A Convenient Synthesis of 3-Aryl-1,2,4-triazolo[4,3-*c*]quinazolines

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The synthesis and characterization of several 3-aryl-1,2,4-triazolo[4,3-*c*]quinazolines is described. The first step comprises the condensation of aromatic aldehydes with 2-(H or Cl)-4-hydrazinoquinazolines **2** to afford the corresponding hydrazones **3**. The second step involves the cyclization to the title compounds **4** in bromine/acetic acid. Reaction of **4** (X = Cl) with cyclic amines gave the corresponding 5-cyclicamino **5** or 5-alkoxy derivatives **6**.

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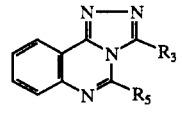
It has been previously demonstrated that triazoloquinazolines such as **1**, where R_3 is hydrogen or alkyl and R_5 is chloro, methoxy or substituted amino, possess antiinflammatory activity [1-3]. In the course of our work on novel antiinflammatory agents, it became of interest to develop a general method for the synthesis of 5-substituted 3-aryl-1,2,4-triazolo[4,3-*c*]quinazolines (*i.e.*, **1**, R_3 = aryl or substituted aryl). We report here the facile cyclization of 1-arylidene-2-(4-quinazolinyl)hydrazines **3** to the desired derivatives of **1** where R_3 = H or Cl. The subsequent displacement of the chloro substituent by a variety of nucleophiles was also investigated.



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Results and Discussion.

4-Hydrazinoquinazoline **2c** [4] and 2-chloro-4-hydrazinoquinazoline **2d** were prepared by reaction of hydra-

Table 1

Characterisation of 1-Arylidene-2-(4-quinazolyl)hydrazines

Compound	MP [a] (°C)	Yield %	Emperical Formula	Analysis Calcd./Found C	H	N	^{1}H-NMR (δ ppm) [b]
3a	227-229	64	$C_{15}H_{11}BrN_4$	55.04 55.09	3.39 3.41	17.12 17.07	7.31-8.48 (m, 10H, Ar-H and Ar-CH=N), 11.46 (s, 1H, NH)
3b	198-200	59	$C_{15}H_{11}ClN_4$	63.70 63.80	3.92 3.96	19.82 19.73	7.46-8.59 (m, 10H, Ar-H and Ar-CH=N), 11.78 (s, 1H, NH)
3c	218-220	68	$C_{15}H_{11}ClN_4$	63.70 63.61	3.92 3.94	19.82 19.77	7.45-8.54 (m, 10H, Ar-H and Ar-CH=N), 11.72 (s, 1H, NH)
3d	246-248	77	$C_{15}H_{10}CL_2N_4$	56.78 56.86	3.17 3.22	17.66 17.65	7.48-8.73 (m, 9H, Ar-H and Ar-CH=N), 11.84 (s, 1H, NH)
3e	172-174	69	$C_{15}H_{11}ClN_4$	63.70 63.62	3.92 3.95	19.82 19.80	7.6-8.9 (m, 10H, Ar-H and Ar-CH=N), 12.25 (s, 1H, NH)
3f	230-232	72	$C_{15}H_{10}BrClN_4$	49.79 49.65	2.78 2.82	15.49 15.38	7.55-8.68 (m, 9H, Ar-H and Ar-CH=N), 12.17 (s, 1H, NH)
3g	217-219	41	$C_{15}H_{10}Cl_2N_4$	56.78 56.72	3.17 3.20	17.66 17.61	7.61-8.7 (m, 9H, Ar-H and Ar-CH=N), 12.20 (s, 1H, NH)
3h	225-227	70	$C_{15}H_{10}Cl_2N_4$	56.78 56.86	3.17 3.19	17.66 17.62	7.55-8.72 (m, 9H, Ar-H and Ar-CH=N), 12.18 (s, 1H, NH)
3i	238-240	78	$C_{15}H_9Cl_3N_4$	51.20 51.36	2.56 2.70	15.93 16.10	7.5-8.83 (m, 8H, Ar-H and Ar-CH=N), 12.28 (s, 1H, NH)

[a] All compounds were recrystallized from acetonitrile except for **2e** which was recrystallized from aqueous methanol. [b] DMSO-d_6 was used as the solvent. All NH signals were exchangeable with deuterium oxide.

