Russian Journal of Organic Chemistry, Vol. 37, No. 5, 2001, pp. 700–703. Translated from Zhurnal Organicheskoi Khimii, Vol. 37, No. 5, 2001, pp. 737–740.

Cyanoacetylene and Its Derivatives: XXVII.* 5,5-Dialkyl-4-azido-2,5-dihydrofuran-2-imines**

A. G. Mal'kina, R. N. Kudyakova, and B. A. Trofimov

Irkutsk Institute of Chemistry, Siberian Division, Russian Academy of Sciences, ul. Favorskogo 1, Irkutsk, 664033 Russia

Received September 16, 1999

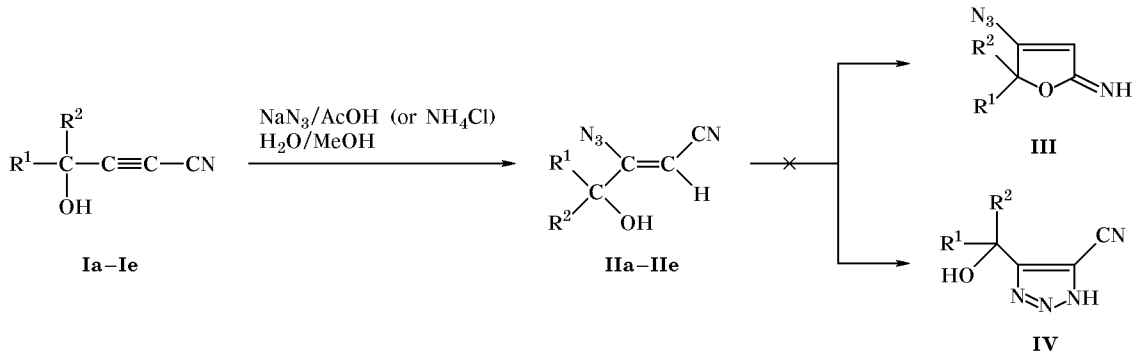
Abstract—The reaction of 3-azido-4-hydroxy-2-alkynenitriles with hydrogen chloride is accompanied by intramolecular ring closure with formation of 5,5-dialkyl-4-azido-2,5-dihydrofuran-2-imine hydrochlorides which can be converted into the corresponding free bases by the action of potassium carbonate in ethanol.

The 4-azido-2-aminofuran fragment is a part of the AZT molecule {1-[4-azido-5-(hydroxymethyl)tetrahydrofuran-2-yl]-5-methyl-1,2,3,4-tetrahydropyrimidine-2,4-dione}, which is now one of the most powerful anti-HIV remedies. Therefore, new ideas concerning reasonable approaches to such structures on the basis of accessible initial compounds may be useful for subsequent systematic development of compounds active against human immunodeficiency viruses.

The present communication reports the results of our study which was aimed at developing a general procedure for preparation of 4-azido-2-iminodihydrofurans from nitriles of α,β-acetylenic γ-hydroxy acids. The latter became available in the recent time [2–4].

Reactions of acids with (*Z*)-4-hydroxy-3-dialkylamino(azolyl)-2-alkenenitriles formed by addition of nitrogen-centered nucleophiles (e.g., secondary amines, imidazole, benzimidazole, etc.) to nitriles derived from α,β-acetylenic γ-hydroxy acids are known [5–7] to take different pathways. 4-Hydroxy-3-dialkylamino-2-alkenenitriles react with HCl to give 5,5-dialkyl-4-dialkylamino-2,5-dihydrofuran-2-imine hydrochlorides [5]. Treatment of 4-hydroxy-3-(1-imidazolyl)-2-alkenenitriles with HCl in acetic acid leads to formation of the corresponding 1-(5-oxo-2,5-dihydrofuran-3-yl)imidazolium salts instead of the expected 4-imidazolyl-2-imino derivatives as a result of concurrent hydrolysis [6]. An analogous reaction of 3-(1-benzimidazolyl)-4-hydroxy-2-alkenenitriles

Scheme 1.



$R^1 = R^2 = Me$ (**a**); $R^1 = Me$, $R^2 = Et$ (**b**); $R^1R^2 = (CH_2)_5$ (**c**); $R^1 = Me$, $R^2 = Bu$ (**d**); *i*-Bu (**e**).

* For communication XXVI, see [1].

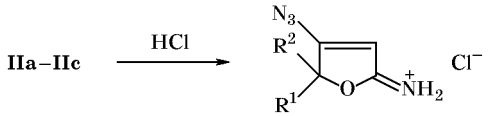
** This study was financially supported by the Russian Foundation for Basic Research (project no. 96-19-97536).

