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An Innovative Approach for the Synthesis of 7-Hydroxyquinolin-2(1*H*)-one: A Key Intermediate of Brexpiprazole

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2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) mediated oxidation of 7-hydroxy-1,2,3,4-tetrahydro-2-quinolinone has been prepared from 3-hydroxy aniline to obtain 7-hydroxyquinolin-2(1*H*)-one in aqueous media. Stoichiometric quantities of DDQ and THF provides a high out put of 7-hydroxyquinolin-2(1*H*)-one and reduces the consumption of organic solvents and discourages by-products. Overall advantage with this approach was reduce the time cycle and cost of the brexpiprazole intermediate.

Keywords: 7-Hydroxyquinolin-2(1*H*)-one, 7-Hydroxy-1,2,3,4-tetrahydro-2-quinolinone, 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone.

INTRODUCTION

7-Hydroxyquinolin-2(1*H*)-one have always been of interest to medicinal chemists and can be found in antipsychotic drug such as brexpiprazole. REXULTI® (brexpiprazole) is a serotonin-dopamine activity modulator (SDAM) for the treatment of schizophrenia and is used as adjunctive therapy to antidepressants for the treatment of major depressive disorder [1,2].

One of the classical synthesis of 7-hydroxyquinolin-2(1*H*)-one starts from commercially available *m*-anisidine reacting with cinnamoyl chloride to give 3-methoxy cinnamaldehyde followed by cyclization with aluminium chloride [3,4]. Another method starting from 7-hydroxyquinoline would be oxidized to offered 7-hydroxyquinoline-1-oxide, further reaction with acetic anhydride followed by saponification with aqueous NaOH solution to obtain 7-hydroxyquinoloine-2(1*H*)-one [5-9]. El-Aal and Koraierm [10] reported the synthesis of 7-hydroxyquinolin-2(1*H*)-one with 7-hydroxy-4-methyl coumarin in presence of ammonium acetate and acetic acid. However above mentioned methods have the disadvantages such as high reaction temperature, more by-product formation, usage of hazardous chemicals in the reaction and low yielding. Therefore, these drawbacks motivated us to consider some alternative approaches to synthesize 7-hydroxyquinolin-2(1*H*)-one (**1**). Herein, we present 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) mediated oxidation of 7-hydroxy-1,2,3,4-tetrahydro-2-quinolinone (**4**) to give 7-hydroxyquinolin-2(1*H*)-one (**1**). This approach enables us the synthesis of brexpiprazole and its intermediate with increased yield and reasonable reaction time.

EXPERIMENTAL

All commercially available materials and solvents were used without any further purification. TLC analyses were performed on Merck silica gel 60 F254 plate. ^{1}H NMR and ^{13}C NMR spectra were recorded at room temperature on a Bruker AMX-400 using TMS as an internal standard. Mass spectra were recorded on a Finnigan MAT-95/711 spectrometer

Synthesis of 3-chloro-N-(3-hydroxyphenyl)propanamide (3): 3-Aminophenol (**2**) (50 g, 0.458 mol, 1.0 eq), $NaHCO_3$ (59.2 g, 0.705 mol, 1.54 eq) and dichloromethane (250 mL) was stirred under a nitrogen atmosphere at room temperature for 30 min. 3-Chloropropionyl chloride was added to the above mixture (66.7 g, 0.52 mol, 1.15 eq) the resulting reaction mixture stirred at room temperature for 2 h, the progress of the reaction is monitored by TLC. The solid thus obtained was filtered, crystallized from water to offered compound **3** (85 g, 0.425 mol, 93 %) as an off-white solid.

Synthesis of 3,4-dihydro-7-hydroxyquinolin-2(1*H*)-one (4): To a solution of compound **3** (50 g, 0.250 mol, 1.0 eq) in N,N-dimethyl acetamide (11 mL) $AlCl_3$ (125 g, 0.936, 3.74 eq) was added portion wise at 70 °C. Stirred the reaction mixture at 140 °C for 4 h. The progress of the reaction was monitored by TLC. After cooling added toluene and water to the reaction mixture, the obtained solid was filtered and washed with water. The solid treated with aq. NaOH and aq. HCl to offered compound **3** (25 g, 0.153 mol, 61 %) as an off-white solid. m.p. 235-237 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 9.91 (br s, 1H), 9.22 (s, 1H), 6.88 (d, *J*) 8.0 Hz, 1H),

6.27-6.30 (m, 2H), 2.71 (t, *J*) 7.8 Hz, 2H), 2.36 (t, *J*) 7.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 170.8, 156.7, 139.2, 128.5, 144.0, 109.1, 102.6, 31.1, 24.2; FTIR (KBr): 3109, 2955, 1655, 1593, 1523, 1433, 1401, 1231, 1166, 1030, 803, 742 cm^{-1}; $C_9H_9NO_2$ [M -1] calcd. 162.86.