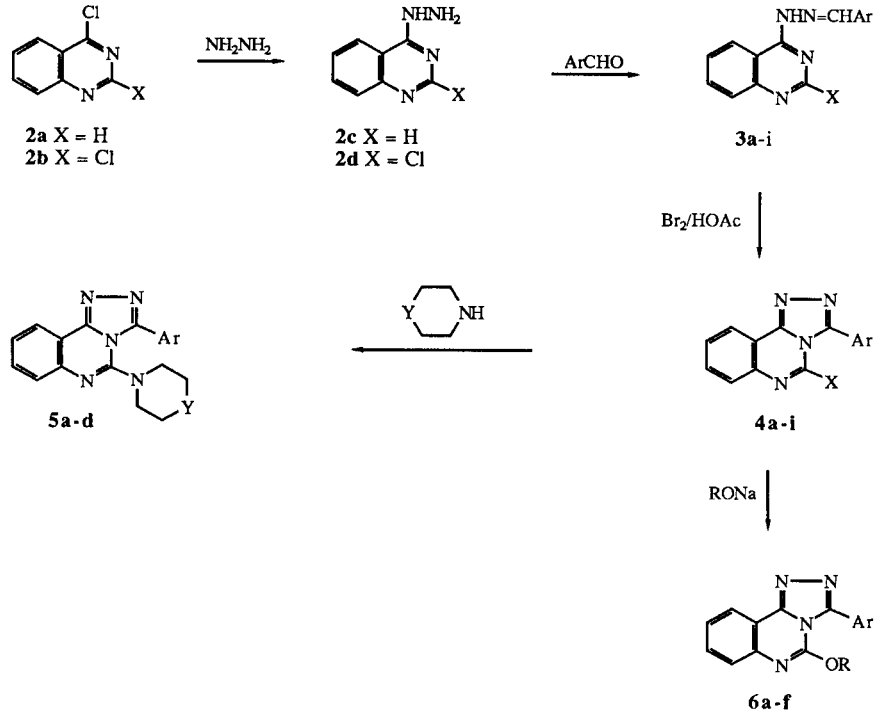
zine with 4-chloroquinazoline [5] or 2,4-dichloroquinazoline [6] (**2a** and **2b** respectively). The reaction of **2c** and **2d** with aromatic aldehydes yielded 1-arylidene-2-(4-quinazolyl)hydrazines **3**. The structures of **3a-i** are supported by their elemental analysis and ^{1}H-nmr spectral data (Table 1). 3-Aryl-5-(H or Cl)-1,2,4-triazolo[4,3-*c*]quinazolines **4** were prepared from the corresponding **3** by treatment with an acetic acid solution of bromine in the presence of sodium acetate followed by pouring the reaction mixture into excess sodium hydroxide solution.

The concentration of sodium hydroxide solution used to achieve cyclization of **3** played a role in terms of the structure of the cyclized product when there is a chloro substituent at 2-position of the quinazoline ring. 1-(4-Chlorobenzylidene)-2-(2-chloro-4-quinazolyl)hydrazine **3h** was subjected to the cyclization reaction utilizing two different concentrations of sodium hydroxide (Scheme 2). The use of 0.5 *N* sodium hydroxide afforded the corresponding 5-chlorotriazoloquinazoline **4h**. However 2 *N* sodium hydroxide resulted in the formation of an unexpected product that was subsequently identified as 3-(4-chlorophenyl)-5,6-dihydro-5-oxo-1,2,4-triazolo[4,3-*c*]quinazoline (**9**). The structure of **9** is supported by its ^{1}H-nmr spectrum and also by a carbonyl stretching band (1750 cm^{-1}) in its infrared spectrum.

