Synthesis of 2-alkylthio-6-methylpyridine-3-carbaldehydes*

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The action of sodium bis(2-methoxyethoxy)aluminum hydride and its complex with piperidine on 2-alkylthio-3-cyano-6-methylpyridines and on their esters in anhydrous ether yielded 2-alkylthio-3-formyl-6-methylpyridines. The aldehydes obtained undergo condensation with malononitrile and methyl cyanoacetate to give the corresponding hetarylidene derivatives.

Key words: 2-alkylthio-3-cyano-6-methylpyridines, 2-alkylthio-3-formyl-6-methylpyridines, aldehydes, sodium bis(2-methoxyethoxy)aluminum hydride, reduction, malononitrile, methyl cyanoacetate, condensation.

Earlier,¹ we demonstrated that the action of lithium aluminum hydride on substituted 3-cyanopyridine-2(1H)-thiones and 2-(alkylthio)-3-cyanopyridines in boiling anhydrous ether affords the corresponding 3-aminomethyl derivatives. The use of sodium bis(2-methoxyethoxy)aluminum hydride (BMA) under analogous conditions leads to various products, depending on the structure of the starting reagent. For instance, pyridine-2(1H)-thiones yield aminomethyl derivatives, 3-cyano-6-methyl-2-methylthiopyridine yields azomethine, and 3-cyano-4,6-dimethyl-2-methylthiopyridine yields a mixture of an amine, azomethine, and dipyridylmethane.²

Apart from amines, aldehydes of the pyridine-2(1H)thione and 2-alkylthiopyridine series are of considerable interest as building blocks in heterocyclic synthesis.

BMA is known³⁻⁷ to be used for the synthesis of not only amines but also aldehydes from both nitriles³ and esters;^{4,7} BMA is employed alone or together with secondary amines such as pyrrolidine, morpholine, and piperidine.^{5,6}

The goal of the present study was to develop methods of preparing aldehydes of the 2-(alkylthio)pyridine series with BMA and its complex with piperidine (BMAP) as reducing agents.

Results and Discussion

We found that the action of BMA on 3-cyano-6-methyl-2-methylthiopyridine (1) in ether at 0 °C gives aldehyde 2a (as a mixture with the starting nitrile 1). The aldehyde content of the mixture is 50% at a nitrile : BMA

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ratio of 1 : 2 (¹H NMR data); use of more BMA leads to by-products. With a milder reducing agent, BMAP, prepared from BMA by the reaction with piperidine,⁵ the yield of the target product was not increased significantly. According to the ¹H NMR data, the content of aldehyde **2a** (in the mixture with the starting nitrile **1**) in this case is 60% at a nitrile : BMAP ratio of 1 : 3 (Scheme 1). An increase in the amount of BMAP causes side processes to occur.

With the aim of increasing the yield of the aldehyde and avoiding side processes, we used esters 3a,b (synthesized according to known procedures^{8,9}) in the reduction instead of the corresponding nitriles.

In contrast to nitrile, the reduction of ester 3a with BMA in ether at 0 °C led to 3-hydroxymethyl-6-methyl-2-methylthiopyridine (4) in 99% yield (see Scheme 1).

The structure of compound **4** was confirmed by data from IR and ¹H NMR spectroscopy and mass spectrometry. Its IR spectrum contains no absorption band of the CO_2Me group but shows a wide band of the hydroxyl group at 3350 cm⁻¹; the ¹H NMR spectrum contains a singlet signal for the methylene group at δ 4.67.

