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Cyanoacetylene and Its Derivatives: XXXI.* Nucleophilic Addition of 2- and 4-Mercaptopyridines to Cyanacetylenes**

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Abstract—Reactions of nucleophilic addition of 2- and 4-mercaptopyridines to 3-phenyl-2-propynonitrile, 4-hydroxy-4-alkyl-2-alkynonitriles, and methyl 2-butynoate (triethylamine, 20—25 or 100°C) give rise to the corresponding S-adducts with Z-configuration (for cyanoethylenes), or to a mixture of *E*- and *Z*-isomers in 60 : 40 ratio for methyl 2-butynoate.

The nucleophilic addition of thiols to acetylene compounds is well documented; it is commonly catalyzed by bases and follows the rule of trans-addition [2, 3]. Results of this research are summed up in books [3–6] and numerous papers, e.g., [7–9]. However the published data on reaction between mercaptopyridines and acetylenes are scanty [10, 11]. For instance, it was reported [10] that 2-mercaptopyridine added to acetylene, phenylacetylene, and diacetylene affording the corresponding vinyl sulfides. The reaction of 2-mercaptopyridine with propiolic and phenylpropiolic acids gave rise to 3-(2-pyridylthio)-2-propenoic acids of *E*- and *Z*-configurations, The use in this process of acetylenedicarboxylic acid furnished thiazolo[3,2-a]pyridinium systems [11]. Therewith there are no published data on reactions between 2- and 4-mercaptopyridines with cyanoacetylenes.

The present report deals with the results of investigation on the nucleophilic addition of 2- and 4-mercaptopyridines (**I, II**) to 3-phenyl-2-propynonitrile (**III**), 4-hydroxy-4-alkyl-2-alkynonitriles (**IVa–c**), and methyl 2-butynoate (**V**) with a goal of preparation of new unsaturated compounds of azine series which would be promising intermediates for fine organic synthesis and biologically active compounds.

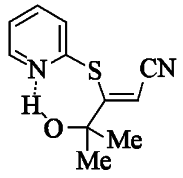
The 2- and 4-mercaptopyridines are known to be tautomers of pyridine-2- and -4-thiones. However mercaptopyridines and pyridinethiones always are alkylated at the sulfur atom [12].

We established that mercaptopyridines **I, II** reacted regioselectively with 3-phenyl-2-propynonitrile (**III**) in the presence of KOH (10 wt%) in dioxane furnishing (*Z*)-3-[2(4)-pyridylthio]-3-phenyl-2-propenonitriles (**VI, VII**) (Scheme 1, Table 1).

The yield of adducts **VI, VII** depends on the position of SH group in the pyridine ring and on the reaction conditions. For instance, 2-mercaptopyridine (**I**) reacts with alkyne **III** at room temperature providing within 10 h propenonitrile **VI** in 64% yield. The reaction of 4-mercaptopyridine (**II**) with alkyne **III** required boiling of the reaction mixture for 20 h, and the yield of propenonitrile **VII** attained 34%.

4-Hyrdoxy-2-alkynonitriles (IVa–c) turned out to be more electrophilic with respect to 2- and 4-mercaptopyridines (**I, II**). Under mild conditions (20–25°C, triethylamine as catalyst and solvent) within 8 h with 2-mercaptopyridine (**I**) and in 20 h with 4-mercaptopyridine (**II**) the reaction resulted in formation of hydroxy-3-[2(4)-pyridylthio]-2-alkenonitriles (**VIIIa–c, IXa–c**) in high yield (77–96%) (Scheme 2, Table 1).

The IR spectra of compounds **VI–IX** contain absorption bands at 2205–2220 cm^{-1} corresponding to



VIIIa

* For communication XXX see [1].

