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A highly efficient and green protocol for the synthesis of 3,3′-(arylmethylene)-bis(2-hydroxynaphthoquinone) derivatives catalyzed by a dicationic molten salt

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Abstract: A highly efficient and green protocol for the synthesis of 3,3′-(arylmethylene)-bis(2-hydroxynaphthoquinone) {3,3′-(arylmethylene)-bis(2-hydroxynaphthalene-1,4-dione)} derivatives has been developed. The reaction of 2-hydroxynaphthoquinone (2-hydroxynaphthalene-1,4-dione) (2 eq.) and arylaldehydes (1 eq.) in the presence of the dicationic molten salt *N*,*N*,*N*′,*N*′-tetramethylethylenediaminium bis-hydrogensulfate ($[TMEDAH_2][HSO_4]_2$) under solvent-free conditions afforded the mentioned compounds in high yields and relatively short reaction times.

Keywords: 3,3′-(arylmethylene)-bis(2-hydroxynaphthoquinone) {3,3′-(arylmethylene)-bis(2-hydroxynaphthalene-1,4-dione)}; dicationic molten salt; *N*,*N*,*N*′,*N*′-tetramethylethylenediaminium bis-hydrogensulfate ($[TMEDAH_2][HSO_4]_2$); solvent-free.

1 Introduction

Compounds bearing a naphthoquinone moiety are of great importance in medicinal and biological chemistry [1–10]. They have shown a wide range of medicinal and biological activities, such as antimalarial [2], antitumor [3], antimicrobial [4], anti-inflammatory [5], antibacterial [6], antiproliferative [7], CDC25 phosphatase inhibitor [8], antifungal [9], antiplatelet [10], and antiallergic [10] properties. A special class of these compounds is 3,3′-(arylmethylene)-bis(2-hydroxynaphthoquinone) {3,3′-(arylmethylene)-bis(2-hydroxynaphthalene-1,4-dione)} derivatives, which could be prepared through the reaction of 2-hydroxynaphthoquinone (2-hydroxynaphthalene-1,4-dione) (2 eq.) and arylaldehydes (1 eq.). See Scheme 1 for the respective reaction with 4-nitrobenzaldehyde. Some catalysts have been reported for this transformation [11–18]. It is noteworthy that only a few catalysts have been reported for the preparation of 3,3′-(arylmethylene)-bis(2-hydroxynaphthoquinone) derivatives from 2-hydroxynaphthoquinone (2 eq.) and arylaldehydes (1 eq.). Therefore, it is highly desirable to develop new efficient catalysts for this transformation.

Salts which comprise organic cations and organic/inorganic anions, and melt below 100 °C are defined as ionic liquids, whereas salts which contain organic/inorganic cations and anions, and melt above 100 °C are commonly referred to as molten salts (MSs) [19]. MSs have a wide range of chemical and industrial applications. For instance, they have been utilized as catalysts [19–25] and reaction medium [26–31] in chemical reactions. MSs have been also applied as electrolyte in rechargeable zinc-air batteries [32], and tubular-receiver for solar power tower [33]. Furthermore, they have been used for separation [34], heat transfer [35], and thermal energy storage [36].

Solvent-free condition is a practical and well-known technique in organic synthesis. The superiority of this technique with respect to reactions in solution consists of compliance with green chemistry principles. Safer reaction profiles, facile workup, easier procedures for purifying the products, higher yield and selectivity of products, shorter reaction times, less energy consumption, and prevention or decrease of by-products/waste formed [37–42] are often realized advantages.

In this work, we have utilized a dicationic molten salt namely *N*,*N*,*N*′,*N*′-tetramethylethylenediaminium bis-hydrogensulfate ($[TMEDAH_2][HSO_4]_2$) as highly efficient catalyst for the synthesis of 3,3′-(arylmethylene)-bis(2-hydroxynaphthoquinone) derivatives through the reaction of 2-hydroxynaphthoquinone (2 eq.) with arylaldehydes (1 eq.) under solvent-free conditions.

