REDUCTIVE LITHIATION OF HALOPYRIDINES USING LITHIUM NAPHTHALENIDE

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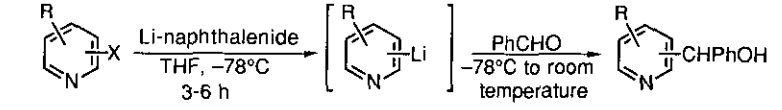
Abstract-Chloropyridines were converted into lithiopyridines *via* reductive lithiation using lithium naphthalenide as an electron transfer reagent.

Organolithium compounds have been widely used as reagents in organic synthesis not only for the fundamental carbon-carbon bond forming reaction, but also for introducing a wide range of functional groups.[1] The chemistry of organolithium compounds is still developing especially in the heteroaromatic field, and new applications are continually being reported.[2a]

Lithiopyridines have been usually prepared *via* metal-halogen exchange using alkyllithium and lithiation of pyridines bearing *o*-directing group. These reactions have been reviewed extensively,[2] however, no example has been reported for reductive lithiation of halopyridines. Recently, Yus reported a convenient preparative method of lithiobenzenes from chlorobenzenes using the combination of lithium and naphthalene.[3] As an extension of our work on the direct preparation of metallopyridines from halopyridines,[4] we investigated the lithiation of halopyridines using lithium naphthalenide.

2-Chloropyridine (**1a**) was treated with 1.1 equivalents of lithium naphthalenide at -78°C in tetrahydrofuran (THF) followed by the action of benzaldehyde to give 1-phenyl-2-pyridinemethanol (**1c**) in 72% yield. The same product (**1c**) was obtained from the reaction of 2-bromopyridine (**1b**) in 74% yield.



1a: X=Cl
1b: X=Br
1c: X=CHPhOH

2a: X=Cl
2b: X=Br
2c: X=CHPhOH

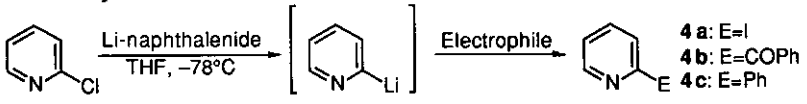
3a: X=Cl
3b: X=Br
3c: X=CHPhOH

The lithiation of 4-chloro- (**3a**) and 4-bromo-2,6-dimethylpyridines (**3b**) proceeded smoothly, and the 4-lithiopyridine was trapped with benzaldehyde to give the pyridinemethanol (**3c**) in moderate yields. To our surprise, the chloropyridines and the bromopyridines showed almost the same reactivity toward the lithiation. On the other hand, the lithiation of 3-chloro- (**2a**) and 3-bromopyridines (**2b**) seemed to be sluggish, and the pyridinemethanol was obtained in low yields (11 and 6%). Even when 3-iodopyridine was employed as a substrate for the lithiation, the yield of **2c** was also low (10%). Thus, the reactivity toward this lithiation is much higher at the α- or γ-position than the β-position.

Table 1 Reaction of Lithiopyridines with Benzaldehyde

Halopyridine	Time (h)	Product	Yield (%)
1a	6	**1c**	72
1b	3	**1c**	74
2a	4	**2c**	11
2b	6	**2c**	6
3a	3	**3c**	63
3b	4	**3c**	41

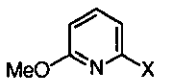
Next, functionalization at the 2-position of pyridine by this lithiation was examined. 2-Lithiopyridine prepared from 2-chloropyridine and lithium naphthalenide reacted with some electrophiles as shown below. Iodination, benzoylation, and transmetallation to the organozinc derivative followed by the palladium catalyzed coupling reaction[4] were successful as expected.



1a

Table 2 Reaction of 2-Lithiopyridine with Electrophiles

Electrophile	Product	Yield (%)
I_2	**4a**	54
PhCONMeOMe	**4b**	50
$ZnCl_2$ / PhI, $Pd(PPh_3)_4$	**4c**	63



5a: X=Cl
5b: X=CHPhOH

Then, effect of substituent on pyridine ring was studied. Methoxyl group at the 6-position did not affect the lithiation and the methoxy derivative (**5a**) was converted into **5b** in 77% yield, while the presence of ethoxycarbonyl group or cyano group made the reaction complicated.

Finally, the lithiation was also carried out using a catalytic amount of naphthalene, and 2-chloropyridine was converted to **1c** in 54% by using a catalytic amount (10%) of naphthalene, however more effort for improving the yield seems to be necessary.

References and Notes

1. B. J. Wakefield, *Organolithium Methods*, Academic Press, London, 1988.
2. a) G. W. Rewcastle and A. R. Katritzky, *Adv. Heterocycl. Chem.*, 1993, ***56***, 155;
   b) G. Queguiner, F. Marsais, V. Snieckus, and J. Epsztajn, *Adv. Heterocycl. Chem.*, 1991, ***52***, 187.
3. A. Guijarro, D. J. Ramon, and M. Yus, *Tetrahedron*, 1993, ***49***, 469.
4. T. Sakamoto, Y. Kondo, N. Murata, and H. Yamanaka, *Tetrahedron Lett.*, 1992, ***33***, 5373.
5. **Lithiation of 2-Chloropyridine Followed by Reaction of 2-Lithiopyridine with Benzaldehyde** : All operations were performed under an Ar atmosphere. A mixture of naphthalene (1.69 g, 13.2 mmol) and lithium (48 mg, 6.6 mmol) in dry THF (10 ml) was stirred for 12 h at room temperature. 2-Chloropyridine (341 mg, 3 mmol) was added at –78°C and the mixture was stirred for 6 h at the same temperature. Benzaldehyde (366 µl, 3.6 mmol) was added and the whole was stirred for 10 min at -78°C. The mixture was allowed to warm to room temperature and quenched with saturated aq. NH_4Cl (5 ml). After removal of the THF *in vacuo*, the residue was partitioned with H_2O and $CHCl_3$. The residue from the $CHCl_3$ extract was purified by silica gel column chromatography using hexane-ether (1:1) as an eluent and the crude material was distilled under reduced pressure to give 1-phenyl-2-pyridinemethanol (401 mg, 72%), bp 130~135°C / 3 mmHg (lit.,[6] bp *127~129°C / 0.3 mmHg*).
6. C. H. Tilford, R. S. Shelton, and M. G. Van Campen, Jr., *J. Am. Chem. Soc.*, 1948, ***70***, 4001.

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