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Directed Lithiation of Unprotected Pyridinecarboxylic Acids

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Abstract: *The lithium salts of 2-, 3- and 4-pyridinecarboxylic acids undergo deprotonation at the position adjacent to the carboxylate group when treated with LTMP in THF at 0 °C, -50 °C and -25 °C, respectively. The lithiation conditions could be extended to chloronicotinic acids, and even to an activated benzoic acid.*

Keywords: *lithiation; pyridines; carboxylic acids; neighbouring group effects*

Lithiation is an important method for the preparation of polyfunctional pyridines since lithiated pyridines display a high reactivity toward many electrophilic functions.[1] From all the directing groups, carboxylic acid-derived functions stand out as being particularly useful for subsequent elaborations. Methodologies based on 2-oxazolino and amide directing groups were developed.[2] Moreover, deprotonation using ester and amide directing groups with Hauser bases or magnesium diamides was investigated.[3] These methodologies require protection and deprotection steps, the latter being difficult in the case of useful sterically demanding groups. This protection could be avoided if free pyridinecarboxylic acids could be metalated.

Since the pioneering work on 3-thiophenecarboxylic acid[4] and 3-furancarboxylic acid[5], lithiation in the position *ortho* to the carboxylate group was fully investigated in the benzene series by Mortier and Bennetau.[6] During the course of a synthesis of 2-bromonicotinic acid from 2-bromopyridine *via* metalation with an excess of LDA and trapping with dry ice, it was noted that 2-bromo-3,4-pyridinedicarboxylic acid was obtained as a by-product.[7] We suspected a metalation of lithium 2-bromo-3-nicotinate during the quenching with dry ice. Consequently, we started a study of the lithiation of the lithium salts of pyridinecarboxylic acids.

Preliminary experiments showed that commercial pyridinecarboxylic acids were not dimetalated at all when treated with *s*BuLi/TMEDA[8] or Schlosser's base LICKOR[9] in THF at -75 °C. So we turned to lithium 2,2,6,6-tetramethylpiperidide (LTMP).

The metalation of picolinic acid (**1**) was achieved with 3 eq. of LTMP in THF at 0 °C, after *in situ* formation of the lithium salt with one eq. of BuLi at -50 °C. Trapping the dilithio derivative with D_2O and dry ice afforded deuterated picolinic acid **2a**[10-11] and quinolinic acid (**2b**)[12] in good yields. The use of benzaldehyde as an electrophile also allowed the synthesis of lactone **2c**[13] after cyclization under acidic conditions (Scheme 1).

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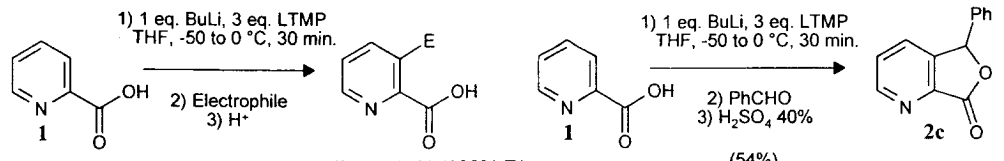
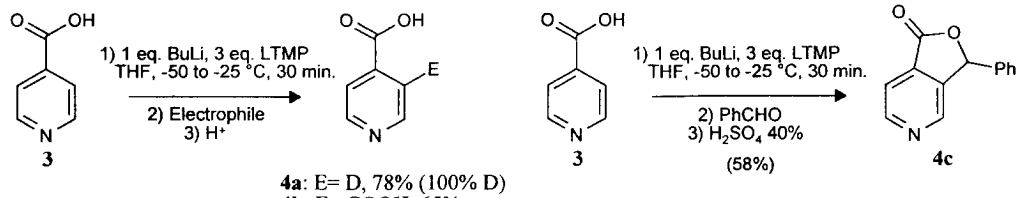