2 Results and discussion

First, the reaction conditions were optimized by studying the influence of the amount of catalyst and the

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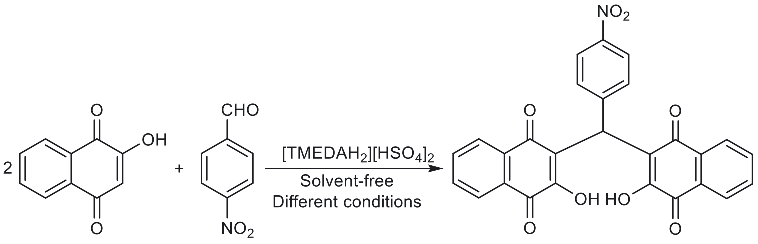


Scheme 1: The reaction of 2-hydroxynaphthoquinone with 4-nitrobenzaldehyde.

Table 1: Optimization of the reaction conditions of the condensation of 2-hydroxynaphthoquinone (2 mmol) with 4-nitrobenzaldehyde.

Entry	Mol% of $[TMEDAH_2][HSO_4]_2$	Temp. (°C)	Time (min)	Yield[a] (%)
1	20	120	60	83
2	25	120	40	96
3	27	120	40	94
4	25	115	40	89
5	25	125	40	94

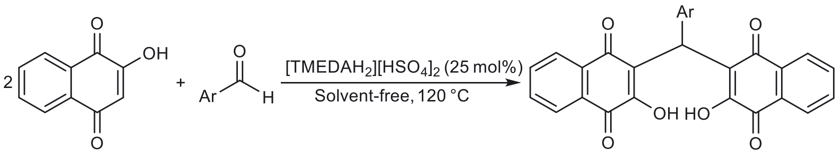
[a]Isolated yields.

temperature on a model reaction, the condensation of 2-hydroxynaphthoquinone (2 mmol) with 4-nitrobenzaldehyde (1 mmol) (Scheme 1). The results are summed up in Table 1. As the data illustrate, the reaction using 20 mol% of $[TMEDAH_2][HSO_4]_2$ at T = 120 °C lead to the desired product in only moderate yield (Table 1, entry 1). Examining the model reaction in the presence of 25 mol% of the molten salt at 115 °C also did not give satisfactory results (Table 1, entry 4). The best results were obtained when 25 mol% of the catalyst was employed at 120 °C (Table 1, entry 2). To improve the results, the amount of catalyst was increased up to 27 mol% and the temperature was raised up to 125 °C. However, no improvement of the reaction time and yield was observed under these conditions (Table 1, entries 3 and 5).

Efficiency and generality of our protocol for the synthesis of 3,3′-(arylmethylene)-bis(2-hydroxynaphthoquinone) derivatives were assessed by the reaction of 2-hydroxynaphthoquinone with diverse arylaldehydes, ranging from unsubstituted benzaldehyde to aromatic aldehydes bearing electron-releasing, electron-attracting, and halogen substituents. The results obtained in these experiments are given in Table 2. The very good results (i.e., production of the products in good to excellent yields and relatively short times) confirmed the high efficiency and generality of the protocol. It should be mentioned that reactions with aliphatic aldehydes are planned.

