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

Feyriel 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-indolylnaphthoquinones.

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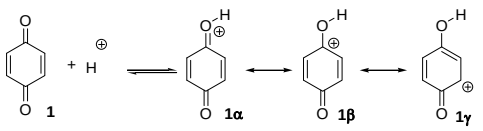
Introduction

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 indoylhydroquinone in the first step.



Scheme 1. Protonation of quinones.

After an oxidation step, the resulting indoylquinone can react in a similar way with a second equivalent of indole providing bisindoylhydroquinones. Moreover, in this step, two isomers are likely to be formed. As hydroquinones, bisindoylhydroquinones can be oxidated to bis(indoyl)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 methylnaphthoquinone (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 protoned quinone. The reaction with indoles depends also of the nucleophilicity of indoles.[11]

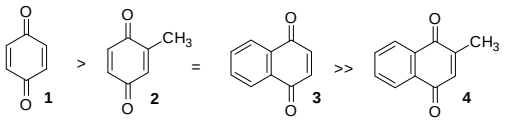


Figure 1. Order of reactivity of quinones.

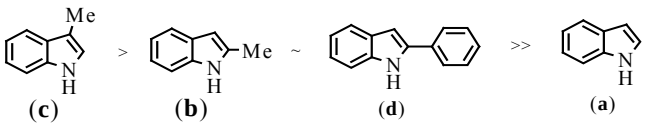


Figure 2. Order of reactivity of indoles.

During our studies on Thiele acetylation of menadione,[11] triflic acid (trifluromethanesulphonic acd, TfOH) was found to be a particularly convenient catalyst, able to broader 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

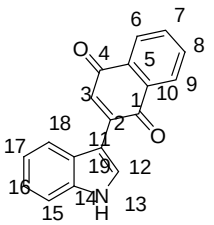
General procedure

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 Na_2SO_4, 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-3yl-benzoquinone. Spectral data for selected products are given below.

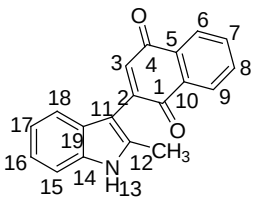
Table 1. Trifluoromethanesulfonic acid catalyzed reaction of indoles to quinones.

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	**2αb, 2βb**	24	36/36
6	c	2	**2αc**	24	45
7	d	2	**2βd**	24	55
8	b	4	**4b 4γ**	24	45/10
9	d	4	**4d**	24	50

[a] Isolated products, except for the mixture 2αb, 2βb determined by NMR (ratio1:1)



(**3a**)



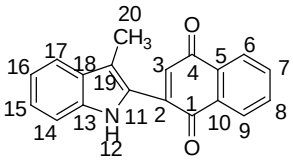
(**3b**)

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

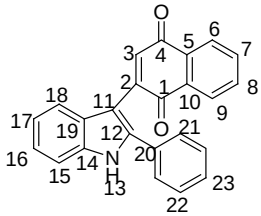
M. P. 205-206 °C. IR: 3239, 1589, 1556, 1255, 1230 cm^{-1}. ^1H NMR ($CDCl_3$) : δ = 8.53 (s, 1H, NH_{13}), 8.05 (d, *J=3.2 Hz* 1H, H_{12}), 7.98-7.95 (m, 1H, H_9), 7.94-7.91 (m, 1H, H_6), 7.81-7.76 (m, 1H, H_{18}), 7.58-7.51 (m, 2H, $H_{7,8}$), 7.29-7.23 (m, 1H, H_{17}), 7.46 (s, 1H, H_3), 7.13-7.06 (m, 2H, $H_{16,17}$). ^{13}C NMR ($CDCl_3$) : 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 $C_{18}H_{12}NO_2$ [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 ($CDCl_3$): δ = 8.36 (s, 1H, NH_{13}), 8.22-8.17 (m, 1H, H_9), 8.18-8.13 (m, 1H, H_6), 7.81-7.74 (m, 2H, $H_{7,8}$), 7.54 (d, *J=6.8 Hz*, 1H, H_{18}), 7.34 (d, *J=6.8 Hz*, 1H, H_{15}), 7.22-7.12 (m, 2H, $H_{16,17}$), 7.10 (s, 1H, H_3), 2.48 (s, 3H, CH_3, H_{20}). ^{13}C NMR ($CDCl_3$): 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 $C_{19}H_{13}NO_2$ [M+1] : 288.1025, found: 288.1018.



