A Mild and Versatile Friedel-Crafts Methodology for the Diversity-Oriented Synthesis of Redox-Active 3-Benzoylmenadiones with Tuneable Redox Potentials

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Leandro Cotos,[a] Maxime Donzel,[a] Mourad Elhabiri,*[a] and Elisabeth Davioud-Charvet,*[a]

Abstract: A series of highly diversified 3-aroylmenadiones was prepared by a new Friedel-Crafts acylation variant/oxidative demethylation strategy. A Mild and versatile acylation was performed between 1,4-dimethoxy-2-methylnaphthalene and various activated/deactivated benzoic and heteroaromatic carboxylic acids, in the presence of mixed trifluoroacetic anhydride and triflic acid, at room temperature and air moisture. The 1,4-dimethoxy-2-methylnaphthalene-derived benzophenones were isolated in high yield, and submitted to oxidative demethylation with cerium ammonium nitrate to produce 3-benzoylmenadiones.

All *1,4*-naphthoquinone derivatives were investigated as redox-active electrophores by cyclic voltammetry. The electrochemical data recorded on 3-acylated menadiones are characterized by a second redox process whose potentials cover a wide range of values (500 mV). These data emphasize the ability of the reached structural diversity at the 3-aroyl chain of these electrophores to fine-tune their corresponding redox potentials. These properties are of significant importance in the context of antimalarial drug development and understanding of the mechanism of bioactivation/action.

Introduction

1,4-Naphthoquinones (NQs) are redox-active compounds widespread in all kingdoms of life, synthesized in microorganisms and plants used in traditional medicine as secondary bioactive metabolites.[1] They are well represented in numerous natural products with biological activities (*e.g.* antibiotic, anticancer, antiparasitic) and are generated in many vital metabolic processes.[2] Structurally, the NQ core, in its oxidized form (NQ_{ox}), is responsible for redox properties due its ability to accept one or two electrons. In the presence of oxygen, the resulting dihydronaphthoquinone (NQ_{red}) can transfer 1 or 2 electrons in reactions regenerating the NQ_{ox} form, and releasing reactive oxygen species.[3] Numerous NAD(P)H-dependent flavoproteins of the oxido-reductase family reduce NQs, and these latter were described as redox-cyclers or "subversive substrates" of these flavoenzymes[4] (Figure 1). A well-known example is menadione (2-methyl-*1,4*-naphthoquinone or vitamin K3). In particular, 3-benzoylmenadiones (**1**) were proven to be highly oxidant compared to the parent menadiones[5] and proposed to be the active principles of potent antimalarial 3-benzylmenadiones.[6] Variation of the substitution pattern at the west or east parts of the electroactive core of NQs[2],[7],[8] modulates the electrochemical properties and thus both their biological and pharmacokinetic activities.

Benzoyl-*1,4*-naphthoquinones are also privileged scaffolds in medicinal chemistry.[6],[7] From a synthetic point of view, they are valuable molecular templates in drug discovery to produce lead compounds or crucial intermediates in multistep synthesis to build complex natural products (Figure 1).[9] As such, 2-benzoyl-NQs have been reported as key intermediates for the synthesis of 7H-benzo[*c*]xanthen-7-ones,[10] or advanced precursors to obtain the complex polycyclic 1,4-dioxygenated xanthone aglycone, IB-00208.[9] These key moieties have also defined a smart strategy in the total 4 step-synthesis of the naturally occurring red pigment radermachol,[11] improving the previous synthetic scheme.[12]

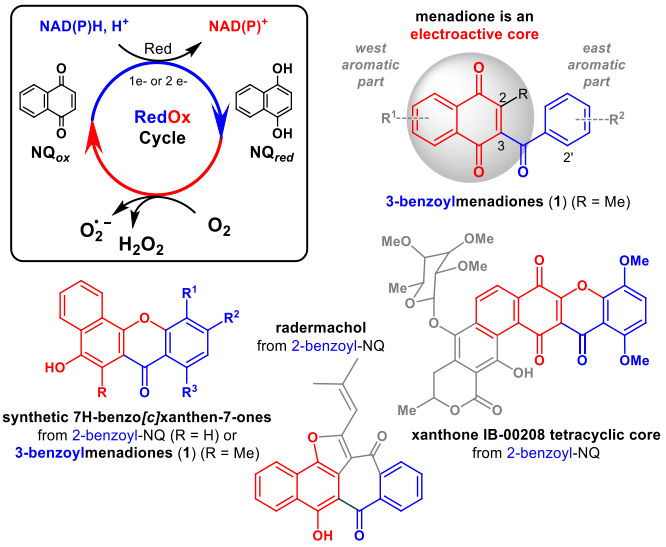

Figure 1. Natural and synthetic menadione derivatives polysubstituted at the aromatic ring including menadione (2-methyl-*1,4*-naphthoquinone).

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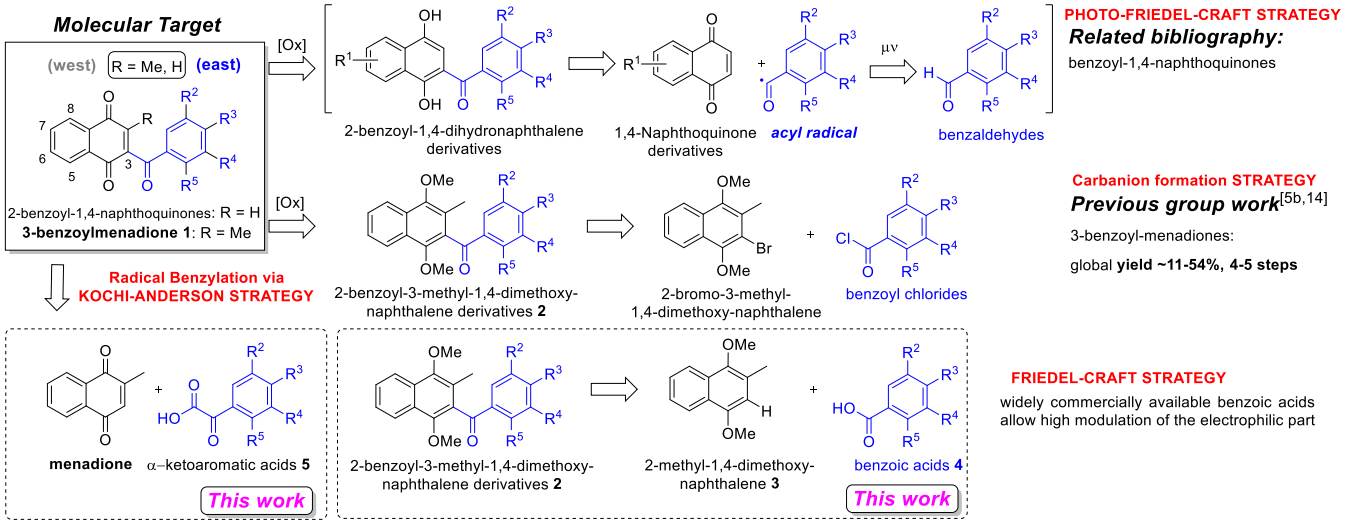


Scheme 1. Synthesis of 3-benzoylmenadione derivatives **1** (R = Me) starting from 1,4-dimethoxy-2-methyl-naphthalene **3** and benzoic acids **4**.

