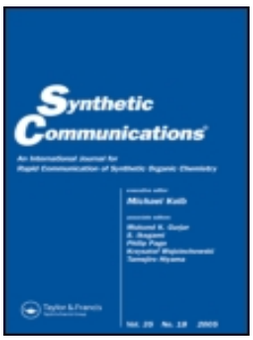


Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

A FACILE SYNTHESIS OF 2,3-DISUBSTITUTED PYRIDO[2,3-h]QUINAZOLIN-4(3H)-ONES

T. Aruna Kumari , M. Satyanarayana Reddy & P. Jaya Prasad Rao

To cite this article: T. Aruna Kumari , M. Satyanarayana Reddy & P. Jaya Prasad Rao (2002) A FACILE SYNTHESIS OF 2,3-DISUBSTITUTED PYRIDO[2,3-h]QUINAZOLIN-4(3H)-ONES, Synthetic Communications, 32:2, 235-240, DOI: 10.1081/SCC-120002007

To link to this article: http://dx.doi.org/10.1081/SCC-120002007

Published online: 16 Aug 2006.

SYNTHETIC COMMUNICATIONS, 32(2), 235–240 (2002)

A FACILE SYNTHESIS OF 2,3-DISUBSTITUTED PYRIDO[2,3-*h*]QUINAZOLIN-4(3H)-ONES

T. Aruna Kumari, M. Satyanarayana Reddy, and P. Jaya Prasad Rao*

Department of Chemistry, Osmania University, Hyderabad, 500 007, A. P., India

ABSTRACT

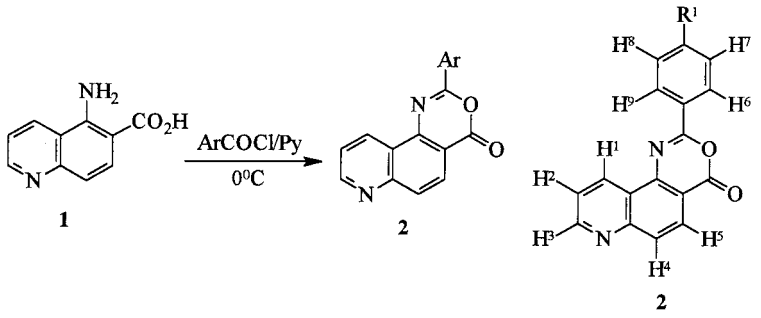
Synthesis of 2-substituted-4H-Pyrido[2,3-*h*]benzoxazin-4-ones (2) from 5-Aminoquinoline-6-carboxylic acid (1) and their conversion to 2,3-disubstituted Pyrido[2,3-*h*]quinazolin-4(3H)-ones(3) is reported.

5-Aminoquinoline-6-carboxylic acid,[1] inspite of its wide potential has been scarcely used in the synthesis of heterocyclic synthesis. It has been successfully used by us[2] for the preparation of 2-methyl-4H-pyrido[2,3-*h*]quinazolin-4(3H)-one. Here in we report the synthesis of 2-aryl-4H-pyrido[2,3-*h*]benzoxazin-4-ones (2a–d) and 2,3-disubstituted pyrido[2,3-*h*]quinazolin-4(3H)-ones (3a–s).

The reaction of 5-aminoquinoline-6-carboxylic acid (1) with 4-methylbenzoyl chloride in pyridine at 0°C gave a crystalline compound in high yield. The mass spectrum of the compound revealed the molecular ion

*Corresponding author.

at m/z 288 indicating to be a 1:1 product formed by the elimination of hydrogen chloride and water. The IR spectrum (KBr) showed the absence of NH and presence of a δ-lactonic carbonyl at 1758 cm^{-1}. The ^{1}H-NMR spectrum (DMSO-d_6) exhibited signals at δ 2.5 (s, 3H, CH_3), 7.4 (d, 2H, Ar-H of H^7, H^8), 7.7 (m, 1H, Ar-H of H^4), 8.2 (d, 1H, Ar-H of H^5), 8.4 (m, 3H, Ar-H of H^2, H^6, H^9), 9.2 (d, 1H, Ar-H of H^1), 9.4 (d, 1H, Ar-H of H^3). Based on the spectral and analytical data the compound has been characterised at 2-(4-methylphenyl)-4H-pyrido[2,3-*h*]3,1-benzoxazin-4-one (2c).



