

Imidoyl isothiocyanates in the synthesis of condensed quinazolines

Preparation of 3-aryl-5-phenyl-*s*-triazolo[4,3-*c*]quinazolines

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N-Phenylbenzimidoyl isothiocyanate easily isomerizes to 2-phenyl-3*H*-quinazoline-4-thione, which upon treatment with hydrazine hydrate converts to 2-phenyl-4-hydrazinoquinazoline. This in turn has been converted by standard procedures to the corresponding 2-phenyl-4-quinazolylhydrazones — starting compounds for the oxidative cyclization, leading to 3-aryl-5-phenyl-*s*-triazolo[4,3-*c*]quinazolines.

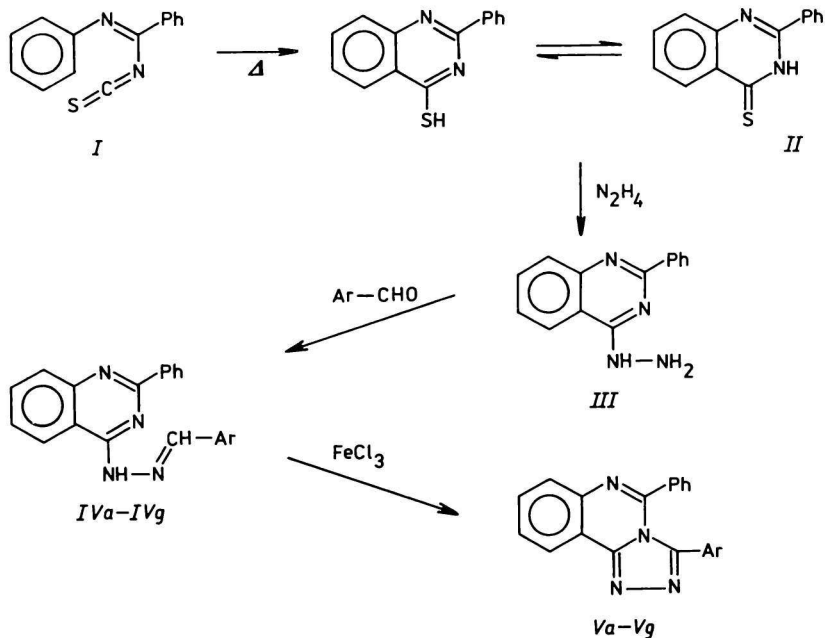
Изотиоцианат *N*-фенилбензимидаоила легко изомеризуется в 2-фенил-3*H*-хиназолин-4-тион, который под действием гидрата гидразина превращается в 2-фенил-4-гидразинохиназолин. Последний, в свою очередь, был путем стандартных процедур превращен в соответствующие 2-фенил-4-хиназолилгидразоны — исходные соединения для окислительной циклизации, ведущей к образованию 3-арил-5-фенил-*s*-триазоло[4,3-*c*]хиназолинов.

A general approach to *s*-triazoloquinazolines involves reaction of the corresponding hydrazinoquinazolines with aliphatic carboxylic acids or with their ortho esters [1—4]. Triazoloquinazolines, carrying an aryl substituent at both triazole and pyrimidine ring have not been described so far.

In 1961 *Huisgen* and coworkers obtained 3-phenyl-*s*-triazolo[4,3-*c*]quinazoline as a result of heating of 4-(3-phenyltetrazolyl)quinazoline [5]. *Sidhu* and *Rao* prepared identical product *via* a cyclization of 4-(benzoylhydrazino)quinazoline with POCl₃ as well as by cyclization of the corresponding hydrazone [6].

Motivated by the well known biological activity of *s*-triazoles [7], we have concentrated on the preparation of some 3-aryl-5-phenyl-*s*-triazolo[4,3-*c*]quinazolines (*Va*—*Vg*). Our approach was based on an oxidative cyclization of the corresponding arylhydrazones (Scheme 1).

As the principal building block of the quinazoline skeleton easily accessible *N*-phenylbenzimidoyl isothiocyanate (*I*) has been used, the thermal isomerization of which furnished spontaneously 2-phenyl-3*H*-quinazoline-4-thione (*II*). Easy enolization of the thioamide group of *II* enables direct substitution of the



Scheme 1

—SH group by a hydrazino group to give derivatives *III*. Condensation of 2-phenyl-4-hydrazinoquinoline with aromatic aldehydes furnished seven aryl aldehyde 2-phenyl-4-quinazolylylhydrazones (*IVa—IVg*) in excellent yields (Table 1).

It is known that 2-azaheterocyclic hydrazones can be transformed by oxidative cyclization to the condensed *s*-triazoles. Thus condensed triazoles derived from 2-pyridyl-, 2-quinolyl-, and 1-isoquinolylarylhydrazones have been prepared by this method [8, 9].

