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A practical approach to highly functionalized benzodihydrofurans[†]

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Abstract

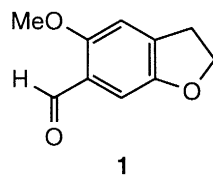
A number of aromatic dibromides have been treated with 2–3 equivalents of *n*-butyllithium in order to initiate two sequential chemical events, a Parham cyclization and an intermolecular reaction with DMF. © 2000 Elsevier Science Ltd. All rights reserved.

As part of our ongoing endothelin antagonist program,¹ we required an efficient practical preparation of aldehyde **1** (Fig. 1). The route chosen to support development is illustrated in Scheme 1² and employed a strategy whereby aromatic bromide **3** was subjected to *n*-butyllithium in THF at –78°C in order to form the corresponding lithium anion. The resultant organometallic was allowed to react with DMF to furnish the aldehyde **1** after acid hydrolysis. On scale-up, however, certain deficiencies were discovered within the route. Principally, selective bromination of benzodihydrofuran **2** was not an easy task because of its propensity to dibrominate. Moreover, the purity of **3** was compromised further because of the formation of regioisomers. These isomers, if not removed by recrystallization, and carried through the entire process, formed impurities structurally similar to our drug which were extremely difficult to remove. This imposed a tight specification on the purity of bromide **3** and even though this was achieved, it was at the expense of yield. For the purpose of supporting development, the short term answer was to arrest the reaction after 70% of **2** had been consumed (HPLC analysis). This gave **3** in 50% isolated yield (after recrystallization from hexane) devoid of significant impurities. However, endeavors were initiated to find a new and more reliable method of making aldehyde **1** as well as an efficient route to highly functionalized benzodihydrofurans in general.

A review of the literature suggested that a chelation controlled deprotonation of **2** with *n*-butyllithium would not be selective.³ Furthermore, when standard formylation procedures were examined, such as the Vilsmeier reaction and its variants, our efforts were challenged by their lack of selectivity towards the ring.⁴ Our next strategy was based on the initial observation of the development route

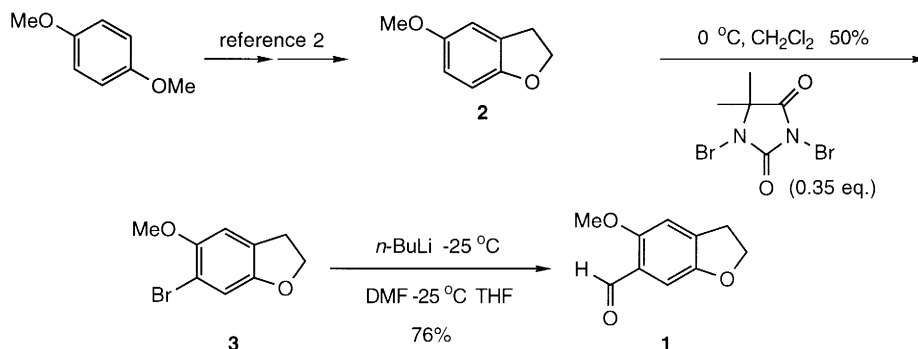
* Corresponding author.

[†] Dedicated to the memory of Ken Tubman and Lendon Pridgen.



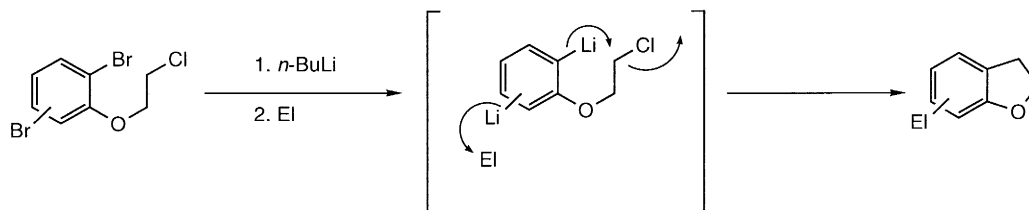
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Fig. 1.



