An efficient and direct synthesis of substituted 2-phenylquinoline-4-carboxamides from 3-substituted-3-hydroxyindolin-2-ones

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Abstract

A simple and direct synthesis of substituted 2-phenylquinoline-4-carboxamides from 3-substituted-3-hydroxyindolines in presence of ammonium acetate is described. The developed protocol also allows synthesis of the carboxamide moiety directly from isatin and acetophenone in one pot under optimized conditions. The protocol has the merits of simple reaction conditions, easy work up process and good yields of products.

Keywords: 2-Phenylquinoline-4-carboxamide, ammonium acetate, 3-hydroxyindolin-2-ones
Introduction

Quinoline derivatives are an important class of structural motif that is posed with diverse chemotherapeutic activities like antimicrobial,\(^1\) antiviral,\(^2\) antimalarial\(^3\) and anti-inflammatory.\(^4\) Since the discovery of cinchophen (I) (2-phenylquinoline-4-carboxylic acid) as an analgesic drug, this pharmacophore has been extensively explored for the synthesis of antibacterial agents.\(^5\)-\(^7\) The structure activity relationship of these molecules have also revealed that the presence of aryl group at 2-position of quinoline ring is crucial for their bioactivity.\(^8\)

In particular, the 2-phenylquinoline-4-carboxamide (II) moiety have been identified and developed as potent and selective non-peptide competitive antagonists for human neurokinin-3 receptor.\(^9\) The 2-phenylquinolines bearing a (S)-N-(1-phenylpropyl)carboxamide functionality at the 4 position (III) represent a class of highly potent antagonists of the NK-3 receptor. They have also been extensively studied for their application as a ligand suitable for radiolabeling. In fact, Many of these radioactive labelled molecules have been evaluated as radiotracer of NK-3 receptor for PET imaging studies.\(^10\) Quinoline-4-carboxamide analogues (IV) have also been studied as a potential type II binding compounds with cytochrome CYP2C9 protein which is mainly responsible for drug metabolism.\(^11,12\)

![Figure 1. Some biologically active 2-phenylquinoline-4-carboxamides.](image)

Despite there being plenty of applications in medicinal chemistry, the direct synthesis of 2-phenylquinoline-4-carboxamide has limited reported methods.\(^13\)-\(^15\) They are usually obtained from 2-phenylquinoline-4-carboxylic acid (Cinchophen) which is usually synthesized by Pfitzinger or Doebner reactions.\(^16\) While the Pfitzinger reaction involves an isatin and an aryl methyl ketone in the presence of potassium hydroxide which allows the synthesis of 2-phenylquinoline-4-carboxylic acid whereas the Doebner reaction gives a similar kind of product by a three-component reaction between pyruvic acid, benzaldehyde, and an aniline. There are limited literature reports for the synthesis of 2-phenylquinoline-4-carboxamide.\(^17\)-\(^19\) An elegant method for one-step synthesis of 2-phenylquinoline-4-carboxylates and carboxamides from arylimines and acrylates or acrylamides were reported under microwave conditions catalyzed by indium chloride.\(^20\)
As a part of our research plan aimed at developing new synthetic methods for the creation of biologically relevant heterocyclic compounds in aqueous media, recently we have reported the synthesis of 3-substituted-3-hydroxyindolin-2-ones by aldol reactions between isatin and acetophenone catalysed by DABCO (Scheme 1). The copper catalysed and Cs$_2$CO$_3$ mediated efficient methods for the synthesis of 3-hydroxyindolin-2-ones have also been documented recently. Now, we wish to report an efficient method for the direct synthesis of 2-phenylquinoline-4-carboxamide derivatives by ring-opening and cyclization of 3-substituted-3-hydroxyindolin-2-ones.

Scheme 1. Synthesis of 3-substituted-3-hydroxy-2-oxindole (3a).

**Results and discussion**

Initially, we began the synthesis by heating of the 3-substituted-3-hydroxyindolin-2-one (3a) in the presence of excess of ammonium acetate in EtOH at 80 °C (Scheme 2). After TLC indicated the complete consumption of 3a, the solvent was evaporated, leaving a brown-colored solid. This brown solid was dissolved in a large volume of dichloromethane with the addition of few drops of methanol. The solution was left for overnight and the product 4a crystallized out as a white solid. The structure of 4a was confirmed by $^1$H, $^{13}$C NMR, IR and mass spectral analysis. Although the TLC indicated the complete conversion of 3a into 4a, the yield of the product was found low. It was realized by TLC that a significant amount of the product (4a) was present in the mother liquor. We therefore purified the reaction mixture by silica gel column chromatography and the product was isolated with 72% yield.

