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A simple and convenient method for synthesis of new aminonaphthoquinones derived from lawsone by catalytic multicomponent Mannich reaction

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ABSTRACT

A clean, efficient and facile one-pot protocol was developed for the synthesis of a series of new aminonaphthoquinones derived from 2-hydroxy-1,4-naphthoquinone (lawsone) by three-component Mannich reaction using catalytic amount of *p*-TsOH in CH_3CN, at room temperature. At the present work, we improved the yield and significantly reduced the reaction time for several Mannich reactions with different amine and aromatic aldehydes using a non-expensive, mild catalyst and suitable solvent.

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Nitrogen-containing compounds are ubiquitous in nature and many of them are biologically active. The nitrogen-containing units of these molecules play important roles in their bioactivity (Fig. 1). For the synthesis of these nitrogen-containing building blocks, the Mannich reaction is one of the most common and convenient routes.[1]

The science of organic synthesis is constantly enriched by the improvement of synthetic methodologies. The paradigms of organic synthesis have shifted from the traditional concept using only chemical yield to define efficiency to one in which the economic and ecological values are also considered.

Recently, multicomponent reactions (MCRs) have received considerable interest among synthetic chemists for the construction of complex molecules.[2] MCRs usually show good atom economy. When compared with conventional organic reactions, MCRs are advantageous because they are highly convergent, requiring minimal time and effort to achieve structural complexity. Thus, MCRs are also considered green chemical processes.

Over the years, hundreds of MCRs have been reported in the literature. These reactions include imine-based MCRs (involving imines as a substrate or an intermediate), which have received considerable attention in recent years.[3] This sudden rise in the popularity of imine-based MCRs may be due to two factors: (i) the substrate-dependent reactivity of imines and (ii) the commercial availability of several hundred amines and aldehydes, which are required to access many imines, thus leading to diverse molecular scaffolds. Therefore, imines are considered to be versatile building blocks for diversity-oriented synthesis using MCRs. Imines primarily act as electrophiles in MCRs. Among these reactions, the Mannich reaction is one of the most widely used three-component reactions which utilizes a non-enolizable aldehyde, a primary or secondary amine and an enolizable carbonyl compound. The resulting β-amino carbonyl compounds are important synthetic intermediates for various pharmaceuticals and natural products and have found wide application in organic synthesis.

Molecules with the quinone structure constitute one of the most interesting classes of compounds in organic chemistry because of their biological properties, including antitumor, molluscicidal, leishmanicidal, anti-inflammatory and antifungal activities (Fig. 2),[4] as well as their industrial applications and their synthetic potential as intermediates to obtain heterocyclic compounds.

Considering the incorporation of amino groups or a nitrogen atom into naphthoquinones often results in increased anticancer,[5]—molluscicidal[6] and antibacterial activities,[7] part of our programme aimed at the synthesis of new aminonaphthoquinone derivatives with potential biological activity. We are currently investigating the synthesis of lawsone **1** derivatives via a simple

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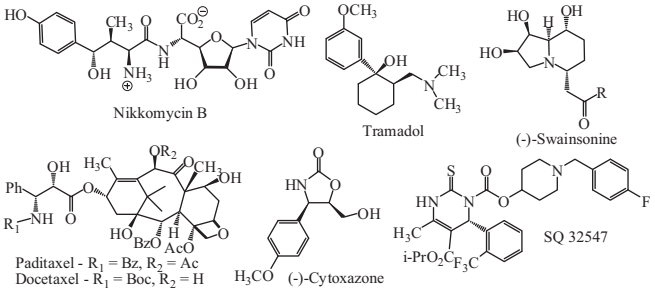


Figure 1. Nitrogen containing bioactive compounds.

and atomically efficient three-component condensation reaction of lawsone, aromatic aldehydes and aromatic and alicyclic amines in the presence of a catalyst at room temperature (Scheme 1).

The Mannich reaction of lawsone was first described by Leffer and Hathaway in 1948,[8] and was performed because certain 2-hydroxy-3-alkyl-1,4-naphthoquinone compounds had shown antimalarial activity. However, this methodology has not been widely utilized to synthesis these molecules.

Our research group has recently described the use of the Mannich reaction to react lawsone with various aldehydes and amines in ethanol at room temperature using the procedure described in the literature, with minor modifications.[9] It should be noted that the reaction times range from 12 to 48 h depending on the aldehyde and the amine used. Subsequently, Dabiri and co-workers published the synthesis of aminonaphthoquinones using the Mannich reaction in an aqueous medium under reflux using $InCl_3$ as a catalyst, and the reaction times varied from 4 to 7.5 h.[10] Recently, Shaterian and co-workers[11] employed ionic liquids as catalyst in multicomponent Mannich reaction derived from lawsone.

