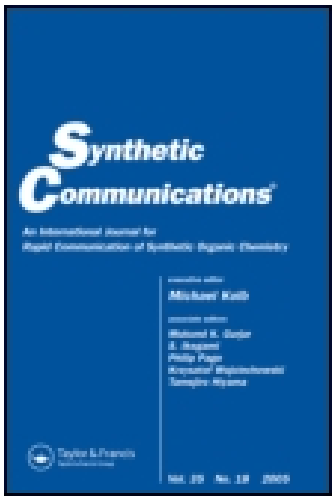

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ABSTRACT

The reaction of 2-substituted-4H-pyrido[2,3-h]benzoxazin-4-ones (1) with hydrazine hydrate resulted in 2-substituted-3-aminopyrido[2,3-h]quinazolin-4(3H)ones (2) and not in the corresponding 3. The Schiff bases (4) of 2 on pyrolysis led to 2-substituted pyrido[2,3-h]quinazolin-4(3H)ones (5).

The potentiality of 5-aminoquinoline-6-carboxylic acid[1] has not been explored fully. It has been used by us earlier in the synthesis of 2,3-disubstituted pyrido[2,3-h]benzoxazin-4-ones.[2] The results of 2-substituted-4H-benzoxazin-4-one and hydrazine hydrate[3–7] have been debated earlier. This prompted us to take up the investigation of 2-substituted-4H-pyrido[2,3-h]benzoxazin-4-one and hydrazine hydrate reaction and the results with spectral, analytical and chemical evidence are presented hereunder (Tables 1 and 2).

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Table 1. Characterisation Data of 2, 4, and 5

Compound	Ar	Ar[1]	M.P. (°C)	Yield (%)
2a	C_6H_5	–	252–253	52
2b	4-CH_3–C_6H_4	–	258	61
2c	4-OCH_3–C_6H_4	–	248–250	57
2d	4-Cl–C_6H_4	–	276–278	58
2e	C_2H_5	–	206	60
2f	CH_3	–	242	63
4a	C_6H_5	C_6H_5	242	62
4b	C_6H_5	4-CH_3–C_6H_4	216–219	61
4c	C_6H_5	4-OCH_3–C_6H_4	214	55
4d	4-CH_3–C_6H_4	C_6H_5	252	52
4e	4-CH_3–C_6H_4	4-CH_3–C_6H_4	228	56
4f	4-CH_3–C_6H_4	4-OCH_3–C_6H_4	254	59
4g	4-OCH_3–C_6H_4	C_6H_5	244	64
4h	4-OCH_3–C_6H_4	4-CH_3–C_6H_4	226–227	62
4i	4-OCH_3–C_6H_4	4-OCH_3–C_6H_4	236	59
4j	4-Cl–C_6H_4	C_6H_5	262	61
4k	4-Cl–C_6H_4	4-CH_3–C_6H_4	228–230	62
4l	4-Cl–C_6H_4	4-OCH_3–C_6H_4	254	56
4m	C_2H_5	C_6H_5	196	64
4n	C_2H_5	4-CH_3–C_6H_4	184–185	61
4o	C_2H_5	4-OCH_3–C_6H_4	210	66
4p	CH_3	C_6H_5	207	60
4q	CH_3	4-CH_3–C_6H_4	205	59
4r	CH_3	4-OCH_3–C_6H_4	248–251	65
5a	C_6H_5	–	> 300	61
5b	4-CH_3–C_6H_4	–	> 300	63
5c	4-OCH_3–C_6H_4	–	> 300	58
5d	4-Cl–C_6H_4	–	> 300	55
5e	C_2H_5	–	268	65
5f	CH_3	–	> 300	66

