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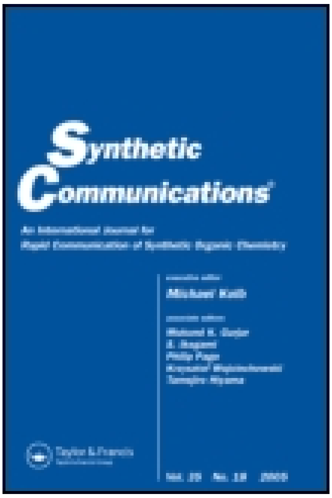

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Room-Temperature Synthesis of Hydroxylnaphthalene-1,4-dione Derivative Catalyzed by Phenylphosphinic Acid

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ROOM-TEMPERATURE SYNTHESIS OF HYDROXYLNAPHTHALENE-1,4-DIONE DERIVATIVE CATALYZED BY PHENYLPHOSPHINIC ACID

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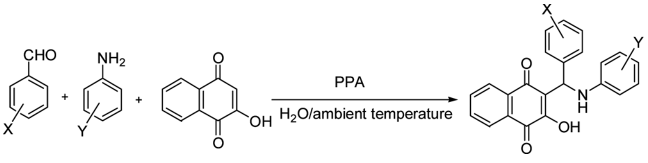
GRAPHICAL ABSTRACT



Abstract *An efficient one-pot synthesis of hydroxylnaphthalene-1,4-dione derivatives is accomplished by a three-component reaction of 2-hydroxynaphthalene-1,4-dione, aromatic aldehydes, and amines in water under ambient temperature catalyzed by phenylphosphinic acid. This method has the advantages of good yield, mild reaction conditions, simple workup, environmental friendliness and cost efficiency.*

Keywords Aldehyde; ambient temperature; amine, 2-hydroxy-1,4-naphthoquinone; phenylphosphinic acid; synthesis

INTRODUCTION

Mannich reaction is one of the most important carbon–carbon bond-forming reactions in organic synthesis because of its atom-economy advantages and application in biologically active molecule syntheses. β-Amino carbonyl compounds are valuable synthetic intermediates for various pharmaceuticals and natural products[1–3] that can be easily formed via a Mannich reaction.[4] Current research focuses on the three-component Mannich reaction from aldehydes, cyclohexanone or acetophenone, and amines that allows for a wide range of structural variations.

2-Hydroxy-1,4-naphthoquinone has been known for the past 4000 years, is found in many natural products, and has been employed as a synthetic intermediate for the preparation of numerous heterocyclic compounds. Molecules containing the heterocyclic quinone group constitute one of the most important classes

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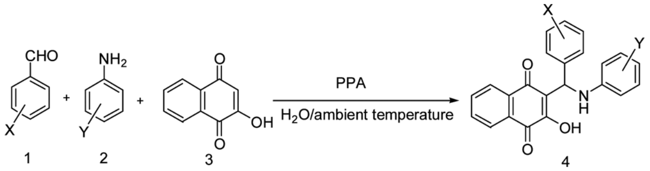


Scheme 1. Synthesis of hydroxylnaphthalene-1,4-dione derivatives.

of compounds in organic chemistry because of their biological properties such as antitumor, antibacterial, antifungal, and anti-inflammatory agents.[5–7] Thus, the development of new and simple synthetic methods for the preparation of the compounds containing napthoquinone fragments would be highly desirable.

Herein, we report a simple and efficient method for the preparation of hydroxylnaphthalene-1,4-dione derivatives by a three-component variant Mannich reaction of 2-hydroxynaphthalene-1,4-dione, aromatic aldehydes, and heterocyclic or carbocyclic amines. A literature survey showed us that the reaction has been improved in the presence of a catalyst. Dabiri et al. synthesized hydroxylnaphthalene-1,4-dione derivatives using Lewis acid $InCl_3$ as catalyst[8], and weak basic ionic liquids were also reported for this reaction[9]. These methods show varying degrees of success as well as limitations such as use of an excess of expensive reagents/catalysts, tedious workup procedures, or harsh reaction conditions. Thus, the development of an alternative procedure is in high demand.

