On the mechanism of the metalation of 2-(pyridin-3-yl)benzoic acid derivatives

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Abstract—The mechanism of the metalation of 2-(pyridin-3-yl)benzoic acid derivatives with strong bases is discussed. © 2005 Elsevier Ltd. All rights reserved.

Recently, Mongin and Quéguiner described\(^1\) the regio-selective directed remote metalation (DreM) of 2-(pyridin-2-yl) and 2-(pyridin-4-yl)benzoic acids (1) and (2) by LDA and LTMP in THF at rt, respectively, in

\[ \text{3a} \quad X = \text{OH} \]
\[ \text{3b} \quad X = \text{Ni-P}\text{Pr}_2 \]
\[ \text{3c} \quad X = \text{OEi} \]

\[ \text{9} \]
\[ \text{10} \]
\[ \text{11a} \]
\[ \text{12a} \]

Scheme 1.

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\[^1\] LDA (3 equiv), rt, THF
\[^2\] H^+
positions C2’ and C3’, which leads, by an in situ cyclization, to 5H-indeno[1,2-b]pyridin-5-one (5) and 9H-indeno[2,1-c]pyridin-9-one (6) in 52% and 67% yield (Scheme 1). The 2-(pyridin-3-yl) isomer 3a either remained unchanged or underwent degradation reactions on exposure to the lithium alkylamides, depending on the conditions used. It was suggested that pyridyllithiums 11a and 12a are less reactive than 9 and 10 towards the internal carboxylate thus preventing cyclization.

This last assumption was questionable because the authors provided no evidence to support their hypothesis. Furthermore, the arguer fails to take into account other facts that might contribute to the results. Thus, whereas the CONR2 group is by far much less electrophilic than CO2Li, the 4’-pyridyllithium anion arising from the metalation of N,N-disopropylbenzamide 3b with LDA (2.5 equiv) in THF at 0 °C undergoes facile cyclization, leading to 5H-indeno[1,2-c]pyridin-5-one (8) exclusively (94%). In the course of research aimed to generalize the synthetic utility of metalation of unprotected benzoic acids,3 we investigated the reactivity of 2-biphenyl carboxylic acid towards strong bases. While s-BuLi/TMEDA deprotonates exclusively the position adjacent to the carboxylate, metalation with the Schlosser–Lochmann superbase (n-BuLi/t-BuOK) takes place in a non-regiospecific fashion in ortho and remote positions. Because the carboxylate group acts as an in situ trap for the arylanion, the equilibrium between the lithiated species is shifted by Le Châtelier’s Principle towards the formation of the remote arylanion, which cyclizes to give the parent fluorenone after acidic hydrolysis.

In light of these observations, the metalation of 2-(pyridin-3-yl)benzoic acid (3a) was reexamined. Acid 3a was prepared (Scheme 2) by cross-coupling reaction of 3-pyridylboronic acid with ethyl 2-iodobenzoate under Suzuki’s conditions followed by saponification. A solution of 3a in THF was then allowed to react with LTMP (3 equiv) at 0 °C and the mixture was stirred for 18 h after which D2O was added. Chromatography (cyclohexane/ethyl acetate 9:1) led to a mixture of 9H-indeno[2,1-b]pyridin-9-one (7) (26%) and 8 (9%). It is notable that neither azafluorenones 7 and 8 nor the recovered starting acid 3a incorporated a deuterium. Taking into account the fact that ethyl ester 3c is exclusively converted into 7 (70%) by treatment with LTMP (3 equiv) in THF at 0 °C,1 potential deprotonation pathways were envisioned as shown in Scheme 3. In these reactions, the formation of azafluorenones is dictated both by the pyridine ring hydrogen acidities7 and by the electrophilicity of the director of lithiation (COX) which acts as an in situ trap for the intermediately formed aryl anion. In each case, there is complexation of the lithium atom of the base with the COX group in a prelithiation complex8 (complex induced proximity effect (CIPE) process)9 that precedes a transition state.

Scheme 2.

