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ortho-Metalation of Unprotected 3-Bromo and 3-Chlorobenzoic Acids with Hindered Lithium Dialkylamides

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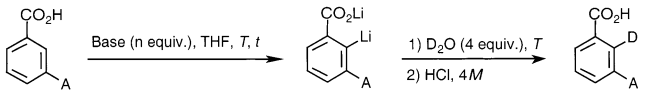
Abstract: Upon treatment of 3-chloro/bromobenzoic acids with hindered lithium dialkylamides (LDA or LTMP) at −50 °C, lithium 3-chloro/bromo-2-lithiobenzoates are generated. These dianions can be trapped as such to afford after electrophilic quenching a variety of simple 2-substituted-3-chloro/bromobenzoic acids. The 3-bromo-2-lithiobenzoate is less stable than the corresponding 3-chloro derivative and partly eliminates lithium bromide, thus setting free lithium 2,3- and 3,4-dehydrobenzoates that can be intercepted in situ with the hindered base.

The deprotonation of arenes usually requires a strong base such as an alkyllithium and a directing group such as a secondary or tertiary amide, an oxazoline, an α-amino alkoxide, or a carbamate.[1] The resulting aryllithium can react with a variety of electrophiles including alkylating agents, aldehydes, ketones, chloroformates, silylating agents, and trialkylborates. Amides and oxazolines can serve as latent carboxylic acids in the directed metalation; nevertheless, they require harsh conditions for their hydrolysis.

The best protective group is the one that can be omitted.[2] The directed *ortho*-metalation of unprotected benzoic acids can be achieved by treatment with 2.2 equiv of *s*-BuLi/TMEDA in THF at −90 °C;[3,4] the resulting dilithiated species easily react with a variety of electrophiles to give the *ortho*-substituted products. Alternatively, 2,3-disubstituted benzoic acids are readily available by lithiating 1,2-disubstituted compounds, metalation occurring to the more effective directing group-neighboring position.[5,6]

The use of alkyllithium bases limits group functionality, for example, by not allowing for the presence of a bromine or iodine atom on the arene due to competing halogen−metal exchange.[7] We record here details of our investigations on the metalation of 3-halobenzoic acids (halo = Cl, Br) by hindered lithium dialkylamides.

TABLE 1. Deprotonation of 3-Chloro and 3-Bromobenzoic Acids with Hindered Lithium Dialkylamides[a]



1 (A = Cl)
2 (A = Br)

2Li-**1**
2Li-**2**

2D-**1**
2D-**2**

entry	reactant	base	n^b	T (°C)	t (h)[c]	2-D (%)	yield (%)[d]	concn (mol/L)
1	1	LDA	2.2	−78	0.5−8	<30	e	0.15
2	1	LDA	2.2	−50	0.5−8	<30	e	0.15
3	1	LDA	4	−50	0.5	37	e	0.15
4	1	LTMP	2.2	−50	4	86	80	0.15
5	1	LTMP	2.2	−50	4	90	79	0.05
6	1	LTMP	3	−50	4	93	62	0.05
7	1	LTMP	3	−60	4	83	69	0.2
8	2	LDA	2.2	−78	2	38	36	0.15
9	2	LDA	2.2	−60	2	42	39	0.15
10	2	LTMP	2.2	−78	1	17	16	0.15
11	2	LTMP	2.2	−60	1	64	47	0.15
12	2	LTMP	2.2	−60	4	72	52	0.15
13	2	LTMP	2.2	−50	1	75	53	0.15
14	2	LTMP	2.2	−50	2	78	37	0.15
15	2	LTMP	3	−50	1	78	37	0.15

[a] General procedure. To a stirred solution of LDA or LTMP (*n* equiv) in anhydrous THF at *T* °C was added dropwise under argon the recrystallized benzoic acid **1** (6.4 mmol) or **2** (5 mmol) dissolved in dry THF (5 mL). After *t* hours at *T* °C, the mixture was treated with an excess of deuterium oxide (5 equiv). Workup in the usual manner (see the Experimental Section) followed by recrystallization provided the benzoic acids 2D-**1** and 2D-**2**, which were characterized by ^{1}H and ^{13}C NMR. [b] Calculated from the starting benzoic acid (**1** or **2**). [c] Reaction time of the lithium dialkylamide with the starting acid. [d] Crude yield. [e] Not determined.

