Nucleophilic addition of 2-hydroxyquinoxaline to acetylenes

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Vinylation of 2-hydroxyquinoxaline affords either 2-vinyloxyquinoxaline or 1-vinyl-2-quinoxalone depending on the reaction conditions. The reactions of 2-hydroxyquinoxaline with 3-phenylprop-2-ynonitrile or 4-hydroxyalk-2-ynonitriles yield 3-phenyl-3-(quinoxalyl-2-oxy)prop-2-enonitrile or 4-hydroxy-3-(quinoxalyl-2-oxy)alk-2-enonitriles, respectively.

Key words: 2-hydroxyquinoxaline, acetylene, nucleophilic addition, 2-vinyloxyquinoxaline, 1-vinyl-2-quinoxalone, 3-phenylprop-2-enonitrile, 4-hydroxyalk-2-ynonitriles, 3-phenyl-3-(quinoxalyl-2-oxy)prop-2-enonitrile, 4-hydroxyalk-2-enonitriles.

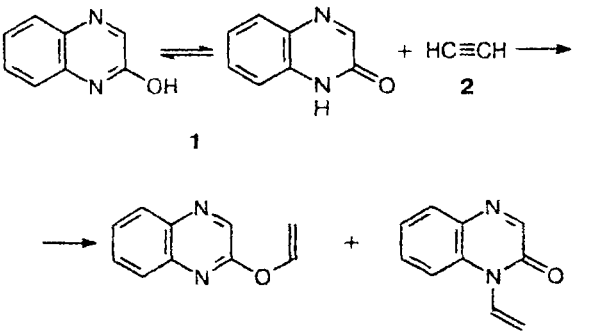
The data on the reactions of hydroxyl-containing azines with acetylene and its derivatives were surveyed in the review.[1] In particular, it is known[2] that 2-hydroxy-4-methylquinoline reacts with acetylene to form either *O*- or *N*-vinyl derivatives depending on the reaction conditions. Hydroxyquinoline derivatives were also studied.[3] However, the reaction conditions and the properties of the resulting vinyl compounds were not reported. The reactions of 2-, 3-, and 8-hydroxyquinolines with substituted acetylenes, in particular, with 3-phenylprop-2-ynonitrile and 4-hydroxyalk-2-ynonitriles, afford *Z*-quinolyloxyalk-2-enonitriles.[4] Data on the reactions of hydroxyquinoxalines with acetylene and substituted cyanoacetylenes are lacking in the literature.

This work is devoted to studies of the nucleophilic addition of 2-hydroxyquinoxaline (**1**) to acetylene (**2**) and its activated derivatives, *viz.*, 3-phenylprop-2-ynonitrile (**3**) and 4-hydroxyalk-2-ynonitriles (**4a—c**), with the aim of preparing new functionally substituted quinoxalines, which may find use as intermediates for fine organic synthesis and for the preparation of biologically active compounds.

It is known[5,6] that monohydroxydiazines (to which quinoxaline **1** belongs) exist predominantly as tautomeric carbonyl compounds. As a result, the nucleophilic addition of acetylenes to quinoxaline **1** can yield both *O*- and *N*-vinyl derivatives.

It appeared that the reaction of quinoxaline **1** with acetylene **2** under conditions described for the vinylation of 2-hydroxy-4-methylquinoline (14 atm, $Cd(OAc)_2 \cdot 3H_2O$, 200—205 °C, 1 h, dioxane)[2] afforded 2-vinyloxyquinoxaline (**5**) and 1-vinyl-2-quinoxalone (**6**) in 48 and 10% yields, respectively (Scheme 1). This reaction in the presence of KOH (14 atm, 220—225 °C, dioxane) gave predominantly 1-vinyl-2-quinoxalone (**6**) (the yield was 43%), while 2-vinyloxyquinoxaline (**5**) was obtained only as a minor product (the yield was 6%).

