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On study of sterically controlled regioselective lithiation of *meta*-halopyridocarboxamides derivatives

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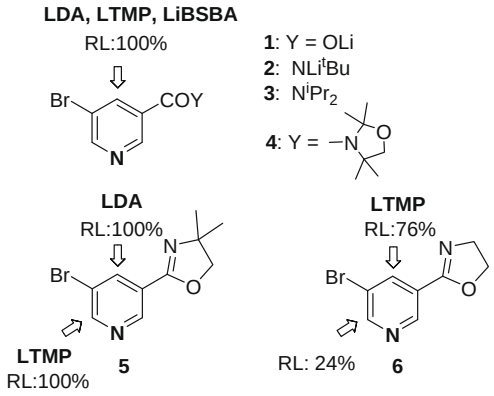
ABSTRACT

Sterically controlled regioselective lithiation of *meta*-halopyridocarboxamides derivatives using deuterated probes is described. A first experimental demonstration that the nitrogen is the main chelating-base approach site onto the oxazoline and *N*-alkoxyamide DMGs is reported.

Directed *ortho*-lithiation (DoM) is widely used as a powerful and efficient method for regioselective functionalization of aromatics and heteroaromatics.[1] Selective *ortho*-metallation of pyridocarboxamides, 3-(4,4′-dimethyloxazolinyl)pyridines, cyanopyridines and the unprotected carboxypyridines has been successfully accomplished with alkyllithium, lithium dialkylamide, Grignard, Hauser, and recently with lithium magnesiate bases.[2] With these achievements, we recently turned our attention to the highly valuable *meta*-halocarboxypyridine scaffolds as the two *meta*-directed DMGs metallation groups providing three possible ortho substitutions using DoM methodology. Furthermore, the halogen and carboxylic groups could be engaged in numerous chemical transformations, such as direct couplings, nucleophilic aromatic substitution reactions, and Buchwald's and Curtius's amination, to access highly substituted pyridines. The regiochemical metallation of the 1,3-inter-related-DMGs system specifically at the less favored ortho position not located between the two DMGs has hardly ever been studied.[3] For this purpose, we reasoned that addition of external and/or internal (DMG) steric effects might drive the challenging ortho lithiation at one of the less sterically hindered sites. To this end, we recently selected from the 3-bromonicotinic acid model the 4,4′-dimethyloxazoline (**5**) versus bulky amides (**1–4**) as carboxylic acid modulation to indifferently drive lithiation at both C-2 and C-4 positions using 2,2′,6,6′-tetramethylpiperidinyl lithium (LTMP) and lithium diisopropylamide (LDA) bases, respectively (Scheme 1 and Table 1, entries 1–6).[4] In this Letter, we further study the extension of the sterically controlled regioselective lithiation methodology using deuterated probes on the *meta*-chloro picolinic and isonicotinic series using both (4,4′-dimethyl)oxazoline and the structurally related secondary *N*-alkoxyamide as carboxylic acid DMG-moduling.



Scheme 1. Previous regiocontrolled lithiation (RL) study of 3-bromonicotinamides and 3-bromo-5-oxazolylpyridines.

The bulky secondary and tertiary picolinamides **7 and 8** and isonicotinamides **9 and 10** were prepared from commercially available 2-chloro- and 4-chloropicolinic acids via acid chlorides, and the 4,4′-dimethyloxazoline protection was installed under Meyer's method[2a] to give the 4-chloro-2-[(4,4′-dimethyl)oxazolinyl] pyridine **11** and 2-chloro-4-[(4,4′-dimethyl)oxazolinyl]pyridine **12,** respectively.