Scheme 2. Synthesis of 2-phenylquinoline-4-carboxamide (4a).

We also investigated the efficiency of the reaction in different solvents for optimal conditions. For this, the reaction was performed with 3a on a 300 mg scale in various solvents (Table 1). Although the expected product was obtained in most of the solvents, EtOH was found a better solvent with respect to reaction time and yield.

During the synthesis of 3a, it was observed that the product separated out as solid in water and it was almost pure. We had also found that the reaction can also be performed in EtOH. Keeping this in view, we
planned to make this two step reaction in one pot. Therefore, isatin (1a) and acetophenone (2a) were heated in EtOH using DABCO as a catalyst for 2 hours. After the TLC indicated the consumption of 1a and 2a, NH₄OAc was added to the reaction mixture portion wise and the mixture heated for a further 4 hours. To our satisfaction, the compound 4a obtained in 60% yield (Scheme 3). It was interesting to note that the portion wise addition of ammonium acetate (4 to 5 eq.) at regular intervals of 2 hours was found more efficient that one-time addition.

Table 1. Optimization of solvents for the synthesis of 4a from 3a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Base</th>
<th>Time (h)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOH</td>
<td>DABCO</td>
<td>6 h</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>CH₃CN</td>
<td>DABCO</td>
<td>10 h</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>DMF</td>
<td>DABCO</td>
<td>10 h</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>CHCl₃</td>
<td>DABCO</td>
<td>12 h</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>DABCO</td>
<td>12 h</td>
<td>25</td>
</tr>
<tr>
<td>6</td>
<td>H₂O</td>
<td>DABCO</td>
<td>10 h</td>
<td>No product</td>
</tr>
</tbody>
</table>

<sup>a</sup> isolated yield

Scheme 3. One pot synthesis of 2-phenylquinoline-4-carboxamide (4a).

The scope of the substrate for this transformation was studied using substituted isatins and acetophenones (Scheme 4). It was observed that the second step of the reaction was generally prolonged by about 3-4 times in comparison to the duration of first step. The reaction time in the table indicates the total reaction time over both the steps (Table 2).

Scheme 4. Synthesis of 4-arylquinoline-4-carboxamides 4a-i.

As reflected in the Table 2, the electronic effect of substituents was also observed during the reaction. The reaction time for unsubstituted isatin was found relatively less (6 h) in comparison to 5-chloro/bromo substitution (10 h) and the yield was found less for 5-bromo isatin. It indicates that chloro/bromo substitution at 5 position of isatin retards the reaction. For acetophenone, the yield was found maximum (74%) with 4-methyl substitution and minimum (68%) for 4-bromo substitution. This indicates that electron donation group
at 4-position of acetophenone is found more reactive substrate for this synthetic transformation (Table 2).

Table 2. Scope of substrate with reaction time and yield of product (4a-i)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Isatin (R₁)</th>
<th>Acetophenone (R₂)</th>
<th>Time (h)</th>
<th>Product (4a-i) (Yield %)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>6</td>
<td>4a (72)</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>CH₃</td>
<td>12</td>
<td>4b (74)</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>OCH₃</td>
<td>12</td>
<td>4c (70)</td>
</tr>
<tr>
<td>4</td>
<td>Cl</td>
<td>H</td>
<td>10</td>
<td>4d (65)</td>
</tr>
<tr>
<td>5</td>
<td>Cl</td>
<td>CH₃</td>
<td>10</td>
<td>4e (74)</td>
</tr>
<tr>
<td>6</td>
<td>Cl</td>
<td>OCH₃</td>
<td>8</td>
<td>4f (75)</td>
</tr>
<tr>
<td>7</td>
<td>Cl</td>
<td>Br</td>
<td>8</td>
<td>4g (68)</td>
</tr>
<tr>
<td>8</td>
<td>Br</td>
<td>H</td>
<td>10</td>
<td>4h (68)</td>
</tr>
<tr>
<td>9</td>
<td>Br</td>
<td>OCH₃</td>
<td>10</td>
<td>4i (70)</td>
</tr>
</tbody>
</table>

