Reactions of 3-cyano-2-(methylthio)pyridines with butyllithium

V. K. Zav´yalova, A. A. Zubarev, and A. M. Shestopalov*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
47 Leninsky prosp., 119991 Moscow, Russian Federation.
Fax: +7 (499) 135 5328. E-mail: zvk@ioc.ac.ru

Reactions of substituted 3-cyano-2-(methylthio)pyridines with butyllithium were studied. The reactions afforded 3-pentanoylpyridines, 2,3-dihydrothieno[2,3-*b*]pyridine, or 1-amino-2,7-naphthyridine, depending on the starting substrate and the reaction conditions.

Key words: 3-cyano-2-(methylthio)pyridines, 3-pentanoylpyridines, butyllithium, 2,3-dihydrothieno[2,3-*b*]pyridine, 1-amino-2,7-naphthyridine.

The pyridine ring is found in many compounds exhibiting various biological activity.[1,2] In a search for new functionalized pyridines, including pyridine-2-thione derivatives, a study of methods for transformations of the cyano group in 3-cyanopyridine-2(1*H*)-thiones is of both theoretical and practical interest. In the last few years, we studied the modification of the cyano group in those compounds under the action of butyl- and methyllithium,[3,4] as well in the presence of such reducing agents[5—7] as lithium aluminum hydride and its derivatives. Substituted 2-alkylthio-3-cyanopyridines were also used in the reduction reaction. We found that the reaction pathway substantially depends on both the structure of the starting reagent and the conditions of the synthesis. These reactions involve not only the cyano group, which can be reduced in different ways, but also adjacent substituents such as 4-methyl and 2-methylthio groups, probably because of the basic character of the reagents employed.

In connection with the aforesaid, the use of 3-cyano-2-(methylthio)pyridines in reactions with organometallic compounds is of interest.

Results and Discussion

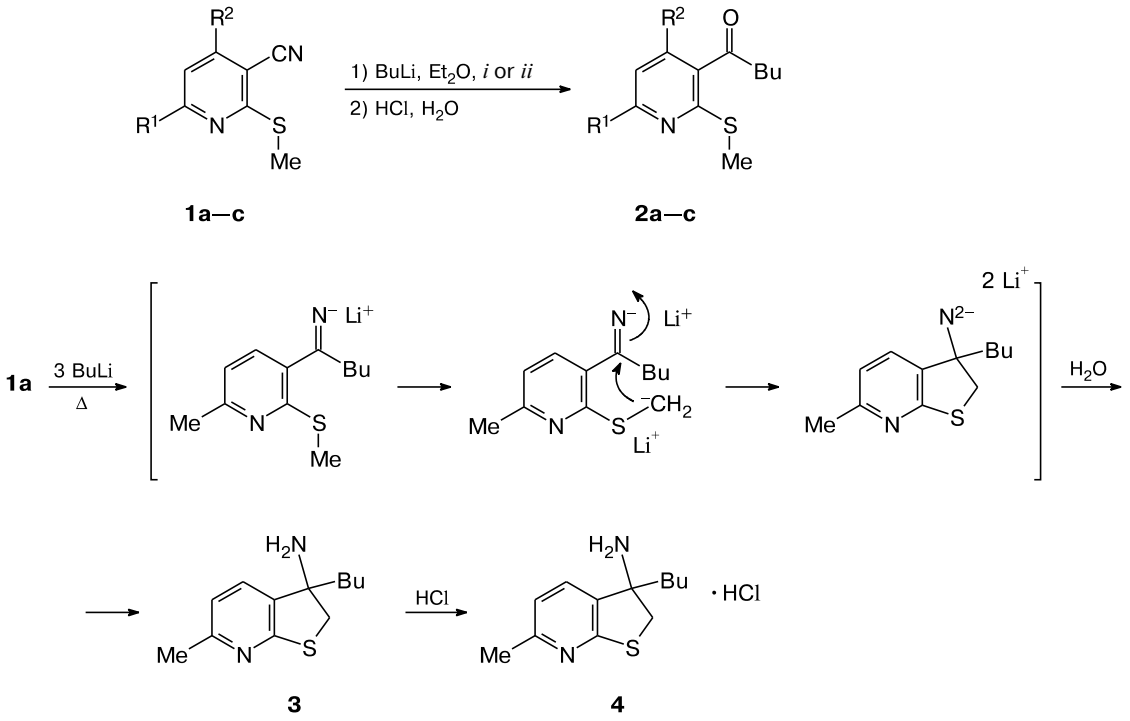
We found that the reaction outcome depends on the structure of 3-cyano-2-(methylthio)pyridines and the reaction conditions. A reaction of 3-cyano-6-methyl-2-(methylthio)pyridine (**1a**) with butyllithium (1 equiv.) in ether at −3 to −5 °C selectively gives, on treatment with dilute HCl, the corresponding 3-pentanoylpyridine **2a** in high yield (Scheme 1). With an excess of butyllithium (BuLi : **1a** = 2—3 : 1) or in boiling ether, a small amount of dihydrothienopyridine **3** is detected (^{1}H NMR data). The high yield of compound **3** was achieved by reflux of pyridine **1a** in ether with a threefold excess of butyllithium. Apparently, the reaction passes through imine formation followed by deprotonation of the SMe group, which is favored by the coordinating properties of both the sulfur atom and the intermediate iminium anion. The resulting dianion undergoes intramolecular cyclization into a dihydrothiophene ring (see Scheme 1). Amine **3** was characterized in the form of hydrochloride **4**. Its structure was confirmed by IR, ^{1}H NMR, and mass spectra. The IR spectrum of compound **3** contains absorption bands at 3360 and 3272 cm^{-1} (NH_2). The ^{1}H NMR spectrum shows, apart from the signals for the pyridine and butyl protons, signals for the protons of the dihydropyridine ring as a classic AB system: a quartet at δ 3.17 and 3.39 (^2J = 11.8 Hz).