Synthesis of 7-hydroxyquinolin-2(1*H*)-one (1): To a solution of compound **4** (25 g, 0.153 mol, 1.0 eq) in THF (125 mL) at room temperature under a nitrogen atmosphere and stirred for 10-15 min, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) added portion wise (37.16 g, 0.163, 1.07 eq) to the reaction mixture. Stirred the reaction at 45-50 °C for 2 h. The progress of the reaction monitored by TLC, reaction mixture was cooled to 25-30 °C, added $NaHCO_3$ (27.5 g, 0.327, 2.14 eq) and water (250 mL) to the reaction mixture, stirred for 1 h at room temperature, solid filtered and washed with water (50 mL). Wet cake was triturated with Isopropyl alcohol (75 mL), filtered and washed with isopropyl alcohol (25 mL) to obtain pure compound **1** (18.5 g, 0.114 mol, 75 %) as an off-white solid, m.p. 233-235 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 11.47 (br s, 1H), 10.07 (s, 1H), 7.73 (d, *J*) 9.44 Hz, 1H), 7.43 (d, *J*) 8.52 Hz, 1H) 6.67 (s, 1H) 6.61 (d, *J*) 6.48 Hz, 1H), 6.20 (d, *J*) 9.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 162.3, 159.5, 140.7, 140.0, 129.2, 117.4, 112.3, 111.5, 99.8; $C_9H_7NO_2$ [M-1] calcd. 160.1.

RESULTS AND DISCUSSION

The target compound 7-hydroxyquinolin-2(1*H*)-one (**1**) could be prepared from commercially available 3-hydroxy aniline (**2**) reaction with 3-chloropropionyl chloride to give 3-(3-hydroxyphenylamino) propanoyl chloride (**3**), followed by intermolecular Friedel-Crafts cyclization to obtain 7-hydroxy-1,2,3,4-tetrahydro-2-quinolinone (**4**), this process previously reported [11]. Finally, DDQ mediated oxidation-dehydrogenation of compound **2** yield the compound **1** (**Scheme-I**).

As part of the reaction, during work up few issues encountered during the quenching and isolation of the product. As per the literature after completion of reaction, quenching with aqueous sodium hydroxide, red colour clear solution observed, a product was not isolated. Due to presence of phenolic group in the compound **2**, it reacts with sodium hydroxide to form corresponding sodium phenoxide, it is highly soluble in water, poor extractability in organic solvents such as dichloromethane and ethyl acetate. This layer would be acidified with hydrochloric acid to get solid but poor yields were observed. To overcome all these challenges sodium hydroxide was replaced with sodium hydrogen carbonate to give precipitate in the direct reaction mass, pure product was isolated with good yields. The reason would be, weak basic nature of sodium hydrogen carbonate was unable to form the sodium phenoxide ion of compound **1**.

The final isolated product was confirmed by spectroscopic techniques such as ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopy. After dehydrogenation reaction, alkene product would be detected in ^{1}H NMR with significant coupling constant 9.4 Hz at 7.73 and 6.62 δ ppm values, it indicates the presence of alkene protons in the compound **1**. ^{13}C NMR significant alkene carbons would be observed at 140.0 and 117.4 δ ppm and peaks at 31.1 and 24.2 δ ppm disappeared, these peaks related to *sp*^{3} carbons in compound **4**.

Oxidation-dehydrogenation reaction depends on the certain parameters such as reaction temperature, solvent, solvent volume and mole equivalents of reagents.

