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Unusual Sterically Controlled Regioselective Lithiation of 3-Bromo-5-(4,4′-dimethyl)oxazolinylpyridine. Straightforward Access to Highly Substituted Nicotinic Acid Derivatives

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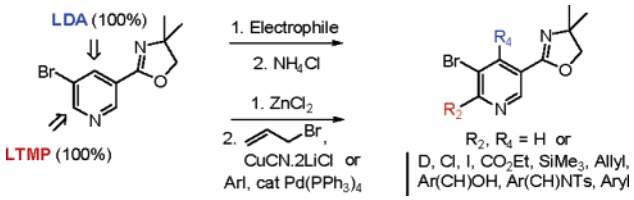
ABSTRACT



Lithiation of 5-bromonicotinic acid protected as secondary or tertiary amide as well as (4,4′-dimethyl)oxazoline with lithium amides is reported. The unusual C-2 and C-4 regioselective lithiation of 3-bromo-5-(4,4′-dimethyl)oxazolinylpyridine using LTMP versus LDA was observed, providing a new route to substituted nicotinic acid scaffolds. The methodology was applied to the synthesis of novel C-4 and C-6 arylated 5-bromonicotinic acids.

Nicotinic acid (Niacin, Vitamin B_3) and nicotinamides are important members of the B-vitamin group and represent the active moiety of both coenzymes NAD/NADP involved in many metabolic processes.[1] Niacin is known also as a very efficient lipid-regulating agent clinically used for the treatment of severe dyslepidemia and the atherosclerotic cardiovascular disease.[2] Moreover, functionalized nicotinic acid derivatives, including amide, ester, and oxazoline, have been used extensively to design pharmacophores in disease states such as obesity,[2] cancer,[3] inflammatory,[4] and pain,[5] as well as pesticides.[6] Such scaffolds are also versatile building blocks for the preparation of complex azaheterocycles. The directed orthometalation (DoM) reaction has been

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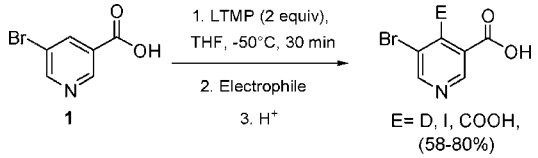
widely used as a powerful and efficient method for regioselective functionalization of aromatics and heteroaromatics.[7] Selective C-4 lithiation of nicotinamides,[8] 3-(4,4′-dimethyl)-oxazolinylpyridine,[9] 3-cyanopyridine,[10] and unprotected nicotinic acid[11] has been successfully accomplished using lithium dialkylamides and Hauser bases. With these achievements, we recently sought to identify the simplest scaffold to prepare highly functionalized niacin analogues. We selected the 5-bromonicotinic acid **1** due to the presence of two meta-directed metalation groups (DMGs), allowing three possible ortho substitutions using DoM methodology. Further functionalizations could be also achieved exploiting the C−Br bond synthetic value.

The regiochemical lithiation of the 1,3-inter-related−DMGs system specifically at the less favored ortho positions not located between the two DMGs has been scarcely studied.[7a,12] The choice of suitable lithiating agents in the case of the lithiation of bromopyridine models as **1** is restricted mainly to lithium amides which avoid competitive side reactions such as C−Br exchange and nucleophilic addition to the pyridine nucleus. The lithiation of 5-bromonicotinic acid **1** using 2,2′,6,6′-tetramethylpiperidinyllithium (LTMP) occurred selectively at the most hindered C-4 position (Scheme 1).[11b] We further reasoned that the

Scheme 1. C-4 Lithiation of 5-Bromonicotinic Acid **1**

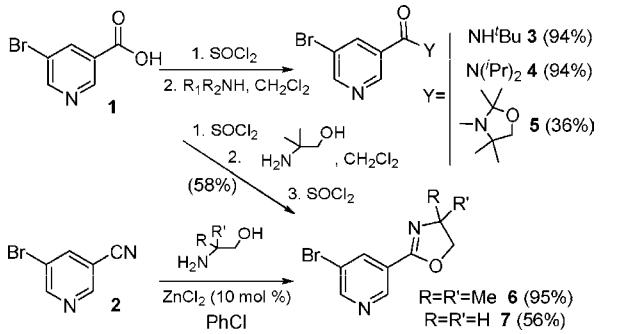


addition of external (base) and/or internal (DMG) steric effects might drive the challenging ortho lithiation at less hindered sites.