1 2 2

This reaction was extended to three other aroyl chlorides and the products obtained were characterised as 2-aryl-4H-pyrido[2,3-*h*]3,1-benzoxazin-4-ones (2a–d) (Table 1) by analogy and on the basis of spectral and analytical data (Tables 1–3). Attempts to isolate *N*-acylamino acid in the reaction of 1 with aroyl chlorides were not successful.

Compounds 2 exhibited intense molecular ions in their mass spectra. The mass spectral fragmentation is characterised by the presence of ions corresponding to the loss of $\dot{A}r$, CO_2. In addition, $\overset{\oplus}{A}r$ and $\overset{\oplus}{Ar}CO$ fragment ions have been observed.

Compounds 2 possess a labile lactone ring which can readily undergo reaction with nucleophiles involving replacement of oxygen in the ring. Thus reaction of 2a with 4-methylaniline in acetic acid afforded a crystalline compound, identified as 2-phenyl-3-(4-methylphenyl)pyrido[2,3-*h*]quinazolin-4(3H)-one (3c) on the basis of mass (M^+ at m/z 363), IR (KBr, υC=O at 1670 cm^{-1}) and ^{1}H-NMR (DMSO-d_6) spectral data [δ 2.4 (s, 3H, CH_3), 7.0–7.4 (m, 9H, Ar-H of C-aryl and N-aryl), 7.6 (m, 1H, Ar-H of H^2), 8.1 (d, 1H, Ar-H of H^4), 8.5 (d, 1H, Ar-H of H^5), 9.1 (d, 1H, Ar-H of H^1) and 9.3 (d, 1H, Ar-H of H^3)]. The reaction of 2a was extended to aniline, 4-nitroaniline and 2-methylanilines and the corresponding 3 (Table 1) were obtained in good yields.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

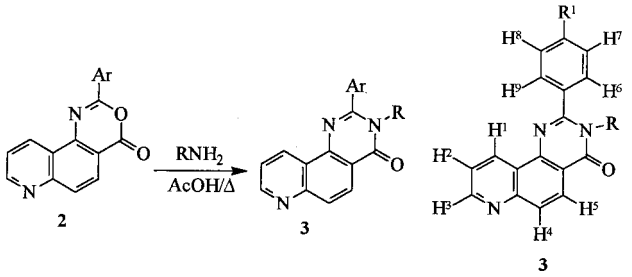


Table 1. Characterisation Data of 2-Substituted-4H-pyrido[2,3-*h*]-3,1-benzoxazin-4-ones (2) and 2,3-Disubstituted Pyrido[2,3-*h*]-quinazolin-4-(3H)-ones(3)

Compound	Ar	R	M.P. (°C)	Yield (%)
2a	C_6H_5	–	204	80
2b	4-Cl-C_6H_4	–	220	75
2c	4-CH_3-C_6H_4	–	215	72
2d	4-OCH_3-C_6H_4	–	258	80
3a	C_6H_5	C_6H_5	> 300	82
3b	C_6H_5	4-NO_2-C_6H_4	> 300	78
3c	C_6H_5	4-CH_3-C_6H_4	260	75
3d	C_6H_5	2-CH_3-C_6H_4	254	80
3e	4-Cl-C_6H_4	C_6H_5	> 300	80
3f	4-Cl-C_6H_4	4-NO_2-C_6H_4	278	75
3g	4-Cl-C_6H_4	4-CH_3-C_6H_4	> 300	78
3h	4-Cl-C_6H_4	2-CH_3-C_6H_4	288	75
3i	4-CH_3-C_6H_4	C_6H_5	> 300	82
3j	4-CH_3-C_6H_4	4-NO_2-C_6H_4	195	80
3k	4-CH_3-C_6H_4	4-CH_3-C_6H_4	> 300	78
3l	4-CH_3-C_6H_4	2-CH_3-C_6H_4	238	74
3m	4-OCH_3-C_6H_4	C_6H_5	> 300	76
3n	4-OCH_3-C_6H_4	4-NO_2-C_6H_4	188	80
3o	4-OCH_3-C_6H_4	4-CH_3-C_6H_4	140	72
3p	4-OCH_3-C_6H_4	2-CH_3-C_6H_4	196	82
3q	4-CH_3-C_6H_4	H	> 300	76
3r	4-CH_3-C_6H_4	CH_2Ph	228	75
3s	4-CH_3-C_6H_4	CH_3	230	80

