Regular Article

ORGANIC CHEMISTRY RESEARCH
Published by the
Iranian Chemical Society
www.orgchemres.org

Org. Chem. Res., Vol. 5, No. 2, 167-173, September 2019.

One-pot Synthesis of Pyrono [2,3] Quinoline *via* the Tandem Cyclization of Algar-Flyn-Oyamanda Reactions

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(Received 6 October 2018, Accepted 21 January 2019)

A new and imaginative technique for the synthesis of substituted pyranoquinoline *via* Algar Flyn Oyamanda oxidation cyclization approach has been achieved by hydrogen peroxide and sodium hydroxide catalyzed of quinoline chalcone with intramolecular cyclization of pyranoquinoline formed. In this reaction, two new C-C bonds were formed in a one step with high atom economy. The possible reaction pathway for the formation of the products was also discussed as a green technique.

Keywords: Algar-Flyn-Oyamanda oxidation, Pyranoquinoline, Intramolecular cyclization, Greener technique

INTRODUCTION

The quinoline alkaloids and substituted quinolines are eye-catching targets for medicinal activity and important implements for marketed drugs, embodying an inclusive variety of biological activities [1]. Some quinoline compounds, especially pyranoquinoline alkaloids are an important class of quinolines in which pyran ring is attached to the B component of quinoline ring, for example, *tabouensinium chloride simulenoline, flindersine (+-)-7-demethoxyzanthodioline* and *huajiaosimuline.* They are commonly distributed considering the plant source of the rutaceae family [2].

The pyrano-quinoline derivatives are drawing considerable interest for synthesis of quinoline products through various strategies are available, but reports on the synthesis of pyranoquinoline derivatives are limited, due to their structural modification widely present in many drugs that have demonstrated a noteworthy range of biological effects such as vitro activity [3] anti-malaria [4], anti-histamine [5], anti-allergic activities [6] and anti-microbial [7]. Some of their derivatives behave as potential protease inhibiting the growth of cancerous cells *via* binding to DNA [8].

Numerous approaches are available in pyranoquinoline derivatives, particularly for indium trichloride which efficiently catalyzes the cycloaddition responses of aryl amines with 3,4-dihydro-2*H*-pyran (DHP) under mild reaction conditions to afford the corresponding pyrano [3,2-*c*]-quinolines in high yields with high diastereoselectivity [10]. Chiefly an ultrasound irradiation and microwave assisted, the cyclocondensation reaction of one-pot preparation of a synthetically valuations pyranoquinolone heterocycle [11]. Lewis-acid-catalyzed aza Diels-Alder reactions have been employed for the preparation of the tri- and tetracyclic pyranoquinolines *via* a domino cyclization approach achieved by chiral salen-AlCl complex [12], iodine and mercuric oxide [13], $FeCl_3$-NaI [14], Fe/HCl [15], glycerol and non-toxic, biodegradable reagent system catalyzed by intramolecular cyclization [16]. The special type of nanostructured catalysts investigate and empower the novel use of silver and some catalysts in such reactions to reach furoquinoline and pyranoquinoline cores [17]. Recently, pyranoquinoline derivatives have been synthesized *via* an efficient three-component condensation reaction [18]. While several methodologies with different

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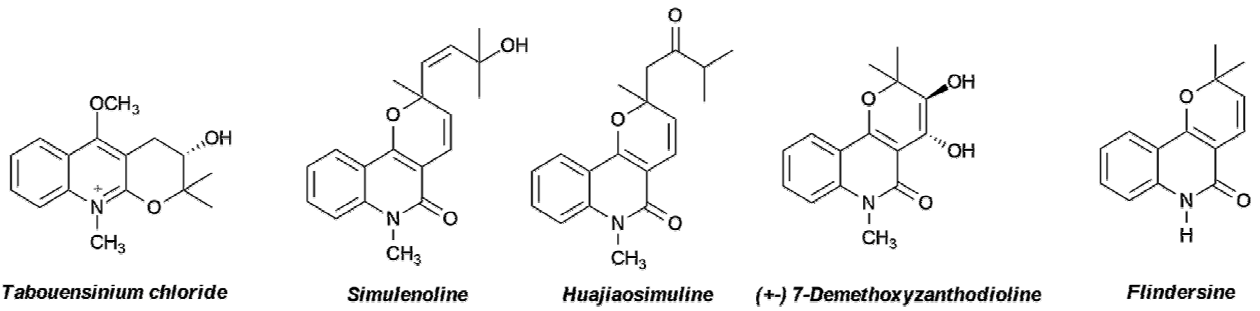


Fig. 1. Some biologically active pyrano -quinoline products.

reaction conditions have been built upon synthesis of pyranoquinoline derivatives, there are still few difficulties to succeed [9]. Some of the methods proposed are suffered from several drawbacks such as harsh reaction conditions, unavailability of starting substantial, multi-step procedures for low yields, and poor atom economy. Therefore, the progress of new approaches for their synthesis, employing efficient and economical routes is currently a popular research area.