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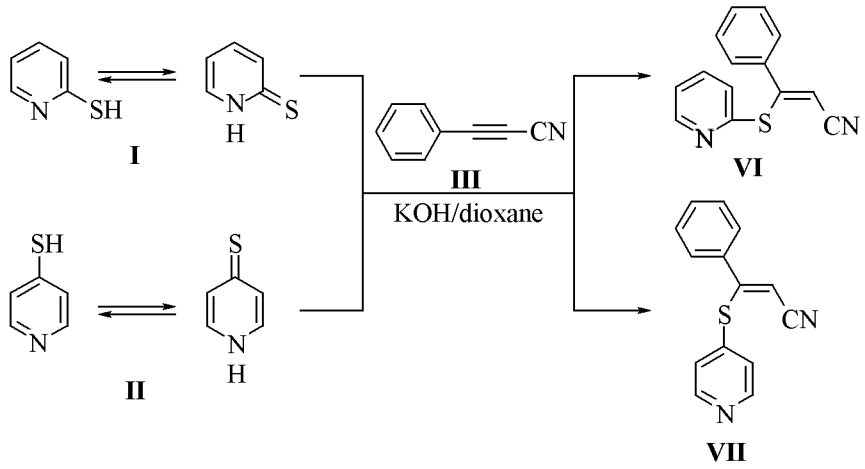
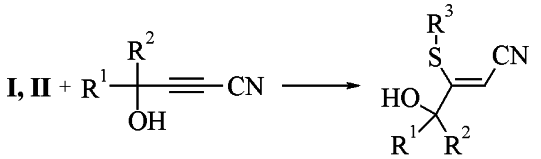
Scheme 1.



Scheme 2.



R^1 = R^2 = Me (**IVa, VIIIa, IXa**); R^1 = Me, R^2 = Et (**IVb, VIIIb, IXb**); R^1, R^2 = $(CH_2)_5$ (**IVc, VIIIc, IXc**); R^3 = 2-pyridyl (**VIIIa**–**c**), 4-pyridyl (**IXa**–**c**).

CN group attached to a double bond, and of exocyclic double bond at 3040–3050, 1620–1650, and 920–960 cm^{-1} (Table 2). At concentrations where the formation of intermolecular hydrogen bonds is totally impossible ($c << 0.001$ mol l^{-1}) in the spectrum of compound **VIII** was observed an absorption band in 3260 cm^{-1} region evidencing the presence of a relatively stable intramolecular hydrogen bond ($\Delta\nu$ 349 cm^{-1}).

In the ^{1}H NMR spectra of compounds **VI**–**IX** the signals of olefin protons are present in a single set indicating formation of an only isomer (Table 2).

We believe that S-adducts **VI**–**IX** exist in *Z*-configuration providing the reaction occurs as a normal *trans*-nucleophilic addition [2, 3]. The *Z*-configuration of compounds **VI**–**IX** is confirmed by their inability to cyclize into aminofurans as has been observed with analogous compounds in [13]. Adducts **VI**–**IX** actually do not suffer transformations when treated at 20–25°C with 30 wt% of KOH in dioxane for 20 h. In the presence of HCl (20–25°C, 20 h, dioxane) occurred polymerization and tarring.

For comparison we carried out reaction of 2-mercaptopyridine (**I**) with methyl 2-butynoate (**V**). The reaction proceeded under mild conditions (triethylamine, 20–25°C, 28 h) giving rise to two isomers, methyl (*E*+ *Z*)-3-(2-pyridylthio)-2-butenoates (**Xa, b**) in an overall yield 89% (Scheme 3).

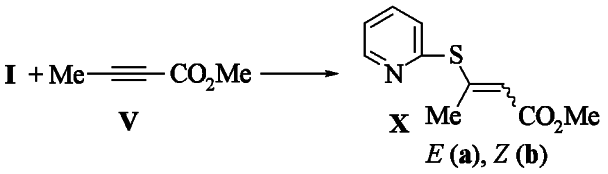
Table 1. Yields, melting points, and elemental analyses of compounds **VI**–**X**