Likewise the reaction of all other 2-aryl-4H-pyrido[2,3-*h*]-3,1-benzoxazin-4-ones (2b–d) with aromatic primary amines in acetic acid also afforded the corresponding 3 (Table 1) characterized by analogy and on the basis of spectral and analytical data (Tables 1–3). The above reaction constitutes

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Table 2. ^{1}H NMR Data of 2 and 3 (DMSO-d_6)

Compound	^{1}H NMR Data (δ)
2b	7.5 (d, 2H, Ar-H of H^7, H^8), 7.7 (m, 1H, Ar-H of H^4), 8.2 (d, 1H, Ar-H of H^5), 8.4 (m, 3H, Ar-H of H^2, H^6, H^9), 9.1 (d, 1H, Ar-H of H^1), 9.4 (d, 1H, Ar-H of H^3).
2c	2.5 (s, 3H, CH_3), 7.4 (d, 2H, Ar-H of H^7, H^8), 7.7 (m, 1H, Ar-H of H^4), 8.2 (d, 1H, Ar-H of H^5), 8.4 (m, 3H, Ar-H of H^2, H^6, H^9), 9.2 (d, 1H, Ar-H of H^1), 9.4 (d, 1H, Ar-H of H^3).
3a	7.1–7.5 (m, 10H, Ar-H of C-aryl and N-aryl), 7.6 (m, 1H, Ar-H of H^2), 8.1 (d, 1H, Ar-H of H^4), 8.5 (1H, Ar-H of H^5), 9.1 (d, 1H, Ar-H of H^1), 9.4 (d, 1H, Ar-H of H^3).
3b	7.2–7.6 (m, 10H, Ar-H of C-aryl & N-aryl and H^2), 8.2 (d, 1H, Ar-H of H^4), 8.5 (d, 1H, Ar-H of H^5), 9.1 (d, 1H, Ar-H of H^1), 9.4 (d, 1H, Ar-H of H^3).
3c	2.4 (s, 3H, CH_3), 7.0–7.4 (m, 9H, Ar-H of C-aryl & N-aryl), 7.6 (m, 1H, Ar-H) of H^2), 8.1 (d, 1H, Ar-H of H^4), 8.5 (d, 1H, Ar-H of H^5), 9.1 (d, 1H, Ar-H of H^1), 9.3 (d, 1H, Ar-H of H^3).
3d	2.1 (s, 3H, CH_3), 7.1–7.5 (m, 9H, Ar-H of C-aryl & N-aryl), 7.7 (m, 1H, Ar-H of H^2), 8.1 (d, 1H, Ar-H of H^4), 8.4 (d, 1H, Ar-H of H^5), 9.1 (d, 1H, Ar-H of H^1), 9.4 (d, 1H, Ar-H of H^3).
3h	2.1 (s, 3H, CH_3), 7.1–7.4 (m, 8H, Ar-H of C-aryl & N-aryl), 7.6 (m, 1H, Ar-H) of H^2), 8.1 (d, 1H, Ar-H of H^4), 8.5 (d, 1H, Ar-H of H^5), 9.1 (d, 1H, Ar-H of H^1), 9.4 (d, 1H, Ar-H of H^3).
3l	2.1 (s, 3H, ortho CH_3), 2.3 (s, 3H, para CH_3), 7.0–7.4 (m, 8H, Ar-H of C-aryl & N-aryl), 7.7 (m, 1H, Ar-H of H^2), 8.1 (d, 1H, Ar-H of H^4), 8.5 (d, 1H, Ar-H of H^5), 9.1 (d, 1H Ar-H of H^1), 9.4 (d, 1H, Ar-H of H^3).
3m	3.9 (s, 3H, OCH_3), 7.0–7.6 (m, 10H, Ar-H of C-aryl & N-aryl and H^2), 8.2 (d, 1H, Ar-H of H^4), 8.8 (d, 1H, Ar-H of H^5), 9.1 (d, 1H, Ar-H of H^1), 9.3 (d, 1H, Ar-H of H^3).
3o	2.5 (s, 3H, CH_3), 3.9 (s, 3H, OCH_3) 7.1–7.3 (m, 8H, Ar-H of C-aryl & N-aryl), 7.7 (m, 1H, Ar-H of H^2), 8.1 (d, 1H, Ar-H of H^4), 8.3 (d, 1H, Ar-H of H^5), 9.1 (d, 1H, Ar-H of H^1), 9.3 (d, 1H, Ar-H of H^3).