Considering these reports, our program aimed at developing selective and simple methodologies for the preparation of hydroxylnaphthalene-1,4-dione derivatives. In this artical, a simple and efficient route using Bronsted acid–polyphosphoric acid (PPA) as catalyst under ambient temperature is developed (Scheme 1).

RESULTS AND DISCUSSION

Initially, based on the current report, two Lewis acids [$FeCl_3{\cdot}6H_2O$, $(CH_3COO)_2Zn{\cdot}2H_2O$] and two Bronsted acids ($NaHSO_4{\cdot}H_2O$, $C_6H_5PO_2H_2$) were chosen to catalyze the reaction of aniline, benzaldehyde, and 2-hydroxy-1,4-naphthoquinone in refluxing water to search for an effective catalyst. A summary of the experiment optimization is provided in Table 1. As can be seen in Table 1, $C_6H_5PO_2H_2$ was

Table 1. Optimization of the reaction conditions for synthesis of 2-hydroxy-3-[phenyl (phenylamino)methyl]naphthalene-1,4-dione

Entry	Catalyst (mol%)	Conditions	Time (h)	Yield (%)
1	$FeCl_3{\cdot}6H_2O$ (15)	H_2O (reflux)	4	58.0
2	$(CH_3COO)_2Zn{\cdot}2H_2O$ (15)	H_2O (reflux)	4	69.2
3	$C_6H_5PO_2H_2$ (15)	H_2O (reflux)	4	75.5
4	$NaHSO_4{\cdot}H_2O$ (15)	H_2O (reflux)	4	40.2
5	$C_6H_5PO_2H_2$ (20)	H_2O (reflux)	4	80.9
6	$C_6H_5PO_2H_2$ (25)	H_2O (reflux)	4	81.2
7	$C_6H_5PO_2H_2$ (20)	H_2O (rt)	4	80.5
8	$C_6H_5PO_2H_2$ (20)	H_2O (rt)	6	87.9
9	—	H_2O (rt)	4	<15.0

Table 2. Synthesis of 2-hydroxyl naphthalene-1,4-dione derivatives catalyzed by PPA

Entry	X	Y	Product	Time (h)	Yield (%)[a]
1	H	H	**4a**	6	87.9
2	4-HO	H	**4b**	6.5	86.4
3	4-NO_2	H	**4c**	6	85.0
4	H	4-Me	**4d**	7.5	87.0
5	4-HO	4-Me	**4e**	7.5	85.8
6	4-NO_2	4-Me	**4f**	6.5	80.0
7	H	4-F	**4g**	7.5	84.1
8	4-NO_2	4-F	**4h**	6	79.5
9	Lauraldehyde	H	**4i**	6	—

[a] Isolated yield.

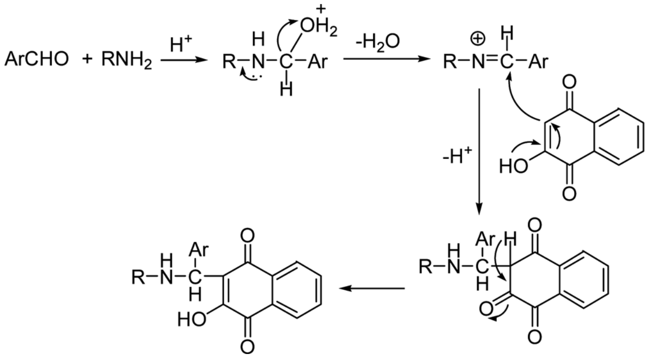
found to be the most efficient catalyst compared with other catalysts. The effect of the amount of catalyst was examined in this reaction. The results showed that a 20% mol amount of $C_6H_5PO_2H_2$ was sufficient to promote the reaction and larger amounts of the catalyst did not lead to any significant changes in the reaction yield. Also we studied the model reaction catalyzed by $C_6H_5PO_2H_2$ (20 mol%) at room temperature. Surprisingly, nearly the same yield was obtained, which indicated the reaction could be efficiently catalyzed by $C_6H_5PO_2H_2$ at ambient temperature. In addition, it should be mentioned that the yield was very poor without catalyst under ambient condition for this reaction (Table 1, entry 9).