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Table 1
Regiocontrolled deuterium incorporation experiments[5] produced via Schemes 1–3

Entry	Compound	Condition	ID[a] (%)	RL[b] (%), site	Yield[c] (%)
1	**1**	LTMP (1.0 equiv), THF, −78 °C, 15 min then D_2O	88	100, C-4	72
2	**2**	LTMP (1.0 equiv), THF, −78 °C, 15 min then D_2O	91	100, C-4	89
3[b]	**3**	LTMP (1.0 equiv), THF, −78 °C, 15 min then D_2O	95	100, C-4	88
4	**4**	LTMP (1.0 equiv), THF, −78 °C, 15 min then D_2O	89	100, C-4	95
5	**5**	LDA (1.0 equiv), THF, −78 °C, 15 min then D_2O	90	100, C-4	91
6	**5**	**LTMP** (1.0 equiv), THF, −78 °C, 15 min then D_2O	85	**100, C-2**	96
7	**6**	*LTMP* (1.0 equiv), THF, −78 °C, 15 min then D_2O	100	*76, C-4*; *24 C-2*	97
8	**7**	LDA[d] (2.0 equiv), THF, −78 °C, 30 min then D_2O	88	100, C-3	89
9	**8**	LDA[d] (2.0 equiv), THF, −78 °C, 30 min then D_2O	90	100, C-3	95
10	**9**	LDA[d] (1.0 equiv), THF, −78 °C, 30 min then D_2O	85	100, C-3	75
11	**10**	LDA[d] (1.0 equiv), THF, −78 °C, 30 min then D_2O	85	100, C-3	85
12	**11**	LDA (1.0 equiv), THF, −78 °C, 30 min then D_2O	93	100, C-3	88
13	**11**	LTMP (1.0 equiv), THF, −78 °C, 30 min then D_2O	96	**25, C-3**; **75 C-5**	71
14	**12**	LDA (1.0 equiv), THF, −78 °C, 30 min then D_2O	85	100, C-3	75
15	**12**	**LTMP** (1.0 equiv), THF, −78 °C, 30 min then D_2O	77	**21, C-3**; **79 C-5**	91
16	**13**	LDA (2.0 equiv), THF, −78 °C, 30 min then D_2O	98	100, C-4	96
17	**13**	**LTMP** (3.0 equiv), THF, −78 °C, 15 min then D_2O	91	**19, C-4**; **81, C-2**	95
18	**14**	LDA (2.0 equiv), THF, −78 °C, 30 min then D_2O	96	100, C-4	96
19	**14**	**LTMP** (3.0 equiv), THF, −78 °C, 15 min then D_2O	96	**16, C-4**; **84, C-2**	95
20	**15**	LDA (2.0 equiv), THF, −50 °C, 30 min then D_2O	93	100, C-3	89
21	**15**	**LTMP** (4.0 equiv), THF, −78 °C, 45 min then D_2O	91	**8, C-3**; **91, C-5**	95
22	**16**	LDA (2.0 equiv), THF, −50 °C, 30 min then D_2O	92	100, C-3	91
23	**16**	**LTMP** (4.0 equiv), THF, −78 °C, 45 min then D_2O	96	**10, C-3**; **90, C-5**	95
24	**17**	LDA (2.0 equiv), THF, −78 °C, 30 min then D_2O	78	100, C-3	92
25	**17**	**LTMP** (4.0 equiv), THF, −30 °C, 45 min then D_2O	80	**34, C-3**; **66, C-5**	89
26	**18**	LDA (2.0 equiv), THF, −78 °C, 30 min then D_2O	85	100, C-3	75
27	**18**	**LTMP** (2.0 equiv), THF, −30 °C, 45 min then D_2O	76	**30, C-3**; **70, C-5**	85

[a] ID = Incorporation of deuterium (%).
[b] RL Regioselective lithiation (%).
[c] Yield of isolated mixture of deuterated compounds and starting material.
[d] LTMP base gave the same results.

