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EFFICIENT SYNTHESIS OF SOME 3-ARYLISOQUINOLIN-1(2H)-ONES

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

Keywords: isocoumarin, isoquinolin-1(2H)-one, methanamide.

Isoquinolin-1(2H)-ones (isocarbostyrils) are the nitrogen analogues of isocoumarins (1H-2-benzopyran-1-ones). Various isoquinolin-1(2H)-one derivatives are found in several bioactive natural products such as thalifoline, doryphorine [1], ruprechstyril [2], narciclasine [3], pancretistatin, lycoricidine [4], alkaloids coryaldine [5], dorianine [6, 7], hydroxyhydrastinine, and thalflavine [8]. The 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 the amino acid phenyl- alanine, exhibits biomimetic characteristics [9]. Substituted isoquinolones are orally effective antagonists of 5-HT_3 receptors, which have shown a high efficacy in the control of cancer models [10], thymidylate synthase (TS) inhibitors [11], human tumor necrosis factor (TNF) inhibitors, and tachykinin receptors [12]. Substituted isocarbostyrils exhibiting antidepressant [13], anti-inflammatory [14], analgesic [15], hypolipidemic [16], and analeptic [17] 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 [18], ring enlargement of phthalimides [19], condensation of amines with homophthalic anhydrides [20], reaction of 2-methoxy-carbonylstyrene oxide with ammonia or methylamine [21], and reaction of coumarin and isocoumarin derivatives [22] with ammonia and amines. The latter method has been used in the synthesis of (±)-licoricidine [23], narciclasine [24], (+)-deoxypancretistatin [25], and the benzophenanthridine alkaloid nitidine [26]. In addition, the [4+2] cycloaddition of the ketenes to cyano ketones [27], treatment of indanones with sodium azide [28], recently reported solid-phase synthesis of isoquinolinones using Bischler–Napieralski cyclization [29], palladium-mediated synthesis of isoquinolinones [30], and syntheses *via* Curtius arrangement of cinnamic acids or *via* an isoquinolone N-oxide have been reported [31].

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 [32–34] except for a recently reported method [35].

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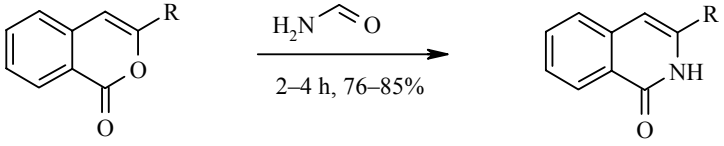
The majority of the natural isocoumarins that are of polyketide origin possess a C-3 alkyl/aryl substituent; consequently, a variety of methodologies are available for rapid access to these bioactive heterocycles [36]. Therefore the conversion of 3-substituted isocoumarins into the analogous isoquinolin-1(2H)-ones could prove to be a synthetically feasible procedure. In continuation of our studies on the synthesis of naturally occurring isocoumarins [37–42] and their synthetic analogues, in this article we describe the conversion of a number of 3-substituted isocoumarins into their nitrogen analogues.

The isocoumarins **1a-j** were synthesized according to the method reported earlier [37]. An equimolar mixture of the isocoumarin and methanamide was refluxed for 2–4 h to afford the corresponding isoquinolin-1(2H)-ones **2a–j.** The products were obtained in 76–85 % yield in high purity (Table 1). The progress of the reaction was followed by TLC. The successful substitution was primarily indicated by the appearance of a fluorescent blue spot under the longer wavelength of a UV lamp, having R_f values lower than those of the parent isocoumarin. The products were further characterized by comparing 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 to 1630–1650 cm^{-1} and appearance of absorption at 3220–3380 cm^{-1} for NH were noted in the IR spectra. In the ^{1}H NMR spectra a downfield shift of the characteristic H-4 proton of the isocoumarins at δ 6.0–6.2 to 6.6–6.9 in isoquinolinones was observed besides the appearance of NH absorption at δ 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**), heterocyclic (**2i**)**,** or a long aliphatic chain (**2j**) at position C-3.



