

Preparation of substituted 2-phenyl-4-anilinoquinazolines through imidoilcarbodiimides

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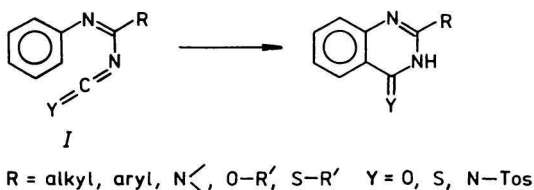
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Preparation of some imidoilthioureas by the reaction of the corresponding imidoil isothiocyanates with anilines has been described. The obtained thioureas, after conversion to unstable imidoilcarbodiimides, served as starting compounds for the preparation of 2-phenyl-4-anilinoquinazolines.

Описано получение некоторых имидоилтиомочевин посредством реакции соответствующих имидоилизотиоцианатов с анилинами. Полученные тиомочевины, после превращения их в нестабильные имидоилкарбодиимиды, служили в качестве исходных веществ для синтеза 2-фенил-4-анилинохиназолинов.

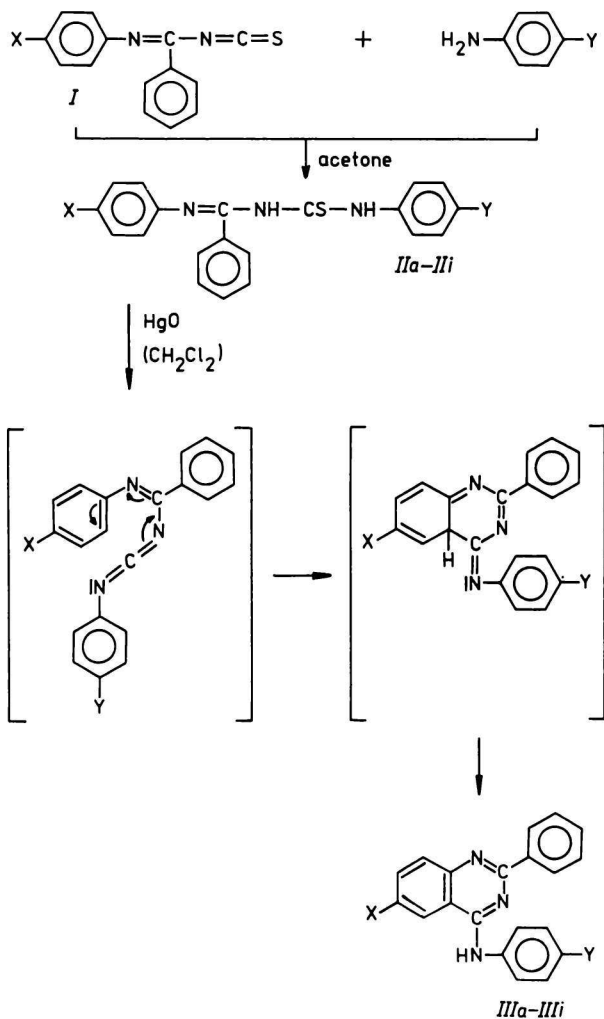
Imidoil isothiocyanates (*I*) [1—3], similarly as other imidoil heterocumulenes [4—6], readily undergo cyclization under the formation of quinazoline derivatives.



This reaction, proceeding as an intramolecular 6π -electron electrocyclic reaction under simultaneous 1,5-sigmatropic rearrangement of hydrogen, makes possible to prepare some unattainable derivatives of quinazoline without using antranilic acid [1].

It has been found that amidinoyl isothiocyanates (*I* where Y = S, R = $N<$) enter the reaction with aromatic isothiocyanates to give an unstable intermediate, amidinoylcarbodiimide, which, on spontaneous cyclization, affords 4-anilinoquinazoline substituted in the position 2 by a secondary amine [7]. In order to prepare some 2-phenyl-4-anilinoquinazolines, we carried out similar reactions with

imidoyl isothiocyanates and found that these reactions had not taken place evidently because of lower reactivity of carbimidoyl isothiocyanates when compared to amidinoyl isothiocyanates. The only obtained products were the isomers of the starting isothiocyanates, i.e. the corresponding 2-phenyl-3*H*-quinazoline-4-thiones [8]. Therefore, the desired 2-phenyl-4-anilinoquinazolines were prepared after the method illustrated on Scheme 1.



