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Regioselective lithiation of aryl benzyl ethers

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Abstract—The lithiation of a series of aryl benzyl ethers containing –F and –OMe groups has been studied. It was found that the presence of one or two fluorine atoms in the *meta* position relative to the oxygen atom prevents the lithiation at the benzyl carbon atom. 3-(3',5'-Dimethoxybenzyloxy)fluorobenzene was lithiated and next reacted with DMF to give 2-(3',5'-dimethoxybenzyloxy)-6-fluorobenzaldehyde. A three-step procedure was applied to remove three hydrogen atoms from 1,3-difluoro-5-(3',5'-dimethoxybenzyloxy) benzyloxy)benzene and replace them with methyl groups by reactions of the lithiated compounds with MeI. © 2005 Elsevier Ltd. All rights reserved.

1. Introduction

The regiospecific introduction of lithium into an aromatic ring a process known as '*ortho* lithiation' is well documented.^{1–5} However, the ortho lithiation of aryl benzyl ethers (ABEs) has not been previously studied. An ABE contains two types of centre which can be metallated: the aromatic rings and the benzylic position. Metallation of either center is of great synthetic potential.^{6–9}

Two generally accepted factors influence the regioselectivity: (1) the inductive effect of a substituent on the phenyl ring which increases the acidity of the ortho hydrogen and, (2) complexation of the metallating agent by a lone pair of electron.¹⁰ The mechanism suggested for this process involves complex formation between a BuLi dimer and an alkoxy group. The metallation of 4-fluoroanisole illustrates this difference well.¹¹ With butyllithium alone, deprotonation of the 2-position ortho to the -OMe group occurs, because the lithium atom interacts with the lone electron pair of the oxygen. Addition of pentamethyldiethylenetriamine (PMDTA), however, coordinatively saturates the butyllithium so the most acidic proton, ortho to the fluorine, is removed. The lithiation of both fluorobenzene and anisole by butyllithium is efficient, but the reaction itself is very slow.^{12,13}

ABE molecules contain benzylic protons which are also α to oxygen. Generally the metallation of protons α to oxygen is unfavourable because of antibonding interactions between the oxygen lone pairs with the C–Li bond. However, the inductive effect of the oxygen atom and the phenyl ring can overcome this effect making lithiation of these compounds easier. Lithiation at the benzylic position can also be accelerated by *ortho* substituents working in conjunction. Napolitano et al. studied the influence of alkoxyalkyl substituents on the regioselective lithiation of a benzene ring and found that the concomitant presence an alkoxyalkyl group and an alkoxy group in a *meta* relationship generally permits easy lithiation by deprotonation at C-2.¹⁴

In this work we have studied the lithiation of ABEs possessing -F and -OMe substituents (Scheme 1). The reaction of 1 with butyllithium is very slow at -60 °C and gives 1a (after trapping with MeI).

Integration of the methylene signals in the ¹H NMR (400 MHz) spectrum of the reaction mixture confirmed that 22% of **1** remained unreacted. The use of other metallating reagents (BuLi/*t*-BuOK or BuLi/PMDTA) gave **1a** (80%, calculated from the ¹H NMR spectrum) and traces of **1b**. Ether **2** was also metallated at the benzylic position using BuLi in THF to give **2a** after trapping with DMF. However when the reaction was carried out in the presence of PMDTA, a mixture of **2a–d** was formed. Integration of the aldehyde proton signals in the ¹H NMR spectrum revealed that **2a** was the main product (50%). This non-selective outcome results from an increase in metallating power of BuLi in the presence

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Scheme 1. Reagents and conditions: (1) (i) *n*-BuLi/THF, $-60 \,^{\circ}$ C, (ii) MeI, H^+/H_2O ; (2) (i) *n*-BuLi/THF/PMDTA, $-60 \,^{\circ}$ C, (ii) MeI, H^+/H_2O ; (3) (i) *n*-BuLi/THF, $-60 \,^{\circ}$ C, (ii) DMF, H^+/H_2O ; (4) (i) *n*-BuLi/THF/PMDTA, $-60 \,^{\circ}$ C, (ii) DMF, H^+/H_2O ; (5) (i) *n*-BuLi/THF, $-60 \,^{\circ}$ C, (ii) DMF, H^+/H_2O ; (6)–(8) (i) *n*-BuLi/THF, $-60 \,^{\circ}$ C, (ii) MeI, H^+/H_2O .

of PMDTA and thus some deprotonation ortho to fluorine is possible. Metallation of 3 with BuLi occurred easily and selectively to give 3a after addition of DMF. Only the hydrogen between the fluorine and the oxygen was removed. This hydrogen is the most acidic and additionally, complexation of the BuLi by the lone electron pair of oxygen is possible. We did not observe any metallation of the carbon atom between two -OMe groups. This would require a higher temperature to occur efficiently. The metallation of 4 is especially interesting because of the presence of three very reactive centres, one between two fluorine atoms and two between fluorine and oxygen atoms. We expected that BuLi would remove the proton between fluorine and oxygen, however, 4 was metallated exclusively between the two fluorine atoms, then reacted with MeI to give 5. Our explanation is that the lithiation of 4 is kinetically controlled and that the most acidic hydrogen is removed. Complexation of the lithium by oxygen must be slower in this case than the deprotonation. When 5 reacted with BuLi and the intermediate was trapped with MeI, 6 was isolated. This, in turn, was also easily metallated by BuLi and then reacted with MeI to give 7.