In our experiments, oxidative cyclizations were performed by using $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ or nitrobenzene as oxidants. It turned out that iron(III) chloride worked best with quinazolylylhydrazones of the type *IVb—IVf*, whereas nitro- and dimethylamino-substituted derivatives *IVa* and *IVg* gave better yields of cycliza-

Table 1

Physical constants and characteristic IR spectral bands of compounds *IVa*—*IVg*

Compound	Formula M_r	$w_i(\text{calc.})/\%$ $w_i(\text{found})/\%$			Yield %	M.p. °C	$\tilde{\nu}/\text{cm}^{-1}$				
		C	H	N			$\nu(\text{NH})$	$\nu(\text{C}=\text{N})$	$\nu(\text{C}-\text{N})$	Other	
<i>IVa</i>	$\text{C}_{23}\text{H}_{21}\text{N}_5$	75.18	5.76	19.06	98	221—222	3375	1627	1366	1475	} $\delta(\text{CH}_3)$
	367.44	75.30	5.49	19.19						1465	
<i>IVb</i>	$\text{C}_{22}\text{H}_{18}\text{N}_4\text{O}$	74.56	5.12	15.80	79	142—143	3390	1627	1373	1465	} $\delta(\text{CH}_3)$
	354.40	74.38	5.03	15.93						1604	
<i>IVc</i>	$\text{C}_{22}\text{H}_{18}\text{N}_4$	77.08	5.36	16.56	98	89—90	3370	1628	1337	1252	} $\nu(\text{C}-\text{O})$
	338.40	77.19	5.40	16.61						1465	
<i>IVd</i>	$\text{C}_{21}\text{H}_{16}\text{N}_4$	77.76	4.76	17.27	86	132—133	3303	1609	1364		
	324.38	77.54	4.59	17.37							
<i>IVe</i>	$\text{C}_{21}\text{H}_{15}\text{N}_4\text{Cl}$	70.29	4.21	15.61	97	171—173	3370	1626	1376		
	358.83	70.13	4.11	15.79						1603	
<i>IVf</i>	$\text{C}_{21}\text{H}_{15}\text{N}_5\text{O}_2$	68.28	4.09	18.96	98	191—193	3380	1623	1363	1539	} $\nu_{\text{as}}(\text{NO}_2)$
	369.38	68.09	4.16	18.87						1603	
<i>IVg</i>	$\text{C}_{19}\text{H}_{14}\text{N}_4\text{O}$	72.59	4.49	17.82	98	142—143	3370	1635	1368	992	} $\nu(\text{C}-\text{O})$
	314.33	72.42	4.53	17.90						1602	

tion with nitrobenzene as oxidant. Both reagents however gave very good yields of 3-aryl-5-phenyl-*s*-triazolo[4,3-*c*]quinazolines (Table 2).

In their infrared spectra the prepared *s*-triazolo[4,3-*c*]quinazolines displayed a complex band at $\tilde{\nu} = 1600\text{--}1635\text{ cm}^{-1}$; the band incorporated two distinct maxima and has been ascribed to $\nu(\text{C}=\text{N})$ vibrations. The observed multiplicity of the band is probably caused by the nonequivalency of the $\text{C}=\text{N}$ bonds, present in the bicyclic skeleton. Comparison of the bands corresponding to the vibrations $\nu(\text{C}=\text{N})$ of compounds *IVa*—*IVg* and *Va*—*Vg* revealed a shift of the higher of the two maxima of *Va*—*Vc* to lower wavenumbers, due to the donor effect of the 3-aryl substituent. Compounds *Vd*—*Vg*, on the other hand, where no such effect was possible, displayed the maximum shifted to higher wavenumbers than the corresponding quinazolyhydrazones *IVd*—*IVg* (Tables 1 and 2).

Cyclic structure, suggested for compounds *Va*—*Vg*, has been corroborated by the fact that their IR spectra failed to show $\nu(\text{NH})$ vibrations, corresponding to a hydrazone.

When heated to their melting temperatures or subjected to acidic or basic environment, *s*-triazolo[4,3-*c*]quinazolines isomerized to *s*-triazolo[1,5-*c*]quinazolines [3]. Study of this phenomenon revealed that the isomerization resembled the Dimroth rearrangement and could not be observed, when the pyrimidine ring carried a phenyl or when reactions were carried out in neutral media.

In order to suppress the formation of the unwanted [1,5-*c*] isomer only phenyl-substituted 4-quinazolyhydrazones were used and the cyclization was carried out at relatively low temperature of the boiling methanol or water. In addition, only oxidants not requiring extreme acidic or basic conditions, were utilized.

