SYNTHESIS OF 5-METHOXY-2(1*H*)-QUINOLINONE

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Abstract-Methylation of 5-hydroxy-2(1*H*)-quinolinone (**1**) is studied. The previous protection of the amide group in **1** is proposed as the more convenient method to obtain 5-methoxy-2(1*H*)-quinolinone (**1a**).

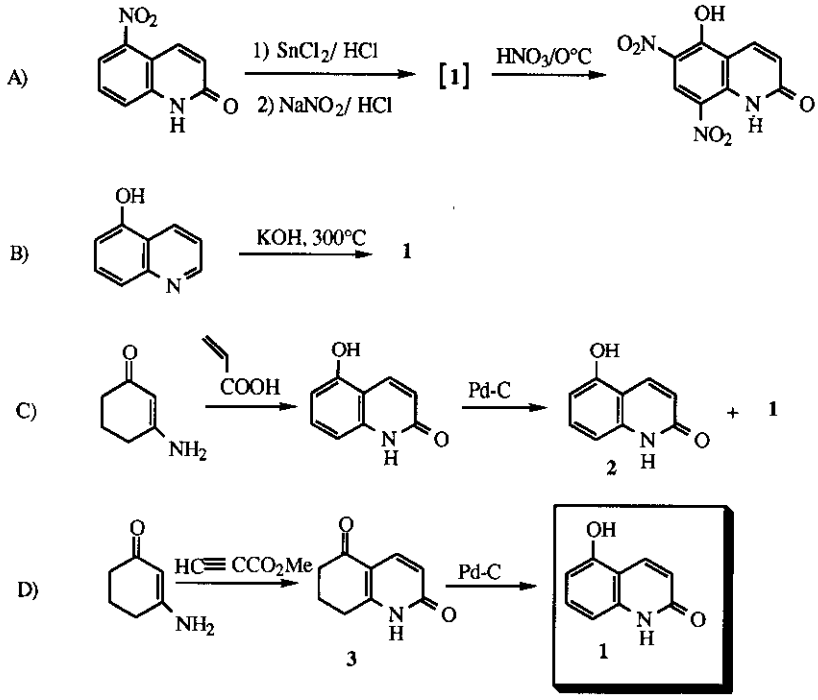
INTRODUCTION

In a project directed to the synthesis of 1,8-diaza-2,9,10-anthracenetriones with potential antitumor activity,[1] 3- and/or 4-substituted carbostyrilquinones were required as dienophiles. In this context, we are evaluating different methods to obtain these systems from 2,5-dimethoxyaniline derivatives,[2] but we considered that the base-catalyzed electrophilic substitution of 5-methoxy-2(1*H*)-quinolinone would be an attractive approach. In a previous work we have shown that 2(1*H*)-quinolinone lithium salt can be regioselectively deprotonated to give 3-substituted 2(1*H*)-quinolinone by alkylation of the dianion.[3] Extension of this methodology to 5-methoxy-2(1*H*)-quinolinone (**1a**) required the synthesis of this compound, that was planned by methylation of 5-hydroxy-2(1*H*)-quinolinone (**1**).

RESULTS

Three different methods have been reported for the synthesis of **1** (A-C, Scheme 1). Method A is related to the synthesis of 5-hydroxy-6,8-dinitro-2(1*H*)-quinolinone,[4] in which **1** was an unisolated intermediate. The other two methods imply either the fusion of 5-quinolinol with potassium hydroxide,[5] or the dehydrogenation of 1,2,3,4,5,6,7,8-octahydroquinoline-2,5-dione, which is obtained by addition-condensation of 3-aminocyclohexenone-2 with acrylic acid.[6] Since 5-nitro-2(1*H*)-quinolinone is not commercially available and 5-quinolinol is very expensive, the method C was chosen to prepare **1**. However, in our hands, its separation from the 3,4-dihydro precursor (**2**), either by recrystallization or column chromatography, was never complete.

