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

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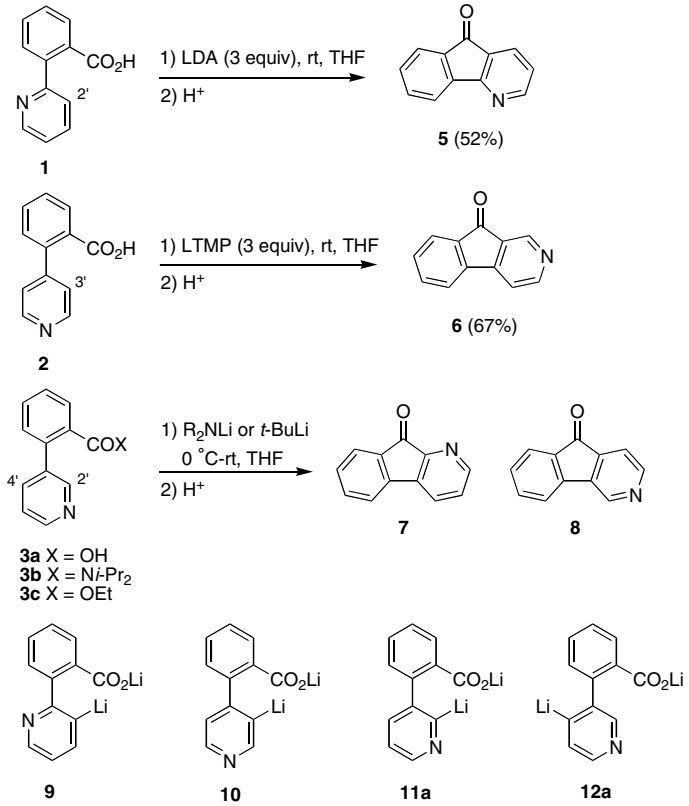
Abstract—The mechanism of the metalation of 2-(pyridin-3-yl)benzoic acid derivatives with strong bases is discussed.

Recently, Mongin and Quéguiner described[1] the regioselective 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



Scheme 1.

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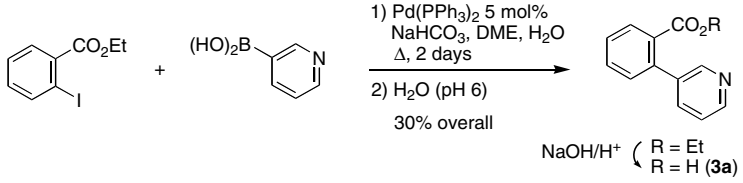
positions C2′ and C3′, which leads, by an in situ cyclization, to 5*H*-indeno[1,2-*b*]pyridin-5-one (**5**) and 9*H*-indeno[2,1-*c*]-pyridin-9-one (**6**) in 52% and 67% yield (Scheme 1). The 2-(pyridin-3-yl) isomer **3a** 'either remained unchanged or underwent degradation reactions on exposure to the 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 $CONR_2$ group is by far much less electrophilic than CO_2Li, the 4′-pyridyllithium anion arising from the metalation of *N*,*N*-diisopropylbenzamide **3b** with LDA (2.5 equiv) in THF at 0 °C undergoes facile cyclization, leading to 5*H*-indeno[1,2-*c*]pyridin-5-one (**8**) exclusively (94%).[2] 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.[4] 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 Chtelier's Principle towards the formation of the remote arylanion, which cyclizes to give the parent fluorenone after acidic hydrolysis.

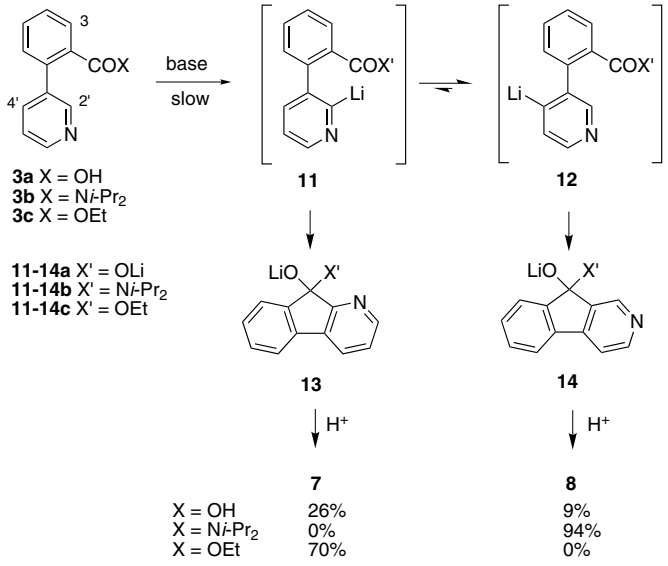
In light of these observations, the metalation of 2-(pyridin-3-yl)benzoic acid (**3a**) was reexamined. Acid **3a** was prepared (Scheme 2) by cross-coupling reaction of 3-pyridylboronic acid with ethyl 2-iodobenzoate under Suzuki's conditions followed by saponification.[5]

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 D_2O was added. Chromatography (cyclohexane/ethyl acetate 9:1) led to a mixture of 9*H*-indeno[2,1-*b*]pyridin-9-one (**7**) (26%) and **8** (9%).[6] 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 acidities[7] 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 complex[8] (complex induced proximity effect (CIPE) process)[9] that precedes a transition state



Scheme 2.



Scheme 3.

leading to the metalated species **11**. Since the CO_2Et group is a weaker binder than CO_2Li and CON*i*-Pr_2, its acidifying effect in remote (C2′) position is moderate. However, CO_2Et 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′-pyridyllithium **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 CON*i*-Pr_2 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 path.[4]

In contrast to strong directors such as amides and oxazolines, the CO_2Li 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 dilithio dialkoxides **13a** and **14a**. Dianions **11a** and **12a** have a too short lifetime to be trapped by D_2O. Removal of H2′ is rate determining[10] whereas cyclization is fast and irreversible. Contrary to what was observed for 2-biphenyl carboxylic acid,[4] 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 metalated further.

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

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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, D_2O (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 ($MgSO_4$), 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.
   9*H*-indeno[2,1-*b*]pyridin-**9**-one (**7**). Mp 125–127 °C (lit. 126–127 °C: Mayor, C.; Wentrup, C. *J. Am. Chem. Soc.* **1975**, *97*, 7467–7480). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.59 (dd, 1H, H_1, $J = 4.9$ Hz, $J = 1.0$ Hz), 7.86 (dd, 1H, H_3, $J = 7.4$ Hz, $J = 1.0$ Hz), 7.73 (d, 1H, H_7, $J = 7.4$ Hz), 7.56–7.54 (m, 2H, H_4 and H_5), 7.37 (m, H_6), 7.34 (dd, 1H, H_2, $J = 7.4$ Hz, $J = 4.9$ Hz). ^{13}C NMR ($CDCl_3$, 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.
   5*H*-indeno[1,2-*c*]pyridin-5-one (**8**). Mp 118–119 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.91 (s, 1H, H_4), 8.71 (d, 1H, H_2, $J = 4.5$ Hz), 7.74 (d, 1H, H_1, $J = 7.4$ Hz), 7.65 (d, 1H, H_5, $J = 7.4$ Hz), 7.6 (td, 1H, H_6, $J = 7.4$ Hz, $J = 8.4$ Hz), 7.51 (m, 1H, H_8), 7.4 (dd, 1H, H_7, $J = 7.4$ Hz, $J = 7.9$ Hz). HRMS, calcd for $C_{12}H_7NO$: 181.0523, found: 181.0520.
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