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[A005]

Synthesis of New 2-(3-Hydroxy-4-oxo-4*H*-naphthalenylidene) acetonitriles in Aqueous Solvent

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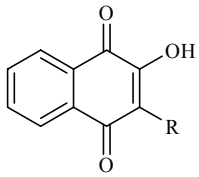
Abstract: *We have prepared a serie of new naphthoquinomethanes: [2-(3-hydroxy-4-oxo-4H-naphthalen-1-ylidene) acetonitriles] by the cascade Michael-elimination reaction of sodium 1, 2-naphthoquinone-4-sulfonate with substituted acetonitriles in basic ethanol-water.*
Keywords*: lawson, antibacterial, Michael addition, 3-hydroxy-1,2-naphthoquinomethane, green chemistry*

Introduction

Hydroxynaphthoquinones are well known substances for their chemical and biological properties [1]. The hydroxynaphthoquinones like lawson [2], phthiocol [3], parvaquone, buparvaquone and atovaquone [4] have gained large interest due to their presence in natural products and their pharmacological properties as antitumoral, antiprotozoal, anti-inflammatory, antiviral and antifungal [5, 6, 7]. Hydroxynaphthoquinone like conocurvone was shown to inhibit the cytopathogenic effects of HIV-1 in human T-lymphoblastic cells [8]. Some have even reached clinical use level. We are interested by antimicrobial and antifungal properties of new hydroxynaphthoquinone derivatives.



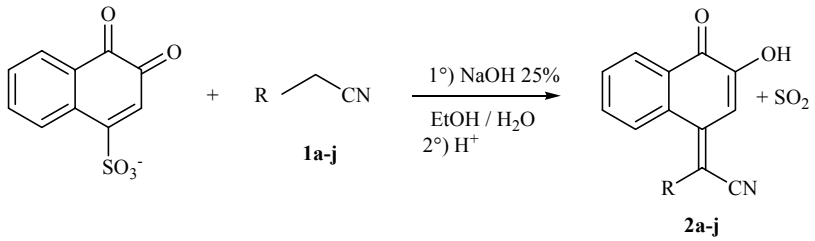
R = H ; lawson
R = Me ; phthiocol
R = cyclohexyl ; parvaquone
R = 4-(4-chlorophenyl) cyclohexyl ; atovaquone

Figure 1

While hydroxynaphthoquinones are well described, hydroxylnaphtho quinomethanes are poorly known [9]. Naphthoquinomethanes are the equivalent of quinomethanes known as reactive intermediate with single aromatic compounds.

Recently, organic reactions under green conditions, in water or benign solvent like ethanol have received considerable attention [10], because of its environmental acceptability, abundance and low cost. We report herein the

synthesis of new hydroxynaphthoquinomethanes from substituted acetonitrile. The synthesis of this type of compounds involves a base in order to catalyse Michael-type addition of the acetonitrile anion on 1,2-naphthoquinone-sulfonate, followed by a protonation and elimination of sulfur dioxide. The reaction was conducted in ethanol-water media and produced 2-hydroxynaphthoquinomethanes (Scheme **1**) in quite good yields.



Scheme 1.

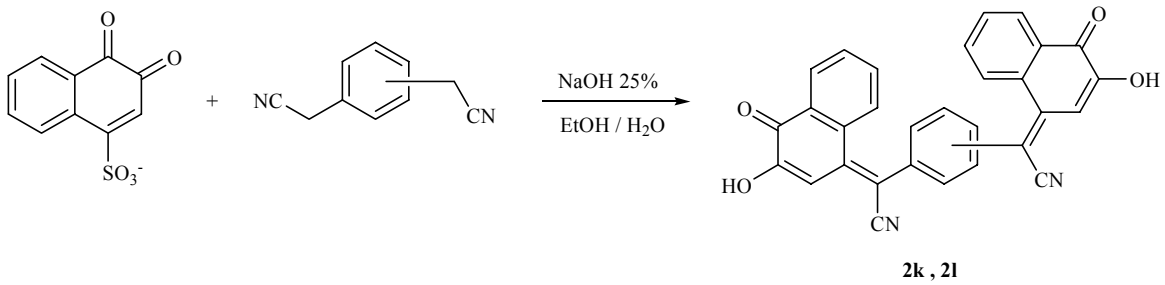
The results are reported in Table **1:**

Entry	**R**	**Product**	**Yield (%)**
1	CN	2a	91
2	COOEt	2b	37
3	$CONH_2$	2c	44
4	SCH_3	2d	30
5	Ph	2e	50
6	2,6-dichlorophenyl	2f	60
7	3,4-dimethoxyphenyl	2g	74
8	4-methoxyphenyl	2h	92
9	4-nitrophenyl	2i	67
10	4-chlorophenyl	2j	51
11	1,3-phenylene	2k	32
12	1,4-phenylene	2l	46

