Journal of the Korean Chemical Society
2012, *Vol. 56, No. 3*
Printed in the Republic of Korea
http://dx.doi.org/10.5012/jkcs.2012.56.3.322

New Efficient Synthesis of 3-Carboxylquinolines

S. Kirankumar, D. Rambabu, N. Chandra Sekhar[†], ASG. Prasad[†], and M. V. Basaveswara Rao[†,*]

Department of Chemistry, K L University, Vaddeswaram Guntur-522 502, A. P, India
[†]Department of chemistry, Krishna University, Machilipatnam-521 001, A. P, India.
[*]E-mail: professormandava@gmail.com

(Received January 20, 2012; Accepted April 17, 2012)

ABSTRACT. Rapid and efficient synthesis of substituted 3-carboxylquinoline derivatives from 4-chloro-3-formylcoumarin and substituted anilines using 30% H_2SO_4 in methanol at room temperature within the duration of 5-30 min., through domino condensation-cyclization-ring opening reaction.

Key words: 3-Carboxylquinoline derivatives, 4-Chloro-3-formylcoumarin, Anilines

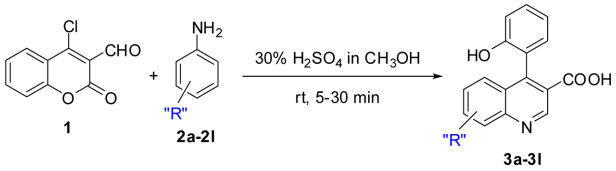
INTRODUCTION

Functionalized quinoline scaffolds obtained from natural sources and their synthetic analogs are of considerable importance due to their wide spectrum of biological profiles. Quinoline derivatives proved to be possessing antimalarial,[1] anti-inflammatory,[2] anticancer,[3] antibiotic,[4] antihypertensive,[5] tyrokinase PDGF-RTK inhibiting agents,[6] anti HIV,[7] DNA binding capability,[8] antitumor activities,[9] and DNA-intercalating carrier[10] activities. In addition to the medicinal significance, multi-substituted quinolines are valuable synthons exploited for the preparation of nano- and mesostructures with enhanced electronic and photonic properties.[11]

The synthesis of quinoline derivatives thus continues to be an attractive area of research,[12] and the synthesis of various substituted quinolines has been largely described in the literature through different strategies.[13,14] For example, preparation of quinolines by Lewis acid catalyzed cyclization of 1,5-diaryl-1,5-diazapentadiene salts have been reported in 1923.[15] These compounds were prepared by the action of primary arylamines on β-chlorovinylaldehydes at room temperature.[16,17] Some diazapentadiene salts undergo intramolecular cyclization when heated under reflux in acetic acid or in alcohols of similar boiling point and are converted into quinolines.[18] The mechanism under these conditions has been rationalized as an electrocyclic ring closure with elimination.[19] Similarly the thermolysis of diazapentadiene analogues gives quinolines.[20] As a consequence, the development of general methods for the synthesis and biological evaluation of new agents, retaining the 'core' quinoline moiety has been the subject of considerable synthetic effort. An essential component of the search for new leads in the drug designing program is the synthesis of molecules, which are novel yet resemble known biologically active molecules by virtue of the presence of some critical structural features. Certain small heterocyclic molecules act as highly functional scaffolds and are known pharmacophores of a number of biologically active and medicinally useful molecules.[21] The Skraup-Doebner-Von Miller quinoline synthesis, which generally refers to the reaction of α,β-unsaturated carbonyl compounds with anilines to give quinolines, has been of great value for constructing the quinoline system since its discovery one and a quarter centuries ago.[22]

