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Regiospecific Synthesis of Mixed 2,3-Dihalobenzoic Acids and Related Acetophenones *via Ortho*-Metalation Reactions

Joël Moyroud,[a] Jean-Luc Guesnet,[a] Bernard Bennetau,[b] and Jacques Mortier*,[a],†

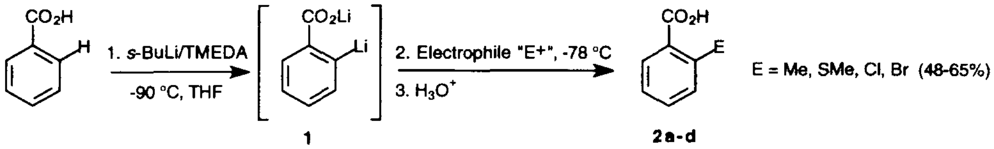
[a] *Rhône-Poulenc Secteur Agro, Centre de recherches de la Dargoire, BP 9163, 69263 LYON Cedex 09, France*
[b] *Laboratoire de chimie organique et organométallique, unité associée au CNRS n°35, université Bordeaux I,*
351 cours de la Libération, 33405 TALENCE, France

Abstract: Concise general routes to mixed 2,3-dihalobenzoic acids and related acetophenones based on directed *ortho*-metalation and ipso-desilylation reactions are described.

The metalation of a variety of aromatic molecules with organolithium reagents has demonstrated that this reaction is often characterized by 1) introduction of the lithium atom at positions adjacent to heteroatoms; 2) good yields, and 3) rapid reaction under mild conditions.[1] As the positions adjacent to heteroatoms are often not the positions involved in other common substitution reactions, the metalation reaction offers a useful and convenient synthetic technique.

We have recently demonstrated that the directed *ortho*-metalation of unprotected benzoic acid can be achieved by treatment with 2.2 equiv. of *s*-BuLi/TMEDA in THF at -90 °C (**Scheme 1**).[2] Quenching the *ortho*-lithiated carboxylate **1** with such electrophiles as methyl iodide, dimethyl disulfide, hexachloroethane, and 1,2-dibromotetrachloroethane led in yields ranging from 48% to 65% to isolated, purified *ortho*-substituted benzoic acids **2a-d**.

Scheme 1



We also examined the metalation of *o*-, *m*-, and *p*-halobenzoic acids and found that the reaction occurred in good yields at the position *ortho* to the carboxylic substituent, and at the position mutually *ortho* to both substituents, respectively.

As a part of recent investigations[3] in the chemistry of 3-arylpyrazoles and derivatives thereof, we required the complete series of 2,3-dihalobenzoic acids and acetophenones **3,4a-f** (**Scheme 2**). Surprisingly, of the six possible acids, only two had already been described in the literature, viz, 2-bromo-3-fluoro and 3-bromo-2-chlorobenzoic acids (**3b,d**), which were prepared from 2-fluoroaniline *via* an isatin intermediate,[4] and by halogen exchange of 2,3-dibromobenzoic acid catalyzed by dichlorocuprate(I) ion,[5] respectively.

Here we report on the first general method for the construction of the title compounds by thematic variation of inter-connecting synthetic methodologies, namely:

1) directed *ortho*-metalation of unprotected 3-fluoro and 3-chlorobenzoic acids **5,6** (reaction i) to

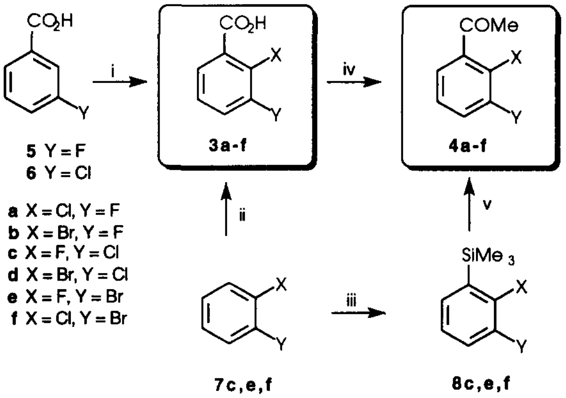
construct 2,3-dihalobenzoic acids **3a**,**b**,**d**[6] (**Table**);

2) sequential treatment of the resulting carboxylic acids with methyllithium in THF at 0 °C followed by quenching with Me_3SiCl (reaction iv/A)[7] or reaction of $EtOMgCH(CO_2Et)_2$ followed by acid hydrolysis (reaction iv/B)[8] to give 2,3-dihaloacetophenones **4a-d**,**f**;

3) the previously unreported directed *ortho*-metalation of 1,2-dihalobenzenes **7c**,**e**,**f** followed by quenching with carbon dioxide (reaction ii) or Me_3SiCl (reaction iii) to afford benzoic acids **3c**,**e**,**f** and aryltrimethylsilanes **8c**,**e**,**f**, respectively;

4) Friedel-Crafts acetylation of arylsilanes **8c**,**f** to prepare acetophenones **4c**,**f** (reaction v).[9]

Scheme 2[a]



[a](i) 2.2 equiv. (1:1 *s*-BuLi/TMEDA), THF, -90 °C; 4 equiv. E^+, THF, -78 °C; 4N HCl. (ii)-(iii) A: 1.1 equiv. *n*-BuLi, THF, -78 °C; 4 equiv. E^+, THF, -78 °C; 4N HCl. B: 1.1 equiv LDA, THF, -78 °C; 4 equiv. E^+, THF, -78 °C; 4N HCl. (iv) A: MeLi, THF, 0 °C; Me_3SiCl H_2O. B: $SOCl_2$, $(CH_2Cl)_2$, Δ; $EtOMgCH(CO_2Et)_2$, Et_2O, Δ; H_2SO_4, AcOH; NaOH, H_2O, pH 7. (v) $AlCl_3$, MeCOCl, 0 °C — 23 °C, CH_2Cl_2.

