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A CONVENIENT METHOD FOR THE PREPARATION OF LINEAR FUROQUINOLIN-2-ONES

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Fries rearrangement of 7-acetoxy-4-methylquinolin-2-one and subsequent condensation of the 6-acetyl-7-hydroxy-4-methylquinolin-2-one obtained with α-chloro ketones gives a series of furo[3,2-g]quinolin-7-ones.

Keywords: 6-acetyl-7-hydroxy-4-methylquinolin-2-one, 3,5-dimethylfuro[3,2-g]quinolin-7-one, Fries rearrangement.

The usage of furocoumarin derivatives in the treatment of various skin disorders is well known [1]. However, despite the high effectiveness of furocoumarins, their use is complicated by a number of side effects, e.g. their significant phototoxicity, the risk of initiating cancerous diseases, and the lowering of immune function [2-4]. If one takes into consideration the case that the therapeutic action of the furocoumarins is generally connected with the intercalation of these compounds on the skin surface then the undesired effects arise because of the formation of interstrand psoralen-DNA cross links. It is proposed that the formation of monofunctional adducts makes it possible to avoid the side effects of the preparations to a significant degree [6]. Currently, a series of nitrogen analogs of the furocoumarins has been synthesized and studied [6-8] and this includes those capable of bonding monofunctionally with DNA [9]. Publications have appeared recently concerning the synthesis of furoquinolinones of linear [10] and angular [11] structures. Data for the absence of interstrand cross links with DNA is present with the use of the angular furoquinolinones.

In this study we report a convenient method for the synthesis of furoquinolinones of a linear structure, making possible the introduction of a carbonyl function into the furan ring. The latter situation is particularly important since only furoquinolinones with alkyl substituents in the furan ring have been obtained up to the present time. With the introduction of electron-acceptor substituents like an acyl group in the furan ring, a lowering of its activity in a [2+2] photocycloaddition reaction (and hence a strengthening of the monofunctionality of the corresponding substrate) might be expected.

The synthesis of the furoquinolinones was carried out by the following scheme which has previously reported by us in detail for a series of coumarin derivatives [12].

Cyclization of *m*-aminophenol and ethyl acetoacetate was brought about by heating the mixture at 140-150°C to solidification [18]. In addition to the target 7-hydroxy-4-methylquinolin-2-one (**1**), a further cyclization product (5-hydroxy-4-methylquinolin-2-one) was found in quite large quantities (approximately

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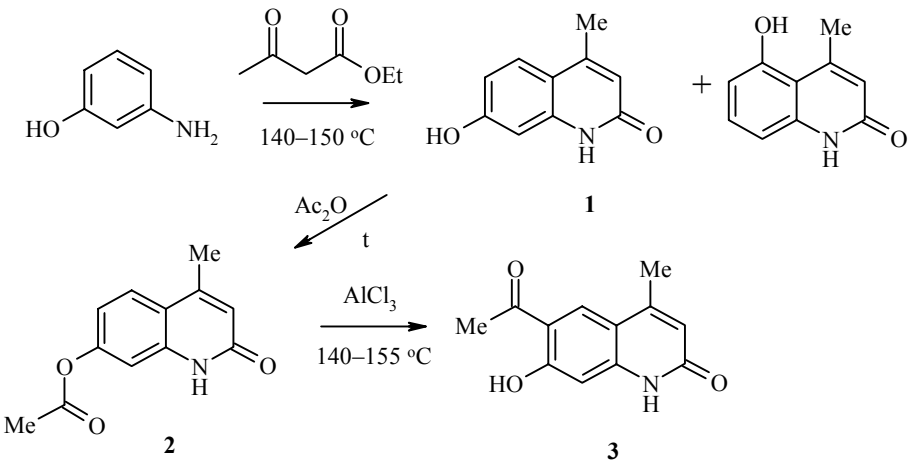
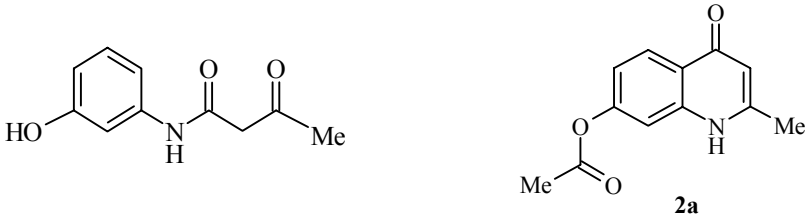
Scheme 1



40%). Evidently the formation of the ring comprises an intramolecular electrophilic aromatic substitution to the intermediate anilide with secondary formation of the 5-hydroxy-4-methylquinolin-2-one as a result of the closing of the ring to the *ortho* position relative to the hydroxyl group. It was interesting to find that, in the process of synthesizing an oxygen analog of the quinoline (7-hydroxy-4-methylcoumarin) by treating resorcinol with ethyl acetoacetate, the formation of an appreciable amount of the corresponding 5-hydroxy-4-methylcoumarin was not observed [13].