A reversal of the standard regiochemistry of the Skraup-Doebner-Von Miller quinoline synthesis was observed when anilines were condensed with γ-aryl-β, γ-unsaturated α-ketoesters in refluxing TFA. The reaction is proposed to involve 1,2-addition of the anilines to γ-aryl-β, γ-unsaturated α-ketoesters to form Schiff's base adducts, followed by cyclization and oxidation. The products were shown to the 2-carboxy-4-arylquinolines by spectroscopy and X-ray crystallographic analysis.[23] Similarly, a variety of substituted quinolines are synthesized from imines and enolizable carbonyl compounds under aerobic conditions, in DMSO, and a catalytic amount of HCl activates carbonyl compounds to give the quinolines.[24] Dieter Heber reported the reaction of 4-chloro-3-formylcoumarin with p-substituted anilines to yield 6-Oxo-6*H*-[1]benzopyrano[4,3-b] quinoline derivatives.[25]

However, most of the synthetic routes suffer from various problems: (1) harsh conditions,[26] (2) multisteps,[27] and (3) a large amount of promoters such as a base,[28] expensive and/or harmful metals,[29] the oxidants for the aromatization,[30] and other additives.[31] Thus, the development



***Scheme* 1.** Synthesis of 3-carboxyl quinolines **3a-3l**.

of simple and practical methods for synthesizing functionally substituted quinolones is of current interest.[32-33] So thrust in framing and developing synthetic methodologies for new and highly functionalized quinoline moieties is of current interest.

RESULTS AND DISCUSSION

In this context herein, we are reporting one pot, acid-catalyzed, new methodology for the fast and efficient synthesis of highly functionalized quinoline derivatives. Reaction of acid-catalyzed (30% H_2SO_4 in methanol) 4-chloro-3-formylcoumarin (**1**) with substituted anilines (**2a-2l**) gave the desired substituted 3-carboxylquinolines (**3a-3l**) at room temperature in the duration of within 5-30 min (*Scheme* 1, *Table* 1). The reaction sequences employed for the synthesis of substituted 3-carboxylquinoline derivatives are shown in *Scheme* 1. The reaction proceeds through the domino Schiff base condensation followed by cyclization-aromatization-ring-opening as shown in *Scheme* 2.

CONCLUSIONS

In conclusion this methodology provides a fast and efficient synthesis of new substituted 3-carboxyquinoline derivatives, which can diversity oriented for the creation of library of these molecules.

EXPERIMENTAL SECTION

General

Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. ^{1}HNMR and ^{13}CNMR spectra were determined in $CDCl_3$ or DMSO-d_6 solution by using 400 and 100 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (*J*) are given in hertz. Infrared spectra were recorded on a FT-IR spectrometer. Melting points were determined using melting point apparatus and are uncorrected. MS spectra were obtained on a mass spectrometer. All chemicals and reagents were purchased from commercial sources and purified before use.

General procedure for the Synthesis of 3-carboxyl Quinolines (3a-3l)

A mixture of 4-Chloro-3-formylcoumarin (1) (1.0 mmol), 30% H_2SO_4 in methanol and anilines (2a-2l) (1.0 m.mol) were stirred at room temperature for 5-30 min. (*Scheme* 1, *Table* 1). After completion of the reaction, the solid obtained (3a-3l) was filtered and washed with methanol. All the compounds (3a-3l) were characterized by their NMR, IR and Mass spectral data.

4-(2-Hydroxyphenyl)quinoline-3-carboxylic acid (3a)

White solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.5 (s, 1H), 10.05 (s, 1H), 9.25 (s, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.55 (dd, *J* = 8.0 Hz, *J* = 2.4 Hz, 1H), 7.36 (dd, *J* = 8.4 Hz, *J* = 2.4 Hz, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 7.02-7.09 (m, 1H), 6.84-6.9 (m, 1H), 6.71 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.9, 154.3, 148.2, 147.1, 140.6, 132.4, 130.5, 129.8, 128.8, 128.5, 128.1, 127.2, 122.2, 121.6, 121.1, 115.8; IR (KBr) ν_{max} 3274, 3204, 3071, 2958, 1644, 1483, 1367, 1224, 1145; EI-MS: m/z 264.1 $(M-H)^+$.