As a preliminary assay, the unprotected nicotinic acid **1** was reacted with the most highly hindered lithium (*tert*-butyldimethylsilyl)-*tert*-butylamide (LiBSBA)[13] in THF for 30 min at −50 °C followed by D_2O quenching to provide exclusively the C-4 deuterated product in 82% yield. Herein we report our results from a thorough screening of bulky carboxylic acid derived DMGs which identified the (4,4′-dimethyl)oxazoline as a suitable DMG to control the ortho lithiation at both C−Br ortho positions.

The bulky secondary and tertiary amides **3**−**5** (Scheme 2) were prepared from 5-bromonicotinic acid **1** via the

Scheme 2



corresponding acid chlorides. Treatment of 3-bromo-5-cyanopyridine **2** with the appropriate amino alcohol in the presence of catalytic amounts of zinc chloride cleanly afforded multigram quantities of 3-bromo-5-(4,4′-dimethyl)-oxazolinylpyridine **6** in excellent 95% yield.[14]

A first set of lithiation experiments was achieved using LTMP at −78 °C in THF. Each lithio intermediate was quenched with D_2O (Table 1, entries 1−4). All bulky carboxamides **3**−**5** showed exclusive deuterium incorporation at the C-4 position (entries 1−3) providing deuterated compounds **3a**−**5a** in high isolated yields. On the other hand, we found that the 3-bromo-5-(4,4′-dimethyl)oxazolinylpyridine **6** was selectively deuterated at the C-2 position (entry 4).[15] We then tried to modify the lithiation regioselectivity of **6** from the C-2 to C-4 position. Thus, deprotonation of **6** with LTMP at −78 °C, warming at different temperatures, and trapping the lithio intermediates with D_2O clearly showed that the C-2 lithio species slowly isomerized to the thermodynamically more stable C-4 lithio isomer at −50 °C (entry 5).

We also observed that the 4-lithiopyridine previously formed at −50 °C underwent degradation at −40 °C (entry 6). The lithiation of 3-bromo-5-(4,4′-dimethyl)oxazolinylpyridine **6** was carried out with a less hindered amide base, lithium diisopropylamine (LDA), at −78 °C in THF. Surprisingly, quenching the lithio intermediate with D_2O led exclusively to isolation of the C-4 deuterated product **6a** in 90% yield (entry 7). Thus, steric hindrance appeared to be the major factor controlling the regioselectivity of deprotonation of **6**. To gain further support for this assumption, we examined the lithiation of the less hindered oxazoline **7**, prepared from 3-bromo-5-cyanopyridine **2** in 56% yield (Scheme 2).

As expected, treatment of **7** with LTMP (entry 8) followed by quenching with D_2O mainly provided the C-4 deuterated compound **7a** (entry 8).

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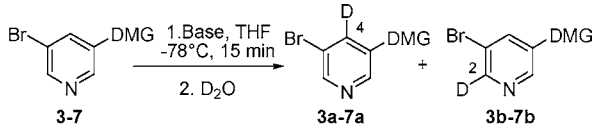
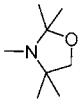
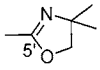
(15) ^1H NMR spectra of C_2 deuterated product **6b** showed two characteristic doublets corresponding to the H-4 and H-6 protons, which both correlate in the HMBC NMR spectra with the quaternary carbon C-5′ of the oxazolinyl group.

Table 1. Lithiation of 3-Bromo-5-carboxypyridines **3**−**7**[a]



entry	DMG		Base			a[a](%)[b]	b[a](%)[b]
1	CONH^{t}Bu	**3**	LTMP	2	-78	88 (91)	0
2	CON(^{i}Pr)$_2$	**4**	LTMP	1	-78	97 (91)	0
3		**5**	LTMP	2	-78	95 (90)	0
4		**6**	LTMP	1	-78	0	85 (94)
5			LTMP	1	-50	95 (83)	0
6			LTMP	1	-40	degradation	
7			LDA	1	-78	90 (93)	0
8		**7**	LTMP	1	-78	76[c]	24[c]

[a] Percent of deuterium incorporation estimated by ^{1}H NMR. [b] Isolated overyields. [c] Isolated overyield is 56%.

