## Note



# Halogen-metal exchange of 3-substituted 1,2-dibromoarenes: The use of long-range *J*<sub>CH</sub> coupling constants to determine regiochemistry

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Regioselective halogen/metal exchange reactions were carried out on a series of 3-substituted- 1,2dibromoarenes. Product mixtures were quenched with CO<sub>2</sub> to form the corresponding benzoic acid analogs to facilitate HPLC and NMR analysis. Substitution at the 3-position could readily be assigned on the basis of 2D HMBC long-range correlations, while assignment at the 2-position was not as straightforward. The use of three-bond  $J_{CH}$  coupling constant measurements, extracted from 1-D <sup>1</sup>H coupled <sup>13</sup>C experiments, were necessary to render unequivocal regio assignments. Copyright © 2006 John Wiley & Sons, Ltd.

**KEYWORDS:** tri-substituted arenes; NMR; <sup>13</sup>C; coupled <sup>13</sup>C; <sup>1</sup>H; <sup>3</sup>J<sub>CH</sub> coupling constants; <sup>2</sup>J<sub>CH</sub> coupling constants; regiochemistry; HMBC

### INTRODUCTION

In the course of our study of halogen/metal exchange reactions of 3-substituted 1,2-dibromoarenes with Grignard reagents, we found that isopropylmagnesiumchloride (iPrMgCl)<sup>1</sup> had a clear advantage over the more commonly used *n*-butyl lithium (nBuLi)<sup>2,3</sup> in providing high assay yield, thermal stability and site selectivity. A series of 3substituted 1,2-dibromobenzene analogs were prepared to examine the effect of R-group substitution on regioselectivity in the transmetalation.<sup>4</sup> To simplify the analysis, the metal analogs were quenched with carbon dioxide to provide the more stable benzoic acid analogs for product yield via HPLC analysis. NMR analysis was used to determine the regiochemistry of these analogs, which required the use of the older, more traditional 1-D technique: <sup>1</sup>H coupled <sup>13</sup>C NMR, whereby long- range three-bond and two-bond JCH coupling constants could be measured.

### **RESULTS AND DISCUSSION**

A series of substituted 1,2-dibromo arenes, 1a-g, were reacted under the conditions presented in Scheme 1 to yield the benzoic acid regioisomers 2a-g and 3a-g; the regioisomeric ratios (2:3) and yields are presented in Table 1.

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Scheme 1. Formation of benzoic acid regioisomers.

For all of the quenched product mixtures, the major regioisomer represented  $\geq$ 90% of the product mixture. A combination of <sup>1</sup>H and <sup>13</sup>C 1D NMR experiments was used to identify the major species in each mixture. The similarity of the aromatic coupling patterns observed in the proton spectra for all products was consistent with a 1,2,3 tri-substituted arene ring where C<sub>3</sub> bore the R-group. Although the literature provides references for proton NMR data<sup>5</sup> for all but one of the products, the chemical shift differences between the regioisomers are too small to make an unequivocal distinction. Solvent effects lend further uncertainty to the assignment differences. Consequently, assignment of the quench site to  $C_1$  or  $C_2$  on the ring required <sup>13</sup>C NMR data. While the decoupled <sup>13</sup>C experiment provided chemical shift information about the aromatic carbons, the coupled <sup>13</sup>C experiment provided multiplicity and long-range coupling data. In compound 2a, the presence of a fluoro group at the C<sub>3</sub> position on the aromatic ring provided a valuable tool for the positional <sup>13</sup>C assignments on the ring. Carbon-fluorine  $(J_{CF})$  couplings were fairly diagnostic for aromatic ring assignments. In general, the  $J_{CF}$  coupling constant for the *ipso* (C<sub>3</sub>) bearing the fluorine was  $\sim$ 250 Hz, whereas those



for ortho, meta and para were approximately 20-25, 6-10 and 2-4 Hz, respectively. The substituted and protic carbons were readily distinguished in the <sup>1</sup>H coupled <sup>13</sup>C spectrum, although the reduced signal intensity of the  $C_1$ - $C_3$  carbons in the decoupled spectrum presented a reliable indicator for substitution as well. Using this combined information, the assignments for the carbons in compound 2a were made, which appear in Table 3. A significant observation in the <sup>1</sup>H coupled <sup>13</sup>C data revealed that the acid carbonyl showed no long-range carbon-hydrogen couplings  $(J_{CH})$ , which strongly suggested its substitution at C<sub>2</sub>. This applied to all the major regioisomers (2a-2f) with the exception of the methyl analog (3g) where a  ${}^{3}J_{CH}$  coupling of 4.5 Hz to the acid carbonyl was observed. The more commonly used 2-D HMBC (heteromultiple bond correlation) experiment would easily have shown this three-bond correlation; however, the absence of these correlations in 2a-2f would not conclusively prove carboxyl substitution at C2. It was necessary to focus on the substituted carbons in the coupled <sup>13</sup>C spectrum. The positional assignment of the C2 carbon (triplet) was readily distinguished from  $C_1$  and  $C_3$ , the former having two similar  ${}^{3}J_{CH}$  couplings. The C<sub>3</sub> carbons were assigned on the basis of one of several strategies: chemical shifts (2b, 2e, 2f), the J<sub>CF</sub> couplings (2c), the symmetry of the compound (2d) and the  $^{2}J_{CH}$  couplings from the C<sub>3</sub>-methyl for (**3g**).