With this optimized procedure in hand, we have extended the condensation reaction of aldehydes and 2-hydroxy-1,4-naphthoquinone under similar conditions, furnishing the respective 2-hydroxyl naphthalene-1, 4-diones. The optimized results are summarized in Table 2. Good yields (79.5–87.9%) were obtained using aromatic aldehydes and aromatic amines carrying electron-donating or electron-withdrawing substituents. Finally, the feasibility of employing aliphatic aldehydes for the synthesis of 2-hydroxy-1,4-naphthoquinone derivatives was also investigated. The result showed that aliphatic aldehyde reacted poorly under the same conditions.

To show the merit of the present work, we summarized the results for the synthesis of 2-hydroxy-3-[phenyl(phenylamino)methyl]naphthalene-1,4-dione obtained by other workers (Table 3). As shown in Table 3, although weak basic ionic liquids have high catalytic activity, they are very expensive. Compared with our catalyst, $InCl_3$ exhibits similar catalytic performance, but the reaction condition is harsh. So our method has the advantages of mild reaction conditions, low cost, and environment friendliness comparison with results in the literature.

Table 3. Comparison of the efficiencies of various catalysts used in the synthesis of 2-hydroxy-3-[phenyl(phenylamino)methyl]naphthalene-1,4-dione

Catalyst	Conditions/T/°C	Time	Yield (%)	Reference
$InCl_3$	Water/refluxing	6 h	90	[8]
Ionic liquids	Solvent-free/rt	5–9 min	89–91	[9]
$C_6H_5PO_2H_2$	Water/rt	6 h	87.9	This work



Scheme 2. Proposed reaction mechanism for the synthesis of hydroxyl naphthalene-1,4-dione derivatives catalyzed by PPA.

Although the detailed mechanism of the reaction remains to be fully clarified, a reasonable possibility is proposed in Scheme 2 according to the mechanism of Mannich reaction.

EXPERIMENTAL

All reagents were of analytical grade and purchased from Sinopharm Chemical Reagent Co., Ltd., and were used without further purification.

General Procedure for the Synthesis of Hydroxylnaphthalene-1,4-dione Derivatives

A mixture of aldehyde (5 mmol), amine (5 mmol), 2-hydroxynaphthalene-1,4-dione (5 mmol), and PPA (1 mmol) was stirred under ambient conditions in water (5 mL) for the specific time. The reaction was monitored by thin-layer chromatography (TLC). After completion, the reaction mixture was filtered, and the precipitate was purified by recrystallization in aqueous EtOH (60 %, v) to afford the product.

All the products are known compounds. The desired pure products were characterized by analytical and spectral data (including infrared spectrum (IR), ^{1}H and ^{13}C nuclear magnetic resonance (NMR), elemental analyses, melting point) and by comparison of their physical and spectral data with those of known compounds.[4,5]

2-Hydroxy-3-[phenyl(phenylamino)methyl]naphthalene-1,4-dione (4a)

Orange powder; mp: 142–145 °C; IR (KBr, cm^{-1}): 3431, 3319, 1660, 1639; ^{1}H NMR (300 MHz, DMSO-d_6): δ=6.00 (s, 1H, CH), 7.26–8.09 (m, 14H, ArH and NH), 9.27 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ=37.4, 113.5, 123.9, 126.0, 126.6, 128.5, 129.7, 130.4, 132.8 133.2, 133.7, 135.1, 138.1, 146.2, 156.9, 157.7, 181.9, 184.2. Anal. calcd. for $C_{23}H_{17}NO_3$: C, 77.73; H, 4.82; N, 3.94. Found: C, 77.66; H, 4.72; N, 3.87.

CONCLUSION

A simple and efficient method for the synthesis of 2-hydroxy-1,4-naphthoquinone derivatives using PPA as catalyst in water under room temperature has been developed, which affords good yield in mild reaction conditions with a simple procedure that is environmentally friendly and utilizes an inexpensive catalyst.

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher’s website.

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