We conclude that a molecule of an ABE can be selectively lithiated on the phenyl ring when it contains a fluorine atom *meta* to the oxygen, or two fluorine atoms in a *meta* orientation. The regioselectivity of the reaction depends on the acidity of the hydrogen atoms. When two fluorine atoms and an oxygen are mutually in a *meta* relationship, as in 4, the hydrogen atom between the two fluorine or the fluorine and oxygen atoms are not in a *meta* relationship, the benzylic position is lithiated selectively, but the yield of the reaction is low. It is worth mentioning that we did not observe a [1,2]-Wittig rearrangement at -60 °C for all the studied reactions.¹⁵ However, we did find that this process occured with 1 at -10 °C.

2. General procedure for lithiation and reaction with electrophiles

To a cooled $(-68 \,^{\circ}\text{C})$ solution of the ABE in 100 mL of THF, butyllithium (1.1 equiv) as a 10 M solution in hexane was added dropwise with stirring while maintaining the temperature below $-60 \,^{\circ}\text{C}$. The stirring was continued for 1 h and then the appropriate electrophile (DMF, MeI) was added maintaining the temperature below $-60 \,^{\circ}\text{C}$. After the addition, the cooling bath was removed and the reaction mixture was allowed to warm to $-40 \,^{\circ}\text{C}$. Water (100 mL) and 3 M sulfuric acid (20 mL) were added to make the mixture slightly acidic. The resulting solution was extracted twice using 50 mL portions of diethyl ether and the extracts were evaporated under reduced pressure. The solid obtained was washed with hexane and recrystallised from hexane.

2.1. 2-(3',5'-Dimethoxybenzyloxy)-6-fluorobenzaldehyde, 3a

2-(3',5'-Dimethoxybenzyloxy)-6-fluorobenzaldehyde, **3a** obtained from 3-(3',5'-dimethoxybenzyloxy)fluorobenzene (8.64 g, 0.033 mol), BuLi (3.5 mL, 0.035 mol) and DMF (2.55 g, 0.035 mol), (9 g, yield 95%). Analysis: ¹H NMR (400 MHz, CDCl₃) δ 10.52 (d, J = 1.2 Hz, 1H), 7.45 (m, J = 6.4 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 6.74 (m, J = 8.4 Hz, 1H), 6.59 (d, J = 2.4 Hz, 2H), 6.43 (t, J = 2.4 Hz, 1H), 5.14 (s, 2H), 3.81 (s, 6H). Anal. Calcd for C₁₆H₁₅FO₄: C, 66.20; H, 5.21. Found: C, 66.01; H, 5.19.

2.2. 2,6-Difluoro-4-(3',5'-dimethoxybenzyloxy)toluene, 5

2,6-Difluoro-4-(3',5'-dimethoxybenzyloxy)toluene, **5** obtained from 1,3-difluoro-5-(3',5'-dimethoxybenzyloxy)benzene (9.40 g, 0.033 mol), BuLi (3.5 mL, 0.035 mol) and MeI, (4.97 g, 0.035 mol), (8.73 g, yield 90%). Analysis: ¹H NMR (400 MHz, CDCl₃) δ 6.54 (d, J = 2.4 Hz, 2H), 6.46 (d, J = 8.8 Hz, 2H), 6.41 (t, J = 2.4 Hz, 1H), 4.92 (s, 2H), 3.78 (s, 6H), 2.09 (t, J = 1.6 Hz, 3H). Anal. Calcd for C₁₆H₁₆F₂O₃: C, 65.30; H, 5.48. Found: C, 65.18; H, 5.51.

2.3. 2,6-Difluoro-4-(3',5'-dimethoxybenzyloxy)-3-methyltoluene, 6

2,6-Difluoro-4-(3',5'-dimethoxybenzyloxy)-3-methyltoluene, **6** obtained from **5** (5.93 g, 0.020 mol), BuLi (2.5 mL, 0.025 mol) and MeI (3.55 g, 0.025 mol), (4.76 g, yield 85%). Analysis: ¹H NMR (400 MHz, CDCl₃) δ 6.56 (d, J = 2.4 Hz, 2H), 6.42 (t, J = 2.4 Hz, 1H), 6.39 (d, J = 1.6 Hz, 1H), 4.96 (s, 2H), 3.78 (s, 6H), 2.13 (t, J = 7.2 Hz, 3H), 2.10 (t, J = 2.0 Hz, 3H). Anal. Calcd for C₁₇H₁₈F₂O₃: C, 66.22; H, 5.88. Found: C, 65.41; H, 5.87.

2.4. 2,6-Difluoro-4-(3',5'-dimethoxybenzyloxy)-3,5-dimethyltoluene, 7

2,6-Difluoro-4-(3',5'-dimethoxybenzyloxy)-3,5-dimethyltoluene, 7 obtained from 6 (3.55 g, 0.011 mol), BuLi (2.5 mL, 0.015 mol) and MeI (2.13 g, 0.015 mol), (2.4 g, yield 68%). Analysis: ¹H NMR (400 MHz, CDCl₃) δ 6.61 (d, J = 2.4 Hz, 2H), 6.45 (t, J = 2.4 Hz, 1H), 4.71 (s, 2H), 3.82 (s, 6H), 2.15 (t, J = 2.0 Hz, 6H), 2.14 (t, J = 2.0 Hz, 3H). Anal. Calcd for C₁₈H₂₀F₂O₃: C, 67.15, H, 6.24. Found: C, 66.57; H, 6.19.

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