(**3c**)



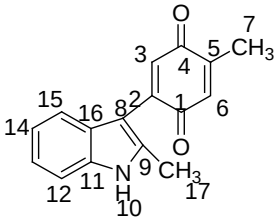
(**3d**)

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

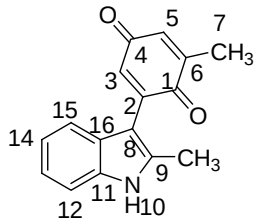
M. P. 205-206 °C. IR: 3385, 1644, 1588, 1563, 1331, 1301, 1253 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 10.45 (s, 1H, NH_{12}), 8.19 (d, *J=6.5 Hz,* 1H, H_6), 8.13 (d, *J=6.5 Hz,* 1H, H_9), 7.81-7.79 (m, 2H, $H_{7,8}$), 7.65 (d, *J= 7.8 Hz*, 1H, H_{17}), 7.43 (d, *J= 7.8 Hz*, 1H, H_{14}), 7.29 (t, *J= 7.8 Hz*, 2H, H_{15}), 7.27 (s, 1H, H_3), 7.14 (t, *J= 7.8 Hz,* 1H, H_{16}), 2.62 (s, 3H, CH_3,H_{20}). ^{13}C NMR ($CDCl_3$): 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 $C_{19}H_{13}NO_2$ [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 ($CDCl_3$): δ = 9.30 (s, 1H, NH_{13}), 8.12 (dd, *J=7.6 Hz, J=1.2 Hz,* 1H, H_6), 7.95 (dd, *J= 7.6 Hz, J=1.2 Hz*, 1H, H_9), 7.75 (td, *J= 7.6 Hz, J= 1.2 Hz*, 1H, H_7), 7.69 (td, *J= 7.6 Hz, J= 1.2 Hz, 1H, H_8),* 7.61 (d, *J=7.2 Hz*, 1H, H_{18}), 7.46-7.42 (m, 2H, H_{21}), 7.39 (d, J=7.2 Hz, 1H, H_{15}), 7.33-7.28 (m, 3H, $H_{22,23}$), 7.24 (t, *J= 7.6 Hz*, 1H, H_{16}), 7.22 (d, *J= 7.6 Hz,* 1H, H_{17}), 7.18 (s, 1H, H_3). ^{13}C NMR ($CDCl_3$): 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 $C_{24}H_{16}NO_2$ [M+H] : 350.1181, found: 350.1194.



(**2αb**)



(**2βb**)

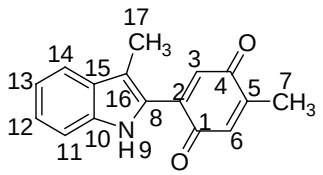
2-Methyl-5-(2-methyl-1H-indol-3-yl)cyclohexa-2,5-diene-1,4-dione (2αb)

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 $C_{16}H_{14}NO_2$ [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)

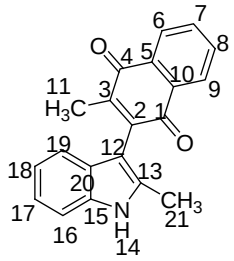


(**2αc**)

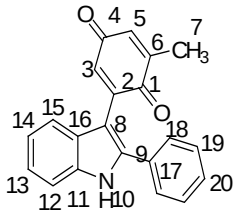
M. P. 190-191 °C. IR: 3378, 1617, 1568, 1505, 1330, 1168. ^1H NMR ($CDCl_3$): 10.28 (s, 1H, NH_9), 7.62 (d, *J= 8.0 Hz*, 1H, H_{14}), 7.39 (d, *J= 8.0 Hz*, 1H, H_{11}), 7.27 (t, *J= 8.0 Hz*, 1H, H_{12}), 7.12 (t, *J= 8.0 Hz*, 1H, H_{11}), 7.03 (s, 1H, H_3), 6.67 (q, *J= 1.6 Hz*, 1H, H_6), 2.56 (s, 3H, H_{16}), 2.11 (d, *J= 1.6 Hz*, 3H, H_7). ^{13}C NMR ($CDCl_3$): δ = 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 $C_{16}H_{14}NO_2$ [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, $H_{12,18,19,20}$), 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 $C_{21}H_{16}NO_2$ [M+1] : 314.1181, found: 314.1177.



(**4αb**)



(**2βd**)

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 ($CDCl_3$): δ = 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, $H_{7,8}$), 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 ($CDCl_3$): δ = 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 $C_{20}H_{16}NO_2$ [M+1] : 302.1181, found: 302.1188.

Results and discussion

The TfOH is a commonly used superacid (*Ho* = -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 indolylnaphtho 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 monoindoylquinone and to

limit the formation of diindoylindoles. In all cases, the reactions proceeded rapidly in DCM, at room temperature. The products were characterized by ^{1}H, ^{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-naphtoquinone **3a** in 55 % yield. All the reactions of indoles **a-d** with naphthoquinone **3** give pure products, monoindoylnaphthoquinones, with similar yields.

Methylbenzoquinone **2** can lead to the formation of different regioisomers **2α** and **2β**. However in the literature, only the regioisomer **2α** 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 **2αc**. Concerning 2-phenylindole, only the stereoisomer **2β** 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 **2β**, 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 **4γ.**

This product **4γ** 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 diindoylquinones[13] 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 monoindolylnaphthoquinones were tested on four types of cancer cells, all of them displayed interesting antiproliferative activity, and the compound **3d** was found as very promising.

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