



HAL
open science

Catalysis by triflic acid: synthesis of the indolyquinones as potential antitumor agent

Feyriél Dridi, Didier Villemin, Nathalie Bar, Messaoud Hachemi, Rémi Legay

► **To cite this version:**

Feyriél Dridi, Didier Villemin, Nathalie Bar, Messaoud Hachemi, Rémi Legay. Catalysis by triflic acid: synthesis of the indolyquinones as potential antitumor agent. *European Chemical Bulletin*, 2015, 4 (10-12), pp.543-590. 10.17628/ecb.2015.4.543-547. hal-02381054

HAL Id: hal-02381054

<https://hal.science/hal-02381054v1>

Submitted on 26 Nov 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



CATALYSIS BY TRIFLIC ACID: SYNTHESIS OF THE INDOLYLQUINONES AS POTENTIAL ANTITUMOR AGENT

Feyriél Dridi^[a,b], Didier Villemin^{[a]*}, Nathalie Bar^[a], Messaoud Hachemi^[b] and Remi Legay^[a]

Keywords: *p*-Quinones, indoles, trifluoromethanesulfonic acid, indol-3-ylbenzoquinones.

Trifluoromethanesulfonic acid efficiently catalyzes the conjugate addition of indoles to *p*-benzoquinones under mild conditions affording the corresponding indolylquinones in high yields with high selectivity. In particular, the poorly reactive menadione underwent reaction with indoles under similar conditions to give 3-indolynaphthoquinones.

* Corresponding Authors

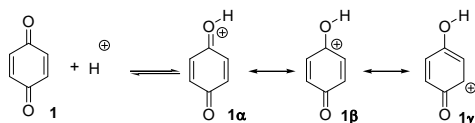
E-Mail: villemin@ensicaen.fr

[a] Laboratoire de Chimie Moléculaire et Thioorganique, UMR CNRS 6507, INC3M, FR 3038, Labex EMC3, Labex Synorg, ENSICAEN & Université de Caen, 14050 Caen, France

[b] Laboratoire de Chimie Moléculaire et Composites, Faculté des Sciences de l'Ingénieur, Université M' Hamed, Boumerdes, Algérie

Introduction

Protonation of quinones with a Bronsted acid (HX) gives a carbocation which can react with different nucleophiles, and after rearomatization the resulting product is a substituted resorcinol. This reaction is well known and already reported for many years with hydrogen halides,² hydrogen cyanide,³ hydrazoic acid,⁴ sulphur acids,⁵ (thiols, thiourea, sulphite) and amines.⁶ The probable mechanism of the reaction of benzoquinone **1** with indole begins by the protonation of benzoquinone, leading to carbon electrophiles (**1β**, **1γ**). Indole reacts with **1γ** as nucleophile and gives indolylhydroquinone in the first step.



Scheme 1. Protonation of quinones.

After an oxidation step, the resulting indolylquinone can react in a similar way with a second equivalent of indole providing bisindolylhydroquinones. Moreover, in this step, two isomers are likely to be formed. As hydroquinones, bisindolylhydroquinones can be oxidated to bis(indolyl)quinones. As a result, the reaction of indoles with quinones is complex and a mixture of products is generally obtained which need laborious separation.⁷

In fact, the nucleophile addition of indoles on quinones is strongly dependant of the nature of the quinone because the limiting step is the protonation of quinone.

With the easily protonated benzoquinone, the reaction can take place without acid, even in water or with poor acidic agent.⁸ With naphthoquinone, a stronger acid is necessary and this reaction was already described with different protic acids,⁹ like hydrochloric acid,^{9a} tosylic acid.^{9c} With methyl-naphthoquinone (menadione) the reaction is very difficult. Concerning the reactivity of quinones, the same results were previously observed with the Thiele reaction which can take place from the same carbocation intermediate.¹⁰ This reactivity depends of the basicity of quinone and the electrophilicity of protonated quinone. The reaction with indoles depends also of the nucleophilicity of indoles.¹¹

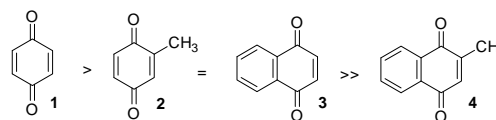


Figure 1. Order of reactivity of quinones.

