Amidinoyl Isothiocyanates in the Synthesis of Condensed Quinazolines Preparation of 3-Aryl-9-chloro-5-morpholino[1,2,4]triazolo-[4,3-*c*]quinazolines and Their [1,5-*c*] Isomers

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Some 3-aryl-9-chloro-5-morpholino[1,2,4]triazolo[4,3-*c*]quinazolines were prepared by oxidative cyclization of corresponding arylhydrazones. The isomerization of these condensed [1,2,4]triazolo[4,3-*c*] derivatives to the [1,5-*c*] isomers was observed. The IR and ^{1}H NMR spectra of final products are presented.

Several biological activities have been attributed to the quinazoline derivatives. They have been found to exhibit pesticidal, anti-inflammatory, herbicidal, analgesic, CNS-depressant, and various other activities [1, 2]. Triazole derivatives have widely ranging activities [3].

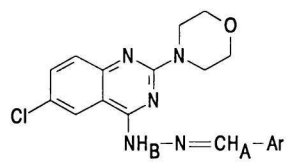
Combining two known biologically active moieties, [1,2,4]triazole and quinazoline, we have arrived at a series of [1,2,4]triazolo[4,3-*c*]quinazolines with the hope that the known activities might add up, potentiate or merge into a novel type of activity. In our previous papers the preparation and physicochemical properties of [1,2,4]triazolo[4,3-*c*]quinazolines without a substituent at the triazole skeleton and with secondary amino group at the pyrimidine ring, as well as of 3-aryl-5,9-disubstituted derivatives have already been reported [4—6].

This contribution describes the synthesis of 5,9-disubstituted [1,2,4]triazolo[4,3-*c*]quinazolines with various aryl and heteroaryl group, respectively, at the triazole ring in position 3.

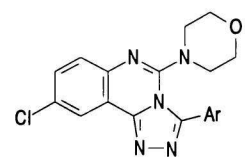
Quinazoline skeleton was built up of an open-chain precursor — amidinoyl isothiocyanate, which in thermal isomerization furnished the corresponding (3*H*)-quinazoline-4-thione [7]. The subsequent treatment with hydrazine hydrate effected the conversion of the mentioned thione to 6-chloro-4-hydrazino-2-morpholinoquinazoline. This in turn has been converted by reaction with aromatic or heteroaromatic aldehyde to the corresponding arylcarbaldehyde 4-quinazolylhydrazones *I* — starting compounds for the oxidative cyclization. This cyclization leading to 3-aryl-9-chloro-5-morpholino[1,2,4]triazolo[4,3-*c*]quinazolines *II* was effected by the method described by *Stanovnik et al.* [8] using bromine in acetic acid. During this cyclization, isomerization of [4,3-*c*] derivatives to the [1,5-*c*] isomers was observed.

Isomerization in ring-fused [1,2,4]triazoles induced by acid, base or heat has been reported for several of these ring systems, especially for the pyrimidines [9—11]. A particularly facile isomerization was observed of the [1,2,4]triazolo[4,3-*c*]quinazoline system, substituted in position 2 with alkyl or aryl group [12]. It was found that this isomerization, which is a variation of Dimroth rearrangement, depends on the nature of these substituents.

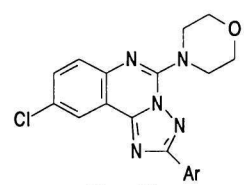
In our case, substituted arylcarbaldehyde 2-morpholino-7-chloro-4-quinazolylhydrazones *I* underwent ring closure in the presence of acetic acid, bromine, and sodium acetate without isomerization and only [1,2,4]triazolo[4,3-*c*]quinazolines *II* were isolated. Isomerization of obtained products *II* to the isomeric [1,5-*c*] system *III* was readily effected by their reflux in acetic acid or also by the prolongation of reaction



Ia—Ig



IIa—IIg



IIIa—IIIg

Aryl

a	Phenyl
b	2-Nitrophenyl
c	4-Nitrophenyl
d	5-Nitro-2-furyl
e	5-Methoxycarbonyl-2-furyl
f	5-Phenylsulfonyl-2-furyl
g	5-Nitro-2-thienyl