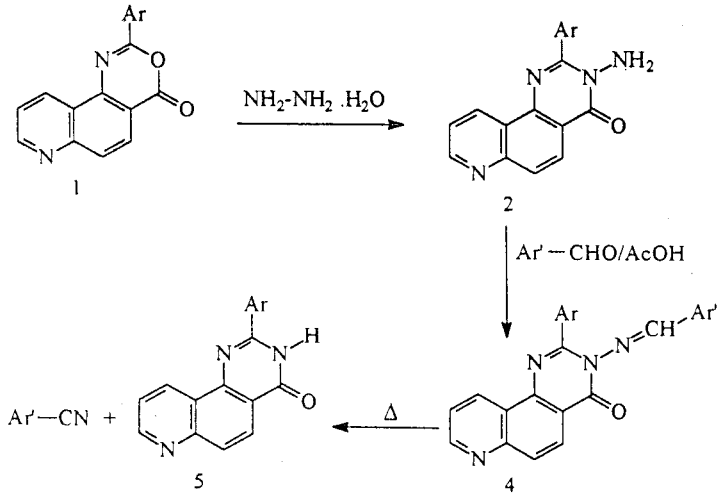
The reaction of 2-*p*-tolyl-4H-pyrido[2,3-h]benzoxazin-4-one (1, Ar = 4-CH_3–C_6H_4) with an excess of hydrazine hydrate under refluxing condition for 2 h gave a crystalline compound with m.p. 258°C. The mass spectrum of the compound revealed the molecular ion at m/z 302. The ^{1}H-NMR spectrum (DMSO–d_6) exhibited signals at δ 2.4 (s, 3H, CH_3), 5.9 (s, 2H, NH_2, D_2O exchangeable), 7.3 (d, 2H, Ar–H, H^7, H^8), 7.7 (m, 1H, Ar–H, H^4), 7.9 (m, 3H, Ar–H, H^2, H^6, H^9), 8.1 (d, 1H, Ar–H, H^5), 9.1 (d, 1H, Ar–H, H^1), 9.3 (d, 1H, Ar–H, H^3). Based on the elemental analysis and spectral data the

Table 2. Analytical Data of 2, 4, and 5

Comp.	Mol. Formula	Found % (Calc.)		
		C	H	N
2a	$C_{17}H_{12}N_4O$	70.84 (70.83)	4.16 (4.17)	19.42 (19.44)
2b	$C_{18}H_{14}N_4O$	71.50 (71.52)	4.61 (4.64)	18.57 (18.54)
2c	$C_{18}H_{14}N_4O_2$	67.91 (67.92)	4.42 (4.40)	17.60 (17.61)
2d	$C_{17}H_{11}N_4ClO$	63.23 (63.26)	3.39 (3.41)	17.33 (17.36)
2e	$C_{13}H_{12}N_4O$	65.02 (65.00)	4.99 (5.00)	23.34 (23.30)
2f	$C_{12}H_{10}N_4O$	63.68 (63.72)	4.44 (4.42)	24.75 (24.78)
4a	$C_{24}H_{16}N_4O$	76.62 (76.60)	4.25 (4.26)	14.90 (14.89)
4b	$C_{25}H_{18}N_4O$	76.93 (76.92)	4.60 (4.62)	14.35 (14.36)
4c	$C_{25}H_{18}N_4O_2$	73.85 (73.89)	4.41 (4.43)	13.81 (13.79)
4d	$C_{25}H_{18}N_4O$	76.91 (76.92)	4.61 (4.62)	14.35 (14.36)
4e	$C_{26}H_{20}N_4O$	77.20 (77.22)	4.94 (4.95)	13.87 (13.86)
4f	$C_{26}H_{20}N_4O_2$	74.27 (74.29)	4.75 (4.76)	13.33 (13.33)
4g	$C_{25}H_{18}N_4O_2$	73.88 (73.89)	4.40 (4.43)	13.80 (13.79)
4h	$C_{26}H_{20}N_4O_2$	74.30 (74.29)	4.72 (4.76)	13.32 (13.33)
4i	$C_{26}H_{20}N_4O_3$	71.54 (71.56)	4.58 (4.59)	12.85 (12.84)
4j	$C_{24}H_{15}N_4ClO$	70.19 (70.16)	3.66 (3.65)	13.61 (13.64)
4k	$C_{25}H_{17}N_4ClO$	70.65 (70.67)	4.01 (4.00)	13.20 (13.19)
4l	$C_{25}H_{17}N_4ClO_2$	68.11 (68.10)	3.85 (3.86)	12.73 (12.71)
4m	$C_{20}H_{16}N_4O$	73.20 (73.17)	4.89 (4.88)	17.08 (17.07)
4n	$C_{21}H_{18}N_4O$	73.65 (73.68)	5.24 (5.26)	16.38 (16.37)
4o	$C_{21}H_{18}N_4O_2$	70.36 (70.39)	5.01 (5.03)	15.65 (15.64)
4p	$C_{19}H_{14}N_4O$	72.62 (72.61)	4.41 (4.46)	17.84 (17.83)
4q	$C_{20}H_{16}N_4O$	73.18 (73.17)	4.85 (4.88)	17.08 (17.07)
4r	$C_{20}H_{16}N_4O_2$	69.76 (69.77)	4.63 (4.65)	16.26 (16.28)
5a	$C_{17}H_{11}N_3O$	74.71 (74.73)	4.01 (4.03)	15.35 (15.38)
5b	$C_{18}H_{13}N_3O$	75.27 (75.26)	4.52 (4.53)	14.61 (14.63)
5c	$C_{18}H_{13}N_3O_2$	71.30 (71.29)	4.26 (4.29)	13.88 (13.86)
5d	$C_{17}H_{10}N_3ClO$	66.32 (66.34)	3.23 (3.25)	13.65 (13.66)
5e	$C_{13}H_{11}N_3O$	69.32 (69.33)	4.85 (4.89)	18.61 (18.67)
5f	$C_{12}H_9N_3O$	68.27 (68.25)	4.22 (4.27)	19.88 (19.91)