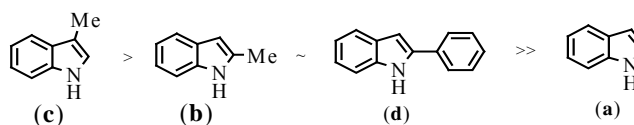


Figure 2. Order of reactivity of indoles.

During our studies on Thiele acetylation of menadione,¹¹ triflic acid (trifluoromethanesulphonic acid, TfOH) was found to be a particularly convenient catalyst, able to broaden the synthetic scope of quinones substituted with electron donating groups.

In this context, we decided to investigate the addition of indoles as nucleophile on quinones, in particular methylquinone, naphthoquinone and methyl-naphthoquinone catalyzed by TfOH which has not been reported in the literature.

Experimental

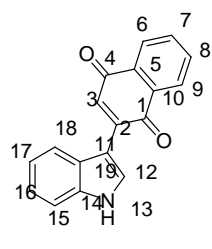
General procedure

A mixture of the quinone (2 mmol) and TfOH (2 mol %) and indole (1 mmol) in dichloromethane (30 mL) was stirred at room temperature under nitrogen for the specified time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was quenched with water (15 mL). Sodium carbonate (2 g) was added to the reaction mixture. After filtration, the reaction mixture was extracted with ethyl acetate (2 x 10 mL). The organic phases were combined, dried over Na₂SO₄, and concentrated in vacuum. The resulting product was purified by column chromatography on silica gel (Merck, 100-200 mesh, ethyl acetate-cyclohexane, 0.5-9.5) to afford pure indol-3-ylbenzoquinone. Spectral data for selected products are given below.

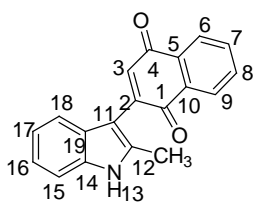
Table 1. Trifluoromethanesulfonic acid catalyzed reaction of indoles to quinones.

No.	Indole	Quinone	Product	Time, h	Yield ^a , %
1	a	3	3a	24	47
2	b	3	3b	0.25	51
3	c	3	3c	0.33	47
4	d	3	3d	0.33	48
5	b	2	2a , 2b	24	36/36
6	c	2	2a	24	45
7	d	2	2b	24	55
8	b	4	4b 4y	24	45/10
9	d	4	4d	24	50

^a Isolated products, except for the mixture **2a**, **2b** determined by NMR (ratio 1:1)



(3a)



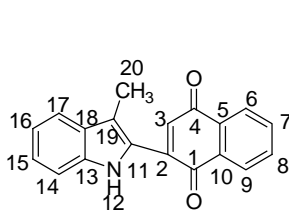
(3b)

2-(1*H*-Indol-3-yl)-1,4-naphthoquinone (**3a**)

