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The Carboxylic Acid Group as an Effective Director of Ortho-Lithiation

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Summary: Treatment of $PhCO_2H$ in tetrahydrofuran with 2.2 equiv of a 1:1 *sec*-butyllithium/*N,N,N',N'*-tetramethyl-1,2-ethylenediamine complex at −90 °C gave *o*-$LiC_6H_4CO_2Li$, which was treated with electrophiles to give *o*-$RC_6H_4CO_2H$ (R = Me, SMe, Cl, Br) in good yields.

The directed ortho-lithiation of substituted benzenes is a powerful method for the preparation of synthetically useful aryllithium intermediates. Early developments, initially by Gilman and Hauser[1] with subsequent contributions from many other laboratories,[2] expanded the scope of this reaction to a variety of substituted aromatic and olefinic systems.

From all the ortho-directing groups one type stands out as being particularly useful for subsequent elaborations, i.e., carboxylic acid-derived directing groups which include amides, esters, α-amino alkoxides, oxazolines, acetals, imidazolidines, imidazoles, and cyclohexylimines.[3] Sterically demanding groups such as *N,N*-diethylbenzamides have been studied the most extensively and have found widespread application;[2b–f,4] however, the major problems associated with their use are their great resistance to hydrolysis[2e,f,5] and the paucity of methods for their transformation to other useful functionalities.

Research in the field of ortho-directed aromatic metalations has also included studies of ortho-directing substituents that undergo side-chain metalation prior to ring ortho-metalation to give dimetalated species.[6] With the discovery that certain derivatives of aromatic carboxylic acids, such as secondary benzamides, thioamides, and arenehydroxamates,[7,8] can be lithiated directly in their ortho-position, a useful, reliable, and simple new method for regiospecific introduction of virtually any substituent became available.

Conventional wisdom indicates that the *carboxylic acid* group itself is incompatible with the lithiation conditions. For example, in their review, Gschwend and Rodriguez[9,10] concluded that "the direct ortho-lithiation of arylcarboxylic acids is generally not feasible because of the increased electrophilicity of the carboxylate group. Thus, treatment of lithium benzoate with an additional equivalent of an organolithium reagent leads to addition rather than metalation, providing useful ketone syntheses".[11] However this situation is not universally true, since the carboxylate group from benzene aromatic systems was described in a few examples to be resistant to addition of the alkyllithium base *at low temperature* (i.e., ≤−78 °C).[12,13] Furthermore, lithiations in the position ortho to the carboxylic acid group were reported in a few special cases: for example, Davies and Davies[14a] have described the formation at −78 °C and trapping by trimethylsilyl chloride of the dianion derived from 3-thiophenecarboxylic acid and LDA, while Knight and Nott have found that sequential treatment of 3-furancarboxylic acid with LDA followed by either deuterium oxide or methyl iodide leads only to the 2-substituted derivative, implying that the corresponding dianion can indeed be formed.[10,14b,c,15] Since it has been well established that the α positions of five-membered heterocycles are generally deprotonated much more readily than benzenoid systems,[16] we rea-

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[1] For a review of the early literature, see: Gilman, H.; Morton, J. W., Jr. *Org. React.* **1954**, *8*, 258.

[2] For recent reviews, see: (a) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1. (b) Snieckus, V. *Heterocycles* **1980**, *14*, 1649. (c) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306. (d) Snieckus, V. *Lect. Heterocycl. Chem.* **1984**, *7*, 95. (e) Snieckus, V. *Bull. Soc. Chim. Fr.* **1988**, 67. (f) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

[3] For a comprehensive list of references, see ref 2f.

[4] (a) Beak, P.; Brown, R. A. *J. Org. Chem.* **1977**, *42*, 1823. For recent examples: (b) Clark, R. D.; Repke, D. B.; Kilpatrick, A. T.; Brown, C. M.; MacKinnon, A. C.; Clague, R. U.; Spedding, M. *J. Med. Chem.* **1989**, *32*, 2036. (c) De Silva, S. O.; Reed, J. N.; Billedeau, R. J.; Wang, X; Norris, D. J.; Snieckus, V. *Tetrahedron* **1992**, *48*, 4863.

