An efficient synthesis of some 3-substituted-isoquinolin(2H)-ones

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Received: 25th June, 2007 ; Accepted: 30th June, 2007

ABSTRACT

A number of 3-aryl-isoquinolin-1(2H)-ones were efficiently prepared from the corresponding 3-aryl isocoumarins by refluxing with methanamide.

KEYWORDS

Isocoumarin;
Isoquinolin-1(2H)-ones;
Methanamide.

INTRODUCTION

1(2H)-isoquinolones(isocarbostyrils) are the nitrogen analogues of isocoumarins (1H-2-benzopyran-1-ones). Various 1(2H)-isoquinoline derivatives are found in several bioactive natural products such as thalifoline, doryphorine[11] ruprechtstyril[12] narciclasine[3], pancratistatin, lycoricidine[4], the alkaloids coryaldine[5], dorianine[6] hydroxyhydrastinine and thalflavine[7]. Isoquinolone nucleus is also an integral part of complex isoquinoline alkaloids and is a useful building block in organic synthesis.

The isoquinolone skeleton biogenetically derived from amino acid phenylalanine, exhibits biomimetic characteristics.[8]. Substituted isoquinolones are orally effective antagonists of receptors 5-HT3, which have shown highly efficacy in the control of cancer models[9], thymidylate synthase (TS) inhibitors[10], human Tumor Necrosis Factor (TNF) inhibitors, and tachykinin receptors[11]. Substituted isocarbostyrils exhibiting antidepressant[12], anti-inflammatory[13], analgesic[14], hypolipidemic[15] and analeptic[16] activities have also been reported.

In view of the great therapeutic value of such motifs in various bioactive molecules, a number of synthetic routes have been developed. These include the Gabriel–Coleman synthesis[17], ring enlargement of phthalimides[18], condensation of amines with homophthalic anhydrides[19], reaction of 2-methoxy carbonylstyrene oxide with ammonia or methyl amine[20], reaction of coumarin and isocoumarin derivatives[21] with ammonia and amines. The latter method has been used in the synthesis of(+)-licoricidine[22], narciclasine[23],(+)-deoxypencratistatin[24], and the benzophenanthridine alkaloid nitidine[25]. In addition, the[+2]-cycloadition of the ketenes to cyano ketones[26], treatment of indanones with sodium azide[27] and recently solid-phase synthesis of isoquinolinones using Bischler–Napieralski cyclization[28], and palladium mediated synthesis of isoquinolinones[29] syntheses via Curtius arrangement of cinnamic acids or via an isoquinolone N-oxide have been reported[30].

The substitution of the oxygen by nitrogen atom is still one of the most important methods. A number of reagents have been used including ammonia, ammonium acetate or amines, but the results are never satisfactory[31-33] except for a recently reported method[34].

Majority of the natural isocoumarins being of
polyketide origin possess a C-3 alkyl/aryl substituent consequently, a variety of methodologies are available for rapid access to these bioactive heterocycles\[35\]. Therefore the conversion of 3-substituted isocoumarins into corresponding isoquinolin-1(2\(H\))-ones could prove a synthetically feasible procedure. As a continuation of our interest towards synthesis of naturally occurring isocoumarins\[36\] and their synthetic analogues in this article, we wish to describe the conversion of a number of 3-substituted isocoumarins into their nitrogen analogues.

RESULTS AND DISCUSSION

The isocoumarins (1a-j) were synthesized according to method reported earlier\[36\]. An equimolar mixture of the isocoumarin and methanamide was refluxed for 2-4 hours to afford corresponding 1(2\(H\))-isoquinolones (2a-j). The products were obtained in 76-85\% yields in high purity (TABLE 1). The progress of the reaction was followed by TLC. The successful substitution was initially indicated by appearance of a fluorescent blue spot under longer wave length of UV lamp, having R\(_f\) values lower than that of the parent isocoumarin. The products were further characterized by comparison of their mp, IR, \(^1\)H NMR and mass spectral data with those of the corresponding isocoumarins. Thus, a shift of lactonic carbonyl absorption from 1710-1730\,cm\(^{-1}\) to 1630-1650\,cm\(^{-1}\) and appearance of absorption at 3220-3380\,cm\(^{-1}\) for NH was noted in the IR spectra. In the \(^1\)H NMR a downfield shift of the characteristic H-4 proton of the isocoumarins at \(\delta\) 6.0-6.2 to \(\delta\) 6.6-6.9 in isoquinolones was observed besides, appearance of NH absorption at \(\delta\) 9.4-10.8. A variety of substituents on the aryl ring are well-tolerated, and the reaction leads to completion in all the cases. The generality of the conversion was indicated by substrates bearing an aralkyl group (2c), heterocycyl(2i) or a long aliphatic chain (2j) at C-3 position.