Scheme 1

By the reaction of *N*-(4-*X*-phenyl)benzimidoyl isothiocyanates (*I*) with chosen anilines the corresponding *N*¹-(*N*-phenylbenzimidoyl)-*N*²-phenylthioureas (*IIa—IIIi*) (Table 1) were prepared. Elimination of hydrogen sulfide was achieved under very gentle conditions by using yellow HgO, however, we have not succeeded in isolation of the corresponding imidoilcarbodiimides. The corresponding 2-phenyl-4-anilinoquinazolines (*IIIa—IIIi*) in about 60 mass % yield were obtained directly (Table 2).

In the infrared spectra (Table 3) characteristic absorption bands belonging to vibrations of C=N bonds of the pyrimidine ring were observed at 1620 cm⁻¹, as well as an absorption band at 3440 cm⁻¹ assigned to ν(NH) vibrations of aniline. The ultraviolet spectra of these compounds revealed three absorption bands of orderly similar intensities. The least intensive band was that appearing at the highest wavelength (partly reaching the visible region), which pointed to a possible conjugation of the quinazoline skeleton with the aromatic ring of aniline.

Goerdeler and Lohmann [9] performed similar reactions with series of imidoilthioureas. The carbodiimides were isolable in those cases only when the *N*-substituent of the imidoil isothiocyanate was a 2,6-disubstituted phenyl, *i.e.* when cyclization could not occur.

Experimental

Infrared absorption spectra of the prepared compounds were measured in saturated chloroform solutions on a double-beam UR-20 spectrophotometer (Zeiss, Jena) using NaCl cells of 0.05 cm thickness.

Electronic spectra in visible and ultraviolet regions (220—800 nm) were taken with a Specord UV VIS (Zeiss, Jena) apparatus. Methanolic solutions of compounds were measured in quartz cells of 10 mm thickness. Spectral characteristics of the final compounds are presented in Table 3.

N-Phenyl- [2], *N*-(4-chlorophenyl)- [2], and *N*-(4-tolyl)benzimidoyl isothiocyanates [10] were prepared by the reaction of the respective imidoil chlorides with KSCN in acetone according to [2].

Substituted imidoilthioureas (*IIa—IIIi*)

To the respective *N*-phenylbenzimidoyl isothiocyanate (*I*) (10 mmol) dissolved in dry acetone (50 cm³), the respective aniline (10 mmol) was added and the mixture was boiled under reflux for 30 min. On cooling of the reaction mixture or after its evaporation the respective thioureas (*II*) crystallized. They were further purified by crystallization from ethanol and used in the subsequent reaction.

Table 1

Characterization of imidoylthioureas (IIa—IIIi)

Compound	X	Y	Formula	M_r	$w_i(\text{calc.})/\%$ $w_i(\text{found})/\%$				Yield/mass %	M.p./°C
					C	H	N	Cl		
IIa	H	H	$C_{20}H_{17}N_3S$	331.09	72.49	5.13	12.69	—	60	122—124
					72.51	5.20	12.65	—		
IIb	H	CH_3	$C_{21}H_{19}N_3S$	345.09	73.02	5.51	12.18	—	50	133—134
					72.94	5.37	12.32	—		
IIc	H	Cl	$C_{20}H_{16}ClN_3S$	365.54	65.66	4.38	11.50	9.70	60	110—112
					65.44	4.45	11.55	9.58		
IId	CH_3	H	$C_{21}H_{19}N_3S$	345.09	73.02	5.51	12.18	—	70	143—145
					73.08	5.50	11.95	—		
IIe	CH_3	CH_3	$C_{22}H_{21}N_3S$	359.09	73.52	5.85	11.70	—	60	130—132
					73.34	5.90	11.78	—		
II f	CH_3	Cl	$C_{21}H_{18}ClN_3S$	379.54	66.40	4.72	11.07	9.34	65	139—142
					66.24	4.83	11.25	9.12		
II g	Cl	H	$C_{20}H_{16}ClN_3S$	365.54	65.66	4.38	11.50	9.70	70	140—143
					65.55	4.49	11.35	9.47		
II h	Cl	CH_3	$C_{21}H_{18}ClN_3S$	379.54	66.40	4.72	11.07	9.34	65	150—152
					66.25	4.54	11.26	9.39		
III i	Cl	Cl	$C_{20}H_{15}Cl_2N_3S$	399.99	60.00	3.75	10.51	17.52	50	167—170
					60.20	3.90	10.31	17.35		

