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Directed *Ortho*-Metalation of Unprotected Benzoic Acids. Methodology and Regioselective Synthesis of Useful Contiguously 3- and 6-Substituted 2-Methoxybenzoic Acid Building Blocks

Thi-Huu Nguyen, Anne-Sophie Castanet, and Jacques Mortier*

Université du Maine and CNRS, Unité de Chimie Organique Moléculaire et Macromoléculaire (UMR 6011), Faculté des Sciences, avenue Olivier Messiaen, 72085 Le Mans Cedex 9, France

jacques.mortier@univ-lemans.fr

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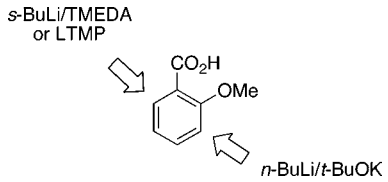
ABSTRACT



By treatment with *s*-BuLi/TMEDA at −78 °C, *unprotected* 2-methoxybenzoic acid is deprotonated exclusively in the position ortho to the carboxylate. A reversal of regioselectivity is observed when the acid is treated with *n*-BuLi/*t*-BuOK. These results are of general utility for the one-pot preparation of a variety of very simple 3- and 6-substituted 2-methoxybenzoic acids that are not easily accessible by conventional means. The potential usefulness of the method is demonstrated by the expedient synthesis of lunularic acid.

3- and 6-substituted 2-hydroxybenzoyl fragments are a characteristic feature of many biologically active natural products of polyketide origin (macrolides, polyene antibiotics, tetracyclines, etc.), and synthetic exploits in this area often require the 3- and 6-substituted 2-hydroxybenzoic acids.[1] Published routes to these materials reveal that the substitution pattern is not easily established. These building blocks have, in the past, been obtained by demanding, invariable, classical, and poorly regioselective electrophilic substitution chemistry and largely inefficient classical sequences which suffer generally from poor overall yields.

In view of their importance, little attention has been paid to their synthesis via lithiation reactions for a simple reason: it is generally accepted that the carbonyl group needs to be protected prior to metalation and deprotection requires drastic conditions which are very often not applicable for delicate structures. The *N*,*N*-dialkylamide group which has been studied the most extensively,[2,3] is stable to refluxing 16 N HCl for 72 h. The problem is especially acute for 2-substituted benzamides, in general, and for *N*,*N*-diethyl-2-methoxybenzamide (**1**), in particular. Directed metalation and subsequent reaction with electrophiles produce 2,6-disubstituted benzamides **5** which are especially inert to hydrolysis except in cases where anchimeric assistance by ortho-introduced electrophiles is capable of forming five- or six-membered-ring tetrahedral intermediates, which greatly enhances amide hydrolytic rates.[3,4]

(1) See, inter alia: (a) Bender, C. L.; Rangaswamy, V.; Loper, J. *Annu. Rev. Phytopathol.* **1999**, *37*, 175. (b) Tyman, J. H. P. *Recent Res. Devel. Lipids* **2001**, *5*, 125. (c) Katz, L. *Chem. Rev.* **1997**, *97*, 2557. (d) Staunton, J.; Weissman, K. J. *Nat. Prod. Rep.* **2001**, *18*, 380.

(2) (a) Beak, P.; Brown, R. A. *J. Org. Chem.* **1977**, *42*, 1823. (b) Comins, D. L.; Brown, J. D. *J. Org. Chem.* **1986**, *51*, 3566. (c) Reitz, D. B.; Massey, S. M. *J. Org. Chem.* **1990**, *55*, 1375.

