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Registry No. 4, 3299-38-5; 5, 105-14-6; 6E, 124267-60-3; 6Z, 124267-61-4; 7, 124267-62-5; 8E, 124267-63-6; 8Z, 124267-64-7; 9Z, 124267-65-8; 9E, 124267-66-9; diethyl(trimethlsilyl)amine, 996-50-9; ethyl vinyl ketone, 1629-58-9.

Supplementary Material Available: Raw ^1H NMR data of a typical enol silane product mixture resulting from the silylation of compounds 4 and 5 as well as NMR spectral data of *N,N*-diethyl-3-((trimethylsilyl)oxy)-(*E*)-2-pentenamine (6 pages). Ordering information is given on any current masthead page.

A Dramatic Solvent Effect during Aromatic Halogen–Metal Exchanges. Different Products from Lithiation of Polyfluorobromobenzenes in Ether and THF

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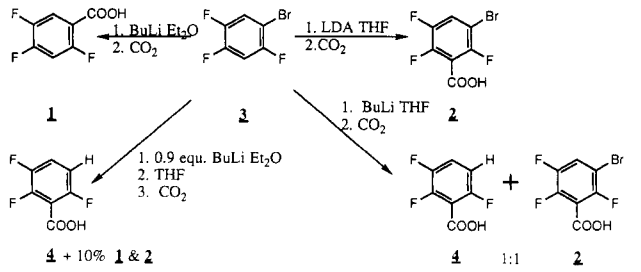
As part of a synthetic program in quinolone antiinfectives, we wished to prepare 2,4,5-trifluorobenzoic acid (1) and 3-bromo-2,5,6-trifluorobenzoic acid (2) from 1-bromo-2,4,5-trifluorobenzene (3). Although acid 1 can be



prepared via cyanation (CuCN) of 3 followed by acid hydrolysis,[1] it appeared that bromine–lithium exchange followed by carboxylation would be operationally simpler. Halogen–metal exchange is a very well-established technique for the regiospecific generation of aromatic anions.[2] Because aromatic bromine–lithium exchange is very rapid, it allows for lithiation to be carried out at positions in the molecule that would not normally be available due to the presence of kinetically or thermodynamically more acidic sites.[3] Conversely, simple metalation of 3 should occur at the most acidic site, and carboxylation should yield acid 2. Although lithiation between two fluorines with butyllithium (BuLi) is known,[4] in this case halogen–metal exchange must be avoided. In this note we wish to report that bromide 3 is acidic enough to be metalated by LDA, that acid 1 can also be prepared from 3 via halogen–metal exchange in ether, and that this latter reaction shows a remarkable solvent effect, such that changing the solvent to THF leads to a mixture of acid 2 and 2,3,6-trifluorobenzoic acid (4). The mechanism of this latter process was shown to be compatible with autometalation.[5]

When lithium diisopropylamide (LDA) was added dropwise to a −78 °C solution of bromide 3 in THF, a clear yellow solution was formed immediately. After a further 2 min this was transferred onto solid CO_2 in ether and yielded after workup 83% of analytically pure bromo acid 2[6] (Table I, entry 1). Although there are reports of ortho lithiation of benzoates[7] and benzonitriles,[8] with lithium amides, such anions were trapped in situ, and are probably never present as major species during the reaction. Most ortho-metalating groups do not decrease aryl pK_as below 38,[9] and aromatics are generally metalated with alkyllithiums, often activated by TMEDA, at −78 °C.[10] Thus, the facile LDA metalation of 3 demonstrates that fluorine shows the same powerful kinetic and thermodynamic acidifying ability on a benzene ring that it shows in the polyhalomethanes.[11]