Scheme 1

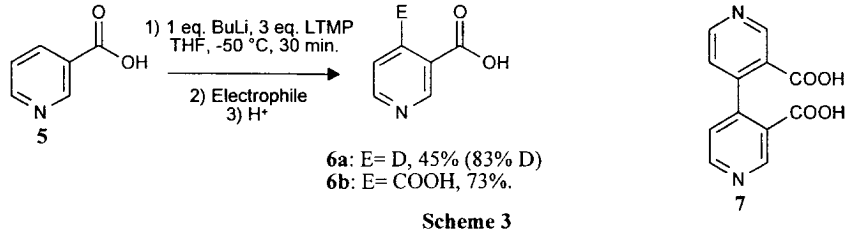
The metalation of isonicotinic acid (**3**) could be performed in the conditions described for picolinic acid, but the reaction mixture had to be kept below -25 °C during the metalation step in order to avoid addition reaction to the carboxylate entity. Quenching the reaction mixture with D_2O, dry ice and benzaldehyde gave, after subsequent acidification, deuterated isonicotinic acid **4a**[10,14], cinchomeronic acid (**4b**)[15] and lactone **4c**.[10,16] Note that the ^1H NMR spectra obtained after evaporation of the reaction mixtures showed lithium carboxylates of **4a** and **4b** as the only pyridinic compounds; yields mainly depend on the isolation of the pyridinecarboxylic acids (Scheme 2).



Scheme 2

From nicotinic acid (**5**), attemps to obtain deprotonation as the exclusive reaction failed since 4,4'-bipyridine-3,3'-dicarboxylic acid (**7**)[10,17] was always formed, probably *via* addition of the 4-lithio derivative to lithium nicotinate and subsequent air oxidation.

Nevertheless, optimization of the reaction conditions (-50 °C, 30 min) allowed after deuteriolysis and carboxylation, the syntheses of compounds **6a**[10,18] and **6b**[15] in respectively 37% and 73% yield (Scheme 3).

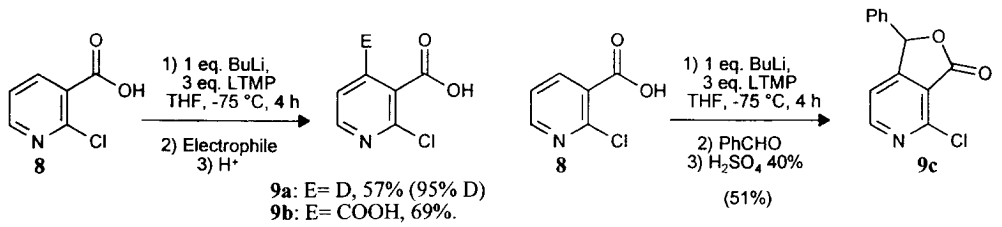


Scheme 3

Note that deprotonation occured at C4 as previously observed from pyridine amides and oxazolines.[2b,d-f]

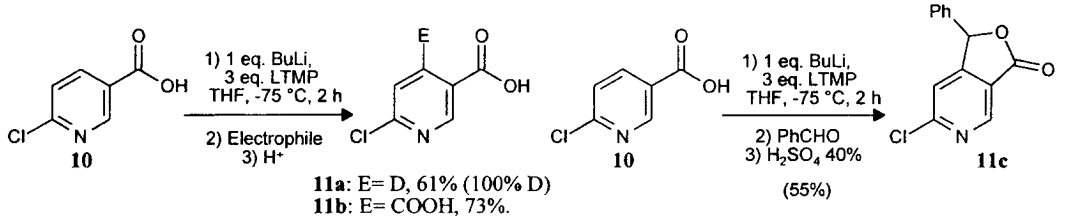
These metalation conditions were also tested on commercial chloronicotinic acids.

From 2-chloronicotinic acid (**8**), deprotonation could be performed at -75 °C owing to the long range effect of chlorine.[19] The 4-pyridyllithium readily reacted with electrophiles to afford compounds **9a-c**.[10,20] Note that addition at C4 of the 4-lithio derivative to the lithium salt of compound **8**, as previously observed from **5**, could be completely avoided (Scheme 4).



Scheme 4

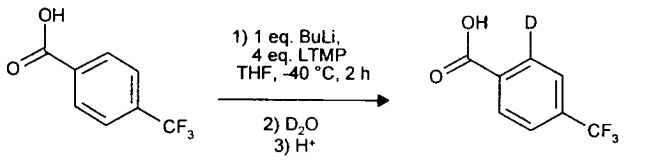
From 6-chloronicotinic acid (**10**), a regioselective metalation also occured at C4 to give compounds **11a-c**[10,21], as demonstrated by the quenching with D_2O, dry ice and benzaldehyde (Scheme 5).