With these assignments in place, the focus returned to the regiochemistry of  $C_1$  and  $C_2$ . From the coupled <sup>13</sup>C data, the three-bond <sup>3</sup>J couplings were measured and

Table 1. Regioisomer ratio and yields

	R	2:3	Yield %
2a	F	99:1	84
2b	Cl	95:5	62
2c	CF <sub>3</sub>	94:6	89
2d	Br	90:10	73
2e	OMe	90:10	75
2f	CO <sub>2</sub> Me	92:8	54
3g	CH <sub>3</sub>	1:99	85

**Table 2.** Three-bond  $({}^{3}J_{CH})$  coupling constants for the major regioisomer

		$C_1$	C	2	C <sub>3</sub>	
	R	${}^{3}J_{15}$	${}^{3}J_{24}$	${}^{3}J_{26}$	${}^{3}J_{35}$	
2a	F	12.5	4.5	4.5	12.5	
2b	Cl	13.1	5.5	5.5	12.5	
2c	CF <sub>3</sub>	11.8	а	а	8.3	
2d	Br	12.5	6.2	6.2	12.5	
2e	OMe	13.1	5.2	5.2	9.3	
2f	CO <sub>2</sub> Me	11.4	6.9 <sup>b</sup>	5.5 <sup>b</sup>	9.0	
3g	CH <sub>3</sub>	7.6	9.8 <sup>c</sup>	9.8 <sup>c</sup>	7.6	

<sup>a</sup> Owing to overlap, the couplings could not be measured.

<sup>b</sup> Using coupled  ${}^{13}$ C with selective irradiation of the C<sub>4</sub>–H, unequivocal assignments of the couplings were made.

<sup>c</sup> A coupled <sup>13</sup>C with selective irradiation of the  $C_3$ -Me was used to obtain these measurements.



tabulated (Table 2) for  $C_1$  through  $C_3$ . There are three general trends from the literature for mono substituted aromatic systems: (i)  ${}^{3}J_{CH}$  couplings are larger (6–12 Hz) than the  ${}^{2}J_{CH}$  couplings (0–4 Hz) and easier to discern; (ii) The magnitude of the <sup>3</sup>J<sub>CH</sub> couplings are directly proportional to the increased electronegativity of the substituent. Thus, for halogen substitution the <sup>3</sup>J<sub>CH</sub> couplings are quite large,<sup>6</sup>  $\sim$ 10–13 Hz; (iii) If a substituent is on the coupling pathway, the <sup>3</sup>J values decrease with increased electronegativity. For halogenated substituents, the <sup>3</sup>J<sub>CH</sub> values decrease<sup>6,7</sup> to ~4-6 Hz. Although our system is tri-substituted, these trends were still applicable and were key to making the regioisomer assignments. For the compound 2a, the  ${}^{3}J_{CH}$ coupling for  $C_3$  ( ${}^{3}J_{35}$ ) and  $C_1$  ( ${}^{3}J_{15}$ ) were both 12.5 Hz indicative of halogen substitution, in this case, F and Br, respectively. Subsequently, the  $C_2$  carbon bearing the carboxylic acid group showed the expected smaller couplings (t,  ${}^{3}J_{24} = {}^{3}J_{26} = 4.5$ ) associated with halogen substitution along the coupling pathway. Consequently C2 was assigned to the quench site. Similar <sup>3</sup>J<sub>CH</sub> coupling constants were obtained for 2b and are illustrated<sup>8</sup> in Fig. 1 (Although the literature<sup>8</sup> indicates that the relative proximity of proton chemical shifts can produce second-order effects in the coupled carbon-13 depending on the field strength used, these only apply to the protic carbons, whereas, the coupled patterns for the quaternary carbons are first order). The  $C_2$  carbon appears as a triplet where  ${}^3J_{24} = {}^3J_{26} = 4.5$ . This trend was observed for compounds 2d-2f. Owing to overlap, the values for compound 2c could not be measured. All (2c-2f) had bromine substitution on the  $C_1$  carbon and yielded the large diagnostic  ${}^{3}J_{15}$  values (11.4–13.1). There was some expected variation in the  ${}^{3}J_{35}$ couplings (9.0-12.5) at C<sub>3</sub> related to the electronegativity of the R group; the least electronegative groups, CH<sub>3</sub> and CF<sub>3</sub>, showed the smallest  ${}^{3}J_{35}$  coupling of 7.6 and 8.3 Hz, respectively. For the methyl analog, compound 3g, the C1 carbon revealed a small  ${}^{3}J_{15}$  coupling of 7.6 Hz relative to the large values observed for the other isomers. This indicated that the carboxylic acid group was now on the C<sub>1</sub> carbon. Additionally, as noted previously, the <sup>3</sup>J to the carbonyl was observed.



