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Note

Solid-state induced heterocyclization under microwave irradiation: Synthesis of 2-phenyl-3-hydroxy-quinolin-4(1*H*)-one

Majid M Heravi[a,*], Hossein A Oskooie[a], Lila Bahrami[a] & Mitra Ghassemzadeh[b]

[a]Department of Chemistry, School of Sciences
Azzahra University, Vanak, Tehran, Iran

[b]Chemistry & Chemical Engineering Research Center of Iran
P.O.Box 14335-186, Tehran, Iran

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Synthesis of 2-phenyl-3-hydroxy-quinolin-4(1*H*)-one under microwave irradiation in solventless system has been described. The mechanism of the reaction is also discussed.

Keywords: Solid state, quinolinone, microwave irradiation, heterocyclization.

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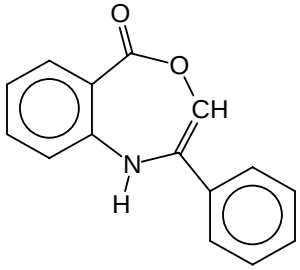
The quinoline system is a prevalent topic in heterocyclic chemistry. It's presence in a variety of biologically active compounds[1] led to the design of numerous approaches towards the construction of this skeleton[2]. For the preparation of 3-hydroxy-quinolin-4-ones several methods have been reported[3]. 3-Hydroxy-2-aryl-quinolin-4(1*H*)-ones **3** has been synthesized via chalcone formation, epoxidation, ring closure and final oxidation[4]. For the construction of this system, thermal reaction of phenacyl anthranilates **2** or reaction in polyphosphoric acid has been employed[5]. This reaction needed high temperature (120°C), long reaction time (1 hr) and tedious work- up procedure.

Microwave irradiation of organic reactions has rapidly gained popularity as it accelerates a variety of organic reactions[6]. Although reagents adsorbed on mineral support have also gained popularity in organic synthesis[7], the solventless procedures[8] without the use of supporting reagents are particularly eco-friendly[9].

Solvent-free organic reactions or dry media techniques under microwave irradiation are one of the main topics of research in our laboratory[10].

Our synthetic approach involves two steps reaction under microwave irradiation starting from anthranilic acid. A mixture of anthranilic acid, phenacyl bromide and potassium carbonate was exposed to microwave irradiation in solventless system. The progress of reaction was monitored by TLC using chloroform as eluent. The reaction was found to complete after 2 min to give a single compound, which was identified to be phenacyl anthranilate **2**. Under classical heating this reaction needs 1 hr at 90°C in dimethylformamide along with tedious work-up procedure and moderate yield[5b]. When **2** was mixed with polyphosphoric acid supported onto silica gel and exposed to microwave irradiation a single TLC compound was obtained in 2 min. The cyclization of phenacyl anthranilates **2** in polyphosphoric acid has been reported to give 2-phenyl-3*H*-benz[e][1,4]oxazepin-5-one[11]. Hradil *et a.l* claimed the formation of 2-substituted-3-hydroxy-quinolin-4(1*H*)-ones **3** from the cyclization of phenacyl anthranilates **2**[5b]. To achieve cyclization, compound **2** has been heated with polyphosphoric acid at 120°C or refluxed in N-methylpyrrolidone for 1 hr to obtain **3** in moderate yield. IR spectrum of our compound showed OH stretching bond at 3450 cm^{-1}, which could rule at the structure **4**. Unambiguous synthesis of 3-hydroxy-2-phenyl-1,4-dihydro-quinolin-4-one **3** has been reported[4]. The product was identical by the comparison of its physical and spectroscopic data. The following mechanism for this transformation has been suggested (**Scheme I**).