Lithiation experiments were achieved using LDA and LTMP bases at −78 °C in THF, and each lithio intermediate was quenched with D_2O.[5] The percentage of regiocontrolled lithiation (RL) is indicated in scheme **2,** and the respective results of deuterium incorporation are depicted in Table 1 (entries 8–15). These results clearly showed that regioselective deprotonation between the two DMGs at the C-3 position of picolinamides **7 and 8** and isonicotinamides **9 and 10** (Table 1, entries 8–11) as well as chlorooxazolinylpyridines **11 and 12** (Table 1, entries 12 and 14) can be achieved with LDA. The chloropyridocarboxamides **7–10** were also exclusively deuterated at the same C-3 position using the more sterically hindered LTMP base with the same results of selective deuterium incorporation as when using the LDA base (Table 1, entries 8–11). Therefore, interestingly, chlorooxazolinylpyridines **11 and 12** were mainly deuterated at the less hindered C-5 positions with 75% and 79% selectivities, respectively (Table 1, entries 13 and 15) using the LTMP base. The steric hindrance turned out to be the main factor for controlling the regioselectivity of deprotonation of **11 and 12**. Indeed, we previously verified this assumption by examining the lithiation of the less hindered 3-bromo-5-oxazolinylpyridine which occurs mainly at the more hindered position 4 (Scheme 1 and Table 1, entry 7).[4] Thus, the present extended study on chlorooxazolinylpyridines **11 and 12** is gaining more support for the sterically controlled regioselective lithiation model depicted in Figure 1. The fact that the nitrogen atom onto the oxazoline DMG versus the oxygen atom onto the alkylamide or dialkylamide DMG is the main chelating-base approach site prior to metallation process is highlighted by experiments for the first time. On the basis of this novel sterically regioselective lithiation model, it appeared interesting to us to further examine the *N*-alkoxyamide group as carboxylic acid DMG-moduling which is structurally related to the oxazoline group since the lithium *N*-alkoxyamide constitutes an identical five-membered cycle by intramolecular lithium–oxygen bond (Fig. 1).

Thereby, interestingly, the steric encumbrance near the nitrogen chelating-base approach site could be modulated by changing

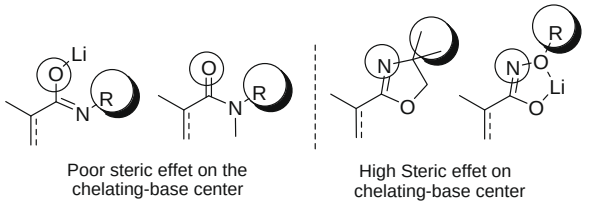
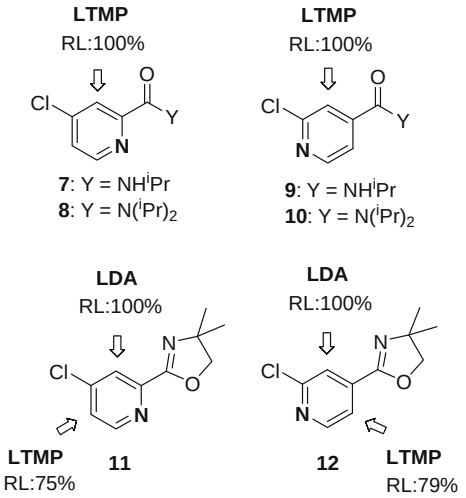
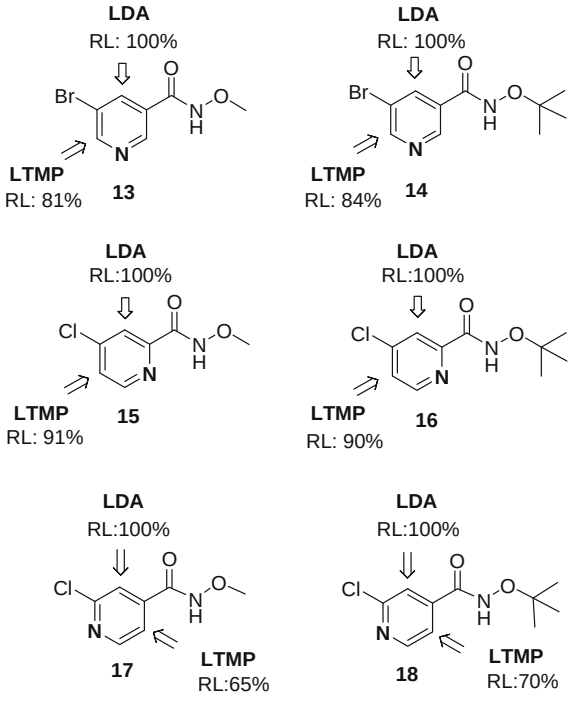


Figure 1. Sterically DMG-moduling model of regiocontrolled lithiation of 1,3-interrelated DMG systems based upon specific base chelating sites.