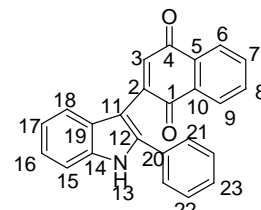
M. P. 205-206 °C. IR: 3239, 1589, 1556, 1255, 1230 cm⁻¹. ¹H NMR (CDCl₃): δ = 8.53 (s, 1H, NH₁₃), 8.05 (d, *J*=3.2 Hz, 1H, H₁₂), 7.98-7.95 (m, 1H, H₉), 7.94-7.91 (m, 1H, H₆), 7.81-7.76 (m, 1H, H₁₈), 7.58-7.51 (m, 2H, H_{7,8}), 7.29-7.23 (m, 1H, H₁₇), 7.46 (s, 1H, H₃), 7.13-7.06 (m, 2H, H_{16,17}). ¹³C NMR (CDCl₃): δ = 185.7 (C1), 185.4 (C4), 142.2 (C11), 136.5 (C14), 133.9 (C7), 133.5 (C8), 133.1 (C10), 132.4 (C5), 131.1 (C12), 129.9 (C3), 127.0 (C9), 125.9 (C6), 125.7 (C19), 123.5 (C16), 122.0 (C17), 120.6 (C18), 112.0 (C15), 109.2 (C2). EIMS: *m/z* (%): 274 M+H (60), 257 (15), 246 (100), 218 (10). HRMS calcd for C₁₈H₁₂NO₂ [M+H]: 274.0868, found: 274.0868.

2-(2-Methyl-3-indolyl)-1,4-naphthoquinone (**3b**)

M. P. 183-184 °C. IR: 3354, 1617, 1667, 1634, 1565, 1296, 1253 cm⁻¹. ¹H NMR (CDCl₃): δ = 8.36 (s, 1H, NH₁₃), 8.22-8.17 (m, 1H, H₉), 8.18-8.13 (m, 1H, H₆), 7.81-7.74 (m, 2H, H_{7,8}), 7.54 (d, *J*=6.8 Hz, 1H, H₁₈), 7.34 (d, *J*=6.8 Hz, 1H, H₁₅), 7.22-7.12 (m, 2H, H_{16,17}), 7.10 (s, 1H, H₃), 2.48 (s, 3H, CH₃, H₂₀). ¹³C NMR (CDCl₃): δ = 185.3 (C1), 184.6 (C4), 144.4 (C2), 136.9 (C12), 135.5 (C14), 134.8 (C3), 133.7 (C7), 133.5 (C8), 132.8 (C10), 132.3 (C5), 127.7 (C19), 127.0 (C9), 125.9 (C6), 122.3 (C16), 120.9 (C17), 119.3 (C18), 110.6 (C15), 107.4 (C11), 14.0 (C20). EIMS: *m/z* (%): 288 M+H (25), 270 (100), 260 (15), 242 (25), 117 (10). HRMS calcd for C₁₉H₁₃NO₂ [M+1]: 288.1025, found: 288.1018.



(3c)



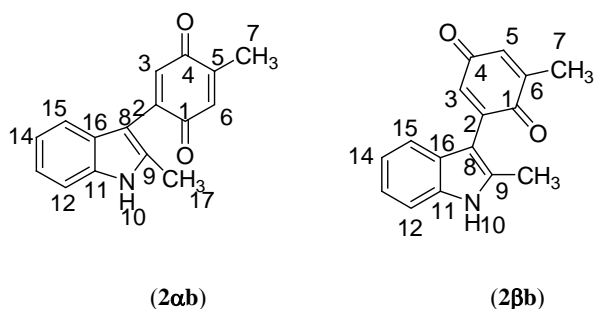
(3d)

1-(3-Methyl-2-indolyl)-1,4-naphthoquinone (**3c**)

M. P. 205-206 °C. IR: 3385, 1644, 1588, 1563, 1331, 1301, 1253 cm⁻¹. ¹H NMR (CDCl₃): δ = 10.45 (s, 1H, NH₁₂), 8.19 (d, *J*=6.5 Hz, 1H, H₆), 8.13 (d, *J*=6.5 Hz, 1H, H₉), 7.81-7.79 (m, 2H, H_{7,8}), 7.65 (d, *J*=7.8 Hz, 1H, H₁₇), 7.43 (d, *J*=7.8 Hz, 1H, H₁₄), 7.29 (t, *J*=7.8 Hz, 2H, H₁₅), 7.27 (s, 1H, H₃), 7.14 (t, *J*=7.8 Hz, 1H, H₁₆), 2.62 (s, 3H, CH₃, H₂₀). ¹³C NMR (CDCl₃): δ = 187.7 (C4), 184.6 (C1), 137.4 (C13), 137.3 (C2), 134.5 (C7), 133.7 (C8), 132.5 (C10), 132.1 (C5), 131.6 (C3), 128.6 (C18), 127.1 (C6), 127.0 (C11), 126.0 (C9), 125.3 (C15), 120.16 (C16), 119.9 (C17), 118.7 (C19), 111.8 (C14), 12.6 (C20). EIMS: *m/z* (%): 288 M+H (80), 270 (100), 260 (20), 242 (15), 235 (5). HRMS calcd for C₁₉H₁₃NO₂ [M+1]: 288.1025, found: 288.1018.