In contrast to nitrile **1a**, a reaction of 3-cyano-4,6-dimethyl-2-(methylthio)pyridine (**1b**) with butyllithium (1 equiv.) is selective only at −20 °C, leading to the corresponding ketone **2b** in 88% yield. At −3 to −5 °C, the yield of the target ketone **2b** does not exceed 35% because of resinification of the reaction mixture. Such a decrease in the yield can be due to both steric hindrance presented by the methyl group in position 4 and side reactions. To verify the influence of steric hindrance, we used in a similar reaction 3-cyano-4-(4-methoxyphenyl)-2-methylthio-6-phenylpyridine (**1c**) containing a bulkier substituent in position 4. The yield of the target ketone **2c** (68%) is only slightly lower than the yield of compound **2a**. The structures of compounds **2a—c** were proved by IR and ^{1}H NMR spectroscopy and mass spectrometry. The IR spectra of ketones **2a—c** show an absorption band at 1656—1672 cm^{-1} (C=O); the ^{1}H NMR spectra exhibit a system of signals for the butyl substituent.

In the case of 4,6-dimethyl derivative **2a**, the reaction at the cyano group is probably accompanied by deprotonation of the 4-methyl group. This parallel process is favored by the coordinating properties of the cyano group,

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 11, pp. 2303—2306, November, 2008.

Scheme 1



i. –3 to –5 °C (**1a,c**); *ii*. –20 °C (**1b**);
1,2: R^1 = Me, R^2 = H (**a**); R^1 = R^2 = Me (**b**); R^1 = Ph, R^2 = 4-$MeOC_6H_4$ (**c**).

Table 1. Characteristics of compounds **2a—c, 3, 5**

Compounds	Molecular weight	Yield (%)	M.p./°C (solvent)	Found / Calculated (%)			Molecular formula
				C	H	N	
2a	223	87	65—67 (C_6H_{14})	64.35 64.54	7.78 7.67	6.20 6.27	$C_{12}H_{17}NOS$
2b	237	88.5	Oil	65.62 65.78	8.18 8.07	5.78 5.90	$C_{13}H_{19}NOS$
2c	391	68	227—230 (EtOH)	73.41 73.63	6.50 6.44	3.45 3.58	$C_{24}H_{25}NO_2S$
3	222	74	Oil*	64.59 64.82	8.27 8.16	12.44 12.60	$C_{12}H_{18}N_2S$
5	356	17	223—226 (Me_2CO)	60.48 60.64	5.73 5.65	15.58 15.72	$C_{18}H_{20}N_4S_2$

* For hydrochloride **4**, m.p. 206—209 °C.

