Pergamon

Tetrahedron Letters 43 (2002) 767–769

TETRAHEDRON LETTERS

Directed lithiation of unprotected quinolinecarboxylic acids

Anne-Sophie Rebstock, Florence Mongin, François Trécourt and Guy Quéguiner*

Laboratoire de Chimie Organique Fine et Hétérocyclique, UMR 6014, IRCOF, Place E. Blondel, BP 08, 76131 Mont-Saint-Aignan Cédex, France

Received 25 July 2001; accepted 28 November 2001

Abstract—The lithium salts of quinoline-2-carboxylic acid and 4-methoxyquinoline-2-carboxylic acid undergo deprotonation at C3 when treated with LTMP in THF at −25 and 0°C, respectively. The lithium salts of quinoline-3- and -4-carboxylic acids are more prone to nucleophilic addition; nevertheless, they are deprotonated at C4 and C3, respectively, when treated with LTMP in THF at −50°C.

Lithiation is an important method for the preparation of polyfunctional azines (pyridines, quinolines…) since lithiated derivatives display a high reactivity toward many electrophilic functions.[1] From all the directing groups, carboxylic acid-derived functions, such as 2-oxazolino and amide groups, stand out as being particularly useful for subsequent elaborations.[2] Moreover, deprotonation using ester and amide directing groups with Hauser bases or magnesium diamides was investigated.[3] The protection and deprotection steps required in these methodologies could be avoided if free carboxylic acids could be metalated.

The lithiation of π-excessive heteroaromatic systems containing the lithium carboxylate group was studied in the isothiazole,[4] thiophene,[5] benzo[*b*]furan,[6] furan,[5c,7] and oxazole[8] series. *Ortho*-metalation directed by the carboxylate group was fully investigated in the benzene series by Mortier and Bennetau.[9] Concerning π-deficient heteroaromatic systems, our group recently found conditions for deprotonation of all isomeric lithium pyridinecarboxylates, avoiding protection and difficult deprotection steps.[10] Compared to lithium 2-lithiobenzoate, the aza-analogues show good stability and can be prepared at a higher temperature; extension of this method to other azinic carboxylic acids seems thus far accessible.

A survey of the literature reveals that metalation of unprotected quinolinecarboxylic acids has never been reported; only one example concerns the deprotonation of a quinoline containing a carboxylic acid-derived function, *N*,*N*-diethylquinoline-4-carboxamide.[11]

Consequently, we started a study of the metalation of the lithium salts of commercially available quinolinecarboxylic acids.

Preliminary experiments showed that BuLi was not suitable to generate the lithium salts of quinolinecarboxylic acids, as used in the case of pyridinecarboxylic acids.[10] Due to its lower LUMO level, quinoline is more prone to nucleophilic attack and addition of BuLi to the quinoline ring was concurrently observed. So, we turned to lithium 2,2,6,6-tetramethylpiperidide (LTMP).

Deprotonation conditions of the lithium salts thus obtained were found to be identical to those already described for pyridinecarboxylic acids (LTMP in THF).[10]

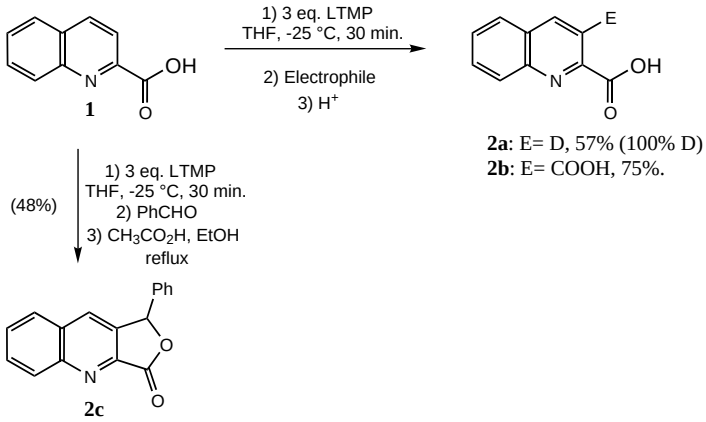
The metalation of quinaldic acid (**1**) was achieved with 2 equiv. of LTMP in THF at −25°C, after in situ formation of the lithium salt with 1 equiv. of LTMP. Trapping the dilithio derivative with D_2O and dry ice afforded deuterated quinaldic acid **2a**[12] and quinoline-2,3-dicarboxylic acid (**2b**)[13] in medium to good yields. The use of benzaldehyde as an electrophile also allowed the synthesis of lactone **2c**[14] after cyclization under acidic conditions (Scheme 1).

From 4-methoxyquinaldic acid (**3**), deprotonation could be performed at 0°C owing to the substituents present at both C2 and C4. Quenching the reaction

Keywords: lithiation; quinolines; carboxylic acids; neighbouring group effects.

