Regioselective *o*-Lithiation of 3-Alkoxypyridines; A Convenient Route to New *o*-Disubstituted Pyridines

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The direct metallation of the substituted pyridine ring can be performed at low temperature either with alkyllithium or with

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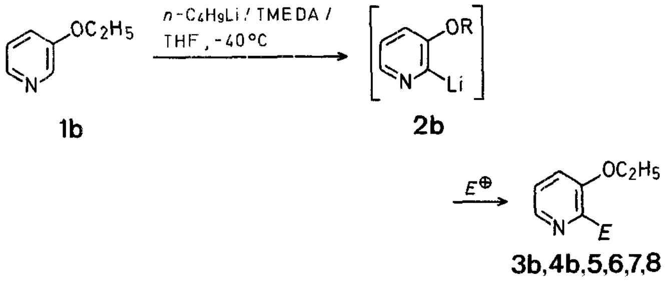
lithium dialkylamides[1-9]. Only tetrachloro- and trichloropyridines had previously been metallated[1] before we could lithiate monosubstituted pyridines regioselectively and thus prepare various *o*-substituted derivatives[2]. Similar results have been reported for 4-(2-oxazolinyl)-pyridine[3], 4-aminocarbonylpyridine[4], and 2-aminocarbonylpyridines[7]. We have recently shown that *o*-lithiation of 2-fluoropyridine[5] and 3-chloropyridine[8] represents a synthetically useful method.

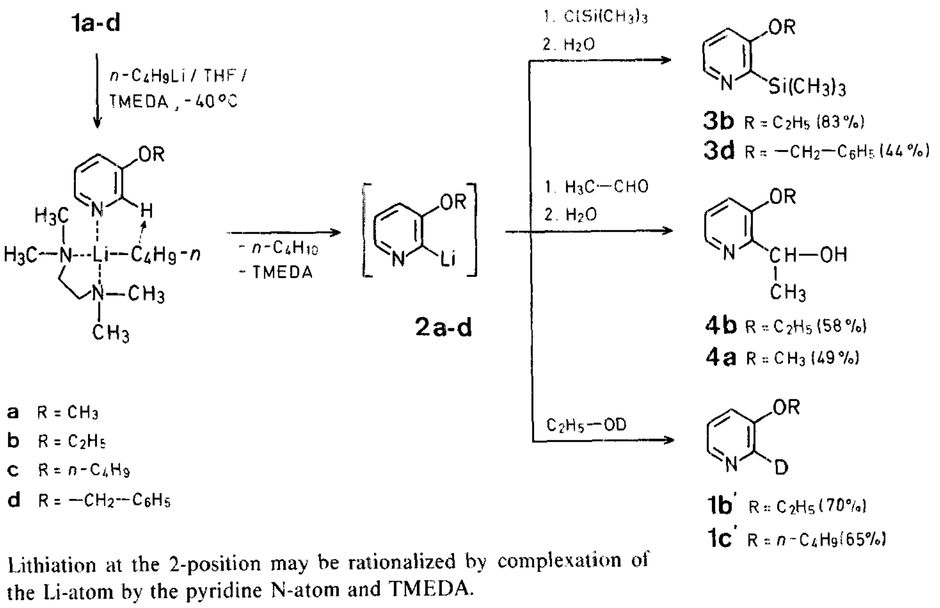
We report here the direct lithiation of 3-alkoxypyridines (**1**). The best metallation conditions found for 3-ethoxypyridine (**1b**) consist of the reaction of **1b** with butyllithium in tetrahydrofuran in the presence of an equimolar amount of *N,N,N′,N′*-tetramethyl-1,2-ethanediamine (TMEDA) at −40 °C. Lithiation takes place at the 2-position as shown by the result of the reaction of the generated lithio derivative **2b** with ethanol-*O-d*; the structure of the resultant deuteration product was established as **1b′** by ^{1}H-N.M.R. spectrometry. Metallation at the 2-position of 3-ethoxypyridine (**1b**) is further confirmed by the reactions of the intermediate alkoxylithiopyridine **2b** with chlorotrimethylsilane and with acetaldehyde, the products obtained upon hydrolysis being 3-ethoxy-2-trimethylsilylpyridine (**3b**) and 3-ethoxy-2-(1-hydroxyethyl)-pyridine (**4b**), respectively.

Metallation experiments with various 3-alkoxypyridines **1** showed that the best yields (as determined by ^{1}H-N.M.R. spectrometry after deuteration or by the yield of isolated **3** or **4**) are obtained with 3-ethoxypyridine (**1b**). The benzene ring of 3-benzyloxypyridine (**1d**) does not favor the metallation reaction.