(3) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

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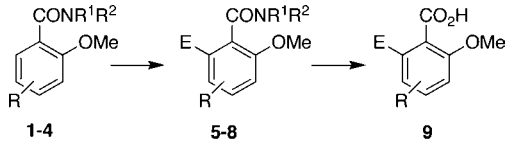
Moreover, while the related secondary benzamides **2** are generally thought to be more susceptible to hydrolysis than tertiary amides,[2b] acid hydrolysis of 2,6-disubstituted secondary benzamides **6** to the corresponding 2,6-disubstituted benzoic acids **9** still presents quite a challenge. The "built-in" TMEDA benzamide **3** is a useful director which offers greater facility in hydrolysis.[2b] However, the procedure for deprotection still requires refluxing **7** in 6 N hydrochloric acid for 7 days in the presence of iodomethane and sodium ethoxide. Reitz and Massey have addressed the hydrolysis problem by developing the *tert*-amide ortho-lithiation directing group **4** which is converted into secondary amide, the cleavage of which, via the *N*-nitrosoamide has long been known.[2c,5]

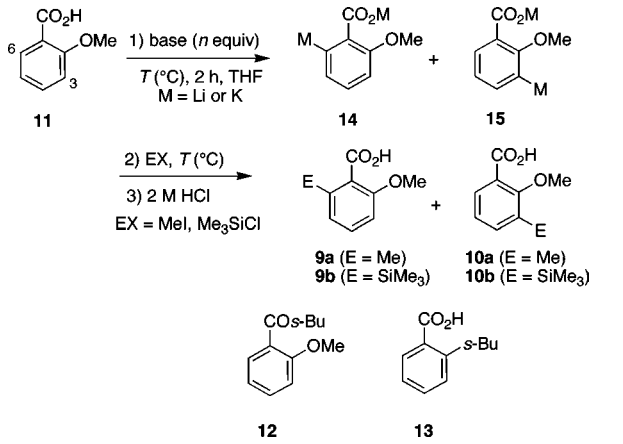


1,5 $R^1 = R^2 = Et$
2,6 R^1 = Alk or Ar, $R^2 = H$
3,7 $R^1 = (CH_2)_2NEt_2$, $R^2 = Et$
4,8 $R^1 = t$-Bu, $R^2 = Me$

The CO_2H group which might be thought to be susceptible to nucleophilic addition by the organolithium bases can retain its structural integrity and function as an effective director under suitable conditions. Despite its relatively recent discovery[6] and adequate recognition,[7] this director has received up to now only moderate methodological attention. In contrast to strong directors such as amides and oxazolines, the carboxylate group moderately activates neighboring positions thus conferring maximum regioflexibility in the aromatic metalation.

Herein we provide a general, short, and regioselective new method for the construction of simple 3- and 6-substituted 2-methoxybenzoic acids, including the growth inhibitor found in *Lunularia cruciata*, lunularic acid (**18**). All of the optimization reactions were carried out using commercially available 2-methoxybenzoic acid (**11**) under argon and THF as the solvent (Scheme 1 and Table 1). The intermediates were trapped with iodomethane or chlorotrimethylsilane. The product ratio was determined by ^1H NMR after acidification and extraction with ether of the crude reaction mixture. Since the recovered starting acid **11** and nonacidic products were also identified in these conditions, the product distribution represents the selectivity and the efficiency of the metalation reactions.

Scheme 1. Site-Selective Deprotonation of 2-Methoxybenzoic Acid (**11**) by Strong Bases (See also Table 1)



After considerable experimentation beforehand, we found that treatment of **11** with the 1:1 complex *s*-BuLi/TMEDA (2.2 equiv)[6] in THF for 2 h at −78 °C provided the dianion **14** (M = Li) exclusively. Quenching with an excess of MeI furnished 2-methoxy-6-methylbenzoic acid (**9a**) in good yield (71%) (entry 1). The ketone **12** arising from the nucleophilic attack of *s*-BuLi to the CO_2Li functionality was also formed as a byproduct.[8,9] At −65 °C with *s*-BuLi alone (entry 2), 1,2-addition competes with ortho-lithiation, and in minor way with an addition−elimination sequence leading to **13**. We have shown recently that ortho-lithiation of 2-fluorobenzoic acid with *s*-BuLi is hampered by the preferential attack of the anion to the C−F position.[7a]