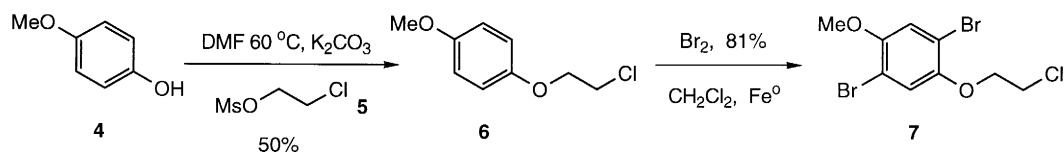
Scheme 1.

that dibromination of these systems was a competing reaction pathway. Therefore we explored an idea whereby a suitably alkylated phenol would be treated with two equivalents of bromine in order to allow complete dibromination. The dibromide would then be exposed to two or more equivalents of *n*-butyllithium in order to trigger two sequential chemical events, a Parham cyclization⁵ and an intermolecular reaction with an electrophile (Scheme 2).



Scheme 2.

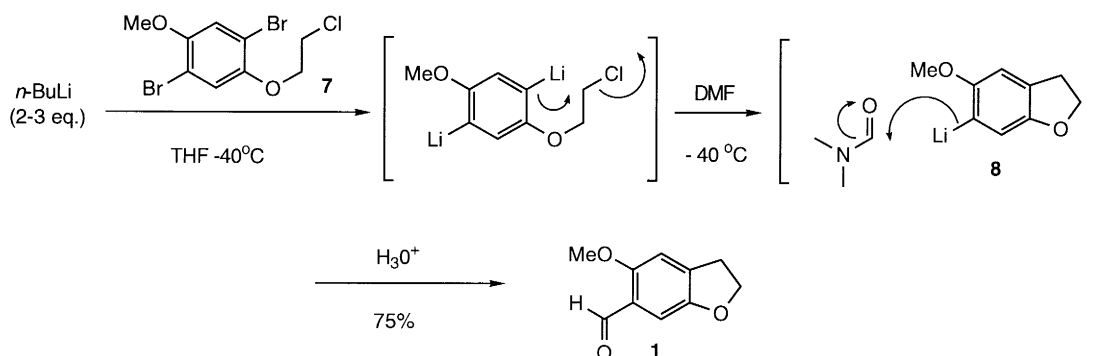
In order to investigate this concept, *p*-methoxyphenol (**4**) was heated in DMF with 2-chloroethylmethanesulfonate (**5**) and K_2CO_3 to give **6** in an unoptimized yield of 50%. Ether **6** was exposed to two equivalents of bromine in dichloromethane in the presence of iron granules to furnish dibromide **7** in 81% yield (Scheme 3).



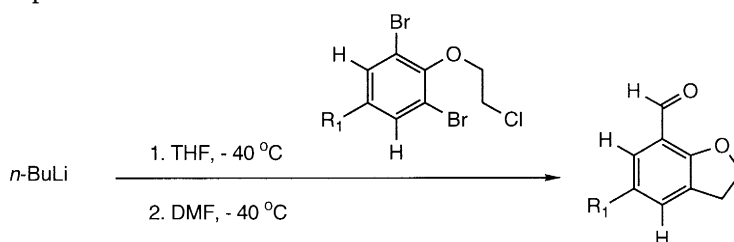
Scheme 3.