In this study, an efficient synthesis is proposed to prepare pyrano[2,3-*b*]-quinoline derivatives from 2,4-dihydroxyquinoline chalcones. We wish to expand the application of the methodology presented, according to the Flan-Algar-Oyamada reaction [19] of benzaldehyde with 2,4-dihydroxy-3-acylquinoline for obtaining desired performance under an eco-friendly and straightforward method.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FTIR spectrophotometer as potassium bromide discs unless otherwise indicated. ^{1}H NMR spectra were obtained on a Brucker (400 MHz) instrument in $CDCl_3$ solutions using tetramethylsilane as an internal standard. *J* values are given in Hz. Mass spectra were obtained at the Vellore Institute of Technology, Vellore, Tamil Nadu, India. In column chromatography, Merck silica gel 60-120 mesh, hexane, and ethylacetate, as eluents, were utilized. All the basic chemicals were purchased from Merck and Avira chemical (India).

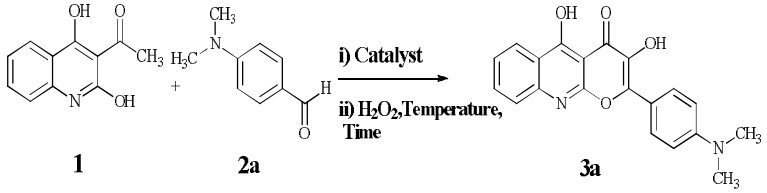
Typical Experimental Procedure for the Synthesis of Pyrono [2,3-*b*] Quinolines 3

A mixture of 3-acyl-2,4-dihydroxy quinoline 1 (2.03 g, 0.1 mol) with benzaldehyde derivatives 2a-e (0.1 mol) in dry ethanol (25 ml) was refluxed with added NaOH (1.0 g) monitoring the progress of the reaction by TLC. Then, the reaction was contacted by the second step of process, 50% H_2O_2 solution 10 ml was added drop wise with stirring to a solution of stopped at the appropriate point 2 h. The mixture was neutralized with 5% HCl to pH 4-6. The precipitate was filtered off and purified by chromatography.

Spectral data of 2-(4-(Dimethylamino)phenyl)-3,5-dihydroxy-4*H*-pyrano[2,3-*b*]-quinolin-4-one (3a). Orange crystal, m. p.: 146 °C yield; 82%; IR (KBr, ν_{max}, cm^{-1}): 3397, 3053, 2924, 1678, 1619, 1560; ^{1}H NMR (500 MHz, $CDCl_3$): δ 15.34 (bs, 1H, pyran-OH), 8.09 (d, 1H, *J* = 8.0, quinoline-C_5-H), 7.99 (d, 1H, *J* = 7.9 quinoline-C_8-H) 7.80 (t, 1H, quinoline C_7-H), 7.55 (t, 1H, quinoline C_6-H), 7.49-7.25 (d, 2H, *J* = 7.2 phenyl,C_3-C_5-H), 6.78 (d, 2H, *J* = 6.7 phenyl, C_2-C_6-H), 3.03 (s, 6H, N-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 180.0, 175.7, 152.0, 145.8, 139.1, 132.1, 130.4, 128.5, 128.4, 128.3, 128.2, 122.7, 117.0, 112.8, 111.8, 103.3, 40.1; GC-MS: m/z [M+1] 394.

3,5-Dihydroxy-2-(4-nitrophenyl)-4*H*-pyrano[2,3-*b*] quinolin-4-one (3b). Red crystal, m. p.:146 °C yield; 59%; IR (KBr, νmax, cm-1): 3440, 3082, 2922, 1656, 1617, 1559; ^{1}H NMR (500 MHz, $CDCl_3$): δ 15.30 (bs,1H, pyran-OH), 8.00 (d, 1H, *J* = 8.0, quinoline-C5-H), 7.99-7.80 (d, 2H, *J* =7.2 phenyl,C_3,C_5-H), 7.77 (d, 1H,quinoline-C_8-H) 7.55 (t, 1H, quinoline-C_7-H), 7.54 (m, 3H, phenyl (C_2-H,C_5-H), quinoline (C_6-H)); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.7, 152.0, 145.8, 139.1, 132.1, 130.4, 128.5, 128.4, 128.3,

Table 1. Optimization of the Reaction Conditions[a]



1 **2a** **3a**

Entry	Catalyst (%)	Temperature (°C)	Time (h)	Yield (%)[b]
1	10%, NaOH	90 °C	5	52
2	15%, NaOH	90 °C	5	63
3	20%, KOH	90 °C	2	81
4	25%, KOH	100 °C	2	60

[a]Reaction conditions: 1a and 2a (0.2 mmol), catalyst, in H_2O_2 (2 m).
[b]Isolated yield.

