Sodium bis(2-methoxyethoxy)aluminum hydride in reactions with 3-cyano-6-methylpyridine-2(1*H*)-thione and 3-cyano-6-methyl(4,6-dimethyl)-2-methylthiopyridines

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The reactions of sodium bis(2-methoxyethoxy)aluminum hydride with 3-cyano-6-methylpyridine-2(1*H*)-thione and 3-cyano-6-methyl-2-methylthiopyridine afforded 3-aminomethyl-6-methylpyridine-2(1*H*)-thione and azomethine of the pyridine series, respectively. The corresponding reaction with 3-cyano-4,6-dimethyl-2-methylthiopyridine gave rise to azomethine, substituted 3-aminomethylpyridine, and substituted dipyridylmethane.

Key words: 3-cyano-6-methylpyridine-2(1*H*)-thione, 3-cyano-2-methylthiopyridines, 3-aminomethyl-4,6-dimethyl-2-methylthiopyridine, 3-aminomethyl-6-methylpyridine-2(1*H*)-thione, azomethines, dipyridylmethane, sodium bis(2-methoxyethoxy)aluminum hydride, reduction.

With the aim of preparing biologically active compounds as well as new building blocks for heterocyclic synthesis, we continued investigations on reduction of 3-cyanopyridine-2(1*H*)-thiones and their derivatives. Earlier,[1] we have demonstrated that reactions of lithium aluminum hydride with substituted 3-cyanopyridine-2(1*H*)-thiones and 3-cyano-2-methylthiopyridines in anhydrous diethyl ether afforded 3-aminomethyl derivatives.

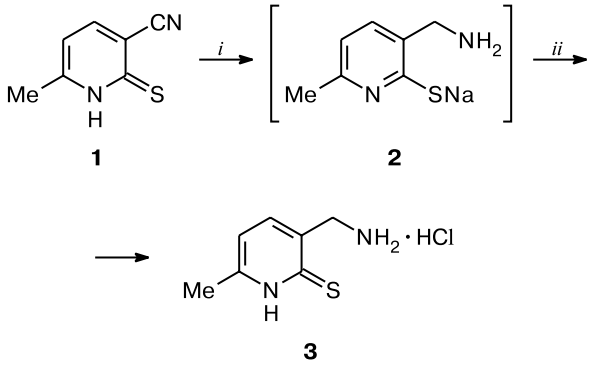
Nitriles can be reduced not only with lithium aluminum hydride but also with other complex metal hydrides, such as sodium bis(2-methoxyethoxy)aluminum hydride (BMA). The latter reagent is widely used for reduction of nitriles to both aldehydes[2—4] and amines.[5—7] In its properties, BMA is similar to lithium aluminum hydride[5,6] and is often recommended as an alternative to the latter reagent. Sodium bis(2-methoxyethoxy)aluminum hydride reduces acids and their esters, amides, and nitriles to the corresponding alcohols and amines in high yields (generally, in yields higher than 90%; sometimes, in quantitative yields)[5—8] using a minimum excess of the hydride. This is a more convenient and safe reducing agent which, unlike lithium aluminum hydride, it is not oxidized in dry air, and its contact with water does not lead to explosion. Being partially hydrolyzed, BMA remains soluble in diethyl ether. Besides, reactions with the use of partially hydrolyzed hydride often afford products in higher yields.

The aim of the present study was to investigate the reactions of BMA with substituted 3-cyanopyridine-2(1*H*)-thiones and their methylthio derivatives.

Results and Discussion

We found that $NaAlH_2(OC_2H_4OCH_3)_2$ (BMA), like $LiAlH_4$, reduces 3-cyanopyridine-2(1*H*)-thiones to the corresponding aminomethyl derivatives. For example, 3-cyano-6-methylpyridine-2(1*H*)-thione (**1**) was reduced to amine **2**, which was isolated as hydrochloride **3** in 85—90% yield (Scheme 1). The yields in reactions with $LiAlH_4$ were rarely higher than 75%.

Scheme 1



i. $NaAlH_2(OC_2H_4OMe)_2$, Et_2O; *ii*. HCl.

The identity of hydrochloride **3** to a specimen prepared earlier was confirmed by IR and ^1H NMR spectroscopy and also by the fact that a mixture of these two compounds showed no melting point depression.