One of the strategies to build 2-benzoyl-*1,4*-naphtoquinone moieties is based on the generation of the 2-benzoyl-1,4-dihydro-naphthalene, this hydroquinone is readily oxidized into the target quinone moiety. Photo-Friedel-Crafts acylation of NQs with a large stoichiometric excess of aromatic aldehydes provided the 2-benzoyl-dihydro-naphthalene derivatives (Scheme 1).[13] Previous work of the group to synthesize 3-benzoylmenadione derivatives **1** was based on the formation of a carbanion after i) bromination of the reduced and protected form of menadione, *i.e.* the 1,4-dimethoxy-2-methylnaphthalene, ii) halogen/metal exchange, followed by iii) addition of benzoic chloride to give 2-benzoyl-3-methyl-1,4-dimethoxy-naphthalene derivatives **2**, and finally, iv) oxidative demethylation by cerium ammonium nitrate (CAN) (Scheme 1).[5b],[14]

Friedel-Crafts acylation process is widely used to synthesize benzophenones moieties (Scheme 1). From the original version[15] based on the use of $AlCl_3$ in stoichiometric amount with a benzoyl chloride at high temperature, the corresponding acylium cation is formed, allowing an electrophilic aromatic substitution (S_EAr) by the corresponding aromatic nucleophile. In this scenario, $HCl_{(g)}$ and toxic aluminium metal waste are generated. Several improvements were further described, *e.g.* solvent-free conditions made the process greener when Zn[16] or ZnO[17] were used as Lewis acids. Alternatively, Brønsted acid to activate the aroyl chloride was reported using a catalytic amount of the non-toxic perfluorinated acid resin Nafion-H[18], trifluoromethanesulfonic acid (or triflic acid, TfOH)[19] and bis(trifluoromethylsulfonylimino)-trifluoromethanesulfonic acid.[20] Combination of Lewis and Brønsted acids was also shown to be an efficient acylation method using benzoyl chlorides.[21] Benzoyl chlorides are known to be substrates for benzoyltriflate generation providing excellent acylating agents.[22] To render the process more efficient, benzoic acids can be used as acylating reactants to avoid the use of chlorinated reagents. Methanesulfonic acid appeared in literature to perform acylations in combination with other reagents, such as Eaton's reagent (P_2O_5)[23], Alumina[24] or Graphite.[25] Also, P_2O_5[26] and the combination P_2O_5/SiO_2[27] was applied to activated and deactivated benzoic acids, and methanesulfonic anhydride[28] was shown to promote acylation of aryl and alkyl carboxylic acids in metal- and halogen free conditions. Most of the cited methodologies required dry conditions, high temperatures, or pre-activation of the reagents. Nevertheless, noticeable progress has been made by using trifluoroacetic anhydride (TFAA)[29] or trifluoroacetic acid/trifluoroacetic anhydride (TFA/TFAA),[11],[30] under mild heating conditions and air moisture, to allow S_EAr of activated and non-strong deactivated benzoic acids, depending on the nucleophilicity strength of the aromatic compound.

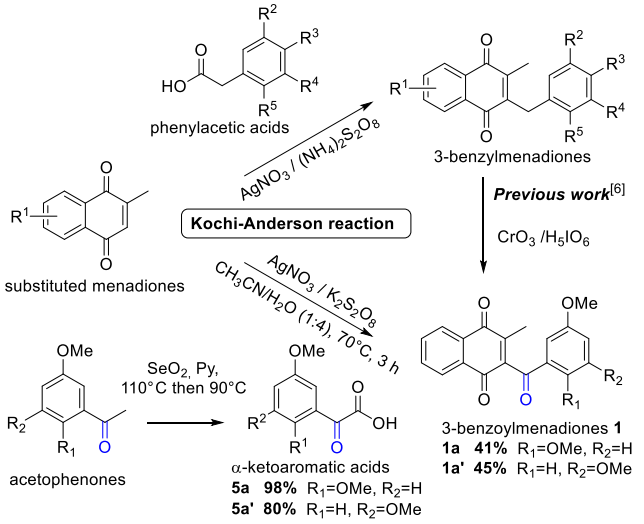
Taking the acylation of 1,4-dimethoxy-2-methylnaphthalene **3** by several activated and (strongly) deactivated benzoic/heteroaromatic carboxylic acids **4** as a model reaction to incorporate a new pattern of substitution at C-3 of menadione, we developed a versatile Friedel-Crafts acylation variant to produce the benzophenone intermediates in mild conditions, *i.e.* air moisture and room temperature, in moderate to excellent yields (Scheme 1). In a second step, the diversified 3-benzoylmenadiones **1** were almost quantitatively produced after demethylation/oxidation with CAN. All the final compounds were evaluated for their electrochemical properties by cyclic voltammetry. Thus, the incorporation of the broad structural diversity in the 3-acylated chain of menadione brought new insights in the understanding of the bioactivation/action mechanisms and the structure-electroactivity relationships of this important new electrophore series at the origin of the potent antimalarial activity of 3-benzylmenadiones.

Results and Discussion

Preliminary Study

Previous strategies developed in the team to obtain polysubstituted 3-benz(o)ylmenadiones at both aromatic parts west (quinonic moiety) and east (benzoic core) were based on the Kochi-Anderson reaction shown in Scheme 2.[6],[7b] Phenylacetic acids in the presence of a catalytic amount of silver salt with stoichiometric excess of an oxidant (peroxodisulfate) undergo radical decarboxylation upon heating. The resulting benzyl radical specifically thus undergoes a nucleophilic radical addition to menadione core at the C-3 position generating the corresponding 3-benzylmenadione. In the next step, 3-benzoylmenadiones **1** were produced by benzylic oxidation using CrO_3/H_5IO_6 reagent system.[6]

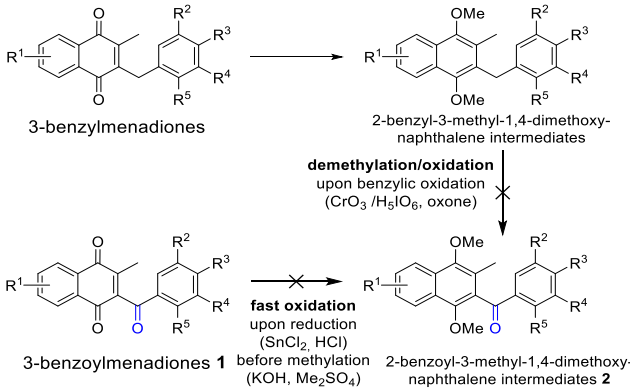
A first straightforward pathway to synthesize 3-benzoylmenadiones **1** was investigated by a silver(I)-catalyzed decarboxylation reaction[31] between menadione and α-ketoaromatic acids **5** according to the reaction shown in Scheme 2. To do so, starting α-keto acids **5a** and **5a'** had to be prepared, first, by a described method[32] and were obtained with 80 and 98%, respectively. When the Kochi-Anderson reaction conditions were applied to menadione and α-ketoaromatic acids **5**, an acyl radical was generated, producing directly the 3-benzoylmenadione derivatives **1a** and **1a'** in 45% and 41% yield, respectively (Scheme 2).



Scheme 2. Kochi-Anderson reactions used to synthesize 3-benz(o)yl-menadiones, in particular 3-benzoylmenadiones **1a** and **1a'**.

However, these strategies to build the 3-benzoylmenadione **1** core displayed several drawbacks to provide a widely diversified chemical library. Phenylacetic and α-ketoaromatic acids are not broadly commercially available. The synthesis of phenylacetic acids from benzaldehydes[33] and benzoic acids[34] are not very convenient to build a chemical library because it involves multiple steps, long time of reactions, expensive reagents with non versatile protocols to achieve their production. In the next step, the benzylic oxidation with CrO_3/H_5IO_6 proceeded with low to moderate yields along with many side-products and high toxicity for the environment.[6] In parallel, synthesis of 3-benzoylmenadiones (*e.g.* **1a**, **1a'**, Scheme 2) from α-ketoaromatic acids **5** resulted in poor yields. The use of the Kochi-Anderson reaction showed incompatibilities with hydroxyl[6] and amino[7c] groups, and low efficiency to introduce pyridine rings[7a].

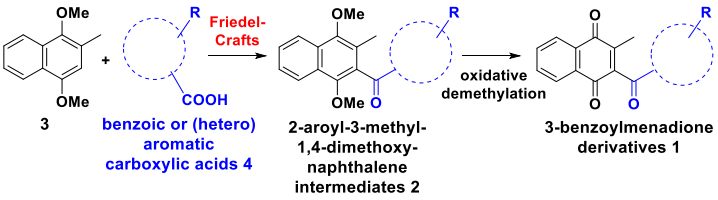
Firstly, the direct functionalization of the benz(o)ylmenadione skeleton has proven to be difficult due the presence of the C2-methyl group attached to the quinone moiety, which is highly base-sensitive. Secondly, the functionalization of the benz(o)ylmenadione derivatives through the 1,4-dihydro- or 1,4-dimethoxy-3-methyl-2-benz(o)yl-naphthalene intermediates was found difficult to handle (Scheme 3). On the one hand, the 1,4-dimethoxy groups of the benzyl intermediate were demethylated using proton assistance as previously described with the benzylic oxidation using CrO_3/H_5IO_6 (or oxone) as reagents, *i.e.* formation of several side products was observed (Scheme 3). On the other hand, in contact with oxygen traces *(i.e.* despite an argon atmosphere), the produced 2-benzoyl-1,4-dihydro-3-methylnaphthalene intermediate was quickly oxidized into its quinone form before methylation occurred (Scheme 3).