2-(2-Phenyl-3-indolyl)-1,4-naphthoquinone (**3d**)

M. P. 213-214 °C. IR: 3406, 1667, 1647, 1591, 1449, 1294 cm⁻¹. ¹H NMR (CDCl₃): δ = 9.30 (s, 1H, NH₁₃), 8.12 (dd, *J*=7.6 Hz, *J*=1.2 Hz, 1H, H₆), 7.95 (dd, *J*=7.6 Hz, *J*=1.2 Hz, 1H, H₉), 7.75 (td, *J*=7.6 Hz, *J*=1.2 Hz, 1H, H₇), 7.69 (td, *J*=7.6 Hz, *J*=1.2 Hz, 1H, H₈), 7.61 (d, *J*=7.2 Hz, 1H, H₁₈), 7.46-7.42 (m, 2H, H₂₁), 7.39 (d, *J*=7.2 Hz, 1H, H₁₅), 7.33-7.28 (m, 3H, H_{22,23}), 7.24 (t, *J*=7.6 Hz, 1H, H₁₆), 7.22 (d, *J*=7.6 Hz, 1H, H₁₇), 7.18 (s, 1H, H₃). ¹³C NMR (CDCl₃): δ = 185.2 (C4), 184.2 (C1), 145.2 (C2), 139.5 (C12), 136.3 (C14), 135.8 (C3), 133.7 (C7), 133.6 (C8), 132.9 (C10), 132.6 (C20), 132.3 (C5), 128.9 (C22), 128.4 (C23), 128.2 (C19), 128.1 (C21), 126.9 (C9), 125.9 (C6), 123.1 (C16), 121.3 (C17), 119.5 (C18), 111.53 (C15), 106.8 (C11). EIMS: *m/z* (%): 350 M+H (100), 332 (40), 304 (30), 280 (20), 133 (10). HRMS calcd for C₂₄H₁₆NO₂ [M+H]: 350.1181, found: 350.1194.



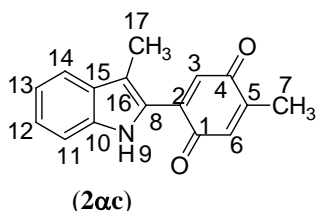
2-Methyl-5-(2-methyl-1H-indol-3-yl)cyclohexa-2,5-diene-1,4-dione (2αb)

M. P. 206-208 °C. IR: 3295, 1646, 1603, 1588, 1575, 1457, 1421, 1302, 1244 cm^{-1} . ^1H NMR (DMSO): 11.56 (s, 1H, NH_{10}), 7.36 (d, $J = 7.6$ Hz, 1H, H_{15}), 7.32 (d, $J = 8.0$ Hz, 1H, H_{12}), 7.07 (t, $J = 7.2$ Hz, 1H, H_{13}), 7.00 (t, $J = 8.0$ Hz, 1H, H_{14}), 6.84-6.82 (m, 1H, H_6), 6.74 (s, 1H, H_3), 2.36 (s, 3H, CH_3 , H_{17}), 2.03 (d, $J = 1.2$ Hz, 3H, CH_3 , H_7). ^{13}C NMR (DMSO): 187.6 (C1), 186.8 (C4), 145.1 (C5), 142.3 (C2), 137.9 (C9), 135.5 (C11), 133.5 (C6), 131.1 (C3), 127.3 (C16), 121.2 (C13), 119.8 (C14), 118.9 (C15), 110.9 (C12), 105.6 (C8), 15.0 (C7), 13.2 (C17). EIMS: m/z (%): 252 M+H (50), 237 (100), 235 (60), 220 (30), 207 (10). HRMS calcd for $\text{C}_{16}\text{H}_{14}\text{NO}_2$ [M+1]: 252.1027, found: 252.1025.