Attempted rationalization of the formation of ortho-lithiated species **14** turned out to invoke in the initial step a prelithiation complex **PLC** (CIPE effect)[10] by a strong coordination of *s*-BuLi with the electron-rich π-system of the carboxylate, TMEDA, and the solvent (Scheme 2). The interaction of the alkyllithium with the p-electrons of the methoxy group would be comparatively weaker.[11] This coordination is followed by a protophilic attack of the carbanionic portion of the lithiating agent on the adjacent hydrogen atom (H_6) in the transition state (**TS**), leading to the dianion **14**.[12]

In the absence of TMEDA, the competing reaction leading to **13** follows a S_NAr mechanism. A critical transition-state geometry **TS′** must be achieved, presumably via a prelithia-

(4) Page, M. I. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 449.
(5) See also: (a) Cuevas, J.-C.; Patil, P.; Snieckus, V. *Tetrahedron Lett.* **1989**, *30*, 5841. (b) Fisher, L. E.; Muchowski, J. M.; Clarck, R. D. *J. Org. Chem.* **1992**, *57*, 2700.
(6) Mortier, J.; Moyroud, J.; Bennetau, B.; Cain, P. A. *J. Org. Chem.* **1994**, *59*, 4042.
(7) (a) Gohier, F.; Castanet, A.-S.; Mortier, J. *Org. Lett.* **2003**, *5*, 1919. (b) Gohier, F.; Mortier, J. *J. Org. Chem.* **2003**, *68*, 2030. (c) Tilly, D.; Samanta, S. S.; De, A.; Castanet, A.-S.; Mortier, J. *Org. Lett.* **2005**, *7*, 827. (d) Tilly, D.; Castanet, A.-S.; Mortier, J. *Chem. Lett.* **2005**, *34*, 446. (e) Gohier, F.; Castanet, A.-S.; Mortier, J. *J. Org. Chem.* **2005**, *70*, 1501. (f) Nguyen, T. H.; Chau, N. T. T.; Castanet, A.-S.; Nguyen, K. P. P.; Mortier, J. *Org. Lett.* **2005**, *7*, 2445.
(8) Jorgenson, M. J. *Org. React.* **1970**, *18*, 1.
(9) Attempted lithiation of **11** with *n*-BuLi alone or chelated to TMEDA gave exclusively the undesired 1,2-addition product. In the presence of the tridental ligand *N*,*N*,*N*′,*N*′,*N*″-pentamethyldiethylenetriamine (PMTDA), a poor yield of **9a** was attained (15%).
(10) (a) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. (b) Whisler, M. N.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem, Int. Ed.* **2004**, *43*, 2206.
(11) Katsoulos, G.; Takagishi, S.; Schlosser, M. *Synlett.* **1991**, 731.
(12) In a recent report (ref 7f), we put forward for consideration that the directing and accelerating effect of the substituents might be due to the stabilization of *both* the initial complex and the transition structure. We also suggested that coordination might be stronger in the transition state than in the initial complex. As a result, complexation would increase the reaction rate by providing a new mechanism that has a smaller activation energy.

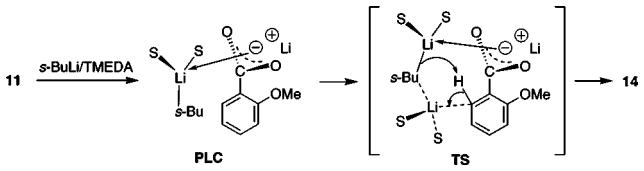
Table 1. Deprotonation of 2-Methoxybenzoic Acid (**11**) with Strong Bases[a,b]

entry	base (*n* equiv)	EX[c]	*T* (°C)	**9a**,**b**	**10a**,**b**	**11**[d]	others
1	*s*-BuLi/TMEDA (2.2)	MeI	−78	71 (61*)	0	4	20 [**12**]
2	*s*-BuLi (2.2)	MeI	−65	6	2	18	45 [**12**], 25 (17*) [**13**]
3	LTMP (4)	MeI	−50	0	0	98	0
4	LTMP (4)	MeI	−30	8	0	80	degradation
5	LTMP (4)	MeI	0	0	0	0	degradation
6	LTMP (3)	Me_3SiCl	−78	92 (89*)	0	0	0
7	*n*-BuLi/*t*-BuOK (4)	MeI	−78	16	51 (40*)	28	0