When 1 equiv of *n*-BuLi was added to a solution of bromide 3 in ether at −78 °C and carboxylated, acid 1 was obtained in 83% yield and 99% purity (entry 2). Thus the halogen–metal exchange reaction in ether provided a very satisfactory preparation of acid 1. However, when we carried out the halogen–metal exchange under the most commonly used conditions, 2 equiv of *t*-BuLi in THF,[12] followed by carboxylation, we did not obtain acid 1 but a material that showed three aromatic resonances in its NMR spectrum (entry 3). Use of 1 equiv of *n*-BuLi in THF (entry 4) gave a cleaner version of the same result, so the change in reaction pathway was due to a solvent effect. Although this product recrystallized essentially unchanged, leading to speculations on benzyne or biphenyl dimers,[13] GC analysis and spectroscopic comparisons showed the product to be an approximately 1:1 mixture of acid 2 and 2,3,6-trifluorobenzoic acid (4), with less than 1% of acid 1 present. With 0.5 equiv of *n*-BuLi in THF, only acid 2 was obtained (entry 5). Furthermore, when bromide 3 was reacted with 0.9 equiv of *n*-BuLi in ether, followed by THF addition prior to carboxylation, the major product was acid 4 (entry 6), but if 1.1 equiv of *n*-BuLi was used in the same protocol, unrearranged acid 1 was the major product (entry 7). All of the experimental results using THF described above could be repeated by adding TMEDA, a good lithium chelator, to the ether solution at an appropriate time.

The likely mechanism of formation of acids 2 and 4, shown in Scheme I, involves autometalation, a process first described by Gilman,[5] in which the initially formed or-

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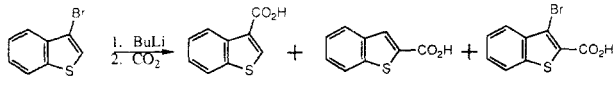
Table I. Product Distribution after Carboxylation

entry	ArBr	conditions	time[a]	products	ratio[b]	yield,[c] %
1	3	1 equiv of LDA THF	2	2	100	83
2	3	1 equiv of Bu^nLi Et_2O	2	1 + 2 + 4	98.8:1.0:0.2	83
3	3	2 equiv of Bu^tLi THF	2	1 + 2 + 4	3.2:33.8:60.5	58
4	3	1 equiv of Bu^nLi THF	2	1 + 2 + 4	0.4:51.8:47.8	55
5	3	0.5 equiv of Bu^nLi THF	2	2	100	71[d]
6	3	0.9 equiv of Bu^nLi Et_2O then THF	2, 60	1 + 2 + 4	10.6:12.6:76.8	62
7	3	1.1 equiv of Bu^nLi Et_2O then THF	2, 15	1 + 2 + 4	95.6:0.2:4.0	80
8	12	1 equiv of Bu^nLi Et_2O	2	14 + 16 + 18	98.8:0.2:0.9	83
9	12	1 equiv of LDA THF	2	16	100	76
10	12	1 equiv of Bu^nLi THF	2	14 + 16 + 18	19:39.1:41.7	75
11	12	0.5 equiv of Bu^nLi THF	2	14 + 16 + 18	6.5:9.2:84.3	73[d]
12	13	1 equiv of Bu^nLi Et_2O	2	15	100	77
13	13	1 equiv of LDA THF	2	17	100	70
14	13	1 equiv of Bu^nLi THF	2	15 + 17	91.7:8.3	68

[a] Time in min after addition of RLi, then ligand when appropriate, before quenching. [b] Determined by GC. [c] Crude total yields of acidic products, based on starting bromide unless otherwise stated. [d] Yield based on RLi added.

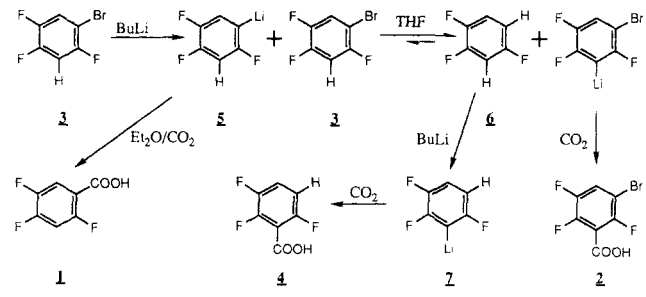
ganolithium can act as a base toward unlithiated substrate. After an initial halogen–metal exchange to form anion **5** (which leads to acid **1** in ether), anion **5** immediately extracts the most acidic proton in the entire system, the 3-proton of bromide **3** itself. When half of the BuLi is added, half of **3** has been consumed by bromine extraction, and the other half through transmetalation. Quenching at this point gives only acid **2** plus 1,2,4-trifluorobenzene (**6**), which is lost in the workup. Addition of further BuLi leads to metalation of **6**, producing anion **7**, which carboxylates to acid **4**. If anion **5** is generated in ether, it can rearrange to anion **7** in the presence of THF, *provided that a suitable proton source is present to catalyze the autometalation.* In entry 6, this is provided by the 10% of unreacted bromide **3**, and when this is not present (entry 7), autometalation is at best a minor pathway.