Scheme 2. Regiocontrolled lithiation (RL) study of *meta*-chloropyridocarboxamides and *meta*-chlorooxazolylpyridines.



Scheme 3. Regiocontrolled lithiation (RL) study of *meta*-chloro-*N*-alkoxypyridocarboxamides.

the nature of the alkoxy group (Fig. 1). Thus, the *N*-methoxy- and *N*-*tert*-butyloxy nicotinamides **13 and 14**, picolinamides **15 and 16** and isonicotinamides **17 and 18** were prepared by treatment of nicotinic, picolinic, and isonicotinic acid chlorides with commercially available methyl- and *tert*-butyl hydroxylamine hydrochlorides following Faul's procedure.[6]

A first set of lithiation experiments followed by D_2O quenching were achieved using 2 equiv of LDA at −78 °C in THF. All *N*-alkoxypyridocarboxamides **13–18** were exclusively deuterated between the two DMGs at C-3 position (Scheme 3). As expected, we found that the use of the more sterically hindered LTMP base led to the incorporation of the deuterium mainly at the less hindered site in a fair to high selectivity (65–91%) (Scheme 3, Table 1, entries 16–27). However, it should be noted that in almost all cases, an increase in the amount of base (3 or 4 equiv) and temperature (−50 and −30 °C) was required to attain a high level of deuterium incorporation (Table 1, entries 17, 19, 21, 23, and 25). In comparison with oxazoline-protecting model results of deuterium incorporation at the less hindered position depicted in Scheme 2, though few lower selectivities of deuteration at C-5 position were obtained from the *N*-methoxy as well as *N*-*tert*-butoxy nicotinamides **13** and **14** (81%, 84% vs 100%) and isoniconinamides **17** and **18** (65%, 70% vs 79%), interestingly, the selectivity of deuterium incorporation at C-5 position improved dramatically from the *N*- methoxy and *N*-*tert*-butoxypicolinamides **15** and **16** (91% and 90% vs 75%). It also clearly appeared that the methyl and the *tert*-butyl as steric group onto alkoxyamide DMGs gave closed results of regiocontrolled deuteration incorporation.

In conclusion, we reported here the sterically controlled regiolithiation of meta-halopyridocarboxamides derivatives based upon the use of (4,4′-dimethyl)oxazoline or *N*-alkoxyamide as carboxylic acid DMG-moduling. High selectivities of regiolithiation were observed at the less hindered position using the common bulky LTMP base, 100%, 91%, and 79% from 3-bromo-5-oxazolinylpyridine **5**, 5-chloro-*N*-methylpicolinamide **15** and 2-chloro-5-(4,4′-dimethyl) oxazolinylpyridine **12,** respectively. Nevertheless interestingly, the position between the two DMGs could be also lithiated in each case using a less steric LDA base. In the field of DMG methodology, this work constitutes the first experimental demonstration to our knowledge that the nitrogen atom is the preferential chelating-base approach site using oxazoline and the *N*-alkoxyamide DMGs. Further works toward 1,3-halocarboxy inter-related DMGs systems installed on various heteroaromatics are now in progress.