Scheme 1



The structures of vinyl derivatives **5** and **6** were confirmed by their IR and ^1H NMR spectra (Table 1). Thus the IR spectra have absorption bands characteristic of vibrations of the double bond in the vinyl group (at 1650, 1350, 1320, 950, and 840 cm^{-1} for compound **5**[7] and at 1640 and 940 cm^{-1} for compound **6**). The absorption bands at 1150 and 1205 cm^{-1} in the spectrum of *O*-vinylquinoxaline (**5**) belong to C—O—C stretching vibrations. The band at 1680 cm^{-1} in the spectrum of *N*-vinyl-2-quinoxalone (**6**) was assigned to the C=O group of the amide fragment.[8]

The ^1H NMR spectra of *O*- and *N*-vinyl derivatives **5** and **6** differ slightly in the vicinal $^1H—^1H$ spin-spin coupling constants of the vinyl group. The values $^3J_{AX}$ = 8—9 Hz and $^3J_{BX}$ = 15—16 Hz correspond to the

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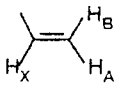
Table 1. Data of IR and ^{1}H NMR spectroscopy for 2-vinyloxyquinoxaline (**5**) and 1-vinyl-2-quinoxalone (**6**)

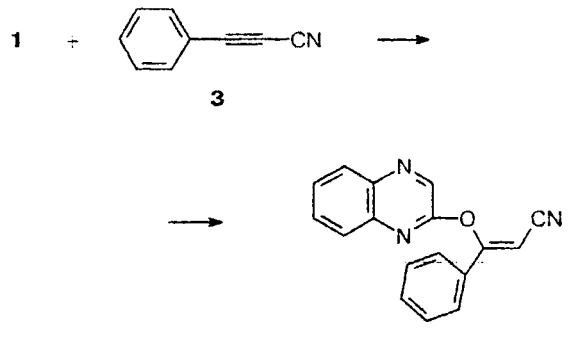
Compound	IR, ν/cm^{-1}	^{1}H NMR (–CH$_X$=CH$_A$H$_B$)					
		δ			J/Hz		
		H$_A$	H$_B$	H$_X$	$^2J_{AB}$	$^3J_{AX}$	$^3J_{BX}$
5	3100, 1645, 1610, 1580, 1550, 1480, 1460, 1400, 1350, 1320, 1300, 1205, 1150, 1105, 1010, 980, 950, 920, 840, 780, 750, 700, 670, 610, 560, 540, 480, 440	4.68 (dd)	5.04 (dd)	7.71 (q)	–1.8	6.0	13.5
6	3100, 1680, 1640, 1600, 1560, 1500, 1480, 1460, 1420, 1390, 1330, 1300, 1270, 1250, 1230, 1100, 970, 940, 900, 760, 740, 670, 650, 610, 550, 470, 440	5.79 (dd)	5.72 (dd)	6.63 (q)	–0.7	8.4	15.9

N-vinyl compounds and the values $^3J_{AX}$ = 6–7 Hz and $^3J_{BX}$ = 13–14 Hz correspond to the *O*-vinyl compounds.[9] The inverse arrangement of the H$_A$ and H$_B$ signals, their downfield shifts, and an increase in the geminal spin-spin coupling constant $^2J_{AB}$ in *N*-vinyl product **6** are attributable to a substantial deviation of the vinyl group from the plane of the heterocycle.[10] A strong upfield shift of the H$_X$ resonance in *O*-vinyl compound **5** is a consequence of an intramolecular specific C–H$_X$...N interaction (see Ref. 11).



As expected, the nucleophilic addition of hydroxyquinoxaline **1** to cyanoacetylenes **3** and **4a–c** occurred under milder conditions than the reactions of nonsubstituted acetylene **2**. At room temperature (dioxane or aqueous dioxane, KOH (0.18 mmol), 20–25 °C, 20 h), the addition of 3-phenylprop-2-ynonitrile (**3**) to hydroxyquinoxaline **1** did not occur. However, this reaction proceeded regio- and stereospecifically at 100 °C to form (*Z*)-3-phenyl-3-(quinoxalyl-2-oxy)prop-2-enonitrile (**7**) (Scheme 2). Under optimum conditions, the yield of adduct **7** reached 69%.