The possibility exists that hydrolysis might have occurred before or after cyclization to **4h**. The possibility of hydrolysis after cyclization was eliminated by treating **4h** with 2 *N* sodium hydroxide at room temperature (*i.e.*, under conditions of cyclization); under these conditions, **4h** was recovered unchanged (Scheme 2). On the other hand, heating **4h** with aqueous sodium hydroxide under reflux resulted in the formation of **9**. It appears that, hydrolysis of **7** (possibly *via* intermediate **8**) occurs prior to cyclization to **9**.

It was expected that the chloro group of the 5-chlorotriazoloquinazolines would be reactive towards nucleophilic displacement reactions due to the electron-withdrawing effect of the triazole ring. Thus, treatment of **4** (X = Cl) with cyclic amines or alkoxides afforded the correspon-

Scheme 1



3 or 4	Ar	X
a	4-BrC_6H_4	H
b	2-ClC_6H_4	H
c	4-ClC_6H_4	H
d	2,4-di-ClC_6H_3	H
e	C_6H_5	Cl
f	4-BrC_6H_4	Cl
g	2-ClC_6H_4	Cl
h	4-ClC_6H_4	Cl
i	2,4-di-ClC_6H_3	Cl

5	Ar	Y
a	4-BrC_6H_4	NCH_3
b	4-ClC_6H_4	NCH_3
c	4-ClC_6H_4	O
d	4-ClC_6H_4	CH_2

6	Ar	R
a	4-ClC_6H_4	CH_3
b	4-ClC_6H_4	C_2H_5
c	4-BrC_6H_4	CH_3
d	4-BrC_6H_4	C_2H_5
e	2,4-di-ClC_6H_3	CH_3
f	2,4-di-ClC_6H_3	C_2H_5