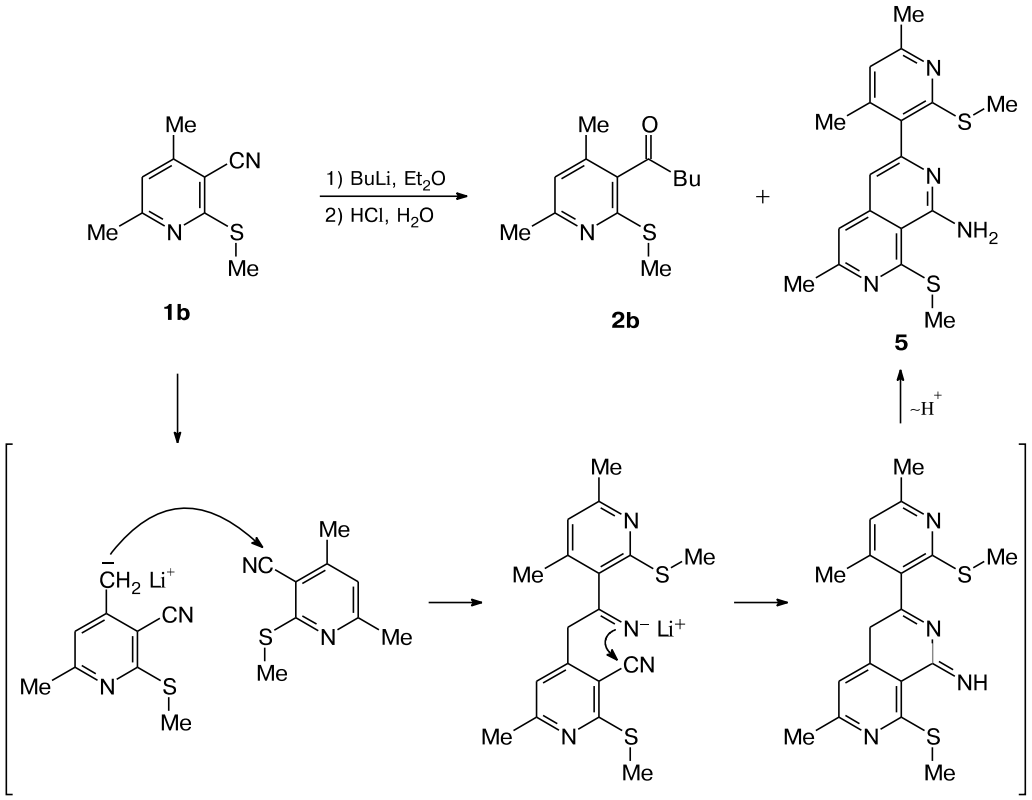
which initiates further substitution and polycondensation reactions. This is confirmed by isolation from the reaction mixture of a small amount of substituted 1-amino-2,7-naphthyridine **5**. Its structure was proved by IR and ^{1}H NMR spectroscopy and mass spectrometry. The IR spectrum of compound **5** contains no signals for the carbonyl or cyano group; instead, the absorption bands appear at 3436, 3284, and 1636 cm^{-1} ($\delta(NH_2)$). The ^{1}H NMR spectrum shows no signal for the butyl substituent; yet it exhibits a broadened singlet at δ 6.20 (2 H, NH_2), five singlets at δ 2.07—2.75 (3 H each, CH_3), and three singlets at δ 6.78—6.98 for the protons of the heteroaromatic rings.

Interestingly, the 6-methyl group remains inert in these reactions in the presence of both the 4-methyl and SMe group, although the latter is much less reactive. The fact