2-Methyl-6-(2-methyl-1H-indol-3-yl)cyclohexa-2,5-diene-1,4-dione (2βb)

M. P. 206-208 °C. IR: 3295, 1646, 1603, 1588, 1575, 1457, 1421, 1302, 1244, 913 cm^{-1} . ^1H NMR (DMSO): 11.56 (s, 1H, NH_{10}), 7.36 (d, $J = 7.6$ Hz, 1H, H_{15}), 7.32 (d, $J = 8.0$ Hz, 1H, H_{12}), 7.07 (t, $J = 7.2$ Hz, 1H, H_{13}), 7.00 (t, $J = 8.0$ Hz, 1H, H_{14}), 6.77-6.75 (m, 1H, H_5), 6.67 (d, $J = 2.4$ Hz, 1H, H_3), 2.36 (s, 3H, CH_3 , H_{17}), 2.07 (d, $J = 1.6$ Hz, 3H, CH_3 , H_7). ^{13}C NMR (DMSO): 187.7 (C1), 186.8 (C4), 146.01 (C5), 142.03 (C2), 135.5 (C9), 135.4 (C11), 132.6 (C6), 130.9 (C3), 127.3 (C16), 121.1 (C13), 119.7 (C14), 118.9 (C15), 110.9 (C12), 105.9 (C8), 15.9 (C7), 13.2 (C17).

2-Methyl-5-(3-methyl-1H-indol-2-yl)cyclohexa-2,5-diene-1,4-dione (2αc)

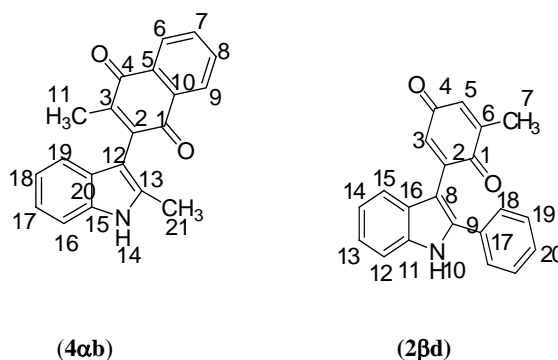


M. P. 190-191 °C. IR: 3378, 1617, 1568, 1505, 1330, 1168. ^1H NMR (CDCl_3): 10.28 (s, 1H, NH_9), 7.62 (d, $J = 8.0$ Hz, 1H, H_{14}), 7.39 (d, $J = 8.0$ Hz, 1H, H_{11}), 7.27 (t, $J = 8.0$ Hz, 1H, H_{12}), 7.12 (t, $J = 8.0$ Hz, 1H, H_{11}), 7.03 (s, 1H, H_3), 6.67 (q, $J = 1.6$ Hz, 1H, H_6), 2.56 (s, 3H, H_{16}), 2.11 (d, $J = 1.6$ Hz, 3H, H_7). ^{13}C NMR (CDCl_3): $\delta = 190.2$ (C1), 187.5 (C4), 146.6 (C5), 137.5 (C10), 135.34 (C2), 133.6 (C6), 128.9 (C3), 128.5 (C15), 126.6 (C8), 125.2 (C12), 120.1 (C13), 119.9 (C14), 118.7 (C16), 111.8 (C11), 15.7 (C7), 12.5

(C17). EIMS: m/z (%): 252 M+H (60), 237 (100), 235 (25). HRMS calcd for $\text{C}_{16}\text{H}_{14}\text{NO}_2$ [M+1]: 252.1025, found: 252.1024.