In conclusion, one pot, conversion of a number of 3-substituted isocoumarins to the corresponding isoquinolones has been achieved by refluxing with methanamide.

EXPERIMENTAL

<table>
<thead>
<tr>
<th>Entry</th>
<th>Comp.</th>
<th>R</th>
<th>Mp (°C)</th>
<th>Yield (%)</th>
<th>Reflux time (h)</th>
<th>(^1)H NMR 8 (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>3-FC(_6)H(_4)</td>
<td>216-218</td>
<td>84</td>
<td>2.5</td>
<td>6.1 6.83 10.25</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>4-FC(_6)H(_4)</td>
<td>222-224</td>
<td>82</td>
<td>3.0</td>
<td>6.4 6.80 10.54</td>
</tr>
<tr>
<td>3</td>
<td>2c</td>
<td>2-CICH(_2)CH(_4)</td>
<td>188-190</td>
<td>85</td>
<td>3.5</td>
<td>6.24 6.66 9.53</td>
</tr>
<tr>
<td>4</td>
<td>2d</td>
<td>2-Br(_6)H(_4)</td>
<td>170-172</td>
<td>82</td>
<td>2.0</td>
<td>6.2 6.63 9.4</td>
</tr>
<tr>
<td>5</td>
<td>2e</td>
<td>3-IC(_6)H(_4)</td>
<td>226-228</td>
<td>84</td>
<td>2.5</td>
<td>6.34 6.8 9.8</td>
</tr>
<tr>
<td>6</td>
<td>2f</td>
<td>2,4-DiClC(_6)H(_3)</td>
<td>213</td>
<td>78</td>
<td>3.0</td>
<td>6.21 6.66 10.89</td>
</tr>
<tr>
<td>7</td>
<td>2g</td>
<td>2-Cl-4-FC(_6)H(_3)</td>
<td>230-232</td>
<td>80</td>
<td>3.5</td>
<td>6.35 6.65 10.05</td>
</tr>
<tr>
<td>8</td>
<td>2h</td>
<td>4-NO(_2)C(_6)H(_4)</td>
<td>210-212</td>
<td>84</td>
<td>4.0</td>
<td>6.26 6.94 8.79</td>
</tr>
<tr>
<td>9</td>
<td>2i</td>
<td>2-Cl-C(_6)H(_3)N</td>
<td>71-73</td>
<td>76</td>
<td>4.0</td>
<td>6.24 6.89 6.62</td>
</tr>
</tbody>
</table>

**TABLE 1:** Physicochemical and spectral data of 1(2\(H\))-isoquinolones (2a-j)

Recrystallization solvent: Ethyl acetate

**SCHEME 1:** Conversion of isocoumarins into 1(2\(H\))-isoquinolones

Melting points were recorded using a digital Gallenkamp(SANYO) model MPD BM 3.5 apparatus and are uncorrected. \(^1\)H NMR spectra were determined as CDCl\(_3\) solutions at 300MHz on a Bruker AM-300 spectrophotometer. FT IR spectra were recorded using an FTS 3000 MX spectrophotometer; mass spectra(El, 70eV) on a GC-MS instrument and elemental analyses with a LECO-183 CHNS analyzer. All compounds were purified by thick layer chromatography using silica gel from Merck.

**General procedure for the conversion of isocoumarins into isoquinolin-1(2\(H\))-ones (2a–j)**

A mixture of isocoumarins (1a-j)(10mmol) and formamide (10mmol) was refluxed for 2-4h(TABLE 1). On completion of the reaction, followed by TLC the solution was poured into water (300mL). The resulting precipitates were filtered out and recrystallized
Synthesis of some 3-substituted-1(2H)-isoquinolinones

from ethyl acetate to afford 1(2H)-isoquinolones (2a–j).