128.2, 122.7, 117.0, 112,8, 111.8.

2-(2,5-Ddihydroxyphenyl)-3,5-dihydroxy-4*H*-pyrano [2,3-*b*]-quinolin-4-one (3c). Yellow, m. p.: 176, 59% yield; IR (KBr, ν_{max}, cm^{-1}): 3446, 3300, 3218, 2920, 2107, 1637, 1583, 1479, 1349, 1058, 784; ^{1}H NMR (500 MHz, $CDCl_3$): δ 16.0 (s, 1H, pyran-OH), 7.99 (d, 1H, *J* = 7.5, quinoline-C_5-H), 7.77 (t, 1H, quinoline-C_7-H) 7.54 (d, 1H, quinoline-C_8-H), 7.49-6,68 (m, 5H, aromatic-H), 6.69 (d, 2H, phenyl-C_3, C_5-H); ^{13}C NMR (120 MHz, $CDCl_3$): δ 198.4, 166.8, 149.2, 138.1, 136.8, 135.3, 134.6, 131.2, 131.1, 128.9, 129.7, 128.3, 128.2, 128.1, 112.5.

2-(2,5-Dihydroxyphenyl)-3,5-dihydroxy-4*H*-pyrano [2,3-*b*]-quinolin-4-one (3d). Yellow, m. p.: 180-186, 56% yield; IR (KBr, ν_{max}, cm^{1}): 3771, 3423, 2921, 1655, 1445, 1018, 873; ^{1}H NMR (500 MHz, $CDCl_3$): δ 16.0 (s, 1H, pyran-OH), 8.0 (d, 1H, *J* = 7.9, quinoline-C_5-H), 7.80 (d, 1H, *J* = 6.8 quinoline-C_8-H) 7.55 (t, 1H, quinoline-C_7-H), 7.49 (t, 1H, quinoline-C_6-H), 7.34-6.68 (m, 3H, *J* =7.2 phenyl,C_3-C_5-H), 5.36 (s, 3H, quinoline-C_4 and phenyl-OH); ^{13}C NMR (120 MHz, $CDCl_3$): δ 198.3, 149.5, 146.5, 139.5, 139.1, 137.3, 135.4, 134.6, 130.8, 130.6, 129.6, 129.4, 128.9, 128.4, 128.3, 128.4, 127.9, 127.5, 127.2; GC-MS: m/z [M+1] 337 (56%).

RESULTS AND DISCUSSION

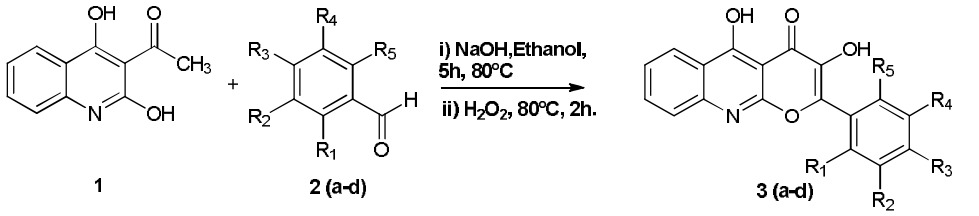
Synthesis of Flan-Alager-Oyamanda Precursor 3

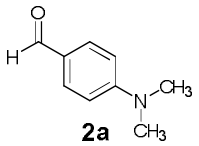
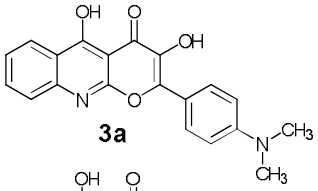
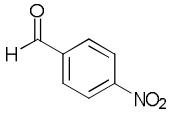
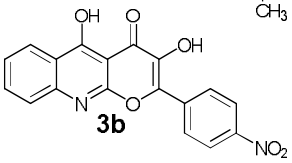
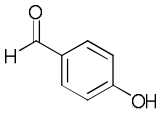
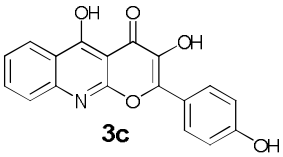
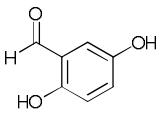
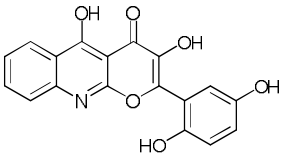
Our strategy to the target heterocycle firstly started by the synthesis of 2,4-dihydroxy-3-acylquinoline 1 *via* a one-pot Claisen ester condensation between equimolar mixture amounts of methyl anthranilate with ethyl acetoacetate catalyzed by sodium hydride [20].