1070-4280/01/3705-0700 $25.00 © 2001 MAIK "Nauka / Interperiodica"

yields only 3-(1-benzimidazolyl)-4-hydroxy-2-alkenenitrile hydrochlorides which do not undergo cyclization into iminodihydrofurans [7]. On the other hand, there are no published data on the reactivity of 3-azido-4-hydroxy-2-alkenenitriles which are readily available via reactions of α,β-acetylenic γ-hydroxy nitriles **Ia**–**Ie** with the system NaN_3–HOAc or NaN_3–NH_4Cl (aqueous methanol, room temperature). We previously reported [8] that in the presence of alkali metal hydroxides MOH (M = Na, K) azidoalkenenitriles **II** are not converted into the corresponding 4-azido-2-iminodihydrofurans **III** or 1,2,3-triazoles **IV** (Scheme 1). As noted above, 4-azido-2-iminodihydrofurans **III** are structurally related to the known anti-HIV compounds; therefore, they attract interest from the viewpoint of physiological activity.

In continuation of our studies on the reactivity of cyanoacetylene derivatives, the present communication reports on the successful cyclization of 3-azido-4-hydroxy-2-alkenenitriles **II** to dihydrofuranimines **III**. We have found that alkenenitriles **II** react with hydrogen chloride under mild conditions (dioxane, 20°C, 3–5 h) to form 5,5-dialkyl-4-azido-2,5-dihydrofuran-2-imine hydrochlorides **V** in quantitative yield (Scheme 2, Tables 1, 2).

Scheme 2.



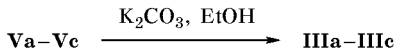
Va–Vc

$R^1 = R^2 = Me$ (**a**); $R^1 = Me$, $R^2 = Et$ (**b**); $R^1R^2 = (CH_2)_5$ (**c**).

Obviously, the cyclization begins with protonation of the cyano group to give mesomeric cation **A** ↔ **B** ↔ **C** in which rotation about the C^2-C^3 bond is facilitated and steric limitation (*Z* configuration of the initial nitrile) to intramolecular nucleophilic attack by the hydroxy group oxygen atom on the emerging heteroallene system is removed (Scheme 3).

4-Azido-5,5-dialkyl-2,5-dihydrofuran-2-imine hydrochlorides **Va**–**Vc** are colorless crystalline substances, soluble in acetone, alcohol, and water and partially soluble in chloroform; they are safe in handling and are stable on storage (5°C) in a closed vessel. The ^1H NMR and IR spectra of **Va**–**Vc** are given in Table 2.

As we showed previously [2], 5,5-dialkyl-4-dialkylamino-2,5-dihydrofuran-2-imine hydrochlorides can readily be converted into the corresponding free bases by treatment with potassium hydroxide in ethanol (20–25°C, 3–5 h). Neutralization of hydrochlorides **V** to 4-azido-5,5-dialkyl-2,5-dihydrofuran-2-imines **III** occurs under milder conditions, by the action of potassium carbonate in ethanol at 20–25°C (2 h):



4-Azido-5,5-dialkyl-2,5-dihydrofuran-2-imines **IIIa**–**IIIc** are yellow oily substances, soluble in most organic solvents and insoluble in water. They readily decompose on storage above 5°C, yielding dark brittle polymeric compounds with partial loss of nitrogen.

The ^1H NMR spectra of compounds **IIIa**–**IIIc** contain a singlet at δ 5.66–5.73 ppm from the olefinic proton (Table 2). In the IR spectra of **III** (film) we observed absorption bands at 3298–3122 and 1671–1655 cm^{-1}, which belong to stretching vibrations of the N−H and C=N bonds, respectively. The band at 2150–2119 cm^{-1} corresponds to the azido group. The double C=C bond gives rise to absorption in the region 1614–1611 cm^{-1} (Table 2).

Thus 3-azido-4-hydroxy-2-alkenenitriles **II** react with HCl in dioxane to afford 4-azido-5,5-dialkyl-

Scheme 3.