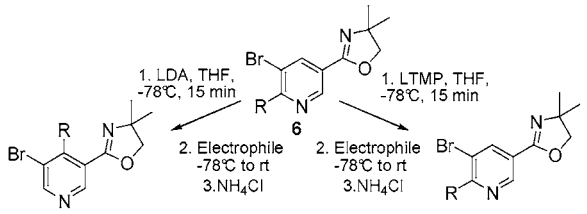
Application of the regiocontrolled lithiation of **6** using LTMP or LDA followed by trapping the respective C-2 or C-4 lithio intermediates at −78 °C with various electrophiles led to a large panel of C-2 and C-4 substituted 3-bromo-5-oxazolylpyridines. Halogenation, carboxyethoxylation, amino and hydroxyl alkylation, and trimethylsilylation of **6** could be thus achieved either at C-2 or C-4 positions in moderate to excellent yields using the appropriate electrophiles as depicted in Scheme 3. However, the C-2 allylated compound **8g** could not be obtained by treating the C-2 lithio derivative of **6** neither with allylbromide nor with allyliodide at −78 °C whatever the reaction time. Allylation of **6** was also successfully realized at the C-4 position, affording **9g** in moderate 56% yield.

Warming the reaction to room temperature led to prior isomerization of the C-2 lithio species to the C-4 lithio isomer with subsequent allylation to give **9g** in 40% yield (Scheme 3).

Regioselective C-2 lithiation of **6** followed by Li/Zn transmetalation and subsequent copper-catalyzed allylation was envisaged for achieving C-2 allylation (Scheme 4).[16] Treatment of **6** with LTMP at −78 °C, reaction with anhydrous $ZnCl_2$, and warming immediately to room temperature for 1 h before addition of allylbromide in the presence of CuCN·2LiCl afforded the expected C-2 allylated

(16) For a unique example of bromopyridine lithiation and subsequent Li/Zn transmetalation followed by Pd-mediated Negishi coupling, see: Karig, G.; Spencer, J. A.; Gallagher, T. *Org. Lett.* **2001**, *3*, 835−838.

Scheme 3. C-2 and C-4 Substitution of **6**[a]

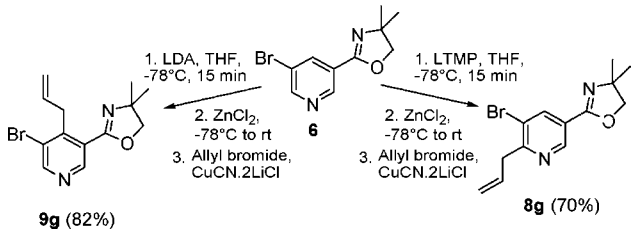


product	yield	R	yield	product
9a	89%[b]	Cl	72%[b]	**8a**
9b	80%[c]	I	77%[c]	**8b**
9c	70%[d]	$SiMe_3$	72%[d]	**8c**
9d	72%[e]	CO_2Et	70%[e]	**8d**
9e	51%[f]	CH(OH)Ph(OMe)$_3$	45%[f]	**8e**
9f	62%[g]	CH(NTs)Ph(OMe)	70%[g]	**8f**
9g	56%[h]	Allyl	0%[h](40%)[i]	**8g**

[a] Base (1 equiv), electrophiles (1−6 equiv). The superscripts *b*−*h* depict the following electrophiles: [b]Cl_2, [c]I_2, [d]$SiMe_3Cl$, [e]$CNCO_2Et$, [f]3,4,5-trimethoxybenzaldehyde, [g]*N*-tosylbenzylimine, [h]allyl bromide. [i]Isolated yield of **9g**. Yields are isolated yields. See the Supporting Information for details.

product **8g** in 70% yield. Interestingly, the same procedure could be used to improve the yield of the C-4 allylation after lithiation with LDA, leading to the C-4 allylated compound **9g** in 82% yield (Scheme 4).

Scheme 4. C-2 and C-4 Allylation of **6**[a]

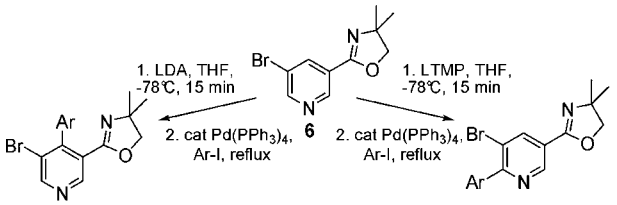


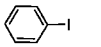
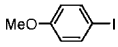
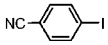
[a] Base (1 equiv), $ZnCl_2$ (1.1 equiv), CuCN·2LiCl (1.1 equiv), allyl bromide (1.1 equiv). See the Supporting Information for details.

The intermediate C-2 and C-4 pyridylzinc chlorides are stable at room temperature and are thus potential candidates for palladium-catalyzed cross-coupling reactions. Thus, both C-2 and C-4 pyridylzinc chlorides were treated with various phenyliodides (1 equiv) in the presence of $Pd(PPh_3)_4$ (5 mol %) as catalyst in refluxing THF for 20 h (Scheme 5). Further treatment with EDTA allowed isolation of expected 2- and 4-phenyl products **10a**−**c** and **11a**−**c** in good to high yields as depicted in Scheme 5.