In contrast to the reaction with BMA, the reactions of BMAP with methyl 6-methyl-2-methylthiopyridine-3carboxylate (**3a**) and ethyl 2-ethylthio-6-methylpyridine-3-carboxylate (**3b**) in boiling ether gave 3-formyl-6-methyl-2-methylthiopyridine (**2a**) and 2-ethylthio-3-formyl-6-methylpyridine (**2b**) in 99 and 80% yields, respectively (see Scheme 1). Such a difference in the properties of the reducing agents used is due to the relative stabilities of aldehydes in the presence of BMAP under the aforementioned conditions.⁵

The structures of aldehydes **2a,b** were confirmed by data from IR and ¹H NMR spectroscopy and mass spectrometry. Their IR spectra show a characteristic absorp-

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Scheme 1

2, 3, 5: R = Me (**a**), Et (**b**) Z = CN (**5**), CO₂Me (**6**)

Reagents and conditions: *i*. NaAlH₂(OC₂H₄OMe)₂, Et₂O, 0 °C; *ii*. NaAlH₂(OC₂H₄OMe)₂/piperidine, boiling Et₂O; *iii*. ZCH₂CN, Et₃N, EtOH.

tion band of the formyl group at 1696 cm⁻¹; the ¹H NMR spectrum contains a singlet signal for the formyl proton at δ 10.20 (**2a**) and 10.21 (**2b**).

Compounds 2a,b exhibit properties typical of aldehydes, *e.g.*, they undergo condensation with malononitrile and methyl cyanoacetate to give the corresponding ylidene derivatives 5a,b and 6 (see Scheme 1).

The structures of compounds **5a,b** and **6** were confirmed by data from IR and ¹H NMR spectroscopy. The IR spectra of ylidenes **5a,b** show an absorption band of the nitrile groups at 2224 (**5a**) and 2236 cm⁻¹ (**5b**). The IR spectrum of compound **6** contains absorption bands at 2224 (CN) and 1720 cm⁻¹ (CO₂Me). In the ¹H NMR spectra of the compounds obtained, the signal for the proton at the double bond is shifted downfield to $\delta 8.14$ (5a), 8.13 (5b), and 8.58 (6). The characteristics of compounds 2 and 4–6 are given in Tables 1 and 2.

Thus, we demonstrated that the action of sodium bis(2-methoxyethoxy)aluminum hydride and its complex with piperidine on 3-cyano-6-methyl-2-methylthiopyridine in anhydrous ether affords the corresponding aldehyde. However, the yields of the aldehyde are low and by-products are formed. A more advisable route to aldehydes involves the reaction of BMAP with the corresponding esters rather than nitriles. The aldehydes obtained undergo condensation with malononitrile and methyl cyanoacetate to give hetarylidene derivatives.

Table 1. Yields and physicochemical characteristics of compounds 2 and 4–6

Com- pound	Yield (%)	M.p./°C (solvent)	Found Calculated (%)				Molecular formula
			С	Н	N	S	
2a	99	31-33	<u>57.29</u> 57.46	<u>5.49</u> 5.42	<u>8.25</u> 8.38	<u>19.28</u> 19.17	C ₈ H ₉ NOS
2b	80	Liquid	<u>59.47</u> 59.64	<u>6.22</u> 6.12	<u>7.61</u> 7.73	<u>17.80</u> 17.69	C ₉ H ₁₁ NOS
4	99	59—61 (C ₆ H ₁₄)	<u>56.64</u> 56.78	<u>6.61</u> 6.55	<u>8.19</u> 8.28	<u>19.09</u> 18.94	C ₈ H ₁₁ NOS
5a	42	(C_6H_{14}) (C_6H_{14})	<u>61.25</u> 61.37	<u>4.26</u> 4.21	<u>19.43</u> 19.52	<u>15.03</u> 14.89	$C_{11}H_9N_3S$
5b	34	64-66 (C ₆ H ₁₄)	<u>62.65</u> 62.86	<u>4.89</u> 4.84	$\frac{18.43}{18.33}$	<u>14.16</u> 13.98	$C_{12}H_{11}N_3S$
6	69	139-141 (C ₆ H ₁₄)	<u>57.89</u> 58.05	<u>4.94</u> 4.87	<u>11.16</u> 11.28	<u>13.03</u> 12.91	$C_{12}H_{12}N_2O_2S$

