Controlling Chemoselectivity in Reactions of Unprotected Naphthalene-1-carboxylic Acid with Strong Bases

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Whereas treatment of unprotected naphthalene-1-carboxylic acid with alkyllithiums (RLi) affords 1,4-addition products, the reaction with LTMP/Me3SiCl under in situ quench conditions provides the arylsilane arising out from the substitution of lithium 2-lithionaphthalene carboxylate with Me3SiCl. With the Lochmann–Schlosser superbase (n-BuLi/t-BuOK), metalation occurs preferentially in the position adjacent to CO2Li although the peri and ortho, peri-dilithiated species are also formed.

Naphthalenes may undergo nucleophilic attack by organolithium compounds,1 though deamortisation of a naphthalene ring requires additional activation by an electron-withdrawing substituent. Naphthalenamines,2 naphthylxazolines3 and very ring requires additional activation by an electron-withdrawing (RLi) at low temperature (Scheme 1).15 Entry of the electrophile proceeds exclusively from the more accessible opposite face to that carrying the alkyl group.

Ortho- and peri-lithiations of naphthalene-carboxylic acid derivatives have received so far less attention.7 The best periliathion-directing groups are those which coordinate to the incoming organolithium but do not acify nearby protons, thereby disfavoring directed ortho-lithiation. Typical periliathion substrates are therefore naphthalenes bearing electron-rich oxygen or nitrogen-based substituents (e.g. OMe, NMe2, or CH2NMe2).3 With the electron withdrawing tertiary amide substituent CO-NR2—only group able to direct metalation in its adjacent position in the naphthalene series—, the ortho-substituted product becomes kinetically and thermodynamically favored.7,8

Although the CO2Li group does activate neighboring positions towards metalation, the effect remains fairly weak.9,10 This enables regioflexibility as most other electronegative substituents outperform a competing carboxylate group by their superior ortho-directing power.11,12 For instance, whereas 4-fluoro benzoic acid is metatalated preferentially in the position adjacent to the carboxylate by treatment with s-BuLi, s-BuLi/TMEDA or t-BuLi at ~78 °C, a complete reversal in regioselectivity is observed with LTMP at ~50 °C.13

We decided to explore metalation conditions using sterically hindered lithium amides (LDA and LTMP) and the Lochmann–Schlosser base (n-butylolithum/t-BuOK)14,15 with the intention of obtaining good chemo- and regiocontrol. It was not only of theoretical, but also of practical interest to test conditions for selective lithiation in ortho- or peri-position to the carboxylate, since the amide counterpart (CONR2) is recalcitrant to hydrolysis.16,17 There is also a real lack of methods for transformation of this group to other useful functionalities.

Acid 1 did not react upon treatment with LDA or LTMP (2.2 equiv.) in THF followed by a D2O quench in the interval of temperature −78 °C → 0 °C [External quench (EQ)]. When LTMP and chlorotrimethylsilane were premixed prior to the addition of 1 [in situ quench (ISQ) technique],18 2-(trimethylsilyl) naphthalene-1-carboxylic acid (4) was isolated in 65% yield.

Scheme 1.

Chlorotrimethylsilane is known to react slowly with bulky bases such as lithium diisopropylamide (LDA) and LTMP,18,19 and with tert-butylolithium and n-butyllithium.20 Nevertheless, s-BuLi and s-BuLi/TMEDA destroy Me3SiCl at −85 °C in THF.11 The deprotonation of 1 by LTMP which produces a small concentration of the trappable aryllithium 3, is sufficiently rapid to make the process competitive in rate with reaction of the hindered base with Me3SiCl. Deuterium oxide destroys the excess LTMP under EQ conditions. Although trisopropyl borate is known to be an effective in situ-trap in the presence of LTMP,21 it did not react under the previous ISQ conditions.