2-methyl-6-(2-phenyl-1H-indol-3-yl)cyclohexa-2,5-diene-1,4-dione (2βd)

^1H NMR (CDCl_3): 8.75 (s, 1H, NH_{10}), 7.55 (d, $J = 8.0$ Hz, 1H, H_{15}), 7.42-7.31 (m, 6H, $\text{H}_{12,18,19,20}$), 7.27 (t, $J = 8.0$ Hz, 1H, H_{13}), 7.22 (t, $J = 8.0$ Hz, 1H, H_{14}), 6.91 (d, $J = 2.6$ Hz, 1H, H_3), 6.64 (dq, $J = 2.6$ Hz, $J = 0.2$ Hz, 1H, H_5); 1.97 (d, $J = 0.2$ Hz, 3H, CH_3 , H_7). ^{13}C NMR (CDCl_3): 187.8 (C4); 186.8 (C1); 146.5 (C6); 143.2 (C2); 139.1 (C9); 136.3 (C11); 133.6 (C5); 133.4 (C3); 132.7 (C17); 129.1 (C19); 128.6 (C20); 128.2 (C16); 128.1 (C18); 123.3 (C13); 121.5 (C14); 119.6 (C15); 111.5 (C12); 107.0 (C8); 16.5 (C7). EIMS: m/z (%): 314 M+H (60), 299 (100). HRMS calcd for $\text{C}_{21}\text{H}_{16}\text{NO}_2$ [M+1]: 314.1181, found: 314.1177.



2-Methyl-3-(2-methyl-1H-indol-3-yl)naphthalene-1,4-dione (4αb)

M. P. 88-86 °C. IR: 3359, 2923, 1692, 1654, 1593, 1458, 1422, 1284 cm^{-1} . ^1H NMR (CDCl_3): $\delta = 8.27$ (s, 1H, NH_{14}), 8.20-8.18 (m, 1H, H_6), 8.16-8.14 (m, 1H, H_9), 7.77-7.72 (m, 2H, $\text{H}_{7,8}$), 7.31 (d, $J = 8.0$ Hz, 1H, H_{16}), 7.18 (d, $J = 8.0$ Hz, 1H, H_{19}), 7.15 (t, $J = 8.0$ Hz, 1H, H_{17}), 7.09 (t, $J = 8.0$ Hz, 1H, H_{18}), 2.28 (s, 3H, H_{21}), 2.10 (s, 3H, H_{11}). ^{13}C NMR (CDCl_3): $\delta = 186.0$ (C4), 184.0 (C1), 145.8 (C3), 141.07 (C2), 135.6 (C15), 134.8 (C13), 133.6 (C7), 133.5 (C8), 132.7 (C10), 132.5 (C5), 128.1 (C20), 126.9 (C9), 126.4 (C6), 121.7 (C17), 120.3 (C18), 119.3 (C19), 110.8 (C16), 106.7 (C18), 15.4 (C12), 13.4 (C21). EIMS: m/z (%): 302 M+H (100), 287 (95), 284 (35), 270 (25), 146 (5). HRMS calcd for $\text{C}_{20}\text{H}_{16}\text{NO}_2$ [M+1]: 302.1181, found: 302.1188.

Results and discussion

The TfOH is a commonly used superacid ($H_o = -14.1$) and is an effective catalyst for many transformations. Its use is preferable to other acids with similar acid strength (e.g. H_2SO_4 , ClSO_3H , FSO_3H) as it does not promote oxidative side reactions.