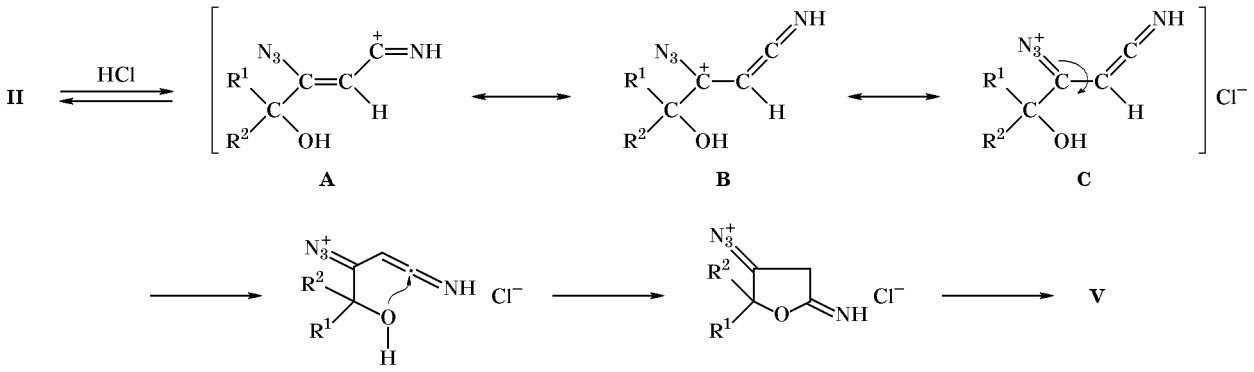


Table 1. Yields, melting points, and elemental analyses of 4-azido-5,5-dialkyl-2,5-dihydrofuran-2-imines **IIIa** and **IIIb** and 4-azido-5,5-dialkyl-2,5-dihydrofuran-2-imine hydrochlorides **Va**–**Vc**

Comp. no.	Yield, %	mp, °C	Found, %				Formula	Calculated, %			
			C	H	Cl	N		C	H	Cl	N
IIIa	80	–	47.77	5.24	–	35.09	$C_6H_{12}N_4O$	47.36	5.30	–	36.82
IIIb	87	–	50.03	6.48	–	32.02	$C_7H_{10}N_4O$	50.59	6.07	–	33.71
Va	98	80–82	37.38	5.04	19.14	28.60	$C_6H_9ClN_4O$	38.21	4.81	18.80	29.70
Vb	97	108–110	41.14	5.69	18.06	26.54	$C_7H_{11}ClN_4O$	41.49	5.47	17.50	27.65
Vc	95	70–74	47.71	5.56	15.13	23.35	$C_9H_{13}ClN_4O$	47.27	5.73	15.50	24.50

Table 2. ^{1}H NMR and IR spectra of 4-azido-5,5-dialkyl-2,5-dihydrofuran-2-imines **IIIa**–**IIIc** and 4-azido-5,5-dialkyl-2,5-dihydrofuran-2-imine hydrochlorides **Va**–**Vc**

Comp. no.	^{1}H NMR spectrum, δ, ppm		IR spectrum (KBr), ν, cm^{-1}
	=CH, s	Alk	
IIIa	5.67	1.41 s (6H, CH_3)	3284–3122, 2982, 2934, 2150–2124, 1655, 1613, 1464, 1440, 1384, 1368, 1342, 1250, 1211, 1153, 1076, 1049, 1002, 940, 910, 880, 803, 731, 683, 643, 539
IIIb	5.73	0.83 t (3H, CH_3), 1.38 s (3H, CH_3), 1.67 m (2H, CH_2)	3295–3168, 3095, 2977, 2936, 2881, 2119, 1671, 1614, 1455, 1375, 1353, 1269, 1248, 1209, 1163, 1144, 1101, 1078, 1061, 1031, 998, 967, 945, 912, 892, 812, 678, 648, 598, 539, 496
IIIc	5.66	1.60 br.s (10H, CH_2)	3298–3175, 3098, 2935, 2860, 2124, 1669, 1611, 1449, 1347, 1256, 1152, 1132, 1093, 1070, 983, 964, 945, 909, 848, 811, 787, 732, 675, 619, 536, 494
Va	6.63	1.58 s (6H, CH_3)	3410–3340, 3200–2770, 2200 m, 2160 s, 2140 s, 2100 m, 2080 m, 1680–1660, 1590, 1420, 1370, 1340, 1240, 1205, 1195, 1150, 1100, 1080, 1050, 995, 970, 870, 840, 805, 570, 550, 540
Vb	6.64	0.83 t (3H, CH_3) 1.54 s (3H, CH_3), 1.86 q (2H, CH_2)	3470–3360, 3110–2720, 2160 s, 2150 s, 2110 m, 1690–1660, 1590, 1405, 1360, 1320, 1260, 1240, 1200, 1150, 1130, 1100, 1070, 1030, 995, 970, 880, 840, 790, 660, 600, 520
Vc	6.60	1.72 br.s (10H, CH_2)	3460–3350, 3130–2720, 2200 m, 2180 s, 2130 s, 2110 m, 1690–1660, 1590, 1430, 1360, 1330, 1260, 1150, 1120, 1070, 1040, 990, 950, 910, 870, 830, 790, 605, 570, 540

2,5-dihydrofuran-2-imine hydrochlorides **V** whose neutralization with K_2CO_3 in ethanol leads to formation of 4-azido-2,5-dihydrofuran-2-imines **III**.