Bradsher has examined the selectivity of *n*-butyllithium towards aromatic dibromides and observed that a bromine adjacent to a Lewis basic site will react preferentially with 1 equiv. of *n*-butyllithium after 1 h at -100°C to initiate a Parham cyclization. After cyclization was achieved he also observed that addition of a second equivalent of *n*-butyllithium followed by DMF at -100°C furnishes an aldehyde.⁶

Besides the fact we had two Lewis basic sites on the aromatic ring to which the alkyl lithium could coordinate, this low temperature procedure was too impractical for our purposes and so we explored a modification of this operation at -40°C . To our dismay we discovered that sequential addition of 2 equiv. of *n*-butyllithium and DMF to dibromide **3** at -40°C led to a complex mixture which contained only a small quantity of the desired product. This result was also observed when the reaction was conducted at -78°C and at -25°C .⁷ The reaction was improved slightly when dibromide **7** and DMF were stirred together at -40°C and *sec*-butyllithium was added last. However, after some experimentation, we discovered that treating a pre-cooled mixture of *n*-butyllithium with dibromide **7** (inverse addition) at -40°C resulted in clean conversion to aldehyde **1** in 75% yield after addition of DMF (Scheme 4).⁸



The scope and utility of this procedure was demonstrated further when applied to a number of readily available dibrominated phenols. Each phenol was alkylated with 2-chloroethyl-methanesulfonate (**5**) and the resultant ether was sequentially exposed to 3 equivalents of *n*-butyllithium and DMF. The results from these studies are presented in Table 1.⁹



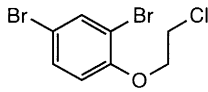
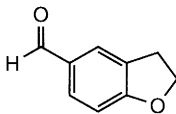
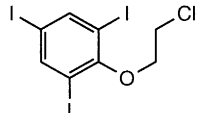
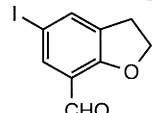
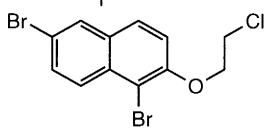
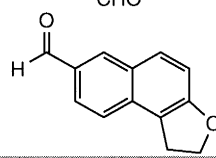
In general, this procedure worked extremely well and provided synthetically useful yields of substituted benzodihydrofurans. More importantly, it provided a practical route to **1** of a purity that could be used in our supply route without the need of further purification.

Conclusion: This dianion strategy provides ready access to highly functionalized benzodihydrofurans in a short number of steps. Furthermore, this chemistry can be applied to a range of other electrophiles some already investigated by us.¹⁰ This method will be applied to other heterocycles and the results will be reported in due course.

Acknowledgements

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Table 1
Reaction of aromatic dibromides with *n*-BuLi and DMF at -40°C

Entry	Dibromide $\text{R}_1 =$	Product $\text{R}_1 =$	Yield (%) ^a
1	H	H	76
2	Me	Me	81
3	tBu	tBu	91
4	F	F	42
5	Br	Br	36 ^b
6			75
7			69 ^b
8			76

^a Yields are based on purified isolated compound (column chromatography).

^b Position of the aldehyde on the ring was determined by nOe.

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- It was observed that when lithiated species **8** was allowed to warm to 0°C (or rt) and then recooled, a mixture of isomeric aldehydes was obtained after sequential addition of DMF and 1.0 M HCl. This is probably due to scrambling of the aryl lithium anion on the ring. This could be avoided if the reaction temperature is maintained below -25°C . At this temperature, the isomerization is suppressed to a level of less than 5%. Therefore the temperature profile of the reaction, prior to DMF addition, should never exceed -25°C .
- A precooled solution of the dibromide (1.73g, 4.67 mmol, entry 3) in THF (4 mL) was added dropwise to a precooled solution of *n*-BuLi (5.61 mL, 14.0 mmol) in 15 mL of THF at -40°C . Upon completion of the addition, DMF (0.76 mL, 9.82 mmol) was added. The cooling bath was removed and the reaction mixture was allowed to warm to rt. After the starting