From our work on the development of the green Mannich reaction, the choice of an appropriate reaction medium is of crucial importance for a successful synthesis. Initially, the three-component reaction of lawsone **1**, *p*-nitrobenzaldehyde **2** and *p*-nitroaniline **3** was investigated as a simple model to establish the feasibility of the strategy and optimize the reaction conditions (Scheme 2).

Experimental protocols were initially tested as described in previous report.[12] The best results were obtained using a slightly modified procedure employing 10 mol % of excess of amine in an order to increase the nucleophilicity of lawsone by deprotonation and 20 mol % of excess of aldehyde which helps to shift the equilibrium towards the formation of the iminium ion.

Initially, different solvents were screened in the model reaction, and the chemical yields and reaction times were evaluated with acetonitrile giving the best results (entry 3, Table 1).

Subsequently, a study was conducted with various Brønsted–Lowry and Lewis acids to assess the effectiveness of these compounds as catalysts for the model reaction (Table 2). Again, the

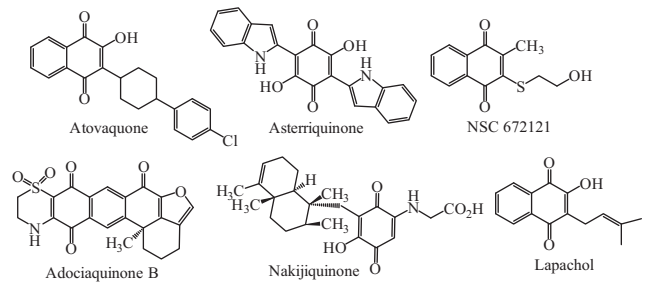
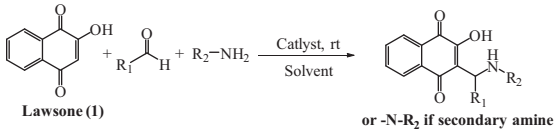
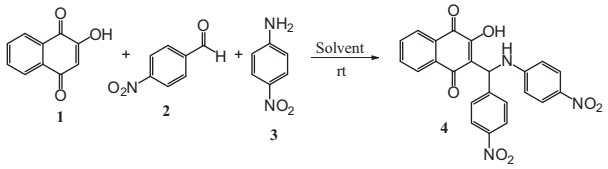


Figure 2. Quinones with biological activity.



Scheme 1. Synthesis of lawsone derivatives.



Scheme 2. Optimization of multicomponent Mannich reaction.

Table 1
Solvents screening for model reaction in Scheme 2[a]

Entry	Solvent/volume[b]	Time (h)	Yield (%)
1	EtOH (10 mL)	24	82
2	H_2O (5 mL)	26	84
3	CH_3CN (3 mL)	6	98
4	Et_2O (4 mL)	26	87
5	Toluene (4 mL)	26	73

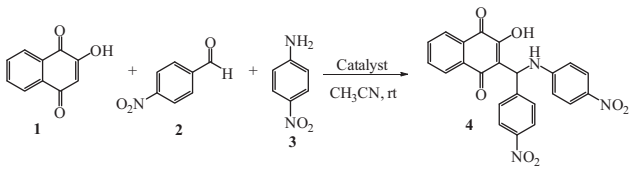
[a] Reaction conditions: lawsone (1 mmol), *p*-nitrobenzaldehyde (1.2 mmol), *p*-nitroaniline (1.1 mmol) and solvent, at room temperature.
[b] The volume of solvent was varied to maintain the homogeneity of the reaction medium.

reaction times and yields were evaluated. Initially, 10 mol % of the catalyst was utilized as a standard. The results showed that Brønsted–Lowry acids were more effective than Lewis acids, most likely because they facilitate the formation of an electrophilic iminium ion. In general, *p*-toluenesulfonic acid (entry 4, Table 2) was the best catalyst for the multicomponent Mannich reaction.

To optimize the amount of catalyst, various trial reactions were performed with 1, 10, 20 and 50 mol % *p*-toluenesulfonic acid as a catalyst. Among them, 10 and 20 mol % of *p*-TsOH provided the best results for the formation of products (Table 3).

Note that increasing the amount of catalyst did not result in an increased yield of product and/or decreased reaction time (entry 4,

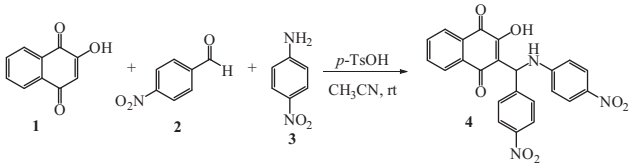
Table 2
Model reaction and catalyst screening[a]



Entry	Catalyst	Time (h)	Yield (%)
1	—	6	60
2	$Fe_2(SO_4)_3{\cdot}xH_2O$	2	66
3	$AlCl_3{\cdot}6H_2O$	0.75	84
4	I_2	1	90
5	CF_3CO_2H	0.75	94
6	*p*-TsOH	2	98

[a] Reaction conditions: lawsone (1 mmol), *p*-nitrobenzaldehyde (1.2 mmol), *p*-nitroaniline (1.1 mmol) and catalyst (10 mol %) in CH_3CN (3 mL), at room temperature.