1a–j **2a–j**

1, 2 a R = 3-FC_6H_4, **b** R = 4-FC_6H_4, **c** R = 2-$ClC_6H_4CH_2$, **d** R = 2-BrC_6H_4, **e** R = 3-IC_6H_4, **f** R = 2,4-$Cl_2C_6H_3$, **g** R = 3-F,4-ClC_6H_3, **h** R = 4-$O_2NC_6H_4$, **i** R = 2-ClC_5H_3N-6, **j** R = $C_{15}H_{31}$

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

TABLE 1. Physicochemical Spectral Characteristics of Isoquinolin-1(2H)-ones **2a**–**j**

Com-pound	mp, °C*	Yield, %	Reflux, time, h	^{1}H NMR spectrum, δ, ppm		
				H-4 (**1**)	H-4 (**2**)	NH (**2**)
2a	216-218	84	2.5	6.10	6.83	10.25
2b	222-224	82	3.0	6.40	6.80	10.54
2c	188-190	85	3.5	6.24	6.66	9.53
2d	170-172	82	2.0	6.2	6.63	9.4
2e	226-228	84	2.5	6.34	6.8	9.8
2f	221-222	78	3.0	6.21	6.66	10.89
2g	213-214	80	3.5	6.35	6.65	10.05
2h	230-232	84	4.0	6.26	6.94	8.79
2i	210-212	82	4.0	6.3	6.84	10.2
2j	71-73	76	4.0	6.24	6.89	6.62

* Recrystallization solvent: ethyl acetate.

EXPERIMENTAL

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 300 MHz on a Bruker AM-300 spectrophotometer. FT IR spectra were recorded using an FTS 3000 MX spectrophotometer; mass spectra (EI, 70 eV) on a GC-MS instrument, and elemental analyses with a LECO-183 CHNS analyzer. All compounds were purified by thin-layer chromatography using silica gel from Merck and solvent system hexane–ethyl acetate, 4:1.

3-(3-Fluorophenyl)isocoumarin (**1a**). R_f 0.65. IR spectrum (KBr), n, cm^{-1}: 2980, 1730, 1615. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.87 (1H, s, H-4); 8.14 (1H, s, H-2'); 7.56-7.70 (2H, m, H-4',5'); 7.4 (1H, d, *J* = 2.1, H-6'); 7.3 (2H, d, *J* = 7.8, H-5,8); 7.22 (1H, dd, *J* = 1.8, *J* = 2.1, H-6); 7.15 (1H, dd, *J* = 2.5, *J* = 2.7, H-7). Mass spectrum, *m/z* (*I*, %): 240 (43), 160 (100), 118 (93).

3-(4-Fluorophenyl)isocoumarin (**1b**). R_f 0.55. IR spectrum (KBr), ν, cm^{-1}: 3020, 1725,1590. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.95 (1H, s, H-4); 8.70 (2H, d, *J* = 7.8, H-3',5'); 7.77 (2H, d, *J* = 3, H-2',6'); 7.72 (1H, d, *J* = 1.2, H-5); 7.51 (3H, m, H-6,7,8). Mass spectrum, *m/z* (*I*, %): 240 (43), 160 (100), 118 (93).

3-(2-Chlorobenzyl)isocoumarin (**1c**). IR spectrum (KBr), ν, cm^{-1}: 2860 (C–H), 1738 (C=O), 1558 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.0 (2H, s, CH_2); 6.52 (1H, s, H-4); 7.48-7.51 (2H, m, H-6,7); 7.58 (1H, d, *J* = 1.6, H-5); 7.65 (1H, d, *J* = 1.5, H-8); 7.81 (1H, dd, *J* = 1.5, *J* = 1.5, H-5'); 7.85 (1H, d, *J* = 1.5, H-6'); 8.1 (1H, dd, *J* = 1.5, *J* = 1.8, H-4'); 8.9 (1H, d, *J* = 8.1, H-3'). Mass spectrum, *m/z* (*I*, %): 272, 270 (43), 160 (100), 118 (93).