compound was assigned the structure 2-*p*-tolyl-3-aminopyrido[2,3-h]quinazolin-4(3H)one (2b). An alternate pyridobenzotriazepin-5-one structure (3, Ar = 4-CH_3–C_6H_4) for this compound is ruled out based on the presence of a doublet around 3250 cm^{-1} corresponding to NH_2 in its IR spectrum (KBr) and also a two proton D_2O exchangeable singlet at δ 5.9 in its ^{1}H-NMR spectrum.

The reaction has been extended to other 2-aryl-4H-pyrido[2,3-h]benzoxazin-4-ones (1) and in each case the product was identified as the



Scheme 1.

corresponding 2-aryl-3-aminopyrido[2,3-h]quinazolin-4(3H)-one (2) based on spectral and analytical data (Scheme 1).

The formation of 2 from 1 probably involves nucleophilic attack by hydrazino nitrogen on carbonyl carbon of the latter, resulting in an open chain intermediate.[6,8] Subsequent loss of elements of water from the tautomeric form of the intermediate involving NH and not NH_2 yields compound 2. Compounds 2 were also obtained from 1 and hydrazine hydrate under variety of conditions like hot acetic acid, refluxing methanol, xylene and pyridine.

Further proof for the structure assigned to compound 2 came from the fact that it formed a Schiff base (4) with aromatic aldehyde. Compound 4 was characterised by the presence of an azomethine signal in its ^{1}H-NMR spectrum (DMSO–d_6, Table 3) and characteristic (M^+–H) peak in its mass spectrum. To ascertain the generality, all the 2 were treated independently with benzaldehyde, 4-methylbenzaldehyde and 4-methoxybenzaldehyde. In each case the corresponding 4 were characterised by spectral and analytical data.

The *N–N* bond is considered to be labile and susceptible to cleavage. To verify this, 2-*p*-tolyl-3-benzylidene aminopyrido[2,3-h]quinazolin-4(3H)-one (4d) was subjected to neat pyrolysis above its melting point. The reaction mixture on processing afforded the benzonitrile and a compound with molecular ion at *m/z* 287. The IR spectrum (KBr) showed the presence of NH (broad at 3200 cm^{-1}), amide C=O (at 1658 cm^{-1}) and C=N

Table 3. ^{1}H-NMR Data of Selected 2, 4, and 5 (DMSO–d_6)