Table 3
Model reaction and screening of amount of catalyst[a]



Entry	Concentration	Catalyst	Time (h)	Yield (%)
1	1 mol %	*p*-TsOH	0.85	90
2	10 mol %	*p*-TsOH	0.75	98
3	20 mol %	*p*-TsOH	0.5	98
4	50 mol %	*p*-TsOH	0.5	97

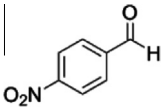
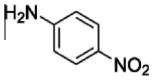
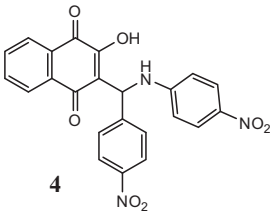
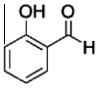
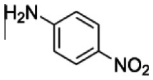
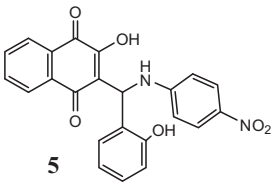
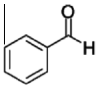
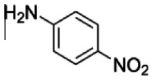
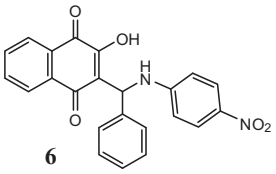
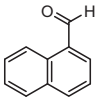
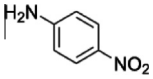
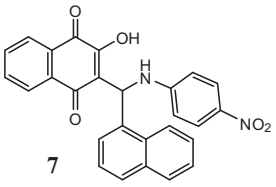
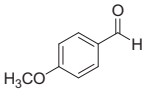
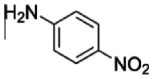
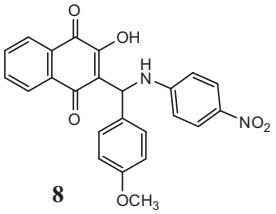
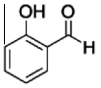
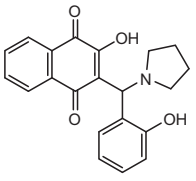
[a] Reaction conditions: lawsone (1 mmol), *p*-nitrobenzaldehyde (1.2 mmol), *p*-nitroaniline (1.1 mmol) and *p*-TsOH (x mol %) in CH_3CN (3 mL), at room temperature.

Table 3), which leads us to believe that the largest amount of the catalyst is not immobilized by amine.

To further extend the scope of this methodology, a one-pot, three component Mannich reaction was performed under the same conditions described previously using *p*-nitroaniline and the alicyclic secondary amine pyrrolidine with substituted aromatic aldehydes containing electron-withdrawing group (nitro) or electron-donating groups (i.e., hydroxyl, methoxyl) and non-substituted aromatic aldehydes (Table 4). Aliphatic aldehydes were also used, although reflux conditions were required for these reactions (entries 11 and 12).

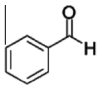
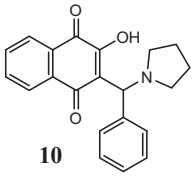
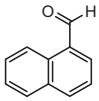
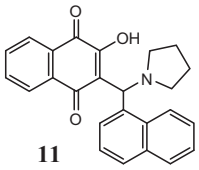
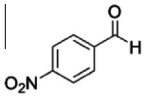
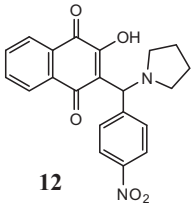
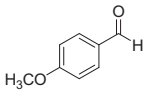
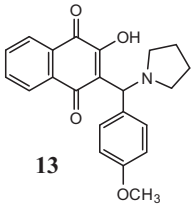
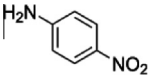
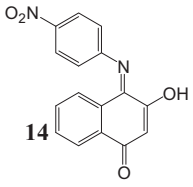
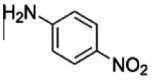
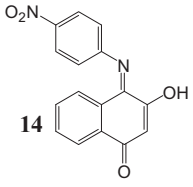
As expected, the reaction works best with aldehydes containing electron-withdrawing by increasing the carbonyl electrophilicity (entries 1 and 9). The reactions with salicylaldehyde also showed good yields despite the hydroxyl group role—electrons donor (entries 2 and 6). It occurs probably owing to the formation of intramolecular hydrogen bond between the hydroxyl and carbonyl