Scheme 3. Side-reactions occurring via the 1,4-dihydro- or 1,4-dimethoxy- 2-methylnaphthalene intermediates.

Preliminary Friedel-Crafts Reaction Study

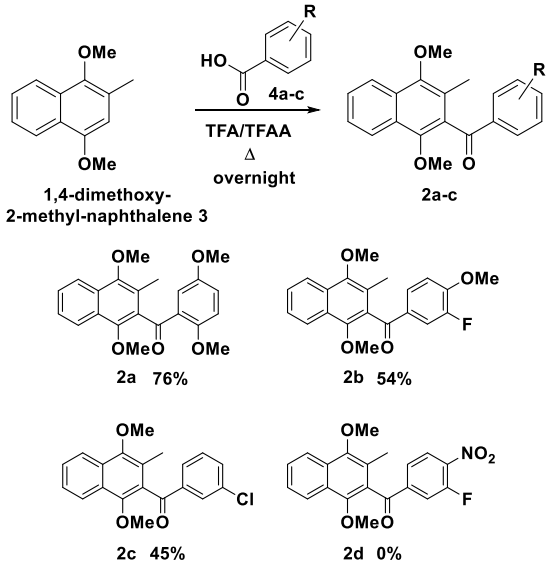
In this work, our objective was to develop a chemical library of structurally diversified electroactive 3-(hetero)aroylmenadiones **1** after incorporation of polysubstituted (hetero)aromatics moieties and to modulate their redox characteristics. Diversity-oriented synthesis (DOS) implies the generation, under efficient and versatile procedures, of functionally diverse small-molecules acting as chemical modulators.[35] In the new strategy reported herein, diversity at the east aromatic part of 3-benzoylmenadione was reached using a large array of readily commercially available benzoic and heteroaromatic carboxylic acids as starting materials. Benzoic acids and heteroaromatic carboxylic acids are acylating substrates for the Friedel-Crafts reaction. The west aromatic part of the 3-benzoylmenadione **1** core was introduced via its 1,4-dimethoxy-2-methylnaphthalene precursor **2** upon the Friedel-Crafts acylation. In the next step, the diversified 3-benzoylmenadiones **1** were generated upon selective oxidative demethylation using CAN (Scheme 4).



Scheme 4. Synthesis of 3-(hetero)aroylmenadione derivatives **1** based on Friedel-Crafts acylation/oxidative demethylation.

The key point is the development of a Friedel-Crafts acylation reaction, which allows electrophilic aromatic substitution from activated or deactivated benzoic and heteroaromatic carboxylic acids under mild conditions, thus promoting an easy experimental protocol, *e.g.* no air moisture-sensitive reagents, no high temperatures, activating the acylating agents *in situ*. TFA/TFAA reagent system has been reported to be an efficient practical system to achieve the S_EAr under mild heating conditions, in open air with air moisture compatibility. As it was reported, this methodology proceeds with non-strongly deactivated and activated benzoic acids **4** (Scheme 5), depending on the nucleophicity of the aromatic nucleophile. Due the high electronic density of 1,4-dimethoxy-2-methylnaphthalene **3**, we first started the screening from activated benzoic acids **4a-c** to generate the 2-benzoyl-3-methyl-1,4-dimethoxy-naphthalene intermediates **2a-c** derivatives with moderate to good yields (Scheme 5). The

mechanism of the reaction likely proceeds through the *in situ* generation of the mixed anhydride, *i.e.* an acyltrifluoroacetyl intermediate,[36] formed between the benzoic acid and TFAA. This intermediate is protically activated by TFA to promote the formation of the corresponding acylium cation. Subsequently, S_EAr of 1,4-dimethoxy-2-methylnaphthalene **3** produced the corresponding 2-benzoyl-3-methyl-1,4-dimethoxy-naphthalene derivatives **2a-c**. Then, following oxidative demethylation by CAN, the 3-benzoylmenadiones **1** were generated in excellent yields. Noteworthy, CAN oxidation is sensitive to the electronic density of the aromatic ring.



Scheme 5. Preliminary study on the Friedel-Crafts reaction to build 2-acylated 3-methyl-1,4-dimethoxy-naphthalene derivatives **2a-c**.

In the 2-benzoyl-3-methyl-1,4-dimethoxy-naphthalene **2a** two pairs of 1,4-dimethoxy moieties are present. Nevertheless, the most electronically rich naphthalene moiety (west aromatic part) promotes faster oxidation than the phenyl fragment (east aromatic part), and only the desired 3-benzoylmenadione **1a** was obtained.

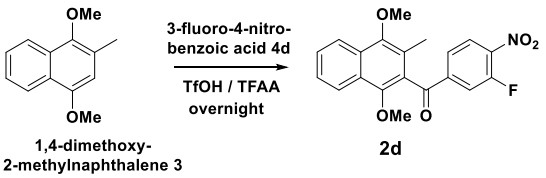
When TFA/TFAA reagent mixture was applied to strongly deactivated benzoic acids, such as 3-fluoro-4-nitrobenzoic acid, the targeted compound was not obtained. Even by increasing the temperature and with longer time of reaction, the acyltrifluoroacetate intermediate was probably not formed with strongly deactivated benzoic acids, despite the presence of the electronically rich aromatic nucleophile, *i.e.* 1,4-dimethoxy-2-methylnaphthalene. Therefore, we directed our acylation study by screening reagents able to activate (strongly) deactivated benzoic acids, like **4d** (Scheme 5), in mild heating conditions and air moisture, to achieve a versatile methodology.

Development of an Optimized Friedel-Crafts Variant

In very specific applied cases, the use of TfOH/TFAA in an equimolecular mixture was used in biological chemistry applications for ferrocene[37] and (D)-biotin[38] acylations. Surprisingly, this reagent system was never applied to perform S_EAr with deactivated aromatic carboxylic acids. Once TfOH and TFAA are combined, the strong trifluoroacetyl agent, *i.e.* trifluoroacetyl triflate (TFAT), is proposed to be generated.[39] We investigated the acylation of 1,4-dimethoxy-2-methylnaphthalene by 3-fluoro-4-nitrobenzoic acid and monitored the progression of the reaction by TLC upon addition of TFAA (4 mL) and TfOH (2 equiv. in 10 mL of dichloromethane) to the reaction mixture at 0°C in open air, and reaction at room temperature without dry conditions (Table 1, entry 1).

