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AN CONVENIENT METHOD FOR THE SYNTHESIS OF 7,8-DIMETHOXY-3-HYDROXYQUINOLIN-2(1*H*)-ONE AND ITS TAUTOMER CONFORMATION STUDY

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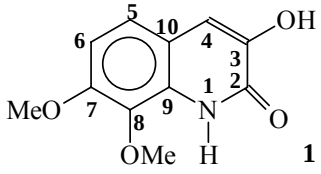
Abstract –3-Hydroxyquinolin-2(1*H*)-one (**1**) was synthesized successfully from readily available 2-nitroveratraldehyde in a three-step reaction. The procedure was based on existing protocol but with slight modification to give a much higher production yield. The tautomer conformation of the quinolinone was studied.

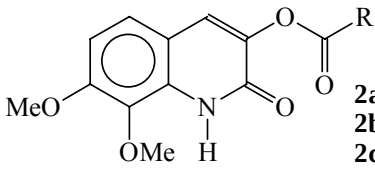
INTRODUCTION

Quinolin-2(1*H*)-one moiety can be found in various alkaloids, and many of them possess interesting biological activity.[1] Much efforts have been made on the biological study of molecules with quinolin-2(1*H*)-one core structure and obtained positive results. It is the biological activity of compounds containing quinolinone unit and the versatile application of quinolinone in various organic synthesis[2] which made this compound important, and thus the development of effective synthetic methods to this compound attracted attention in recent studies. Apart from the older methods for the synthesis of quinolin-2(1*H*)-one which involved the ring-expansion of isatins,[3] recent developments in the synthesis included one pot synthesis *via* tandem Ugi-Knoevenagel condensation,[4] radical cyclisation of secondary amide,[5] palladium-catalyzed annulation,[6] and electron transfer-initiated photocyclization of benzoquinolinone.[7] As a part of our project on the total synthesis of metabolites from marine microorganisms,[8] we therefore study the synthesis of 7,8-dimethoxy-3-hydroxyquinolin-2(1*H*)-one (**1)** and its derivatives (**2**). The synthetic approach adopted in our scheme was similar to the existing protocol for the synthesis of hydroxyquinolin-2(1*H*)-one[9] but with minor modifications (Scheme 1).

Chloroacetylation according to the reported method only gave a 20% yield, while our method gave an 80% yield which allowed a more convenient synthesis for 3-hydroxyquinolin-2(1*H*)-ones.



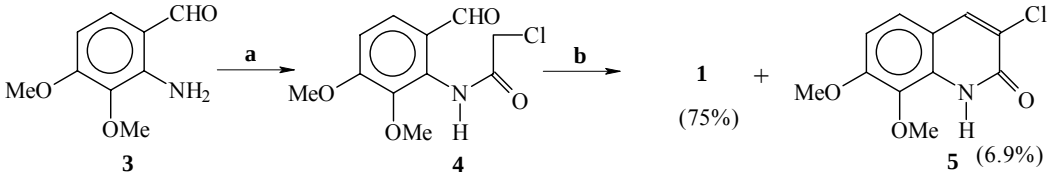
1



2a: R = isopropenyl
2b: R= cyclopropanyl
2c: R = 3-chlorophenyl

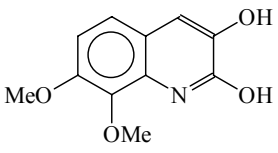
RESULTS AND DISCUSSION

Readily available **3** was prepared by the reduction of 2-nitroveratraldehyde[10] obtained from vanillin.[11] **3** was relatively unstable[10] and was directly used for chloroacetylation with chloroacetyl chloride without further purification.

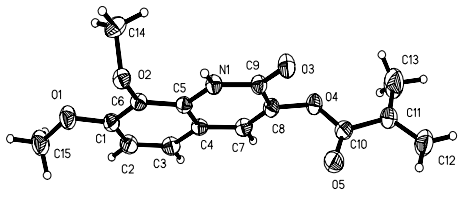


Scheme 1 Reagents: (a) $ClCH_2COCl$, AcONa, AcOH (b) 1% KOH, aq. propanol, reflux