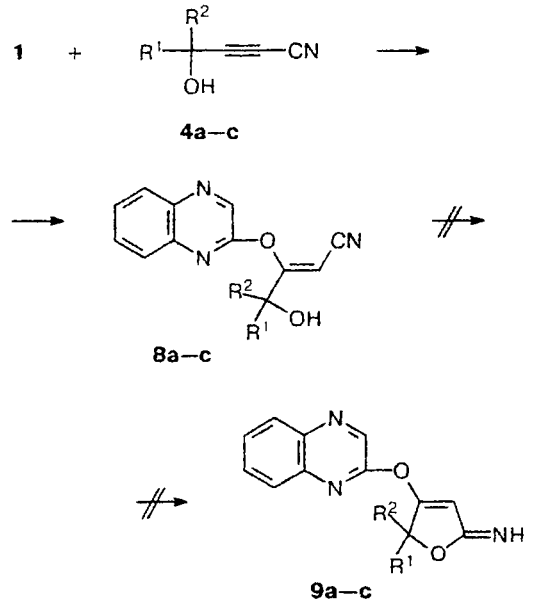
Scheme 2



The addition of quinoxaline **1** to 4-hydroxyalk-2-ynonitriles **4a–c** (Scheme 3) occurred even at 20–25 °C to form (*Z*)-4-hydroxy-3-(quinoxalyl-2-oxy)alk-2-enonitriles (**8a–c**, respectively) (Table 2).

Attempts to increase the yields of 4-hydroxyalkenonitriles **8a–c** by varying the reaction conditions did not gave the desired results. Thus boiling of the reaction mixture, the use of KOH instead of LiOH, or an

Scheme 3



R^1 = R^2 = Me (**a**); R^1 = Me, R^2 = Et (**b**); R^1–R^2 = (CH$_2$)$_5$ (**c**)

Table 2. Yields, melting points, and data from elemental analysis of the synthesized compounds

Compound	Yield (%)	M.p./°C (solvent)	Found / Calculated (%)			Molecular formula
			C	H	N	
5	48	67–69 (hexane)	69.30 / 69.75	4.61 / 4.68	16.54 / 16.27	$C_{10}H_8N_2O$
6	43	123–125 (ether)	69.15 / 69.75	4.23 / 4.68	16.72 / 16.27	$C_{10}H_8N_2O$
7	69	Oil	74.05 / 74.71	4.27 / 4.06	15.10 / 15.38	$C_{17}H_{11}N_3O$
8a	50	174–176 (chloroform–hexane, 1 : 10)	65.34 / 65.87	5.27 / 5.13	16.58 / 16.46	$C_{14}H_{13}N_3O_2$
8b	36	Oil	66.52 / 66.90	5.35 / 5.61	15.27 / 15.60	$C_{15}H_{15}N_3O_2$
8c	20	185–187 (chloroform–hexane, 1 : 10)	69.30 / 69.13	5.96 / 5.80	13.93 / 14.23	$C_{17}H_{17}N_3O_2$

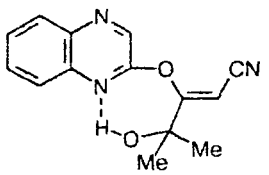
Table 3. Data of IR and ^{1}H NMR spectroscopy for adducts **7** and **8a—c**