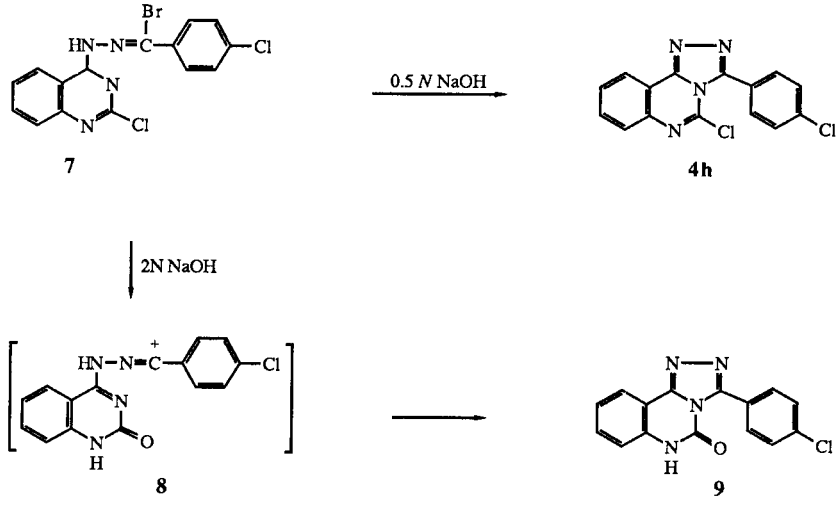
Table 2

Characterisation of 3-Aryl-1,2,4-triazolo[4,3-*c*]quinazolines

Compound	Rs [a]	MP (°C)	Yield %	Emperical Formula	Analysis Calcd./Found C	H	N	^{1}H-NMR (δ ppm) [b]
4a	M	280-282	54	$C_{15}H_9BrN_4,1/2H_2O$	53.89 54.16	3.01 2.66	16.77 16.79	7.72-8.64 (m, 8H, Ar-H), 9.65 (s, 1H, 5-position proton)
4b	E	158-160	57	$C_{15}H_9ClN_4,2/3H_2O$	61.52 61.72	3.56 3.19	19.15 18.64	7.62-8.53 (m, 8H, Ar-H), 9.13 (s, 1H, 5-position proton)
4c	M	290-292	79	$C_{15}H_9ClN_4$	64.15 63.98	3.23 3.25	19.96 19.89	7.62-8.52 (m, 8H, Ar-H), 9.68 (s, 1H, 5-position proton)
4d	I	218-220	40	$C_{15}H_8Cl_2N_4$	57.14 57.25	2.56 2.60	17.77 17.77	7.65-8.61 (m, 7H, Ar-H), 9.0 (s, 1H, 5-position proton)
4e	E	248-250	62	$C_{15}H_9ClN_4,1/2H_2O$	62.16 61.78	3.48 3.30	19.34 19.21	7.60-8.62 (m, 4H and 5H Ar-H)
4f	E	227-229	33	$C_{15}H_8BrClN_4$	50.06 49.96	2.24 2.25	15.57 15.50	7.61-8.65 (m, 4H and 4H Ar-H)
4g	I	176-178	50	$C_{15}H_8Cl_2N_4$	57.14 57.06	2.56 2.56	17.77 17.70	7.60-8.68 (m, 4H and 4H Ar-H)
4h	E	215-217	80	$C_{15}H_8Cl_2N_4$	57.14 57.22	2.56 2.58	17.77 17.71	7.58-8.57 (m, 4H and 4H Ar-H)
4i	I	228-230	47	$C_{15}H_7Cl_3N_4$	51.51 51.56	2.01 2.06	16.03 15.97	7.71-8.65 (m, 3H and 4H Ar-H)

[a] Rs (Recrystallization solvents); E = Ethanol, I = 2-Propanol, M = Methanol. [b] DMSO-d_6 was used as the solvent.

Scheme 2



ding **5** or **6** under relatively mild conditions and in comparatively good yield (Scheme 1).

In summary then, 3-aryl-1,2,4-triazolo[4,3-*c*]quinazolines can be readily prepared by the cyclization of 1-arylidene-2-(4-quinazolyl)hydrazines, which in turn, are easily prepared by condensation of the appropriately substituted aldehyde with 4-hydrazinoquinazolines. Cyclization is effected by bromine in acetic acid, followed by treatment of the crude intermediate bromohydrazone with 0.5 *N* sodium hydroxide solution. If the triazoloquinazoline bears a 5-chloro substituent, this can be readily displaced by alkoxide or an amine to afford the corresponding alkoxy or amino derivatives.

Table 3

Characterisation of 5-Alkoxy-3-aryl-1,2,4-triazolo[4,3-*c*]quinazolines

Compound	MP [a] (°C)	Yield %	Emperical Formula	Analysis Calcd./Found C	H	N	^{1}H-NMR (δ ppm) [b]
6a	220-222	60	$C_{16}H_{11}ClN_4O$	61.82 61.78	3.57 3.59	18.04 18.04	4.4 (s, 3H, OCH_3), 7.26-8.35 (m, 8H, Ar-H)
6b	176-178	72	$C_{17}H_{13}ClN_4O$	62.84 62.77	4.03 4.06	17.26 17.21	1.62 (t, 3H, CH_3), 4.85 (q, 2H, CH_2), 7.38-8.52 (m, 8H, Ar-H)
6c	222-224	60	$C_{16}H_{11}BrN_4O$	54.08 54.02	3.12 3.15	15.78 15.74	4.48 (s, 3H, OCH_3), 7.34-8.38 (m, 8H, Ar-H)
6d	185-187	70	$C_{17}H_{13}BrN_4O$	55.27 55.19	3.55 3.59	15.18 15.16	1.63 (t, 3H, CH_3), 4.87 (q, 2H, CH_2), 7.60-8.51 (m, 8H, Ar-H)
6e	242-244	60	$C_{16}H_{10}Cl_2N_4O$	53.55 53.44	3.23 2.98	15.62 15.53	4.43 (s, 3H, OCH_3), 7.29-8.36 (m, 7H, Ar-H)
6f	145-147	68	$C_{17}H_{12}Cl_2N_4O$	56.82 56.80	3.36 3.39	15.60 15.57	1.62 (t, 3H, CH_3), 4.87 (q, 2H, CH_2), 7.30-8.52 (m, 7H, Ar-H)