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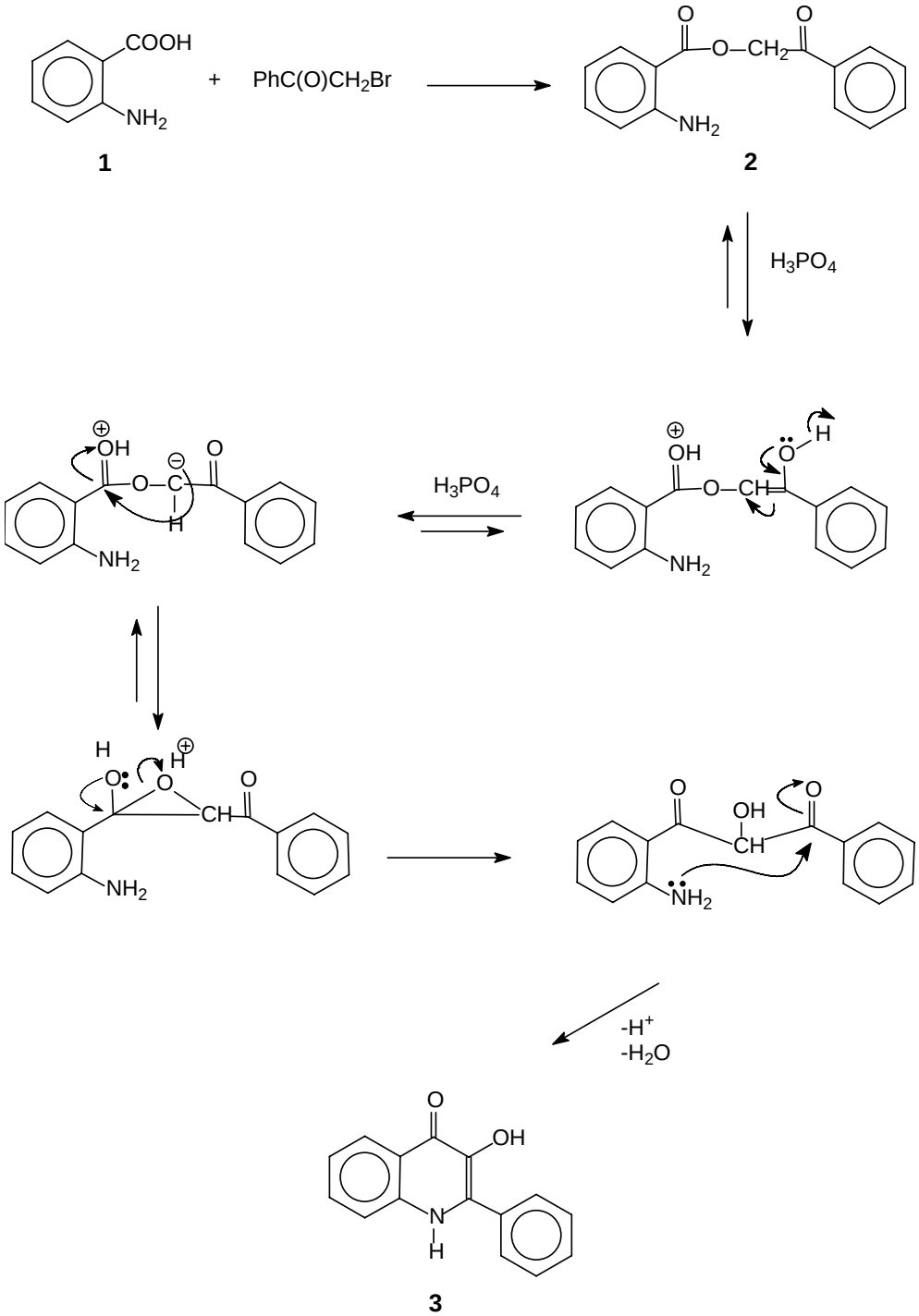
Substituted phenacyl bromide reacts with anthranilic acid to afford the condensed product under microwave irradiation but heterocyclization did not take place under forementioned condition. Chloro-acetone did not condense under microwave irradiation with anthralinic acid.



Scheme I

Synthesis of **3** from 2-nitrobenzaldehyde and phenacyl bromide based on modification of Darzen's reaction and formation of an epoxide has been already reported[3a].

In conclusion we have developed the cyclization of anthranilate **2** to 3-hydroxy-quinolinone **3** under microwave irradiation in solventless system. The reactions are found to be very fast, relatively benign with high yields and has easy work-up procedures.

Experimental Section

^{1}H NMR spectra were recorded on a Bruker 90 MHz spectrometer using TMS as internal standard in $CDCl_3$. IR spectra were recorded on a PU9714 Philips

spectrometer. Mass spectral analyses were obtained using GC-Mass HP, GC 6890N network GC system, mass 5973. Melting points (uncorrected) were recorded on Electrochem.

Phenacyl anthranilates 2

Anthranilic acid **1** (0.20 g, 1.5 mmole), potassium carbonate (0.14 g, 1.07 mmole) and phenacyl bromide (0.24 g, 1.25 mmole) were grinded throughly using pestel and mortar. The mixture was transferred to a beaker and placed in a household microwave oven for 2 min. The progress of the reaction was monitored by TLC using $CHCl_3$ as eluent. After the completion of reaction, to the crude, water (10 mL) was added. The mixture filtered and washed with water (5 mL). The solid was dried and crystallized from ethanol to give the titled compound. Yield: 0.15 g (75%); m.p. 124-26°C (lit. 124-28°C[5b]); ^{1}H NMR (DMSO-d_6): δ 5.75 (s, 2H, CH_2), 6.9(m, 4H, ArH), 7.2-8.1(m, 5H, ArH), 7.3 (s, 2H, NH_2); IR, (KBr disc): 3500, 3400, 1710, 1600, 920, 790 cm^{-1}; MS: m/z, 859(92), 120(100), 105(80), 92(42), 77(35), 66(30), 51(15), 39(11).

2-Phenyl-3-hydroxy-quinolin-4(1*H*)-one 3

Compound **2** (0.12 g, 0.5 mmole), polyphosphoric acid (1 g) and silica gel (0.5 g) were grinded using pestle and mortar. This mixture was transferred to a beaker and placed in a household microwave oven for 2 min. The progress of the reaction was monitored by TLC using methanol:chloroform 9:1 as eluent. After completion of reaction, to the crude $CHCl_3$ (15 mL) was added and heated. The hot solution was filtered off. The filtrate was evaporated to dryness. To the crude water (10 mL) was added. The *p*H of the solution was adjusted to 7-8 by addition of NaOH. The precipitated solid was collected, washed with water, dried and crystallized from acetone:DMF 7:3 to yield the titled compound as yellow crystals. Yield: 0.97 g (76%); m.p. 278-182°C[4]; ^{1}H NMR (DMSO-d_6): δ 3.42(s, 1H, OH), 7.25-8.15(m, 9H, ArH), 11.8 (s, br, 1H, NH); IR, (KBr disc): 3450, 3243, 1640, 1600, 1490 cm^{-1}; MS: m/z, 238(18), 237(85), 236(100), 208(11), 180(18), 152(8), 104(9), 77(17).

Caution. Although we did not observed any accident using polyphosphoric acid in microwave oven, use of microwave oven in an efficient hood is highly recommended.

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