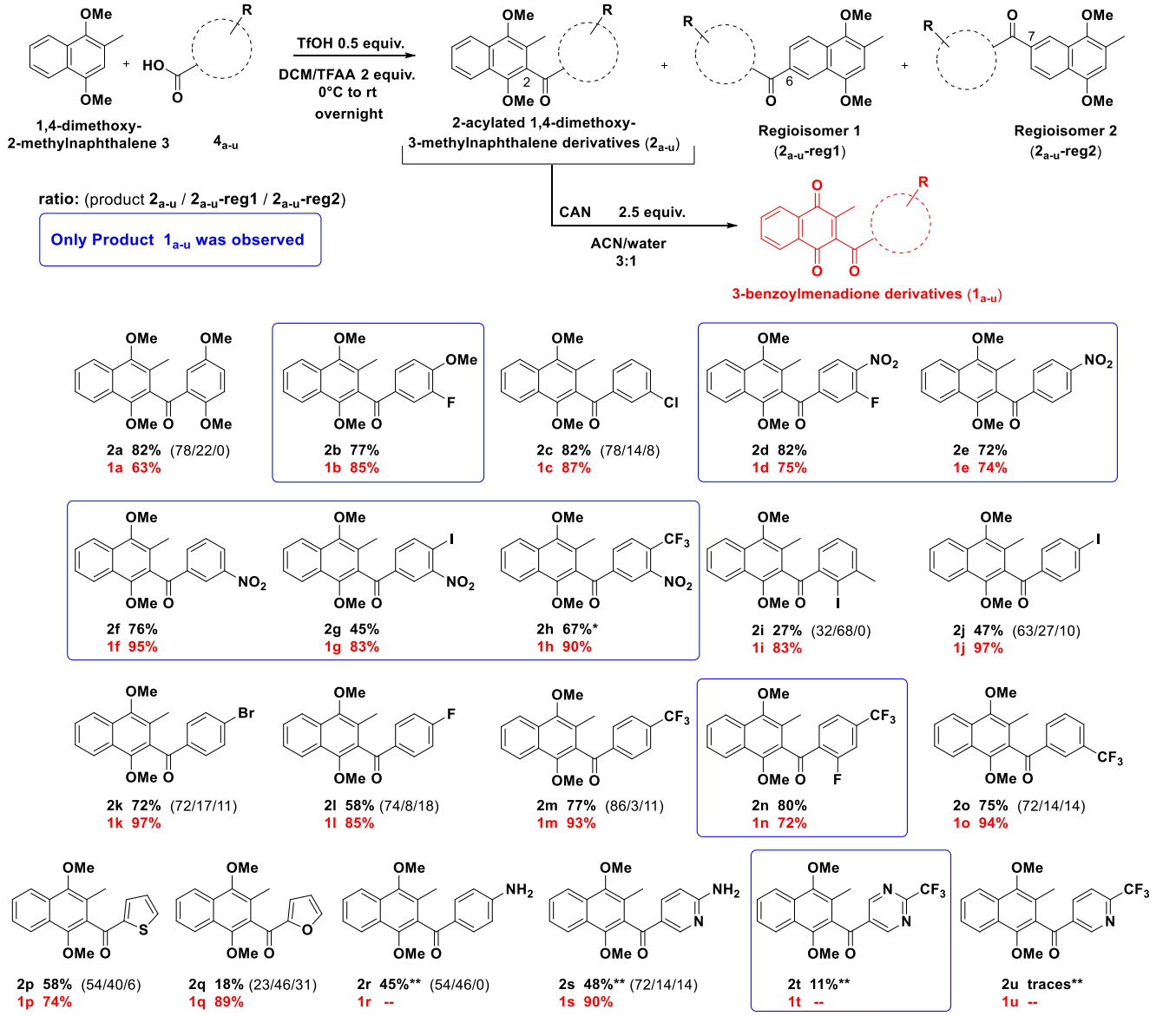
The formation of the targeted compound was clearly evidenced after one hour of reaction, and the desired diarylketone intermediate was isolated in 73 % yield after overnight time of reaction at room temperature. The effect of TfOH on the acylation reaction was then investigated by adding different amounts of TfOH (Table 1, entries 1-4). Catalytic amount of TfOH (0.1 equiv.) provided the product only in traces (entry 4), and the unreactive starting materials was mainly observed in the crude by NMR. Increasing the TfOH amount up to 20% allowed the reaction to proceed but with less than 50% conversion and in low yield (entry 4). Finally, by adding 0.5 equiv. of TfOH, a full conversion was achieved and the benzophenone was isolated in 82% yield (entry 2). Reducing the quantity of TFAA up to 2 equiv. (entry 5) with the optimized TfOH amount (0.5 equiv.) afforded the product with the same yield and with a much cleaner reaction crude. Furthermore, we checked that TFAA or TFAT did not react with 1,4-dimethoxy-2-methylnaphthalene in the absence of the benzoic acid. An excess of 1.5 equiv. of 1,4-dimethoxy-2-methylnaphthalene was required toward benzoic acid because it enhanced the rate of the reaction under these conditions to observe completion of the reaction overnight. Thus, with an easy defined experimental procedure, these experimental conditions at room temperature allowed us to build a wide variety of 2-benzoyl-3-methyl-1,4-dimethoxy-naphthalene derivatives **2a-u**, including those from strongly deactivated benzoic acids, through an efficient Friedel-Crafts acylation variant (Scheme 6). In the next step, the corresponding 3-aroylmenadiones **1a-u** diversified at their east aromatic part were prepared following CAN oxidation with moderate to good yields (72-97%) in the majority of the cases (Scheme 6).

Table 1. Optimization of the model Friedel-Crafts reaction conditions with 1,4-dimethoxy-2-methylnaphthalene **3**[a] and 3-fluoro-4-nitrobenzoic acid **4d**[b].



Entry	TfOH (equiv.)	TFAA (equiv.)	Yield %[c]
1	2	53	73
2	0.5	53	82
3	0.2	53	50
4	0.1	53	trace
5	0.5	2	82

[a] 1.5 equiv., [b] 1.0 equiv., [c] yield after purification.



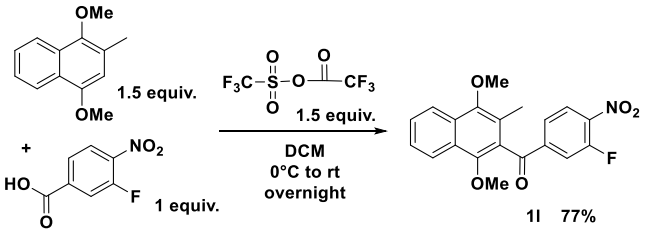
Scheme 6. Scope of the Friedel-Crafts reaction variant between 3-methyl-1,4-dimethoxy-naphthalene **3** and benzoic acids, heteroaromatic carboxylic acids **4** with base sensitive moieties. The ratio between the formed Friedel-Crafts products acylated at C-2, C-6 or C-7 was deduced from a regioisomeric analysis based on carbonyl signals of ^{13}C-NMR of the reaction crude. *: 1.5 equiv. of TfOH was used and the reaction duration was 48h. **: upon addition of 4 equiv. of a mixture TfOH/TFAA (1:1). Abbrev.: The product code of the desired product is 1a-u; 1a-u-reg1 stands for regioisomer 1 (position C-6, *vide infra*), and 1a-u-reg2 for regioisomer 2 (position C-7, *vide infra*).

In parallel, an analysis of the regioisomers was performed by ^{13}C NMR from the crude of the reaction to quantify their nature and the corresponding ratio formed during the acylation reaction (Scheme 6, and the Supporting Information for details from page S13) by integrating the carbonyl signals of the acylated compounds.[40] After isolation and purification of each regioisomer from the crude of the reactions to produce **2i**, **2p**, and **2q** it was possible to attribute the carbonyl signals of each isolated regioisomers upon their ^{13}C NMR analysis. Their structures were found to correspond to the acylated products in position C-6 (regioisomer 1) or C-7 (regioisomer 2) of the 1,4-dimethoxy-2-methylnaphthalene core. The new experimental conditions led to improved (or similar) yields of the acylation products **2a**-**2c** with respect to the previously reported cases using the non-deactivated benzoic acids depicted in Scheme 5. In the case of **2c** with a Cl atom in *meta*, the yield was improved from 45 to 82 % yield. The acylation reaction was observed to be sensitive to steric effects when a bulky group is adjacent to the carboxylic acid (*ortho*), like in the example **2i** the desired benzophenone is obtained in low yield (27%), supporting the formation of another regioisomer isolated in 71 % yield, by acylation of the 1,4-dimethoxy-2-methylnaphthalene in position C-6. With halogens (I, Br, F) in *para,* benzophenones **2j**-**2k**-**2l** were produced in moderate to good yields (47-72-58%, respectively), with a regioselectivity of about 70%. With a Cl atom in *meta* position, the corresponding benzophenone **2c** was obtained in 82% yield with minor regioisomers. Examples with deactivated benzoic acids, incorporating strong electron-withdrawing groups (NO_2 and CF_3) in *para* or *meta*, combined or not with other functionalities (iodo or fluoro), provided excellent yields and regioselectivity. The example **2h**, where a strong deactivated benzoic acid including CF_3 (*para*) and NO_2 (*meta*),

has to be highlighted with the resulting 67% yield of the isolated benzophenone upon addition of 1.5 equiv. of TfOH, attested by the observation of only one carbonyl signal in the crude of the ^{13}C NMR spectrum. The use of non activated heteroaromatic carboxylic acids, like 2-thiophene carboxylic acid or 2-furoic acid led to acylated products **2p** and **2q** incorporating thiophene and furan moieties in the east aromatic part (Scheme 6), from moderate to low yields of the desired product. However, in both cases, i.e. **2p** and **2q**, and also in the case of **2i**, the formation of regioisomers was obtained in higher proportion, probably due to steric effects. However, benzophenone **2q** was obtained with easier experimental conditions compared to the reported reaction using polyphosphoric acid at high temperature.[41] Direct introduction of acid-sensitive moieties like amino group, pyridine and pyrimidine rings could be achieved after addition of 4 equiv. of a mixture TfOH/TFAA (1:1). Examples **2r** and **2s** incorporate an amino group in *para* in the aromatic and pyridine moiety. The excess of generated TFAT allowed the transient protection of the amino group through a trifluoroacetyl amide group. Consequently, in both cases, moderate yields were obtained with low regioselectivity. The trifluoroacetyl amide group was removed in basic conditions. Pyrimidine fragment incorporating CF_3 was introduced in product **2t** formed in 11% yield but no regioisomer was detected. With the CF_3 group in the same position located in the pyridine fragment, only traces of product **2u** were observed. While the oxidative demethylation by CAN produced the 3-acylated menadiones **1a**-**1q** in 63-97% yields (Scheme 6), only two nitrogen-based benzophenones (**2r**-**2t**) led to complex mixtures under these deprotection conditions.