Compound	IR, ν/cm^{-1}	^{1}H NMR, δ			
		Alk	=CH—CN	OH	Ar
7	3040, 2210, 1660, 1610, 1590, 1540, 1480, 1450, 1440, 1340, 1290, 1110, 1060, 990, 910, 860, 840, 750, 690, 550, 520, 450	—	6.43	—	7.33—8.34 (m, 10 H)
8a	3420—3340, 3060, 2970, 2920, 2220, 1650, 1625, 1600, 1580, 1540, 1450, 1350, 1330, 1310, 1290, 1190, 1140, 1120, 1090, 1030, 970, 910, 850, 820, 800, 750, 660, 550, 530, 510, 450	1.42 (s, Me); 1.57 (s, Me)	6.30	3.44 (br.s)	7.11—8.34 (m, 5 H)
8b	3470—3340, 3070, 2980, 2930, 2870, 2210, 1650, 1590, 1550, 1540, 1490, 1450, 1430, 1360, 1320, 1290, 1170, 1130, 1050, 1020, 990, 930, 880, 860, 770, 740, 650, 590, 540, 520, 500, 460	0.93 (t, Me); 1.44 (s, Me); 1.71 (q, CH_2)	6.29	2.75 (br.s)	7.21—8.31 (m, 5 H)
8c	3460—3380, 3050, 2940, 2920, 2830, 2220, 1650, 1630, 1600, 1590, 1550, 1450, 1430, 1350, 1340, 1320, 1300, 1250, 1170, 1150, 1140, 1050, 1030, 1000, 910, 830, 800, 770, 760, 670, 580, 550, 530, 500, 460	1.62 (br.s, 5 CH_2)	6.27	3.08 (br.s)	7.14—8.34 (m, 5 H)

increase in the reaction time led to a sharp decrease in the yields (by a factor of two or three) and resinification, due, apparently, to the instability of hydroxyacetylenes **4a—c** under strongly alkaline conditions.

The IR spectra of adducts **7** and **8a—c** have intense absorption bands of the nitrile group and the C—O—C bonds at 2210—2220 and 1000—1200 cm^{-1}, respectively (Table 3). The absence of bands of the carbonyl group (at 1680 cm^{-1}) indicates that only the hydroxy tautomer of quinoxaline **1** was involved in the reaction. In this case, we did not observe the formation of *N*-adducts.

The IR spectra of solutions of compound **8a** in $CHCl_3$ and CCl_4 at concentrations which completely exclude an intermolecular hydrogen bond have two absorption bands at 3463 and 3597 cm^{-1}. The low-frequency band belongs to an intramolecular hydrogen bond between the N(1) atom and the OH group and the high-frequency band belongs to the free nonassociated OH group.



8a

The ^{1}H NMR spectra of adducts **7** and **8a—c** (see Table 3) have single signals for the olefin protons (at δ 6.43, 6.30, 6.29, and 6.27, respectively). This is indicative of the formation of one isomer, which adopts, apparently, the *Z* configuration, if the reaction proceeds as the normal concerted *trans*-nucleophilic addition.[12] The *Z* configuration of the resulting alkenonitriles **8a—c** is also confirmed by the fact that these compounds cannot undergo intramolecular cyclization to form the corresponding iminodihydrofurans **9a—c** (see Refs. 13 and 14).

To summarize, we developed a procedure for the synthesis of new unsaturated compounds based on quinoxaline **1**, acetylene **2**, and its cyano derivatives **3** and **4a—c**. *O*-Vinyl, *N*-vinyl, and 2-cyanovinyl derivatives of quinoxaline were prepared (**5**, **6**, **7**, and **8a—c**). It was demonstrated that it is only the hydroxy tautomeric form of compound **1** that enters into reactions with cyanoacetylenes **3** and **4a—c**, unlike the vinylation reactions.

Experimental

The IR spectra were recorded on a Specord IR-75 spectrometer in KBr pellets, in a thin layer, and in $CHCl_3$ and CCl_4 solutions (c = 0.01—0.001 mol L^{-1}, d = 50—100 mm). The ^{1}H NMR spectra were measured on Jeol FX-90Q (90 MHz) and Bruker DPX-250 (250 MHz) instruments in $CDCl_3$ with HMDS as the internal standard.