[a] All compounds were recrystallized from methanol. [b] Deuteriochloroform used as the solvent.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were obtained with a JOEL FX 90 Q spectrometer. Tetramethylsilane (TMS) was used as internal standard, and chemical shifts are expressed in ppm (δ units). Infrared spectra were recorded with a Nicolet 5 ZDX FT-IR spectrometer. Microanalysis was performed by Atlantic Microlab. (GA, USA). Compounds **2a** and **2b** were prepared according to literature procedures [5,6].

1-Benzylidene-2-(4-quinazolyl)hydrazines **3a-i**.

General Procedure.

A mixture of the appropriate (4-quinazolyl)hydrazine (1.54 mmoles), the properly substituted benzaldehyde (1.62 mmoles) and absolute ethanol (25 ml) was allowed to stir at room temperature for 30 minutes. The product was collected by filtration, dried, and recrystallized from the appropriate solvent. For percent yields, melting points, microanalytical and ^{1}H-nmr data, See Table 1.

3-Aryl-5-(H or chloro)-1,2,4-triazolo[4,3-*c*]quinazolines **4a-i**.

General Procedure.

A solution of bromine (0.02 ml) in glacial acetic acid (0.1 ml) was added to a suspension of anhydrous sodium acetate (0.3 g) and the appropriate 1-arylidene-2-(4-quinazolyl)hydrazine **3** (0.39 mmole) in acetic acid (1 ml). The reaction mixture was allowed to stir at room temperature for 30 minutes, and poured into excess ice cooled 0.5 *N* sodium hydroxide; the product was collected by filtration, washed with water, dried and recrystallized from the appropriate solvent. Recrystallization solvent, percent yield, melting points, elemental analysis and ^{1}H-nmr data are shown in Table 2.

3-(4-Bromophenyl)-5-(4-methyl-1-piperazinyl)-1,2,4-triazolo[4,3-*c*]-quinazoline **5a**.

A mixture of 3-(4-bromophenyl)-5-chloro-1,2,4-triazolo[4,3-*c*]-quinazoline (0.1 g, 0.31 mmole), 1-methylpiperazine (0.25 ml), and absolute ethanol (10 ml) was heated under reflux for 2 hours. After cooling the reaction mixture to room temperature, the product was collected by filtration, air dried, and recrystallized from methanol to give 0.05 g (39%) of **5a** mp 242-244°; ^{1}H-nmr (deuteriochloroform): 2.08 (t, 4H, CH_3-N(CH_2)$_2$), 2.18 (s, 3H, CH_3), 3.10 (t, 4H, Ar-N(CH_2)$_2$), 7.58-8.60 (m, 8H, Ar-H).

Anal. Calcd. for $C_{20}H_{19}BrN_6$: C, 56.72; H, 4.52; N, 19.68. Found: C, 56.66; H, 4.59; N, 19.85.

3-(4-Chlorophenyl)-5-(4-methyl-1-piperazinyl)-1,2,4-triazolo[4,5-*c*]-quinazoline **5b**.

The title compound was prepared in a manner similar to that used in the preparation of **5a**. The product was recrystallized from methanol to give a 42% yield of **5b** mp 243-245°; ^{1}H-nmr (deuteriochloroform): 2.08 (t, 4H, CH_3-N(CH_2)$_2$), 2.18 (s, 3H, CH_3), 3.15 (t, 4H, Ar-N(CH_2)$_2$), 7.46-8.68 (m, 8H, Ar-H).