Mechanistic Insight

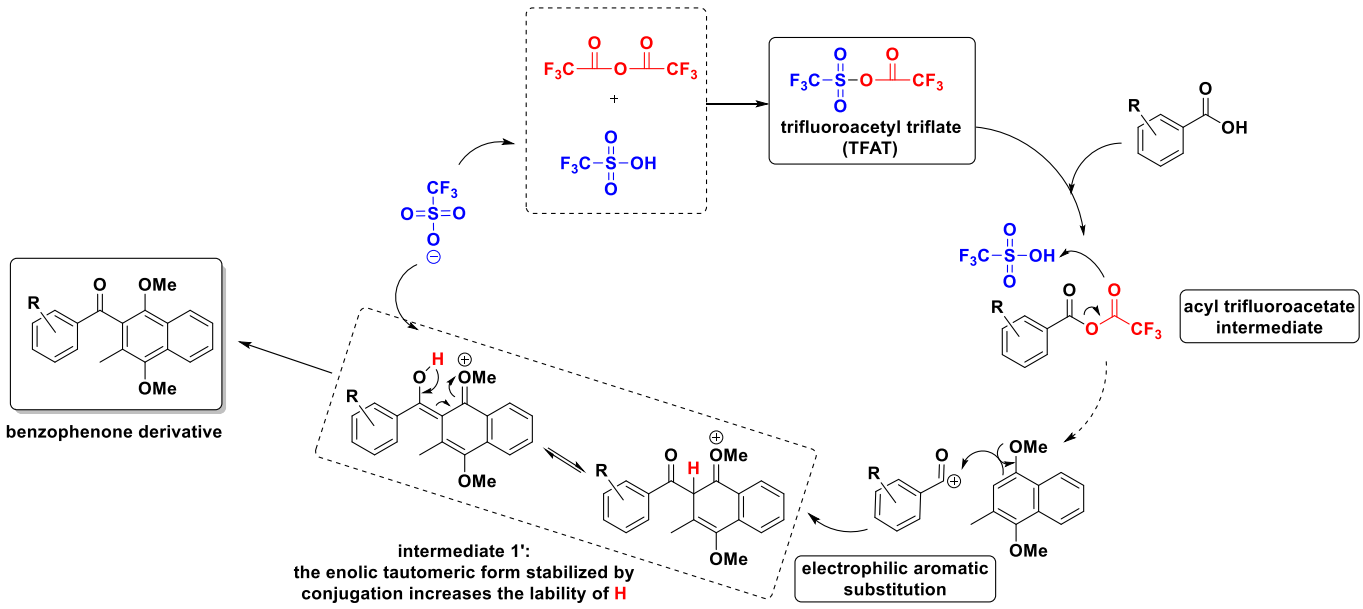
Based on our present results and a literature report, a possible acylation reaction pathway is depicted in Scheme 7, with the reaction between the 1,4-dimethoxy-2-methylnaphthalene and a substituted benzoic acid representative. The mechanism of the reaction is proposed to proceed through the formation of an acyltrifluoroacetyl intermediate from benzoic acid, promoted by the *in situ* generation of the reactive trifluoroacetyl triflate (TFAT) reagent, generated by mixing TfOH and TFAA. TFAT was indeed described as more reactive than TFAA.[39] In this scenario, the acyltrifluoroacetyl intermediate might be formed for deactivated benzoic acids. During the process of trifluoroacetylation, one molecule of TfOH is produced, which, due to its excellent proton donor properties, efficiently activates the acyltrifluoroacetate at low temperature and promotes the formation of the acylium cation, allowing the S_EAr of 1,4-dimethoxy-2-methylnaphthalene. Upon acylation, the intermediate **2'** (Scheme 7), which is in equilibrium with the enolic form (more stable by conjugation), is generated. The OH-enol function likely allowed the regeneration of TfOH and then, release of the targeted benzophenone derivative. *In situ* TFAT formation from TfOH and TFAA was supported by reacting the costly and highly unstable commercial TFAT with 1,4-dimethoxy-2-methylnaphthalene and 3-fluoro-4-nitrobenzoic acid, under the same experimental conditions of the herein described Friedel-Crafts acylation variant. The reaction afforded the desired benzophenone in 77% yield (Scheme 8).



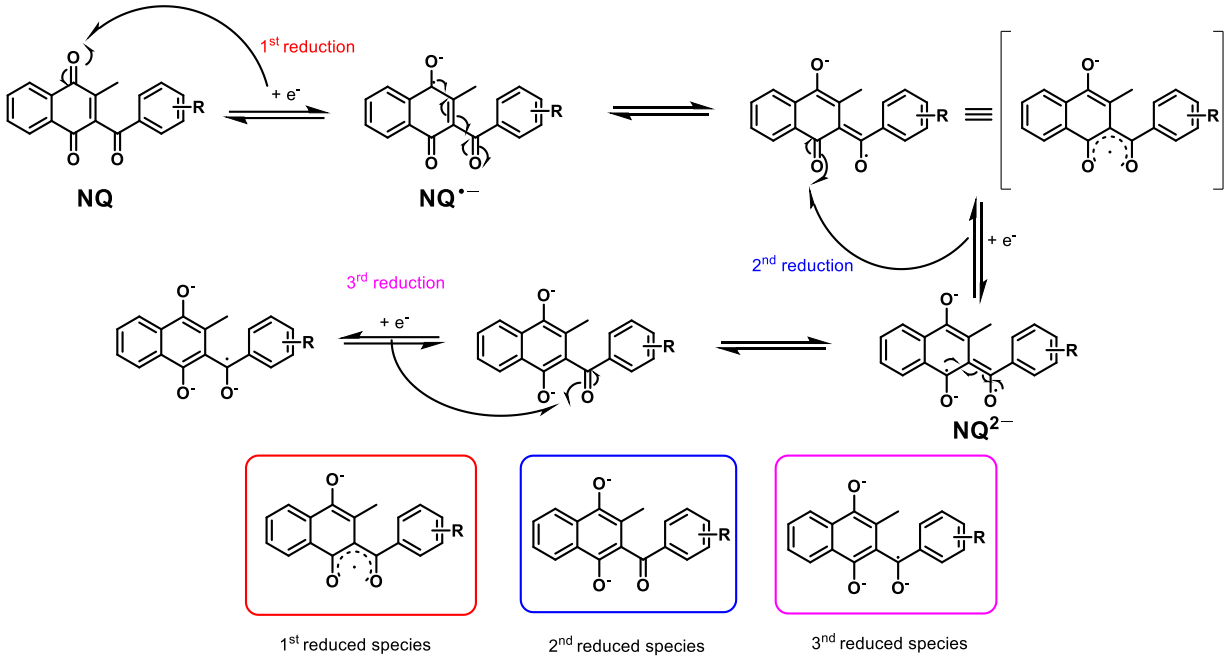
Scheme 8. TFAT as the key reagent for Friedel-Crafts acylation of 1,4-dimethoxy-2-methylnaphthalene by the deactivated 3-fluoro-4-nitrobenzoic acid.

Redox Properties

We will herein discuss the electrochemical data of our homogenous series of 3-acylated-menadiones (Scheme 6). These redox-active compounds only differ by the substitution pattern of their aroyl subunit on the east part of the molecule thus allowing evidencing the key role of this moiety (electronic and steric effects) on the redox modulation of the NQ core.



Scheme 7. Putative mechanism of the Friedel-Crafts variant reaction.



Scheme 9. Proposed mechanism for the consecutive 1-electron transfers centred on 3-benzoylmenadiones derivatives.

