CMC Catalyzed Multicomponent Mannich Reaction for Synthesis of Lawsone Family Pigments

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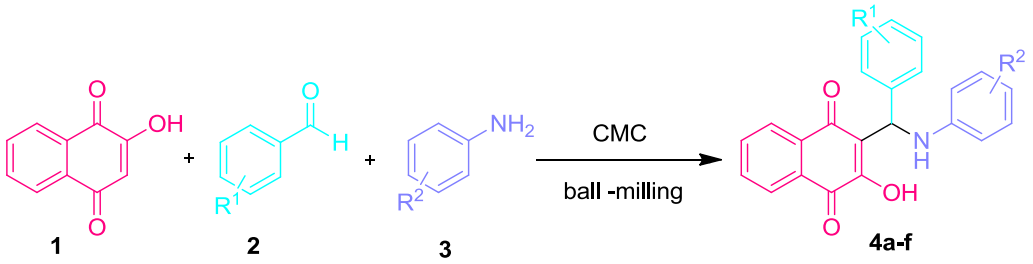
Abstract

A clean, efficient and facile one-pot protocol was utilized for the synthesis of Lawsone family pigments by three-component Mannich reaction with different amines and aromatic aldehydes using an inexpensive catalyst under ball milling method.

Keywords: Lawsone, CMC, Mannich reaction, solvent free

1. Introduction

Molecules with the naphthoquinone structure receives great attention because of their biological properties [1], industrial application and as intermediates in heterocyclic compounds synthesis. 2-hydroxy-1,4-naphthoquinone (HNQ: Lawsone) is the principal active ingredient of the henna plant [2]. Three component Mannich reaction is a one-pot reaction of a non-enolizable aldehyde, a primary or secondary amine and an enolizable carbonyl compound. This reaction provides β-aminocarbonyl compounds [3]. Herein, we wish to report the synthesis of these derivatives under solvent-free and mild reaction conditions (Scheme 1). For first time, we report here a fast, efficient and green route for synthesis of the Lawsone derivatives under ball milling condition and using Carboxymethyl Cellulose (CMC) as a heterogeneous catalyst. CMC is the water-soluble derivative of cellulose with carboxymethyl groups (-CH_2-COOH) that is used widely in medicine, cosmetics and foods [4]. CMC is inexpensive, biodegradable, and non-toxic with good chemical stability [5]. Advantages of using mechanochemistry are shorter reaction times and reduction of waste production especially from solvents used in the reactions or during the separation and purification [6].



Scheme 1. Synthesis of 2-hydroxy-1,4- naphtoquinone derivatives.

2. Experimental

2.1. General

Melting points were determined on an Electrothermal 9100 apparatus. Reactions were performed by using a ball mill MM-400 from RETSCH company equipped with stainless steel grinding jars (10 mL). Two stainless steel balls with 7 mm diameter were used, and the milling frequency was set at ca. 28 Hz.

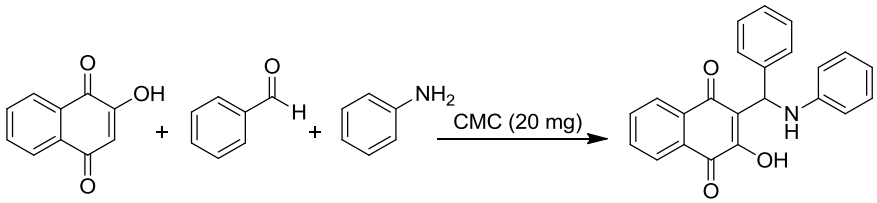
2.2. General procedure for synthesis of 2-hydroxy-1,4-naphtoquinones 4

A mixture of 2-hyroxy-1,4-naphtoquinone (1 mmol), an amine (1 mmol), an aldehyde (1 mmol) and CMC (20 mg) were ball milled for the appropriate time. After Completion of the reaction confirmed by TLC, $CHCl_3$ was added, and the catalyst was separated by filtration. The solvent was evaporated at reduced pressure to afford the pure product (**4a-f**). The catalyst reused after washing with EtOAc and acetone and drying at 70 ℃.

