$ = $NO_2$ | 17 | 80 |
| 8 | $R_1$, $R_2$ = Et | $R_3$ = H | $R_1$, $R_2$ = Et, $R_3$ = H | 09 | 75 |
| i | $R_1$, $R_2$ = Et | $R_3$ = $CH_3$ | $R_1$, $R_2$ = Et, $R_3$ = $CH_3$ | 08 | 77 |
| j | $R_1$, $R_2$ = H | $R_3$ = Ph | $R_1$, $R_2$ = H, $R_3$ = Ph | 10 | 72 |

[a]Time in minutes, [b]Isolated yield after crystalization.

*Table* 3. Recyclability of phosphomolybdic acid for quinoxaline synthesis.

| Run | Yield (%) |
|---|---|
| 1 | 89 |
| 2 | 89 |
| 3 | 88 |
| 4 | 87 |
| 5 | 87 |

were recorded on VXR-300 MHz instrument using TMS as an internal standard.

**General Experimental Procedure**

A mixture of 1.2-diketones (0.01 mole), 1.2-benzenediamines (0.01 mole) and phosphomolybdic acid (0.0002 mole), was stirred at room temperature in methanol (3.6 mL) for appropriate time mentioned in *Table* 2. The progress of reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, the reaction mass was concentrated to dryness. The solid was washed with water, the crude quinoxaline was crystallized from ethanol. Phosphomolybdic acid was recovered by concentrating the aqueous layer.

**Representative data (3a)**

**M.P: 123 - 125 °C, (lit. 126 - 127 °C)**

**IR (KBr):** 3051, 1506, 1493, 1478, 1439, 1392, 1342, 1287, 1243, 1219, 1177, 1155, 1075, 1058, 977, 771, 817, 801, 771, 730, 697 $cm^{-1}$.

**$^1$H-NMR ($CDCl_3$):** δ = 7.33- 7.44 (6H, m, Ar-H), 7.44-7.51 (4 H, m, Ar-H), 7.87-7.92 (2H, m, Ar-H), 8.14-8.20 (2H, m, Ar-H) ppm.

**$^{13}$C NMR ($CDCl_3$):** δ = 124.6, 129.2, 130.4, 131.2, 131.8, 137.7, 141.5, 151.6 ppm.

**Mass:** *m/z* = 282 ($M^+$).

**Elemental Analysis** : $C_{20}H_{14}N_2$ Calculated: C = 85.10; H = 5.00; N= 9.92. Found: C = 85.20; H = 4.91; N = 9.89.

## CONCLUSION

In conclusion, we have developed a simple, convenient and efficient method for synthesis of quinoxaline and its derivatives from various 1.2-diketones and 1.2-benzenediamines using safe, stable and easily available phosphomolybdic acid as a solid acid catalyst. The advantages of this procedure are simplicity of operation, short reaction time, high atom economy, recyclability of catalyst, and eco-

friendly nature.

We believe this will provide a better and more practical alternative to the existing methodologies for synthesis of Quinoxaline and its derivatives.

**Acknowledgments.** Authors are grateful to University Grant Commission, New Delhi and University of Mumbai for financial support. Thanks to Dr. S. T. Gadade, Principal, C. K. Thakur College for providing laboratory and other facilities.

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