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Synthesis of 4-Alkyl-3,5-dibromo-, 3-Bromo-4,5-dialkyl- and 3,4,5-Trialkylpyridines via Sequential Metalation and Metal-Halogen Exchange of 3,5-Dibromopyridine

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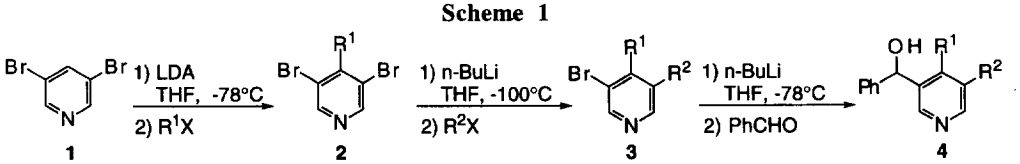
Abstract: Lithiation of 3,5-dibromopyridine with LDA and subsequent reaction with electrophiles provided 4-alkyl-3,5-dibromopyridines **2** in high yield. 3-Bromo-4,5-dialkylpyridines **3** were synthesized by metal-halogen exchange of **2** with one equivalent n-BuLi and reaction with a second electrophile. Further metal-halogen exchange of **3** and reaction with a third electrophile provided 3,4,5-trisubstituted pyridines **4**. Copyright © 1996 Elsevier Science Ltd

In the course of our studies devoted to the synthesis of therapeutically interesting compounds, we required an efficient and general synthesis of 3-bromo-4,5-dialkylpyridines. The existing literature methodology for preparing these compounds utilizes the direct bromination of 3,4-disubstituted pyridines and suffers from either poor regioselectivity[1] or lack of generality.[2]

The nucleophilic reaction of *ortho*-halolithiopyridines, which are usually prepared *in situ* at low temperature by the direct metalation of halopyridine, provides ready access to various *ortho*-alkylhalopyridines and has been extensively documented.[3] For example, lithiation of 3-halopyridines with LDA at -78°C followed by reaction with electrophiles produces the corresponding 4-alkyl-3-halopyridines.[4] Metalation of 2,3-dihalopyridines and 2,3,4-trihalopyridines has also been extensively studied,[5] and a "halogen-dance" phenomenon is often observed.[6] In this communication, we wish to report a versatile synthesis of 4-alkyl-3,5-dibromo-, 3-bromo-4,5-dialkyl- and 3,4,5-trialkylpyridines by metalation of 3,5-dibromopyridine followed by reaction with various electrophiles.

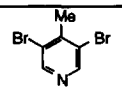
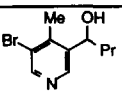
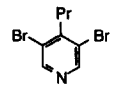
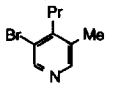
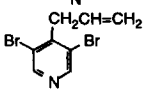
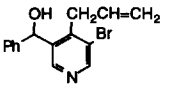
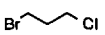
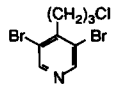
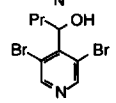
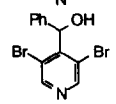
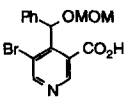
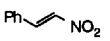
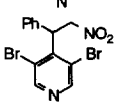
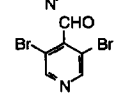
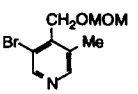
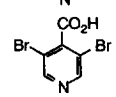
Scheme 1



Addition of a solution of commercially available 3,5-dibromopyridine (**1**) in THF to LDA at -78°C and subsequent nucleophilic reaction of the 3,5-dibromo-4-lithiopyridine intermediate with various electrophiles provided 4-alkyl-3,5-dibromopyridines (**2**)[7] (Scheme 1) in high yield (Table 1). Both iodides and bromides can be used as electrophiles, and selective alkylation with a bromide in the presence of a chloride is possible (**2d**). Addition to aldehydes gave rise to secondary alcohols in high yield (**2e** and **2f**). However, the reaction with a ketone or lactone resulted only in the recovery of the starting material (**2k** and **2l**), presumably due to more rapid enolization relative to the addition reaction.[4] Acylation with methyl formate and carbon dioxide afforded

3,5-dibromo-4-pyridinecarboxaldehyde **2i** and 3,5-dibromo-4-pyridinecarboxylic acid **2j** in 81% and 59% yield respectively. A similar reaction of 3,5-dichloro-4-lithiopyridine with carbon dioxide has been reported but with the corresponding 3,5-dichloro-4-pyridinecarboxylic acid being obtained in only 29% yield.[8] Michael addition to nitroalkene and reaction with isocyanate also gave the desired addition products in high yield (**2g** and **2h**).

Table 1. The Reaction of 3,5-Dibromo-4-lithiopyridine With Various Electrophiles

entry	R^1X	product **2**	yield(%)[a]	R^2X	product **3**	yield(%)[a]
a	MeI		89	PrCHO		81
b	n-PrI		83	MeI		82
c			93	PhCHO		79
d			62			
e	PrCHO		94			
f	PhCHO		89	CO_2		52[b]
g			94			
h	t-BuNCO		76			
i	HCO_2Me		81	MeI		70[c]
j	CO_2		59			
k		SM[d]				
l		SM[d]				

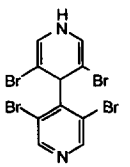
[a] Yields are isolated yields and were not optimized.

[b] Overall yield of a two-step sequence in which the OH was first protected as the MOM ether.

