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A convenient method for the synthesis of 3,5,7-trimethoxy-2-phenyl-4-quinolones

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Abstract

The synthesis of 2-aryl-3,5,7-trimethoxy-4-quinolones was accomplished in three steps starting from 3,5-dimethoxyaniline and an aroyl chloride. These structures might be used as potential flavonol analogs.

Keywords: 3-methoxyphenylquinolones; synthesis.

Since the discovery that flavonoids possess good inhibitory activity toward protein tyrosine kinases,[1,2] the synthesis and SAR studies on flavonoids have been the goal of many research groups.[3] Among the flavonoid analogs studied, 2-phenyl-4-quinolones were found to be particularly interesting (Fig. 1).[4] They are structurally similar to flavonoids, and they also have an available nitrogen for further extension and for branching different substituents. In flavonoids, 3,5,7-trihydroxyl groups are often required for good activity and this was correlated with their ability to mimic the adenine moiety of ATP. This analogy was recently demonstrated by the high-resolution X-ray structure of cyclin-dependent protein kinase 2 co-crystallized with an 8-substituted flavone (L868276).[5] The recent co-crystallization of quercetin (5,7,3′,4′-tetrahydroxyflavonol) with tyrosine kinase Hck confirmed the role of 3-, 5- and 7-hydroxy groups for mimicking the adenine moiety of nucleotides.[6]

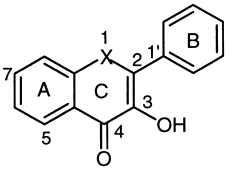

Figure 1. X = O: flavonol; X = N: 3-hydroxy-2-phenyl-4-quinolone

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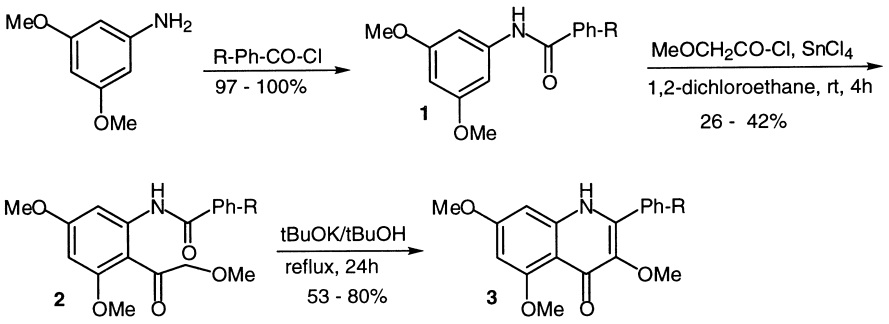
If the synthesis of flavonols can now be accomplished through convenient methods,[7] to the best of our knowledge, there is no available synthesis of quinolones having 3,5,7-hydroxyl groups. The search for an approach to 3,5,7-trihydroxy-4-quinolones as potential analogs of quercetin was undertaken in the framework of a project related to the synthesis of biologically active flavonol analogs.

2-Phenyl-4-quinolones can be synthesized by several pathways.[8] The most convenient method is the one using *ortho*-aminoacetophenones as starting building blocks prepared by nitration of the corresponding acetophenone, followed by hydrogenation in the presence of active carbon.[4c] However, the introduction of an oxygen atom at position 3 requires an oxidation of the assembled quinolones, which might be incompatible with the presence of oxidant-sensitive substituents. In our method, the oxygen atom at position 3 was introduced early in the synthesis via a Friedel–Crafts reaction, as shown in Scheme 1.



Scheme 1.

Reaction of 3,5-dimethoxyaniline with a benzoyl chloride derivative in the presence of Et_3N gave quantitatively the 3,5-dimethoxyphenyl-*N*-phenylamide **1**. Friedel–Crafts acylation with methoxyacetyl chloride in 1,2-dichloroethane and in the presence of stannic chloride ($SnCl_4$) gave the corresponding *N*-phenylamido methoxyacetophenone **2** in 26–42% yield. It should be mentioned that anhydrous 1,2-dichloroethane and high dilution (30 ml solvent/mmol of **1**) are very important for the success of this step. Cyclization of **2** in the presence of *t*-BuOK in *t*-butanol at 80°C gave quinolones **3** in 53–80% yield (Table 1).

Table 1
Preparation of 2-aryl-3,5,7-trimethoxy-4-quinolones **3**

Entry	R	Yield of 2 from 1 (%)	Yield of 3 from 2 (%)
1	H	35	62
2	4-F	30	72
3	4-OMe	26	53
4	2,4-Cl	28	79
5	4-n-octyl	42	80
6	2-F	32	64
7	4-I	40	65

In conclusion, a three-step synthesis of 3,5,7-trimethoxy-2-phenyl-4-quinolones is reported starting from commercially available materials. These quinolones **3** can be used as analogs of methoxylated flavones, they can be demethylated to give hydroxylated flavones and, more interestingly, *N*-substituted quinolones can be easily prepared, since the hydroxyls are fully protected.

(4,6-Dimethoxy-2-benzamido)methoxyacetophenone 2. To an ice-cooled solution of *N*-(3,5-dimethoxyphenylbenzamide **1** (prepared from 3,5-dimethoxyaniline and a benzoyl chloride) in anhydrous 1,2-dichloroethane (30 ml/mmol) under N_2 was slowly added $SnCl_4$ (2 equiv.). Freshly distilled methoxyacetyl chloride (1 equiv.) was added dropwise as a solution in 1 ml of 1,2-dichloroethane and the reaction was allowed to warm to room temperature and stirred for 4 h. After this time, the solution was poured onto ice and the product was extracted with AcOEt (three times). The organic layers were washed with water, dried and evaporated. Compound **2** (more polar than **1**) was isolated by silica gel column chromatography, eluting with cyclohexane:ethyl acetate (9:1).

3,5,7-Trimethoxy-2-phenyl-4-quinolones 3. To a solution of **2** in distilled *t*-butanol (2 ml/mmol) was added *t*-BuOK (5 equiv.) and the mixture was heated at 80°C under N_2 for 24 h. The mixture was cooled to room temperature, poured onto an aqueous NH_4Cl saturated solution and extracted with AcOEt. The organic layers were washed with water, brine, dried and concentrated. The mixture was purified by silica gel flash chromatography, eluting with cyclohexane:ethyl acetate (8:2), to afford quinolones **3**.

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