Compd. no.	Yield, %	mp, °C	Found, %				Formula	Calculated, %			
			C	H	N	S		C	H	N	S
VI	64	77–79	70.24	4.22	11.60	13.05	$C_{14}H_{10}N_2OS$	70.56	4.23	11.76	13.46
VII	34	170–172	70.73	4.10	11.44	13.21	$C_{14}H_{10}N_2OS$	70.56	4.23	11.76	13.46
VIIIa	96	103–105	60.19	5.59	12.74	14.31	$C_{11}H_{12}N_2OS$	59.97	5.49	12.72	14.56
VIIIb	86	80–81	61.23	5.96	11.88	13.47	$C_{12}H_{14}N_2OS$	61.51	6.02	11.96	13.68
VIIIc	96	99–100	64.19	6.10	10.52	12.05	$C_{14}H_{16}N_2OS$	64.58	6.19	10.76	12.32
IXa	91	109–111	59.52	5.66	12.85	14.06	$C_{11}H_{12}N_2OS$	59.97	5.49	12.72	14.56
IXb	86	101–103	61.85	6.02	12.11	13.46	$C_{12}H_{14}N_2OS$	61.51	6.02	11.96	13.68
IXc	77	128–130	64.31	6.30	10.93	12.60	$C_{14}H_{16}N_2OS$	64.58	6.19	10.76	12.32
Xa, b	89	Oily substances	57.01	5.14	6.32	15.44	$C_{10}H_{11}NOS$	57.39	5.30	6.69	15.32

Table 2. IR and ^{1}H NMR spectra of compounds **VI–X**

Compd. no.	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm			
		Alk	=CH–CN (–CO_2CH_3)	OH	Ar
VI	3040, 2220, 1640, 1620, 1560, 1550, 1480, 1450, 1420, 1320, 1270, 1230, 1170, 1140, 1120, 1070, 1040, 980, 930, 890, 820, 770, 760, 740, 720, 690, 620, 590, 480, 440	–	5.87 s	–	6.93–8.32 m (9H)
VII	3040, 2205, 1650, 1620, 1570, 1550, 1480, 1440, 1330, 1320, 1290, 1230, 1170, 1150, 1070, 1030, 980, 960, 920, 910, 890, 850, 810, 805, 750, 740, 680, 670, 610, 580, 540, 450	–	5.92 s	–	7.00–8.31 m (9H)
VIIIa	3230, 3050, 2970, 2940, 2210, 1650, 1630, 1570, 1550, 1450, 1410, 1370, 1350, 1270, 1250, 1180, 1140, 1120, 1080, 1040, 980, 960, 820, 810, 750, 730, 710, 610, 590, 560, 480	1.50 s ($2CH_3$)	6.23 s	4.67 br.s	7.13–8.39 m (4H)
VIIIb	3240, 3040, 2970, 2940, 2870, 2210, 1620, 1570, 1550, 1440, 1420, 1360, 1310, 1280, 1250, 1170, 1150, 1120, 1090, 1070, 1040, 980, 920, 820, 810, 760, 720, 660, 610, 550, 490	0.89 t, 1.44 s ($2CH_3$), 1.77 q (CH_2)	6.19 s	4.31 br.s	7.12–8.40 m (4H)
VIIIc	3250, 3050, 2940, 2930, 2850, 2215, 1630, 1570, 1560, 1550, 1440, 1410, 1370, 1340, 1320, 1270, 1240, 1160, 1150, 1140, 1120, 1070, 1050, 1040, 990, 970, 900, 840, 810, 750, 720, 680, 630, 580, 480	1.74 m ($5CH_2$)	6.24 s	4.74 br.s	7.11–8.37 m (4H)
IXa	3140, 3050, 2970, 2940, 2230, 1640, 1570, 1540, 1480, 1450, 1420, 1400, 1370, 1350, 1260, 1200, 1180, 1090, 1050, 1000, 980, 830, 820, 750, 710, 620, 580, 490	1.50 s (CH_3)	6.53 s	3.69 br.s	7.22–8.45 m (4H)
IXb	3140, 3050, 2970, 2940, 2930, 2220, 1630, 1560, 1540, 1470, 1450, 1410, 1400, 1350, 1270, 1240, 1170, 1120, 1080, 1050, 980, 910, 800, 700, 660, 650, 620, 600, 550, 480	0.90 t, 1.45 s ($2CH_3$), 1.76 t (CH_2)	6.51 s	4.73 br.s	7.22–8.43 m (4H)
IXc	3170, 3050, 2950, 2980, 2225, 1620, 1570, 1540, 1480, 1440, 1410, 1340, 1320, 1270, 1230, 1210, 1160, 1110, 1090, 1050, 1030, 970, 930, 900, 820, 800, 730, 710, 660, 590, 510, 480	1.68 m ($5CH_2$)	6.53 s	4.10 br.s	7.18–8.43 m (4H)
Xa, b	3040, 2980, 2940, 2920, 2840, 1730, 1710, 1700, 1610, 1570, 1550, 1450, 1420, 1380, 1340, 1280, 1200, 1140, 1120, 1100, 1090, 1040, 990, 920, 900, 840, 830, 760, 720, 700, 650, 620, 540, 480, 450	1.99 s, 2.45 s ($2CH_3$), 3.64 s, 3.72 s ($2OCH_3$)	5.80 s, 5.91 s (2CH)	–	7.07–8.61 m (8H)