a simple one-step synthesis for a variety of pyrido[2,3-*h*]quinazolin-4-(3H)-ones (3). Pyrolysis of 2 with aromatic primary amines also resulted in corresponding 3. However, the yields were relatively low. The formation of 3 from 2 probably involves nucleophilic attack by anilino nitrogen on carbonyl carbon of the latter, resulting in an open chain intermediate. Subsequent loss of elements of water from the tautomeric form of the intermediate yields 3. All the 3 exhibited intense molecular ions in their mass spectra indicating the stability of ring system. Generally $M^{+\cdot}$ or $M^{+\cdot} - 1$ is observed as the base peak.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Table 3. Analytical Data of 2 and 3

Compound	Molecular Formula	Found % (Calc.)		
		C	H	N
2a	$C_{17}H_{10}N_22O_2$	74.42 (74.45)	3.62 (3.65)	10.20 (10.22)
2b	$C_{17}H_9N_2O_2Cl$	66.10 (66.13)	2.89 (2.92)	9.06 (9.08)
2c	$C_{18}H_{12}N_2O_2$	75.03 (75.00)	4.16 (4.17)	9.73 (9.72)
2d	$C_{18}H_{12}N_2O_3$	71.02 (71.05)	3.97 (3.95)	9.23 (9.21)
3a	$C_{23}H_{15}N_3O$	79.10 (79.08)	4.28 (4.30)	12.00 (12.03)
3b	$C_{23}H_{14}N_4O_3$	70.07 (70.05)	3.57 (3.55)	14.19 (14.21)
3c	$C_{24}H_{17}N_3O$	79.30 (79.34)	4.66 (4.68)	11.57 (11.57)
3d	$C_{24}H_{17}N_3O$	79.37 (79.34)	4.69 (4.68)	11.55 (11.57)
3e	$C_{23}H_{14}N_3OCl$	71.97 (71.97)	3.66 (3.65)	10.98 (10.95)
3f	$C_{23}H_{13}N_4O_3Cl$	64.39 (64.41)	3.06 (3.03)	13.09 (13.07)
3g	$C_{24}H_{16}N_3OCl$	72.44 (72.45)	4.05 (4.03)	10.59 (10.57)
3h	$C_{24}H_{16}N_3OCl$	72.48 (72.45)	4.01 (4.03)	10.56 (10.57)
3i	$C_{24}H_{17}N_3O$	79.32 (79.34)	4.66 (4.68)	11.56 (11.57)
3j	$C_{24}H_{16}N_4O_3$	70.56 (70.59)	3.94 (3.92)	13.72 (13.73)
3k	$C_{25}H_{19}N_3O$	79.54 (79.58)	5.06 (5.04)	11.11 (11.14)
3l	$C_{25}H_{19}N_3O$	79.57 (79.58)	5.06 (5.04)	11.12 (11.14)
3m	$C_{24}H_{17}N_3O_2$	75.98 (75.99)	4.46 (4.49)	11.06 (11.08)
3n	$C_{24}H_{16}N_4O_4$	67.93 (67.92)	3.79 (3.77)	13.18 (13.21)
3o	$C_{25}H_{19}N_3O_2$	76.31 (76.34)	4.85 (4.83)	10.70 (10.69)
3p	$C_{25}H_{19}N_3O_2$	76.31 (76.34)	4.80 (4.83)	10.71 (10.69)
3q	$C_{18}H_{13}N_3O$	75.23 (75.26)	4.51 (4.53)	14.61 (14.63)
3r	$C_{25}H_{19}N_3O$	79.56 (79.58)	5.01 (5.04)	11.11 (11.14)
3s	$C_{19}H_{15}N_3O$	75.72 (75.75)	4.96 (4.98)	13.92 (13.95)