In this report, we wish to report a simple, convenient and efficient protocol for the synthesis of indolynaphtho and benzoquinones using a catalytic amount of TfOH under mild conditions. We have used a ratio quinone/indole = 2:1 in order to favour the formation of monoindolylquinone and to

limit the formation of diindolylindoles. In all cases, the reactions proceeded rapidly in DCM, at room temperature. The products were characterized by ^1H , ^{13}C NMR, IR and mass spectroscopic data. We have not studied benzoquinone itself because it reacts rapidly and it is known that benzoquinone is easily protonated by weak acids or even by water.^{8,10}

Treatment of 1,4-naphthoquinone **3** with indole in the presence of 2 mol % of TfOH at room temperature gave 2-(3-indolyl)-1,4-naphthoquinone **3a** in 55 % yield. All the reactions of indoles **a-d** with naphthoquinone **3** give pure products, monoindolyl-naphthoquinones, with similar yields.

Methylbenzoquinone **2** can lead to the formation of different regioisomers **2 α** and **2 β** . However in the literature, only the regioisomer **2 α** corresponding to a 1,4 attack relative to the methyl has been reported with indole and 2-methylindole. According to the nature of indoles, different results are obtained with triflic acid. For the 3-methylindole, the condensation takes place on the opposite side of the methyl probably due to steric hindrance, and conducts to the expected regioisomer **2 α** . Concerning 2-phenylindole, only the stereoisomer **2 β** is produced. On the other hand, 2-methylindole affords the two regioisomers, in equal amount with a total yield of 72 %. In fact, it is not surprising to obtain the regioisomer **2 β** , the carbocation corresponding to its formation is the most stabilized by the presence of the methyl group.

In a similar way, 2-methyl-1,4-naphthoquinone (**4**, menadione) afforded 2-(3-indolyl)-1,4-naphthoquinones derivatives **4b** and **4d**. Menadione is less reactive in Thiele-Winter reaction in which the intermediate is the same as in reaction of quinone with indole.

Surprisingly, different results were obtained from the reaction of menadione **4** with 2-methylindole **b**. The naphthoquinone **4** afforded the expected 3-indolylquinone **4b** (2-methyl-3-(2-methyl-1H-indol-3-yl) naphthalene-1,4-dione (45% of yield), along with a small amount (10%) of 2-methyl-4-(2-methyl-1H-indol-3-yl) naphthalen-1-ol **4y**.

This product **4y** was already reported in literature and a mechanism of formation has been proposed.¹² The condensation takes place on the carbonyl group of the quinone, followed by an elimination of a molecule of water. A similar reactivity, rather rare, have been observed with hydroxyquinones but not with menadione.

The monoindolyl products, prepared from different indoles and quinones exhibit sometimes pharmaceutical properties as antitumoral properties. Yet, relatively little attention has been focused on this type of compounds contrary to natural diindolylquinones¹³ which are well known for their antitumoral properties. Preliminary results show that all products (**3a-3d**) were found active against four types of cancer cell types but **3c** was found particularly active (0.1 μMol) against B16F10.¹⁴

Conclusion

In conclusion, triflic acid is an excellent catalyst for the synthesis of indolylquinones. Triflic acid exhibits an unusual reactivity with methylquinone and menadione leading to new derivatives which are fully characterized. The monoindolyl-naphthoquinones were tested on four types of cancer cells, all of them displayed interesting antiproliferative activity, and the compound **3d** was found as very promising.

Acknowledgments

We gratefully acknowledge the CNRS (National Center for Scientific Research), the "Region Basse Normandie", the University of Boumerdes (Algeria), the Franco-Algerian program for the Superior Education (PROFS), and the Algerian-French cooperation for a BAF grant for Feyriél Dridi. Also the authors thank Baptiste Rigaud for NMR spectra and Mrs. Karine Jarsalé for ESIMS and HRMS analysis. The authors thanks Pr. Marc Lecouvey and Odile Sainte-Catherine (CSPBAT, Bobigny, France) for the preliminary screening on human cell line