3-(3-Fluorophenyl)iso cou marin (1a)
R<sub>f</sub>=0.65. IR(KBr):=2990, 1705, 1595 cm<sup>-1</sup>; <sup>1</sup>H NMR δ 6.77 (1H, s, H-4'), 7.80 (1H, s, H-3'), 7.78 (1H, d, J=2.7 H-5'), 7.19 (1H, d, J=2.4, H-6'), 7.15 (4H, m, H-5,6,7,8). MS (70 eV): m/z (%) =274.5 (M<sup>+</sup>+100), 226 (44) 109.5 (37), 145 (62). MS (70 eV): m/z (%) =274.02 (100.0%), 276.02 (32.4%).

3-(3-Nitrophenyl)isoquinolin-1(2H)-one (1h)
IR(KBr):=1734 (C=O), 1543 (C=C) cm<sup>-1</sup>; <sup>1</sup>H NMR δ: 7.1 (1H, s, H-4), 7.2-7.5 (3H, m, H-5-H-8), 7.6 (1H, d, J=1.6 H-3'), 8.7 (1H, d, J=1.6 H-3'), 145 (60). MS (70 eV): m/z (%) =336.5 (M<sup>+</sup>+100), 314.3 (63.7), 160 (100%).

3-(2-Chloro-4-fluorophenyl)isoquinolin-1(2H)-one (1f)
IR(KBr):= 2990, 1705, 1595 cm<sup>-1</sup>; <sup>1</sup>H NMR δ =6.95 (1H, s, H-4), 7.6 (1H, d, J=0.9, H-3'), 7.5 (1H, d, J= 13.2, H-5'), 7.4 (1H, d, J=8.5 H-6'), 7.1-7.35 (4H, m, H-5-H-8). MS (70 eV): m/z (%) =289.1 (64.3%), 290.9 (16.3%).
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OCAIJ, 4(1) January 2008

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(1H, d, J=1.2, H-8), 7.7(2H, d, J=1.8, H-2',H-6'), 8.4(2H, d, J=8.4, H-3',H-5'), 10.54(1H, s, NH); EIMS(70eV):m/z(%)=240, 239[M⁺](61.3), 144(53), 117(98.1).

3-(2-Chlorobenzyl)isoquinolin-1(2H)-one (2c)
IR(KBr):=3348(NH), 1638(C=O), 2860(C-H), 1558(C=C) cm⁻¹; ¹HNMR δ: 2.19(2H, s, CH₂), 6.66(1H, s, H-4), 7.5-7.55(2H, m, H-6,H-7), 7.6(1H, d, J=1.5,H-5), 7.7(1H, d, J=1.5, H-8), 7.85(1H, dd, J=1.5, H-5'), 7.89(1H, d, J=1.5,H-6'), 8.3(1H, dd, J=1.5, 1.8,H-4'), 9.1(1H, d, J=8.1,H-3'), 9.53(1H, s, NH); EIMS(70eV):m/z(%)=271, 269[M⁺](43.7), 144(53.5), 117(59.2).

3-(2-Bromophenyl)isoquinolin-1(2H)-one (2d)
IR(KBr):=3341(NH), 1635(C=O), 2864(C-H), 1535(C=C)cm⁻¹; ¹HNMR δ: 6.635(1H, s, H-4), 7.34(1H, d, J=1.8, H-5), 7.45-7.55(2H, d, m, H-6,7), 7.63(1H, d, J=2.7, H-8), 7.66-7.75(2H, m, H-4',H-5'), 8.38(1H, d, J=1.5,H-6'), 9.12(1H, d, J=8.4,H-3'), 9.4(1H, s, NH); EIMS(70eV):m/z(%)=301, 299[M⁺](71.3),144(62), 117(87.4).