Chloroacetylation was conducted in various organic solvents in the presence of organic base and gave only 10-20% yield of **4**. Amazingly, the yield was elevated to 80% in acetic acid in the presence of sodium acetate. The reaction was particularly facile and straightforward. Cyclization was achieved by refluxing **4** in an aqueous propanol solution of KOH to give the predominant product (**1**) and a small amount of the side product, 3-chloro-7,8-dimethoxyquinolin-2(1*H*)-one (**5**). Due to the high solubility of **1** in alkaline solution, **5** was easily removed from the reaction mixture by washing with ethyl acetate. 3-Hydroxyquinolin-2(1*H*)-one (**1)** was then precipitated out in high purity by acidification with concentrated hydrochloric acid (75% yield). The present procedure allowed a much more convenient work-up process compared with other methods in a similar synthesis.[9]



6 (lactim-form)



2a The view of the molecule (lactam-form)

It was reported quinolin-2(1*H*)-ones could exist in both lactam and lactim tautomer forms.[12] The tautomeric equilibrium of lactam-lactim attracts attention owing to its chemical, biological, and theoretical importance.[13] It was reported that the *N*-alkylated lactam-form of 2(1*H*)-quinolones had a strong IR signal of amido carbonyl group around 1648-1665 cm^{-1} [14] and the strong signal of **1** at 1665

cm^{-1} indicated its lactam-form in solid state. This lactam-form was further confirmed by the absolute conformation of the single crystal structure of an ester derivative, 7,8-dimethoxy-2(1*H*)-oxoquinolin-3-yl 2-methylprop-2-enoate (**2a**).[15] Esterification of C3-OH proceeded smoothly, simply by treating **1** with an appropriate carboxylic acid, such as 2-methacrylic acid, cyclopropanecarboxylic acid and 3-chorobenzoic acid in the presence of DCC and 4-pyrrolidinopyridine to give a 80-92% yield of the corresponding esters.

Conformation of **1** was deduced from the 1D and 2D NMR spectra in $CDCl_3$ (Table 1). In the ^1H NMR spectra, both **1** and **2a** have the same signal at δ 9.28, indicating that it is due to either the N-H of **1** (lactam-form**)** or the C2-OH of **6** (lactim-form). The multiple correlations of the HMBC of proton to carbon unambiguously defined the quinolinone ring system of **1**. The correlations of the proton at δ 9.28 to both C-3 and C-10 revealed that the proton is attached to the nitrogen atom.

Table 1. NMR data of **1**

^{13}C	^1H	HMBC
159.0(C)		
150.2(C)		
143.7(C)		
134.2(C)		
127.3(C)		
121.1(CH)	7.14-7.17 (d, *J*=9.0 Hz)	C-6,7,9
115.7(C)		
112.2(CH)	6.85-6.88 (d, *J*=9 Hz)	C-7,8,10
108.8(CH)	7.07 (s)	C-2,3,5,9,10
60.6(CH_3)	3.97 (s)	
56.0(CH_3)	3.93 (s)	
OH	6.61(br)	
NH	9.28 (s)	C-3,10

EXPERIMENTAL

Melting points were uncorrected. IR spectra were recorded on a Bruker Equinox55-FTIR spectrophotometer. NMR spectra were recorded on a Varian Inova 300 NMR spectrometer. Mass spectra were recorded on a VG ZAB-HS mass spectrometer. X-Ray data were generated on a Bruker Smart 1000CCD system diffractometer. Elemental analyses were carried out on a Vario EL elemental analyzer.

3,4-Dimethoxy-2-(*N*-chloroacetamino)benzaldehyde (4)

To a boiling solution of ferrous sulfate heptahyrate (35.0 g, 0.13 mol) in water (75 mL) was added 3,4-dimethoxy-2-nitrobenzaldehyde (2.32 g, 0.011 mol), and then slowly added saturated aqueous sodium carbonate solution with vigorous stirring until the reaction mixture was permanently alkaline to litmus paper. The black-color mixture was boiled for 20 min and then filtered while hot. The residue was washed with hot water (2 x 25 mL). All aqueous solution were combined and extracted with ethyl acetate (3 x 80