Table 2

Characterization of 4-anilinoquinazolines (IIIa—IIIi)

Compound	X	Y	Formula	M_r	$w_i(\text{calc.})/\%$ $w_i(\text{found})/\%$				Yield/mass %	M.p./°C
					C	H	N	Cl		
IIIa	H	H	$C_{20}H_{15}N_3$	297.03	80.80 80.99	5.05 5.10	14.15 14.00	—	62	155—157*
IIIb	H	CH_3	$C_{21}H_{17}N_3$	311.03	81.02 81.23	5.47 5.43	13.51 13.50	—	63	159—162
IIIc	H	Cl	$C_{20}H_{14}ClN_3$	331.48	72.40 72.65	4.22 4.18	12.68 12.53	10.69 10.58	65	184—187
IIId	CH_3	CH_3	$C_{22}H_{19}N_3$	325.03	81.22 81.33	5.85 5.80	12.93 12.93	—	60	158—159
IIIe	CH_3	H	$C_{21}H_{17}N_3$	311.03	81.02 80.85	5.47 5.54	13.51 13.33	—	56	153—155
IIIf	CH_3	Cl	$C_{21}H_{16}ClN_3$	345.48	72.94 73.20	4.63 4.73	12.17 11.95	10.26 10.39	65	178—180
IIIg	Cl	Cl	$C_{20}H_{13}Cl_2N_3$	365.93	65.59 65.63	3.55 3.73	11.49 11.35	19.38 19.23	65	195—198
IIIh	Cl	H	$C_{20}H_{14}ClN_3$	331.48	72.40 72.25	4.22 4.16	12.68 12.45	10.69 10.32	60	150—152
IIIi	Cl	CH_3	$C_{21}H_{16}ClN_3$	345.48	72.94 73.10	4.63 4.50	12.17 12.13	10.26 10.14	68	177—178

* Ref. [9] gives m.p. = 152 °C.

Table 3

Spectral characteristics of the prepared 4-anilinoquinazolines (IIIa—IIIi) (ϵ in $\text{dm}^3 \text{mol}^{-1} \text{cm}^{-1}$)

Compound	IR		UV			
	C=N	$\tilde{\nu}_{\text{C}=\text{C}}$ cm^{-1}	NH	$\lambda_{1\text{max}}/\text{nm}$ ($\log \{ \epsilon_1 \}$)	$\lambda_{2\text{max}}/\text{nm}$ ($\log \{ \epsilon_2 \}$)	$\lambda_{3\text{max}}/\text{nm}$ ($\log \{ \epsilon_3 \}$)
IIIa	1622	3070	3445	250 (4.663)	271 (4.431)	340 (4.322)
IIIb	1623	3010	3445	251 (4.627)	275 (4.326)	343 (4.255)
IIIc	1623	3005	3445	251 (4.690)	270 (4.423)	339 (4.352)
IIId	1630	3030	3445	253 (4.615)	275 (4.310)	345 (4.236)
IIIe	1630	3065	3445	252 (4.521)	277 (4.246)	344 (4.170)
IIIf	1630	3030	3445	253 (4.672)	271 (4.380)	344 (4.301)
IIIg	1615	3070	3445	250 (4.593)	281 (4.387)	347 (4.204)
IIIh	1615	3020	3445	251 (4.606)	284 (4.471)	349 (4.204)
IIIi	1620	3015	3445	253 (4.674)	277 (4.415)	351 (4.283)

Substituted 2-phenyl-4-anilinoquinazolines (IIIa—IIIi)

Suspension of dry imidoylthiourea (*II*) (10 mmol) and yellow HgO (4.4 g) in dichloromethane (30 cm³) was stirred vigorously at room temperature. After 1 h stirring, further HgO (2.2 g) was added and stirring was continued for 1 h. Then the reaction mixture was percolated through a silica gel column to remove colloidal HgS and evaporated to dryness. The compounds obtained were purified by crystallization from benzene using charcoal.

References

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