Table 2. Electrochemical data measured using cyclic voltammetry (CV)[a] and Square Wave Voltammetry (SWV)[b] for all 3-benzoylmenadione derivatives examined in this work. Solvent: DMSO; *I* = 0.1 M *n*-Bu_4NPF_6, *v* = 200 mV s^{-1}. ($E_{1/2}$ (V), ΔE (mV), $\Delta E_{1/2} = E^1_{1/2}$-$E^2_{1/2}$ (V))

	Quinone		Carbonyl group	Nitro group		
Cpds	$E^1_{1/2}(\Delta E)$[a] $E^1_{1/2}$[b] [V(mV)][a] [V][b]	$E^2_{1/2}(\Delta E)$ $E^2_{1/2}$[b] [V(mV)][a] [V][b]	$E^3_{1/2}(\Delta E)$[a] $E^3_{1/2}$[b] [V(mV)][a] [V]b	$E^4_{1/2}(\Delta E)$[a] $E^4_{1/2}$[b] [V(mV)][a] [V][b]	$E^5_{1/2}(\Delta E)$[a] $E^5_{1/2}$[b] [V(mV)][a] [V][b]	$\Delta E_{1/2}$ $E^1_{1/2} - E^2_{1/2}$ (V)
3-benzoyl-menadione 1[5]	-0.47(92)	-1.19(72)		-	-	0.72
1a	-0.529(90) / *-0.526(78)* -0.505	-1.131(94) / *-1.128(87)* -1.106	br	-	-	0.601
1b	-0.467(90) / *-0.463(73)* -0.447	-1.172(88) / *-1.166(73)* -1.147	-1.610	-	-	0.700
1c	-0.444(88) / *-0.445(73)* -0.427	-1.152(92) / *-1.157(82)* -1.139	-1.638(85) -1.594	-	-	0.712
1d	-0.418(125) / *-0.409(91)* -0.469	-0.773(99) / *-0.778(97)* -0.755	br	-1.002(102) / *-0.997(61)* 0.977	-1.285(111) / *-1.273(85)* -1.249	0.286
1e	-0.412(92) / *-0.413(77)* -0.390	-0.812(96) / *-0.808(77)* -0.789	-1.484	-1.178(105) / *-1.22 (92)* -1.192	-	0.399
1f	-0.409(89)/ *-0.408(86)* -0.385	-0.942(95)/ *-0.945(86)* -0.914	br	-1.148(96) / *-1.140(74)* -1.128	-	0.533
1g	-0.419(82) / *-0.422(76)* -0.396	-0.948(60) / *-0.938(52)* -0.933	br	-1.28(86) / *-1.291(67)* -1.24		0.519
1h	-0.387(94) / *-0.403(78)* -0.362	-0.822(87) / *-0.826(82)* -0.798	-1.728	nd / *-0.985(52)* -0.952	-1.182(84) / *-1.24(72)* -1.158	0.436
1i	-0.434(80) / *-0.425(76)* -0.404	-1.056(76) / *-1.055(70)* -1.038	-1.615	-	-	0.634
1j	-0.455(90) / *-0.444(77)* -0.435	-1.110(96) / *-1.094(77)* -1.091	-1.573	-	-	0.656
1k	-0.450(88) / *-0.449(64)* -0.424	-1.134(92) / *-1.131(73)* -1.102	-1.613	-	-	0.678
1l	-0.457(90) / *-0.451(74)* -0.433	-1.196(92) / *-1.192(80)* -1.176	-1.624	-	-	0.743
1m	-0.431(87) / *-0.417(80)* -0.397	-1.021(86) / *-1.005(80)* -0.984	-1.87	-	-	0.587
1n[b]	E_{1red} = -0.45	E_{2red} = -1.065	nd	-	-	na
1o	-0.423(90) / *-0.420(74)* -0.397	-1.055(94) / *-1.053(80)* -1.029	-1.607	-	-	0.632
1p	-0.462(96) / *-0.460(79)* -0.489	-1.168(100) / *-1.168(79)* -1.202	-1.750	-	-	0.713
1q	-0.468(100) / *-0.464(82)* -0.447	-1.159(92) / *-1.211(76)* -1.135	*-1.631* -1.577			0.691
1s	-0.488(88) / *-0.485(70)* -0.466	-1.093(102) / *-1.117(79)* -1.069	-1.953	-	-	0.603

[a] CVs and [b] SWVs measured in DMSO with 0.1 M *n*-Bu_4PF_6 electrolyte support at 25°C. *v* = 200 mV s^{-1}; reference electrode = KCl(3 M)/Ag/AgCl; working electrode = glassy carbon disk of 0.07 cm^2 area. $E^1_{1/2}$ and $E^2_{1/2}$ are related to the quinone-centred redox processes, $E^3_{1/2}$ is related to the carbonyl benzoyl unit while $E^4_{1/2}$ and $E^5_{1/2}$ characterize the nitro-centred redox processes. br = broad. nd = not determined. na = not applicable. [b] Measured at *v* = 500 mV s^{-1}. The values in italics correspond to measurements at 50 mV s^{-1}.

The redox potentials of the substituted 3-aroyl-menadiones **1** (Table 2 and Figures S1-19 in the Supporting Information) were measured by cyclic voltammetry (CV) and square wave voltammetry (SWV, Table 2) at 23 ± 1 °C using a glassy carbon (GC) working electrode in DMSO solvent and tetra-*n*-butylammonium hexafluorophosphate (*n*-NBu_4PF_6) as the supporting/inert electrolyte. The electrochemical properties measured by SWV were found to be in good agreement with those measured by CV (Table 2). Furthermore, the data recorded for **1f**, **1g**, **1h** and **1a** were found to be in excellent agreement with those measured in a previous communication.[5]

Irrespective of the substitution pattern of the aroyl subunit, no alteration of the global electrochemical profile of the NQ core was observed. Two consecutive one-electron quasi-reversible waves ($E^1_{pc} - E^1_{pa}$ ~80-125 mV and $E^2_{pc} - E^2_{pa}$ ~ 72-100 mV) have been systematically observed under our experimental conditions. NQ reduction indeed occurs *via* two successive one-electron transfers. The monoradical-anion $NQ^{\bullet-}$ is formed in the E_{pc1} reduction step, and is then reduced to its related dihydro-naphthoquinone dianion NQ^{2-} in a second E_{pc2} step. The 3-benzoylmenadiones **1a-s** examined in this work were not subjected to any inter- or intramolecular proton transfers and therefore the electrochemical properties were considered to be strictly associated to the successive formation of the two anionic reduced species.

In addition to these consecutive one-electron transfers, a third (*i.e.* in some cases as for **1h** and **1d**, a fourth redox wave is also observed) redox wave at potential value $E^3_{1/2}$ of about -1 to -1.2 V was also observed for the nitro-benzoyl-menadiones **1d, 1e, 1f**, **1g** and **1h** (Figures S4-S8, S19 in the Supporting Information and Table 2). These additional redox signals most likely result from the reduction of the nitro function.[42] Finally, a last weak, broad and ill-defined wave was often observed at much more negative values ($E^3_{1/2}$ >> -1.5 V) and was attributed to oxidation/reduction processes centred on the benzoyl carbonyl unit (*e.g.* Figure 3).

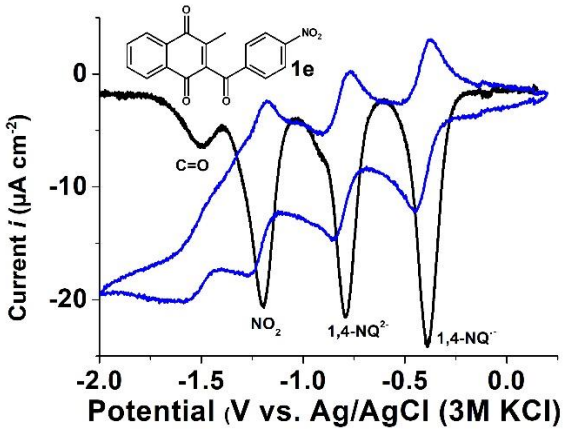


Figure 3. CV (blue) and SWV (black) profiles of **1e** (1.40 mM) measured in DMSO with 0.1 M *n*-Bu_4PF_6 electrolyte support at 25°C. v = 50 mV s^{-1}; reference electrode = KCl(3 M)/Ag/AgCl; working electrode = glassy carbon disk of 0.07 cm^2 area.

Compound **1n** bearing a 2'-fluoro substituent stands in an interesting contrast with the other systems. Reduction at 1 (or 2) electrons afforded an anionic species which can rapidly trigger (at the time scale of the electrochemical experiment) a nucleophilic substitution, at the 2'-position, leading to a benzoxanthone product (Figure 1).[10c] Increasing the voltage sweep rate up to 5 V (Figure S14) indeed allowed us to evidence in the first cycle the characteristic reduction peaks of the benzoquinone unit which then faded completely in the following cycles as a result of the reaction.