mL). The ethyl acetate extract was dried over anhydrous sodium sulfate and then evaporated to dryness to give an yellow oily residue of aminobenzaldehyde (**3**). The aminobenzaldehyde (**3**) was dissolved in a mixture of glacial acetic acid (8 mL) and saturated solution of sodium acetate (8 mL) and then cooled to 0 ^{o}C. To the solution was added dropwise chloroacetyl chloride (3.70 g, 0.033 mol) and was vigorously stirred for 1h at 0 ^{o}C, and then the resultant solution was allowed to warm to room temperature and continuously stirred for 10 h. Then to the stirring mixture added ice water (50 mL), and the solid formed was filtered off and washed with ice water to give the crude product, which was recrystallized from ethanol to give **4** (2.26g, 8.8mmol; overall 80% yield). mp 118-119 ºC; IR (KBr): 3320, 1697, 1678, 1598 cm^{-1}; ^{1}H-NMR (300MHz, $CDCl_3$): δ = 9.83 (s, 1H), 7.59 (d, 1H, *J*=9 Hz), 6.94 (d, 1H, *J*=9 Hz), 4.26 (s, 2H), 3.97 (s, 3H), 3.90 (s, 3H); ^{13}C-NMR (300MHz, $CDCl_3$): δ = 189.9, 165.6, 158.0, 143.0, 130.9, 128.3, 123.6, 110.0, 60.9, 56.5, 43.3; MS (EI): *m/z* = 258 $(M+1)^+$; *Anal*. Calcd for $C_{11}H_{12}NO_4Cl$: C, 51.27; H, 4.69; N, 5.44. Found: C, 51.25; H, 4.83; N, 5.36.

7,8-Dimethoxy-3-hydroxyquinoline-2 (1*H*)-one (1)

To a refluxing aqueous potassium hydroxide solution (1.00 g in 100 mL) was added dropwise over a ten-minute period a solution of **4** (0.9 g, 3.50 mmol in 20 ml of hot propyl alcohol) with stirring. The solution was refluxed and stirred for 2h, and then was concentrated to 30 mL. The concentrated solution was extracted with ethyl acetate (2 x 10 mL), and the aqueous solution was acidified with concentrated hydrochloric acid to give white precipitate. The precipitate was collected and recrystallized from acetone to give **1** (0.58 g, 2.63 mmol; 75% yield). mp 163-164 ºC; IR (KBr): 3442, 3169, 1665, 1638, 1616 cm^{-1}; ^{1}H-NMR (300MHz, $CDCl_3$): δ = 9.28 (s, NH), 7.14, 7.17 (d, *J*=9.0 Hz, 1H), 7.07 (s, 1H), 6.85, 6.88 (d, 1H, *J*=9 Hz), 6.61(br, OH), 3.97 (s, 3H), 3.93 (s, 3H); ^{13}C-NMR (300MHz, $CDCl_3$): δ = 159.0, 150.2, 143.7, 134.2, 127.2, 121.1, 115.7, 112.2, 108.8, 60.6, 56.0; MS (EI): *m/z* = 222 $(M+1)^+$; *Anal*. Calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33. Found: C, 59.98; H, 5.23; N, 6.14.

The ethyl acetate extract was dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified on prep. TLC (silica-gel) [ethyl acetate/petroleum ether, 1:1, Rf (TLC) = 0.3] to give the white solid of 3-chloro-7,8-dimethoxyquinoline-2(1*H*)-one (**5**) (58 mg, 0.24 mmol; 6.9% yield). mp 231-232 ºC; ^{1}H-NMR (300MHz, $CDCl_3$): δ = 9.31 (s, NH), 7.86 (s, 1H), 7.20, 7.23 (d, *J*=9.0 Hz, 1H), 6.86, 6.89 (d, 1H, *J*=9 Hz), 3.97 (s, 3H), 3.97 (s, 3H); MS (EI) m/z: 240$(M+1)^+$, 147, 136, 109, 95,81, 55, 43; *Anal*. Calcd for $C_{11}H_{10}NO_3Cl$: C, 55.13; H, 4.21; N, 5.84. Found: C, 55.29; H, 4.01; N, 5.63.

General Procedure for the Esterification of 1

A solution of carboxylic acid (1.10 mmol), *N*,*N*-dicyclohexylcarbodimide (1.10 mmol), **1** (1.00 mmol) and 4-pyrrolidinopyridine (0.1 mmol) in dichloromethane was allowed to stand at rt until esterification was completed. The *N*,*N*-dicyclohexyl urea was filtrated and the filtrate was washed with water (2 × 5

mL), 5% acetic acid solution (2 × 5 mL), and again with water (2 × 5 mL), dried (Na_2SO_4) and evaporated in vacuo to give the ester.