Although our results can be explained by a known process, they provide an exceptionally clear and dramatic example of the mechanism. Gilman[5] induced thermal rearrangement, and the results were variable, with rather low yields usually isolated. The ability of both THF and TMEDA to depolymerize aryllithium oligomers is well documented,[14] as is the enhancement of basicity of aryllithiums in the presence of these ligands.[15,16] In fact, the switch to an autometalation mechanism in THF is also precedented in the work of Dickenson and Iddon,[17] in the lithiation of 3-bromothiophene **8**. In ether at −70 °C

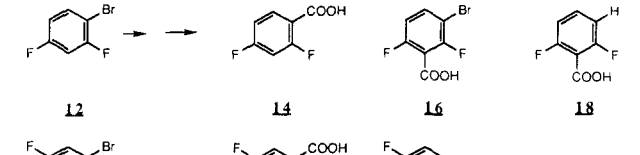


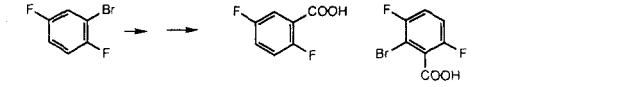
lithiation–carboxylation gave only one acid, the expected 3-thiophenecarboxylic acid (**9**). However, upon holding the initial anion at 20 °C prior to carboxylation, or by running the reaction at −70 °C in THF, acid **9** was contaminated with both the 2-carboxylic acid **10** and the 3-bromo 2-carboxylic acid **11**. Our results exhibit the same behavior but show an essentially complete changeover of reaction paths upon changing solvents. Another very interesting parallel comes in the elegant studies of metalation of (2-halo)-3-bromopyridines by Mallet and Queguiner.[18] Generation of anions at −60 °C in THF followed by quenching led to the normal products of halogen–metal exchange, but allowing anions to be generated at, or warmed up to, −40 °C converted the product mixture entirely to autometalation derived products, some of which subsequently rearranged via a halogen dance mechanism of bromine transfers,[19] a process we did not observe.

Scheme I



The carboxylations of 1-bromo-2,4-difluorobenzene (**12**), 2-bromo-1,4-difluorobenzene (**13**), and 1-bromo-3-fluorobenzene were also examined. Both **12** and **13** carboxylated





normally in ether with *n*-BuLi as base, giving acids **14** and **15**, respectively (entries 8 and 12), and both gave the expected bromo acids **16** and **17** when LDA in THF was employed (entries 9 and 13). Use of *n*-BuLi in THF with bromide **12** gave a 1:2:2 mixture of acids **14**, **16**, and **18**, respectively (entry 10). When 0.5 equiv of *n*-BuLi was used the major product was bromo acid **16** (entry 11). In THF bromide **13** was converted mainly to acid **15**, containing only 8% of bromo acid **17** (entry 14), the anion rearrangement being degenerate in this system. When 1-

(14) PhLi is a tetramer in ether. See: Hope, H.; Power, P. P. *J. Am. Chem. Soc.* **1983**, *105*, 5320. In the presence of TMEDA it is a dimer. See: Thoennes, D.; Weiss, F. *Chem. Ber.* **1978**, *111*, 3157. Fraenkel, G.; Hsu, H.; Su, B. M. Presented at the ACS S.E. Regional Meeting, Charlotte, NC, Nov 1983. In THF it is also a dimer. See: Jackman, L. M.; Scarmoutzos, L. M. *J. Am. Chem. Soc.* **1984**, *106*, 4627.

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bromo-3-fluorobenzene was carboxylated with *n*-BuLi in THF followed by CO_2, only 3-fluorobenzoic acid was detected.

We also examined briefly the carboxylation of two other compounds using *n*-BuLi in THF. Carboxylation of 1-bromo-3,5-dichlorobenzene (the optimal chloride system for rearrangement) gave a mixture of 3,5- and 2,6-dichlorobenzoic acids, plus some minor unidentified products. In contrast, 1-bromo-2,4-dimethoxybenzene gave 2,4-dimethoxybenzoic acid as the only detectable product (>98% pure).