Table 2. Spectroscopic characteristics of compounds **2a—c**, **3**, and **5**

Compound	IR ν/cm^{-1}	MS *m/z*, (*I*(%))	^1H NMR (δ, *J*/Hz)
2a	1672 (C=O)	223 (19.6) $[M]^+$, 208 (35.4), 194 (30.2), 190 (32.6), 166 (100), 138 (20.1), 92 (27.4).	0.95 (t, 3 H, Me-δ, *J* = 7.5); 1.40 (m, 2 H, $C(3)H_2$); 1.71 (m, 2 H, $C(2)H_2$); 2.51 (s, 3 H, SMe); 2.56 (s, 3 H, Me(6)); 2.89 (t, 2 H, $C(1)H_2$, *J* = 7.3); 6.90 (d, 1 H, H(5), *J* = 7.4); 7.95 (d, 1 H, H(4), *J* = 7.4)
2b	1656 (C=O)	236 (2.8) $[M-1]^+$, 221 (61.4), 178 (100), 164 (26.4), 118 (26.3), 106 (64.6), 95 (77.8).	0.94 (t, 3 H, Me-δ, *J* = 7.5); 1.40 (m, 2 H, $C(3)H_2$); 1.64 (m, 2 H, $C(2)H_2$); 2.14 (s, 3 H, SMe); 2.46 (s, 3 H, Me(4)); 2.51 (s, 3 H, Me(6)); 2.57 (t, 2 H, $C(1)H_2$, *J* = 7.3); 6.69 (s, 1 H, H(5))
2c	1668 (C=O)	375 (100), 331 (53.5), 242 (15.9), 128 (28.1), 101 (31.9), 80 (38.9).	0.76 (t, 3 H, Me-δ, *J* = 7.5); 1.22 (m, 2 H, $C(3)H_2$), 1.53 (m, 2 H, $C(2)H_2$); 2.60 (m, 2 H, $C(1)H_2$); 2.77 (s, 3 H, SMe); 3.89 (s, 3 H, OMe); 7.05 (d, 2 H, H(2)+H(6), $MeOC_6\underline{H}_4$, *J* = 8.5); 7.40—7.51 (m, 6 H; H(3)+H(5), $MeOC_6\underline{H}_4$; H(3), H(4), H(5), Ph; H(5), Py); 8.10 (m, 2 H, Ph, H(2)+H(6))
3	3360 (NH_2) 3272 (NH_2)	222 (9.7) $[M]^+$, 207 (20.1), 165 (100), 150 (13.3), 138 (48.6), 132 (14.2), 119 (17.1), 92 (11.5).	0.87 (m, 3 H, Me-δ); 1.28 (m, 4 H, $C(2)H_2$ + $C(3)H_2$); 1.80 (m, 4 H, $C(1)H_2$ + NH_2); 2.46 (s, 3 H, Me); 3.17 (d, 1 H, $H_{eq}(2)$, *J* = 11.8); 3.39 (d, 1 H, $H_{ax}(2)$, *J* = 11.8); 6.82 (d, 1 H, H(5), *J* = 7.3); 7.25 (d, 1 H, H(4), *J* = 7.3)
5	3436 (NH_2) 3284 (NH_2) 1636 (δ NH_2)	356 (4.1) $[M]^+$, 341 (100), 323 (6.3), 307 (6.5), 295 (6.3), 153 (6.3), 110 (8.3), 99 (22.2).	2.07 (s, 3 H, Me(6′); 2.48 (s, 3 H, SMe(2′)); 2.50 (s, 3 H, Me(4′)); 2.56 (s, 3 H, Me(6)); 6.20 (br.s, 2 H, NH_2); 6.78 (s, 1 H, H(5′)); 6.79 (s, 1 H, H(4)); 6.98 (s, 1 H, H(5))

Scheme 2



that the reactions described above occur at the last two substituents can be explained by intramolecular stabilization of the reaction intermediates *via* coordination to the cyano group or products of its modification.[8]

To sum up, we demonstrated that the reactions of 3-cyano-2-(methylthio)pyridines with butyllithium give various products, depending on the reaction conditions. A low-temperature reaction at an equimolar reagent—substrate ratio yields 2-methylthio-3-pentanoylpyridines. With an increase in the temperature and in the amount of butyllithium, intra- and intermolecular condensation processes lead to 2,3-dihydrothieno[2,3-*b*]pyridines and 1-amino-2,7-naphthyridines.

Experimental

Melting points were determined on a Kofler hot stage. IR spectra were recorded on a Specord M-80 spectrophotometer (in KBr pellets). ^{1}H NMR spectra were recorded on a Bruker WM-250 spectrometer (250.13 MHz) in $CDCl_3$. The signal of the solvent (δ_H 7.25) served as the internal standard. Mass spectra were measured on a Finnigan MAT INCOS-50 instrument (ionizing energy 70 eV).

Synthesis of 6-methyl-2-methylthio-3-pentanoylpyridine (2a) and 4-(4-methoxyphenyl)-6-methyl-2-methylthio-3-pentanoylpyridine (2c) (general procedure). An ethereal solution of BuLi (3.8 mL, 6.5 mmol; c = 0.11 g mL^{-1}) was added dropwise at −3 to −5 °C for 10 min to a solution of nitrile **1a,c** (6 mmol) in ether (25 mL). The solution was stirred at −3 to −5 °C for 1 h. Then 3% aqueous HCl (15 mL) was added. The resulting two-phase system was vigorously stirred without cooling for 30 min. The organic layer was separated, washed with water, dried over $MgSO_4$, and concentrated. The product was crystallized from 70% aqueous ethanol. The yields of ketones **2a** and **2c** as yellow crystals were 1.18 g (87%) and 1.59 g (68%), respectively.