Scheme 5

2-Chloropyridine is metalated at C3.[1a] In this work, metalation of nicotinic acid (**5**) occured at C4. 6-Chloronicotonic acid (**10**) is also deprotonated at C4, probably due to the stabilizing effect of the carboxylate group.

We wondered if the conditions here described could be extended in the benzene series. Activated[22] lithium benzoate of **12a** could be deprotonated using an excess of LTMP in THF at -40 °C and quenched with D_2O. No addition side compound was observed in this case (Scheme 6).



Scheme 6

It was observed that these conditions could be used for an activated benzoic acid, but were not suitable to dimetalate unsubstituted benzoic acid.

Compared to lithium 2-lithiobenzoate, the aza-analogous show good stability and they can thus be prepared at higher temperature. LTMP is particularly suitable for a clean deprotonation. Compared to the corresponding lithio amides, dilithio derivatives obtained from picolinic and isonicotinic acids show a good stability since no side reaction was observed at 0 °C and -25 °C, respectively. Moreover, our work shows that protection steps of pyridinecarboxylic acids to afford amide and oxazoline moities can be successfully avoided.

Metalation; Typical Procedure: BuLi (32 mL of a 2.5 M solution in hexane, 80 mmol) and, 5 min later, isonicotinic acid (2.5 g, 20 mmol) were added to a solution of 2,2,6,6-tetramethylpiperidine (10 mL, 60 mmol) in THF (100 mL) at -50 °C. After 10 min at -50 °C, the mixture was allowed to reach -25 °C and stirred at this

temperature for 30 min. The mixture was poured onto an excess of freshly crushed dry ice. After concentration under reduced pressure, the residue was washed with a cyclohexane/ether (30/70) mixture (500 mL) and dried. It was then treated with 2.5 M hydrochloric acid until pH 4, washed with dichloromethane (3 x 50 mL), acidified to pH 1 and stirred for 3 days. Filtration and drying of the precipitate afforded compound **4b** (65% yield).