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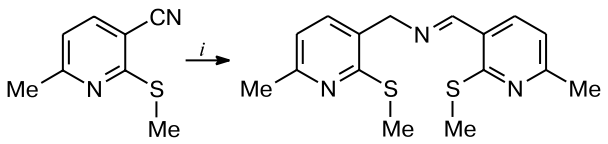
Like in the reaction with $LiAlH_4$,[1] thione **1** was reduced by adding a solution of the hydride in benzene to a boiling suspension of thione **1** in anhydrous diethyl ether (method *A*). The best yield of amine **3** was achieved with the use of 3 moles of BMA per mole of the starting nitrile **1** and with the gradual addition of the reducing agent. Apparently, this is favorable for a more complete conversion of the starting thione into intermediate complex aluminum thiolates.[9]

A different order of addition of the reagents (addition of the solid thione to a solution of the hydride in diethyl ether) also led to reduction of 3-cyanopyridine-2(1*H*)-thione **1** to amine **3** (method *B*). Under these conditions, $LiAlH_4$, unlike BMA, does not reduce the nitrile group in 3-cyanopyridine-2(1*H*)-thiones.[1]

It was also found that the reaction of BMA with substituted 3-cyano-2-methylthiopyridines differs from that of $LiAlH_4$, which reduces 3-cyano-2-methylthiopyridines to the corresponding 3-aminomethyl-2-methylthiopyridines in good yields.[1]

Refluxing of BMA with 3-cyano-6-methyl-2-methylthiopyridine (**4a**) in diethyl ether in a molar ratio of 2 : 1 afforded azomethine **5** in 90% yield (Scheme 2). At room temperature, the reaction produced compound **5** in 82% yield.

Scheme 2



4a **5**

i. 2 $NaAlH_2(OC_2H_4OCH_3)_2$, Et_2O.

The structure of compound **5** was confirmed by IR and ^1H NMR spectroscopy and mass spectrometry. The IR spectrum of *N*-(6-methyl-2-methylthiopyridin-3-yl)methyl(6-methyl-2-methylthiopyridin-3-yl)methylideneamine (**5**) has an absorption band of the C=N group at 1640 cm^{-1}. The ^1H NMR spectrum shows singlets of the $—CH_2N=$ and —N=CH groups (δ 4.77 and 8.70), four doublets of the pyridine protons at δ 6.85, 6.90, 7.50, and 7.95, and four singlets of the methyl groups at δ 2.51, 2.54, 2.61, and 2.62, which is indicative of the presence of two substituted pyridine rings.

The reaction of BMA with 3-cyano-4,6-dimethyl-2-methylthiopyridine (**4b**) in a molar ratio of 2 : 1, unlike that with monosubstituted derivative **4a**, afforded a mixture containing (according to the ^1H NMR spectroscopic data) 65% of amine **6**, 5% of azomethine **7**, and 30% dipyridylmethane **8** (Scheme 3).

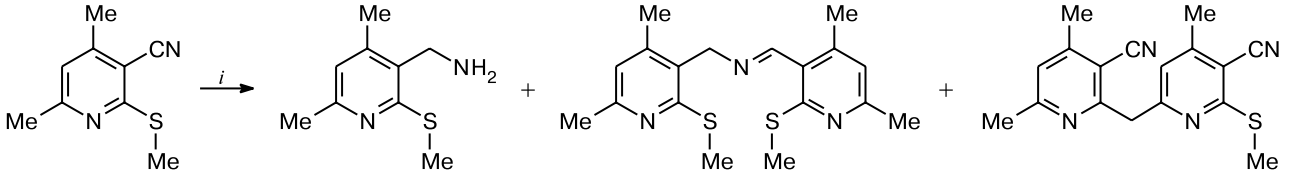
The identity of amine **6** to a sample prepared earlier[1] was established by IR and ^1H NMR spectroscopy. The structure of *N*-(4,6-dimethyl-2-methylthiopyridin-3-yl)methyl(4,6-dimethyl-2-methylthiopyridin-3-yl)methylideneamine (**7**) was confirmed by IR and ^1H NMR spectroscopy and mass spectrometry. The IR spectrum of compound **7** has an adsorption band of the C=N group at 1632 cm^{-1}. The ^1H NMR spectrum shows singlets of the $—CH_2N=$ and —N=CH groups (δ 4.93 and 8.67), two singlets of the pyridine protons at δ 6.68 and 6.73, and six singlets of the methyl groups at δ 2.36, 2.42, 2.45, 2.46, 2.53, and 2.56.

Compound **8** was also identified as a 2,2′-bispyridylmethane derivative rather than as an isomeric 2-pyridyl(2′-pyridylmethyl)sulfide (**9**) (Scheme 4) based on spectroscopic data.