2-Hydroxyquinoxaline (**1**) was a commercially available reagent of chemically pure grade. 3-Phenylprop-2-ynonitrile (**3**) and 4-hydroxyalk-2-ynonitriles (**4a—c**) were prepared according to procedures reported previously.[15,16] Column and thin-layer chromatography was carried out on Al_2O_3 in a 20 : 4 : 1 chloroform—benzene—ethanol solvent mixture. The physicochemical constants of the synthesized compounds are given in Tables 1—3.

2-Vinyloxyquinoxaline (5). 2-Hydroxyquinoxaline (**1**) (4.1 g, 28 mmol), $Cd(OAc)_2 \cdot 3H_2O$ (2.5 g, 8.8 mmol), and dioxane (80 mL) were placed into a 0.25-L autoclave and the mixture was saturated with acetylene at 14 atm. The reaction mixture was kept at 200—205 °C for 1 h and then cooled. The solvent was distilled off and the residue was distilled *in vacuo*. The distillate (4.0 g, b.p. 90—140 °C (3 Torr)) was chromatographed. Vinyl ether **5** and 1-vinyl-2-quinoxalone (**6**) were isolated in yields of 2.3 g (48%) and 0.5 g (10%), respectively.

1-Vinyl-2-quinoxalone (6). Analogously, 1-vinyl-2-quinoxalone (**6**) and 2-vinyloxyquinoxaline (**5**) were prepared from quinoxaline **1** (4.1 g, 28 mmol) in the presence of KOH (1.2 g, 21 mmol) at 200—225 °C in 2 h in yields of 2.1 g (43%) and 0.3 g (6%), respectively.

3-Phenyl-3-(quinoxalyl-2-oxy)prop-2-enonitrile (7). A solution of 3-phenylprop-2-ynonitrile (**3**) (0.06 g, 0.5 mmol) in dioxane (3 mL) was added dropwise to a solution of quinoxaline **1** (0.07 g, 0.5 mmol) and KOH (0.02 g, 0.36 mmol) in water (9 mL). The reaction mixture was stirred at 100 °C for 10 h. After cooling, the solvents were removed. Column chromatography of the residue gave compound **7** in a yield of 0.09 g (69%).

4-Hydroxy-4-methyl-3-(quinoxalyl-2-oxy)pent-2-enonitrile (8a). A solution of 4-hydroxy-4-methylpent-2-ynonitrile (**4a**) (0.11 g, 1 mmol) in dioxane (5 mL) was added dropwise to a solution of quinoxaline **1** (0.15 g, 1 mmol) and LiOH (0.04 g, 1.67 mmol) in dioxane (10 mL). The reaction mixture was stirred at 20—25 °C for 30 h and then passed through a thin layer (3—5 cm) of Al_2O_3 to remove LiOH. The solvent was removed and column chromatography of the residue afforded compound **8a** in a yield of 0.13 g (50%).

4-Hydroxy-4-methyl-3-(quinoxalyl-2-oxy)hex-2-enonitrile (8b). Analogously, compound **8b** was prepared from quinoxaline **1** (0.15 g, 1 mmol) and 4-hydroxy-4-methylhex-2-ynonitrile (**4b**) (0.12 g, 1 mmol) in the presence of LiOH (0.04 g, 1.67 mmol) in dioxane (15 mL) in a yield of 0.10 g (36%).

3-(1-Hydroxycyclohexyl)-3-(quinoxalyl-2-oxy)prop-2-enonitrile (8c). Analogously, compound **8c** was prepared from quinoxaline **1** (0.15 g, 1 mmol) and 3-(1-hydroxycyclohexyl)prop-2-ynonitrile (**4c**) (0.15 g, 1 mmol) in the presence of LiOH (0.05 g, 2.09 mmol) in dioxane (15 mL) in a yield of 0.06 g (20%).

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