4-(2-Hydroxyphenyl)-6-methylquinoline-3-carboxylic acid (3b)

Off White solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.4 (s, 1H), 10.01 (s, 1H), 9.21 (s, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.52 (s, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* =7.6 Hz, 1H), 7.01-7.08 (m, 1H), 6.83-6.90 (m, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.5, 154.8, 147.2, 146.9, 140.2, 137.8, 134.2, 129.1, 128.9, 128.2, 127.9, 127.2, 122.4, 121.3, 121.1, 116.8, 25.1; IR (KBr) ν_{max} 3276, 3208, 3074, 2960, 1646, 1480, 1366, 1220, 1145; EI-MS: m/z 278.1 $(M-H)^+$.

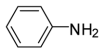
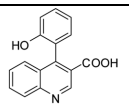
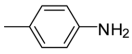
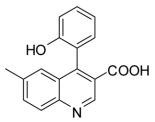
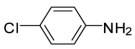
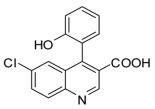
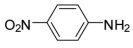
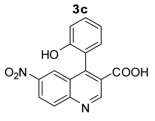
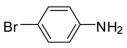
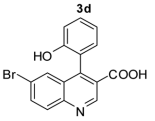
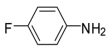
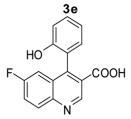
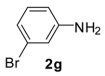
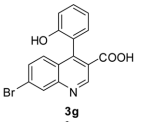
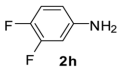
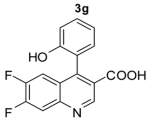
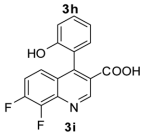
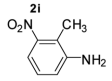
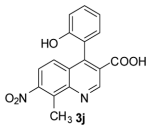
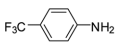
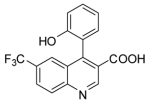
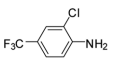
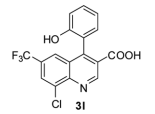
6-Chloro-4-(2-hydroxyphenyl)quinoline-3-carboxylic acid (3c)

White solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.5 (s, 1H), 10.02 (s, 1H), 9.27 (s, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.72 (s, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.03-7.11 (m, 1H), 6.85-6.92 (m, 1H), 6.80 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.1, 155.3, 148.4, 147.1, 139.8, 134.4, 133.5, 131.1, 130.3, 129.1, 128.9, 127.5, 122.5, 122.1, 121.9, 116.8; IR (KBr) ν_{max} 3272, 3206, 3070, 2956, 1646, 1484, 1367, 1224, 1145; EI-MS: m/z 298.5 $(M-H)^+$.

4-(2-Hydroxyphenyl)-6-nitroquinoline-3-carboxylic acid (3d)

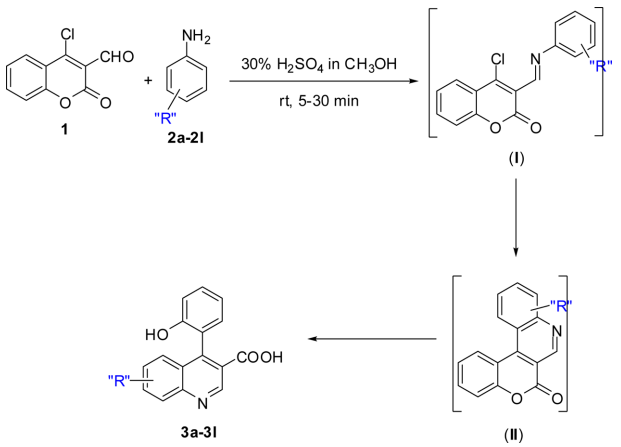
Yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.5