Scheme 3.
leading to the metalted species 11. Since the CO₂Et group is a weaker binder than CO₂Li and CONH-Pr₂, its acidifying effect in remote (C₂) position is moderate. However, CO₂Et is highly electrophilic. The kinetic anion 11c, which is destabilized by electronic repulsion between the carbanion and the pair of the azine nitrogen, has not a long-enough lifetime to isomerize the thermodynamically more stable (less basic) 4’-pyridyl-lithium 12c; it cyclizes instantaneously with the highly electrophilic centre to give monolithium salt 13c. Hydrolysis of the latter gave azafluorenone 7 as a sole product. Since CONH-Pr₂ is a stronger director but a much weaker electrophile, isomerization (11b→12b) has time to take place before cyclization (11b→13b) and azafluorenone 8 is formed exclusively after acidic workup via the stable tetrahedral gem-aminoalkoxide 14b. Isomerization 11b→12b most probably occurs by an intermolecular pathway. 4

In contrast to strong directors such as amides and oxazolines, the CO₂Li group activates moderately neighbouring positions thus conferring maximum regioflexibility in the metalation of the aromatic ring. 3,4 Compound 3a displays a reactivity pattern intermediate between those of the two previous limiting cases. Both azafluorenones 7 and 8 are formed via the doubly charged geminal dimetallo dialkoxides 13a and 14a. Di-anions 11a and 12a have a too short lifetime to be trapped by D₂O. Removal of H₂ is rate determining 10 whereas cyclization is fast and irreversible. Contrary to what was observed for 2-biphenyl carboxylic acid, 3 the deprotonation of 3a by LTMP is site-selective (the ortho position C3 is not lithiated) and the doubly charged geminal dimetallo dialkoxides 13a and 14a are not metalted further.

The results reported herein by no means diminish the value of the otherwise remarkable and meritorious work of Mongin and Quégüiner, but should be corrected for reasons of mechanistic importance.

References and notes

6. LTMP (5.1 mmol) in THF (5 mL) was added dropwise to a solution of 2-(pyridin-3-yl)benzoic acid (3a) (333 mg, 1.67 mmol) in dry THF (5 mL) at 0 °C. After 18 h at rt, D₂O (620 µL, 31 mmol) was added. Stirring was maintained for 15 min, water (10 mL) was added and pH was adjusted to 12 with aq 2 M NaOH. The aqueous layer was washed with ethyl acetate (3 × 15 mL), and aq 2 M HCl was added until pH reached an approximate value of 7. The organic layer was dried (MgSO₄), concentrated in vacuo and the residue was chromatographed (cyclohexane/ethyl acetate 9:1). 7 (79 mg, 0.43 mmol, 26%) and 8 (27 mg, 1.50 mmol, 9%) were isolated as yellow solids. 9H-indeno(2,1-b)pyridin-9-one (7). Mp 125–127 °C (lit. 126–127 °C: Mayor, C.; Wentrup, C. J. Am. Soc. Chem. 1975, 97, 7467–7480). 1H NMR (CDCl₃, 400 MHz) δ: 8.59 (dd, 1H, H₁, J = 4.9 Hz, J = 1.0 Hz), 7.86 (dd, 1H, H₅, J = 7.4 Hz, J = 1.0 Hz), 7.73 (d, 1H, H₄, J = 7.4 Hz, J = 5.6–7.54 (m, 2H, H₄ and H₅), 7.37 (m, H₆), 7.34 (dd, 1H, H₆, J = 7.4 Hz, J = 4.9 Hz). 13C NMR (CDCl₃, 100 MHz) δ: 191.3, 151.7, 149.1, 140.2, 138.6, 134.3, 130.9, 128.8, 126.6, 125.8, 123.4, 120.0. 5H-indeno(1,2-c)pyridin-5-one (8). Mp 118–119 °C. 1H NMR (CDCl₃, 400 MHz) δ: 8.91 (s, 1H, H₈), 8.71 (d, 1H, H₂, J = 4.5 Hz), 7.74 (d, 1H, H₅, J = 7.4 Hz), 7.65 (d, 1H, H₆, J = 7.4 Hz, J = 7.4 Hz), 7.51 (m, 1H, H₆), 7.44 (dd, 1H, H₅, J = 7.4 Hz, J = 7.9 Hz). HRMS, calcd for C₃₂H₂₅NO: 181.0523, found: 181.0520.
8. Complexation between Li and the pyridine nitrogen is believed to play a role in the metalation only at a former stage. The COX group and the pyridine nitrogen seem too far to ensure double complexation. See: Gros, P.; Choppin, S.; Fort, Y. J. Org. Chem. 2003, 68, 2243–2247, and Ref. 4b.