Reductive desulfurization of 3-cyano-2-methylthiopyridines under the action of Raney nickel

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The action of Raney nickel on substituted 3-cyano-2-methylthiopyridines was studied. Under conditions of catalytic hydrogenation, the reaction yields a mixture containing the aminosulfide resulting from reduction of the nitrile group with retention of the methylthio group, the nitrile resulting from elimination of the methylthio group, and the amine resulting from both reduction of the nitrile group and elimination of the methylthio group. Treatment of 3-cyano-2-methylthiopyridines with a large amount of Raney nickel under desulfurization conditions induces simultaneous elimination of the methylthio group and reduction of the nitrile group to the aminomethyl group. When reductive desulfurization is carried out in methanol or THF, primary amines are formed, while the reactions in isopropyl or ethyl alcohol give secondary or tertiary amines, which are formed upon alkylation of the amino group with alcohols.

Key words: 3-cyano-2-methylthiopyridines; 3-aminomethylpyridines; primary, secondary, and tertiary amines; Raney nickel; reduction; desulfurization; salts of amines.

Aminoalkyl groups are present in the molecules of many natural biologically active compounds and drugs.[1—3] In particular, *N*-substituted 3-aminomethylpyridines possess anticholinesterase activity and exhibit insecticide properties, similar to those of nicotine and anabasine.[4] Compounds of this type are usually prepared from nicotinic acid derivatives.[4,5] The use of 3-cyano-2-methylthiopyridines containing various substituents in the pyridine ring seems to have good prospects for the synthesis of 3-aminomethylpyridines. These starting compounds are readily available and the synthesis of the target amines includes elimination of the methylthio group and reduction of the nitrile group to the aminomethyl group.

Raney nickel is widely used to carry out desulfurization of various sulfur-containing organic compounds.[6] The removal of sulfur may be accompanied by the reduction of various functional groups, *e.g.*, nitro and carbonyl groups. In addition, Raney nickel is used as the catalyst for hydrogenation of the nitrile group.[7]

The purpose of this work is to study the action of Raney nickel on substituted 3-cyano-2-methylthiopyridines. The resulting 3-aminomethylpyridines containing various substituents in the pyridine nucleus may be of substantial interest both for their biological activities and as structural blocks in organic synthesis.

Results and Discussion

We found that during catalytic hydrogenation of nitrile **1a** under conditions described for nicotinonitrile,[5] both reduction of the nitrile group and desulfurization may take place. According to ^{1}H NMR spectroscopy, the reaction mixture contains amine **2** resulting from reduction of the nitrile group, nitrile **3** formed upon elimination of the MeS group, and amine **4a**, the product of simultaneous reduction of the nitrile and elimination of the MeS groups. The ratio of the reaction products **2**, **3**, and **4a** was 5 : 4 : 1. No reduction of the pyridine ring was detected.

The fact that compounds **2** and **3** are the major reaction products suggests that the nitrile group reduction and MeS group elimination occur in parallel, while amine **4a** is formed upon the subsequent transformations of **2** and **3** under the reaction conditions.

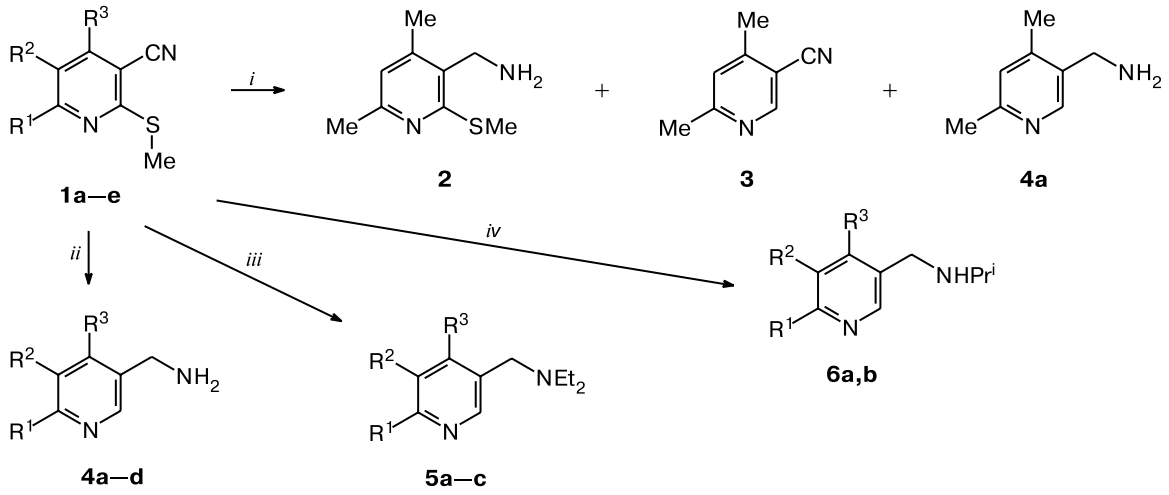
To increase the yield of 3-aminomethylpyridines containing no methylthio group, we carried out the reaction of 3-cyano-2-methylthiopyridines **1a—e** with an excess of Raney nickel under conditions described for reductive desulfurization.[6]