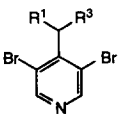
[c] Overall yield of a three-step sequence in which the aldehyde was reduced with $NaBH_4$ and the OH group then protected as the MOM ether.

[d] Starting material (**1**) was recovered.

A small amount (<5%) of the dimerization product **5** was observed in all reactions, as reported previously with other *ortho*-halolithiopyridines.[9,10] The amount of the coupling reaction product **5** increases significantly (up to 20%) if the addition sequence is reversed, i.e. adding LDA solution to a solution of **1** in THF at -78°C, suggesting that compound **5** results from the addition of 3,5-dibromo-4-lithiopyridine to 3,5-dibromopyridine. Raising the reaction temperature also increases the amount of **5** formed. When the electrophile is an alkyl or allyl halide, excess LDA can further lithiate the benzylic hydrogen[9] on the reaction products (**2a-d**) and the reaction of the resultant anions with additional halide (usually used in excess) gives compounds **6**. Thus, a 94:6 mixture of **2a** and 3,5-dibromo-4-ethylpyridine was obtained when the reaction was run with 1.15 equivalent LDA and excess methyl iodide.



5



6

Metal-halogen exchange of **2a-c** with one equivalent n-BuLi at -100°C (ether/N_2 bath) in THF followed by nucleophilic reaction of the intermediate lithiopyridines with a second electrophile R^2X provided 3-bromo-4,5-dialkylpyridines **3**[7] in high yield (Scheme 1 and Table 1). Low reaction temperature (-100°C) is necessary as a complex mixture was obtained when the reaction was conducted at -78°C, presumably due to an intermolecular transmetalation process.[6a,11] On the other hand, if the intermediate lithiopyridine is stabilized by coordination with a neighboring oxygen atom, the metal-halogen exchange can be performed at -78°C and products can be isolated in high yield (**3f** and **3i**).[12]

The products can be further elaborated upon metal-halogen exchange of the second bromine atom and subsequent reaction with a third electrophile to provide 3,4,5-trisubstituted pyridines. This was demonstrated by the metal-halogen exchange of **3b** with n-BuLi at -78°C in THF and subsequent addition of benzaldehyde to provide compound **4** (R^1=Pr, R^2=Me) in 56% yield. Metal-halogen exchange of **3b** proceeds well at -78°C which is in contrast to that of **2a-c** where a lower temperature (-100°C) is required.

In a typical experiment for the synthesis of **2c** and **3c**:[13] A cooled (-78°C) solution of 3,5-dibromopyridine (1.02g, 4.31 mmol) in 35mL THF was added via cannula to a freshly prepared solution of LDA (4.40 mmol) in 25 mL THF at -78°C at such a rate that the internal reaction temperature does not exceed -60°C. After stirring for 5 min at -78°C, allyl bromide (6.0 mmol) was added and stirring was continued at -78°C for 2h. Saturated aqueous NH_4Cl (20 mL) was added and the mixture was warmed to room temperature. Standard workup and flash column chromatography on silica gel, eluting with 10-20% EtOAc in hexane, provided 1.12g (93%) of compound **2c**.

n-BuLi (2.25mmol) was added dropwise to a solution of **2c** (0.617 g, 2.23 mmol) in 35 mL THF cooled to -100°C (ether/N_2). The mixture was stirred for 4 min at -100°C. Benzaldehyde (3.00 mmol) was added and the mixture was slowly warmed to -78°C over 30 min and stirred for 1h at -78°C. Saturated NH_4Cl (10 mL) was added and the mixture was warmed to room temperature. Standard workup and flash column chromatography on silica gel, eluting with 25-50% EtOAc in hexane, provided 0.537 g (79%) of compound **3c**.

In summary, we have developed a versatile synthetic method which allows for the synthesis of 4-alkyl-3,5-dibromo-, 3-bromo-4,5-dialkyl- and 3,4,5-trialkylpyridines in high yield. The different regioisomers can be synthesized by simply changing the sequence of electrophile addition.

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7. All compounds have been characterized by proton NMR (300 MHz, $CDCl_3$) and mass spectra.
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12. Selective replacement of one of the two bromine atoms of 3,5-dibromopyridine by metal-halogen exchange with n-BuLi has been achieved at higher temperature in ether.(Gilman, H.; Spatz, S. M. *J. Org. Chem.* **1951**, *16*, 1485.) However, the reactivity of 4-alkyl-3-bromo-5-lithiopyridine seems to be retarded in ether. For example, the reaction of 3-bromo-5-lithio-4-propylpyridine with MeI in ether at -78°C for 5h gave rise to a mixture (ca. 1: 1) of **3b** and 3-bromo-4-propylpyridine after the reaction was quenched with saturated NH_4Cl, whereas **3b** was isolated as a sole product in 82% yield when the same reaction was conducted in THF at -78°C for less than 2h.
13. Spectra data: **2c**, MS: 278 $(M+H)^+$; ^{1}HNMR ($CDCl_3$) δ 8.60 (s, 2H), 5.94-5.80 (m, 1H), 5.20-5.09 (m, 2H), 3.74 (d, J=6.0 Hz, 2H). **3c**, MS: 304 & 306 $(M+H)^+$; ^{1}HNMR ($CDCl_3$) δ 8.65 (s, 1H), 8.63 (s, 1H), 7.40-7.28 (m, 5H), 6.07 (s, 1H), 5.87-5.72 (m, 1H), 5.09 (d, J=10.5 Hz, 1H), 4.91 (d, J=16.5 Hz, 1H), 3.68-3.42 (m, 2H), 2.40 (s br, 1H).

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