Table 1. Characterization of the Prepared Compounds

Compound	Formula M_r	w_i(calc.)/% w_i(found)/% C	H	N	Yield/%	M.p./°C
Ia	$C_{19}H_{18}ClN_5O$ 367.5	62.00 61.78	4.90 4.89	19.04 18.76	76	181—183
Ib	$C_{19}H_{17}ClN_5O_3$ 412.5	55.30 55.55	4.12 4.20	20.04 20.09	90	232—235
Ic	$C_{19}H_{17}ClN_6O_3$ 412.5	55.30 54.96	4.12 4.08	20.04 20.11	93	258—261
Id	$C_{17}H_{15}ClN_6O_4$ 402.5	50.70 50.38	3.70 4.08	20.90 20.85	87	225—227
Ie	$C_{19}H_{18}ClN_5O_4$ 415.5	55.00 54.89	4.30 4.45	16.80 16.99	52	241—243
If	$C_{23}H_{20}ClN_5O_4S$ 497.5	55.40 55.34	4.00 3.95	14.00 14.36	89	223—225
Ig	$C_{17}H_{15}ClN_5O_3S$ 418.8	48.74 48.35	3.60 3.84	18.73 18.71	72	234—238
IIa	$C_{19}H_{16}ClN_5O$ 365.5	65.20 64.89	4.60 4.32	20.00 19.68	94	289—291
IIb	$C_{19}H_{15}ClN_6O_3$ 410.5	55.50 54.84	3.70 3.61	20.50 20.38	97	239—241
IIc	$C_{19}H_{15}ClN_6O_3$ 410.5	55.50 54.83	3.70 3.54	20.50 20.34	96	278—280
IId	$C_{17}H_{13}ClN_6O_4$ 400.5	50.90 50.81	3.20 3.32	21.00 20.92	94	233—235
IIe	$C_{19}H_{16}ClN_5O_4$ 413.5	55.10 55.07	3.90 3.87	16.90 16.72	97	225—228
IIf	$C_{23}H_{18}ClN_5O_4S$ 495.5	55.70 55.49	3.60 3.76	14.10 13.98	95	221—223
IIg	$C_{17}H_{13}ClN_6O_3S$ 416.8	48.98 48.48	3.14 3.07	20.16 20.24	89	190—192
IIIa	$C_{19}H_{16}ClN_5O$ 365.5	65.20 64.93	4.60 4.53	20.00 19.82	95	211—213
IIIb	$C_{19}H_{15}ClN_6O_3$ 410.5	55.50 55.30	3.70 3.63	20.50 20.39	90	213—215
IIIc	$C_{19}H_{15}ClN_6O_3$ 410.5	55.50 55.29	3.70 3.61	20.50 20.38	97	240—246
IIId	$C_{17}H_{13}ClN_6O$ 400.5	50.90 50.73	3.20 3.18	21.50 21.68	93	199—201
IIIe	$C_{19}H_{16}ClN_5O_4$ 413.5	55.10 54.98	3.90 3.82	16.90 16.76	97	183—185
IIIf	$C_{23}H_{18}ClN_5O_4S$ 495.5	55.70 55.51	3.60 3.51	14.10 13.89	96	163—165
IIIg	$C_{17}H_{13}ClN_6O_3S$ 416.8	48.98 48.69	3.14 3.09	20.16 19.93	88	175—178

time of oxidative cyclization from 1 h to 48 h (see Experimental). Different melting point for [4,3-*c*] isomers and [1,5-*c*] isomers, respectively, as well as their R_f values of TLC, and different NMR chemical shifts of H-10 can be regarded as evidence of two isomers, to which we assigned the structures according to Ref. [12].

The infrared spectra of compounds *II* and *III* show a very intense absorption band at $\tilde{\nu}$ = 1615 cm^{-1} associated with ν(C=N) vibrations. The high intensity and complexity of this band indicates that it cumulates the C=N vibrations of both the [1,2,4]triazole and pyrimidine rings. In the ^1H NMR spectra of compounds *II* and *III* the protons H-3 and H-4 of the furan rings as well as the thiophene rings could be well identified in the aromatic multiplet according to different coupling constants, $J(3,4)_{Fu}$ = 3.5—3.9 Hz, $J(3,4)_{Th}$ = 3.7—4.3 Hz.

