SYNTHESIS OF 2,6-DISUBSTITUTED PYRIDINES BY LITHIATION OF PYRAZOLO[1,5-*a*]PYRIDINES

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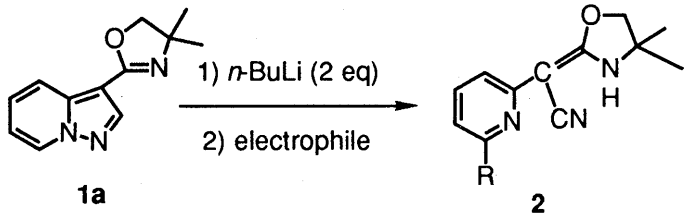
Lithiation of 3-(4,4-dimethyl-2-oxazolin-2-yl)pyrazolo[1,5-*a*]pyridine (**1a**) with 2 molar equivalents of *n*-BuLi followed by reaction with benzaldehyde yielded α-(4,4-dimethyl-2-oxazolidinylidene)-6-(α-hydroxybenzyl)-2-pyridineacetonitrile (**2a**). Upon similar treatment of other electrophiles, the corresponding 2,6-disubstituted pyridines **2** were produced. The formation of the pyridines proceeded through lithiation, reaction with an electrophile, and ring-cleavage of the pyrazole ring.

KEYWORDS pyrazolo[1,5-*a*]pyridine; lithiation; 2,6-disubstituted pyridine; electrophile; ring cleavage

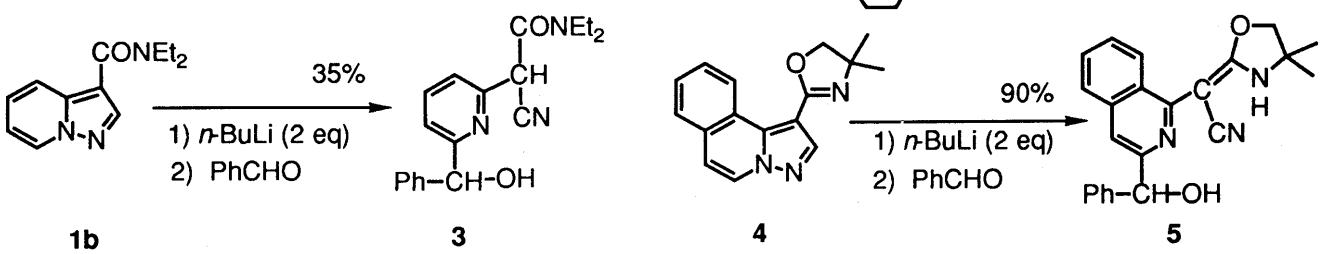
We have reported that the lithiation of pyrazolo[1,5-*a*]pyridine with *n*-BuLi proceeded selectively at the 7-position, and a subsequent reaction with electrophiles gave 7-substituted derivatives.[1] However, it is difficult to produce 2-substituted pyrazolo[1,5-*a*]pyridines by lithiation. We expected that the introduction of a functional group at the 2-position on a pyrazolo[1,5-*a*]pyridine could be achieved by use of the *ortho*-directing effect of a substituent at the 3-position. Several substituents, such as 2-oxazolin-2-yl, *N,N*-dimethylaminomethyl, and carbamoyl groups, efficiently promote *ortho*-lithiation.[2] In order to introduce a functional group at the 2-position, we synthesized 3-(4,4-dimethyl-2-oxazolin-2-yl)pyrazolo[1,5-*a*]pyridine (**1a**).[3]

Treatment of **1a** with 2 molar equivalents of *n*-BuLi at -78°C for 0.5 h followed by the reaction with benzaldehyde unexpectedly yielded α-(4,4-dimethyl-2-oxazolidinylidene)-6-(α-hydroxybenzyl)-2-pyridineacetonitrile (**2a**).[4] The structure of **2a** was supported by the following result: the characteristic absorptions at 2186 cm^{-1} (CN), 3178 cm^{-1}, and 3442 cm^{-1} (OH or NH) in the IR spectrum and characteristic signals at 9.62 ppm, 5.77 ppm, and 2.70 ppm due to NH, and CHOH in the ^{1}H-NMR spectrum were observed. Elemental analysis and MS measurement also supported the proposed structure.[5]



1a **2**

electrophile		R	yield (%)
PhCHO	**2a**	PhCH(OH)-	49
C_2H_5CHO	**2b**	$C_2H_5CH(OH)$-	41
$(Ph)_2CO$	**2c**	$(Ph)_2C(OH)$-	83
n-$C_3H_7COCH_3$	**2d**	n-$C_3H_7(CH_3)C(OH)$-	64
PhCN	**2e**	PhCO-	83
n-C_3H_7CON	**2f**	n-C_3H_7CO-	45



1b **3** **4** **5**

Chart 1

In order to examine the scope and limitations of this method for synthesis of 2,6-disubstituted pyridines, we used various electrophiles

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such as propionaldehyde, benzophenone, methyl propyl ketone, benzonitrile, and *N*-butyrylpiperidine, and the corresponding 2,6-disubstituted pyridines **2** were obtained in moderate yields. Moreover, treatment of 3-(*N,N*-diethylcarbamoyl)pyrazolo[1,5-*a*]pyridine (**1b**) with 2 molar equivalents of *n*-BuLi followed by reaction with benzaldehyde gave ring-opening product **3**. A similar result was obtained in the reaction of **4**, whose structure includes a pyrazolo[1,5-*a*]pyridine moiety.