¹Isolated yield

The characterization of all the compounds was done by ¹H, ¹³C NMR and IR spectra as well as HRMS analysis. The mass spectra of all synthesized compounds showed a characteristic [M+H]⁺ peak. The IR spectra of 4a showed characteristic two peaks of amide carbonyl (CONH₂) at 1660 cm⁻¹ and 1588 cm⁻¹ and two peaks for NH₂ were observed at 3373 cm⁻¹ and 3150 cm⁻¹. A similar pattern was observed for all the other compounds. The ¹H NMR spectra of compound 4a showed the disappearance of –CH₂ and OH protons which were observed in 3a. The chemical shifts of all the aromatic protons of quinoline and phenyl ring were observed in between δ 7.2 ppm to 8.5 ppm. The NH₂ protons of amide were observed at approx. δ 8.0 ppm. The ¹³C NMR showed a characteristic peak at δ 168 ppm in 4a amide carbonyl (CONH₂). The melting point of compound 4a was found in good agreement with the literature report.²⁴

In this way, a series of 9 molecules was synthesized and fully characterized by various spectral analysis bearing substitution on both isatin and acetophenone. The synthesized molecules with their reaction times and yields are given in Scheme 4 and Table 2.

A plausible route to the formation of 4a from the intermediate 3a can be explained as the ammonium acetate decomposes to give ammonia which attacks the carbonyl to give imine (5) which undergoes tautomerization to provide an enamine (6). The amino group then attacks the carbonyl of the indolinone to give an intermediate pyrrolenone with aniline residue (7). Further cyclization of the aniline with imine provide benzodiazepinone (8) which after ring-opening and release the amide group provides 4-hydroxydihydroquinoline (9) and further elimination of water provides the product 4a. This sequence is shown in Scheme 5. The DABCO is used as a base for aldol reaction between isatin (1a) and acetophenone (2a) in the first step for the synthesis of 3-substituted-3-hydroxyindolin-2-one (3a).
Scheme 5. A plausible mechanism for formation of 2-phenylquinoline-4-carboxamide (4a).

**Conclusion**

In summary, we have developed an efficient and direct method for the synthesis of substituted 2-phenylquinoline-4-carboxamide by ring opening and cyclization of 3-hydroxyindolines. This method is applicable to a wide substrate scope for both the isatin and acetophenone and provides a series of quinoline-4-carboxamides which represent a pharmaceutically important scaffold. The reaction conditions and work up procedure is very simple with good yield of products. Further exploration of this methodology is currently under way in our laboratory and findings will be reported with due course.

**Experimental section**

**General.** Commercially available isatins, acetophenones and ammonium acetate from Spectrochem were used. Progress of reactions was monitored by thin layer chromatography (TLC). NMR spectra were recorded in DMSO d$_6$ at 400 MHz for $^1$H and 100 MHz for $^{13}$C on Bruker Avance DPX-400 MHz. Chemical shifts were reported in $\delta$ (ppm) relative to DMSO-d$_6$ ($^{13}$C) as internal standards. Integrals are in accordance with assignments, coupling constants are given in Hz. The HRMS was recorded on a JOEL-AccuTOF JMS-T100LC Mass spectrometer having a DART source. The IR spectra were recorded on Spectrum RX-1 FTIR, Perkin Elmer. Yields refer to quantities obtained after chromatography. Melting points of compounds were recorded on Labindia make melting point apparatus.
Synthesis of 2-phenylquinoline-4-carboxamide (4a)

A solution of 0.3 gm (1.12 mmol) of 3a and 0.432 gm of ammonium acetate (5.6 mmol) was heated to 80 °C in EtOH for 6 hours. The ammonium acetate was added in portion wise at regular interval. After the TLC indicated the complete consumption of 3a, the solvent was evaporated on rotatory evaporator to provide dark brown solid which was purified by silica gel column chromatography using hexane:EA (7:3) as an eluent to provide 4a as white colour solid. All the experiments for substituted compounds were performed in similar manner. The reaction times and yields of all the synthesized compounds are mentioned in the Results and Discussion section of the paper.

2-phenylquinoline-4-carboxamide (4a). White solid; 72%, 195 mg, mp 190-191 °C; IR (KBr): ν_{max} 3373, 3150, 1669, 1588 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.31 (dd, J 8 Hz, 4 Hz, 2H, Ar-H), 8.27 (d, J 8 Hz, 1H, Ar-H), 8.16 (s, 1H), 8.13 (d, J 8 Hz, 1H, Ar-H) 7.93 (bs 1H, NH) 7.82 (t, J 8 Hz, 1H) 7.65 (t, J 8 Hz, 1H, Ar-H) 7.60-7.53 (m, 3H, Ar-H); ^13C NMR (100 MHz, DMSO-d_6): δ 168.6, 155.7, 147.9, 143.0, 138.2, 130.0, 129.8, 129.4, 128.8, 127.2, 127.0, 125.4, 123.2, 116.5; HRMS (ESI) m/z for C_{16}H_{13}N_{2}O [M+H]^+, calcd., 249.1027, found, 249.1053

