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First synthesis of aminonaphthoquinones derived from lawsone in a colloidal dispersion system created by a Brønsted acid-surfactant-combined catalyst in water: An environmentally friendly protocol

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ABSTRACT

Environmentally friendly one-pot protocol was developed for the first synthesis of aminonaphthoquinones derived from 2-hydroxy-1,4-naphthoquinone (lawsone) via a multicomponent Mannich reaction in aqueous media using a catalytic amount of dodecyl benzenesulfonic acid (DBSA), exploring a Brønsted acid-surfactant catalyst (BASC) concept, at room temperature.

The Mannich reaction and related reactions provide one of the most basic and useful methods for the synthesis of β-aminocarbonyl compounds, which constitute various pharmaceuticals, natural products, and versatile synthetic intermediates. A large number of biologically active compounds with nitrogen in the structure are found in nature [1].

The science of organic synthesis is constantly being developed and providing new methodologies to obtain every possible type of molecule. The scientific community has been looking for mild, facile, economic and ecological procedures that lead to a desired product with good chemical yields and low reaction times, factors which are in agreement with the green chemistry concept.

One subject that has drawn the attention of researchers interested in green chemistry is that of multicomponent reactions (MCRs) because of their high atom economy, reproducibility, and versatility, among others [2]. Typically, MCRs are one-pot reactions with three or more components in which the majority of the reactant atoms are incorporated in the product structure [3]. Several MCRs are found in the literature using the most varied types of reagents. To construct nitrogen-containing molecules, the imine-based MCRs are the most explored type in recent years [4]. Usually, imines are electrophiles in MCRs.

The Mannich reaction is an important example of an imine-based MCR because it provides β-aminocarbonyl compounds useful synthetic intermediates for several pharmaceuticals and natural products. The one-pot reaction of a non-enolizable aldehyde, a primary or secondary amine and an enolizable carbonyl compound is classified as a classical, multicomponent Mannich reaction.

Additionally, in regard to biological properties, the pharmacophoric quinone group receives great attention due to its extensive use and its presence in compounds with confirmed antitumour, molluscicidal, leishmanicidal, anti-inflammatory and antifungal activities [5], as well as its industrial applications and their potential as intermediates in the synthesis of heterocyclic compounds. Lawsone is a *p*-naphthoquinone containing an enol group, which is susceptible to a multicomponent Mannich reaction.

Recently, our research group has described the multicomponent Mannich reaction with lawsone in different non-aqueous solvents [6]. A Mannich reaction in aqueous media using lawsone and $InCl_3$ as a catalyst under reflux was reported by Dabiri and co-workers [7]. Moreover, Shaterian and co-workers [8] employed ionic liquids as catalysts in a multicomponent Mannich reaction derived from lawsone.

Regarding environmentally friendly factors, the choice of the solvent is quite important. In view of sustainable chemistry, water is the best choice, despite possible problems with the solubility of substrates.

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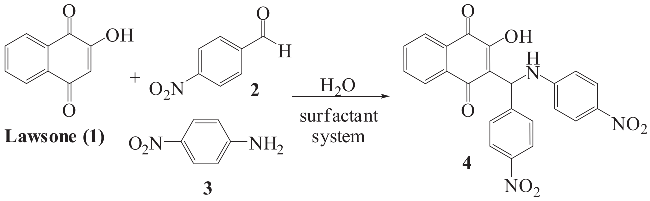
Table 1
Effect of catalyst/surfactant on the synthesis of aminonaphthoquinone **4**.



Entry	Surfactant system	Time (h)	Yield (%)
1	SDS		
2	*p*-TsOH/SDS	26	Not isolated
3	DBSA	48	71
4	Tween 80®	48	57

Otherwise, water can enhance the reactivity and selectivity of organic reactions of hydrophobic substances due to the hydrophobic effect [9].

It is known from the literature that the Mannich reaction in aqueous media is mainly catalysed by Lewis acids [10], such as triflates and chlorides, and Brønsted acids [11], e.g., sulfonic, hydrochloric and heteropolyacids. However, vigourous stirring and high temperatures normally essential to a reaction's success due to the poor solubility of the substrates [12].

To improve the experimental conditions of reactions using water as the medium, surfactants can be used to build micelles and provide better chemical yields and shorter reaction times. This can be explained by certain factors: (a) the distance between molecules of the reactants is diminished by the presence of droplet-like vesicles of the surfactant, which trap the substrates; and (b) the hydrophobicity of the products allows them to interact with the core of the micelles and shift the equilibrium towards progress of the reaction [9].