Lithiation of **1a** with equimolar *n*-BuLi at -78°C followed by reaction with benzaldehyde produced only the 7-substituted pyrazolo[1,5-*a*]pyridine **7a**. Subsequent lithiation of 7-substituted pyrazolo[1,5-*a*]pyridine **7a** led to the 2,6-disubstituted pyridine **2a**. Furthermore, lithiation of **1a** with 2 molar equivalents of *n*-BuLi at -78°C for 0.5 h gave ring-opening product **6a**; however, lithiation with equimolar *n*-BuLi under the same conditions recovered the starting **1a**. Similar results were obtained in the lithiation at -50°C and -10°C. We considered that the pyridine **2a** is produced by the sequential reaction involving lithiation, reaction with benzaldehyde, and cleavage of the pyrazole ring, as shown in Chart 2. But the details are not clear.

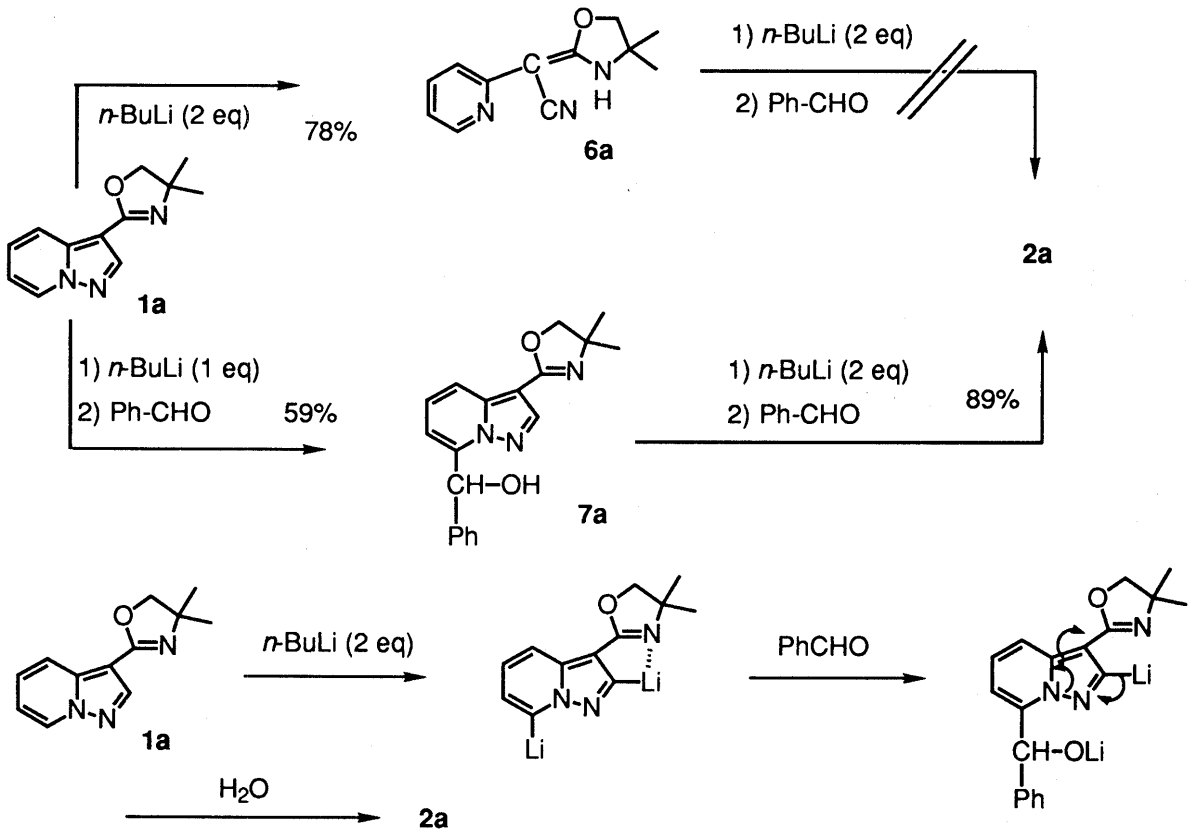

Chart 2

Lithiation of 3-(*N,N*-dimethylaminomethyl)pyrazolo[1,5-*a*]pyridine with 2 molar equivalents of *n*-BuLi followed by reaction with benzaldehyde produced only the 7-substituted pyrazolo[1,5-*a*]pyridine in 72% yield. This result indicates that ring-opening of the pyrazolo[1,5-*a*]pyridines requires an electron-withdrawing substituent at the 3-position. Sufficient acidity of the C^2-hydrogen achieved the ring-opening through the formation of 2-lithiopyrazolo[1,5-*a*]pyridine by chelation and the electron-withdrawing effect of the substituent.