With the n-butyllithium/t-BuOK mixture (LICKOR), initial results from our laboratories were interesting though not synthetically useful. After much experimental manipulation, the best

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conditions involved forming the metalated species with LICKOR (4 equiv.) in THF at −78 °C (Scheme 2). The reaction was allowed to warm up to −50 °C, quenched with deuterium oxide (10 equiv.), and acidified at rt with 6 M HCl until pH reached 1. The deuterated products 2D-1, 8D-1, and 2D,8D-1 were formed in a 43:14:9 ratio, via the intermediacy of the organometallic species 3, 5, and 6 (M = Li or K) resulting from the metatation of the substrate in ortho, peri, and ortho-peri positions, respectively. The nature of the cations M involved in these species is not known with certainty. Both the structure of bases in solution as well as the nature of the actual reactive species have been the objects of controversial discussions. The deuterated products 2D-1, 8D-1, and 2D,8D-1 were formed in a 43:14:9 ratio, via the intermediacy of the organometallic species 3, 5, and 6 (M = Li or K) resulting from the metatation of the substrate in ortho, peri, and ortho-peri positions, respectively. The nature of the cations M involved in these species is not known with certainty. Both the structure of bases in solution as well as the nature of the actual reactive species have been the objects of controversial discussions.

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Scheme 2.

With these optimized conditions in hand, we proceeded to evaluate the scope of the process. Since the separation of the major ortho-substituted products was readily accomplished by fractional recrystallization, the reported method provides an easy access to very simple 2-substituted naphthalene-1-carboxylic acids (Table 1).24

Table 1. Synthesis of 2-substituted naphthalene-1-carboxylic acids (7a–f)

<table>
<thead>
<tr>
<th>Entry</th>
<th>EX</th>
<th>E</th>
<th>Product/%a</th>
<th>mp/°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me1</td>
<td>Me</td>
<td>7a (48)</td>
<td>125–127</td>
</tr>
<tr>
<td>2</td>
<td>EtI</td>
<td>Et</td>
<td>7b (38)</td>
<td>118–119</td>
</tr>
<tr>
<td>3</td>
<td>ClCl</td>
<td>Cl</td>
<td>7c (29)</td>
<td>148–150</td>
</tr>
<tr>
<td>4</td>
<td>BrBrCl</td>
<td>Br</td>
<td>7d (32)</td>
<td>136–139</td>
</tr>
<tr>
<td>5</td>
<td>I2</td>
<td>I</td>
<td>7e (30)</td>
<td>185–187</td>
</tr>
<tr>
<td>6</td>
<td>Me2S2</td>
<td>MeS</td>
<td>7f (34)</td>
<td>105–109</td>
</tr>
</tbody>
</table>

a Isolated (recrystallized) yields.

Reaction with iodomethane and iodoethane gave the anticipated products (Entries 1 and 2). Quenching with such electrophiles as hexachloroethane, 1,2-dibromotetrachloroethane, and iodine provided the ortho-halogenated benzoic acids 7c–e (Entries 3–5). Addition of dimethyl disulfide afforded the methylsulfonylated derivative 7f (Entry 6). In each entry, the ortho, peri, and ortho-peri product distribution was similar to that observed with D2O (Scheme 2).

The results reported in this letter corroborate the recent concept of how to achieve chemo or regiocontrol in hydrogen/metal exchange processes through mechanism-based matching of substituents and reagents. Although the yields of 2-substituted naphthalene-1-carboxylic acids are modest, the present method is direct and does not require protection and deprotection of the CO2H group. Extensions of the manipulation of carboxylic functional group are ongoing in our laboratories and will be reported upon in due course.

References and Notes
22 Isotope ratios were determined by 1H NMR and FIMS. The error is taken to be ±5%.
24 General procedure: To a stirred solution of naphthalene-1-carboxylic acid (1) (300 mg, 1.74 mmol) in anhydrous THF (15 mL) at −78 °C, was added the precooled (−78 °C) THF solution (10 mL) of the LiCKOR base (6.96 mmol, 4 equiv.). The reaction mixture was allowed to warm up to −50 °C and stirred at this temperature for 3 h. The electrophile (6–10 equiv.) in THF (8 mL) was then added. The reaction mixture was allowed to warm to room temperature over a period of 2 h. Acidification and standard workup led to a residue which was purified by chromatography on silica gel using cyclohexane/ethyl acetate (90:10) followed by recrystallization (heptane/ethyl acetate).

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