In this case, the action of Raney nickel on substituted 3-cyano-2-methylthiopyridines **1a—e** results in elimination of the MeS group and reduction of the nitrile group

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 11, pp. 2497—2500, November, 2005.

1066-5285/05/5411-2578

Scheme 1

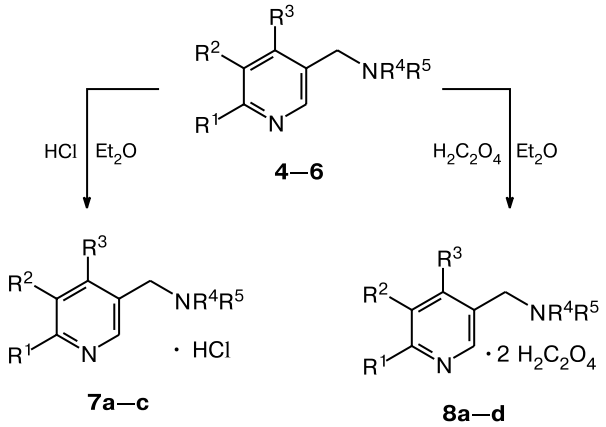


Compound	$R^1 = R^3$	R^2	Compound	$R^1 + R^2$	R^3
1a, **4a**, **5a**, **6a**	Me	H	**1c**, **4c**	$(CH_2)_3$	H
1b, **4b**, **5b**, **6b**	Ph	H	**1d**, **5c**	$(CH_2)_4$	H
			1e, **4d**	$(CH_2)_5$	H

i. H_2 (200 atm), Raney Ni (125 g mol^{-1} nitrile), EtOH, 130 °C.
ii. Raney Ni (1.25 kg mol^{-1} nitrile), MeOH or THF, Δ.
iii. Raney Ni (1.25 kg mol^{-1} nitrile), EtOH, Δ.
iv. Raney Ni (1.25 kg mol^{-1} nitrile), Pr^iOH, Δ.

to give the aminomethyl group. The synthesis was carried out by refluxing compounds **1a—e** with a suspension of a large amount of Raney nickel in an organic solvent. It was found that the structure of the reaction products depends appreciably on the nature of the solvent used. The reaction carried out in methanol or tetrahydrofuran gives primary amines **4a—d**. When ethanol is used as the solvent, tertiary amines **5a—c** are formed, and in isopropyl alcohol, the reaction gives secondary amines **6a,b**. The IR spectra of the resulting compounds exhibit no band for the nitrile group but contain an N—H absorption band (except for compounds **5a—c**) at 3330—3450 cm^{-1}.

Scheme 2



7a—c: $R^1 = R^3$ = Ph, R^2 = H, $R^4 = R^5$ = H (**a**), Et (**b**), R^4 = H, $R^5 = Pr^i$ (**c**)
8a—d: $R^2 = R^4$ = H, R^5 = H (**a—c**), Pr^i (**d**), $R^1 = R^3$ = Me (**a**, **d**), $R^1 + R^2 = (CH_2)_3$ (**b**), $(CH_2)_5$ (**c**)

Amines **4—6** are colorless liquids or low-melting compounds, which were characterized as salts. 4,6-Diphenyl-substituted amines **4b**, **5b**, and **6b** were isolated as hydrochlorides by treatment with a saturated solution of HCl in ether.

Amines **4a,c,d** and **6a**, whose hydrochlorides are highly hygroscopic, were isolated as oxalates by treatment with a saturated solution of oxalic acid in ether.