Combining previously published data[5] with the present ones, a clear relationship between the half-wave potentials of the first ($E^1_{1/2}$) and second ($E^2_{1/2}$) electrochemical processes can be proposed (Figure). Exceptions have been, however, observed for the 2'-substituted benzoyl-menadiones (*i.e.* steric effect) or proton-donor substituent such as 4'-OH.[5] This feature suggests that the substituents borne by the benzoyl core induce sizeable electronic effects both on the NQ unit or on its 1-electron reduced semi-quinone, $NQ^{\bullet-}$. With respect to the first redox process ($E^1_{1/2}$) of 4'-substituted benzoyl-menadiones, the gap in potential was, however, measured to be only ~ 80 mV between the menadione substituted with a methoxy group[5] in the 4' position and that substituted with a nitro group at the same position (**1e**). This likely suggests weak to no influence of the benzoyl substitution pattern on the first electron transfer of the naphthoquinone redox active core. It is noteworthy, that under its oxidized state, the NQ is poorly conjugated with its benzoyl counterpart.

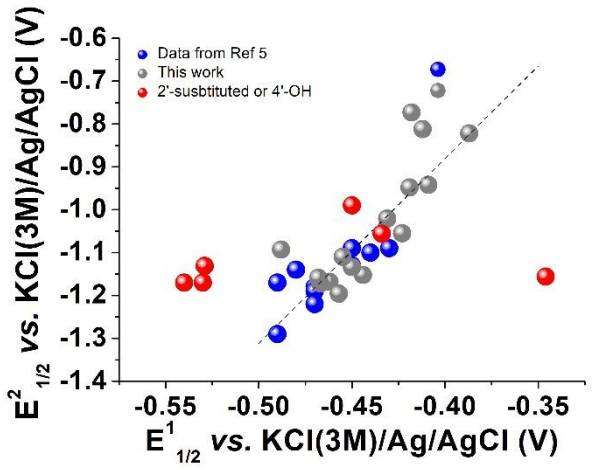


Figure 4. Variation of $E^2_{1/2}$ (V, second redox step) as a function of $E^1_{1/2}$ (V, first redox step). v = 200 mV s^{-1}; reference electrode = KCl(3 M)/Ag/AgCl; working electrode = glassy carbon disk of 0.07 cm^2 area; auxiliary electrode = Pt wire. The dashed line is only provided as a guide for the eyes. ● Data taken from ref [5]. ● Data from this present work. ● Compound with particular behaviour (*e.g.* 2'-substituted or 4'-OH benzoylmenadiones, see text).

By contrast, a marked impact of the 4'-benzoyl substitution can be observed on the second electron transfer leading to the dihydro-naphthoquinone dianion NQ^{2-}. Interestingly, the gap in potential amounts to up 500 mV between the menadione substituted with a carboxylic group in the 4' position[5] and that substituted with a nitro group at the same position (**1e**) (Figure 5). To rationalize this behaviour, we therefore hypothesized that upon the first one electron reduction of the benzoyl-menadiones, the radical is stabilized by the benzoyl carbonyl unit thus allowing electronic communication between the redox-active NQ core and the benzoyl subunit (Scheme 9). Consequently, the second one-electron transfer leading to the dihydro-naphthoquinone dianion NQ^{2-} is thus highly sensitive to the nature of the benzoyl substitution (Figure 5 and Figure S1-S19). Within this series of molecules, the presence of the benzoyl carbonyl function thus allows significantly modulating over a large potential (~ 500 mV)

span the oxidant character of the semi-quinone NQ$^{\bullet-}$ while slightly affecting that of the NQ analogue (~ 80 mV). These properties are of significant importance in the context of antimalarial drug development and understanding of the mechanism of action of the early lead plasmodione.[6]

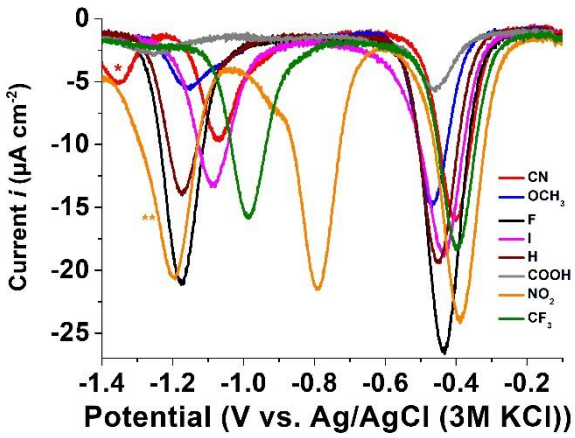
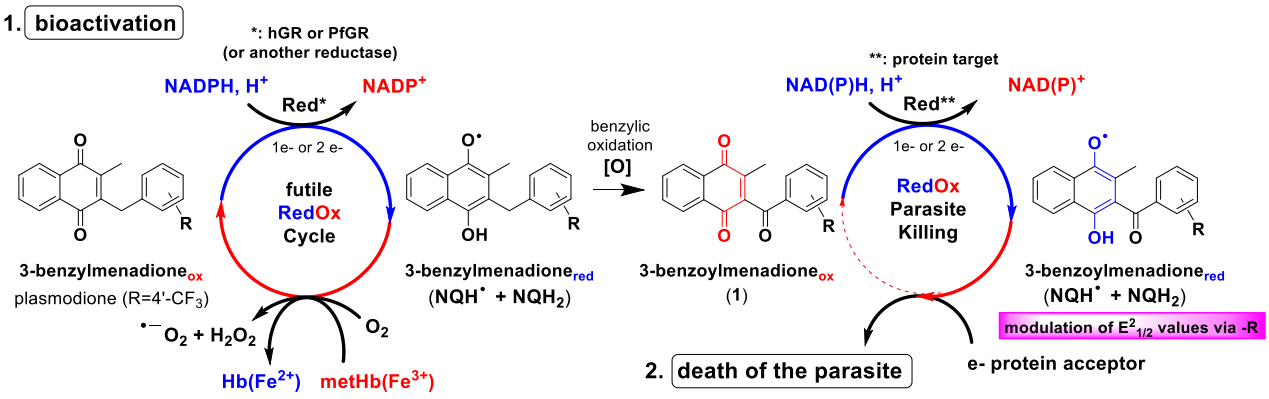


Figure 5. SWV profiles of compound cited as **3k** in ref.[5] (1.06 mM, 4'-CN), compound cited as **3l** in ref.[5] (1.03 mM, 4'-OCH_3), **1l** (1.38 mM, 4'-F), **1j** (1.20 mM, 4'-I), compound cited as **3h** in ref.[5] (1.19 mM, 4'-H), compound cited as **3f** in ref.[5] (0.94 mM, 4'-COOH), **1e** (1.40 mM, 4'-NO_2), **1m** 1.16 mM, 4'-CF_3) measured in DMSO with 0.1 M *n*-Bu_4PF_6 electrolyte support at 25°C. *v* = 200 mV s^{-1}; reference electrode = KCl(3 M)/Ag/AgCl; working electrode = glassy carbon disk of 0.07 cm^2 area.

Bioactivation through redox-cycling of NQ mediated by one- or two-electron transferring oxido-reductase enzymes is an oxygen-dependent process (Scheme 10).[4-6] Under aerobic conditions, we previously showed that both major cytosolic NADPH-dependent glutathione reductases (and possibly other reductases) from *P. falciparum*-parasitized red blood cells participate in a futile redox cycle in which the production of the protonated NQH$^{\bullet}$ species from NQ is rapidly back-oxidized to its parent compound, NQ, at near diffusion-limited rates.[5] Oxygen and methemoglobin(Fe^{3+}), the major hemoglobin catabolite and nutriment generated in *Plasmodium* parasites, play the role of one-electron acceptors from the semi-quinone NQH$^{\bullet}$. Upon 1-e$^-$ and 2-e$^-$-reduction, NQH$^{\bullet}$ and NQH_2 react rapidly with O_2 to regenerate the non-toxic parent prodrug, NQ, superoxide radicals and hydrogen peroxide as by-products. Therefore, our expectation is that under aerobic conditions, NQH$^{\bullet}$ *per se* does not contribute significantly to killing the cells, as it has been observed for plasmodione by the absence of toxicity against various human cell lines.[6] This bioactivation process was also reported for the anticancer quinonic mitomycin C.[43] It is well documented that, while the concentration of O_2 in arterial blood is approximately 13%, O_2 concentrations below 7.5% are found in most organs to which *Plasmodium*-parasitized red blood cells sequester, including the bone marrow, brain, and liver.[44] Therefore, in the hypoxic conditions where malaria parasites can survive, the half-life of NQH$^{\bullet}$ might be extended, allowing it to participate in several metabolic transformations, such as the benzylic oxidation (Scheme 10). Thus, after transport to the parasitic compartment, NQH$^{\bullet}$ can undergo further reduction by other key-protein targets to produce the toxic NQH_2 (Scheme 10). Observed parasite killing might be therefore attributable to the combined flux from both one- and two-electron reducing pathways generating the protonated NQH$^{\bullet}$ and NQH_2 species, which undergo a series of spontaneous rearrangements (in particular, phenolic oxidative coupling to form the benzoxanthones, see structures of 7H-benzo[*c*]xanthen-7-ones from Figure 1).[10c] By diversifying the molecular diversity at the benzoyl chain of 3-benzoylmenadiones **1a-u** our data showed that this aroyl substitution can markedly alter the redox properties of the NQ electrophore and thus modulate the second one-electron transfer leading to the dihydro-naphthoquinone NQH_2 species. This toxic species resulting from 3-benzoylmenadiones **1** is likely generated *in situ* in parasites from the antimalarial 3-benzylmenadione prodrugs and significantly contributes to the antimalarial activity.