We have embarked on a detailed investigation of the deprotonations of 3-chlorobenzoic acid (**1**) and 3-bromobenzoic acid (**2**), varying the base, metalation temperature, and exposure times (Table 1). Lithium diisopropylamide (LDA) is not suitable for the generation of lithium 2-lithio-3-chloro and 2-lithio-3-bromobenzoates (2Li-**1** and 2Li-**2**, respectively): deuteriation (deuterium oxide quench) at the position flanked by both substituents does not exceed 42% (entries 1−3, 8, and 9).[8] Clean lithiation was achieved with lithium 2,2,6,6-tetramethylpiperidide (LTMP, 2.2 equiv) in THF at −50 °C for a concentration of the reactant of 0.15 mol/L (entries 4 and 13). D_2O trapping (4−10 equiv/−50 °C → rt/2 h) provided 2D-**1** and 2D-**2** in satisfying yields. The ^{1}H and ^{13}C NMR

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(8) LDA deprotonates more effectively 4-bromo-3-fluoro and 4-bromo-3-chlorobenzoic acids. See ref 3b.

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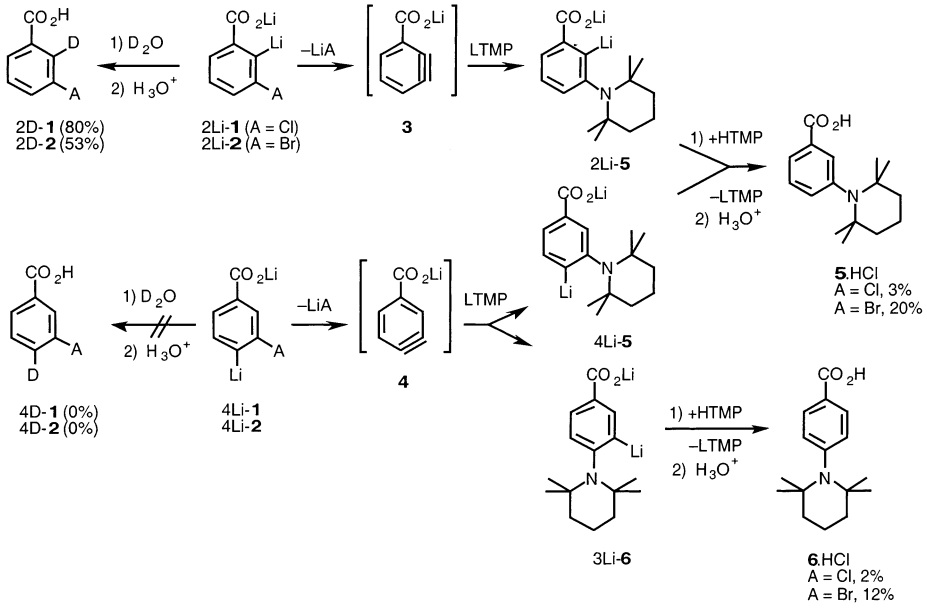
SCHEME 1



data allow assignment of the correct deuterium regiochemistry of the reaction products.[9] Lower concentrations of the reactant or use of an increasing amount of LTMP did not improve the results (entries 5−7 and 15).