Generally, the surfactants (ionic and non-ionic) are substances with long, hydrophobic chains and hydrophilic, polar extremities, e.g., sodium dodecyl sulphate (SDS) and dodecyl benzenesulfonic acid (DBSA). Tween 80® is a crown ether, and polysorbate is derived from sorbitol and very useful as a phase-transfer catalyst, non-ionic surfactant and important carrier of cations of varying sizes through the micellar medium [13]. It is a highly polar compound employed as a catalyst in various types of reactions [13].

In aqueous media, the surfactants organise themselves, creating droplet-like vesicles. The long, hydrophobic chains are situated inside the vesicles structure, while the polar and hydrophilic extremities align on the outside surface, interacting with water and providing the most stable configuration possible. Usually, the organic reaction occurs inside the droplet-like vesicles, in a colloidal dispersion system created by the surfactants. Manabe and Kobayashi [11] described the multicomponent Mannich reaction of aldehydes, amines and ketones in aqueous media for the synthesis of β-aminoketones using DBSA as a catalyst.

However, there were no studies in the literature reporting the synthesis of β-aminonaphthoquinone compounds derived from lawsone via a water-mediated multicomponent Mannich reaction using a colloidal dispersion system. In this context, we started to develop a methodology to reach those compounds in a greener manner, using aqueous media with surfactants and Brønsted acids. As a model reaction, lawsone (1), *p*-nitrobenzaldehyde (2) and *p*-nitroaniline (3) were chosen to establish the surfactants efficiency in terms of reaction times and chemical yields.

We studied the influence of the SDS/*p*-TsOH, DBSA and Tween 80® systems in a model reaction and the results are presented in Table 1. The reactions were performed with lawsone (1 mmol), *p*-nitrobenzaldehyde (1 mmol) and *p*-nitroaniline (1 mmol) with 20 mol% catalyst (Entries 13) in H_2O (10 mL) at room temperature. The quantity of Tween 80® (entry 4) was established based on its critical micelle concentration (CMC) 0.012 $mmol\cdot L^{-1}$ (0.012 mol%) in water at room temperature [14].

As presented in Table 1, the most effective catalyst for the multicomponent Mannich reaction studied above was DBSA. This reaction possibly occurs due its Brønsted acid/surfactant combined (BASC) activity [11b] because DBSA establishes a stable colloidal dispersion and donates a H^{+} species simultaneously.

Acid catalysis is usually required for the Mannich reaction. Thus, when SDS was tested as a surfactant, *p*-TsOH was also added as a proton source (Entry 2, Table 1). However, after the complete consumption of lawsone, shown by chromatography, a complex mixture of products was observed. On the other hand, the result obtained for Tween 80® (Entry 4, Table 1) shows that the surfactant is very efficient for the

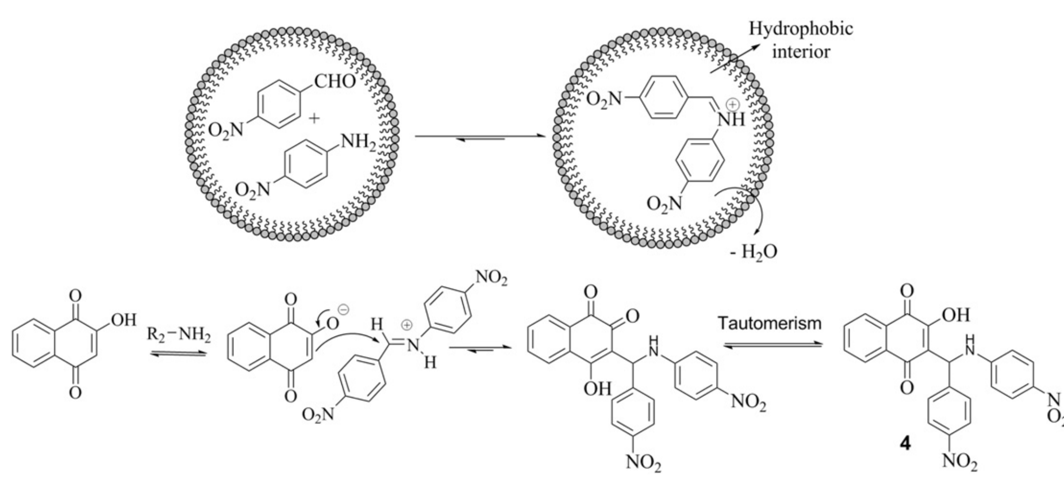


Fig. 1. Interference of the droplet-like vesicles of surfactants during the reaction.