***Table* 1.** 3-Carboxyl quinoline derivatives **3a-3l** produced via *Scheme* 1

Entry	Anilines	Quinoline Product	Time (min)	Mp (°C)	(%) Yield[a]
1	 **2a**	 **3a**	30	170-172	98
2	 **2b**	 **3b**	20	153-154	98
3	 **2c**	 **3c**	5	173-175	97
4	 **2d**	 **3d**	5	184-186	99
5	 **2e**	 **3e**	15	180-182	98
6	 **2f**	 **3f**	15	186-188	96
7	 **2g**	 **3g**	30	120-122	95
8	 **2h**	 **3h**	15	151-153	97
9	 **2i**	 **3i**	5	136-138	98
10	 **2j**	 **3j**	5	179-181	99
11	 **2k**	 **3k**	5	173-175	98
12	 **2l**	 **3l**	5	177-179	99

[a]Isolated yields. All products (3a-3l) were characterized by NMR, IR and mass spectral data

(s, 1H), 10.03 (s, 1H), 9.65 (s, 1H), 8.71 (s, 1H), 8.49 (d, J = 8.8 Hz, 1H), 8.31 (d, J = 8.8 Hz, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.04-7.12 (m, 1H), 6.86-6.93 (m, 1H), 6.83 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.4, 155.5,



***Scheme* 2.** Proposed reaction mechanism for new quinolines **3a-3l**.

152.1, 151.5, 147.6, 143.3, 131.2, 130.5, 129.2, 128.9, 126.2, 125.3, 123.7, 122.1, 120.6, 116.9; IR (KBr) ν_{max} 3274, 3206, 3074, 2958, 1644, 1483, 1367, 1224, 1145; EI-MS: m/z 309.1 $(M\text{-}H)^+$.

6-Bromo-4-(2-hydroxyphenyl)quinoline-3-carboxylic acid (3e)

Red solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.5 (s, 1H), 10.02 (s, 1H), 9.27 (s, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.97 (s, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 7.03-7.11 (m, 1H), 6.85-6.92 (m, 1H), 6.81 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.3, 155.3, 150.1, 148.3, 140.2, 136.3, 131.2, 130.9, 130.5, 129.1, 128.9, 122.6, 122.2, 122.1, 119.9, 116.7; IR (KBr) ν_{max} 3280, 3208, 3074, 2958, 1648, 1485, 1367, 1224, 1150; EI-MS: m/z 343.0 $(M\text{-}H)^+$.

6-Fluoro-4-(2-hydroxyphenyl)quinoline-3-carboxylic acid (3f)

White solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.4 (s, 1H), 10.01 (s, 1H), 9.31 (s, 1H), 8.15 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.36 (dd, J = 8.0 Hz, J = 1.6 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 7.01-7.09 (m, 1H), 6.83-6.91 (m, 1H), 6.77 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.2, 162.1, 155.4, 147.5, 146.0, 140.5, 131.6, 130.9, 129.1, 128.9, 122.5, 122.3, 122.1, 121.9, 111.5, 116.8; IR (KBr) ν_{max} 3276, 3210, 3074, 2960, 1644, 1483, 1367, 1224, 1145; EI-MS: m/z 282.1 $(M\text{-}H)^+$.

7-Bromo-4-(2-hydroxyphenyl)quinoline-3-carboxylic acid (3g)

White solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.5 (s, 1H), 10.02 (s, 1H), 9.41 (s, 1H), 8.31 (s, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 7.03-7.11 (m, 1H), 6.85-6.92 (m, 1H), 6.81 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.3, 155.3, 149.2, 147.3, 140.4, 132.3, 131.8, 130.9, 130.6, 129.1, 128.9, 126.7, 122.3, 122.0, 121.5, 116.5; IR (KBr) ν_{max} 3278, 3206, 3076, 2958, 1648, 1483, 1367, 1224, 1145; EI-MS: m/z 343.0 $(M\text{-}H)^+$.