Potential deprotonation pathways were envisioned as shown in Scheme 1. The dianion 2Li-**1** is presumably more stable than 2Li-**2**, which partly decomposed over a period of 2 h at −50 °C (entry 14 vs entry 13). Benzoic acids **1** and **2** react regiospecifically to give 2D-**1** and 2D-**2** where CO_2Li and the halogen groups completely control the deprotonation site. Analysis of the side-products found in the aqueous layer after acidic workup (HCl, 4 M) was informative. After water removal, appreciable amounts of the anilinium chlorides **5** and **6** were isolated from the reaction of **2** (in 20 and 12% yields, respectively). The two isomers were easily separated by chromatography. Formation of anilines from benzynes is well precedented.[10,11] Steric encumbrance of the amine was said to lower yields considerably.[12] However, LTMP was recently reported to be a good trap for benzynes.[13] The side-product **6** most reasonably arises by *para*-addition of LTMP to benzyne **4**. Formation of **5** proceeds by addition of LTMP to either **3** or **4**. Since **5** and **6** were not deuterated in these conditions (D_2O quench), 2Li-**5**, 4Li-**5**, and/or 3Li-**6** are protonated more likely in situ by a hydrogen donor such as 2,2,6,6-tetramethylpiperidine (HTMP). 4D-**1** and 4D-**2** were not isolated presumably because 4Li-**1** and 4Li-**2** are less stable than 2Li-**1** and 2Li-**2**, respectively, and rapidly decompose to form benzyne **4**. In the case of **2**, warming the reaction mixture to ambient temperature prior to the hydrolysis step led to **5** and **6** in 34 and 12% yield, respectively. Below −60 °C, the deprotonation rate is slow and yields are poor (entries 7−12).

The relative stability of unsubstituted *ortho*-halogenated phenyllithiums toward elimination of LiX follows the order LiBr (−100 °C) < LiCl (−90 °C).[14] It is highly dependent on the overall electronic effects induced in the ring by the substituents. Consistently, only traces of **5** and **6** were obtained when **1** was allowed to react at −50 °C under the same conditions (3 and 2%, respectively). Benzoates 2Li-**1** and 2Li-**2** are stabilized in these transformations presumably by chelation of lithium with the adjacent carboxylate moiety.[14] The higher temperature required to generate the lithium 2-lithio-3-chlorobenzenecarboxylate aryne precursor as compared to its bromo counterpart probably reflects the poorer leaving group ability of chloride ion vs bromide ion.[15,16]

According to the optimized conditions noted in Table 1 (entries 4 and 13), benzoic acids **1** and **2** were allowed to react with a variety of electrophiles to give the corresponding *ortho*-substituted benzoic acids **9a**−**d**,**f**−**i** and **10a**−**i** (Table 2). Reaction with iodomethane gave the anticipated result of methylation at the site mutually *ortho* to both substituents. Yields decreased when iodo-

(9) 3-Chloro-2-deuteriobenzoic acid (2D-**1**). ^{1}H NMR (400 MHz, $CDCl_3$) δ TMS: 8.00 (dd, J = 7.9, 1.0 Hz; 1H), 7.59 (dd, J = 7.9, 1.0 Hz; 1H), 7.43 (t, J = 7.9 Hz; 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 166.0, 133.2, 132.8, 132.6, 130.5, 128.5 (t, J = 25.8 Hz), 127.8. 3-Bromo-2-deuteriobenzoic acid (2D-**2**). ^{1}H NMR (400 MHz, $CDCl_3$) δ TMS: 8.04 (d, J = 7.9 Hz; 1H), 7.74 (d, J = 7.9 Hz; 1H), 7.36 (t, J = 7.9 Hz; 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 170.8, 136.8, 132.9 (t, J = 26 Hz), 131.2, 130.0, 128.8, 122.5.

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SCHEME 2

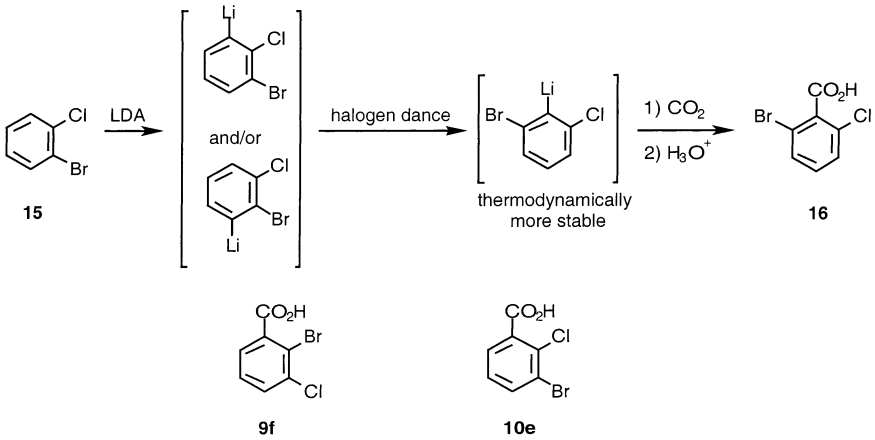
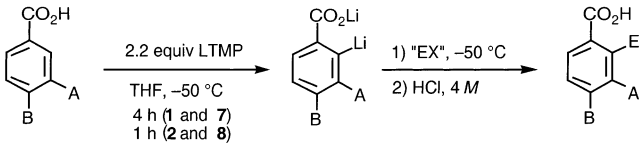