EXPERIMENTAL

Infrared spectra (KBr discs) were taken with a Philips PU-9800 FTIR spectrometer. ^1H NMR spectra of hexadeuterodimethyl sulfoxide solutions containing tetramethylsilane as an internal standard were recorded with Varian VXR-300 (300 MHz) spectrometer.

Preparation of the starting 6-chloro-2-morpholino-4-hydrazinoquinazoline was reported in Ref. [5].

Characterization of the prepared compounds and their spectral data are given in Tables 1 and 2.

Arylcarbaldehyde-6-chloro-2-morpholino-4-quinazolylhydrazones (*Ia—Ig*)

6-Chloro-2-morpholino-4-hydrazinoquinazoline (1.7 g; 5 mmol) and arylcarbaldehyde (5 mmol) in

Table 2. Spectral Data of Compounds *I—III*

Compound	IR, $\tilde{\nu}$/cm^{-1}			^{1}H NMR, δ				
	ν(C=N)	ν(N—H)	Other	H_A s	H_B s	H_{arom} m	H_{Mn} m	H-3/H-4 d
Ia	1616	3304		8.48	11.45	8.37—7.25	3.73 3.67	
Ib	1616	3296	1520[a] 1347[b]	8.49	11.68	8.43—7.25	3.73 3.67	
Ic	1616	3350	1518[a] 1334[b]	8.51	11.65	8.37—7.33	3.97 3.79	
Id	1616	3288	1532[a] 1346[b]	8.25	11.58	8.02—7.18	3.62 3.50	7.53 6.90
Ie	1616	3280	1724[e]	8.38	11.53	8.11—7.25	3.71 3.60	7.18 6.88
If	1616	3136	1350[c] 1150[d]	8.32	11.55	7.85—7.20	3.63 3 52	7.26 6.90
Ig	1614	3314	1547[a] 1367[b]	9.92	11.92	8.61—7.70	3.65 3.77	7.51 8.13
IIa	1632			8.74[f]		8.62—7.52	3.78 3.64	
IIb	1616		1520[a] 1347[b]	9.04[f]		8.46—7.84	3.83 3.78	
IIc	1616		1532[a] 1349[b]	8.74[f]		8.40—7.84	3.82 3.07	
IId	1616		1540[a] 1349[b]	8.88[f]		8.67—7.53	3.71 3.25	7.62 7.42
IIe	1612		1736[e]	8.59[f]		8.42—7.26	3.90 3.77	7.62 7.27
IIf	1612		1360[c] 1152[d]	8.84[f]		8.82—7.69	3.94 3.84	7.61 7.28
IIg	1609		1514[a] 1358[b]	8.86[f]		8.48—7.12	3.85 3.68	7.79 7.72
IIIa	1638			8.65[f]		8.37—7.56	3.43 3.10	
IIIb	1612		1527[a] 1352[b]	8.58[f]		8.33—7.56	3.83 3.78	
IIIc	1626		1529[a] 1358[b]	8.66[f]		8.07—7.33	3.84 3.36	
IIId	1635		1535[a] 1332[b]	8.71[f]		8.67—7.53	3.85 3.39	7.48 7.32
IIIe	1620		1736[e]	8.44[f]		7.84—7.72	3.85 3.67	7.57 7.33
IIIf	1633		1385[c] 1143[d]	8.66[f]		8.11—7.29	3.86 3.78	7.42 7.28
IIIg	1635		1535[a] 1332[b]	8.42[f]		8.40—7.78	3.85 3.68	8.05 8.03

Mo — morpholine, *a*) $\nu_{as}(NO_2)$, *b*) $\nu_s(NO_2)$, *c*) $\nu_{as}(SO_2)$, *d*) $\nu_s(SO_2)$, *e*) ν(CO), *f*) H-10.