All of these results are consistent with the degree of autometalation being controlled mainly by the pK_a of the substrate bromide. Thus, the most fluorinated, and hence most acidic substrate, **3** shows complete autometalation under our standard conditions. Removal of the fluorine β to the extractable proton in bromide **12** slows the autometalation, so that both autometalation products and the unrearranged product are present in comparable amounts, a rather similar case to that of Iddon.[17] However, loss of a fluorine next to the acidic proton in **13** leads to autometalation becoming a very minor pathway, and loss of two fluorines made autometalation undetectable. The results from the dichloro- and dimethoxybenzene substrates confirm that the substituents must provide a powerful kinetic acidification, and not mainly a chelating stabilization.

In conclusion, we have demonstrated that the polyhalobenzenes described in this note can be usefully lithiated and trapped with electrophiles and that it is very easy to selectively metalate between two fluorines. We have also shown a powerful solvent effect between ether and THF in some of these systems and that an unusually facile and straightforward autometalation occurs in THF. The effect has been delimited *under our very mild conditions* and shown to be allowed by the high acidity of benzenes with at least two halogens meta to one another. Finally, our work does suggest that the structures of products derived from aromatic halogen–metal exchange in highly acidified systems should not be taken for granted and that, if generation of such species appears to be unsatisfactory, going to less polar solvents may prove advantageous.

Experimental Section

General. All reagents were commercial grade and not purified prior to use. The structures of 3-fluoro, 2,4-, 2,5-, and 2,6-difluoro, and 2,3,6- and 2,4,5-trifluorobenzoic acids were all confirmed by spectroscopic and chromatographic comparison with commercial samples obtained from Aldrich, from whom melting points were also obtained. Glassware was flame dried in an N_2 stream; syringes and catheters were kept in a 110 °C oven. Ethyl ether was obtained from freshly opened Fisher ACS certified anhydrous grade cans, and THF was freshly distilled from benzophenone ketyl. Melting points were obtained on an Electrothermal melting point apparatus and are uncorrected. NMR spectra were obtained on a Varian EM390 or Bruker AM250 NMR spectrometer in $CDCl_3$. IR spectra were obtained on a Nicolet MX-1FT IR instrument. Mass spectra were obtained on a VG Analytical 7070/HF mass spectrometer using EI at 70 eV.

GC analysis was carried out on ethyl esters that were prepared as follows: 5-mg samples of the acid were reacted with 0.5 mL of preformed EtOH/CH_3COCl[20] (4:1) in vials with Teflon-lined caps at 25 °C initially, followed by 20 min at 100 °C. Samples (1 μL) of this mixture were injected through a 50 mL/min split injector onto a DB wax capillary column (30 m × 0.25 mm i.d., 0.25 μm layer) in a Varian 6000 GC, with 10 psi H_2 as the carrier gas, flow rate 60 cm/min, detecting by FID. GC response factors were calculated from standard esterifications of all acids.

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General Experimental. Unless otherwise stated, all reactions were carried out by using the following general procedure.

n-Butyllithium (2.0 mmol) in hexanes was added dropwise over 2 min to a solution of the aryl bromide (2.0 mmol) in THF or ether (5 mL), stirred under N_2 at −78 °C. After a further 2 min the reaction mixture was blown rapidly through a cannula[21] onto solid CO_2 (about 5 mL) in ether (50 mL). When the reaction mixture had warmed up close to 0 °C, it was washed with dilute HCl (1 M, 10 mL) and water (10 mL) and was extracted with dilute NaOH solution (0.2 M, 2 × 10 mL). The combined basic extracts were washed with ether (10 mL), acidified with dilute HCl (1 M, 10 mL), and extracted with ether (3 × 10 mL). The combined organic extracts were washed with water (2 × 10 mL) and saturated brine (10 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure at 50 °C to give a crystalline solid, which was analyzed without purification.

For entries 6 and 7, the anion was generated in ether (4 mL), and after 2 min, THF (4 mL) was added dropwise over 10 min and the anions were left a further 15 or 60 min prior to CO_2 quench. LDA was generated from 2.2 mmol of Pr^i_2NH and 2.0 mmol of *n*-BuLi in 2 mL of solvent under N_2 at 0 °C for 10 min and was added over 2 min to the bromide in 3 mL of the same solvent.