TABLE 2. Synthesis of 2-Substituted 3-Chloro and 3-Bromobenzoic Acids



1, **9** A = Cl, B = H
2, **10** A = Br, B = H
7, **11** A = Cl, B = F
8, **12** A = Br, B = F

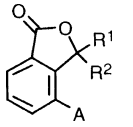
a E = Me
b E = Et
c E = PhCH(OH)
d E = CHO
e E = Cl
f E = Br
g E = I
h E = Me_3Si
i E = MeS

entry	reactant	A	B	EX	E	product	yield (%)[a]
1	1	Cl	H	MeI	Me	**9a**	61
2	1	Cl	H	EtI	Et	**9b**	41[b]
3	1	Cl	H	PhCHO	PhCH(OH)	**9c**[c]	63
4	1	Cl	H	DMF	CHO	**9d**[d]	63
5	1	Cl	H	$C_2Br_2Cl_4$	Br	**9f**	68
6	1	Cl	H	I_2	I	**9g**	55
7	1	Cl	H	Me_3SiCl	Me_3Si	**9h**	75[e]
8	1	Cl	H	Me_2S_2	MeS	**9i**	69
9	2	Br	H	MeI	Me	**10a**	44
10	2	Br	H	EtI	Et	**10b**	15
11	2	Br	H	PhCHO	PhCH(OH)	**10c**[f]	46
12	2	Br	H	DMF	CHO	**10d**[g]	45
13	2	Br	H	C_2Cl_6	Cl	**10e**	43
14	2	Br	H	$C_2Br_2Cl_4$	Br	**10f**	43
15	2	Br	H	I_2	I	**10g**	50
16	2	Br	H	Me_3SiCl	Me_3Si	**10h**	38
17	2	Br	H	Me_2S_2	MeS	**10i**	42
18	7	Cl	F	MeI	Me	**11a**	71
19	7	Cl	F	Me_3SiCl	Me_3Si	**11h**	69
20	8	Br	F	MeI	Me	**12a**	53

[a] Recrystallized yield except otherwise noted. [b] Crude yield. [c] Product **9c** cyclized into lactone **13c**. [d] Product **9d** cyclized into hydroxyphthalide **13d**. [e] LDA was used in this example. [f] Product **10c** was directly cyclized into lactone **14c**. [g] Product **10d** was directly cyclized into phthalide **14d**.

ethane was reacted under the same conditions (entries 2 and 10).[17]

Clean hydroxyalkylation was achieved with benzaldehyde to give **9c** and **10c**, which were directly transformed into lactones **13c** and **14c** (entries 3 and 11). Condensation of the dilithio intermediates with DMF followed by acid-catalyzed cyclization gave hydroxyphthalides **13d** and **14d** via *ortho*-formyl products **9d** and **10d**. Quenching with electrophiles such as hexachloroethane, 1,2-dibromotetrachloroethane, and iodine led to the corresponding *ortho*-halogenated benzoic acids (entries 5, 6, and 13−15). Reaction of C_2Cl_6 with 3-bromobenzoic acid gave 2-chloro-3-bromobenzoic acid (**10e**), albeit in moderate yield (43%). It is worthy of note that previous lithiation methods were inefficient for preparing **10e**. Thus, LDA deprotonates *ortho*-bromochlorobenzene (**15**) randomly at the two halogen-adjacent positions (Scheme 2). Both anions presumably isomerize to the less basic and hence thermodynamically more stable 2-bromo-6-chlorophenyllithium, which can be trapped as the acid **16**.[5,18] As established by Schlosser, trace amounts of 1,3-dibromo-2-chlorobenzene most probably act as a turntable for a base-catalyzed "halogen dance".[18] The isomeric 2-bromo-3-chlorobenzoic acid **9f** was prepared from acid **1** and $C_2Br_2Cl_4$ (entry 5).