Com-	IR,	MS,	¹ H NMR,
pound	v/cm ⁻¹	m/z(I(%))	δ (<i>J</i> /Hz)
2a	1696 (CH=O)	167 [M] ⁺ (36.5), 150 (16.5), 139 (48.3),	2.58 (s, 3 H, SMe); 2.60 (s, 3 H, Me); 7.00 (d, 1 H, H(5),
		125 (16.8), 111 (23.8), 85 (47.1),	J = 7.4; 7.89 (d, 1 H, H(4), $J = 7.4$);
		69 (62.5), 57 (93.4), 43 (100)	10.20 (s, 1 H, CH=O)
2b	1696 (CH=O)	_	1.40 (t, 3 H, CH ₂ C <u>H₃</u>); 2.58 (s, 3 H, Me);
			$3.29 (q, 2 H, CH_2); 6.99 (d, 1 H, H(5), J = 7.4);$
			7.89 (d, 1 H, H($\overline{4}$), $J = 7.4$); 10.21 (s, 1 H, C <u>H</u> =O)
4	3350 (OH)	169 [M] ⁺ (35.7), 154 (100), 136 (58.9),	2.50 (s, 3 H, SMe); 2.50 (s, 3 H, Me);
		122 (35.6), 106 (15.5), 92 (36.3),	4.67 (s, 2 H, CH_2OH); 6.87 (d, 1 H, H(5), $J = 7.4$);
		77 (12.2), 73 (12.9), 65 (25.4)	7.48 (d, 1 H, $H(\bar{4})$, $J = 7.4$)
5a	2224 (CN)	215 [M] ⁺ (100), 200 (22.1), 189 (80.5),	2.60 (s, 3 H, SMe);
		182 (22.6), 175 (32.4), 156 (23.4),	2.67 (s, 3 H, Me);
		150 (67.3), 142 (17.4), 118 (17.5),	7.02 (d, 1 H, H(5), $J = 7.4$);
		91 (20.3), 64 (10.6), 47 (10.7),	8.14 (s, 1 H, C=C <u>H</u>);
		43 (21.7), 39 (19)	8.19 (d, 1 H, H(4), J = 7.4)
5b	2236 (CN)	229 [M] ⁺ (72.7), 214 (60.9), 200 (55),	1.39 (t, 3 H, CH ₂ C <u>H₃</u>);
		196 (59.5), 175 (71.4), 169 (66.5),	2.59 (s, 3 H, Me);
		164 (100), 142 (46.2), 131 (32.5),	3.31 (q, 2 H, CH ₂);
		118 (53.2), 114 (56.4), 93 (19.8),	7.01 (d, 1 H, H(5), $J = 7.4$);
		88 (21.8), 77 (14.6), 69 (15.5),	8.13 (s, 1 H, C=CH);
		57 (16), 43 (25.1)	8.18 (d, 1 H, H(4), J = 7.4)
6	2224 (CN);	248 [M] ⁺ (17.6), 233 (9.8), 217 (7.2),	2.58 (s, 3 H, SMe); 2.64 (s, 3 H, Me);
	1720 (CO ₂ Me)	189 (100), 174 (7.6), 156 (24.7),	3.95 (s, 3 H, CO ₂ Me);
		150 (20.4), 144 (10.6), 117 (8.7),	6.99 (d, 1 H, H(5), $J = 7.4$);
		104 (13.7), 91 (13.4), 77 (7), 63 (9.4),	8.25 (d, 1 H, H(4), $J = 7.4$);
		45 (6.2), 43 (16.2), 39 (15.2)	8.58 (s, 1 H, C=CH)

Table 2. Spectroscopic characteristics of compounds 2 and 4-6

Experimental

Melting points were determined on a Kofler hot stage. IR spectra were recorded on a Specord M-80 spectrophotometer (KBr pellets); ¹H NMR spectra were recorded on a Bruker WM-250 spectrometer (250 MHz) in CDCl₃ with a signal for the solvent as the internal standard ($\delta_{\rm H}$ 7.25). Mass spectra were recorded on a Finnigan MAT INCOS-50 instrument (ionizing energy 70 eV). Elemental analysis was carried out with a Perkin—Elmer 2400 instrument. 3-Cyano-6-methyl-2-methylthiopyridine (1)¹⁰ and esters **3a,b**^{8,9} were prepared according to known procedures. A commercial 70% solution of BMA (Synthesia kolin Co.) in benzene was used.