[5] Cuevas, J.-C.; Patil, P.; Snieckus, V. *Tetrahedron Lett.* **1989**, *30*, 5841.

[6] Related dimetalations include those of arenesulfonic acids, benzyl alcohols, secondary amides, thioamides, hydroxamates, sulfonamides, isonitriles, anilides, sulfonylhydrazones, phenols, and thiophenols. For leading references, see: Figuly, G. D.; Loop, C. K.; Martin, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 654, refs 3 and 4.

[7] Puterbaugh, W. H.; Hauser, C. R. *J. Org. Chem.* **1964**, *29*, 853.

[8] Secondary amides: (a) Forbes, I.; Pratt, R. A.; Raphael, R. A. *Tetrahedron Lett.* **1978**, 3965. (b) Baldwin, J. E.; Bair, K. W. *Ibid.* **1978**, 2559. (c) Dellacoletta, B. A.; Ligon, W. V., Jr.; Verbicky, J. W., Jr.; Williams, L. *J. Org. Chem.* **1981**, *46*, 3923. Thiobenzamides: (e) Fitt, J. J.; Gschwend, H. W. *Ibid.* **1976**, *41*, 4029. Arenehydroxamates: (f) Fisher, L. E.; Caroon, J. M.; Jahangir; Stabler, S. R.; Lundberg, S.; Muchowski, J. M. *Ibid.* **1993**, *58*, 3643.

[9] Reference 2a, p 68.

[10] Yu, S.; Keay, B. A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2600 and references cited therein.

[11] (a) For a review of the early literature on the reaction of carboxylic acids with organolithium reagents, see: Jorgenson, M. J. *Org. React.* **1970**, *18*, 1. (b) See: Ahn, T.; Cohen, T. *Tetrahedron Lett.* **1994**, *35*, 203 for recent leading references.

[12] Oddly, as early as in 1947 Gilman reported the formation and the stability at −78 °C of lithium *o*-lithiobenzoate derived from *o*-bromobenzoic acid and *n*-butyllithium in diethyl ether! See: Gilman, H.; Arntzen, C. E. *J. Am. Chem. Soc.* **1947**, *69*, 1537.

[13] (a) Harper, R. J., Jr.; Solosky, E. J.; Tamborski, C. *J. Org. Chem.* **1964**, *29*, 2385. (b) Tamborski, C.; Soloski, E. J. *Ibid.* **1966**, *31*, 743 and 746. (c) Hauser, F. M.; Rhee, R. *J. Am. Chem. Soc.* **1977**, *99*, 4533. (d) Beak, P.; Brown, R. A. *J. Org. Chem.* **1979**, *44*, 4463. (e) Beak, P.; Brown, R. A. *Ibid.* **1982**, *47*, 34. (f) Winkle, M. R.; Ronald, R. C. *Ibid.* **1982**, *47*, 2101. (g) Palmer, B. D.; Boyd, M.; Denny, W. A. *J. Org. Chem.* **1990**, *55*, 438. (h) Cantegril, R.; Croisat, D.; Desbordes, P.; Guigues, F.; Mortier, J.; Peignier, R.; Vors, J.-P. Wo. Pat. 932287, 1993. (i) Bennetau, B.; Cain, P. A. Continuation-in-Part of co-pending U.S. Pat. 7850128, filed on March 12, 1992.

[14] (a) Davies, G. M.; Davies, P. S. *Tetrahedron Lett.* **1972**, 3507. (b) Knight, D. W.; Nott, A. P. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1125. (c) Knight, D. W.; Nott, A. P. *Ibid.* **1983**, 791.

[15] (a) Gammill, R. B.; Hyde, B. R. *J. Org. Chem.* **1983**, *48*, 3863. (b) Carpenter, A. J.; Chadwick, D. J. *Tetrahedron Lett.* **1985**, 1777.

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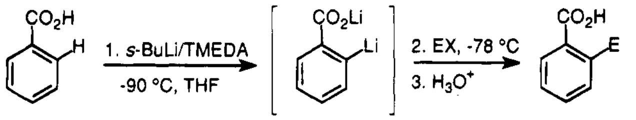
soned that under suitable conditions the oxygen atom of lithium benzoate might still coordinate with an organolithium reagent (kinetic effect)[2a] and/or might stabilize an *o*-lithium atom (thermodynamic effect)[17] thus facilitating dianion formation. It was, therefore, not only of theoretical, but also of considerable practical interest to test the feasibility of this concept.