2-(p-toly1)quinoline-4-carboxamide (4b). Light yellow solid; 74%, 206 mg; Mp 203-205 °C; IR (KBr): ν_{max} 3355, 3152, 1669, 1596 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.31 (bs, 1H) 8.26-8.21 (m, 3H, Ar-H), 8.11 (t, J 8 Hz, 1H, Ar-H), 7.92 (bs, 1H, NH), 7.80 (t, J 8 Hz, 1H, Ar-H) 7.63 (t, J 8 Hz, 1H, Ar-H) 7.38 (d, J 8 Hz, 1H, Ar-H) 2.40 (s, 3H, CH_3); ^13C NMR (100 MHz, DMSO-d_6): δ 168.6, 155.6, 147.9, 142.9, 139.5, 135.5, 130.0, 129.3, 127.1, 126.8, 125.4, 123.1, 116.2, 20.8; HRMS (ESI) m/z for C_{17}H_{15}N_{2}O [M+H]^+, calcd., 263.1184, found, 263.1164

2-(4-methoxyphenyl)quinoline-4-carboxamide (4c). White solid; 70%, 196 mg; mp 235-237 °C; IR (KBr): ν_{max} 3336, 3155, 1665, 1584 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.30-8.22 (m, 3H, Ar-H), 8.23 (d, J 12 Hz, 1H, Ar-H) 8.11 (bs, 1H) 8.08 (d, J 8 Hz, 1H, Ar-H), 7.91 (bs, 1H, NH) 7.79 (t, J 8 Hz, 1H, Ar-H), 7.60 (t, J 8 Hz, 1H, Ar-H), 7.12 (d, J 8 Hz, 2H, Ar-H), 3.86 (s, 3H, OCH_3); ^13C NMR (100 MHz, DMSO-d_6): δ 168.7, 160.8, 155.4, 147.9, 142.8, 130.7, 129.9, 129.2, 128.7, 126.5, 125.4, 122.9, 116.0, 114.2, 55.3 HRMS (ESI) m/z for C_{17}H_{15}N_{2}O + [M+H]^+, calcd., 279.1133, found, 279.1144

6-chloro-2-phenylquinoline-4-carboxamide (4d). White solid; 65%, 182 mg; mp 270-272 °C; IR (KBr): ν_{max} 3372, 3153, 2980, 1647, 1584 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.41 (bs, 1H), 8.35 (d, J 4 Hz, 1H, Ar-H), 8.32 (d, J 4 Hz, 2H, Ar-H), 8.26 (s, 1H Ar-H), 8.15 (d, J 8 Hz, 1H, Ar-H), 8.00 (bs, 1H, NH), 7.84 (dd J 8 Hz, 4Hz, 1H, Ar-H), 7.61-7.54 (m, 3H, Ar-H); ^13C NMR (100 MHz, DMSO-d_6): δ 168.0, 156.3, 146.5, 141.5, 137.8, 131.6, 131.5, 130.6, 130.1, 128.9, 127.3, 124.2, 124.0, 117.8 HRMS (ESI) m/z for C_{16}H_{12}ClN_{2}O [M+H]^+, calcd., 283.0638, found, 283.0645

6-chloro-2-(p-toly1)quinoline-4-carboxamide (4e). White solid; 74%, 208 mg; mp 242-244 °C; IR (KBr): ν_{max} 3355, 3150, 1648, 1584 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.40 (bs, 1H), 8.33 (d, J 4 Hz, 1H, Ar-H), 8.22 (d, J 8 Hz, 2H, Ar-H), 8.12 (d, J 12 Hz, 1H, Ar-H), 7.99 (bs, 1H, NH), 7.83 (dd J 8 Hz, 4Hz, 1H, Ar-H), 7.39 (d, J 8 Hz, 2H, Ar-H), 2.40 (s, 3H, CH_3); ^13C NMR (100 MHz, DMSO-d_6): δ 168.3, 155.2, 147.3, 142.9, 127.8, 131.2, 131.0, 129.3, 126.4, 127.1, 124.6, 124.1, 116.4, 20.6; HRMS (ESI) m/z for C_{17}H_{14}ClN_{2}O [M+H]^+, calcd., 297.0794, found, 297.0761