Experimental

Infrared spectra were taken with a Perkin—Elmer spectrophotometer, model 783, of KBr discs. Starting *N*-phenylbenzimidoyl isothiocyanate (*I*) was prepared from the corresponding imidoyl chloride according to [10], its isomer (*II*) was obtained in almost quantitative yield by refluxing *I* in xylene [10]. 2-Phenyl-4-hydrazinoquinazoline (*III*) was prepared by the hydrazinolysis of *II* with 32 % hydrazine hydrate in methanol in a manner described in [2].

Aryl aldehyde 2-phenyl-4-quinazolyhydrazones (IVa—IVg)

A solution, prepared from *III* (1.2 g; 0.005 mol) and the corresponding aryl aldehyde (0.005 mol) in 20 cm³ of ethanol, was refluxed for 1 h at water bath. The product started

Table 2

Physical constants and characteristic IR spectral bands of the prepared 3-aryl-5-phenyl-*s*-triazolo[4,3-*c*]quinazolines *Va*—*Vg*

Compound	Formula M_r	$w_i(\text{calc.})/\%$ $w_i(\text{found})/\%$			Yield %	M.p. °C	$\tilde{\nu}_i/\text{cm}^{-1}$		
		C	H	N			$\nu(\text{C}=\text{N})$	$\nu(\text{C}-\text{N})$	Other
<i>Va</i>	$\text{C}_{23}\text{H}_{19}\text{N}_5$	75.59	5.24	19.17	70	178—179	1613	1370	1465 } $\delta(\text{CH}_3)$ 1350 }
	365.81	75.49	5.27	19.30			1590		
<i>Vb</i>	$\text{C}_{22}\text{H}_{16}\text{N}_4\text{O}$	74.98	4.58	15.90	85	191—193	1625	1374	1478 } $\delta(\text{CH}_3)$ 1453 }
	352.40	74.79	4.47	15.83			1607		
<i>Vc</i>	$\text{C}_{22}\text{H}_{16}\text{N}_4$	78.56	4.79	16.66	79	204—205	1624	1375	1252 } $\nu(\text{C}-\text{O})$ 1474 } $\delta(\text{CH}_3)$ 1450 }
	336.40	78.39	4.60	16.51			1616		
<i>Vd</i>	$\text{C}_{21}\text{H}_{14}\text{N}_4$	78.24	4.38	17.38	82	187—189	1655	1330	
	322.37	78.11	4.19	17.41			1628		
<i>Ve</i>	$\text{C}_{21}\text{H}_{13}\text{N}_4\text{Cl}$	70.69	3.67	15.70	78	240—241	1628	1330	
	356.81	70.62	3.65	15.75			1602		
<i>Vf</i>	$\text{C}_{21}\text{H}_{13}\text{N}_5\text{O}_2$	68.61	3.56	19.02	88	278	—	1520	$\nu_{\text{as}}(\text{NO}_2)$ $\nu_{\text{s}}(\text{NO}_2)$
	367.36	68.51	3.40	19.19		(decomp.)			
<i>Vg</i>	$\text{C}_{19}\text{H}_{12}\text{N}_4\text{O}$	73.06	3.87	17.94	86	209—210	1623	1365	1003 } $\nu(\text{C}-\text{O})$
	312.31	72.96	3.59	18.01			1603		

to precipitate already during the reflux, the precipitation was completed by the addition of 20 cm³ of cold water. Pure quinazolyhydrazones *IVa—IVg* were obtained after crystallization from ethanol. Physical data of compounds *IV* are given in Table 1.

3-Aryl-5-phenyl-s-triazolo[4,3-c]quinazolines (Va—Vg)

a) Oxidative cyclization by FeCl₃ · 6H₂O

FeCl₃ · 6H₂O (1.35 g; 0.005 mol) dissolved in 25 cm³ of methanol was added, three portions in 15 min intervals, to the refluxing methanolic solution (30 cm³), containing the corresponding quinazolyhydrazone *IVb—IVf* (0.001 mol). The mixture was heated for another 2 h, methanol was then evaporated almost to dryness and 5 cm³ of water was added. The mixture was stirred and its pH adjusted to neutral by ammonia. The aqueous layer was then decanted and the rest washed repeatedly with water. Crystallization from ethanol gave pure triazolo[4,3-*c*]quinazolines *Vb—Vf* in yields, given in Table 2.

b) Oxidative cyclization by nitrobenzene

The mixture of quinazolyhydrazone *IVa* or *IVg* (0.002 mol), nitrobenzene (3 cm³) and water (15 cm³) was refluxed for 2 h at oil bath. When the mixture has cooled down to room temperature the supernatant liquid was decanted and the solid rest mixed with small amount of water, filtered and dried. Pure triazolo[4,3-*c*]quinazolines *Va*, *Vg* were obtained by crystallization from ethanol (Table 2).

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