In order to avoid the above mentioned contamination, we performed the reaction of 3-aminocyclohexenone-2 with methyl propiolate as Michael substrate (D). The bicyclic ketone (**3**), has been previously used as a key intermediate in the preparation of 4-aza-19-noresteroids[7] and 6-hydroxy-2,5,8(1*H*)-quinolinetrione,[8] but we show here that its aromatization to **1** is quantitative.



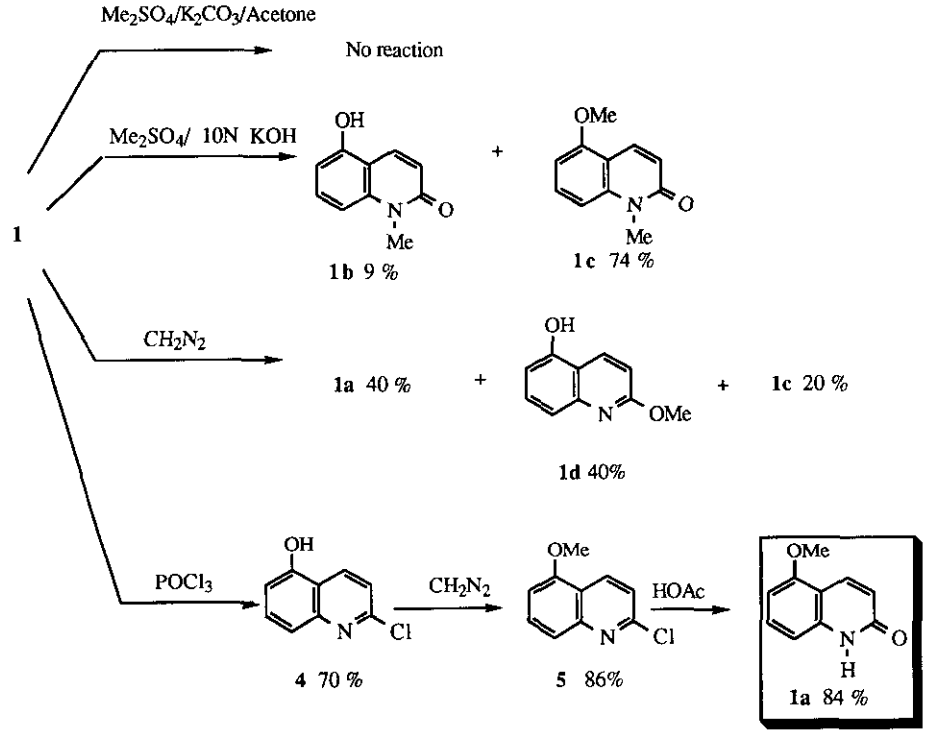
Scheme 1

The reaction of 3-aminocyclohexenone-2 with methyl propiolate gave **3** in 40 % yield. The dehydrogenation of **3** by treatment with Pd-C gave pure **1** in quantitative yield and therefore, we propose method D instead of C to avoid the difficult separation of compounds (**2**) and (**1**).

Methylation of **1** was attempted by standard procedures (Scheme 2). No reaction was observed with Me_2SO_4 (K_2CO_3/acetone) because of the insolubility of the potassium salt of **1** in the solvent, while treatment of **1** with Me_2SO_4 in 10 N KOH gave a 1: 8 mixture of the undesirerd *N*-methyl and *N,O*-dimethyl derivatives (**1b**) and (**1c**), respectively. This last result contrasts with that found in the analogous methylation of 8-hydroxy-2(1*H*)-quinolinone, that gives a 50% mixture of 8-methoxy-2(1*H*)-quinolinone and the *N,O*-dimethyl derivative.[9] In the case of **1**, the electron withdrawing effect of the conjugated carbonyl group at the 2-position probably lowers the nucleophillicity of the 5-phenoxide anion.