2,4,5-Trifluorobenzoic acid (1), 0.30 g (83%), was obtained from bromide **3** as white needles, mp 94–5 °C (lit. mp 99–101 °C), using 1 equiv of *n*-BuLi in ether.

3-Bromo-2,5,6-trifluorobenzoic acid (2) was prepared on a 10-mmol scale from bromide **3** using LDA in THF to give 2.12 g (83%) of white crystals, mp 109–118 °C. Recrystallization from heptane gave **2** (1.59 g, 62%) as transparent rods, mp 116.5–118.5 °C. Anal. Calcd for $C_7H_2BrF_3O_2$: C, 32.98; H, 0.78; Br, 31.37; F, 22.35. Found: C, 33.00; H, 0.75; Br, 31.08; F, 21.93. IR (KBr): 3200–2300, 1710, 1626, 1480, 1441, 1406, 1287, 1197, 949, 875, 827, 784, 660 cm^{-1}. NMR: 11.6 (1 H, br s), 7.62 (1 H, ddd, J = 6.2, 8.0, 9.0 Hz) ppm. Mass spectrum: m/e 256 (98, $^{81}BrM^+$), 254 (100, $^{79}BrM^+$).

2,3,6-Trifluorobenzoic Acid (4). Lithiation of **3** with 0.9 equiv of *n*-BuLi in ether, followed by THF prior to carboxylation, gave **4** (0.23 g, 65%) contaminated with 10% of both **1** and **2** as white crystals, mp 114–6 °C (lit. mp 130–1 °C).

3-Bromo-2,6-difluorobenzoic Acid (16). Lithiation of bromide **12** with 1.0 equiv of LDA in THF gave **16** (0.36 g, 76%) as white needles, mp 140–4 °C. Recrystallization from heptane gave white needles, mp 140–1 °C. Anal. Calcd for $C_7H_3BrF_2O_2$: C, 35.47; H, 1.37; Br, 33.76; F, 16.03. Found: C, 35.17; H, 1.35; Br, 33.68; F, 16.72. IR (KBr): 1715, 1619, 1470, 1410, 1306, 1028, 851, 820, 656 cm^{-1}. NMR: 9.0 (1 H, br s), 7.71 (1 H, ddd, J = 5.5, 7.3, 9.1 Hz), 6.95 (1 H, ddd, J = 1.5, 8.7, 9.1 Hz) ppm. Mass spectrum: m/e 238 (98, $^{81}BrM^+$), 236 (100, $^{79}BrM^+$).

2-Bromo-3,6-difluorobenzoic Acid (17). Lithiation of bromide **13** with 1.0 equiv of LDA in THF gave **17** (0.33 g, 70%) as pale yellow needles, mp 104–8 °C. Recrystallization from heptane gave small white needles, mp 111–3 °C. Anal. Calcd for $C_7H_3BrF_2O_2$: C, 35.47; H, 1.37; Br, 33.76; F, 16.03. Found: C, 35.07; H, 1.32; Br, 34.30; F, 16.66. IR (KBr): 1709, 1471, 1445, 1300, 1280, 1266, 1243, 871, 826, 760 cm^{-1}. NMR: 10.9 (1 H, br s), 7.25 (1 H, ddd, J = 3.1, 4.4, 9.1 Hz), 7.15 (1 H, ddd, J = 4.1, 9.1, 13.2 Hz) ppm. Mass spectrum: m/e 238 (98, $^{81}BrM^+$), 236 (100, $^{79}BrM^+$).

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Registry No. 1, 446-17-3; **2**, 118829-12-2; **3**, 327-52-6; **4**, 2358-29-4; **12**, 348-57-2; **13**, 399-94-0; **14**, 1583-58-0; **15**, 2991-28-8; **16**, 28314-81-0; **17**, 124244-65-1; **18**, 385-00-2.

(21) A referee has suggested that some rearrangements may have occurred during catheter transfer, or on warming up prior to acid quench. The high yields of acids from 1-bromo-2-lithio compounds and kinetic lithiations suggest that catheter transfer is not problematic. Several of the reactions in this note, and many similar cases, have been quenched at −78 °C with TFA, but results were essentially unchanged from a 0 °C quench.