Anal. Calcd. for $C_{20}H_{19}ClN_6$: C, 63.38; H, 5.05; N, 22.19. Found: C, 63.34; H, 5.08; N, 22.16.

3-(4-Chlorophenyl)-5-(4-morpholinyl)-1,2,4-triazolo[4,3-*c*]quinazoline **5c**.

A mixture of 5-chloro-3-(4-chlorophenyl)-1,2,4-triazolo[4,3-*c*]-quinazoline (0.1 g, 0.31 mmole), morpholine (0.25 ml), anhydrous sodium carbonate (60 mg), and absolute ethanol (10 ml) was heated under reflux for 8 hours. After cooling the reaction mixture to room temperature, the product was collected by filtration, washed with water, dried and recrystallized from methanol to give 40 mg (34%) of **5c** mp 205-207°; ^{1}H-nmr (deuteriochloroform): 4.08 (m, 8H, N(CH_2)$_2$, O(CH_2)$_2$), 7.45-8.50 (m, 8H, Ar-H).

Anal. Calcd. for $C_{19}H_{16}ClN_5O$: C, 62.38; H, 4.41; N, 19.15. Found: C, 62.80; H, 4.72; N, 18.72.

3-(4-Chlorophenyl)-5-(1-piperidinyl)-1,2,4-triazolo[4,3-*c*]quinazoline **5d**.

Compound **5d** was prepared according to the procedure used

for the preparation of **5c**. The product was crystallized from methanol to yield 43% of **5d**, mp 177-179°; ^{1}H-nmr (deuteriochloroform): 1.86 (m, 6H, $(CH_2)_3$-piperidine), 4.05 (t, 4H, $N(CH_2)_2$), 7.46-8.48 (m, 8H, Ar-H).

Anal. Calcd. for $C_{20}H_{18}ClN_5$: C, 66.00; H, 4.99; N, 19.25. Found: C, 65.96; H, 5.08; N, 19.17.

5-Alkoxy-3-aryl-1,2,4-triazolo[4,3-*c*]quinazolines **6a-f**.

General Procedure.

Metallic sodium (50 mg) was added to the appropriate absolute alcohol (15 ml) keeping the solution cool. After all the sodium had reacted, the appropriate 3-aryl-5-chloro-1,2,4-triazolo[4,3-*c*]quinazoline (0.31 mmole) was added. The reaction mixture was allowed to stir at room temperature for 30 minutes, the product was collected by filtration, air-dried, and recrystallized from the appropriate solvent. For yield, melting points, analytical and ^{1}H-nmr data see (Table 3).

3-(4-Chlorophenyl)-5,6-dihydro-5-oxo-1,2,4-triazolo[4,3-*c*]quinazoline **9**.

Method A.

Compound **9** was prepared from **3h** employing the same general procedure used for the preparation of compounds **4** except that the reaction mixture was poured into 2 *N* sodium hydroxide instead of 0.5 *N* sodium hydroxide, yield 75%, mp >340°; ^{1}H-nmr (DMSO-d_6): 7.32-8.32 (m, 8H, Ar-H), 12.32 (s, 1H, NH exchangeable with deuterium oxide); ir (potassium bromide): 3121 (NH), 1750 (C=O) cm^{-1}.

Anal. Calcd. for $C_{15}H_9ClN_4O$: C, 60.69; H, 3.05; N, 18.89. Found: C, 60.61; H, 3.09; N, 18.80.

Method B.

Compound **9** was also prepared by heating **4h** with 2 *N* sodium hydroxide at reflux for 1 hour. Compound **9** was not isolated but by tlc, compound **9** co-chromatographed in 3 different solvent systems with an authentic sample. It appeared, however that the major product was unreacted starting material.

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