When **1** was treated with diazomethane the desired **1a** was obtained in a 2:2:1 mixture with **1d** and **1c**. After separation of **1c**, the two *O*-methyl derivatives (**1a**) and (**1d**) could not be properly isolated because they have similar solubility. Since pure **1a** was obtained in other experimental conditions, ^{1}H and ^{13}C nmr spectral data of compound (**1d**) could be attributed in the expectrum of its mixture with **1a**.

These results prompted us to prepare **1a** through the previous protection of the amide group of **1** with $POCl_3$ to give **4**; subsequent methylation to **5** and deprotection. In this way, **1a** is obtained in a 51% overall yield from compound(**1**).



Scheme 2

Structural assignment of **1a**, **1b** and **1d** was mainly based on ^{1}H- and ^{13}C-nmr spectroscopy (Tables **1** and **2**). Compound (**1c**) has been previously reported in the alkylation of 2-(2,6-dimethylpiperidino)acetonitrile with *N*-(3-methoxyphenyl)-*N*-methyl-2-bromoacetamide followed by hydrolysis and cyclisation,[10] and has been obtained in very poor yields in the homolysis and intramolecular cyclisation of *cis*-*o*-methoxy-*N*-iodo-*N*-methylcinnamamide.[11]

Table 1. ^{1}H-Nmr Spectral Data of Compounds (**1**)-(**5**) [250 MHz, DMSO-d$_6$, δ, multiplicity, *J* (Hz)].

Compound	Me	H-3	H-4	H-6	H-7	H-8	OH	NH
1	---	6.35, d (9.7)	8.00, d (9.7)	6.56, d (7.3)	7.25, t (8.1)	6.72, d (8.2)	10.35, s	11.60, s
1a	3.88, s	6.41, d (9.7)	8.02, d (9.7)	6.72, d (8.1)	7.41, t (8.2)	6.87, d (8.2)	-----	11.74, s
1b	3.55, s	6.47, d (9.7)	8.04, d (9.7)	6.71, d (7.4)	7.39, t (8.2)	6.91, d (8.5)	10.52, s	------
1c	3.59, s and 3.91, s	6.54 , d (9.7)	8.06, d (9.7)	6.86, d (8.1)	7.56, t (8.3)	7.12, d (8.5)	-----	------
1d	3.89, s	6.27, d (9.6)	8.06, d (9.6)	6.48, d (8.0)	7.16, t (8.1)	6.55, d (8.1)	n.o.	
4	-----	7.47, d (8.7)	8.51, dd (8.7 and 0.8)	6.98, dd (7.7 and 0.9)	7.61, t (8.4)	7.38, dd (8.4 and 0.8)	10.76, s	------
5	3.99, s	7.54, d (8.8)	8.54, dd (8.8 and 0.5)	7.12, d (7.85)	7.75, t (8.3)	7.51, d (8.5)	-----	------

n.o.: not observed

Table 2. ^{13}C-Nmr Spectral Data of Compounds (**1**)-(**5**) (63 MHz, DMSO-d$_6$, δ)

Compound	Me	C2	C3	C4	C4a	C5	C6	C7	C8	C8a
1	---	170.08	119.51	134.70	108.88	154.21	105.80	131.19	106.57	140.22
1a	56.0	162.13	120.66	134.31	109.48	155.72	102.80	131.58	107.97	140.29
1b	29.45	161.42	118.82	133.59	109.80	154.88	105.51	131.90	107.57	141.35
1c	29.60 and 56.23	161.29	119.73	132.98	110.28	156.04	103.59	132.05	107.47	141.55
1d	56.05	162.58	118.43	135.93	110.08	157.75	103.70	131.60	107.59	140.68
4	---	150.20	120.16	134.32	118.42	153.46	109.13	130.90	118.32	148.48
5	56.32	150.45	121.66	134.48	118.87	155.09	106.07	131.73	119.97	148.33

EXPERIMENTAL

All reagents were of commercial quality from freshly opened containers and reagent quality solvents were used without further purification. Melting points are uncorrected and were measured with a Büchi capillary melting

point apparatus. ^{1}H-Nmr spectra were obtained on a Bruker AC-250 (250 MHz for ^{1}H and 63 MHz for ^{13}C) spectrometer, using $CDCl_3$ or DMSO-d_6 as solvents, and TMS as internal standard. Microanalyses were obtained by the Servicio de Microanálisis, Universidad Complutense, using a Perkin-Elmer 2400 CHN elemental analyzer.