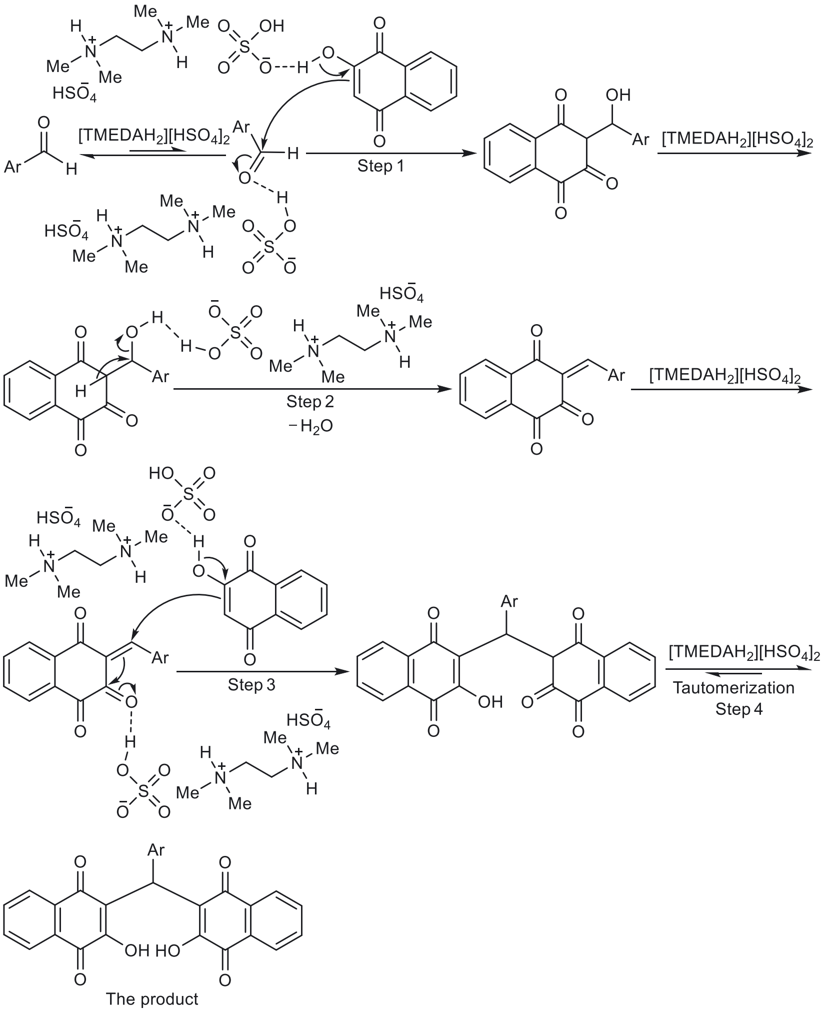
Because of the coexisting weakly acidic and basic groups in the structure of $[TMEDAH_2][HSO_4]_2$ (the hydrogen and oxygen atoms of hydrogensulfate are acidic and weakly basic, respectively, $[TMEDAH_2]^{2+}$ is weakly acidic), it can act as a dual-functional (acid-base) catalyst. Given this and based on arguments put forward in the literature [14–16], a plausible mechanism was proposed for the

Table 2: The synthesis of 3,3′-(arylmethylene)-bis(2-hydroxynaphthoquinone) derivatives catalyzed by $[TMEDAH_2][HSO_4]_2$.



Product No.	Ar	Time (min)	Yield[a] (%)	M.p. (in °C) found (reported) [ref.]
1	C_6H_5	40	94	205–207 (202–204) [12]
2	$4\text{-}CH_3C_6H_4$	60	86	169–171 (170–172) [12]
3	$3,4\text{-}(CH_3O)_2C_6H_3$	60	93	178–180 (143–145) [17]
4	$4\text{-}CH_3OC_6H_4$	60	85	223–225 (220–222) [12]
5	$4\text{-}O_2NC_6H_4$	40	96	179–181 (177–178) [12]
6	$3\text{-}O_2NC_6H_4$	60	94	156–158 (151–152) [17]
7	$2\text{-}ClC_6H_4$	60	89	220–222 (218–220) [13]
8	$4\text{-}ClC_6H_4$	30	96	180–182 (180–182) [14]
9	$2,4\text{-}Cl_2C_6H_3$	60	85	198–200 (200–202) [18]
10	$4\text{-}FC_6H_4$	60	83	181–183 (177–178) [18]

[a]Isolated yields.



Scheme 2: The proposed reaction mechanism.

reaction (Scheme 2). The catalyst tasks are clearly reflected in this mechanism. The acidic hydrogen can activate the electrophiles to accept nucleophilic additions in steps 1 and 3. Additionally, the acidic group can facilitate removal of H_2O in step 2, and tautomerization in step 4. The basic oxygen can activate the nucleophiles to perform steps 1 and 3. The dual functionality of catalysts possessing hydrogensulfate (or similar anions) has been discussed in the literature [20, 43].

The reaction conditions and the results of $[TMEDAH_2][HSO_4]_2$ for the synthesis of compound **1** were compared with those of other reported catalysts (Table 3). As Table 3

Table 3: The preparation of compound **1** using $[TMEDAH_2][HSO_4]_2$ and the reported catalysts.