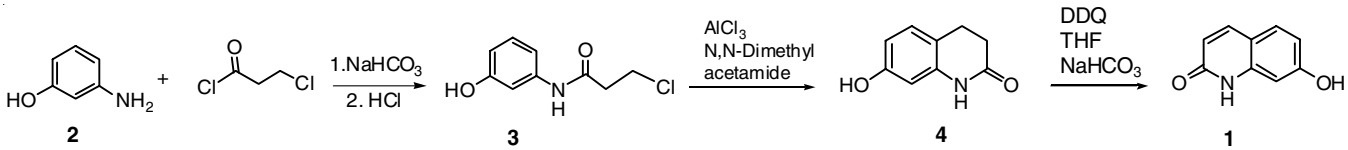
In our initial study, the oxidation of 7-hydroxy-1,2,3,4-tetrahydro-2-quinolinone was carried out in higher dilution of solvent (20 volumes of THF) at room temperature with 1.8 eq of DDQ, reaction not gone for the completion even after 24 h, corresponding compound **1** was isolated in 45 % yield (entry 1, Table-1). Another set of experiment conducted at 45-50 °C, other conditions same as mentioned in the entry 1, reaction completed after 8 h, quenched the reaction with sodium hydrogen carbonate, yield was 63 %, due to the presence of more quantity of THF, yield was dropped. To improve the yield, sequentially reaction optimization carried out by reducing the DDQ reagent equivalents from 1.8 to 1.1 eq and solvent volume from 20 volumes to 5 volumes, finally reaction conversion time reduced drastically from 8 to 2 h, all the results captured in the Table-1. While THF was used as solvent in all these cases, other solvents screened in the reaction such as dioxane, dichloroethane and DMF, however these solvents were found to be less effective in the synthesis of compound **1** (entries 6, 7 & 8 in Table-1).

TABLE-1
REAGENT MOLE EQUIVALENT OPTIMIZATION TABLE

Entry	DDQ (mol. Eq)	Temp. (°C)	Solvent	Time (h)	Yield (%)[e]
1	1.8	25-30	THF[a]	24	45
2	1.8	45-50	THF	12	60
3	1.1	45-50	THF[b]	8	65
4	1.1	45-50	THF[c]	4	70
5	1.1	45-50	THF[d]	2	75
6	1.1	45-50	Dioxane	8	55
7	1.1	45-50	DCE	6	70
8	1.1	45-50	DMF	8	64

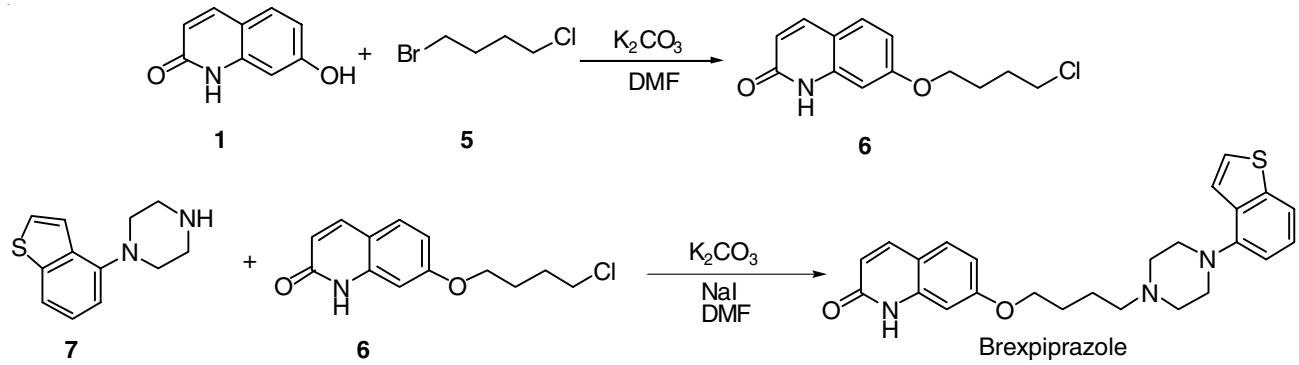
[a]THF 20 volumes, [b]THF 15 volumes, [c]THF 10 volumes, [d]THF 5 volumes, [e]Isolated yield.

To demonstrate the further scope of compound **1** structure elaboration was carried out *via* reaction with 1-bromo-4-chloro butane (**5**) in the presence of K_2CO_3 and DMF to give 7-(4-chlorobutoxy)quinolin-2(1*H*)-one (**6**), compound **6** further reaction with 1-(benzo[*b*]thiophen-4-yl)piperazine (**7**) in the presence of potassium carbonate, sodium iodide in DMF to give brexpiprazole [12] (**Scheme-II**).



2 **3** **4** **1**

Scheme-I: Synthesis of 7-hydroxyquinoline-2(1*H*)-one (**1**)



Scheme-II

Conclusion

In conclusion, a new efficient and practical approach for the synthesis of 7-hydroxyquinoline-2(1*H*)-one has been accomplished *via* a simple DDQ mediated oxidation in THF. This route enables us to synthesize the brexpiprazole API, it reduces the process cost and time enormously.

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