We report evidence for the ortho-lithiation of the lithium salts of benzoic acids to give new members in the family of dilithiated species. The directed metalation of commercial benzoic acid was achieved conventionally with 2.2 equiv of *s*-BuLi/TMEDA in THF at −90 °C.[18] Quenching the orange ortho-lithiated carboxylate **1** with such electrophiles as methyl iodide, dimethyl disulfide, hexachloroethane, and 1,2-dibromotetrachloroethane led in 48−65% yields[19] to isolated, purified ortho-substituted benzoic acids **2a−d**.[20] Under the very basic conditions of this reaction, no benzylic deprotonation of the product *o*-toluic acid (**2a**) occurred as indicated by the absence of any *o*-ethylbenzoic acid product. The dilithiation which provides the dianion **1** may be considered as a new example of the *complex-induced proximity effect* process (CIPE).[21]

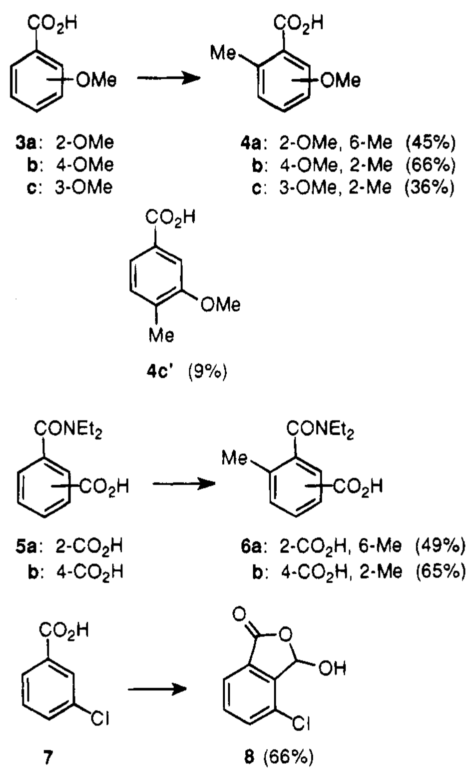


1

2a: E = Me (65%)
b: E = SMe (52%)
c: E = Cl (48%)
d: E = Br (55%)

To assay quantitatively the ability of a carboxylic acid functionality to direct ortho-lithiation, an intramolecular competition was carried out by using *o*- and *p*-methoxybenzoic acids (**3a,b**). Exposure of **3a,b** to *s*-BuLi and TMEDA and then quenching with methyl iodide led in 45 and 66% isolated yields, respectively, to methylation exclusively adjacent to the carboxylic acid group (Scheme 1).[19,22] Metalation of *m*-chlorobenzoic acid (**7**) gave the anticipated result of metalation at the site mutually ortho to both substituents. Condensation of the dilithio intermediate with DMF followed by acid-catalyzed cyclization gave as a sole product a 66% yield of phthalide **8**. The 1,3-CO$_2$LiOMe system showed an astonishingly low regioselectivity: metalation of *m*-anisic acid (**3c**) using *s*-BuLi/TMEDA followed by condensation with methyl iodide produced a crude product which appeared to be a mixture of two isomers **4c** and **4c′**, in a ratio of approximately 80:20.[19,23]

Scheme 1



3a: 2-OMe
b: 4-OMe
c: 3-OMe

4a: 2-OMe, 6-Me (45%)
b: 4-OMe, 2-Me (66%)
c: 3-OMe, 2-Me (36%)

4c′ (9%)

5a: 2-CO$_2$H
b: 4-CO$_2$H

6a: 2-CO$_2$H, 6-Me (49%)
b: 4-CO$_2$H, 2-Me (65%)

7

8 (66%)

The tertiary amide, which was reported first by Beak and Brown to be a very good ortho-directing function,[4a,13d,e] seems to be more activating than the carboxylic acid group: reaction of *N,N*-diethylphthalamic acid (**5a**)[4c] and *N,N*-diethylterephthalamic acid (**5b**)[13d,e] gave predominantly methylation adjacent to the amide function and **6a,b** were isolated in 49 and 65% yields, respectively.