Catalyst	Conditions	Time (min)	Yield (%)	Ref.
$[TMEDAH_2][HSO_4]_2$	Solvent-free, 120 °C	40	94	–
LiCl	H_2O, 25 °C, ultrasonic irradiation	5	91	[12]
LiCl	H_2O, 75 °C, microwave irradiation	15	87	[12]
H_2SO_4	H_2O-EtOH, reflux	15	90	[13]
LiCl	H_2O, reflux	720	83	[14]
Lipase	EtOH, 60 °C	120	88	[15]
O-Carboxymethyl chitosan	H_2O-MeOH, 70 °C	50	89	[16]
H_2O-[bmim]$[BF_4]$[a, b]	90 °C	240–360	85–92	[17]
Sulfamic acid	H_2O-EtOH, r.t.	960	92	[18]

[a] Aqueous 1-Butyl-3-methylimidazolium tetrafluoroborate. [b] In this work [17], the particular synthesis of compound **1** has not been reported. Therefore, the ranges of the reaction times and yields as given in the study by Li et al. [17] have been tabulated here.

indicates, the yields with $[TMEDAH_2][HSO_4]_2$ as catalyst in our work were higher than with other catalysts, and the reaction times were shorter than with most of the other reported catalysts. Additionally, the reaction has been carried out under solvent-free conditions in our work. However, the reaction temperature in our work is higher than in the other catalytic systems employed due to the higher melting point of $[TMEDAH_2][HSO_4]_2$.

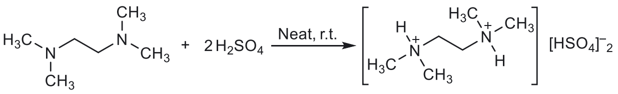
3 Conclusion

In summary, we have developed a new protocol for the preparation of 3,3′-(arylmethylene)-bis(2-hydroxynaphthoquinone) derivatives using a dicationic molten salt as a dual-functional catalyst. The promising points of this protocol include high yields, relatively short reaction times, generality, efficiency, easy preparation of the catalyst, simple workup, facile purification of the products by recrystallization, solvent-free reactions and, hence, good agreement with green chemistry principles.

4 Experimental section

4.1 Materials and instruments

The reactants and solvents were purchased from Fluka or Merck Chemical Companies. $[TMEDAH_2][HSO_4]_2$ was prepared according to our published method (Scheme 3) [20]. For the identification of the products, their melting points/spectral data were compared with those reported in the literature. Thin-layer chromatography (TLC) using silica gel SIL G/UV 254 plates was utilized for observing progress of the reactions. FT-IR spectra were recorded by a Shimadzu IR-60 instrument. ^1H NMR (400 or 500 MHz) and ^{13}C NMR (100 or 125 MHz) were run on Bruker Avance DPX, FT-NMR spectrometers. Melting points were measured using a Thermo Scientific 9200 instrument in open capillary tubes. Mass spectra were obtained with Shimadzu GC-MS-QP 1100 Ex.



Scheme 3: The preparation of $[TMEDAH_2][HSO_4]_2$.

4.2 General procedure for the synthesis of 3,3′-(arylmethylene)-bis(2-hydroxynaphthoquinone) derivatives

A mixture of 2-hydroxynaphthoquinone (2 mmol), aldehyde (1 mmol) and $[TMEDAH_2][HSO_4]_2$ (0.25 mmol, 0.078 g) was vigorously stirred by a small rod at $T = 120$ °C. Upon completion of the reaction as indicated by TLC (eluted by *n*-hexane-ethyl acetate: 2:1, *v*/*v*), the reaction mixture was cooled to room temperature, and the resulting precipitate was recrystallized from hot ethanol-H_2O (7:3, *v*/*v*) to afford the pure product.

5 Supplementary Material

Selected spectral data and original spectra of the synthesized 3,3′v-(arylmethylene)-bis(2-hydroxynaphthoquinone) derivatives are given as Supplementary Material available online (https://doi.org/10.1515/znb-2020-0174).

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