Acknowledgments

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References and notes

1. (a) Schlosser, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 376–393; (b) Anctil, E. J. G.; Snieckus, V. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., de Meijere, A., Eds., 2nd ed.; Wiley-VCH: Weinheim, 2004; p 761; (c) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933.
2. For deprotonation of pyridocarboxamides with alkyllithium and lithium dialkylamide bases see the following reviews: (a) Epsztajn, J.; Jóźwiak, A.; Szcześniak, A. K. *Curr. Org. Chem.* **2006**, *10*, 1817–1848; (b) Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4059–4090; For deprotonation of 3-(4,4′-dimethyloxazolinyl)pyridine and cyanopyridines with dialkylamide bases see: (a) Meyers, A. I.; Gabel, R. A. *J. Org. Chem.* **1982**, *47*, 2633–2637; (b) Cailly, T.; Fabis, F.; Lemaître, S.; Bouillon, A.; Rault, S. *Tetrahedron Lett.* **2005**, *46*, 135–137; For deprotonation of pyridocarboxamides with Grignard and Hauser bases see: (c) Bonnet, V.; Mongin, F.; Trécourt, F.; Quéguiner, G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4245–4249; (d) Schlecker, W.; Huth, A.; Ottow, E.; Mulzer, J. *J. Org. Chem.* **1995**, *60*, 8414–8416; For deprotonation of unprotected carboxypyridines with lithium dialkylamides: (e) Lazaar, J.; Rebstock, A.-S.; Hoarau, C.; Mongin, F.; Trécourt, F.; Godard, A.; Marsais, F.; Quéguiner, G. *Tetrahedron Lett.* **2005**, *46*, 3811–3813; (f) Lazaar, J.; Rebstock, A.-S.; Mongin, F.; Godard, A.; Trécourt, F.; Marsais, F.; Quéguiner, G. *Tetrahedron* **2002**, *58*, 6723–6728; For deprotonation of pyridocarboxamides with lithium magnesiate bases see: (g) Hawad, H.; Bayh, O.; Hoarau, C.; Trécourt, F.; Quéguiner, G.; Marsais, F. *Tetrahedron* **2008**, *64*, 3236–3245.
3. (a) Nguyen, T.-N.; Chau, N. T. C.; Castanet, A.-S.; Nguyen, K. P. P.; Mortier, J. *J. Org. Chem.* **2007**, *72*, 3419–3429; (b) Chau, N. T. C.; Nguyen, T.-N.; Castanet, A.-S.; Nguyen, K. P. P.; Mortier, J. *Tetrahedron* **2008**, *64*, 10552–10557; (c) Schlosser, M.; Mongin, F. *Chem. Soc. Rev.* **2007**, *36*, 1161–1172; (d) Heiss, C.; Marzi, E.; Mongin, F.; Schlosser, M. *Eur. J. Org. Chem.* **2007**, 669–675; (e) Nguyen, T.-N.; Chau, N. T. C.; Castanet, A.-S.; Nguyen, K. P. P.; Mortier, J. *Org. Lett.* **2005**, *7*, 2445–2448.
4. Robert, N.; Bonneau, A.-L.; Hoarau, C.; Marsais, F. *Org. Lett.* **2006**, *8*, 6071–6074.
5. *Typical regiocontrolled deuterium incorporation procedure*: To a stirred solution of LDA (or LTMP) (*n* equiv, Table 1) in dry THF (10 mL) was added dropwise at −78 °C or −50 °C (Table 1) a solution of carboxypyridine derivatives **1**–**18** (1 mmol) in THF (5 mL) under N_2. After 15 or 30 min (Table 1) at this temperature, D_2O (20 mmol) was added. The resulting solution was stirred for 30 min at the same temperature, and was then slowly allowed to warm to room temperature for 15 min. Saturated aqueous NH_4Cl (5 mL) and CH_2Cl_2 (10 mL) were added. The separated aqueous layer was extracted with CH_2Cl_2. The combined organic extract was dried ($MgSO_4$), concentrated in vacuo, and the crude product was purified by flash column chromatography on silica gel using a mixture of AcOEt and petroleum ether as eluent. The incorporation of deuterium (ID, Table 1) and the respective regioselectivity of the lithiation (RL, Table 1) were determined by ^1H NMR analysis of the isolated mixture of deuterated compounds and starting material.
6. Faul, M. M.; Razt, A. M.; Trankle, K. A.; Sullivan, W. G.; Winneroski, L. L. *J. Org. Chem.* **2001**, *66*, 5772–5782.