3. Results and Discussion

At first, the three-component reactin of lawsone, benzaldehyde **2** and aniline **3** in the presence of 20 mg CMC was studied as model reaction to optimize the reaction conditions (Table 1). Different solvents were screened in the model reaction.

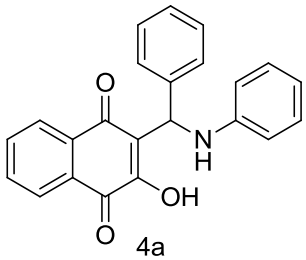
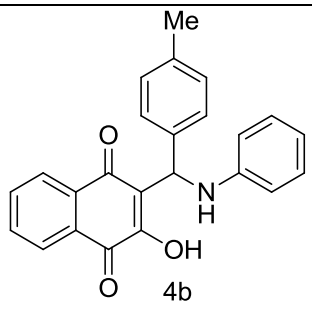
Table 1. Model reaction and screening of the reaction conditions**.**

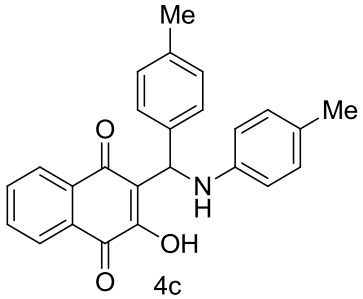
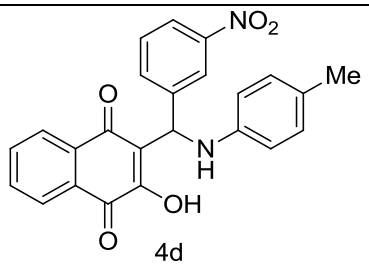
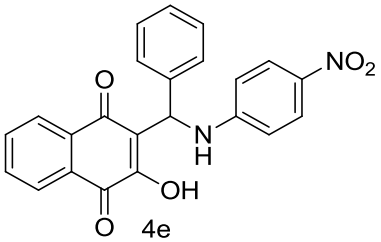
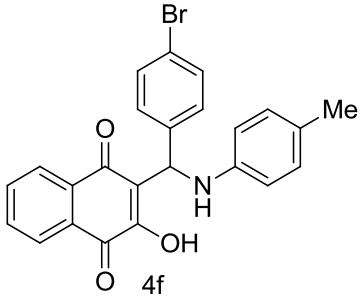


Entry	Condition	T (°C)	Time (h)	Isolated Yield (%)
1	H_2O	r.t	3.5	70
2	EtOH	r.t	6	65
3	CH_3CN	r.t	8	32
4	$CHCl_3$	r.t	12	20
5	H_2O	reflux	3.5	45
6	Ball-milling	r.t	3 min	96
7	Solvent-free	r.t	24	trace

Under the optimized conditions (entry 6, Table 1), various aromatic aldehyde and amines containing either electron-withdrawing or electron-donating groups for preparation of 2-hydroxy-1,4-nahtoquinone derivatives were employed. The results are summarized in Table 2.

Table 2. Synthesis of Lawsone derivatives in the presence of CMC[a].

Entry	R^1	R^2	Product	Time (min)	Yield[b] (%)	Mp (℃)
1	H	H	 4a	3	96	145
2	4-Me	H	 4b	5	95	146

3	4-Me	4-Me	 4c	7	91	144
4	3-NO_2	4-Me	 4d	2	96	147
5	H	4-NO_2	 4e	15	90	185
6	Br	Me	 4f	9	95	150

[a] Reaction conditions: 2-hyroxy-1,4-naphtoquinone (1 mmol) , amine (1 mmol), aldehyde (1 mmol), CMC (20 mg).
[b] Isolated yield

4. Conclusions

In summary, we have described that CMC can be used as an available and environmentally friendly catalyst for synthesis of Lawsone derivatives under ball mill condition. The advantages of this procedure are solvent-free conditions, short reaction times, high yield, easy work up, recovery and reusability of the catalyst.

Acknowledgements

The authors gratefully acknowledge from Iran University of Science and Technology (IUST) for partial financial support of this work.

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