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Efficient synthesis of substituted quinoline-5,8-quinones from 8-hydroxyquinolines by photooxygenation

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Abstract—Substituted quinoline-5,8-quinones were obtained in good yield by photooxygenation of substituted 8-hydroxyquinolines.

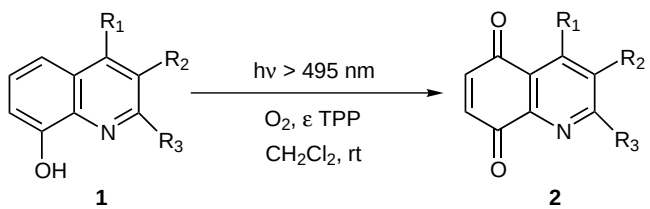
Natural products that bear a 9,10-diazaanthracenedione moiety show interesting antitumor properties. Anthracyclines,[1] pluramycins[2] as well as some enediyne antibiotics such as dynemicin A and deoxydynemicin A[3] are typical examples. The antitumour activity of these quinones is probably due to multiple mechanisms, normally initiated by DNA intercalation. Formation of DNA damaging anion-radical intermediates by reduction of the quinone unit is probably involved in their cytotoxicity, at least in the case of anthracycline.[4] Natural products such as azabenzisochromanquinones,[5] streptonigrinone,[6] lavendamycin,[7] and cystodamine,[8] in which a carbon of the benzene ring of the anthraquinone is replaced by a nitrogen, also show antitumor antibiotic activities. These compounds have geometries similar to those of the parent anthraquinones and hence are capable of intercalation but with sites suitable for hydrogen bonding or ionic interactions they show an increased affinity for DNA. Additionally, the electron-withdrawing properties of the heterocyclic rings must facilitate the formation of anion-radicals. For these reasons, quinoline-5,8-quinones are important synthetic intermediates for the synthesis of a variety of biologically active compounds such as azaanthraquinones.[9]

A great number of reagents or methods suited for the preparation of substituted quinoline-5,8-quinones has been developed.[10–13] Among these, Fremy's salt is the most widely used oxidizing agent for the transformation of substituted 8-hydroxyquinolines to substituted quinoline-5,8-quinones.[14] However, this reagent is best suited to small scale experiments.[15]

In this letter, we report the synthesis of substituted quinoline-5,8-quinones in good yield, by photosensitized oxidation of readily available substituted 8-hydroxyquinolines of type 1 (Scheme 1).

meso-Tetraphenylporphine (TPP) is well known to be a highly effective triplet state photosensitizer[16] and to be able to efficiently produce singlet molecular oxygen, O_2 ($^1\Delta_g$), under illumination in the presence of oxygen.[17] TPP-sensitized photooxygenation of compounds of type **1** in methylene chloride, at room temperature, resulted in the formation of quinoline-5,8-quinones of type **2** after treatment of the crude reaction mixture with dry Na_2SO_4 and purification by chromatography on silica gel.[18] The results are reported in Table 1.

The structures of **2a–j** were assigned by ^{1}H NMR, ^{13}C NMR and by mass spectra. The most conspicuous features in the ^{1}H NMR spectra of quinoline-5,8-quinones are two distinct doublets which correspond to two olefinic protons in the range of 7.0–7.3 ppm with a coupling constant of 10.0–11.0 Hz. Electron-donating or electron-withdrawing substituants on C(2), C(3) or C(4) can be present on 8-hydroxyquinolines without



Scheme 1.

Keywords: quinolines; phenols; quinones; oxygenation; photochemistry.

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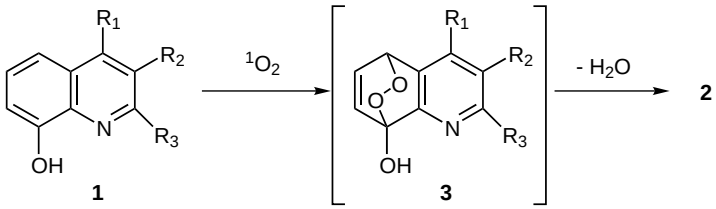
Table 1. Synthesis of quinoline-5,8-quinones **2** from 8-hydroxyquinolines **1**

Entry	R^1	R^2	R^3	Time[a] (h)	Yield% of **2**[b]
a	H	H	H	2.5	82
b	H	H	CH_3	2.5	80
c	H	CH_3	H	2.0	82
d	CH_3	H	H	2.0	72
e	H	H	CN	8.0	73 (86)[c,d]
f	H	H	CHO	5.5	51 (68)[c,e]
g	H	H	CO_2Me	2.0	81
h	H	H	$CON(i\text{-}Pr)_2$	2.0	89
i	H	H	$CH_2N(Boc)CH_2Ph$	2.5	53
j	H	H	$CH_2N(Boc)CH_2CO_2Me$	2.0	50 (63)[c,f]

[a] All reactions were performed in CH_2Cl_2 on a 2 mmol scale. Reactions can be performed on a 20 mmol scale by irradiating for 10–12 h.
[b] Yield of isolated product after purification by chromatography on silica gel.
[c] Yield based on the transformed starting material.
[d] 15% of the starting material was recovered.
[e] 25% of the starting material was recovered.
[f] 21% of the starting material was recovered.



Scheme 2.

affecting their transformation to quinoline-5,8-quinones. The mechanism for the formation of the quinoline-5,8-quinones **2** from 8-hydroxyquinolines **1** was assumed to be a [4+2] cycloaddition of singlet oxygen to the phenolic ring which can afford hydroxy-endoperoxides of type **3**. This latter compound could lead to quinoline-5,8-quinones after decomposition in the presence of dry Na_2SO_4. All efforts to isolate **3** were unsuccessful (Scheme 2).

In conclusion, we have developed a very efficient synthesis of quinoline-5,8-quinones from 8-hydroxyquinolines by using a photooxygenation in the presence of TPP. This methodology allowed for the preparation of new substituted quinoline-5,8-quinones on multigram scale and in a highly concise way.

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18. General procedure: A solution of substituted 8-hydroxyquinoline (2 mmol) and TPP (6 mg, 0.01 mmol) in CH_2Cl_2 (20 mL) was irradiated, under oxygen bubbling, with a 1800 W xenon lamp through a UV cut-off glass filter (λ>495 nm) at 20°C. After 2–8 h (TLC monitoring), the resulting mixture was treated with dry Na_2SO_4 (3 g) for 3 h and then filtered. The solvent was evaporated in vacuo and the residue was purified by flash column chromatography on silica gel to give pure substituted quinoline-5,8-quinone.