13c (R^1 = Ph, R^2 = H, A = Cl)
14c (R^1 = Ph, R^2 = H, A = Br)
13d (R^1 = OH, R^2 = H, A = Cl)
14d (R^1 = OH, R^2 = H, A = Br)

Reaction of dibromotetrachloroethane with 2Li-**2** provided 2,3-dibromobenzoic acid (**10f**) (entry 14), a compound that was attained with difficulty in the past, by demanding, invariably and classically poorly regioselective electrophilic substitution chemistry.[19] The previously unknown 2-iodo-3-chloro and 2-iodo-3-bromobenzoic acids (**9g** and **10g**) were synthesized from iodine (entries 6, 15).[20] Silylation of such systems was cleanly achieved. The smooth and high-yield reaction of chlorotrimethylsilane with **1** affording **9h** is indoubtedly related to the in situ compatibility of TMSCl with lithium dialkyl amides.[21] The process is less efficient with 2Li-**2** possibly

(17) 2-Ethylated product **10b** was prepared in higher yield (76%) by treatment of **10a** with LDA (3 equiv, −50 °C/THF) and trapping with iodomethane.

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due to its thermal instability. Addition of dimethyl disulfide to the dilithiated benzoates gave the methylsulfenylated derivatives **9i** and **10i** (entries 8 and 17). A fluorine atom located *meta* to the deprotonation site shows acidifying effects (entries 18−20). Quenching with iodomethane and chlorotrimethylsilane led to the corresponding *ortho*-substituted benzoic acids **11a**, **11h**, and **12a**.

In summary, a general and convenient route to 2-substituted-3-chloro/bromobenzoic acids has been devised using the directed *ortho*-metalation protocol. The fact that this method gives such simple compounds that were previously unknown is a testament to its future potential. The directed *ortho*-metalation tactic of unprotected benzoic acids should see wide utility in the synthesis of aromatic compounds by coupling chemistry, among other things.[3,22]

Experimental Section

For standard working practice, see recent publications (e.g., refs 1c and 22).

Synthesis of 2-Substituted 3-Chlorobenzoic Acids 9. General Procedure. To a stirred solution of *n*-butyllithium 1.6 M in hexanes (17.5 mL, 28.1 mmol) was added 2,2,6,6-tetramethylpiperidine (4.7 mL, 28.1 mmol) in anhydrous THF (40 mL) at −20 °C under argon. After the mixture was cooled (−50 °C), 3-chlorobenzoic acid **1** (12.8 mmol) in anhydrous THF (10 mL) was added dropwise and the mixture was stirred for 4 h. The mixture was then treated with an excess of the appropriate electrophile (50.4 mmol, 4 equiv). The resulting solution was allowed to warm to ambient temperature, after which water was added. The aqueous layer was washed with diethyl ether, shaken, and then acidified with 4 M HCl. The mixture was diluted with diethyl ether, and the organic layer was separated and dried with $MgSO_4$. Filtration and concentration in vacuo gave the crude benzoic acids, which were purified by recrystallization for characterization in each case.

Synthesis of 2-Substituted 3-Bromobenzoic Acids 10. General Procedure. To a stirred solution LTMP (21.8 mmol) in anhydrous THF (35 mL) was added dropwise 3-bromobenzoic acid **2** (9.9 mmol) in THF (10 mL) at −50 °C under argon. The mixture was stirred for 1 h and then treated with an excess of the appropriate electrophile (39.6 mmol) in THF (8 mL). Workup in the usual manner followed by recrystallization provided benzoic acids **10a**−**i**.

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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.

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