The IR spectrum of this compound has an absorption band of the nitrile group at 2224 cm^{-1}. The ^1H NMR spectrum shows a singlet of the methylene group at δ 4.43, two singlets of the pyridine protons at δ 6.54 and 7.05, and four singlets of the methyl groups at δ 2.49, 2.51, 2.52, and 2.62, which is evidence for the presence of two substituted pyridine rings. However, neither structure **8** nor structure **9** can be rejected based on these data. Apparently, both these compounds can be formed because BMA possesses both reducing and basic properties.

It is known that the methylthio group in 3-cyano-2-methylthiopyridines can be replaced in reactions with different nucleophilic agents.[10] Hence, the mechanism of formation of compounds **8** or **9** involves, presumably, generation of the RCH_2^- anion from the starting 3-cyano-2-methylthiopyridine followed by its nucleophilic at-

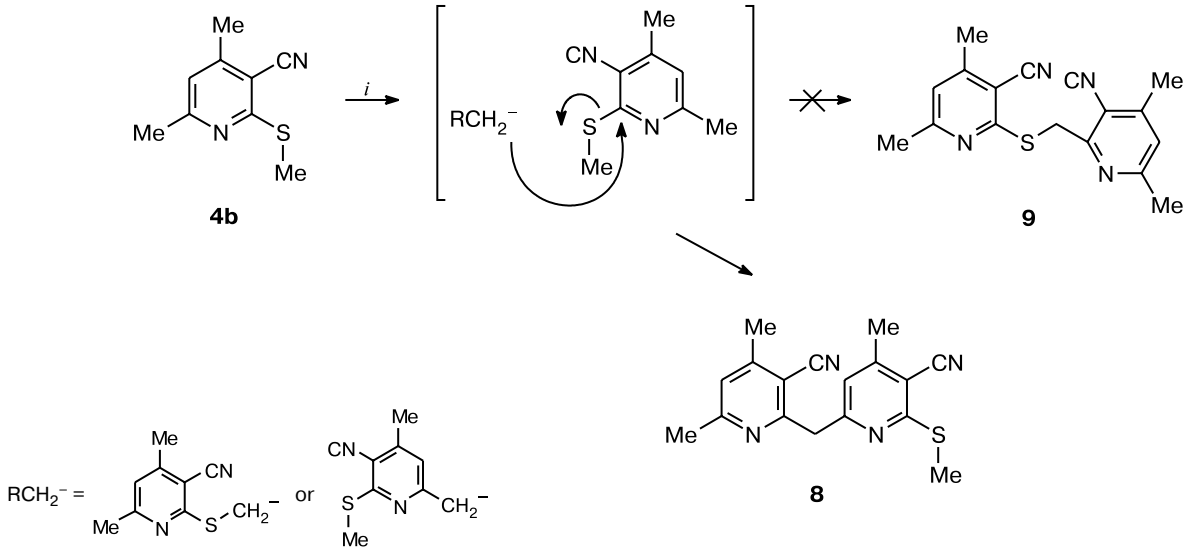
Scheme 3



4b **6** **7** **8**

i. $NaAlH_2(OC_2H_4OMe)_2$, Et_2O.

Scheme 4



i. $NaAlH_2(OC_2H_4OCH_3)_2$, Et_2O.

tack at position 2 of another molecule (see Scheme 4), the anionic center being generated either from the 6-methyl group to give compound **8** (such reactions are known[11—13]) or from the methylthio group to give compound **9**, which has also been described in the literature.[13,14] The reaction can, in principle, follow both pathways because BMA is a strong base and is able to generate anions from various compounds.[15]

Thorough examination of the ^{1}H NMR spectrum provided evidence that the reaction under consideration afforded compound **8**. Analysis of the chemical shifts of the methyl and methylthio groups in the ^{1}H NMR spectra of compounds synthesized earlier[1] (3-cyano-6-methyl-2-methylthio-, 3-cyano-4,6-dimethyl-2-methylthio-, 3-aminomethyl-6-methyl-2-methylthio-, and 3-aminomethyl-6-(2,2-dimethylvinyl)-2-methylthiopyridines) as well as of compounds **5** and **7** demonstrated that the signal of the 6-Me group appears at δ 2.60—2.70, the signal of the methylthio group is observed at δ 2.50—2.54, and the signal of the 4-Me group appears at δ 2.50 or at higher field. In some cases (compound **7**), the signal of the 6-Me group is shifted to the region of 2.53—2.56 ppm. However, in such cases, other signals are also shifted upfield. Two signals in the region of δ 2.60 (6-Me groups) and two signals in the region of δ 2.50 (4-Me groups) would be expected to appear in the ^{1}H NMR spectrum of compound **9** by analogy with compound **5**. In the case under consideration, the spectrum has only one singlet at δ 2.62 and three singlets at δ 2.49, 2.51, and 2.52, which corresponds to the structure of 3-cyano-6-(3-cyano-4,6-dimethyl-2-pyridyl)methyl-4-methyl-2-methylthiopyridine (**8**). Structure **8** is indirectly confirmed by the fact that this compound did not undergo intramolecular heterocyclization giving rise to thienopyridines, which is characteristic of compounds analogous to **9**.[10]

It should be noted that 3-cyano-4,6-dimethyl-2-methylthiopyridine (**4b**), unlike 3-cyano-6-methyl-2-methylthiopyridine (**4a**), is not reduced at room temperature. After standard work-up, we isolated the starting nitrile. The characteristics of compounds **3** and **5—8** are given in Tables 1 and 2.