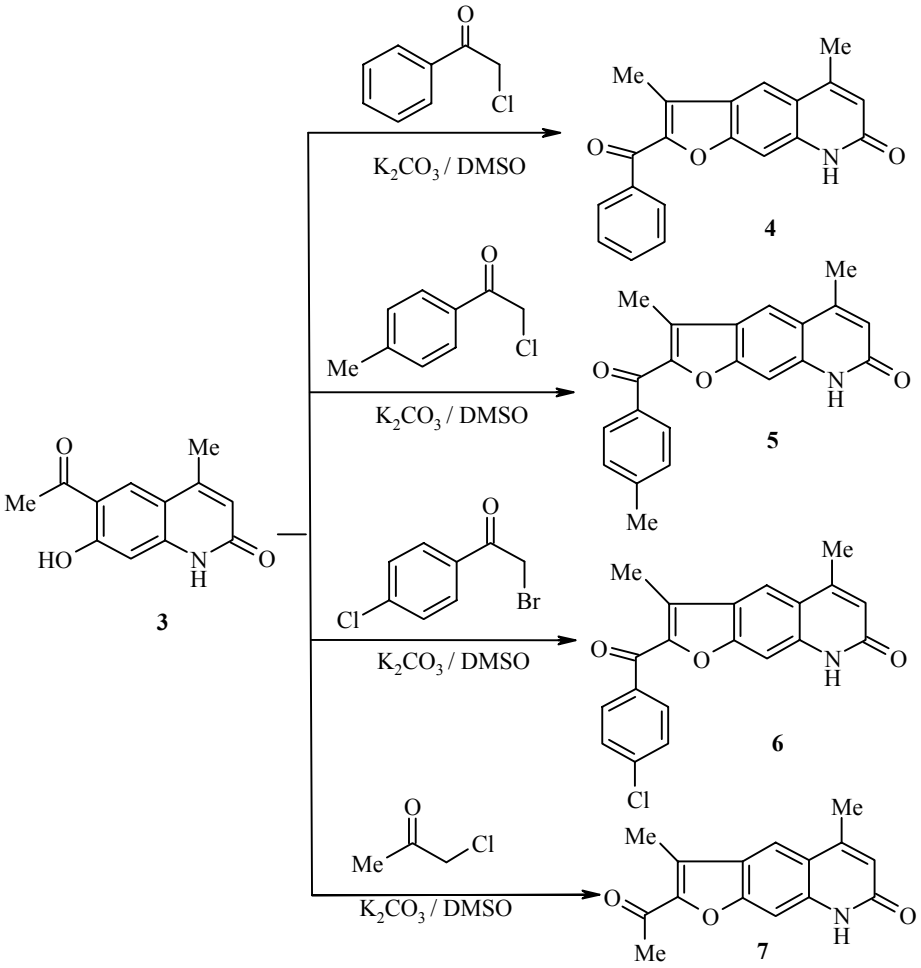


A series of studies are reported in the literature in which the synthesis of 4-methylquinolin-2-ones is described with special mention of the possibility of forming 4-methylquinolin-2-one together with its structurally isomeric 2-methylquinolin-4-one (**2a**) during the cyclization process. The suggestion was made that both products are involved in equilibrium conversions [14], hence it was particularly important to establish clearly the structure of the obtained cyclization product.

Compound **2** was synthesized by refluxing **1** in acetic anhydride and analysis of its structure was carried out by us using NMR together with the NOE method. When carrying out the NOE experiment for compound **2** it was found that irradiation of the methyl group signal at 2.41 ppm caused a 17% increase in the intensity of the 3-H proton singlet (6.36 ppm) together with a 10% increase for the 5-CH proton doublet at 7.73 ppm and this unambiguously indicates support to structure **2**.

The Fries rearrangement is widely used for the preparation of *ortho*-hydroxy ketones including the coumarin series and their analogs [15-17]. Features of the Fries rearrangement of compound **2** in the preparation of compound **3** have been reported by us previously [19]. Since the aromatic protons of compound **3** appear in the spectrum as two singlets, both substituents must be mutually *ortho*-related. In order to establish the position of the substituent in the ring and the position of the methyl group we carried out an NOE experiment. This showed that irradiation of the signal at 2.43 ppm caused both a response in the 3-H proton signal (a 9% increase in intensity) as well as a response in the aromatic proton singlet at 8.14 ppm (a 19% increase in intensity). In addition, irradiation of the acetyl group signal at 2.69 ppm caused a 17% increase in the same aromatic proton singlet at 8.14 ppm. Combination of this data allows one to assign compound **3** the structure 6-acetyl-7-hydroxy-4-methylquinolin-2-one unambiguously.

