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Amidinoyl Isothiocyanates in the Synthesis of Condensed Heterocycles: Tetrazolo-azidoazomethine Tautomerism in Substituted Tetrazolo[1,5-c]quinazolines

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Summary. Isomerization of available amidinoyl isothiocyanates has been elaborated into a viable synthetic approach to sec. amine substituted tetrazolo[1,5-c]quinazolines. The method involves isomerization to quinazoline-4-thiones, their hydrazinolysis, followed by a nitrosation to give the title tetrazoloquinazolines. Infrared spectra of both solid samples and their solutions were used to assess the stability of the tetrazole ring.

Keywords. Amidinoylisothiocyanate; Tetrazolo-azidoazomethine tautomerism; Tetrazolo[1,5-c]quinazolines.

Amidinoylisothiocyanate als Bausteine in der Synthese von kondensierten Heterozyklen. Tetrazolo-azidoazomethine Tautomerie von substituierten Tetrazolo[1,5-c]chinazolinen

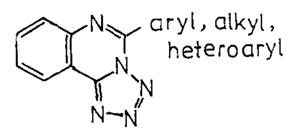
Zusammenfassung. Die Isomerisierung von gut zugänglichen Amidinoylisothiocyanaten wurde zu einer synthetischen Methode für die durch sek. Amine substituierten Tetrazolo[1,5-c]chinazoline entwickelt. Die Methode beinhaltet Isomerisierung von Chinazolin-4-thionen, deren Hydrazinolyse und anschließende Nitrosierung. Die Stabilität des Tetrazolringes in den Tetrazolochinazolinen wurde aus den Infrarotspektren abgeschätzt.

Introduction

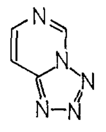
An azide group attached to a carbon-nitrogen double bond of a heterocyclic ring can in principle exist in both cyclic and acyclic form; usually an equilibrium of these two forms is established, namely azido-tetrazolo tautomerism (compare formulas in Table 1).

Such equilibria have been found to accompany solution or melting of azaheterocycles with an annelated tetrazole ring, whereby the character of the annelated heterocycle, solvent polarity and temperature account for the principal factors affecting the equilibrium [1, 2].

Studies on 5-aryl and 5-alkyl substituted tetrazolo[1,5-c]-quinazolines (**1**) revealed that both in the crystalline state and in solution only the tetrazole form was present [3–5]. Tetrazolo-[1,5-c]pyrimidines (**2**) behaved in a similar manner, except that the introduction of donor substituents in position 5 or 7 of the pyrimidine ring facilitated the isomerization and hence the formation of the azido form [6].



1



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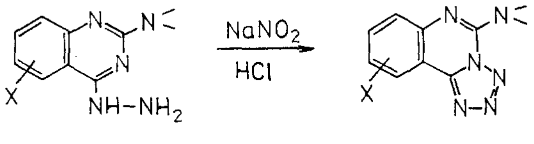


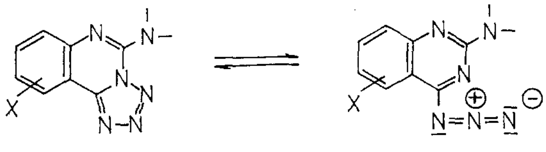
3 a-i **4 a-i**

Results and Discussion

In order to gain insight into the behaviour of an annelated tetrazole ring we have synthesized nine substituted tetrazolo-[1,5-c]quinazolines (**4 a–i**), which in the position 5 carry groups various donor qualities. For this purpose secondary amines were chosen in which the basicity of the donor effect varied in a wide range of pK_B value (pK_B2–10). The donor effect was further enhanced by the presence of a halogen atom or a methyl group at the aromatic ring.

The target tetrazoloquinazolines were prepared by a procedure described in Ref. [7]; the procedure involves an isomerization of amidinoyl isothiocyanates to quinazoline-4-thiones, which in turn were converted in good yields to 4-hydrazinoquinazolines **3 a–i**. On diazotization of the latter we obtained the target tetrazoloquinazolines **4 a–i** as colourless crystalline compounds. Prior to the measurement

Table 1. Characteristic IR vibrations of the substituted tetrazolo[1,5-c]quinazolines **4** in solid state and solution



