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Synthesis of 2-alkenyl-3-hydroxyquinolin-4(1*H*)-ones as promising antimicrobial and fluorescent agents

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ABSTRACT

2-Alkenyl-3-hydroxyquinolin-4(1*H*)-ones were prepared by the rearrangement of anthranilic acid esters synthesized by two alternative methods. The prepared derivatives were screened for their antimicrobial activities against representative Gram-positive and Gram-negative bacteria, displaying notable minimum inhibitory concentration values against specific strains. The emission spectra of the target quinolines exhibited two well-separated emission bands, and the maximum excitation wavelengths of the selected compounds were detected at relatively high values.

1. Introduction

Quinolin-4(1*H*)-ones are pharmacologically attractive compounds with a wide range of biological effects. In this regard, quinolin-4(1*H*)-one-3-carboxylic acids are particularly attractive due to their highly potent antimicrobial activities.[1] A report on the synthesis and screening of oxolinic acid and pefloxacin analogues, which bear 3-hydroxy groups instead of carboxylic groups, toward different bacterial strains revealed only negligible activity.[2] This indicated the negative influence of such structural modification, and therefore, 3-hydroxy-4(1*H*)-quinolines (3HQs) have not been considered promising antimicrobial agents for a long period. Nevertheless, the discovery of a simple synthetic route for the routine preparation of 2-phenyl-3HQs[2,3] as flavonol isosteres initiated a detailed investigation of their biological properties. To date, a number of different 2-phenyl-3HQs with significant cytotoxic[4–6] and immunosuppressive effects[7] have been reported. Regarding their biomolecular targets, 2-phenyl-3HQs have been shown to act as topoisomerase and microtubule polymerization inhibitors with a resulting effect on mitosis.[8] These specific 3HQs also inhibited inosine monophosphate dehydrogenase (IMPDH)[9] and reverse transcriptase of human immunodeficiency viruses.[10] In contrast, significant antibacterial properties of 3HQs have not been reported to date.

In addition to biological effects, 2-aryl-3HQs exhibit interesting fluorescent properties and have been suggested as compounds for the labeling of molecules.[6,11–14] This presumption was supported by the fact that 3HQs typically exhibit two well-separated emission bands, resulting in dual fluorescence. Dual fluorescent labels are not dependent on concentration because the ratio of the intensities of the two bands can be applied as a signal. This is advantageous in complex biological systems, such as cells or tissues, in which the local concentration of the label cannot be controlled easily because of its inhomogeneous distribution.[15,16] On the other hand, the excitation of previously reported 2-aryl-3HQs requires relatively low-wavelength light (usually approximately 350 nm),[12,13] which is not beneficial due to the interfering fluorescence of intrinsic fluorophores as well as harmful effects of UV radiation. For this reason, excitation with higher-wavelength light is considerably more advantageous with respect to possible biological applications.

In this paper, we focus on the preparation of novel 3HQs bearing an alkenyl or alkyl moiety in the 2 position. The introduction of an

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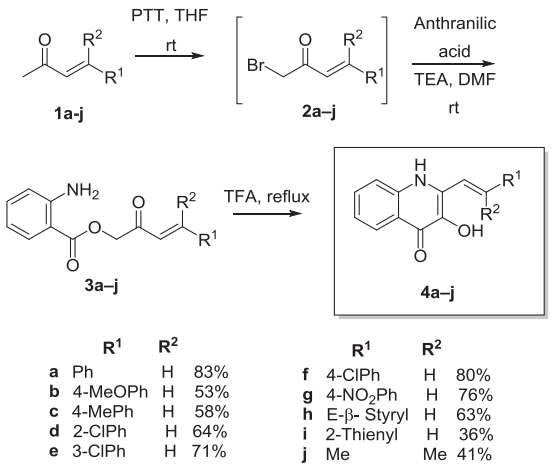
alkene conjugated with an additional aromatic ring was suggested to produce a bathochromic shift of the absorption, thus possibly increasing the excitation wavelength energy. Furthermore, 2-alkyl-3HQs represent biologically relevant compounds, with 2-heptyl-3-hydroxyquinolin-4(1*H*)-one (PQS, Pseudomonas quinolone signal) being the most important derivative. PQS acts as a signaling molecule used by resistant bacteria *Pseudomonas aeruginosa* in the virulence regulatory system,[17–19] which is one of the possible targets for treating diseases caused by resistant bacteria.[20–22]

2. Results and discussion

2.1. Synthesis

The synthetic approach leading to target compounds **4** was inspired by a previously reported method for 2-aryl-3HQs.[2] Nevertheless, the limited availability and stability of unsaturated intermediates **2** or **7** in comparison to analogous α-haloacetophenones required substantial modification. In the first stage, the synthesis of key intermediates **3a**–**o** was performed. These esters were prepared by the alkylation of anthranilic acid with α-haloketones. Two alternative methods were developed depending on the resulting substitution pattern. Method A (Scheme 1) was applicable for aryl (R^1 = Ar) or dialkyl ($R^{1,2}$ = CH_3) intermediates. It was based on the condensation of commercially available aldehydes with acetone[23] and subsequent bromination of the resulting α,β-unsaturated ketones **1a**–**i** with phenyl trimethylammonium tribromide (PTT).[24] Haloketone **2j** was prepared from commercially available mesityl oxide **1j** using a similar procedure. In contrast, the bromination of monoalkyl or pyridyl unsaturated ketones prepared from aldehydes **6k-o**, **6s**, and **6t** (see the structure of aldehydes in Scheme 2) by method A was unsuccessful.