Scheme 2



Compound **4-7** were prepared by us *via* gentle heating of compound **3** in DMSO with phenacyl chloride, 4-methylphenacyl chloride, 4-chlorophenacyl bromide, and chloroacetone respectively. Such a method for the formation of a furan ring had already been used by us in the synthesis of furocoumarins [12]. It is likely that the formation of the furoquinolinones, in the same way as the furocoumarins, occurs in the two stages of alkylation of the hydroxyl group by the phenacyl bromide followed by cyclization of the product obtained in the presence of a base such as potassium carbonate. An undoubted advantage of the method is the convenience of carrying out the alkylation and cyclization without the separation of the intermediate products and also the potential introduction of a carbonyl group into the furan ring. Up to the present time it has only been possible to synthesize furoquinolinones with alkyl substituents in the furan ring.

The yields and spectroscopic parameters for the synthesized compounds are given in Table 1.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker AC 200 (200 MHz) instrument with TMS internal standard. The course of the reaction was monitored using TLC on Silufol UV-254 plates.

The methods for preparing compounds **1-3** are given in [18, 19].

TABLE 1. Physicochemical and Spectroscopic Properties of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %		mp, °C	Chemical shift, δ, ppm (*J*, Hz)*	Yield, %
		C	H			
4	$C_{20}H_{15}NO_3$	74.23 / 75.70	4.61 / 4.76	316-318	2.55 (3H, s, 5-CH_3); 2.62 (3H, s, 3-CH_3); 6.41 (1H, s, 6-H); 7.44 (1H, s, 9-H); 7.74-7.56 (1H, s, *p*-H); 7.62 (2H, d, $J_{m\text{-, }o\text{-H}}$ = 7.8, 2 *m*-H); 8.00 (2H, d, $J_{o\text{-, }m\text{-H}}$ = 7.8, 2 *o*-H); 8.20 (1H, s, 4-H); 11.68 (1H, s, NH)	52
5	$C_{21}H_{17}NO_3$	75.46 / 76.12	5.10 / 5.17	317-319	2.54 (3H, s, *p*-CH_3); 2.61 (3H, s, 5-CH_3); 2.61 (1H, s, 3-CH_3); 6.40 (1H, s, 6-H); 7.40 (2H, d, $J_{2',3'}$ = 7.88, 2 *m*-H); 7.91 (2H, d, $J_{3',2'}$ = 7.88, 2 *o*-H), 8.17(1H, s, 4-H), 11.68 (1H, s, NH)	62
6	$C_{20}H_{14}ClNO_3$	66.13 / 68.29	3.99 / 4.01	309-311	2.62 (3H, s, 5-CH_3); 2.71 (3H, s, 3-CH_3); 6.58 (1H, s, 6-H); 7.44 (1H, s, 9-H); 7.49 (2H, d, $J_{2',3'}$ = 7.88, 2'-H); 7.97 (1H, s, 4-H); 8.11 (2H, d, $J_{3',2'}$ = 7.88, 3'-H); 11.07 (1H, s, NH)	84
7	$C_{15}H_{13}NO_3$	70.08 / 70.58	5.11 / 5.13	280 (sublimes)	2.55 (3H, s, 5-CH_3); 2.59 (3H, s, CH_3CO); 2.63 (3H, s, 3-CH_3); 6.38 (1H, s, 6-H); 7.43 (1H, s, 9-H); 8.14 (1H, s, 4-H); 11.64 (1H, s, NH)	59

* Compounds **4** and **7** were recorded in DMSO-d_6 and compounds **5** and **6** in $CDCl_3$.

2-Benzoyl-3,5,dimethylfuro[3,2-*g*]quinolin-7-one (4). Phenacyl chloride (0.44 g, 2.84 mmol) and ignited potassium carbonate (1.0 g) were added to a solution of **3** (1.0 g, 2.84 mmol) in the minimum amount of DMSO. The mixture was vigorously stirred for 6-8 h. The reaction mixture was then poured into water and the precipitate obtained was filtered off. The dried product was recrystallized from a mixture of ethanol and DMSO.

Compounds **5** and **6** were prepared by this method and recrystallized from acetic acid.

2-Acetyl-3,5-dimethylfuro[3,2-*g*]quinolin-7-one (7). Chloroacetone (0.26 g, 2.84 mmol) and ignited potassium carbonate (1.0 g) were added to a solution of **3** (1.0 g, 2.84 mmol) in the minimum amount of DMSO. The mixture was vigorously stirred with gently heating for 6-8 h. The reaction mixture was then poured into water and the precipitate obtained was filtered off. The dried product was recrystallized from a mixture of ethanol and DMSO.

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