The convenient general synthesis of pyrono[2,3-*b*]-quinoline derivatives 3 is involved on Algar-Flynn-Oyamada (AFO) and Clasisen-Schmidt combined reaction [21] for united the alkaline mediated newly condensation mechanism. Among them, 2,4-dihydroxyquinoline oxygenated functions, were studied because their ability to carbonyl groups are of particular interest. Tandem reactions with nucleophiles can occur in this function, broadening the structural panel of the products formed, which according to the classical methodology involves the oxidation of 2,4-dihydroxyquinolinechalcones intermediate with hydrogen peroxide in alkaline alcohol solution.

In a first attempt, the reaction of 2,4-dihydroxy-3-

Table 2. Reaction of 1 with Different Benzaldehyde Derivatives 2[a-e]

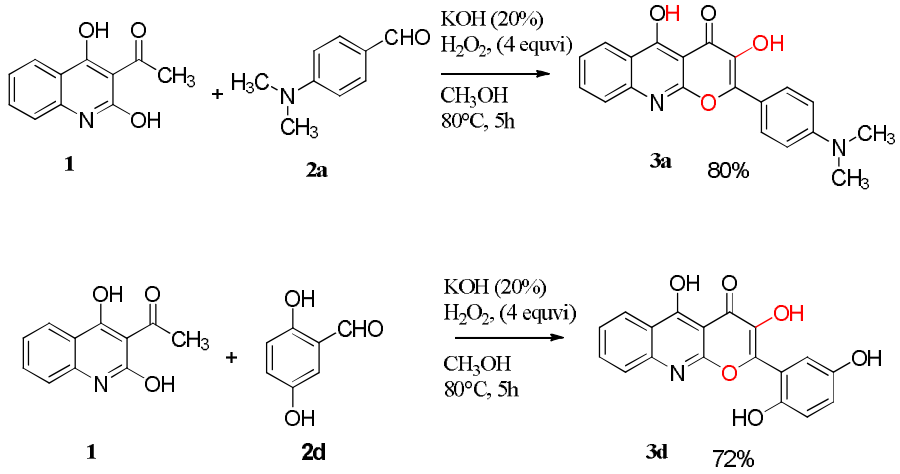


Entry	Benzaldehyde 2	Pyranoquinoline derivatives 3	Yields (%)
1	 2a	 3a	80
2	 2b	 3b	56
3	 2c	 3c	59
4	 2d	 3d	72