Scheme 3.



In the IR spectrum of the isomers **Xa, b** mixture appear the absorption bands of a double bond at 3040, 1610 and 920 cm^{-1} and no absorption is observed at 2240 cm^{-1} corresponding to the triple bond in the initial 2-butynoate **V**.

In the ^1H NMR spectrum of the mixture of isomers **Xa, b** all signals are present in a double set: Me, OMe, =CH, and those of aromatic protons (Table 2). The assignment of the signals to individual isomers was performed with the use of two-dimensional spectroscopic procedures NOESY (2D ^1H, ^1H), COSY, HSQC. For instance, in the spectrum 2D ^1H, ^1H NOESY a cross peak was observed between the signal of the olefin proton (5.91 ppm) and methyl group protons (1.99 ppm) that suggest the assignment of these signals to *Z*-isomer. In the *E*-isomer a similar peak is lacking due to the *trans*-location of the olefin proton and the methyl group.

These data indicate that the olefin signal in the *Z*-isomer resonates downfield (5.91 ppm) with respect to the similar proton in the *E*-isomer (5.80 ppm) where this effect cannot be present. The assignment of the aromatic signals for each isomer relayed on COSY and HSQC methods. The ratio of *E*- and *Z*-isomers is equal to 60 : 40 (Table 3).

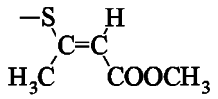
This ratio is conserved when the reaction between 2-mercaptopyridine (**I**) and 2-butynoate **V** is carried out in boiling triethylamine for 6 h; therewith the yield of compounds **Xa, b** is reduced by half due to stronger tarring. In dioxane this reaction does not occur, and in the presence of a basic catalyst (10 wt% KOH, 20 h) the fraction of *Z*-isomer grows to the ratio $E : Z = 1 : 5$. At boiling of the reaction mixture (dioxane, 100°C, 12 h) only tarring was observed.

We failed to obtain any reaction products from 4-mercaptopyridine (**II**) and 2-butynoate **V**.

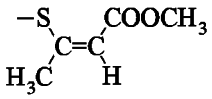
EXPERIMENTAL

IR spectra were measured on spectrophotometer Specord 75IR from samples pelletized with KBr or from thin films, and also in CCl_4 and $CHCl_3$ solution ($c << 0.001$ mol l^{-1}, d 5–10 cm). ^1H NMR spectra of compounds **VI–IX** were registered on spectrometer Bruker DPX-400 (400 MHz), ^1H and ^{13}C NMR spectra of compounds **Xa, b** on Bruker DPX-250 instrument (at 250.1 and 62.4 MHz respectively). Spectra were taken from solutions in $CDCl_3$, internal reference HMDS.

Table 3. ^1H and ^{13}C NMR spectra (NOESY) of *E*- and *Z*-isomers of methyl 3-(2-pyridylthio)-2-butenoates (**Xa, b**)



Xa (*E*)



Xb (*Z*)

Compd. no.	^1H NMR spectrum, δ, ppm				^{13}C NMR spectrum, δ_C, ppm					
	CH_3	OCH_3	=CH	Ar	CH_3	OCH_3	=CH	C–S	C=O	Ar
Xa	2.45 s	3.64 s	5.80 s	7.48 d (H^3), 7.70 t.d (H^4), 7.27 q (H^5), 8.62 d.t (H^6)	20.52	51.06	115.14	153.88	165.49	155.98 (C^2), 128.50 (C^3), 137.52 (C^4), 123.02 (C^5), 150.88 (C^6)
Xb	1.99 s	3.72 s	5.91 s	7.59 d (H^3), 7.62 t.d (H^4), 7.27 q (H^5), 8.62 d.t (H^6)	24.97	51.22	113.90	154.20	166.24	155.52 (C^2), 129.31 (C^3), 137.43 (C^4), 123.10 (C^5), 150.42 (C^6)