Reaction of the lithio intermediate **2b** with various electrophiles affords the corresponding 2,3-disubstituted pyridines.



3-Ethoxypyridine (**1b**) and 3-butoxypyridine (**1c**) were prepared from 3-hydroxypyridine in 79 and 78% yield, respectively, using the phase-transfer-catalyzed method of Ref.[10] (the Williamson ether synthesis cannot be applied to 3-hydroxypyridine[10]). 3-Ethoxypyridine is also obtained as a by-product in the synthesis of 3-fluoropyridine from 3-aminopyridine ac-



Lithiation at the 2-position may be rationalized by complexation of the Li-atom by the pyridine N-atom and TMEDA.

Table 1. 2-Substituted 3-Alkoxypyridines prepared from 3-Alkoxypyridines (**1**)

R	Electrophile	Product	*E*	Yield [%]	m.p. or b.p./torr [°C]	Molecular formula[a]	
C_2H_5	$ClSi(CH_3)_3$[b]	**3b**	$—Si(CH_3)_3$	83	b.p. 85°/4	$C_{10}H_{17}NOSi$	(195.3)
C_2H_5	$JAs(CH_3)_2$	**5**	$—As(CH_3)_2$	65	b.p. 95°/4	$C_9H_{14}AsNO$	(227.1)
C_2H_5	$H_3C—CHO$	**4b**	$—CHOH—CH_3$	58	m.p. 67°	$C_9H_{13}NO_2$	(167.2)
C_2H_5	$C_2H_5—CO—C_2H_5$	**6**	$—COH(C_2H_5)_2$	60	b.p. 115°/4	$C_{12}H_{19}NO_2$	(209.3)
C_2H_5	$4\text{-}H_3CO—C_6H_4—CHO$	**7**	$—CHOH—C_6H_4—OCH_3\text{-}4$	39	m.p. 117°	$C_{15}H_{17}NO_3$	(259.3)
C_2H_5	$(H_3C)_2N—CHO$	**8**	$—CHO$	27	b.p. 107°/5	$C_8H_9NO_2$	(151.2)
CH_3	$H_3C—CHO$	**4a**	$—CHOH—CH_3$	49	— —	$C_8H_{11}NO_2$	(153.2)
$—CH_2—C_6H_5$	$ClSi(CH_3)_3$	**3d**	$—Si(CH_3)_3$	44	b.p. 178°/4	$C_{15}H_{19}NOSi$	(257.4)

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[a] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.28; H, ±0.29; N, ±0.19. Exceptions: **6**, C, −0.37; H, −0.50; **8**, H, −0.50; N, −0.42.

[b] Treatment of 3-ethoxypyridine (**1b**) with methyllithium at room temperature leads to lithiation at the 2- and 4-positions in a 1 : 1 ratio. Subsequent reaction with chlorotrimethylsilane affords (after vacuum distillation) 3-ethoxy-2-trimethylsilylpyridine and 3-ethoxy-4-trimethylsilylpyridine in a 1 : 1 ratio and in an overall total yield of 85% (conditions of G.L.C. analysis of the product mixture: column 1 m, 6 mm ∅, Apiezon-L, ethylbenzene as internal standard).

cording to Ref.[14]. The attempted phase-transfer catalyzed synthesis of 3-methoxypyridine and 3-benzyloxypyridine failed. 3-Methoxypyridine (**1a**) was prepared in 60% overall yield from 3-chloropyridine via the *N*-oxide[11] whereas 3-benzyloxypyridine (**1d**) was obtained in 65% yield by alkylation of the sodium salt of 3-hydroxypyridine in dimethyl sulfoxide according to Ref.[12].

Table 2. ^{1}H-N.M.R. Spectra ($CDCl_3$/TMS_{int}) of 2-substituted 3-Alkoxypyridines

Product	6-H	4-H, 5-H	OR	Substituent at the 2-position
3b	8.2 (dd)	7.0 (m)	3.95 (q); 1.45 (t)	Si—CH_3: 0.3 (s)
5	8.25 (dd)	7.05 (m)	4.05 (q); 1.45 (t)	As—CH_3: 1.25 (s)
4b	8.0 (dd)	7.1 (m)	4.0 (q); 1.35 (t)	CH: 5.0 (q); OH: 4.5 (s); CH_3: 1.4 (d)
6	8.05 (dd)	7.15 (m)	4.05 (q); 1.45 (t)	OH: 5.0 (s); CH_2: 2.0 (q); CH_3: 0.6 (t)
7	8.0 (dd)	6.75 (m)	3.9 (q); 1.2 (t)	C_6H_4: 7.2 (m); CH: 5.9 (d); OH: 5.4 (d); OCH_3: 3.6 (s)
8	8.35 (dd)	7.35 (m)	4.2 (q); 1.5 (t)	CHO: 10.4 (s)
4a	8.1 (dd)	7.15 (m)	3.8 (s)	CH: 4.95 (q); OH: 4.3 (s); CH_3: 1.30 (d)
3d	8.15 (dd)	6.9 (m)	7.1 (s); 4.8 (s)	$SiCH_3$: 0.1 (s)
9	8.15 (dd)	7.25 (m)	4.05 (q); 1.45 (t)	—CO—CH_3: 2.55 (s)