References

- Finley, K.T. "The addition and substitution chemistry of quinone", in *The chemistry of quinonoid compounds*, chap.17, pages 878-1126, S. Patai editor, J. Wiley and Sons, **1974**.
- Hinsberg O., Himmelschein A., *Ber.*, **1896**, 29, 2023-2029.
- Thiele J., Meisenheimer J., *Ber.*, **1900**, 33, 675-676.
- Oliveri-Mandala, E., Calderaro E., *Gaz. Chim. Itat.*, **1915**, 45, 120, 307.
- Hinsberg O., *Ber.*, **1894**, 27, 3259-3261 ; Hinsberg O., *Ber.*, **1895**, 28, 1315-1320 ; Snell, J. M., Weissberger, A., *J. Am. Chem. Soc.* **1939**, 6, 450-453 ; Porter, R. F., Rees, W. W., Frauenglass, H., Wilgus, S., *J. Org. Chem.* **1964**, 29, 588-594.
- Suida, H., Suida, W., *Ann. Chem.*, **1918**, 416, 113-163.
- We are unable to reproduce the selectivities and the yields claimed by Yadav *et al.*: Reddy A.V., Ravinder K., Venkateshwar Goud T., Krishnaiah P., Raju T.V., Venkateswarlu Y., *Tetrahedron Letters*; **2003**, 44, 6257-6260; Yadav J.S., Reddy B.V.S, Swamy.T., *Synthesis*. **2004**, 1, 106-110.
- Hai-Bo Zhang, Li Liu, Yong-Jun Chen, Dong Wang, Chao-Jun Li, *Eur. J. Org. Chem.*, **2006**, 4, 69-873.
- (a) Mohlaur R., Redlich R. *Ber.* **1911**, 44, 3605-3608; (b) Bu'Lock J. D., Harley-Mason J., *J. Chem. Soc.* **1951**, 703-711; (c) Bruce J. M., *J. Chem. Soc.* **1959**, 2366-2375 ; (c) Maiti A. K., Bhattacharya P., *J. Chem. Res. (S)* **1997**, 424-425 (d) Henrion J.C, Jacquet B., Hocquaux M., Lion C., *Bull. Soc. Chem. Belges.*, **1994**, 103, 163-168
- (a) Villemin, D.; Hammadi, M.; Bar, N. *Tetrahedron Lett.*, **1997**, 38, 4777-4778; (b) Villemin, D.; Bar, N.; Hammadi, M.; Hachemi, M. *J. Chem. Res. (S)*, **2000**, 356-358.
- The classification of the nucleophilicities of indols presented here was based on the level of the LUMO of indols obtained by semiempirical MP6 computation: 3-methylindole: -8.16 eV; 2-phenylindole: -8.27 eV; 2-methylindole -8.29 eV; Indole: -8.41 eV. For experimental studies of nucleophilicities of indols see: Lakhdar S., Westermaier M., Terrier F., Goumont R., Boubaker T., Ofial A. R., Mayr H., *J. Org. Chem.*, **2006**, 71, 9088-9095.

- ¹²Kouloouri S., Malamidou-Xenikaki E., Spyroudis S., *Tetrahedron Lett.*, **2005**, 10894-10902.
- ¹³(a) Shimizu S., Yamamoto Y., Inagaki J., Koshimura S., *Gan.* **1982**, 73, 642-8; (b) Pirrung M. C., Park K., Li Z., *Org. Lett.* **2001**, 3, 365-367; Pirrung M. C., Deng L., Li Z., Park K. J., *Org. Chem.* **2002**, 67, 8374-8388; c) Kouloouri S., Malamidou-Xenikaki E., Spyroudis S., *Tetrahedron.* **2005**, 61, 10894-10902.
- ¹⁴(a) Dridi F., Bar N., Sainte-Catherine O., Hachemi M., Lecouvey M., Villemain D., *Eur. Chem. Bull.*, **2014**, 3, 1020-1026, (b) F. Dridi, Ph. D., University of Boumerdès, 2015.

Received: 12.11.2015.

Accepted: 04.02.2016.