Scheme 10. Proposed mechanism of action of antimalarial 3-benzylmenadione prodrugs generating toxic 3-benzoylmenadione **1** metabolites in *P. falciparum*-parasitized red blood cells. The first one-electron transfer leading to the semi-quinone NQH$^{\bullet}$ is proposed to be involved in the drug bioactivation (step 1.) while the second one-electron transfer leading to the dihydro-naphthoquinone NQH_2 might be responsible for parasite killing (step 2). For the sake of clarity, only the 1-e$^-$-reduced NQ species were drawn. Abbrev.: hGR: human glutathione reductase; *Pf*GR: *P. falciparum* glutathione reductase.

Conclusions

In conclusion, we have developed a mild and convenient Friedel-Crafts variant for acylation of 1,4-dimethoxy-2-methylnaphthalene by diversely substituted activated or deactivated benzoic and (hetero)aroyl acids, using the TfOH/TFAA reagent system through versatile conditions (room temperature, overnight, air moisture). The Friedel-Crafts reaction is a very useful reaction to prepare benzophenones derivatives, and the application of a versatile and mild protocol, suitable for any starting substituted benzoic acid, to produce diversely functionalized benzophenone derivatives in satisfactory yields, renders this reaction attractive for organic synthesis and medicinal chemistry. Thus, this new variant allowed us to reach a broad library diversity, both in terms of molecular structure of 3-acylated menadiones and function – expressed here by tuneable $E^2_{1/2}$ values spanning over a broad 500 mV-range of redox potentials. Because the antimalarial 3-benzylmenadiones are thought to be activated through a cascade of redox reactions via the 3-benzoylmenadiones **1**, the library diversity will allow us to subtly modulate the physico(electro)chemical properties of our lead antimalarial agents, which is a crucial step in any drug discovery program.

Experimental Section

Detailed descriptions of experimental procedures, data on product characterization including spectral data and ^{1}H and ^{13}C NMR spectra of all new compounds are given in the Supporting Information.

Typical Procedure for preparing 2-(2,5-dimethoxyphenyl)-2-oxoacetic acid (5a) or 2-(3,5-dimethoxyphenyl)-2-oxoacetic acid (5a'): A round bottom flask which had been flushed with argon was charged with 5 mL (31.6 mmol) of 2,5-dimethoxyacetophenone, 7.01 g (63.2 mmol) of SeO_2, and 16 mL of pyridine. The solution was heated at 120 °C. The temperature gradually dropped to 90°C over 1 h and was heated for an additional 4h. The solution was concentrated by rotary evaporator until a small amount of liquid was present. The black selenium residue was rinsed several times with ethyl acetate. The combined organic layers were transferred to a separatory funnel containing 100 mL of 0.1 M HCl. The aqueous layer was extracted three times with ethyl acetate. The aqueous layer was discarded, and the organic layers were combined and extracted several times with saturated aqueous $NaHCO_3$. The aqueous layers were combined, adjusted to pH 1 with conc. HCl, and extracted three times with ethyl acetate. The final organic layers were dried over Na_2SO_4 and concentrated, producing the 2-(dimethoxyphenyl)-2-oxoacetic acid **5a** or **5a'**.

Kochi-Anderson reaction

General procedure of the for the Silver(II)-Catalyzed Kochi-Anderson reaction between menadione and α-keto carboxylic acids: A mixture of menadione (131 mg,0.50 mmol), 2-oxopropionic acid (133 mg, 1.51 mmol), silver(I) nitrate (34 mg, 0.20 mmol), and potassium persulfate (484 mg, 1.79 mmol) in acetonitrile (2 mL) and H_2O (6 mL) was heated at 70 °C for 3 h. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water (3 x 50 mL), dried (Na_2SO_4), and concentrated in vacuum. The crude product was purified by column chromatography over silica gel (20 g; ethyl acetate/hexane, 1:15) followed by recrystallization (ethyl acetate/hexane) to give **1a** or **1a'**.

Friedel & Crafts Method

General procedure for the Friedel-Crafts acylation using the reagent mixture TFA-TFAA: 1,4-dimethoxy-2-methylnaphthalene (1.0 mmol) and 3-chlorobenzoic acid (0.66 mmol) were mixed to a solution of TFAA (2 mL). Then, 1 mL of TFA was added and the mixture was heated under reflux for overnight. When the time described for the reaction finished, the system was cold down and 10 mL of water was added smoothly. At that point, ethyl acetate (3 x 50 mL) was added, and the organic layers were combined, dried over magnesium sulfate. The solid was discarded by filtration, and the excess of the solvent removed under reduced pressure. The crude was absorbed on silica gel and purified by flash chromatography with toluene-cyclohexane eluent system.

General procedure for the Friedel-Crafts acylation using the reagent mixture TfOH-TFAA: 1,4-dimethoxy-2-methylnaphthalene (1.5 mmol) and benzoic acid (1 mmol) were dissolved in dichloromethane (0.2 M). At 0°C, TFAA (2 mmol) was added. After stirring for 10 minutes, TfOH (0.5 mmol) was added cautiously and the reaction mixture was allowed to warm up slowly at room temperature and stirred for 16h. Then, the reaction was quenched by an aqueous saturated $NaHCO_3$ solution and the aqueous phase was extracted three times by dichloromethane. The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The reaction crude was purified by silica gel chromatography using a mixture of cyclohexane and toluene as eluent to afford analytically pure Friedel & Crafts products.

Oxidative demethylation

General procedure: 2-Aroyl-3-methyl-1,4-dimethoxy-naphthalene derivative **2** (1 mmol) was dissolved in stirring MeCN (3 mL). Then, at room temperature, CAN (2.1 mmol) dissolved in water (2 mL) was added drop by drop. The mixture was stirred at room temperature during 1h. Then, most of the organic solvent was removed under reduced pressure and the aqueous phase was extracted three times with dichloromethane. Combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by silica gel chromatography was performed using cyclohexane/EtOAc as eluent.

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Keywords: acylation • acyltrifluoroacetate • benzoyl • electrochemistry • Friedel-Crafts

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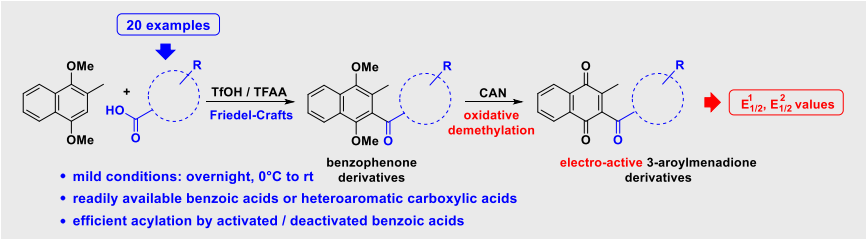

A new Friedel-Crafts acylation variant/oxidative demethylation pathway allowed the introduction of a broad structural diversity at the aroyl chain of 3-benzoylmenadiones **1**. The electrochemical study highlighted an electronic communication between the redox-active NQ core and the 3-aroyl subunit, upon the second one-electron transfer, under the control of the R groups.

Leandro Cotos, Maxime Donzel, Mourad Elhabiri and Elisabeth Davioud-Charvet**

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A Mild and Versatile Friedel-Crafts Methodology for the Diversity-Oriented Synthesis of Redox-Active 3-Benzoylmenadiones with tuneable Redox Potentials