The usefulness of this strategy was later illustrated by the synthesis of 4- and 6-arylated 5-bromonicotinic acids as

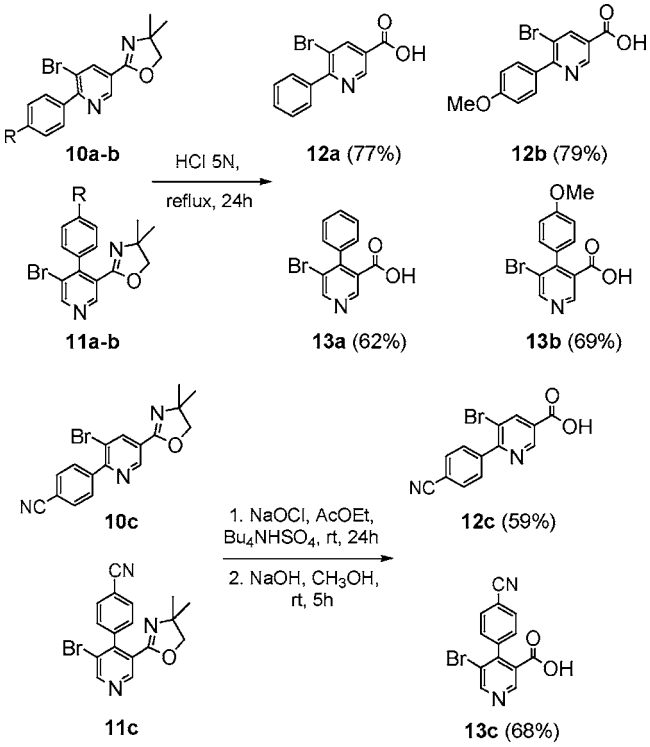
Scheme 5. C-4 and C-6 Arylation of **6**[a]



product	yield	Ar-I	yield	product
11a	90%		81%	**10a**
11b	65%		65%	**10b**
11c	70%		89%	**10c**

[a] Base (1 equiv), Ar−I (1 equiv), $Pd(PPh_3)_4$ (5% mol). Yields are isolated yields. See the Supporting Information for details.

Scheme 6. Niacin Analogue Synthesis[a]



[a] Yields are isolated yields. See the Supporting Information for details.

niacin analogues. The 4-arylated 5-bromonicotinic acids may be also selected precursors to design new 5-bromo-4-aryl-*N*-benzylnicotinamide as neurokinin-1 (NK_1) receptor antagonists.[17] Hydrolysis of the oxazoline group was achieved under either acidic or basic conditions after prior specific chlorination[18] of the oxazoline nitrogen atom. Expected nicotinic acids **12a**−**c** and **13a**−**c** were obtained in 59−43% overall yields in four-step synthesis from **2** (Scheme 6).

In summary, we have developed a regioselective lithiation of 3-bromo-5-(4,4′-dimethyloxazolynyl)pyridine **6** which provides a new versatile pathway to various substituted 5-bromonicotinic acid derivatives by electrophilic quench, Cu(II)-catalyzed allylation, or Negishi cross-coupling after Li/Zn transmetalation. The method was used as an efficient entry to novel 4- and 6-aryl-5-bromonicotinic acids as novel niacin analogues. Further substitutions of these unprotected nicotinic acid analogues at the C-5 position may be considered, taking advantage of the broad synthetic value of the C−Br bond.[19]

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Supporting Information Available: Experimental details. The material is available free of charge via the Internet at http://pubs.acs.org.

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(19) For C−Br arylation of 5-bromonicotinic acid, see: (a) Fernàndez, J.-C.; Feu, L. S.; Fernández, D.; de la Figuera, N.; Forns, P.; Alberico, F. *Tetrahedron Lett.* **2005**, *46*, 581−585. (b) Daku, K. M. L.; Newton, R. F.; Pearce, S. P.; Vile, J.; Williams, J. M. J. *Tetrahedron Lett.* **2003**, *44*, 5095−5098. (c) Hone, N. D.; Payne, L. J.; Tice, C. M. *Tetrahedron Lett.* **2001**, *42*, 1115−1118. (d) Chamoin, S.; Houldsworth, S.; Snieckus, V. *Tetrahedron Lett.* **1998**, *39*, 4175−4178.