4 a-i

Compound **4**	*X*	$\mathrm{N{-}\overset{|}{N}{-}}$	KBr (cm^{-1}) $\nu_{C=N}$	ν_{NNN}	$CHCl_3$ (cm^{-1}) $\nu_{C=N}$	ν_{NNN}
a	H	*Mo*	1 620	–	1 613	2 127 s
b	H	*DFA*	1 613	–	1 613	2 120 s
c	9-Cl	*Mo*	1 626	–	1 620	2 127 s
d	9-Cl	*Pi*	1 635	2 137 w	1 631	2 141 w
e	9-Cl	*DE*	1 620	2 140 m	1 625	2 140 s
f	9-Cl	*NPP*	1 626	–	1 601	2 139 m
g	9-Br	*Mo*	1 620	2 125 vw	1 620	2 126 m
h	9-CH_3	*Mo*	1 620	–	1 613	2 126 s
i	10-CH_3	*Mo*	1 615	2 120 vw	1 610	2 120 s

Table 2. Experimental Data for the tetrazolo[1,5-c]quinazolines **4a–i**

Compound 4	Mol. formula[a]	*M*	*X*	N[c]	M.p., °C	Yield, %
a	$C_{12}H_{12}N_6O$	256.25	H	*Mo*	*150–152*[b]	47
b	$C_{20}H_{14}N_6$	338.36	H	*DFA*	161–162	37
c	$C_{12}H_{11}N_6OCl$	290.69	9-Cl	*Mo*	112–114	59
d	$C_{13}H_{13}N_6Cl$	288.72	9-Cl	*Pi*	168–172	35
e	$C_{12}H_{13}N_6Cl$	276.71	9-Cl	*DE*	116–119	53
f	$C_{18}H_{16}N_7Cl$	365.79	9-Cl	*NPP*	230–238	77
g	$C_{12}H_{11}N_6OBr$	335.14	9-Br	*Mo*	126–130	56
h	$C_{13}H_{14}N_6O$	270.28	9-CH_3	*Mo*	169–170	60
i	$C_{13}H_{14}N_6O$	270.28	10-CH_3	*Mo*	96–98	45

[a] All compounds gave satisfactory elemental analyses (C, H, N)

[b] Ref. [8], m.p. 159–160°C

[c] >N: *Mo*—morpholine; *Pi*—piperidine; *DE*—diethylamine; *DFA*—diphenylamine; *NPP*—4-phenylpiperazine

of infrared spectra, compounds 4 were crystallized from ethanol. The results of IR measurements are presented in Table 1.

An inspection of Table 1 shows that all studied compounds display in their IR spectra in solution an absorption band corresponding to asymmetric valence vibrations of the azido group ν_{as}NNN. Moreover, the high intensity (60–80%) of this band relative to the intensity of the most intensive band in the spectrum ($\nu_{C=N}$ 1 620 cm^{-1}) testifies the high content of the azide in the mixure. Although vibrations belonging to the tetrazole ring (found at about 1 100 cm^{-1}) are overlapped by other vibrations, they can unequivocally be identified and confirm the presence of the tetrazole ring. The intensity of azido vibrations correlates well with the donor properties (basicity) of substituents $DE \gg Pi > Mo > NPP \gg DFA$, a fact that is in accord with earlier observations for tetrazolopyrimidines [6] and tetrazoloquinazolines [8].

Interestingly, the spectra of solid samples of compounds with strong donor substituents (**4e, d, g, i**) also showed a fairly high (30–40%) content of the azide form.

Infrared spectra were repeatedly taken after a period of several weeks (KBr discs); the spectra showed in all cases a more or less intense azide peak (10–40% increase in intensity). Most samples also showed a decrease in the melting point by 5–10 deg. After the samples were recrystallized from ethanol, azide bands vanished in all but those carrying strong donor substituents (**4e, d, g, i**).

Even though no quantitative data on the tetrazolo-azidoazomethine tautomerism in the title tetrazoloquinazolines were obtained, there is enough evidence for the existence of such tautomerism in tetrazolo[1,5-c]quinazolines, substituted by donor substituents at position 5, existing in chloroform solutions.

Experimental

Infrared spectra of saturated chloroform solutions or KBr discs were taken with a double-beam Zeiss Jena spectrophotometer, model M80.

The preparation of starting 4-hydrazinoquinazolines was described in Ref. [7].

Diazotization Procedure

To a suspension of 0.01 mol of 4-hydrazinoquinazolines (**4 a–i**) in 15 ml water and 3 ml 2 *N* hydrochloric acid, stirred at laboratory temperature, was dropwise added a solution of 0.7 g (0.01 mol) of sodium nitrite in 5 ml H_2O. After the mixture was stirred for another hour it was separated, the solid part filtered off and recrystallized from ethanol. Reaction yields and product characteristics are given in Table 2.

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