4,6-Dimethyl-2-methylthio-3-pentanoylpyridine (2b) was obtained analogously from nitrile **1b** (1.1 g, 6 mmol) at −20 °C. The yield was 1.25 g (88%).

3-Amino-3-butyl-6-methyl-2,3-dihydrothieno[2,3-*b*]pyridine (3). An ethereal solution of BuLi (5.2 mL, 9 mmol; c = 0.11 g mL^{-1}) was added to ether (25 mL). Then nitrile **1a** (0.5 g, 3 mmol) was added in portions at −3 to −5 °C for 10 min. The resulting solution was stirred without cooling for 30 min, heated to boiling, and refluxed with stirring for 30 min. On cooling, 5% aqueous HCl (20 mL) was added and the mixture was stirred without cooling for 30 min. The organic layer was separated, washed with water, dried over $MgSO_4$, and concentrated. The yield of ketone **2a** was 0.1 g (15%). The aqueous layer was alkalified with NaOH and the product was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated. The yield of amine **3** was 0.5 g (73.5%), a light brown oil. The oil was dissolved in CH_2Cl_2 (15 mL) and precipitated with an excess of a solution of HCl in ether. The precipitate of hydrochloride **4** (0.53 g, 91%) was filtered off.

1-Amino-3-[4,6-dimethyl-2-(methylthio)pyridin-3-yl]-6-methyl-8-methylthio-2,7-naphthyridine (5). An ethereal solution of BuLi (3.8 mL, 6.5 mmol; c = 0.11 g mL^{-1}) was added dropwise at −3 to −5 °C for 10 min to a solution of nitrile **1b** (1.1 g, 6 mmol) in ether (25 mL). The solution was stirred at −3 to −5 °C for 1 h. Then 3% aqueous HCl (15 mL) was added. The resulting two-phase system was vigorously stirred without cooling for 30 min. The organic layer was separated, washed with water, dried over $MgSO_4$, and concentrated. The yield of ketone **2b** was 0.49 g (35%). The aqueous layer was alkalified with NaOH and the product was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated. The dark brown resinous residue was triturated with acetone (5 mL), filtered off, and washed with acetone. The yield of amine **5** was 0.19 g (17%), a light gray powder.

This work was financially supported in part by the Presidium of the Russian Academy of Sciences (Program P-8, 2008).

References

1. M. D. Mashkovskii, *Lekarstvennye sredstva* [*Drugs*], Meditsina, Moscow, 1984 (in Russian).
2. V. P. Litvinov, *Usp. Khim.*, 2006, **75**, 645 [*Russ. Chem. Rev.*, 2006 (Engl.Transl.)].
3. V. K. Zav´yalova, A. A. Zubarev, V. P. Litvinov, *Izv. Akad. Nauk, Ser. Khim.*, 2008, 1504 [*Russ. Chem. Bull., Int. Ed.*, 2008, 1534].
4. N. G. Frolova, V. K. Zav´yalova, V. P. Litvinov, *Khim. Geterotsikl. Soedin.*, 1996, 231 [*Chem. Heterocycl. Compd.*, 1996, **32** (Engl. Transl.)].
5. A. A. Zubarev, V. K. Zav´yalova, V. P. Litvinov, *Izv. Akad. Nauk, Ser. Khim.*, 2003, 926 [*Russ. Chem. Bull., Int. Ed.*, 2003, **52**, 978].
6. A. A. Zubarev, V. K. Zav´yalova, V. P. Litvinov, *Izv. Akad. Nauk, Ser. Khim.*, 2004, 597 [*Russ. Chem. Bull., Int. Ed.*, 2004, **53**, 626].
7. A. A. Zubarev, V. K. Zav´yalova, V. P. Litvinov, *Izv. Akad. Nauk, Ser. Khim.*, 2005, 1195 [*Russ. Chem. Bull., Int. Ed.*, 2005, **54**, 1229].
8. *Organic Reactions*, John Wiley and Sons, New York, 1954, Vol. 8, p. 258.

Received April 1, 2008;
in revised form July 3, 2008