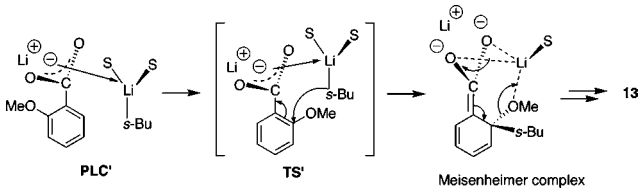
[a] The structures were confirmed by IR, MS, ^{1}H NMR (NOESY), and ^{13}C NMR spectroscopy. [b] NMR yields (%). Isolated yields (recrystallized or chromatographed) are followed by an asterisk (*). See the Supporting Information. [c] External quench (EQ) technique for MeI. In situ quench (ISQ) method for Me_3SiCl (entry 6). The base and Me_3SiCl were premixed prior to addition of **11**. Hydrolysis was carried out at rt. [d] Recovered 2-methoxybenzoic acid (**11**).

tion complex **PLC′**, between *s*-BuLi and the substrate for direct, rate-determining nucleophilic addition of RLi leading to a cyclohexadienyl anion, or Meisenheimer type complex (Scheme 3).[13] This intermediate is no longer aromatic, possessing a sp^3 hybridized carbon. However it is stabilized by delocalization of the negative charge on the ring and the carboxylate. The final step is the loss of the methoxy group to give **13**.

Scheme 2. Proposed Mechanism for Lithiation of **11** via a Prelithiation Complex PLC and a Transition State TS (S: Solvent, TMEDA, or RLi Aggregate)



Scheme 3. Addition−Elimination Sequence. Pre-Lithiation Complex PLC′ and Transition State TS′ (S: Solvent or RLi Aggregate)



Deprotonation of 2-methoxybenzoic acid (**11**) by LTMP was then considered (entries 3−6 of Table 1). Astonishingly, whereas iodomethane quenches at −50 °C left **11** unreacted, trapping with Me_3SiCl (in situ quench technique)[14] at −78 °C led to **9b** free of any isomers (92%).[7a] The deprotonation which produces a small concentration of the trappable aryllithium **14** (M = Li) is sufficiently rapid to make this process competitive in rate with reaction of the hindered base with the in situ electrophile (Me_3SiCl). When MeI was added at −30 °C, a small amount of **9a** was produced (∼8%), while most of the starting acid was recovered unchanged. At 0 °C, only degradation products were recovered.

When **11** was treated with *n*-BuLi/*t*-BuOK[15] (1:1 ratio, 4 equiv) in THF at −78 °C (entry 7), the dianion **15** arising from metalation in C-3 formed preferentially. Quenching with iodomethane followed by hydrolysis provided the acids **9a** and **10a** in 16% and 51% yield, respectively. The major C-3 isomer **10a** was readily isolated by fractional crystallization in cyclohexane/ethyl acetate (40%). Increasing the amount of base or the temperature was detrimental to the yield. *t*-BuOK is a strong ligand powerful enough to break up the ordinary tight tetrameric aggregates of *n*-BuLi[16] to dimers or even monomers. Under these circumstances, the intramolecular solvation is no longer competitive and the reagent deprotonates the position ortho to the most electronegative substituent.[11]

Table 2 summarizes the results of reactions of metalated species **14** and **15** with a variety of electrophiles to give products **9a**−**j** and **10a**−**f**,**h**. The conditions (*s*-BuLi/TMEDA, 2.2 equiv/THF/−78 °C/2 h) and (*n*-BuLi/*t*-BuOK, 4 equiv/THF/−78 °C/2 h) have been standardized and are considered to be optimum. Although numerous preparations of **9a** have been reported,[17] they are all multistep syntheses.[1b,18] 2-Methoxy-6-(trimethylsilyl)benzoic acid (**9b**) was prepared efficiently using the ISQ protocol (vide supra). Regioisomerically pure chlorine, bromine, and iodine derivatives (**9c**−**e** and **10c**−**e**) were conveniently obtained albeit in somewhat moderate yields from reactions with hexachloroethane, 1,2-dibromotetrachloroethane, and iodine. Simple compounds such as **9b** and **10b**,**c**,**e**,**f**,**h** were previously unknown. Prior to this work, syntheses of **9d** were reported

(13) Buncel, E.; Park, K.-T.; Dust, J. M.; Manderville, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 5388.