Condensation of 2c with ammonia, methylamine and benzylamine afforded the corresponding pyridoquinazolin-4-(3H)-ones (3q–s). Compound 3s on treatment with aniline in acetic acid resulted in 3i. The ready replacement of the methylamino moiety by phenylamino component in the above reaction may be attributed to the enhanced conjugation in the resulting product. The formation of 3i from 3s probably involves nucleophilic attack by anilino nitrogen on carbonyl carbon of the latter, resulting in an open chain intermediate. Subsequent loss of elements of methylamine from the tautomeric form of the intermediate yields 3i. The 3-unsubstituted (3q) and 3-benzyl (3r) 2-(4-methylphenyl) pyrido[2,3-*h*]quinazolin-4(3H)-ones proved to be exceptional in their reaction with aniline. In both cases replacement of nitrogen function did not occur. Thus ring NH and NCH_2Ph are found to be resistant to replacement by NPh, which may be attributed to relatively less electrophilic nature of carbonyl carbon in

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

the former (3q) and due to tautomerism in N–H free compound and to steric factors in 3r.

EXPERIMENTAL SECTION

Melting points are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer 1605 spectrophotometer, ^{1}H-NMR (200 MHz) spectra on Varian Gemini-200 spectrometer using TMS as internal standard and mass spectra on Micromass 70-70H instrument.

2-Aryl-4H-pyrido[2,3-*h*]benzoxazin-4-ones (2): 5-Aminoquinoline-6-carboxylic acid (1, 1 mmol) was dissolved in pyridine (5 ml) and cooled at 0°C. To this the appropriate aroyl chloride (1 mmol) was added dropwise with stirring and stirred for 2 h. The mixture was poured into ice-cold water (25 ml) and the compound separated was filtered, washed with small volumes of cold water and few drops of ethanol and dried. The characterisation data of crystalline compounds 2 thus obtained are included in Tables 1–3.

Condensation of 2 with Primary Amines: A mixture of appropriate 2 (1 mmol), primary amine (1 mmol) and glacial acetic acid (5 ml) was heated on steam bath for 5 h. The reaction mixture was cooled and poured into water (25 ml) with stirring. The compound separated was filtered, washed with small volumes of cold water and few drops of ethanol and dried. The characterisation data 2,3-disubstituted pyrido[2,3-h]-quinazolin-4-(3H)-ones(3) thus obtained are given in Tables 1–3.

IR spectra of 2 showed υC=O around 1750 cm^{-1} while those of 3 exhibited around 1670 cm^{-1}.

ACKNOWLEDGMENT

One of the authors (TAK) is thankful to the UGC, New Delhi, for the award of a senior research fellowship.

REFERENCES

1. Bogert, M.T.; Fisher, H.L. J. Am. Chem. Soc. **1912**, *34*, 1570.
2. Satyanarayana Reddy, M.; Ratnam, C.V. Ind. J. Chem. **1983**, *22B*, 1100.

Received in the UK June 12, 2000