3-(3-Iodophenyl)isoquinolin-1(2H)-one (2e)
IR(KBr):=3353(NH), 1643(C=O), 2892(C-H), 1533(C=C)cm⁻¹; ¹HNMR δ: 6.8(1H, s, H-4), 7.5-7.54(2H, m, H-6,H-7), 7.51(1H, d, J=1.2,H-5), 7.6(1H, d, J=1.2,H-8), 7.74(1H, d, J=1.2,H-6'), 8.1(1H, t, J=1.8,H-5'), 8.2(1H, d, J=13.8,H-4'), 8.44(1H, s, H-2'), 10.6(1H, s ,NH); EIMS(70eV):m/z(%)=348, 347[M⁺](16.5), 144(51), 117(59.6).

3-(2,4-Dichlorophenyl)isoquinolin-1(2H)-one (2f)
IR(KBr):=3330(NH), 1650(C=O), 2862(C-H), 1550(C=C) cm⁻¹; ¹HNMR δ: 6.63(1H, s, H-4), 7.5(1H, d, J=5.7, H-5), 7.61-7.67(2H, m, H-6,H-7), 7.71(1H , d, J=6.9, H-8), 7.88(1H, s, H-3'), 8.457(1H, d, J=7.8,H-6'), 9.06(1H, d, J=8.1, H-5'), 10.89(1H, s, NH); EIMS(70eV):m/z(%)=355[M⁺](82.3), 145(43.6), 118(43.3).

3-(2-Chloro-4-Flourophenyl)isoquinolin-1(2H)-one(2g)
IR(KBr):=3381cm⁻¹(NH), 1655(C=O), 2876(C-H), 1550(C=C); ¹HNMR δ: 6.65(1H, s,H-4), 7.5-7.6(2H, m,H-6,H-7), 7.7(1H,J d.=1.2,H-5), 7.8(1H, d, J=1.2,H-8), 7.9(1H, d, J=1.2,H-6'), 8.2(1H, s,H-3'), 8.4(1H, d, J=8.1,H-5'), 10.0(1H, s, NH), 11(H-3') EIMS(70eV):m/z(%)=275, 273[M⁺](72.8), 145(53), 117(84.4).

3-(3-Nitrophenyl)isoquinolin-1(2H)-one (2h)
IR(KBr):=3339(NH), 1634(C=O), 2821(C-H), 1512(C=C) cm⁻¹; ¹HNMR δ: 6.841(1H, s, H-4), 7.5-7.6(2H, m, H-5',H-6'), 8.4 1H, d, J=8.4,H-4'), 8.61(1H, s, H-2'), 8.75(1H, s, NH); EIMS(70eV):m/z(%)=266[M⁺](82.3), 145(12), 117(43.0).

3-(2-Chloropyridyl)isoquinolin-1(2H)-one (2i)
IR(KBr):=3353(NH), 1663(C=O), 2882(C-H), 1543(C=C) cm⁻¹; ¹HNMR δ: 6.84(1H, s, H-4), 7.5-7.6(2H, m, H-5, H-6), 7.8(1H, d, J=1.5, H-8), 8.1(1H, dd, J=2.4, J=2.3, H-4'), 8.7(1H, d, J=2.2, H-5'), 8.8(1H, d, J=1.8,H-3'), 10.2(1H, s, NH); EIMS(70eV) :m/z(%)=258, 256[M⁺](6.9), 145(32), 118(63.8).

3-Pentadecylisoquinolin-1(2H)-one (2j)
IR(KBr):=3323(NH), 1652(C=O), 2876(C-H), 1513(C=C)cm⁻¹; ¹HNMR δ: 0.9(3H, t, J=5.1, H-15'), 1.5-1.7(26H, m, H-2'-H-14'), 2.3(2H, t, J=7.5, H-1'), 6.89(1H, s, H-4), 7.6(1H, d, J=1.2, H-5), 7.7-7.74(2H, m, H-6,H-7), 8.2(1H, d, J=13.5, H-8), 6.62(1H, s, NH) EIMS(70eV):m/z(%)=355[M⁺](82.3), 145(43.6), 118(43.3).

Solvent system Rf values(Hexane:Ethyl acetate 4:1)

ACKNOWLEDGMENT

The authors are grateful to Pakistan Science Foundation for a Research grant under Project No. PSF/Res/C-QU/Chem(395).

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