2- and 4-Mercaptopyridines (**I, II**) are commercial products of "pure" grade. 3-Phenyl-2-propynonitrile (**III**) and 4-hydroxy-2-alkynonitriles (**IVa–c**) were prepared by methods [14, 15]. Methyl 2-butynoate (**V**) was obtained by procedure [16]. Column and thin-layer chromatography was carried out on Al_2O_3, eluent chloroform–benzene–ethanol, 20 : 4 : 1. Compounds **VI–IX** were purified by reprecipitation from chloroform into hexane. Physical constants of compounds synthesized **VI–X** are presented in Tables 1–3.

3-(2-Pyridylthio)-3-phenyl-2-propenonitrile (VI). To a solution of 0.11 g (1 mmol) of 2-mercaptopyridine (**I**) and 0.02 g of KOH in dioxane was added at stirring a solution of 0.13 g (1 mmol) of alkyne **III** in 5 ml of dioxane. The mixture was stirred for 20 h at 20–25°C. The dioxane was removed, and the residue was subjected to chromatography. Yield 0.15 g.

3-(4-Pyridylthio)-3-phenyl-2-propenonitrile (VII) was prepared in the same way from 0.11 g (1 mmol) of 4-mercaptopyridine (**II**), 0.02 g of KOH, and 0.13 g (1 mmol) of alkyne **III** at 100°C within 20 h. Yield 0.08 g.

4-Hydroxy-4-methyl-3-(2-pyridylthio)-2-pentenonitrile (VIIIa). To a dispersion of 0.11 g (1 mmol) of 2-mercaptopyridine (**I**) in 5 ml of triethylamine was added at stirring 0.11 g (1 mmol) of alkyne **IVa** in 5 ml of triethylamine. The reaction mixture was stirred for 8 h at 20–25°C, triethylamine was removed. Yield 0.21 g.

4-Hydroxy-4-methyl-3-(2-pyridylthio)-2-hexenonitrile (VIIIb) was likewise prepared from 0.11 g (1 mmol) of 2-mercaptopyridine (**I**) and 0.12 g (1 mmol) of alkyne **IVb**. Yield 0.2 g.

3-[(1-Hydroxycyclohexyl)-3-(2-pyridylthio)]-2-propenonitrile (VIIIc) was likewise prepared from 0.11 g (1 mmol) of 2-mercaptopyridine (**I**) and 0.15 g (1 mmol) of alkyne **IVc**. Yield 0.25 g.

4-Hydroxy-4-methyl-3-(4-pyridylthio)-2-pentenonitrile (IXa) was similarly prepared from 0.11 g (1 mmol) of 4-mercaptopyridine (**II**) and 0.11 g (1 mmol) of alkyne **IVa**. Yield 0.2 g.

4-Hydroxy-4-methyl-3-(4-pyridylthio)-2-hexenonitrile (IXb) was similarly prepared from 0.11 g (1 mmol) of 4-mercaptopyridine (**II**) and 0.12 g (1 mmol) of alkyne **IVb**. Yield 0.2 g.

3-[(1-Hydroxycyclohexyl)-3-(4-pyridylthio)]-2-propenonitrile (VIIIc) was likewise prepared from 0.11 g (1 mmol) of 4-mercaptopyridine (**I**) and 0.15 g (1 mmol) of alkyne **IVc**. Yield 0.2 g.

Methyl (*E*+ *Z*)-3-(2-pyridylthio)-2-butenoates (Xa, b). A mixture of 0.03 g (0.3 mmol) of 2-mercaptopyridine (**I**), 0.03 g (0.3 mmol) of methyl 2-butynoate (**V**) and 10 ml of triethylamine was stirred for 28 h at 20–25°C. Then triethylamine was removed. Yield of isomers **Xa, b** mixture 0.05 g.

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