EXPERIMENTAL

The ^{1}H NMR spectra were obtained on Jeol (90 MHz) and Bruker DPX-250 (250 MHz) spectrometers in $CDCl_3$ and CD_3OD using HMDS as internal reference. The IR spectra of compounds **IIIa**–**IIIc** as thin films were recorded on a Bruker IFS-25 instrument, and of compounds **Va**–**Vc** (in KBr), on a Specord IR-75 instrument. The progress of reactions was monitored by TLC on Al_2O_3 using chloroform–benzene–ethanol (20:4:1) as eluent.

Initial alkenes **IIa**–**IIc** were synthesized by the procedure reported in [8]. The yields, constants, elemental analyses, and spectral data of compounds **IIIa**–**IIIc** and **Va**–**Vc** are given in Tables 1 and 2.

4-Azido-5,5-dimethyl-2,5-dihydrofuran-2-imine hydrochloride (Va). Gaseous hydrogen chloride was passed over a period of 8 h through a solution of 0.43 g (2.5 mmol) of 3-azido-4-hydroxy-4-methyl-2-pentenenitrile (**IIa**) in 5 ml of anhydrous dioxane,

maintained at 20–25°C. The solvent was removed under reduced pressure, and the crystalline product was washed with diethyl ether. Yield 0.52 g.

Following a similar procedure, from 0.28 g (1.7 mmol) of 3-azido-4-hydroxy-4-methyl-2-hexenenitrile (**IIb**) in 3 ml of anhydrous dioxane we obtained 0.34 g of 4-azido-5-ethyl-5-methyl-2,5-dihydrofuran-2-imine hydrochloride (**Vb**).

From 0.5 g (2.6 mmol) of 3-azido-3-(1-hydroxycyclohexyl)-2-propenenitrile (**IIc**) in 3 ml of anhydrous dioxane we obtained 0.56 g of 4-azido-5,5-pentamethylene-2,5-dihydrofuran-2-imine hydrochloride (**Vc**).

4-Azido-5,5-dimethyl-2,5-dihydrofuran-2-imine (IIIa). To a suspension of 0.056 g (0.4 mmol) of K_2CO_3 in 3 ml of ethanol we slowly added a solution of 0.07 g (0.37 mmol) of hydrochloride **Va**, and the mixture was kept for 2 h at 20–22°C. The precipitate was filtered off, and the filtrate was evaporated under reduced pressure to obtain 0.04 g of compound **IIIa** as a light yellow substance.

4-Azido-5-ethyl-5-methyl-2,5-dihydrofuran-2-imine (IIIb) was synthesized in a similar way from 0.1 g (0.49 mmol) of hydrochloride **Vb** and 0.07 g (0.5 mmol) of K_2CO_3 in 5 ml of ethanol. Yield 0.07 g, light yellow oily substance.

4-Azido-5,5-pentamethylene-2,5-dihydrofuran-2-imine (IIIc) was synthesized in a similar way from 0.2 g (0.8 mmol) of hydrochloride **Vc** and 0.14 g (1.0 mmol) of K_2CO_3 in 6 ml of ethanol. Yield 0.12 g, dark yellow oily substance.

REFERENCES

1. Mal'kina, A.G., Nosyreva, V.V., Kudyakova, R.N., Sokolyanskaya, L.V., and Trofimov, B.A., *Russ. J. Org. Chem.*, 2001, vol. 37, no. 5, pp. 649–654.
2. Trofimov, B.A., Mal'kina, A.G., and Skvortsov, Yu.M., *Zh. Org. Khim.*, 1993, vol. 29, no. 6, pp. 1268–1291.
3. Trofimov, B.A., Abstracts of Papers, *10th European Symp. on Organic Chemistry*, Basel, 1997, p. 35.
4. Trofimov, B.A. and Mal'kina, A.G., *Heterocycles*, 1999, vol. 51, no. 10, pp. 2485–2522.
5. Skvortsov, Yu.M., Mal'kina, A.G., Moshchevitina, E.I., Kositsyna, E.I., and Trofimov, B.A., *Zh. Org. Khim.*, 1992, vol. 28, no. 7, pp. 1371–1376.
6. Skvortsov, Yu.M., Mal'kina, A.G., Trofimov, B.A., Kositsyna, E.I., Voronov, V.K., and Baikalova, L.V., *Zh. Org. Khim.*, 1984, vol. 20, no. 5, pp. 1108–1115.
7. Skvortsov, Yu.M., Trofimov, B.A., Volkov, A.N., Glazkova, N.P., Proidakov, A.G., and Modonov, V.B., *Zh. Org. Khim.*, 1982, vol. 18, no. 5, pp. 983–986.
8. Trofimov, B.A., Mal'kina, A.G., and Kudyakova, R.N., *Zh. Org. Khim.*, 1993, vol. 29, no. 10, pp. 1942–1946.