To summarize, we demonstrated that BMA, like $LiAlH_4$, reduces substituted 3-cyanopyridine-2(1*H*)-thiones in anhydrous diethyl ether to give 3-aminomethyl derivatives. The reaction of BMA with 3-cyano-2-methylthiopyridines proceeds differently from that of $LiAlH_4$. The latter reduces 3-cyano-2-methylthiopyridines to the corresponding 3-aminomethyl-2-methylthiopyridines in good yields. The reaction of BMA with 3-cyano-6-methyl-2-methylthiopyridine gives rise to azomethine of the pyridine series as the only product. The reaction with 3-cyano-4,6-dimethyl-2-methylthiopyridine yields azomethine along with 3-aminomethylpyridine and dipyridylmethane.

Experimental

The melting points were determined on a Kofler stage. The IR spectra were recorded on a Specord M-80 spectrophotometer in KBr pellets. The ^{1}H NMR spectra were measured on a Bruker WM-250 spectrometer (250 MHz) in $CDCl_3$. A signal of the solvent (δ_H = 7.25) was used as the internal standard. The mass spectra were obtained on a Finnigan MAT INCOS-50 instrument; the ionization energy was 70 eV. A 70% BMA solution in benzene was purchased from Synthesia kolin.

Table 1. Yields and characteristics of compounds **3—8**

Compound	Molecular weight	Yield (%)	M.p./°C (solvent)	Found / Calculated (%)					Molecular formula
				C	H	N	S	Cl	
3	190.5	88	292—296 (EtOH)	43.87 / 44.09	5.89 / 5.81	14.57 / 14.69	16.99 / 16.81	18.68 / 18.59	$C_7H_{11}ClN_2S$
5	317	90	81—84 (C_6H_{14})	60.90 / 60.53	6.22 / 6.03	13.11 / 13.24	20.43 / 20.20	—	$C_{16}H_{19}N_3S_2$
6	182	55	70—72 (C_6H_{14})	59.19 / 59.30	7.81 / 7.74	15.24 / 15.37	17.76 / 17.59	—	$C_9H_{14}N_2S$
7	345	5.5	109—111 (C_6H_{14})	62.43 / 62.57	6.78 / 6.71	12.36 / 12.16	18.16 / 18.56	—	$C_{18}H_{23}N_3S_2$
8	308	29	162—164 (EtOH)	66.04 / 66.21	5.21 / 5.23	18.49 / 18.17	9.91 / 10.40	—	$C_{17}H_{16}N_4S$

Table 2. Spectroscopic characteristics of compounds **3—8**

Compound	IR, ν/cm^{-1}	MS, *m/z* (*I* (%))	^{1}H NMR (δ, *J*/Hz)
3	3456 (NH_2), 3480 (NH_2), 3504 (NH)	—	2.40 (s, 3 H, Me); 4.00 (m, 2 H, CH_2); 6.70 (d, 1 H, H(5), *J* = 7.4); 7.70 (d, 1 H, H(4), *J* = 7.4); 8.60 (s, 3 H, NH_3^+); 13.75 (s, 1 H, NH)
5	1640 (CH=N)	317 $[M]^+$ (0.85), 302 (35.6), 165 (7.1), 152 (100), 138 (16.2), 118 (4.3), 106 (40.2), 92 (5.8), 77 (19.1), 65 (6.3), 51 (8.4), 39 (9.3)	2.51, 2.54, 2.61, 2.62 (all s, 3 H each, 4 Me); 4.77 (s, 2 H, CH_2); 6.85, 6.90, 7.50, 7.95 (all d, 1 H each, H(4), H(4′), H(5), H(5′), *J* = 7.4); 8.70 (s, 1 H, CH)
6	3408 (NH_2), 1628 (NH_2)	—	1.63 (br.s, 2 H, NH_2); 2.3 (s, 3 H, Me(4)); 2.37 (s, 3 H, Me(6)); 2.47 (s, 3 H, SMe); 3.72 (s, 2 H, CH_2); 6.75 (s, 1 H, H(5))
7	1632 (CH=N)	345 $[M]^+$ (0.78), 330 (21.9), 166 (100), 152 (7.3), 120 (36.1), 91 (12.2), 77 (17.3), 65 (9.8), 51 (7.2), 39 (11.2)	2.36, 2.42, 2.45, 2.46, 2.53, 2.56 (all s, 3 H each, 6 Me); 4.93 (s, 2 H, CH_2); 6.68, 6.73 (both s, 1 H each, H(5), H(5′)); 8.67 (s, 1 H, CH)
8	2224 (CN)	308 $[M]^+$ (100), 293 (42), 275 (35.5), 266 (15.9), 188 (39.9), 177 (59.4), 163 (17), 146 (20.8), 125 (24.7), 96 (18.6), 77 (39.4), 63 (15.7), 51 (23.4), 40 (80.3)	2.49, 2.51, 2.52, 2.62 (all s, 3 H each, 4 Me); 4.43 (s, 2 H, CH_2); 6.54, 7.05 (both s, 1 H each, H(5), H(5′))