We have shown here that suitable conditions have indeed been found under which lithium benzoate anions can be made to undergo effective and regiospecific ortho-lithiation, as evidenced by several trapping experiments. Despite the moderate strength of CO$_2$Li functionality as an ortho-lithiation director, the synthetic potential of metalated compounds bearing a carboxylic acid group, which can be used for subsequent modification, is clearly enormous.[13h,i] Development of this metalative approach for synthesis of contiguously tri- and tetrasubstituted benzoic acids, as well as studies of the underlying

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[16] Wakefield, B. J. *The Chemistry of Organolithium Compounds*; Pergamon: New York, 1974; pp 26 and 44.

[17] For some reactions of ortho-lithiated lithium benzoate prepared via bromine−lithium exchange, see: (a) Gilman, H.; Melstrom, D. S. *J. Am. Chem. Soc.* **1948**, *70*, 4177. (b) Parham, W. E.; Sayed, Y. A. *J. Org. Chem.* **1974**, *39*, 2051 and 2053. (c) Raynolds, P. W.; Manning, M. J.; Swenton, J. S. *Tetrahedron Lett.* **1977**, 2383. (d) Parham, W. E.; Bradsher, C. K.; Edgar, K. J. *J. Org. Chem.* **1981**, *46*, 1057 and ref 12.

[18] The general conditions were chosen on the basis of preliminary experiments with methyl iodide: benzoic acid could not be dimetalated by reaction with 2.2 equiv of *n*-BuLi/TMEDA in THF at −78 °C. Reaction with 2.2 equiv of *s*-BuLi/TMEDA at −78 °C, followed by quenching with methyl iodide, afforded a mixture of *o*-toluic acid (52%) and *s*-butyl phenyl ketone (22%). Under the same conditions but at −90 °C, **2a** in 65% yield and the undesired ketone in only 8% yield were obtained.

[19] A typical procedure is represented by preparation of *o*-toluic acid (**2a**). To a 500-mL round-bottomed flask equipped with a condenser and a rubber septum under argon was added 12.8 g (0.110 mol) of redistilled (bp 120.5−121.0 °C) *N,N,N′,N′*-tetramethyl-1,2-ethylenediamine and 100 mL of dry THF. The mixture was stirred magnetically and cooled to −90 °C. After consecutive addition of *sec*-butyllithium (0.110 mol, 80 mL of 1.4 M cyclohexane/hexanes solution) and recrystallized benzoic acid (mp 122−123 °C, 6.1 g, 0.050 mol) in 30 mL of dry THF at −90 °C, the orange solution was stirred for 60 additional min. Methyl iodide (28.4 g, 0.200 mol) was added dropwise at −78 °C during 30 min. The mixture was then treated with water, washed with diethyl ether, and shaken, and the aqueous layer was acidified with 2 N HCl. The mixture was diluted with diethyl ether, and the organic layer was separated and dried with MgSO$_4$. Filtration, concentration in vacuo, and recrystallization (heptane/ethyl acetate) gave **2a** (purified yield 4.4 g, 65%): mp 104−105 °C.

[20] Characterization was done by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy and by matching melting points with those of authentic samples. For data, see the supplementary material.

[21] The carboxylate group could provide a residence site for the lithium cation giving rise to a lithium species which could act to direct the second deprotonation in an aggregated species. Complexation enforces proximity, resonance, stereoelectronic, inductive, and steric effects, and the resulting CIPE process could be more important than the classical effects in controlling the course of a reaction. See: Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356.

[22] For earlier methods of preparation of **4a** and **4b**, see respectively: (a) Kanakam, C. C.; Mani, N. S.; Ramanathan, H.; Rao, G. S. R. S. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1907. (b) Hartmann, R. W.; Vom Orde, H.-D.; Schönenberger, H. *Arch. Pharm.* **1990**, *323*, 73.

[23] Box, V. G. S.; Yiannikouros, G. P. *Heterocycles* **1990**, *31*, 971.

structure–stability relationships of ortho-lithiated lithium benzoate, are currently in progress in our laboratories.

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Supplementary Material Available: Experimental procedures and spectra data for compounds **2a–d**, **4a–c**, **4c′**, **6a**, **6b**, and **8** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.