3-(2-Bromophenyl)isocoumarin (**1d**). IR spectrum (KBr), ν, cm^{-1}: 3025, 1710, 1590. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.75 (1H, s, H-4); 7.81 (1H, d, *J* = 2.4, H-3'); 7.55–7.65 (3H, m, H-4'–6'); 7.2-7.3 (4H, m, H-5–8). Mass spectrum, *m/z* (*I*, %): 300 $[M]^+$ (100), 226 (40) 109 (37), 145 (60).

3-(3-Iodophenyl)isocoumarin (**1e**). IR spectrum (KBr), ν, cm^{-1}: 3010, 1725, 1580. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.96 (1H, s, H-4); 8.15 (1H, s, H-2'); 7.96 (1H, d, *J* = 9, H-4'); 7.67 (1H, d, *J* = 8.1, H-6'); 7.61 (1H, dd, *J* = 4.8, *J* = 3.3, H-5'); 7.55 (4H, m, H-5–8). Mass spectrum, *m/z* (*I*, %): 348.9 (16.4), 347.9 (100.0).

3-(2,4-Dichlorophenyl)isocoumarin (**1f**). IR spectrum (KBr), ν, cm^{-1}: 2970, 1705, 1620. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 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-5–8). Mass spectrum, *m/z* (*I*, %): 291.9 (64.3), 290.9 (16.3).

3-(2-Chloro-4-fluorophenyl)isocoumarin (**1g**). IR spectrum (KBr), ν, cm^{-1}: 2990, 1705, 1595. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 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-5–8). Mass spectrum, *m/z* (*I*, %): 276.02 (32.4), 274.02 $[M]^+$ (100.0).

3-(3-Nitrophenyl)isocoumarin (**1h**). IR spectrum (KBr), ν, cm^{-1}: 2893 (C–H), 1734 (C=O), 1512 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.1 (1H, s, H-4); 7.2–7.4 (4H, m, H-5–8); 7.7–7.5 (2H, m, H-5',6'); 8.2 (1H, d, *J* = 8.2, H-4'); 8.4 (1H, s, H-2'). Mass spectrum, *m/z* (*I*, %): 267 $[M]^+$ (97.7), 160 (100).

3-(2-Chloro-6-pyridyl)isocoumarin (**1i**). IR spectrum (KBr), ν, cm^{-1}: 2882 (C–H), 1743 (C=O), 1543 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.95 (1H, s, H-4); 7.2–7.5 (3H, m, H-5–7); 7.6 (1H, d, *J* = 1.5, H-8); 8.0 (1H, dd, *J* = 2.2, *J* = 2.4, H-4'); 8.5 (1H, d, *J* = 2.1, H-5'); 8.7 (1H, d, *J* = 1.6, H-3'). Mass spectrum, *m/z* (*I*, %): 336 (34.2), 314 (63.7), 259, 257 $[M]^+$ (97.7), 160 (100), 118 (97.7).

3-Pentadecylisocoumarin (**1j**). IR spectrum (film), ν, cm^{-1}: 2918, 2849, 1728, 1712, 1656, 1604, 1160, 642. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.87 (3H, t, *J* = 6.3, H-15'); 1.28 (24H, br. s, H-3'–14'); 1.70 (2H, qu, *J* = 8.4, H-2'); 2.52 (2H, t, *J* = 7.1, H-1'); 6.24 (1H, s, H-4); 7.34 (1H, d, *J* = 8.2, H-5); 7.49 (1H, td, *J* = 0.9, *J* = 7.3, H-7); 7.65 (1H, m, H-6); 8.25 (1H, d, *J* = 8.2, H-8). Mass spectrum, *m/z* (*I*, %): 356 $[M]^+$ (97.7), 336 (34.2), 314 (63.7), 160 (100), 118 (97.7).

Conversion of isocoumarins into isoquinolin-1(2H)-ones (General procedure). A mixture of apropriate isocoumarin **1a**–**j** (10 mmol) and methanamide (10 mmol) was refluxed for 2–4 h (Table 1). On completion of the reaction, followed by TLC, the solution was poured into water (300 ml). The resulting precipitates were filtered off and recrystallized from ethyl acetate to afford isoquinolin-1(2H)-ones **2a**–**j**.