In addition, we examined the ring-cleavage of several pyrazolo[1,5-*a*]pyridines with or without an electron-withdrawing group at the 3-position using a base. When 3-cyano-, 3-ethoxycarbonyl, and 3-benzoylpyrazolo[1,5-*a*]pyridines were treated with NaH in DMF at 140°C for 2 h, the corresponding ring-cleavage products, α-cyano- (**6c**), α-ethoxycarbonyl– (**6d**), α-benzoyl-2-pyridineacetonitrile (**6e**), were produced in moderate yields. On the other hand, similar treatment of unsubstituted pyrazolo[1,5-*a*]pyridine with either NaH and *n*-BuLi failed to cleave the ring. The ring-cleavage of the pyrazole ring by base action has already been reported.[6]

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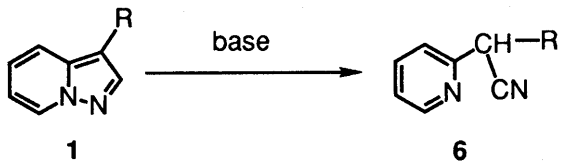

1 6

	R	base	yield (%)
6c	CN	NaH / DMF	39
6d	COOEt	NaH / DMF	35
6e	COPh	NaH / DMF	49
6f	H	NaH / DMF	—
6f	H	*n*-BuLi / THF	—

Chart 3

We found a new method for synthesis of 2,6-disubstituted pyridines from pyrazolo[1,5-*a*]pyridines. In general, the direct introduction of carbon-functional groups at the 2- or 6-position on pyridine ring by lithiation is difficult;[7] nevertheless, pyrazolo[1,5-*a*]pyridines are easily lithiated at the 7-position, which corresponds to the 2- or 6-position on a pyridine ring.

REFERENCES AND NOTES

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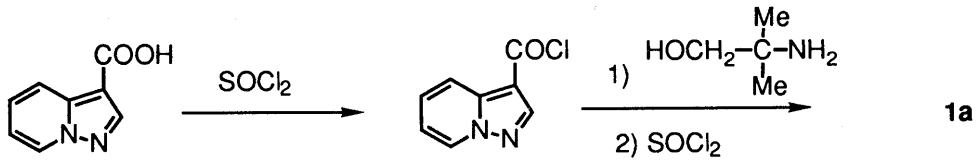
3) Starting compound **1a** was synthesized through two steps, as shown below.



4) A typical procedure: To a solution of **1a** (300 mg, 1.4 mmol) in 10 ml of THF was slowly added *n*-BuLi (1.8 ml, 1.6 mol / l in hexane) at -78°C, and the solution was further stirred for 30 min. A solution of benzaldehyde (456 mg, 4.2 mmol) in 1 ml of THF was added to the solution, and the resulting mixture was stirred for 30 min at -78°C. After the reaction mixture was stirred at room temperature for 1 h, the mixture was poured into H_2O. The mixture was extracted with $CHCl_3$, and the extract was dried over Na_2SO_4 and concentrated. Purification of the residue by column chromatography on SiO_2 gave **2a**.

5) **2a**: *Anal.* Calcd for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.07. Found: C, 71.00; H, 5.87; N, 13.05. IR (KBr) cm^{-1}: 2186 (CN), 3178 (OH), 3442 (NH). ^{1}H-NMR ($CDCl_3$) δ: 9.62 (1H, bs, NH), 7.60 (1H, t, *J* = 7.8 Hz, pyridine), 7.39-7.30 (5H, m, Ph), 7.21 (1H, d, *J* = 7.8 Hz, pyridine), 7.16 (1H, d, *J* = 7.8 Hz, pyridine), 5.77 (1H, s, CH), 4.14 (2H, s, CH_2), 2.70 (1H, bs, OH), 1.29 (3H, s, Me), 1.21 (3H, s, Me). ^{13}C-NMR ($CDCl_3$) δ: 167.6 (s), 159.5 (s),154.9 (s), 143.5 (s), 137.3 (d), 128.8 (d), 128.0 (d), 127.0 (d), 119.6 (s), 117.2 (d), 114.2 (d), 79.3 (t, $\underline{C}H_2$), 76.7 (d, -$\underline{C}$H-OH), 59.2 (s), 26.77 (q), 26.72 (q). The spectral data supported the oxazolidinylidene structure **2a**, but the stereochemistry has not yet been determined.

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