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Facile synthesis of aminonaphthoquinones Mannich bases by

non-catalytic multicomponent reaction

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ABSTRACT

Mannich bases are formed in a non-catalytic multicomponent reaction, which is promoted by ultrasound irradiation. The procedure avoid the use of toxic solvents, catalyst and purification, generating the desired compounds in excellent yields and short reaction times.

GRAPHICAL ABSTRACT



KEYWORDS: aminonaphthoquinone, green reaction, lawsone, Mannich bases, ultrasound irradiation

Introduction

Naphthoquinones are important compounds that are widely distributed in different families of plants, fungi and some animals.^[1] Many naphthoquinones and synthetic analogues have interesting biological activities like antibacterial, antifungal, antiviral, trypanocidal, antimalarial, leishmanicidal, molluscicidal and insecticidal properties.

Also their anticancer activity has attracted research interest.^[2] An important derivative of 1,4-naphthoquinone is 2-hydroxy-1,4-naphthoquinone or lawsone, commonly known as henna, this has been used in cosmetics as hair dye, body paint and tattoo dye. The leaves are used as a prophylactic against skin diseases,^[3] another very interesting use is as ultraviolet filter in sunscreen formation.^[4] Moreover, lawsone is associate with antitumor, antibacterial and antifungal activities.^[5] Also, there is reported that amino substitution in 1,4-naphthoquinone increase the biological activity.^[6]

3-(Aminomethyl)-2-hydroxy-1,4-naphthoquinone known as Mannich base was first synthesized in 1947 by Leffler and Hathaway by the condensation reaction of lawsone, a nonenolizable aldehyde and a primary or secondary amine. They also described their antimalarial activity.^[7a] Vaughan and coworkers reported the reaction between lawsone, several amines with formaldehyde and acetaldehyde, they show moderat to low yields.^[7b] Mannich reaction is a classic method for the preparation of α -amino carbonyl compounds and a principal alternative to generate C-C bonds.

There is reported improvements in the three component reaction to prepare Mannich Bases.^[8] Reactions carried out in Brönsted acids,^[9] Lewis acids,^[10] Lewis bases,^[11] or organic molecules^[12] as catalysts have shown moderate yields but long reaction times, also it is required toxic reagents or catalysts that are atmosphere sensitive. Recently, Allochio Filho and coworkers presented the synthesis of aminonaphthoquinones derived from lawsone via a multicomponent Mannich reaction in aqueous media utilizing a Brønsted acid-surfactant catalyst (BASC) at room temperature, in this case the yields were from moderate to good but the reaction times were between 12-216hours.^[13a] Mannich reaction was used in the synthesis of 3,4-dihydro-2*H*-naphtho[2,3-*e*][1,3]oxazine-5,10-dione derivatives using ionic liquid, ^[13b] and also in the synthesis of naphthoquinone dendrimers as potential antimalarial drugs.^[13c]

Multicomponent reactions have received considerable interest since they show good atom economy, they are highly convergent, and require minimal time and effort to obtain complex molecules.^[14] Ultrasound irradiation is considered an alternative source of energy and has been established as a versatile technique in synthetic chemistry. The phenomenon observed is known as "acoustic cavitation", and generates high temperatures and pressures in localized zones of the liquid creating a rate acceleration in many organic reactions.^[15]

We present the synthesis of Mannich Bases via a multicomponent reaction (threecomponent) ultrasound assisted between lawsone (1), benzaldehyde (2) and primary amines (3ae), Scheme 1. Initial experiments carried out using 2-hydroxy-1,4-naphthoquinone (1), benzaldehyde (2) and 3-chloroaniline (3a) to optimize the experimental conditions. The results are summarized in **Table 1**. The methodology presented is easy, atom-economical, fast and environmentally benign.

Results and Discussion

The expected Mannich base 4a was obtained in good yields using 15, 30 and 60minutes of irradiation time (**Table 1**, entries 1-3). The results revealed that irradiation time higher than 15minutes has not significant effect, therefore, subsequent experiments were performed at 15minutes of irradiation considering the importance of minimized energy requirements in order to present an economic and environmentally friendly reaction. We also tested different solvents (**Table 1**, entries 4-6), these were selected based on their health, safety and environment criteria.^[16] The best result was obtained with ethanol, 90%, (**Table 1**, entry 1), methanol slightly decreased the yield, 80% (entry 4), finally water and water:ethanol mixture yielded the expected product in 43% and 40%, respectively (entries 5,6).

As mentioned above, Brönsted acids, Lewis acids and bases, or catalysts improved the yields and reaction times.^[10–12] Therefore, we also investigated the effect of CeCl₃•7H₂O. **Table 2** shows the yield of 4a with different amounts of catalyst (entries 1-4). Contrary to the results reported in literature,^[10b,c] the reaction efficiency decreased. In fact, the amount of the corresponding compound was 81% with 0.1 mmol of catalyst, 79% with 0.2 mmol and 65% with 0.3 mmol. In order to corroborate this fact, we performed the same experiments with 2,4-difluoroaniline 3d, in this case the Mannich base 4d was obtained in 28, 26 and 13%, respectively (**Table 2**, entries 6-8). The reduction is attributed to the formation of two additional products, one of them in substantial amount. According to lawsone reactivity, this secondary product

corresponds to Michael addition of aniline to 2-hydroxy-1,4-naphthoquinone. To confirm this theory, a reaction between 2-hydroxy-1,4-naphthoquinone (1) and 2,4-difluoroaniline (3d) was carried out. The compounds obtained in both reactions (with and without benzaldehyde) had the same melting point, color and retention factor (Rf) indicating that the reaction mechanism with CeCl₃•7H₂O corresponds to Michael addition, generating 2-hydroxy-3-(2,4-difluoroanilino)-1,4-naphthoquinone.