20 cm^3 of ethanol were refluxed for 1 h. The solution was then moderately cooled: after addition of 20 cm^3 of cold water the separated precipitate was filtered off and crystallized from dimethylformamide.

3-Aryl-9-chloro-5-morpholino[1,2,4]triazolo[4,3-*c*]-quinazolines (*IIa—IIg*)

Sodium acetate (0.5 g) was added to the stirred solution of the substituted hydrazone (2 mmol) in acetic acid (20 cm^3) at room temperature to which bromine (0.32 g; 2 mmol) in acetic acid (10 cm^3) was introduced dropwise. The reaction went through during 1 h: the mixture was then poured on crushed ice (100 g), the separated precipitate was filtered off and crystallized from ethanol—dimethylformamide.

5-Aryl-8-chloro-2-morpholino[1,2,4]triazolo[1,5-*c*]-quinazolines (*IIIa—IIIg*)

Method A. When in the above-mentioned method of oxidative cyclization the reaction went through during 48 h, the substituted [1,2,4]triazolo[1,5-*c*]quinazoline derivatives were formed.

Method B. 3-Aryl-9-chloro-5-morpholino[1,2,4]triazolo[4,3-*c*]quinazolines (2 mmol) in acetic acid (30 cm^3) were refluxed for 48 h. Then acetic acid was removed under reduced pressure. The raw product was recrystallized from dimethylformamide.

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Dihydropyrans from the Heterodienic Reaction of 5-Arylidenerhodanine Derivatives with Isoprene

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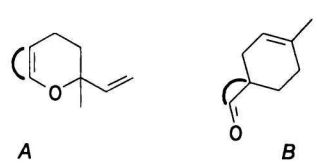
The reaction of α,β-unsaturated carbonyl system in 5-arylidenerhodanines with isoprene furnishes, in a stereoselective heterodienic reaction, the dihydropyran adducts rather than spirocyclohexene adducts. The reaction is accelerated by using aluminium chloride catalyst.

Hetero Diels—Alder reaction with inverse electron demand, pericyclic ($4\pi + 2\pi$) cycloaddition, is one of the most important methods for construction of the polyfunctionalized cyclic compounds. Therefore, various heterodienes [1—3] and heterodienophiles [4, 5] are developed for this purpose.

The ($4\pi + 2\pi$) cycloaddition reaction between a diene and α,β-unsaturated carbonyl compound leads either to heterodienic adduct A (dihydropyran) from the heterodiene pathway or to dienic adduct B (cyclohexenes) from the Diels—Alder pathway [6—10] (Scheme 1).



A B

Scheme 1

In the heterocyclic field it was found that the Diels—Alder pathway is always preferred to the heterodiene pathway. On the other hand, the heterodiene pathway is more favourable in terms of FMO's theory [4, 5, 11].

Hereafter the results of the reaction of isoprene (*II*) with 5-arylidenerhodanine derivatives *Ia—Id* as an α,β-unsaturated carbonyl system attached to heterocyclic ring are reported.

The thermal cycloaddition reactions between 5-arylidenerhodanines *Ia—Id*, as heterodienes and *II* lead to the corresponding aryl 2,3-dihydropyrano[2,3-*b*]rhodanine derivatives *IIIa—IIId* by means of heterodiene pathway [11]. The reaction is carried out in benzene under nitrogen and in the presence of few crystals of hydroquinone. The reaction under these conditions provides a poor yield of the cycloadducts *IIIa—IIId* in long time (several days). To avoid these problems a variety of modified methods are tested. Lewis acid [12—15] and certain lanthanides complexes [16] extremely help in promoting the reaction of labile dienes at low temperature. Remarkable acceleration of enone—diene interaction by aluminium chloride was first reported by *Yates* and *Eaton* [17].

It is known that Lewis acid affects not only the rate but also the regioisomerism and stereoisomerism of the Diels—Alder reaction. In addition, *Ismail* and *Hoffmann* [18] found that crotonoyl cyanide and 4-methyl-1,3-pentadiene, which did not react under thermal conditions, gave the heterodienic adduct under $AlCl_3$ catalysis.