**Figure 1.** (a) Aromatic region of <sup>13</sup>C spectrum of **2b** with labeled quaternary carbons; (b) Corresponding coupled <sup>13</sup>C spectrum with  ${}^{3}J_{CH}$  coupling constants and multiplicities.

Table 3.	<sup>1</sup> H/ <sup>13</sup> C assignments <sup>a,b</sup>	of 3-R-substituted-	1,2-dibromo benzenes
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	2a	2b	2c	2d	2e	2f	3g
	F	Cl	CF <sub>3</sub>	Br	OMe	CO <sub>2</sub> Me	CH <sub>3</sub>
C <sub>1</sub>	120.48	120.12	121.09	119.95	119.77	120.66	136.56
	d, 4.8	_	_	_	_	_	_
C <sub>1a</sub>	_	_	_	_	_	_	170.85
C <sub>2</sub>	127.13	138.15	136.49	140.09	128.39	139.42	123.31
	d, 21.5	_	q, 2.1	_	_	_	_
C <sub>2a</sub>	167.01	168.58	168.94	169.22	169.75	170.70	-
C <sub>3</sub>	160.48	132.10	129.58	119.95	158.36	130.60	140.80
	d, 244.3	_	q, 32.9	_	_	_	-
C <sub>3a</sub>	_	_	124.93	_	_	166.84	23.90
	_	_	q, 273.3	_	_	_	-
OMe	_	_	-	_	56.84	53.29	_
$C_4$	116.02	129.65	126.41	132.78	111.53	130.21	134.01
	d, 21.5	_	q, 4.5	_	_	_	-
$C_5$	133.12	132.36 <sup>c</sup>	131.96	132.62	132.44	131.61	128.24
	d, 9.0	_	_	_	_	_	_
C <sub>6</sub>	129.98	132.42 <sup>c</sup>	137.82	132.78	125.52	138.20	128.72
	d, 3.5	_	_	_	_	_	-
H-4	7.20, td 8.2, 0.8	7.47, dd	7.92, d 8.1	7.63 <i>,</i> d	7.05,br d	7.99, dd	7.41 <i>,</i> m
	_	8.1,1.2	_	8.1	8.4	8.0, 0.9	-
H-5	7.37, td	7.30, t	7.51, tq	7.23, t	7.28, t	7.43, t	7.30, t
	8.2,5.9	8.1	8.1,0.8	8.1	8.2	8.0	7.7
H-6	7.47, d	7.59, dd	7.92 <i>,</i> d	7.63 <i>,</i> d	7.18, dd	7.87, dd	7.46,dd
	8.2	8.1, 1.2	8.1	8.1	8.0, 0.7	8.0, 0.9	7.1,1.2
OMe	-	-	_	_	3.85	3.89	_

<sup>a</sup> Coupling constant multiplicities: d = doublet, t = triplet, q = quartet, m = multiplet.

<sup>b</sup> The  $J_{CF}$  coupling constants for **2a** and **2c** are tabulated with the <sup>13</sup>C assignments.

<sup>c</sup> Assignments may be interchanged.

With this final assignment of regiochemistry for **3g**, all seven benzoic acid analogs were assigned. The full carbon-13 assignments are presented in Table 3.

#### **EXPERIMENTAL**

Proton and carbon-13 spectra were recorded at 27 °C in CD<sub>3</sub>OD on a Bruker DPX 300 instrument at a frequency of 300.13 and 75.47 MHz, respectively, using a 5 mm QNP probe. The chemical shifts are reported in ppm relative to residual CD<sub>2</sub>HOD for proton ( $\delta$  = 3.31) and CD<sub>3</sub>OD for carbon ( $\delta$  = 49.15). The *J*<sub>CH</sub> and *J*<sub>CF</sub> coupling constants are reported in Hz.

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