Table 3 shows the results of the synthesis of five Mannich bases under optimized conditions, also the results of reaction under stirring at room temperature were presented. In both cases, the corresponding Mannich bases, 4a-e, were obtained in good yields, above 80%, but the reaction time is considerable less using ultrasonic irradiation, from 15hours to 15minutes .

A possible mechanisms for the formation of 4a is presented in Scheme 2. First, nucleophilic attack of 3-chloroaniline (3a) to the electrophilic carbon in benzaldehyde (2) with the subsequent dehydration generated the imine intermediate (1b). Then, an excess of amine promoted the lawsone enol form (1a) which attacked the imine 1b to yield the desired product 4a.

As mentioned, the presence of $CeCl_3 \cdot 7H_2O$ facilitated the Michael reaction, we assume that the catalyst coordinated with the lawsone oxygen activating the C-2 position in the 2-hydroxy-1,4-naphthoquinone, where the aniline attacked to generate the secondary product.

Conclusion

To conclude, we have developed a non-catalytic effective procedure to prepare Mannich bases lawsone derivatives using one-pot synthesis promoted by ultrasound irradiation with short reaction times, high yields, and cleaner products by avoiding by-products formation. As a matter of fact, the products obtained were recovered by filtration without further purifications. Mannich bases lawsone derivatives are important intermediates in the synthesis of compounds with pharmacological properties, therefore this procedure represents a potential technique for synthesis of compounds with important applications.

Experimental

General experimental

All chemicals were obtained from commercial suppliers and used without further purification. Melting points were determined using a Fisher-Scientific Melting Point Tester and were no corrected. Silica gel (Kieselgel 60 F₂₅₄, Merck) plates were used for thin layer chromatography (TLC). ¹H NMR spectra were recorded on Varian Mercury 400 spectrometer at 400MHzand ¹³C spectra were recorded at 100MHz using DMSO-d₆ and CDCl₃ as solvent. Chemical shifts are reported in parts per million (ppm, δ), relative to the internal standard of tetramethylsilane (TMS). Mass spectra were performed on a Jeol JMS-100D mass spectrometer equipped with electrospray ionization (ESI) interface and ion trap analyzer. The ultrasound assisted reactions were carried out in a Branson 5510 bath cleaner (45 KHz, 135W).

General synthesis

To a suspension of lawsone (2.5 mmol) and primary amine (2.75 mmol, 3a-e) in ethanol (7.5mL) at room temperature, benzaldehyde (3 mmol) was added. The mixture was placed in the center of an ultrasound cleaner bath at room temperature. The progress of the reaction was monitored by TLC. After reaction completion, the reaction mixture was cooled in an ice-bath and the solid formed was filtered, washed with cold ethanol and dried under vacuum.

Characterization data for compounds 4a

2-[(3-chlorophenylamino)phenylmethyl]-3-hydroxy-1,4-naphthoquinone (4a).



Light green powder, Mp, 136°C. ¹H NMR (400MHz, CDCl₃): δ (ppm) 10.02 (s, 1H), 8.52 (s, 1H), 8.07 (d, 2H), 7.75 (t, 1H), 7.68 (t, 1H), 7.51 (d, 2H), 7.33 (t, 2H), 7.26 (t, 1H), 7.05 (t, 1H), 6.74 (s, 1H), 6.68 (d, 1H), 6.62 (d, 1H), 6.13 (s, 1H); ¹³C NMR (100MHz, CDCl₃): δ (ppm) 135.3, 133.3, 130.3, 128.7, 127.6, 127.0, 126.6, 126.4, 118.3, 113.7, 111.9, 52.7. IR (ATR): 3441, 3319, 1660, 1599, 1497, 1351, 1274, 1009, 704cm ⁻¹. ESI-MS: m/z [M]⁺ calcd for C₂₃H₁₆ClNO₃: 389.0819; found: 389.0813.

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characterization.

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Entry	Time (min)	Solvent	Yield (%)
1	15	EtOH	90
2	30	EtOH	89
3	60	EtOH	91
4	15	МеОН	80
5	15	H2O	43
6	15	H2O:EtOH (1:1)	40

Table 1. Synthesis of 4a under various conditions^a.

^aLawsone (2.5 mmol), benzaldehyde (3 mmol) and 3-chloroaniline (2.75 mmol).

Entry	Product	CeCl ₃ •7H ₂ O	Yield (%)
1	4a	0	94
2	4a	0.1	81 ^b
3	4a	0.2	79 ^b
4	4a	0.3	65 ^b
5	4d	0	80
6	4d	0.1	28 ^b
7	4d	0.2	26 ^b
8	4d	0.3	13 ^b

Table 2. Effect of CeCl₃•7H₂O amount in synthesis of Mannich bases^a.

^aLawsone (2.5 mmol), benzaldehyde (3 mmol) and aniline (2.75 mmol).

^bThe isolated product presented two additional products.

Entry	Primary amine	Product	Yield (%) ^b	Yield (%) ^c
1	3-Chloroaniline	4a	93	94
2	4-Nitroaniline	4b	98	90
3	2,4-Dichloroaniline	4c	94	91
4	2,4-Difluoroaniline	4d	66	80
5	Hexylamine	4e	83	90

Table 3. Mannich reaction of lawsone, primary amine and benzaldehyde.^a

^aLawsone (2.5 mmol), benzaldehyde (3 mmol) and primary amine (2.75 mmol).

^bThe reagents were mixed and left stirring at room temperature for 15 hours.

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"The reagents were mixed and irradiated under ultrasonic irradiation for 15 minutes.