* Corresponding author. Fax: +33 (0) 2 35 52 29 62; e-mail: guy.queguiner@insa-rouen.fr

0040-4039/02/$ - see front matter
PII: S0040-4039(01)02265-1



Scheme 1.

mixture with D_2O, dry ice and iodine gave, after subsequent acidification, deuterated 4-methoxyquinaldic acid **4a**,[15] 4-methoxyquinoline-2,3-dicarboxylic acid (**4b**)[16] and 3-iodo-4-methoxyquinoline-2-carboxylic acid (**4c**)[17] (Scheme 2).

Note that the ^1H NMR spectra obtained after evaporation of the reaction mixtures showed lithium carboxylates of **2a**–**b** and **4b**–**c** as the only quinolinic compounds; yields mainly depend on the isolation of the quinolinecarboxylic acids.

From quinoline-3-carboxylic acid (**5**), attempts to obtain deprotonation as the exclusive reaction failed when LTMP was used at 0 or −25°C,[18] due to the easy addition at C2 and C4 of the 4-lithio derivative to the lithium salt of compound **5**. Nevertheless, this side reaction could be avoided by working at a lower temperature (−50°C) and the syntheses of compounds **6a**[19] and **6b**,[20] in, respectively 59 and 80% yield, were allowed (Scheme 3).

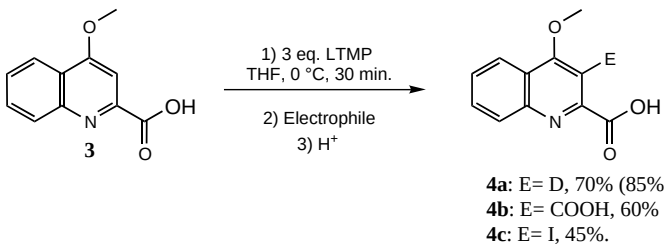
Remark that deprotonation occurred at C4 as previously observed from nicotinic acid.[10]

Concerning the lithium salt of quinoline-4-carboxylic acid (**7**), no lithiation was observed using less than 5 equiv. of LTMP at −50°C. A large excess of metalating agent was required; when 6 equiv. of LTMP were used, the 3-lithio derivative formed reacted with D_2O to afford compound **8**[21] in a low yield of 35% (Scheme 4).

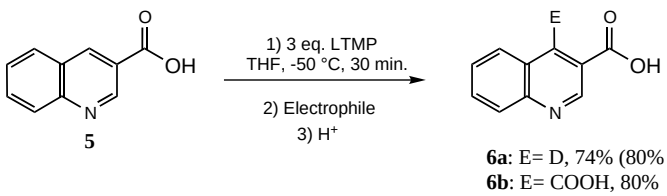
The dihedral angle between the hydrogen at C3 and the carbonyl oxygen could be responsible for the decreased efficiency of the directing power of the lithium carboxylate.[22]

Note that a lack of reactivity was also observed by Kelly during the metalation of *N*,*N*-diethylquinoline-4-carboxamide.[11]

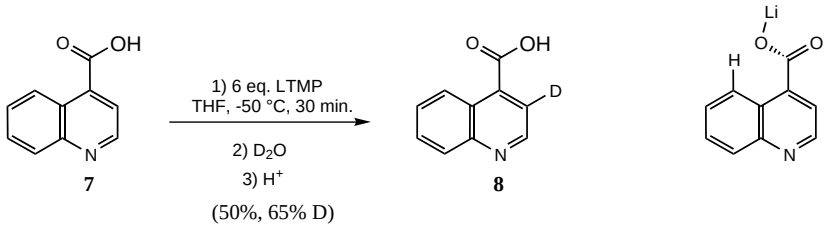
Metalation; **typical procedure**: BuLi (24 mL of a 2.5 M solution in hexane, 60 mmol) and, 5 min later, quinaldic acid (3.5 g, 20 mmol) were added to a solu-



Scheme 2.



Scheme 3.



Scheme 4.

tion of 2,2,6,6-tetramethylpiperidine (10 mL, 60 mmol) in THF (100 mL) at −25°C. The mixture was stirred at this temperature for 30 min and 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 (3×50 mL), acidified to pH 2–3 and stirred for 3 days. Filtration and drying of the precipitate afforded compound **2b** (75% yield).