The results (see **Table**) illustrate the usefulness and generality of the method. Entries 1,3,9 demonstrate that the lithium carboxylate group in *meta* relationship with Cl and F shows exclusive metalation in the common *ortho*-site.

LDA metalates *o*-bromofluorobenzene (**7e**) and *o*-bromochlorobenzene (**7f**) exclusively at the position adjacent to fluorine and chlorine respectively, as demonstrated by quenching with carbon dioxide and Me_3SiCl to give the corresponding benzoic acids **3e**,**f** (entries 11,14) and arylsilanes **8e**,**f** (entries 12,17).[10] When the organometallic intermediate generated from *o*-chlorofluorobenzene (**7c**) and *n*-BuLi is trapped with carbon dioxide and Me_3SiCl, 3-chloro-2-fluorobenzoic acid (**3c**) and (3-chloro-2-fluoro)phenyl trimethylsilane (**8c**) are obtained respectively in 70 and 83% yields (entries 5,6).[11] Carboxylic acids[7-9] **3a-d**,**f** (reaction iv) and arylsilanes **8c**,**e**,**f** (reaction v) lead to acetophenones **4a-f** in good yields under standard conditions.

Table. Synthesis of 2,3-Halobenzoic Acids/Acetophenones **3,4a-f**

entry	substrate	route	electrophile	X	Y	product	yield (%)[a]	mp (°C)
1	**5**	i	C_2Cl_6	Cl	F	**3a**	71	169-171[b]
2	**3a**	iv/A	-	Cl	F	**4a**	61	oil[c]
3	**5**	i	$(CCl_2Br)_2$	Br	F	**3b**	77	165-168[b,d]
4	**3b**	iv/B	-	Br	F	**4b**	84	oil[c]
5	**7c**	ii/A	CO_2	F	Cl	**3c**	70	179-181[b]
6	**7c**	iii/A	Me_3SiCl	F	Cl	**8c**	83	oil[e]
7	**3c**	iv/A	-	F	Cl	**4c**	48	oil[c]
8	**8c**	v	-	F	Cl	**4c**	75	oil[c]
9	**6**	i	$(CCl_2Br)_2$	Br	Cl	**3d**	51	146-147[b]
10	**3d**	iv/B	-	Br	Cl	**4d**	80	oil[c]
11	**7e**	ii/B	CO_2	F	Br	**3e**	73	166-168[b]
12	**7e**	iii/B	Me_3SiCl	F	Br	**8e**	88	oil[e]
13	**8e**	v	-	F	Br	**4e**	75	oil[c]
14	**7f**	ii/B	CO_2	Cl	Br	**3f**	55	170-172[b]
15	**3f**	iv/B	-	Cl	Br	**4f**	78	oil[c]
16	**8f**	v	-	Cl	Br	**4f**	56	oil[c]
17	**7f**	iii/B	Me_3SiCl	Cl	Br	**8f**	60	oil[e]

[a] Isolated yields based on starting material. [b] Purification by crystallization in heptane/ether (70/30—100/0). [c] Purification by liquid chromatography on silica gel with heptane/ethyl acetate. [d] lit. (ref 4) = 157-158 °C. [e] Purification by distillation.

In summary, this paper describes a very flexible and rapid method for the preparation of mixed 2,3-dihalobenzoic acids/acetophenones. The strategy relies on the ability of chlorine and fluorine atoms and the CO_2Li group to acidify the neighboring aromatic proton(s), allowing for an electrophile to be introduced *via* lithiation. The sequence also relies on the ability of the trimethylsilyl group to undergo ipso-desilylation and Friedel-Crafts substitution.

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† Present address: Groupe de recherches de physicochimie structurale, unité associée au CNRS n°704, Université de Rennes I, avenue du Général Leclerc, 35042 RENNES Cedex, France.

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6. All new compounds show ^1H, ^{13}C NMR and combustion analysis in full agreement with the proposed structures. Selected data: **3a** ^1H NMR (250 MHz, DMSO-d_6) δ: 12.8 (broad, 1H), 8.02 (m, 1H), 7.30 (m, 1H), 7.25 (m, 1H). ^{19}F NMR (235.4 MHz, DMSO-d_6) δ: -113.3. ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 165.7, 157.7, 133.5, 128.6, 126.3, 119.2, 118.9. Anal. Calcd for $C_7H_4ClFO_2$: C, 48.17; H, 2.31; Cl, 20.31; F, 10.88. Found: C, 48.42; H, 2.35; Cl, 20.50; F, 10.69. **3b** ^1H NMR (250 MHz, CD_3COCD_3) δ: 11.75 (broad, 1H), 7.67 (dd, J = 7.6, 1.0 Hz; 1H), 7.50 (m, 2H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 160.5, 158.6, 136.0, 129.4, 126.1, 118.7, 107.3. Anal. Calcd for $C_7H_4BrFO_2$: C, 38.39; H, 1.84; Br, 36.48; F, 8.68. Found: C, 38.69; H, 1.79; Br, 36.38; F, 8.71.
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