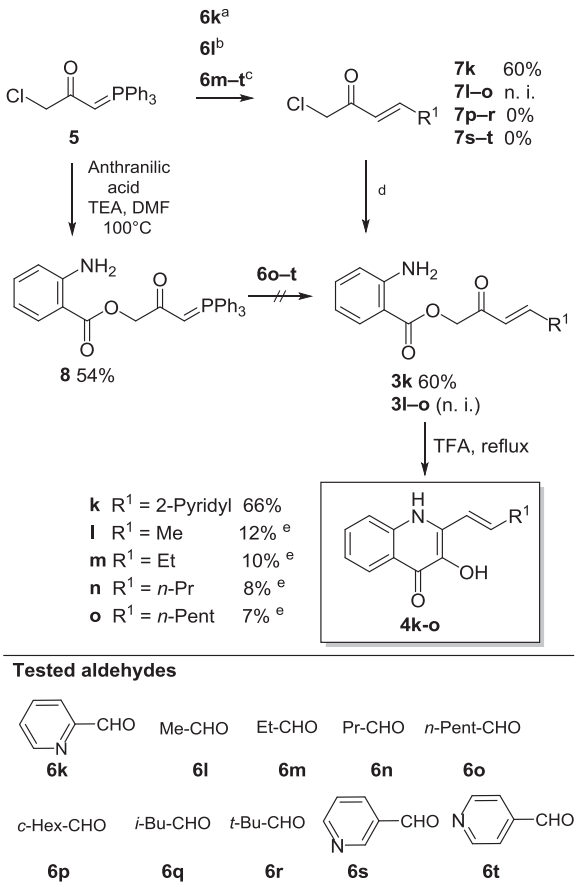
For this reason, intermediates **7k-o** were synthesized by Method B based on a Wittig reaction of phosphorane **5** with pyridine 2-carboxaldehyde **6k**[25] or aliphatic aldehydes **6l**–**o** (Scheme 2). However, reaction conditions to react α-branched aldehydes **6p**–**r** (pivaloyl aldehyde, isobutyraldehyde or cyclohexanecarboxaldehyde) or pyridyl aldehydes **4s** and **4t** with **5** were not found. In contrast to stable compounds **3a**–**k**, anthranilates **3l-o** were prone to spontaneous dimerization during their preparation. We managed to suppress this side-reaction by decreasing the reaction temperature from 25 °C to −5 °C and changing the base (K_2CO_3 was used instead of triethylamine). Despite this fact, esters **3l**–**o** were obtained in limited purity (~70%, LCMS) and used immediately in the next reaction step without purification and characterization.



	R^1	R^2	
a	Ph	H	83%
b	4-MeOPh	H	53%
c	4-MePh	H	58%
d	2-ClPh	H	64%
e	3-ClPh	H	71%
f	4-ClPh	H	80%
g	4-NO_2Ph	H	76%
h	E-β- Styryl	H	63%
i	2-Thienyl	H	36%
j	Me	Me	41%

Displayed yields of **4a-j** were calculated after 3 reaction steps (based on ketones **1**).

Scheme 1. Synthesis of 3HQs **4a**–**j** by method A.



[a]Dichloromethane, rt. [b] Excess aldehyde **6l** was used as the solvent, 35°C, sealed tube. [c]1,2-Dichloroethane, reflux, inert atmosphere. [d]For **7k**: anthranilic acid, TEA, DMF, rt; for **7l–o**: anthranilic acid, K_2CO_3, DMF, -5°C. [e] Yield was calculated after 3 reaction steps (based on ylide **5**). n. i.: Not isolated.

Scheme 2. Synthesis of hydroxyquinolones **4k**–**o** by method B.

The use of anthranilate **8** as an alternative intermediate for the preparation of anthranilates **3** was also tested (Scheme 2). Nevertheless, its reaction with various aliphatic, aromatic or heteroaromatic aldehydes under the Wittig reaction conditions was unsuccessful. To prepare the target 3HQs, the original conditions[2] (using PPA or solvent-free cyclization) were initially applied. However, the cyclization of anthranilates **3a**–**o** failed or led to the formation of inseparable impurities. On the other hand, 3HQs **4a-k** were prepared in good yields by the cyclization of the corresponding anthranilates using trifluoroacetic acid.[6] This method was also applicable for products **4l-o**, however with limited yields 7–12% (calculated after 3 steps).

To test the applicability of the reaction sequence for the preparation of 2-alkyl-3HQs, two representative compounds **4a** and **4h** were reduced using catalytic hydrogenation (Scheme 3). In both cases, the hydrogenation yielded the corresponding target compounds **9a** and **9h**.

2.2. Antibacterial activity

The prepared 3HQs were screened for antibiotic activity against representative Gram-positive (*B. subtilis*, ATCC 6633; *M. luteus*,