References

1. (a) Quéguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.* **1992**, *52*, 187–304; (b) Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4059–4090.
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. (a) Eaton, P. E.; Lee, C.-H.; Xiong, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8016–8018; (b) Schlecker, W.; Huth, A.; Ottow, E.; Mulzer, J. *Liebigs Ann.* **1995**, 1441–1446; (c) Shilai, M.; Kondo, Y.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 442–444.
4. Caton, M. P. L.; Jones, D. H.; Slack, R.; Wooldridge, K. R. H. *J. Chem. Soc.* **1964**, 446–451.
5. (a) Davies, G. M.; Davies, P. S. *Tetrahedron Lett.* **1972**, *33*, 3507–3508; (b) Knight, D. W.; Nott, A. P. *J. Chem. Soc., Perkin Trans. 1* **1983**, 791–794; (c) Carpenter, A. J.; Chadwick, D. J. *Tetrahedron Lett.* **1985**, *26*, 1777–1780.
6. Costa, A. M. B. S. R. C. S.; Dean, F. M.; Jones, M. A.; Smith, D. A.; Varma, R. J. *J. Chem. Soc., Chem. Commun.* **1980**, 1224–1226.
7. (a) Knight, D. W.; Nott, A. P. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1125–1131; (b) Yu, S.; Keay, B. A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2600–2601.
8. Meyers, A. I.; Lawson, J. P. *Tetrahedron Lett.* **1981**, *22*, 3163–3166.
9. (a) Mortier, J.; Moyroud, J.; Bennetau, B.; Cain, P. A. *J. Org. Chem.* **1994**, *59*, 4042–4044; (b) Bennetau, B.; Mortier, J.; Moyroud, J.; Guesnet, J.-L. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1265–1271; (c) Moyroud, J.; Guesnet, J.-L.; Bennetau, B.; Mortier, J. *Tetrahedron Lett.* **1995**, *36*, 881–884; (d) Moyroud, J.; Guesnet, J.-L.; Bennetau, B.; Mortier, J. *Bull. Soc. Chim. Fr.* **1996**, *133*, 133–141.
10. Mongin, F.; Trécourt, F.; Quéguiner, G. *Tetrahedron Lett.* **1999**, *40*, 5483–5486.
11. Kelly, T. R.; Zhao, Y.; Cavero, M.; Torneiro, M. *Org. Lett.* **2000**, *2*, 3735–3737.
12. Compound **2a** ^{1}H NMR (DMSO-d_6): 8.54 (s, 1H), 8.17 (d, 1H, $J=8.7$), 8.08 (d, 1H, $J=8.7$), 7.86 (t, 1H, $J=7.5$), 7.77 (t, 1H, $J=7.5$).
13. Compound **2b** mp 270–272°C. Godard, A.; Quéguiner, G.; Pastour, P. *Bull. Soc. Chim. Fr.* **1971**, 906–912, mp 274°C.
14. Compound **2c** mp 200–202°C. Haddadin, M. J.; Zahr, G. E.; Rawdah, T. N.; Chelhot, N. C.; Issidorides, C. H. *Tetrahedron* **1974**, *30*, 659–666, mp 203°C.
15. Compound **4a** ^{1}H NMR (DMSO-d_6): 8.26 (d, 1H, $J=$ 8.3), 8.17 (d, 1H, $J=8.3$), 7.92 (t, 1H, $J=7.7$), 7.76 (t, 1H, $J=7.7$), 4.20 (s, 3H, OCH_3).
16. Compound **4b** ^{1}H NMR (DMSO-d_6): 8.16 (d, 1H, $J=$ 7.9), 8.06 (d, 1H, $J=7.9$), 7.85 (t, 1H, $J=7.7$), 7.71 (t, 1H, $J=7.7$), 4.10 (s, 3H, OCH_3).
17. Compound **4c** ^{1}H NMR (DMSO-d_6): 8.01 (d, 1H, $J=$ 8.0), 7.94 (d, 1H, $J=8.0$), 7.75 (t, 1H, $J=7.6$), 7.60 (t, 1H, $J=7.6$), 4.05 (s, 3H, OCH_3).
18. This result was already observed starting from nicotinic acid.[10]
19. Compound **6a** ^{1}H NMR (DMSO-d_6): 9.14 (s, 1H), 8.04 (d, 1H, $J=8.4$), 7.96 (d, 1H, $J=8.4$), 7.77 (t, 1H, $J=7.7$), 7.55 (t, 1H, $J=7.7$).
20. Compound **6b** mp 246–250°C. Hohenlohe-Oehringen, K.; Rhomberg, A.; Bretschneider, H. *Monatsh. Chem.* **1966**, *97*, 135–144, mp 250–255°C.
21. Compound **8** ^{1}H NMR (DMSO-d_6): 9.02 (s, 1H), 8.68 (d, 1H, $J=8.4$), 8.10 (d, 1H, $J=8.4$), 7.82 (t, 1H, $J=7.5$), 7.70 (t, 1H, $J=7.5$).
22. Beak, P.; Kerrick, S. T.; Gallagher, D. J. *J. Am. Chem. Soc.* **1993**, *115*, 10628–10636.