References and notes

1. (a) Quéguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.* **1992**, *52*, 187-304; (b) Godard, A.; Marsais, F.; Plé, N.; Trécourt, F.; Turck, A.; Quéguiner, G. *Heterocycles* **1995**, *40*, 1055-1091; (c) Trécourt, F.; Gervais, B.; Mongin, O.; Le Gal, C.; Mongin, F.; Quéguiner, G. *J. Org. Chem.* **1998**, *63*, 2892-2897; (d) Pasquinet, E.; Rocca, P.; Marsais, F.; Godard, A.; Quéguiner, G. *Tetrahedron* **1998**, *54*, 8771-8772.
2. (a) Gschwend, H.W.; Hamdan, A. *J. Org. Chem.* **1975**, *40*, 2008-2009; (b) Meyers, A.I.; Gabel, R.A. *Tetrahedron Lett.* **1978**, *19*, 227-230; (c) Puterbaugh, W.H.; Hauser, C.R. *J. Org. Chem.* **1964**, *29*, 853; (d) Katritzky, A.R.; Rahimi-Rastgoo, S.; Ponkshe, N.K. *Synthesis* **1981**, 127-129; (e) Epsztajn, J.; Bieniek, A.; Brzezinski, J.Z.; Jozwiak, A. *Tetrahedron Lett.* **1983**, *24*, 4735-4738; (f) Epsztajn, J.; Bieniek, A.; Plotka, M.C. *J. Chem. Res. (S)* **1986**, 20-21.
3. Eaton, P.E.; Lee, C.-H.; Xiong, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8016-8018; Schlecker, W.; Huth, A.; Ottow, E.; Mulzer, J. *Liebigs Ann.* **1995**, 1441-1446.
4. Davies, G.M.; Davies, P.S. *Tetrahedron Lett.* **1972**, *13*, 3507-3510.
5. Knight, D.W.; Nott, A.P. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1125-1131.
6. Mortier, J.; Moyroud, J.; Bennetau, B.; Cain, P.A. *J. Org. Chem.* **1994**, *59*, 4042-4044; Bennetau, B.; Mortier, J.; Moyroud, J.; Guesnet, J.-L. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1265-1271; Moyroud, J.; Guesnet, J.-L.; Bennetau, B.; Mortier, J. *Tetrahedron Lett.* **1995**, *36*, 881-884; .Moyroud, J.; Guesnet, J.-L.; Bennetau, B.; Mortier, J. *Bull. Soc. Chim. Fr.* **1996**, *133*, 133-141.
7. Levacher, V.; unpublished result.
8. These conditions were used by Mortier and Bennetau to dimetalate benzoic acid.
9. Concerning LICKOR (BuLi/*t*BuOK), see : Katsoulos, G.; Schlosser, M. *Tetrahedron Lett.* **1993**, *34*, 6263-6266.
10. Satisfactory microanalyses were obtained.
11. Compound **2a** ^{1}H NMR (DMSO-d_6): 8.69 (d, 1H, J = 4.7), 7.98 (d, 1H, J = 6.8), 7.61 (dd, 1H, J = 7.0, 4.6).
12. Compound **2b** mp 188-191 °C. Cochran, J.C.; Little, W.F. *J. Org. Chem.* **1961**, *26*, 808-811 : mp 188-192 °C.
13. Compound **2c** mp 122-124 °C. Villacampa, M.; De la Cuesta, E.; Avendaño, C. *Tetrahedron* **1995**, *51*, 1259-1264 : mp 121-123 °C.
14. Compound **4a** ^{1}H NMR (DMSO-d_6): 8.69 (m, 2H), 7.73 (d, 1H, J = 4.8).
15. Compound **4b** mp 260-262 °C. Schlittler, E.; Spitaler, U. *Tetrahedron Lett.* **1978**, *19*, 2911-2914 : mp 262 °C.
16. Compound **4c** mp 128-130 °C; ^{1}H NMR ($CDCl_3$): 8.79 (d, 1H, J = 4.9), 8.69 (s, 1H), 7.74 (dd, 1H, J = 5.0, 1.0), 7.31 (m, 3H), 7.19 (m, 2H), 6.47 (s, 1H). Humphrey, G.L.; Dalton, L.; Joule, J.A.; Scopes, D.I.C. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2413-2416.
17. Compound **7** mp 240-242 °C. Rebek, J. Jr; Costello, T.; Wattley, R. *J. Am. Chem. Soc.* **1985**, *107*, 7487-7493.
18. Compound **6a** ^{1}H NMR (DMSO-d_6): 9.08 (s, 1H), 8.80 (d, 1H, J = 4.7), 7.55 (d, 1H, J = 4.5).
19. Schlosser, M. *Angew. Chem. Int. Ed.* **1998**, *110*, 1496-1513.
20. Compound **9a** ^{1}H NMR (DMSO-d_6): 8.53 (d, 1H, J = 4.8), 7.52 (d, 1H, J = 4.9); compound **9b** ^{1}H NMR (DMSO-d_6): 8.60 (d, 1H, J = 5.0), 7.81 (d, 1H, J = 5.0); compound **9c** ^{1}H NMR ($CDCl_3$): 8.46 (d, 1H, J = 5.1), 7.29 (m, 3H), 7.21 (d, 1H, J = 5.0), 7.15 (m, 2H), 6.31 (s, 1H).
21. Compound **11a** ^{1}H NMR (DMSO-d_6): 8.87 (s, 1H), 7.65 (s, 1H); compound **11b** ^{1}H NMR (DMSO-d_6): 8.94 (s, 1H), 788 (s, 1H); compound **11c** ^{1}H NMR ($CDCl_3$): 8.98 (s, 1H), 7.43 (m, 3H), 7.34 (s, 1H), 7.25 (m, 2H), 6.41 (s, 1H).
22. Schlosser, M.; Mongin, F.; Porwisiak, J.; Dmowski, W.; Büker, H.H.; Nibbering, N.M.M. *Chem. Eur. J.* **1998**, *4*, 1281-1286.