Compound	Data (δ)
2a	5.7 (s, 2H, NH_2, D_2O exchangeable), 7.3–7.5 (m, 5H, c-phenyl), 7.7 (m, 1H, Ar–H, H^4), 7.9 (m, 2H, Ar–H, H^2, H^5), 9.1 (d, 1H, Ar–H, H^1), 9.4 (d, 1H, Ar–H, H^3).
2c	3.7 (s, 3H, OCH_3), 5.9 (s, 2H, NH_2, D_2O exchangeable), 7.2 (d, 2H, Ar–H, H^7, H^8), 7.7 (m, 1H, Ar–H, H^4), 7.9 (m, 3H, Ar–H, H^2, H^6, H^9), 8.0 (d, 1H, Ar–H, H^5), 9.2 (d, 1H, Ar–H, H^1), 9.3 (d, 1H, Ar–H, H^3).
2e	1.1 (t, 3H, CH_3 of ethyl), 1.3 (q, 2H, CH_2 of ethyl), 5.8 (s, 2H, NH_2, D_2O exchangeable), 7.3 (d, 2H, Ar–H, H^7, H^8), 7.7 (m, 1H, Ar–H, H^4), 7.9 (m, 3H, Ar–H, H^2, H^6, H^9), 8.1 (d, 1H, Ar–H, H^5), 9.1 (d, 1H, Ar–H, H^1), 9.3 (d, 1H, Ar–H, H^3).
4b	2.4 (s, 3H, CH_3), 7.7 (m, 1H, Ar–H, H^4), 7.2–7.6 (m, 9H, Ar–H, phenyl & *p*-tolyl), 8.1 (d, 1H, Ar–H, H^2), 8.4 (d, 1H, Ar–H, H^5), 9.1 (s, 2H, Ar–H, H^1 and azomethine), 9.3 (d, 1H, Ar–H, H^3).
4c	3.9 (s, 3H, OCH_3), 7.8 (m, 1H, Ar–H, H^4) 7.2–7.5 (m, 9H, Ar–H, phenyl & anisyl), 8.2 (d, 1H, Ar–H, H^2) 8.4 (d, 1H, Ar–H, H^5), 9.2 (s, 2H, Ar–H, H^1 and azomethine), 9.3 (d, 1H, Ar–H, H^3).
4n	1.1 (t, 3H, CH_3 of ethyl), 1.3 (q, 2H, CH_2 of ethyl), 2.5 (s, 3H, CH_3), 7.8 (m, 1H, Ar–H, H^4), 7.4 (m, 4H, Ar–H, *p*-tolyl), 8.1 (d, 1H, Ar–H, H^2), 8.4 (d, 1H, Ar–H, H^5), 9.1 (s, 2H, Ar–H, H^1 and azomethine), 9.2 (d, 1H, Ar–H, H^3).
5a	7.3 (s, 1H, NH_2, D_2O exchangeable), 7.5 (m, Ar–H of phenyl), 8.2 (m, 1H, Ar–H, H^2), 8.4 (d, 1H, Ar–H, H^4), 8.7 (d, 1H, Ar–H, H^5), 9.3 (m, 2H, Ar–H, H^1, H^3).
5c	3.8 (s, 3H, OCH_3), 7.1 (s, 1H, NH, D_2O exchangeable), 7.2 (d, 2H, Ar–H, H^7, H^8), 7.7 (m, 1H, Ar–H, H^4), 7.8 (m, 3H, Ar–H, H^2, H^6, H^9), 8.2 (d, 1H, Ar–H, H^5), 9.1 (d, 1H, Ar–H, H^1), 9.3 (d, 1H, Ar–H, H^3).

(at 1599 cm^{-1}). The ^{1}H-NMR spectrum (DMSO–d_6) exhibited signals at δ 2.4 (s, 3H, CH_3), 7.2 (s, 1H, NH, D_2O exchangeable), 7.5 (d, 2H, Ar–H, H^7, H^8), 8.2 (m, 3H, Ar–H, H^2, H^6, H^9), 8.4 (d, 1H, Ar–H, H^4), 8.7 (d, 1H, Ar–H, H^5) and 9.4 (m, 2H, Ar–H, H^1, H^3). Based on the spectral and analytical data the compound has been characterised as 2-*p*-tolyl-pyrido[2,3-h]quinazolin-4(3H)-one (5b). Similarly all the 4 on pyrolysis afforded the corresponding arylnitrile and 5.

Formation of 5 and arylnitrile from 4 probably involves a six-membered cyclic transition state involving H-transfer and the *N–N* bond cleavage. Compounds 5 were also obtained from 2 in the presence of

$KMnO_4$ and dry acetone under refluxing conditions. In this reaction, the compound 2 undergoes oxidative coupling to give dipyridoquinazolinyl hydrazine[9] followed by the loss of nitrogen through a six-membered cyclic transition state to yield 5. Reaction of 1 with an excess of ammonia under refluxing conditions also afforded 5.

EXPERIMENTAL SECTION

2-Substituted-3-aminopyrido[2,3-h]quinazolin-4(3H)ones (2): A mixture of 2-substituted-4H-pyrido[2,3-h]benzoxazin-4-one (1, 10 mmol) and hydrazine hydrate (99%, 5 mL) was heated under reflux for 2 h, cooled and diluted with water. The compound (2) that separated was filtered, washed with a few drops of alcohol and dried.

2-Substituted-3-arylidene aminopyrido[2,3-h]quinazolin-4(3H)-ones (4): A mixture of 2 (1 mmol) and aromatic aldehyde (1 mmol) in ethanol (5 mL) was warmed on steam bath for 15 min and cooled to give crystalline 4.

2-Substituted pyrido[2,3-h]quinazolin-4(3H)-ones (5): 1 mmol of 4 was heated 20°C above its melting point for 1 h. Later it was dissolved in chloroform and subjected to chromatography. Elution with benzene–ethylacetate (1 : 1) mixture yielded pure 5.

Oxidation of 2-substituted-3-aminopyrido[2,3-h]quinazolin-4(3H)ones (2) to give 5.

Compounds 2 were oxidised by $KMnO_4$ following a similar oxidation reaction reported in literature.[9]

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