3-Aminomethyl-6-methylpyridine-2(1*H*)-thione hydrochloride (3). ***A.*** A BMA solution (1.4 mL, 5 mmol) was added with stirring to a boiling suspension of pyridinethione **1** (0.75 g, 5 mmol) in anhydrous Et_2O (50 mL) over 15 min. The reaction mixture was refluxed with stirring for 1.5 h and then a BMA solution (2.8 mL, 10 mmol) was added. The reaction mixture was refluxed with stirring for 4 h and then cooled. Water (200 mL) was added dropwise with vigorous stirring. After 24 h, the precipitate that formed was filtered off, the organic layer was washed with water, and the combined aqueous fractions were acidified with concentrated HCl to pH 2—3. The precipitate of the unconsumed thione (0.05—0.1 g) was filtered off, the aqueous solution was concentrated, the residue was treated with hot ethanol, and the solvent was distilled off to give hydrochloride **3** in a yield of 0.81—0.86 g (85—90%). An analytical sample was prepared by recrystallizing three times from ethanol.

B. Pyridinethione **1** (0.75 g, 5 mmol) was added portionwise to a boiling mixture of a BMA solution (4.2 mL, 15 mmol) and anhydrous Et_2O (50 mL) for 10 min. The reaction mixture was refluxed with stirring for 4 h and worked up as described in the method ***A***, after which hydrochloride **3** was obtained in a yield of 0.6 g (63%).

N*-(6-Methyl-2-methylthiopyridin-3-yl)methyl(6-methyl-2-methylthiopyridin-3-yl)methylideneamine (5).** ***A. A solution of nitrile **4a** (1 g, 6 mmol) in Et_2O (20 mL) was added to a boiling mixture of a BMA solution (3.4 mL, 12 mmol) and Et_2O (30 mL) for 15 min. The resulting pale-brown solution was refluxed with stirring for 1.5 h and then cooled. Water (100 mL) was added dropwise to the solution. The organic layer was separated, washed with water, and dried with $MgSO_4$. The solvent was distilled off. Azomethine **5** was obtained in a yield of 0.87 g (90%) as yellow crystals.

B. A solution of nitrile **4a** (1 g, 6 mmol) in Et_2O (20 mL) was added to a mixture of a BMA solution (3.4 mL, 12 mmol) and Et_2O (30 mL) at 20 °C for 15 min. The resulting pale-brown solution was stirred at 20 °C for 3 h and worked up as described

in the method ***A***. Azomethine **5** was obtained in a yield of 0.79 g (82%).

Reaction of nitrile 4b with BMA. A solution of nitrile **4b** (1.8 g, 10 mmol) in Et_2O (40 mL) was added to a boiling mixture of a BMA solution (5.6 mL, 20 mmol) in boiling Et_2O (70 mL) over 15 min. The resulting transparent dark-red solution was refluxed with stirring for 1.5 h and then cooled. Water (200 mL) was added dropwise to the solution. The organic layer was separated, washed with water, and dried with $MgSO_4$. The solvent was distilled off. The product was recrystallized from ethanol (10 mL). Dipyridylmethane **8** was obtained in a yield of 0.45 g (29%) as a yellow powder. The filtrate was slowly concentrated (for 2 days), after which white fibrous crystals precipitated. The crystals were filtered off and azomethine **7** was obtained in a yield of 0.1 g (5.5%). The residual solvent was distilled off and the resulting mixture was treated with hot hexane. After evaporation, amine **6** was obtained in a yield of 1.01 g (55%).

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