material was consumed the reaction was quenched with 1.0 M HCl (20 mL) and the solvent volume was reduced (in vacuo). The organics were extracted with TBME (4×20 mL), washed with brine (25 mL), dried (MgSO₄), filtered and concentrated to produce a crude yellow solid, which was purified by chromatography to give the substituted benzaldehyde (0.87g, 91%) as a white solid: ¹H NMR (400 MHz, CDCl₃) δ 10.19 (s, 1H), 7.57 (s, 1H), 7.48 (s, 1H), 4.72 (t, J=8.7 Hz, 2H), 3.24 (t, J=8.7 Hz, 2H), 1.30 (s, 9H); ¹³C NMR (100.62 MHz, CDCl₃) δ 189.20, 160.37, 143.83, 129.28, 128.61, 123.29, 118.69, 72.81, 34.37, 31.42, 28.83; IR (KBr disc, cm⁻¹) 3100, 2762, 1675, 1460, 888; MS(ESP) 205 (M+H)⁺, 149 (M+H-(tBu)+H)⁺.

9. Data for entry 2. ¹H NMR (400 MHz, CDCl₃) δ 10.14 (s, 1H), 7.35 (s, 1H), 7.21 (s, 1H), 4.69 (t, J=8.8 Hz, 2H), 3.19 (t, J=8.8 Hz, 2H), 2.29 (s, 3H); ¹³C NMR (100.62 MHz, CDCl₃) δ 189.00, 160.4, 131.9, 130.0, 129.5, 126.9, 119.1, 72.7, 28.7, 20.5; IR (KBr disc, cm⁻¹) 3428, 2771, 1675, 1613, 871; MS(CI) 163 (M+H)⁺, 177 (M+CH₅)⁺. Data for entry 4. ¹H NMR (400 MHz, CDCl₃) δ 10.15 (s, 1H), 7.35 (s, 1H), 7.24 (ddt, J=8.9, 2.7, 1.3, 1H), 7.14 (ddt, J=7.5, 2.7, 1.3, 1H), 4.75 (t, J=8.7 Hz, 2H), 3.25 (ddt, J=8.7, 1.3, 1.0 Hz, 2H); ¹³C NMR (100.62 MHz, CDCl₃) δ 187.7, 158.8, 157.1, 131.5, 118.9, 118.9, 111.3, 73.1, 22.8; IR (KBr disc, cm⁻¹) 2777, 1680, 1620, 1173 (C-F), 875; MS(CI) 167 (M+H)⁺. Data for entry 5. ¹H NMR (400 MHz, CDCl₃) δ 10.12 (s, 1H), 7.69 (s, 1H), 7.49 (s, 1H), 4.76 (t, J=8.7 Hz, 2H), 3.25 (t, J=8.7 Hz, 2H); IR (KBr disc, cm⁻¹) 2778, 1680, 1591, 1070 (C-Br), 868; 1675, 1613, 871; MS(CI) 227 (M+H)⁺, 148 (M+H-Br)⁺. Data for entry 7. ¹H NMR (360 MHz, CDCl₃) δ 10.03 (s, 1H), 7.78 (s, 1H), 7.58 (s, 1H), 4.67 (t, J=8.7 Hz, 2H), 3.15 (t, J=8.7 Hz, 2H); IR (KBr disc, cm⁻¹) 1668, 1584, 1434, 1097 (C-I), 870; MS(CI) 275 (M+H)⁺, 148 (M+H-Br)⁺. Data for entry 8. ¹H NMR (400 MHz, CDCl₃) δ 10.08 (s, 1H), 8.28 (d, J=1.6 Hz, 1H), 7.94 (dd, J=8.6, 1.6 Hz, 1H), 7.84 (d, J=8.7 Hz, 1H), 7.66 (d, J=8.6 Hz, 1H), 7.20 (d, J=8.7 Hz, 1H), 4.82 (t, J=9.0 Hz, 2H), 3.52 (t, J=9.0 Hz, 2H); ¹³C NMR (100.62 MHz, CDCl₃) δ 192.0, 160.7, 135.6, 134.0, 131.6, 131.2, 131.2, 128.1, 123.8, 123.8, 119.5, 72.3, 28.3; MS(CI) 199 (M+H)⁺, 227 (M+C₂H₅)⁺.

10. Unpublished results.