(14) The base and Me_3SiCl were premixed prior to addition of the acid. See: Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155.

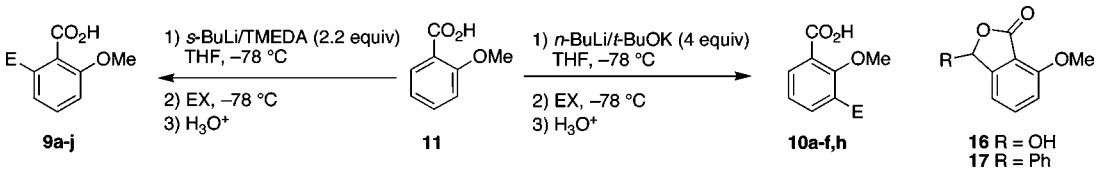
(15) (a) Lochmann, L. *Eur. J. Inorg. Chem.* **2000**, 1115. (b) Schlosser, M. *Mod. Synth. Methods* **1992**, *6*, 227.

(16) Quirck, R. P.; Kester, D. E. *J. Organomet. Chem.* **1974**, *72*, C23.

(17) Hauser, F. M.; Pogany, S. A. *Synthesis* **1980**, 814 and references therein.

(18) **9a** is a useful intermediate for natural product syntheses in particular for the preparation of anacardic acids which are widely distributed in many botanical and biological families. See: Seijas, J. A.; Vazquez-Tato, M. P.; Montserrat Martınez, M.; Santiso, V. *Tetrahedron Lett.* **2004**, *45*, 1937.

Table 2. Preparation of 3- and 6-Substituted 2-Methoxybenzoic Acids **9a**−**j** and **10a**−**f**,**h**[a]



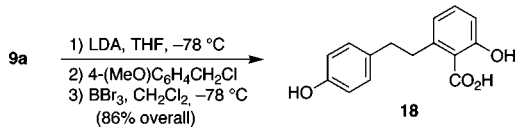
EX[b]	E	product	yield,[c] % (mp °C)	product	yield,[c] % (mp °C)
MeI	Me	**9a**	61 (138.5−139)[d]	**10a**	40 (81−83)[e]
Me_3SiCl	Me_3Si	**9b**[f]	89 (85.5−87)	**10b**	40 (96−98)
C_2Cl_6	Cl	**9c**	58 (142.5−144)[g]	**10c**	39 (114−116)
$C_2Br_2Cl_4$	Br	**9d**	59 (127−129)[h]	**10d**[i]	34 (119−121)[j]
I_2	I	**9e**	46 (129−131)[k]	**10e**[i]	27 (122−124)
Me_2S_2	MeS	**9f**	47 (182−184)[l]	**10f**	45 (77−79)
DMF	CHO	**9g**[i]	43 (155−157)[m]	**10g**	degradation
PhCHO	PhCH(OH)	**9h**[i]	52 (136−138)[n]	**10h**[i]	41 (124−126)
$BrCH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	**9i**[i]	45 (89−91)°	**10i**	degradation
$BrCH_2Ph$	CH_2Ph	**9j**[i]	47 (148−149.5)	**10j**	degradation