The structure of compounds **5a,c, 7a—c**, and **8a—d** was confirmed by ^{1}H NMR data. The ^{1}H NMR spectra of all compounds exhibit a signal for methylene group protons in the region of 3.4—4.4 ppm and no signal for the MeS group; the signal of H(2) is a singlet located in a lower field (δ 8.0—9.4) than the other signals for the pyridine ring protons. In addition, the spectra of compounds **5a,c** contain signals for two ethyl groups as a triplet at δ 0.93—0.95 and a quartet at δ 2.4—2.9; the spectra of compounds **7c** and **8d** show isopropyl group signals as doublets at δ 1.15—1.30 and a sextet at δ 3.2—3.4. The characteristics of compounds **5a,c, 7a—c**, and **8a—d** are summarized in Tables 1 and 2.

Thus, we demonstrated that treatment of substituted 3-cyano-2-methylthiopyridines with Raney nickel under conditions of catalytic hydrogenation induces elimination of the methylthio group and reduction of the nitrile group to the aminomethyl group. Under catalytic hydrogenation conditions, the reaction affords a mixture of three possible products: the aminosulfide resulting from the reduction of the nitrile group, the nitrile formed upon

Table 1. Characteristics of compounds **5a,c, 7a—c**, and **8a—d**

Compound	Mol. weight	Yield** (%)	M.p. /°C	Found / Calculated (%)			Molecular formula
				C	H	N	
5a	192	43.2	*	74.83	10.55	14.49	$C_{12}H_{20}N_2$
				74.95	10.48	14.57	
5c	218	60.8	*	77.05	10.18	12.70	$C_{14}H_{22}N_2$
				77.01	10.16	12.83	
7a	296.5	50.9	224—228	72.77	5.86	9.35	$C_{18}H_{16}N_2 \cdot HCl$
				72.84	5.77	9.44	
7b	352.5	57	198—201	74.80	7.25	7.86	$C_{22}H_{24}N_2 \cdot HCl$
				74.88	7.14	7.94	
7c	338.5	75.8	213—216	74.48	6.89	8.21	$C_{21}H_{22}N_2 \cdot HCl$
				74.43	6.84	8.27	
8a	316	36.5	183—186	45.51	5.18	8.81	$C_8H_{12}N_2 \cdot 2\ H_2C_2O_4$
				45.57	5.10	8.86	
8b	328	54.3	176—178	47.52	5.01	8.49	$C_9H_{12}N_2 \cdot 2\ H_2C_2O_4$
				47.56	4.91	8.53	
8c	356	53.7	169—172	50.52	5.78	7.85	$C_{11}H_{16}N_2 \cdot 2\ H_2C_2O_4$
				50.56	5.66	7.86	
8d	358	47.7	173—177	50.29	6.42	7.86	$C_{11}H_{18}N_2 \cdot 2\ H_2C_2O_4$
				50.28	6.19	7.82	

* Liquid.
** The yields of salts **7**, **8** are based on the starting nitriles **1**.