6-chloro-2-(4-methoxyphenyl)quinoline-4-carboxamide (4f). White solid; 75%, 212 mg; mp 265-267 °C; IR (KBr): ν_{max} 3389, 3155, 2980, 1650, 1578 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.39 (bs, 1H), 8.32 (d, J 4 Hz, 1H, Ar-H), 8.29 (d, J 8 Hz, 1H, Ar-H), 8.21 (s, 1H, Ar-H), 8.10 (d, J 8 Hz, 1H, Ar-H), 7.98 (bs, 1H, NH), 7.81 (dd, J 8 Hz, 4Hz, 1H, Ar-H), 7.13 (d, J 8 Hz, 2H, Ar-H), 3.86 (s, 3H, OCH_3); ^13C NMR (100 MHz, DMSO-d_6): δ 168.1, 161.0, 156.0, 146.5, 141.3, 131.4, 131.0, 130.4, 128.7, 124.2, 123.7, 117.3, 114.3, 55.3; HRMS (ESI) m/z for C_{17}H_{14}ClN_{2}O + [M+H]^+, calcd., 313.0743, found, 313.0736

2-(4-bromophenyl)-6-chloroquinoline-4-carboxamide (4g). White solid; 68%, 193 mg; mp 260-262 °C; IR (KBr): ν_{max} 3365, 3180, 2980, 1655, 1586 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.41 (bs, 1H), 8.35 (d, J 4 Hz,
1H, Ar-H), 8.28 (d, J 8 Hz, 1H, Ar-H), 8.15 (d, J 8 Hz, 1H, Ar-H), 8.02 (bs, 1H, NH), 7.85 (dd, J 8 Hz, 4 Hz, 1H, Ar-H), 7.79 (d, J 8 Hz, 2H, Ar-H); 13C NMR (100 MHz, DMSO-d6) δ 172.3, 167.9, 155.2, 146.4, 141.7, 136.9, 131.9, 131.6, 130.7, 129.3, 124.3, 123.9, 117.6 HRMS (ESI) m/z for C16H11BrClN2O [M+H]^+, calcd., 360.9743, found, 360.9755

6-bromo-2-phenylquinoline-4-carboxamide (4h). White solid; 68%, 192 mg; mp 276-278 °C; IR (KBr): ν max 3367, 3181, 2980, 1648, 1584 cm⁻¹; 1H NMR (400 MHz, DMSO-d6): δ 8.51 (d, J 4 Hz, 1H, Ar-H), 8.41 (bs, 1H), 8.32 (s, 1H, Ar-H), 8.08 (d, J 12 Hz, 1H, Ar-H), 8.00 (bs, 1H, NH), 7.95 (dd, J 8 Hz, 4 Hz, 1H, Ar-H), 7.60-7.55 (m, 3H, Ar-H); 13C NMR (100 MHz, DMSO-d6) δ 168.0, 156.4, 146.7, 141.4, 137.8, 133.1, 131.7, 130.1, 128.9, 127.5, 127.3, 124.5, 120.2, 117.7; HRMS (ESI) m/z for C16H12BrN2O [M+H]^+, calcd., 327.0132, found, 327.0138

6-bromo-2-(4-methoxyphenyl)quinoline-4-carboxamide (4i). White solid; 70%, 199 mg; mp 186-188 °C; IR (KBr): ν max 3375, 3180, 2980, 1650, 1578 cm⁻¹; 1H NMR (400 MHz, DMSO-d6) δ 8.46 (s, 1H, Ar-H), 8.39 (bs, 1H), 8.29 (dd, J 8 Hz, 2H, Ar-H), 8.20 (s, 1H, Ar-H), 8.02 (d, J 8 Hz, 1H, Ar-H), 7.98 (bs, 1H, NH), 7.92 (d, J 8 Hz, 1H, Ar-H), 7.12 (d, J 12 Hz, 2H, Ar-H), 3.86 (s, 3H, OCH3) 13C NMR (100 MHz, DMSO-d6) δ 168.5, 156.2, 146.2, 142.4, 130.1, 129.7, 128.2, 126.9, 125.8, 122.6, 116.2, 114.8, 55.6 HRMS (ESI) m/z for C17H14BrN2O2 [M+H]^+, calcd., 357.0238, found, 357.0276

Acknowledgments

R.C., S.S., and P.G. are thankful to the Department of Pharmaceuticals, Ministry of Chemical and Fertilizers, Govt. of India for providing fellowship. The authors are thankful to Dr. S. J. S. Flora, Director, NIPER, Raebareli for his support and encouragement in carrying out this research work. SAIF-CSIR-CDRI, Lucknow is greatly acknowledged for providing spectral data NIPER-R/Communication/020.

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