Table 4
Scope of the multicomponent Mannich reaction

Entry	Aldehyde	Amine	Adduct	Time (h)	Yield (%)	Time (h)/yield (%) (classical method)[a]
1			 **4**	0.5	98	24/82
2			 **5**	6.0	73	20/69
3			 **6**	10.0	95	24/93
4			 **7**	8.0	90	24/90
5			 **8**	18.0	78	24/68
6			 **9**	1.6	99	24/77

(*continued on next page*)

Table 4 (*continued*)

Entry	Aldehyde	Amine	Adduct	Time (h)	Yield (%)	Time (h)/yield (%) (classical method)[a]
7			 **10**	4.0	89	24/32
8			 **11**	6.0	85	24/38
9			 **12**	1.2	94	24/46
10			 **13**	48	55	96/44
11			 **14**	8.0 (reflux)	89	—
12			 **14**	8.0 (reflux)	82	—

[a] Classical method conditions: lawsone (1 mmol), aldehyde (1.2 mmol), amine (1.1 mmol) and ethanol (10 mL) as solvent, at room temperature.

oxygen in salicylaldehyde making it more electrophilic. The methoxyl group in the *para* position of the aromatic ring decreases the reactivity of the aldehyde carbonyl (entries 5 and 10). Surprisingly, with aliphatic aldehydes, the expected Mannich adducts were not obtained, but the same product was observed in both reactions (entries 11 and 12).

This product was poorly soluble in commonly used NMR solvents, possibly due to zwitterion form of the imine **14** (Fig. 3). It was characterized via electrospray ionization coupled to Fourier transform ion cyclotron resonance mass spectrometry (ESI(−)-FT-ICR MS), showing an unambiguous molecular formula of $C_{16}H_{10}N_2O_4$ and a ion $[M-H]^-$ of *m*/*z* 293.0570.

The formation of this product likely occurs through nucleophilic addition of the amine to the activated carbonyl of naphthoquinone in the acidic medium. The molecular structure was confirmed by ESI(−)-MS/MS experiments, which showed the losses of ·OH (293→276), NO (276→246) and HNO_2 (293→246).

We have not established an exact mechanism for the formation of the aminonaphthoquinones derived from lawsone using catalyst, however; a reasonable possibility is shown in Scheme 3. First, the catalyst protonates the carbonyl oxygen of the aldehyde favoring the formation of the iminium ion which reacts with the nucleophilic species, that may be the ion formed from deprotonation of lawsone by the amine. Finally, the product is obtained after tautomerism and the catalyst is regenerated.

In conclusion, we describe the first use of *p*-toluenesulfonic acid as an inexpensive and readily used catalyst for the multicomponent Mannich reaction derived from lawsone. It has provided excellent reaction times and within the reactions tested, the best results were with aromatic aldehydes, provided Mannich bases were in good and excellent yields.

Acknowledgments

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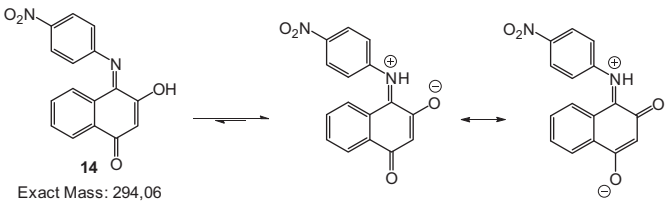
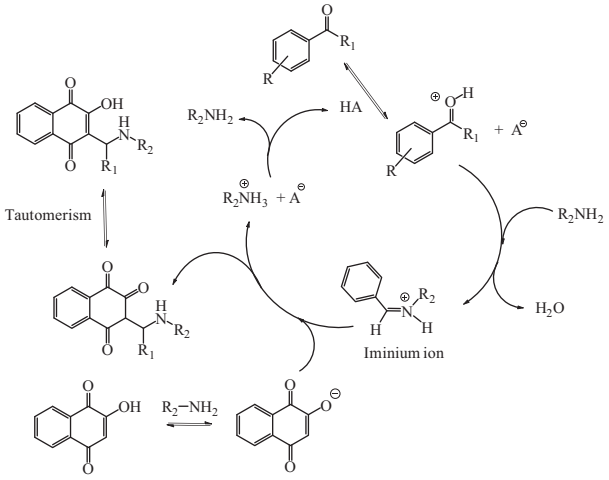


Figure 3. Product obtained with aliphatic aldehydes.



Scheme 3. Proposed mechanism for catalytic Mannich reaction.

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Supplementary data

Supplementary data (materials, analytical methods, general procedures and characterization of all synthesized compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.06.031. These data include MOL files and InChiKeys of the most important compounds described in this article.

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