3-Formyl-6-methyl-2-methylthiopyridine (2a). *A.* Sodium bis(2-methoxyethoxy)aluminum hydride (1.7 mL, 6.5 mmol) was added for 30 min to a stirred solution of nitrile **1** (0.5 g, 3 mmol) in Et₂O (30 mL), while maintaining the reaction temperature at 0 °C. The red solution was stirred at the same temperature for 3 h and then 10% aqueous H_2SO_4 (15 mL) was added dropwise. The organic layer was separated, washed with water, dried over MgSO₄, and concentrated to give the product (0.47 g) as an opaque yellow liquid. The content of aldehyde **2a** in the liquid was 50% (¹H NMR data).

B. A 1 *M* solution of BMAP (9 mL, 9 mmol) in Et₂O was added dropwise for 20 min to a stirred boiling solution of nitrile 1 (0.5 g, 3 mmol) in Et₂O (25 mL). The resulting red solution was refluxed with stirring for 3 h and cooled and 10% HCl (10 mL) was added dropwise. The organic layer was sepa-

rated, washed with water, dried over MgSO₄, and concentrated to give the product (0.48 g) as a yellow liquid. The content of aldehyde **2a** in the liquid was 60% (¹H NMR data).

C. A 1 *M* solution of BMAP (6 mL, 6 mmol) in Et_2O was added dropwise for 20 min to a stirred boiling solution of ester **3a** (0.4 g, 2 mmol) in Et_2O (20 mL). The yellow solution was refluxed with stirring for 3.5 h and cooled and 10% HCl (10 mL) was added dropwise. The organic layer was separated, washed with water, dried over MgSO₄, and concentrated to give aldehyde **2a** (0.335 g, 99%) as yellow crystals.

2-(Ethylthio)-3-formyl-6-methylpyridine (2b) was obtained from ester **3b** as described in procedure *B* for aldehyde **2a**.

3-Hydroxymethyl-6-methyl-2-methylthiopyridine (4). Sodium bis(2-methoxyethoxy)aluminum hydride (1.15 mL, 4.1 mmol) was added dropwise for 25 min to a stirred solution of ester 3a (0.4 g, 2 mmol) in Et₂O (20 mL), while maintaining the reaction temperature at 0 °C. The resulting light green solution was stirred at the same temperature for 2.5 h and 10% HCl (15 mL) was added dropwise. The organic layer was separated, washed with water, dried over MgSO₄, and concentrated to give alcohol **4** (0.34 g, 99%) as colorless crystals.

2-(2-Alkylthio-6-methylpyridin-3-ylmethylene)propanedinitriles (5a,b). A drop of Et_3N was added to a solution of aldehyde **2a** or **2b** (2 mmol) and malononitrile (0.13 g, 2 mmol) in EtOH (5 mL). The resulting mixture was stirred at room temperature for 12 h. The precipitate that formed was filtered off and recrystallized from hexane to give ylidenes **5a** or **5b**, respectively, as yellow crystalline powders. The characteristics of compounds **5a,b** are given in Tables 1 and 2. Methyl [2-cyano-3-(6-methyl-2-methylthiopyridin-3yl)]prop-2-enoate (6). A drop of Et_3N was added to a solution of aldehyde 2a (0.33 g, 2 mmol) and methyl cyanoacetate (0.2 g, 2 mmol) in EtOH (5 mL). The resulting mixture was refluxed with stirring for 1 h and cooled. The precipitate that formed was filtered off and washed with hexane to give ylidene 6 (0.35 g, 69%) as a light orange crystalline powder.

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