6,7-Difluoro-4-(2-hydroxyphenyl)quinoline-3-carboxylic acid (3h)

White solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.4 (s, 1H), 10.02 (s, 1H), 9.33 (s, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 7.01-7.09 (m, 1H), 6.85-6.91 (m, 1H), 6.78 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.3, 157.2, 155.8, 155.3, 148.7, 147.1, 140.5, 130.9, 129.1, 128.9, 122.8, 122.2, 119.1, 116.9, 114.5, 113.8; IR (KBr) ν_{max} 3274, 3204, 3071, 2958, 1644, 1483, 1367, 1224, 1145; EI-MS: m/z 300 $(M\text{-}H)^+$.

7,8-Difluoro-4-(2-hydroxyphenyl)quinoline-3-carboxylic acid (3i)

White solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.4 (s, 1H), 10.02 (s, 1H), 9.35 (s, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.32 (d, J =7.6 Hz, 1H), 7.17 (dd, J = 8.4 Hz, J = 1.6 Hz, 1H), 7.02- 7.09 (m, 1H), 6.84-6.91 (m, 1H), 6.79 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.3, 155.7, 151.3, 150.2, 144.1, 141.9, 141.3, 140.7, 130.9, 129.1, 128.9, 128.3, 122.2, 121.9, 118.5, 116.5; IR (KBr) ν_{max} 3278, 3208, 3074, 2960, 1644, 1483, 1367, 1226, 1148; EI-MS: m/z 300 $(M\text{-}H)^+$.

4-(2-Hydroxyphenyl)-8-methyl-7-nitroquinoline-3-carboxylic acid (3j)

Yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.5 (s, 1H), 10.03 (s, 1H), 9.65 (s, 1H), 8.19 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 7.04-7.12 (m, 1H), 6.86-6.93 (m, 1H), 6.83 (d, J = 8.0 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.3, 156.2, 155.7, 152.6, 150.3, 141.9, 132.3, 131.2, 130.1, 129.2, 128.9, 125.1, 124.2, 122.3, 121.7, 116.9, 11.5; IR (KBr) ν_{max} 3276, 3208, 3073, 2956, 1646, 1485, 1368, 1224, 1146; EI-MS: m/z 323.1 $(M\text{-}H)^+$.

4-(2-Hydroxyphenyl)-6-(trifluoromethyl)quinoline-3-carboxylic acid (3k)

White solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.4 (s, 1H), 10.01 (s, 1H), 9.61 (s, 1H), 8.32 (d, J = 8.4 Hz, 1H), 8.18 (d, J = 7.6 Hz, 1H), 7.95 (dd, J = 8.4 Hz, J = 2.0 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 7.01-7.09 (m, 1H), 6.85-6.91 (m, 1H), 6.81 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.2, 155.7, 150.6, 150.3, 142.4, 130.9, 130.5, 130.3, 129.1, 128.1, 127.5, 125.2, 123.1, 122.3, 121.9, 120.8, 116.8; IR (KBr) ν_{max} 3278, 3206, 3074, 2956, 1644, 1483, 1370, 1234, 1148; EI-MS: m/z 332.0 $(M\text{-}H)^+$.

8-Chloro-4-(2-hydroxyphenyl)-6-(trifluoromethyl)quinoline-3-carboxylic acid (3l)

White solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.4 (s, 1H), 10.01 (s, 1H), 9.76 (s, 1H), 8.21 (d, J = 8.8 Hz, 1H), 8.12 (d, J = 7.6 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 7.01-7.09 (m, 1H), 6.85-6.91 (m, 1H), 6.81 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.5, 155.7, 151.6, 146.5, 142.4, 134.9, 130.9, 130.5, 129.1, 128.1, 127.9, 126.8, 126.1, 124.7, 122.2, 12.5, 116.8; IR (KBr) ν_{max} 3276, 3210, 3071, 2958, 1648, 1482, 1366, 1226, 1148; EI-MS: m/z 366.5 $(M-H)^+$.

Acknowledgments. The authors thank University Grants Commission for the financial assistance under Major Research Project. N.Chandra Sekhar thanks CSIR for the Junior Research Fellowship.

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