Table 2. Spectroscopic characteristics of compounds **5a,s, 7a—s**, and **8a—d**

Compound	IR*, ν/cm^{-1}	^1H NMR (δ, J/Hz)
5a	—	0.94 (t, 6 H, 2 $CH_2\underline{CH_3}$, J = 6.7); 2.28 (s, 3 H, Me(4)); 2.37 (s, 3 H, Me(6)); 2.40 (q, 4 H, 2 $\underline{CH_2}CH_3$, J = 6.7); 3.42 (s, 2 H, $\underline{CH_2}NEt_2$); 6.99 (s, 1 H, H(5)); 8.18 (s, 1 H, H(2))
5c	—	1.04 (t, 6 H, 2 $CH_2\underline{CH_3}$, J = 6.7); 1.78 (m, 4 H, CH_2); 2.49 (q, 4 H, 2 $\underline{CH_2}CH_3$, J = 6.7); 2.76 (m, 4 H, CH_2); 3.43 (s, 2 H, $\underline{CH_2}NEt_2$); 7.14 (s, 1 H, H(5)); 8.01 (s, 1 H, H(2))
7a	3448 (NH_2)	4.09 (m, 2 H, $\underline{CH_2}NH_2$); 7.50—7.60 (m, 8 H, 4-Ph: H(2), H(6) + 6-Ph: H(3), H(5)); 8.00 (s, 1 H, H(5)); 8.19 (m, 2 H, 6-Ph: H(2), H(6)); 9.14 (s, 1 H, H(2))
7b	—	0.95 (m, 6 H, 2 $CH_2\underline{CH_3}$); 2.89 (m, 4 H, 2 $\underline{CH_2}CH_3$); 4.43 (s, 2 H, $\underline{CH_2}NEt_2$); 7.50—7.62 (m, 8 H, 4-Ph: H(2), H(6) + 6-Ph: H(3), H(5)); 8.02 (s, 1 H, H(5)); 8.21 (m, 2 H, 6-Ph: H(2), H(6)); 9.40 (s, 1 H, H(2))
7c	3356 (NH)	1.14 (d, 6 H, $CH(\underline{CH_3})_2$, J = 6.8); 3.18 (m, 1 H, CH); 4.21 (s, 2 H, $\underline{CH_2}NHPr^i$); 7.55—7.70 (m, 8 H, 4-Ph: H(2), H(6) + 6-Ph: H(3), H(5)); 7.86 (s, 1 H, H(5)); 8.24 (m, 2 H, 6-Ph: H(2), H(6)); 9.41 (s, 1 H, H(2))
8a	3408 (NH_2)	2.32 (s, 3 H, Me(4)); 2.41 (s, 3 H, Me(6)); 4.11 (s, 2 H, $\underline{CH_2}NH_2$); 7.15 (s, 1 H, H(5)); 8.38 (s, 1 H, H(2))
8b	3387 (NH_2)	2.18 (m, 2 H, CH_2(2)); 2.39 (m, 4 H, CH_2); 4.12 (s, 1 H, $\underline{CH_2}NH_2$); 7.41 (s, 1 H, H(4)); 8.25 (s, 1 H, H(2))
8c	3374 (NH_2)	1.54 (m, 4 H, CH_2); 1.96 (m, 2 H, CH_2(2)); 2.53 (m, 4 H, CH_2); 4.09 (s, 2 H, $\underline{CH_2}NH_2$); 7.21 (s, 1 H, H(4)); 8.13 (s, 1 H, H(2))
8d	3328 (NH)	1.28 (d, 6 H, $CH(\underline{CH_3})_2$, J = 6.8); 2.34 (s, 3 H, Me(4)); 2.42 (s, 3 H, Me(6)); 3.42 (m, 1 H, CH); 4.15 (s, 2 H, $\underline{CH_2}NHPr^i$); 7.18 (s, 1 H, H(5)); 8.43 (s, 1 H, H(2))

* IR spectra were recorded for free amines.

abstraction of the MeS group, and the amine produced by both processes taking place simultaneously. The last-mentioned amines are formed as the only products when substituted 3-cyano-2-methylthiopyridines are treated with excess Raney nickel under desulfurization reaction conditions. The reactions in methanol or tetrahydrofuran yield

primary amines, and those in isopropyl or ethyl alcohol, secondary or tertiary amines due to alkylation of the amino group with alcohols.

Experimental

The melting points were determined on a Koeffler hot stage. IR spectra were recorded on a Specord M-80 spectrophotometer in KBr pellets, ^{1}H NMR spectra were run on a Bruker AC-200 instrument (200 MHz) in DMSO-d_6. The solvent signal was used as the internal standard (δ_H = 2.50). Elemental analysis was carried out on a Perkin—Elmer 2400 instrument. 3-Cyano-2-methylthiopyridines **1a—e** were prepared by a known procedure.[8]

Hydrogenation. Freshly prepared Raney nickel (prepared by treatment of a suspension of 0.5 g of a Ni/Al alloy in H_2O with NaOH) was added to a solution of nitrile **1a** (0.35 g, 2 mmol) in EtOH (20 mL), and the mixture was hydrogenated in an autoclave at 130 °C and a hydrogen pressure of 200 atm. The light-green solution was filtered off from the catalyst, and the solvent was evaporated to give 0.25 g of a light-green liquid containing, according to ^{1}H NMR data, compounds **2**, **3**, and **4a** in 5 : 4 : 1 ratio.

3-(Aminomethyl)pyridines (4—6). Freshly prepared Raney nickel (prepared by treatment of a suspension of 5 g of a Ni/Al alloy in H_2O with NaOH) was added to a solution of nitrile **1a—e** (2 mmol) in the desired solvent (30 mL). The mixture was refluxed for 5 h and cooled. Nickel was filtered off and the solvent was evaporated to give amines **4—6** as colorless liquids or low-melting compounds in 45—85% yields.

Salts 7, 8. Amines **4—6** were dissolved in 10 mL of ether, the solution was mixed with 20 mL of a saturated ether solution of HCl or oxalic acid, and the precipitate was filtered off to give salts **7** and **8** as colorless crystals in 85—95% yields.

This work was performed with the financial support of the Russian Foundation for Basic Research (Project No 05-03-32031).

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Received June 2, 2005;
in revised form September 6, 2005