3-(3-Fluorophenyl)isoquinolin-1(2H)-one (**2a**). IR spectrum (KBr), ν, cm^{-1}: 3332 (NH), 2825 (C–H), 1656 (C=O), 1517 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.83 (1H, s, H-4); 7.1–7.2 (3H, m, H-5-7); 7.23 (1H, d, *J* = 2.4, H-8); 7.54 (1H, dd, *J* = 1.8, *J* = 1.6, H-5'); 7.70 (1H, d, *J* = 1.5, H-6'); 7.72 (1H, d, *J* = 0.9, H-2'); 8.4 (1H, d, *J* = 1.2, H-4'); 10.3 (1H, s, NH). Mass spectrum, *m/z* (*I*, %): 240, 239 $[M]^+$ (82.3), 144 (53), 117 (97.7). Found, %: C 75.30; H 4.26; N 5.78. $C_{15}H_{10}FNO$. Calculated, %: C 75.30; H 4.21; N 5.85.

3-(4-Fluorophenyl)isoquinolin-1(2H)-one (**2b**). IR spectrum (KBr), ν, cm^{-1}: 3320 (NH), 2870 (C–H), 1630 (C=O), 1527 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.8 (1H, s, H-4);7.4 (1H, dd, *J* = 1.2, *J* = 1.1, H-5); 7.5–7.6 (2H, m, H-6,7); 7.63 (1H, d, *J* = 1.2, H-8); 7.7 (2H, d, *J* = 1.8, H-2',6'); 8.4 (2H, d, *J* = 8.4, H-3',5'); 10.54 (1H, s, NH). EI mass spectrum, *m/z* (*I*, %): 240, 239 $[M]^+$ (61.3), 144 (53), 117 (98.1). Found, %: C 70.29; H 4.03; N 5.52. $C_{15}H_{10}ClNO$. Calculated, %: C 70.46; H 3.94; N 5.48.

3-(2-Chlorobenzyl)isoquinolin-1(2H)-one (**2c**). IR spectrum (KBr), ν, cm^{-1}: 3348 (NH), 2860 (C–H), 1638 (C=O), 1558 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.19 (2H, s, CH_2); 6.66 (1H, s, H-4); 7.5-7.55 (2H, m, H-6,7); 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, *J* = 1.5, H-5'); 7.89 (1H, d, *J* = 1.5, H-6'); 8.3 (1H, dd, *J* = 1.5, *J* = 1.8, H-4'); 9.1 (1H, d, *J* = 8.1, H-3'); 9.53 (1H, s, NH). Mass spectrum, *m/z* (*I*, %): 271, 269 $[M]^+$ (43.7), 144 (53.5), 117 (59.2). Found, %: C 71.29; H 4.33; N 5.23. $C_{16}H_{12}ClNO$. Calculated, %: C 71.25; H 4.48; N 5.19.

3-(2-Bromophenyl)isoquinolin-1(2H)-one (**2d**). IR spectrum (KBr), ν, cm^{-1}: 3341 (NH), 2864 (C–H), 1635 (C=O), 1535 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.64 (1H, s, H-4); 7.34 (1H, d, *J* = 1.8, H-5); 7.45–7.55 (2H, m, H-6,7); 7.63 (1H, d, *J* = 2.7, H-8); 7.66–7.75 (2H, m, H-4',5'); 8.38 (1H, d, *J* = 1.5, H-6'); 9.12 (1H, d, *J* = 8.4, H-3'); 9.4 (1H, s, NH). Mass spectrum, *m/z* (*I*, %): 301, 299 $[M]^+$ (71.3), 144 (62), 117 (87.4). Found, %: C 60.02; H 3.36; N 4.67. $C_{15}H_{10}BrNO$. Calculated, %: C 60.02; H 3.36; N 4.67.

3-(3-Iodophenyl)isoquinolin-1(2H)-one (**2e**). IR spectrum (KBr), ν, cm^{-1}: 3353 (NH), 2892 (C–H), 1643 (C=O), 1533 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.8 (1H, s, H-4); 7.5-7.54 (2H, m, H-6,7); 7.5 (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'); 8.45 (1H, s, H-2'); 10.6 (1H, s, NH). Mass spectrum, *m/z* (*I*, %): 348, 347 $[M]^+$ (16.5), 144 (51), 117 (59.6). Found, %: C 52.10; H 2.97; N 4.08 %. $C_{15}H_{10}INO$. Calculated, %: C 51.90; H 2.90; N 4.03.