7,8-Dimethoxy-2(1*H*)-oxoquinolin-3-yl 2-methylprop-2-enoate (2a)

Crystallization from acetone (yield 92%). mp 209-210 ºC; IR (KBr): 2999, 1740, 1663, 1614 cm^{-1}; ^{1}H-NMR (300MHz, $CDCl_3$): δ = 9.28 (s, NH), 7.49 (s, 1H), 7.20, 7.23 (d, *J*=9Hz, 1H), 6.85, 6.88 (d, *J*=9Hz, 1H), 6.40 (s, 1H), 5.79 (s, 1H,), 3.96 (s, 3H), 3.95 (s, 3H), 2.08 (s, 3H); ^{13}C-NMR (300MHz, $CDCl_3$): δ = 165.3, 157.6, 152.7, 139.6, 135.3, 134.1, 131.1, 128.9, 128.3, 123.1, 113.9, 108.8, 61.3, 56.6, 18.8; *Anal*. Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.43; H, 5.45; N, 4.89.

7,8-Dimethoxy-2(1*H*)-oxoquinolin-3-yl cyclopropanecarboxylate (2b)

Crystallization from ethanol (yield 89%). mp 172-173 ºC; IR (KBr): 3001, 1750, 1665, 1612 cm^{-1}; ^{1}H-NMR (300MHz, $CDCl_3$): δ = 9.15(s, NH), 7.48 (s, 1H), 7.21, 7.24 (d, *J*=9Hz, 1H), 6.85, 6.88 (d, *J*=9Hz, 1H), 3.96 (s, 3H), 3.96 (s, 3H), 1.89-1.98 (m, 1H), 1.23-1.26 (m, 2H), 1.05-1.10 (m, 2H); ^{13}C-NMR (300MHz, $CDCl_3$): δ = 173.0, 157.6, 152.6, 139.3, 133.9, 131.0, 128.9, 123.2, 113.9, 108.8, 61.317, 56.6, 13.2, 10.1; *Anal*. Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.59; H, 5.65; N, 4.70.

7,8-Dimethoxy-2(1*H*)-oxoquinolin-3-yl 3-chlorobenzoate (2c)

Crystallization from chloroform/acetone (1:2) (yield 80%). mp 231-232 ºC; IR (KBr): 3002, 1741, 1664, 1612 cm^{-1}; ^{1}H-NMR (300MHz, $CDCl_3$): δ = 9.26 (s, NH), 8.20 (s, 1H), 8.09, 8.12 (d, *J*=9Hz, 1H), 7.59-7.60 (m, 2H), 7.42, 7.45, 7.47 (t, 1H), 7.25, 7.28 (d, *J*=9Hz, 1H), 6.88, 6.91 (d, *J*=9Hz, 1H,), 3.99 (s, 3H), 3.97 (s, 3H); ^{13}C-NMR (300MHz, $CDCl_3$): δ = 163.5, 157.3, 152.8, 139.3, 134.9, 133.9, 131.2, 131.3, 130.7, 130.2, 130.1, 129.2, 128.8, 123.3, 113.8, 108.9, 61.3, 56.6; *Anal*. Calcd for $C_{18}H_{14}NO_5Cl$: C, 60.09; H, 3.92; N, 3.89; Found: C, 60.21; H, 4.16; N, 3.86.

ACKNOWLEDGEMENTS

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15. X-Ray Diffraction Analysis of **2a** ($C_{15}H_{15}NO_5$): Single crystals suitable for X-Ray structure analysis were prepare by recrystallization from chloroform/acetone =1:2. Crystal Date: $C_{15}H_{15}NO_5$; MW=289.28, Monoclinic, space group P2(1)/c, Unit cell dimensions a =12.976(5)Å, α=90deg, b=11.070(4)Å, β=105.685(6)deg, c=10.406(4)Å, γ=90deg. Volume= 1439.1(9)Å^3, Z = 4, D_{calcd}=1.335 mg·m^{-3}, *m*=0.101 mm^{-1}, F(000)= 608. All single-crystal data were collected using the hemisphere technique on a Bruker SMART 1000CD system diffractometer with graphite monochromated Mo Kα radiation λ= 0.71073 at 293(2) K. The structures were solved by direct methods using SHELXTLV5.0 (Simemens Industrail Automation Inc, Madision.WI) and refined using full-matrix least-squares difference Fourier techniques. All non-hydrogen atoms were refined with anisotropic displacement parameters and all hydrogen atoms were placed in idealized positions and refined as riding atoms with the relative isotropic parameters. Absorption corrections were applied with the Siemens Area Detector ABSorption program (SADABS). The final value of R was 0.0487, *w*R_2=0.1364[I>2sigma(I)]. The structure data have been deposited at the Cambridge Crystallographic Data Centre under the reference number CCDC 279684.