[a] Analytical and spectra data (IR, NMR, MS) data are in accord with the structures of all new compounds. For general procedures, see the Supporting Information. [b] Normal addition except whereotherwise noted. [c] Recrystallized yields. [d] See also entry 1 of Table 1 (lit.[2c] mp 137−138 °C). [e] See also entry 7 of Table 1 (lit. mp 83−83.5 °C: Letsinger, R. L.; Schnizer, A. W. *J. Org. Chem.* **1950**, *15*, 869). [f] In situ quench technique. [g] Lit. mp 140−141 °C: Postmus, C., Jr.; Kaye, I. A.; Craig, C. A.; Matthews, R. S. *J. Org. Chem.* **1964**, *29*, 2693. [h] Lit.[20b] mp 124−127 °C. [i] Reverse addition (see: Mortier, J.; Vaultier, M.; Cantegril, R.; Dellis, P. *Aldrichim. Acta* **1997**, *30* (2), 34). [j] Lit. mp 121 °C: Pudleiner, H.; Laatsch, H. *Synthesis* **1989**, 286. [k] Lit. mp 128−130 °C: Lewis, A.; Stefanuti, I.; Swain, S. A.; Smith, S. A.; Taylor, R. J. K. *Org. Biomol. Chem.* **2003**, *1*, 104. [l] Lit. mp 184−185 °C: Cabiddu, S.; Melis, S.; Piras, P. P.; Secci, M. *J. Organomet. Chem.* **1977**, *132*, 321. [m] Product cyclized into hydroxyphthalide **16** (lit. mp 155−156 °C: Freskos, J. N.; Morrow, G. W. Swenton, J. S. *J. Org. Chem.* **1985**, *50*, 805). [n] Product cyclized into lactone **17** (lit. mp 131.5−132 °C: Harland, P.; Hodge, P. *Synthesis* **1983**, 419. lit. mp 91 °C: Yang, K. L.; Balckman, B.; Diedrich, W.; Flaherty, P. T.; Mossman, C. J.; Roy, S.; Ahn, Y. M.; Georg. G. I. *J. Org. Chem.* **2003**, *68*, 10030).

by tedious and largely inefficient classical multistep sequences which suffer from poor overall yields (10−39%).[19] The products obtained with DMF and benzaldehyde provide chemical confirmation of the site of metalation with *s*-BuLi/TMEDA. Based on NMR analysis (see the Supporting Information), **9g** and **9h** were directly transformed into hydroxyphthalide **16** and lactone **17** after acidic hydrolysis, whereas **10h** arising from the metalation with *n*-BuLi/*t*-BuOK was recovered unchanged. Of special interest is the ability of the carboxylate to introduce an allyl substituent. Whereas allylation of tertiary benzamides can only be achieved by prior transformation to the corresponding softer ortho Grignard reagents,[20,21] benzoic acids do not require this transmetalation tactic.[22]

The potential usefulness of the method was demonstrated by the expedient synthesis of lunularic acid (**18**), a growth inhibitor found in *Lunularia cruciata*.[23] The benzyl anion of **9a** was generated by the procedure previously developed by Creger (Scheme 4).[24] The orange anion reacted slowly with 4-methoxybenzyl chloride at −78 °C; however, on warming to ambient temperature, the color dissipated and the crude dimethyl ether of lunularic acid was directly treated with boron tribromide to provide pure **18** in 87% overall yield after chromatography. This synthesis of **18** compares very favorably to the syntheses previously reported.[2c,17]

Scheme 4. Synthesis of Lunularic Acid (**18**)



Therefore, we believe that the chemistry reported herein represents a preferable alternative to the tertiary and secondary benzamide systems previously discussed. The above results indicate that the carboxylic acid group deserves to occupy a prominent position in the repertoire of directed metalation strategies. Its use in conjunction with other directing groups opens new methodological possibilities. Further structure−reactivity relationships vis-à-vis other directed metalation groups and applications in synthesis are currently under investigation.

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Supporting Information Available: Details of compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0530427

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(20) Sibi, M. P.; Miah, M. A. J.; Snieckus, V. *J. Org. Chem.* **1984**, *49*, 737.

(21) Attempted alkylation of *N*,*N*-diisopropylbenzamide with allylbromide under standard conditions provides *N*, *N*-diisopropyl-2-bromobenzamide: Beak, P.; Brown, R. A. *J. Org. Chem.* **1982**, *47*, 34.

(22) Bennetau, B.; Mortier, J.; Moyroud, J.; Guesnet, J.-L. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1265.

(23) Valio, I. F. M.; Burdon, R. S.; Schwabe, W. W. *Nature* **1969**, *223*, 1176.

(24) Creger, P. L. *J. Am. Chem. Soc.* **1970**, *92*, 1396.