Table 1. Synthesis of 2-hydroxynaphthoquinomethanes in aqueous solvent

Results and discussion

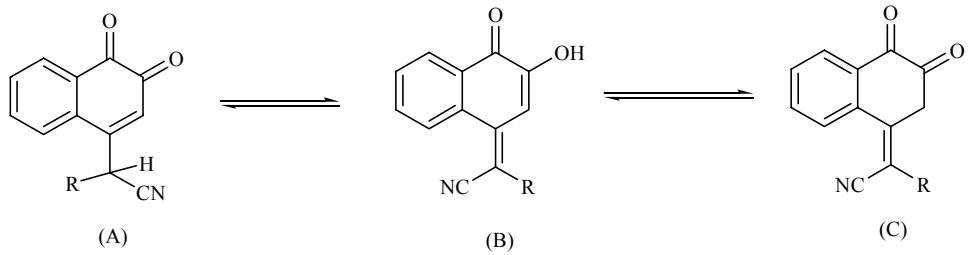
The one-pot two component condensation-elimination reactions of 1,2-naphthoquinone-4-sulfonate with acetonitrile compounds, in the presence of sodium hydroxide as a base, proceeded rapidly by heating the mixture in water-ethanol. It is noteworthy that different bases (triethylamine, potassium tert-butoxide, sodium ethoxide and potassium carbonate) have been tried in this reaction, before choosing 25% NaOH in the water-ethanol mixture, for its convenient use corresponding to the criteria of the “green chemistry”.



Scheme 2

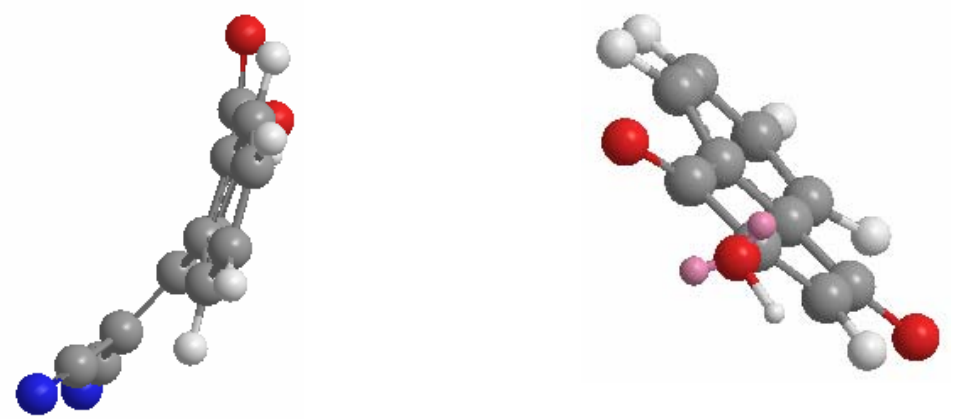
The *meta* and *para*-phenylenediacetonitriles afford new bis-hydroxynaphthoquinomethanes (**2k**, **2l**) (Scheme **2**). These molecules can be of interest, some bisquinones are natural products which possess a diverse array of biological activities [8].

Because of the tautomeric equilibrium (Scheme **3**), hydroxynaphtho quinomethane can be obtained in three different forms. Thus, the structures exactly obtained by our method were confirmed to be **2a-l** in the enolic form (B) by several techniques (^{1}H NMR, ^{13}C NMR, IR and MS).



Scheme 3

The structures of 2-(3-hydroxy-4-oxo-4*H*-naphthalen-1-ylidene) acetonitriles were computed. Equilibrium geometry were optimized first by molecular mechanic by using the force field MMFF and then by semi-empirical calculation with PM3 [11]. The best geometry obtained were used in computation with density functional B3LYP (6-31G *). Whereas the Lawson has a plane structure, the structures of the hydroxynaphthoquinomethanes are concave. The structures obtained with **2a** (R = CN) and lawson were presented in Figure **2**.



dicyano derivative **2a** lawson

Figure 2

The in vitro antibacterial activity of compounds **2a-l** against four bacteria (*Escherichia coli, Staphylococcus aureus, Enterococcus faecalis and Pseudomonas aerogenosa)* was investigated and compared to gentamycin. Compounds **2i** and **2j** showed a very interesting antibacterial effect against *Staphylococcus aureus* and *Enterococcus faecalis*. This research must be sustained for further optimizations.

In conclusion, we have synthesized and screened the vitro antibacterial activity of new series of functionalized hydroxynaphthoquinomethane acetonitriles. A mild base in water medium, respecting ecological criteria, was used. The obtained results are very promising since two of the compounds showed activity comparable with the current used antibiotic drug gentamycin.

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