5-Hydroxy-2(1*H*)-quinolinone (1). A solution of 1,2,5,6,7,8-hexahydroquinoline-2,5-dione (**3**)[8] (3.4 g, 20.8 mmol) in decalin (40 ml) containing 10% Pd-C (1.04 g) was refluxed for 6 days. After cooling, the solution was filtered and the solvent was removed under reduced pressure. Both filtrate and residue were extracted with MeOH and the extract concentrated to give quantitatively **1** (3.35 g) as a solid; mp > 300 °C (MeOH), (lit.,[5] 336-341 °C).

Methylation on **1.** *Methylation with dimethyl sulfate*

To a solution of **1** (0.2 g, 1.24 mmol) in 10N KOH (10 ml, 9.9 mmol), Me_2SO_4 (1 ml, 7.92 mmol) was added dropwise and the mixture was stirred at room temperature for 24 h. The precipitate was removed by filtration giving **1b** (20 mg, 9 % yield), mp (decomp.) 290 °C (MeOH) and the solution was neutralized with 2N HCl (24 ml). The precipitated compound (**1c**) was collected by filtration; yield: 161 mg (74%), mp 129-130 °C (MeOH/ether), (lit.,[11] 129-130 °C).

1-Methyl-5-hydroxy-2(1*H*)-quinolinone (1b). Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 7.99. Found: C, 68.38; H, 4.88; N, 7.63.

Methylation with diazomethane

To a stirred suspension of **1** (1 g, 6.20 mmol) in MeOH (20 ml) a 1.4N solution of CH_2N_2 in ether (50 ml, 0.07 mol) was added dropwise. The light yellow solution was stirred at room temperature for 12 h. After addition of water, the filtered precipitate was extracted with MeOH leaving a 1:1 unseparable mixture of **1a** (400 mg, 40%) and **1d** (400 mg, 40%) as the insoluble residue. Evaporation of methanol gave **1c** 200 mg (20%)with traces of **1a**.

Methylation previous protection of the amide group

2-Chloro-5-hydroxyquinoline (4). A solution of **1** (725 mg, 4.5 mmol) in DMF (0.5 ml) and phosphorus oxychloride (3 ml, 31.6 mmol) was allowed to stand for 12 h. After subsequent heating at 115 °C for 2 h, the reaction mixture was poured onto ice and neutralized with 25 % NH_4OH. The precipitate was filtered and extracted with acetone. The acetone solution concentrated *in vacuo* gave compound **4**; yield 0.6 g (70%), mp 159-160 °C (ethyl acetate). Anal. Calcd for C_9H_6NOCl: C, 60.19; H, 3.36; N,7.79. Found: C, 59.78; H, 3.74; N, 7.85.

2-Chloro-5-methoxyquinoline (5). To a solution of **4** (0.6 g, 3.34 mmol) in MeOH (20 ml) a 0.35N solution of diazomethane in ether (50 ml, 175 mmol) is added dropwise . The light yellow solution is stirred at room temperature for 12 h. After addition of water, the precipitate was filtered to give **5**; yield 0.48 g (86 %), mp 70 °C (ethyl acetate). Anal. Calcd for $C_{10}H_8NOCl$: C, 62.03; H, 4.16; N, 7.23. Found: C, 62.35; H, 4.22; N, 7.15.

5-Methoxy-2(1*H*)-quinolinone (1a). A solution of **5** (0.2 g, 1.33 mmol) in acetic acid (3 ml) and water (1 ml) was refluxed for 5 h and poured onto ice. The filtered precipitate yielded **1a**, 152 mg (84 %); mp 240 °C (MeOH). Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 7.99. Found: C, 68.38; H, 5.52; N, 7.69.

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