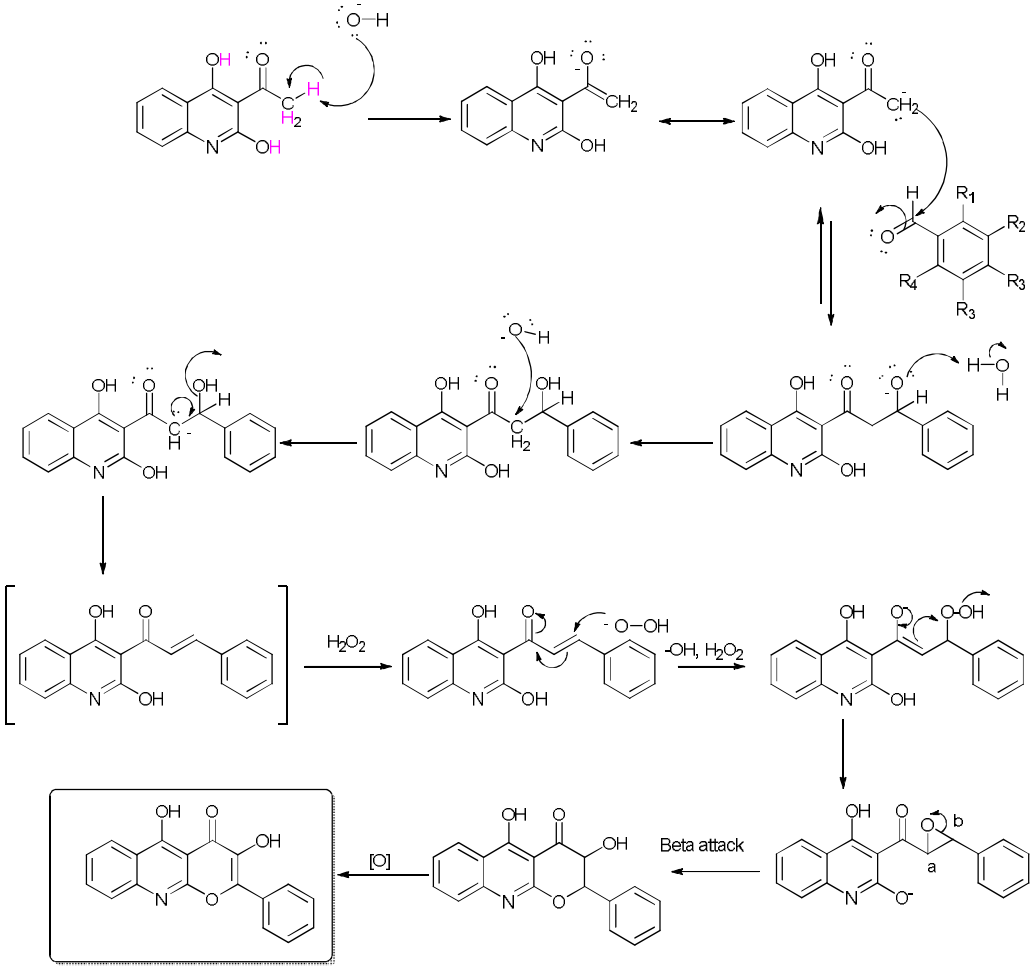
NaOH catalyzed pyranoquinoline synthesis conditions: 1 (0.01 mol), 2 (0.01 mol), 20% KOH in ethanol at 70 °C for 2 h, 10% H_2O_2, isolated yields.

acylquinoline 1 condensation with a variety of benzaldehydes 2 as our model reaction, initially, the stirring of an equimolar mixture of both compounds in methanol with 40% NaOH as catalysis to access the pyranoquinoline 3 was studied at different temperatures. At room temperature, no reaction observed after stirring for 24 h. The reaction temperature increased to 90 °C with respect to the intermediate of quinolinechalcone formed, evidenced by TLC. The intermediate was treated with 10% H_2O_2 to give the pyrono[2,3-*b*]-quinoline derivatives 3a-d. However, the isolated product during this one-pot concurrent condensation cyclisation found to be in a good yield. The results are concise in Table 1.

In the ^{1}H NMR spectrum of compounds 3a-d, the chemical shift is observed at δ 16.00 for pyran hydroxyl hydrogen bored singlet and multiplet for aromatic protons at



Scheme 1. Control experiment



Scheme 2. The possible reaction mechanism is outlined 3

6.72-8.09. The ^{13}C NMR spectrum further supports the structure; the ketonic carbon at δ 180-190 (3a-d), methyl carbon at δ 40.1 (3a), and finally mass spectrum confirmed compounds 3.

Intramolecular attack by the quinoxide anion can then proceed by nucleophilic addition routes at the beta-position of the keto epoxide delivers an intermediate dihydropyrroquinoline derivative that oxidatively converted to pyranoquinoline derivatives 3a-d.

A possible mechanism for the formation of selected product 3 is deprotonation of enolized 2,4-dihydroxy-3-acylquinoline 1 at the acetyl carbon by the base to give the enolate anion which is stabilized by resonance. The next step is the nucleophilic addition of the enolate anion to the carbonyl group of another, non-enolized benzaldehyde molecule 2a-d. If the initially formed hydroxy carbonyl still has hydrogen, a subsequent elimination of water can take place, leading to a 2,4-dihydroxyquinolinechalcone intermediate involving the alkaline mediated hydrogen peroxide oxidation to give pyranoquinoline.

CONCLUSIONS

In conclusion, we have described a trivial and efficient method for the synthesis of pyranoquinoline derivatives *via* a one-pot convenience of the AFO reaction of 2,4-dihydroxy-3-acylquinoline and various kinds of benzaldehydes with sodium hydroxide and hydrogen peroxide under thermal conditions. This is a facile method for the synthesis of fused pyranoquinoline derivatives. This reaction allows direct C-C bond formation under environmentally friendly conditions with an excellent atom economy. A further bid for this reaction in organic synthesis is still an ongoing project in our laboratory.

ACKNOWLEDGMENTS

The author gratefully acknowledges the financial support from the Annai Group of Institute, Kumbakonam, India for this research work.

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