3-(2,4-Dichlorophenyl)isoquinolin-1(2H)-one (**2f**). IR spectrum (KBr), ν, cm^{-1}: 3330 (NH), 2862 (C–H), 1650 (C=O), 1550 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.63 (1H, s, H-4); 7.5 (1H, d, *J* = 5.7, H-5); 7.61-7.67 (2H, m, H-6,7); 7.71 (1H, d, *J* = 6.9, H-8); 7.88 (1H, s, H-3'); 8.46 (1H, d, *J* = 7.8, H-6'); 9.06 (1H, d, *J* = 8.1, H-5'); 10.89 (1H, s, NH). Mass spectrum, *m/z* (*I*, %): 291, 289 $[M]^+$ (5.7), 144 (53), 117 (97.7). Found, %: C 62.17; H 3. 24; N 4.79. $C_{15}H_9Cl_2NO$. Calculated, %: C 62.09; H 3.13; N 4.83.

3-(2-Chloro-4-fluorophenyl)isoquinolin-1(2H)-one (**2g**). IR spectrum (KBr), ν, cm^{-1}: 3381 (NH), 2876 (C–H), 1655 (C=O), 1550 (benzene ring). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.65 (1H, s, H-4); 7.5-7.6 (2H, m, H-6,7); 7.7 (1H, d, *J* = 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, H-3'). Mass spectrum, *m/z* (*I*, %): 275, 273 $[M]^+$(72.8), 145 (53), 117 (84.4).. Found, %: C 65.91; H 3.32; N 5.06. $C_{15}H_9ClFNO$. Calculated, %: C 65.83; H 3.31; N 5.12

3-(3-Nitrophenyl)isoquinolin-1(2H)-one (**2h**). IR spectrum (KBr), ν, cm^{-1}: 3339 (NH), 2821 (C–H), 1634 (C=O), 1512 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.9 (1H, s, H-4); 7.4-7.6 (4H, m, H-5–8); 7.7-7.2 (2H, m, H-5',6'); 8.4 (1H, d, *J* = 8.4, H-4'); 8.6 (1H, s, H-2'); 8.75 (1H, s, NH). Mass spectrum, *m/z* (*I*, %): 266 $[M]^+$ (82.3), 145 (12), 117 (43.0). Found, %: C 67.70; H 3.41; N 10.42. $C_{15}H_{10}N_2O_3$. Calculated, %: C 67.67; H 3.79; N 10.52.

3-(2-Chloro-6-pyridyl)isoquinolin-1(2H)-one (**2i**). IR spectrum (KBr), ν, cm^{-1}: 3353 (NH), 2882 (C–H), 1663 (C=O), 1543 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.84 (1H, s, H-4), 7.5-7.7 (3H, m, H-5,6,7); 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). Mass spectrum, *m/z* (*I*, %): 258, 256 $[M]^+$ (6.9), 145 (32), 118 (63.8). Found, %: C 65.49; H 3.50; N 10.97. $C_{14}H_{19}ClN_2O$. Calculated, %: C 65.51; H 3.53; N 10.91.

3-Pentadecylisoquinolin-1(2H)-one (**2j**). IR spectrum (KBr), ν, cm^{-1}: 3323 (NH), 2876 (C–H), 1652 (C=O), 1513 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.9 (3H, t, *J* = 5.1, H-15'); 1.5-1.7 (26H, m, H-2'–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-6,7); 8.2 (1H, d, *J* = 13.5, H-8); 6.62 (1H, s, NH). Mass spectrum, *m/z* (*I*, %): 355 $[M]^+$ (82.3), 145 (43.6), 118 (43.3). Found, %: C 81.12; H 10.41; N 3.98. $C_{24}H_{37}NO$. Calculated, %: C 81.07; H 10.49; N 3.94.

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