Preparation of 3-Ethoxy-2-lithiopyridine (2b) and its Reaction with Electrophiles; General Procedure:

A solution of TMEDA (6.6 g, 0.055 mol) in tetrahydrofuran (20 ml) is added to a stirred solution of butyllithium (0.055 mol) in tetrahydrofuran (250 ml) at −60 °C under dry nitrogen and the mixture stirred at −60 °C for 15 min. Then, a solution of 3-ethoxypyridine (**1b**; 6.15 g, 0.055 mol) in tetrahydrofuran (20 ml) is added dropwise, stirring of the red solution is continued for 30 min at −40 °C, and finally, a solution of the electrophilic reagent (0.055 mol) in tetrahydrofuran (20 ml) is added slowly. Stirring is continued for 1 h at −40 °C and the mixture then hydrolyzed by the addition, with stirring, of water (50 ml) and ethanol (50 ml) at −20 °C. The mixture is extracted with ether (2 × 100 ml) and dried with magnesium sulfate. The solvent is removed in vacuo and the residual crude product purified by vacuum distillation or recrystallization.

2-Acetyl-3-ethoxypyridine (9) by Oxidation of 3-Ethoxy-2-(1-hydroxyethyl)-pyridine (4b):

A solution of 3-ethoxy-2-(1-hydroxyethyl)-pyridine (**4b**; 1.7 g, 0.01 mol) in anhydrous acetone (150 ml) is cooled to −60 °C and chromium(VI) oxide (3 g, 0.03 mol) is added portionwise with vigorous stirring. The mixture is stirred for 3 h at room temperature. Then, 2-propanol (50 ml) is added with stirring followed by the addition of aqueous 10% sodium carbonate (200 ml). The mixture is filtered, the filtrate extracted with ether (3 × 150 ml), the extract washed with water (2 × 50 ml), and dried with magnesium sulfate. The solvent is removed and the residual product recrystallized from ether/ligroin (1/3) to afford **9** as a colorless solid; yield: 1.2 g (72%); m.p. 126 °C.

$C_9H_{11}NO_2$	calc.	C 65.44	H 6.71	N 8.48
(165.2)	found	65.30	6.35	8.70

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[1] J. D. Cook, B. J. Wakefield, *J. Chem. Soc.* [C] **1969**, 1973.

[2] F. Marsais, M. Mallet, G. Quéguiner, P. Pastour, *C. R. Acad. Sci.* [C] **275**, 1535 (1972).

[3] A. I. Meyers, R. A. Gabel, *Tetrahedron* **34**, 227 (1978).

[4] S. O. de Silva, V. Snieckus, *Tetrahedron Lett.* **1978**, 5103.

[5] T. Güngör, F. Marsais, G. Quéguiner, *J. Organomet. Chem.* **215**, 139 (1981).

[6] G. W. Gribble, M. G. Saulnier, *Tetrahedron Lett.* **21**, 4137 (1980).

[7] A. R. Katritzky, S. Rahimi-Rastgoo, N. K. Ponkshe, *Synthesis* **1981**, 127.

[8] F. Marsais, P. Bréant, G. Quéguiner, *J. Organomet. Chem.* **216**, 139 (1981).

[9] Neighbouring-group effects in metallation reactions: H. W. Gschwend, H. R. Rodriguez, *Org. React.* **26**, 1 (1979).

[10] H. J. M. Dou, P. Hassanaly, J. Metzer, *J. Heterocycl. Chem.* **1977**, 321.

[11] D. A. Prins, *Recl. Trav. Chim. Pays-Bas* **76**, 58 (1957).

[12] P. Nedenskov et al., *Acta Chem. Scand.* **23**, 1791 (1969).

[13] G. H. Postner, C. M. Lentz, *Tetrahedron Lett.* **1977**, 3211.

[14] T. Talik, Z. Talik, *Roczn. Chem.* **28**, 777 (1964).

0039-7881/82/0332-0237 $ 03.00