Pergamon

Tetrahedron Letters 39 (1998) 8377–8380

TETRAHEDRON LETTERS

Controlling the Regioselectivity of Lithiation using Kinetic Isotope Effects: Deuterium as a Protecting Group for Carbon

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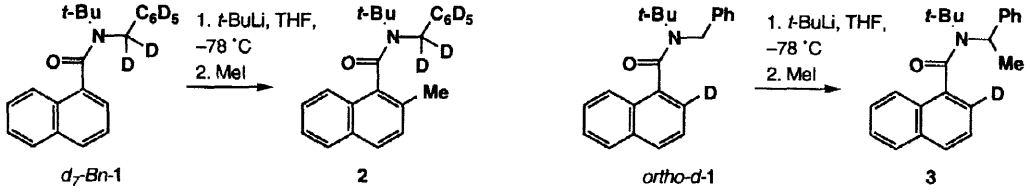
Received 11 August 1998; accepted 9 September 1998

Abstract: By substituting deuterium for hydrogen at positions of high kinetic acidity in amides and carbamates, the usual regiochemical course of their reactions with alkyllithiums (ortholithiation *vs.* lateral lithiation *vs.* nucleophilic addition) can be altered or overturned by the kinetic isotope effect. The deuterium substituent functions in these reactions as a protecting group for carbon.

The lithiation of aromatic amides or carbamates is an important technique for the construction of aromatic compounds.[1] Lithiation of amides by alkyllithium reagents is directed by complexation of the alkyllithium with the electron-rich amide oxygen atom,[2,3] and because of this it takes place adjacent to the amide group, for example at the *ortho* position of the aromatic ring. Benzylic positions are also particularly susceptible to lithiation: 2-alkyl benzamides usually undergo benzylic (lateral) lithiation[4] rather than ortholithiation,[5] and Snieckus has employed silyl substituents to block acidic lateral positions.[6] Lithiation α to the nitrogen atom is preferred in *N*-benzylamides.[7] In some circumstances, a certain degree of control over regioselectivity may be obtained by choice of base – α-lithiation, for example, appears to be favoured by LiTMP[8] – but in general the site of lithiation is determined by the substitution pattern of the starting material.

In this Letter, we show that sites in amides and carbamates which are usually prone to lithiation can be protected using a kinetic isotope effect (KIE): replacing hydrogen by deuterium at an acidic position can divert the usual regioselectivity exhibited by organolithiums and favour alternative reaction pathways.



d_7-*Bn*-1 **2** *ortho*-*d*-1 **3**

Scheme 1: Using deuterium to control ortho vs α-lithiation

During some mechanistic studies[9] on an anionic cyclisation[10] we found that we could direct lithiation of an *N*-benzyl naphthamide **1** to either the *ortho* (**2**) or the α-position (**3**) simply by replacing hydrogen atoms in the starting material with deuterium (Scheme 1). Hoppe has reported values of k_H/k_D >70 for the lithiation of a carbamate at –78 °C,[11] and has employed the powerful kinetic preference for de-protonation over de-deuteration to control stereochemistry. Others have found that replacement of H by D can perturb the stereochemistry of, or completely shut down, lithiation reactions.[12] We decided to investigate the potential of this strategy as general method for promoting ortholithiation over lateral lithiation, and started by using intramolecular competition experiments to assess the magnitude of the KIE for amide lithiations (Scheme 2).[13]

We made the 2-deutero and 2-ethyl benzamides **5** and **7** by ortholithiation of *N*,*N*-diisopropylbenzamide **4**. Ortholithiation of **5** at –78 °C, followed by a methyl iodide quench, gave a product **6**

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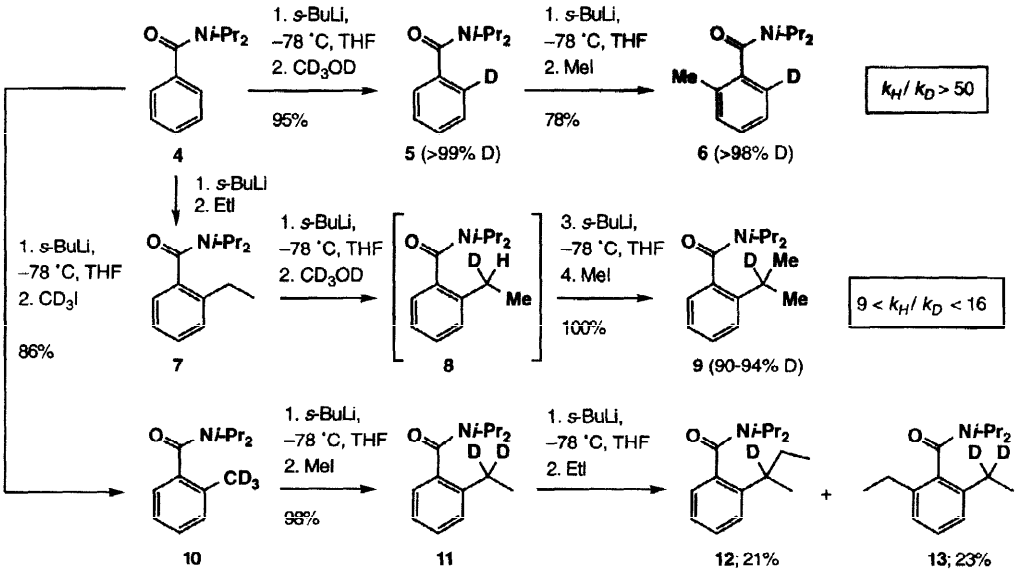
PII: S0040-4039(98)01930-3

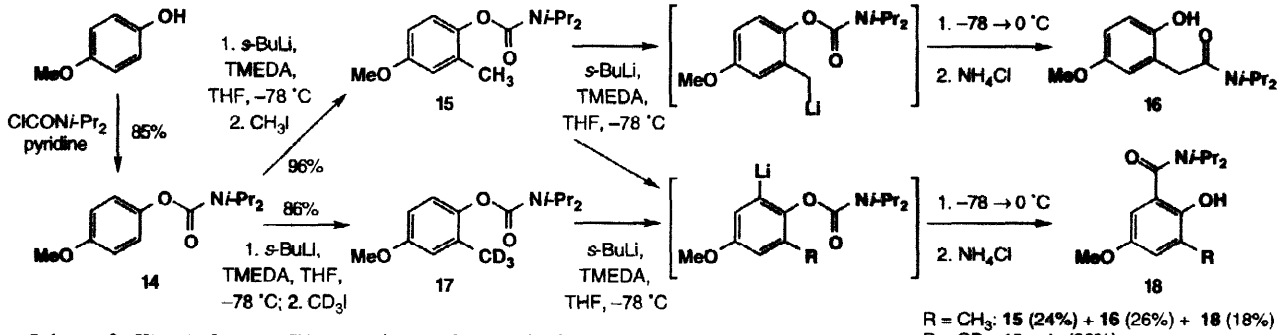
which mass spectrometry showed was still at least 98% deuterated: the value of k_H/k_D for ortholithiation at –78 °C appears to be at least 50.[14] The 2-ethyl benzamide **7** was laterally lithiated and deuterated with CD_3OD to give **8**. A second equivalent of *s*-BuLi was then added to **8**, followed by a methyl iodide quench: the product **9** was isolated in quantitative yield and contained no *ortho* methylated material by HPLC. NMR and mass spectrometry showed that 90-94% of this material was deuterated, indicating a KIE for lateral lithiation at –78 °C between 9 and 16.[15]



Scheme 2: Kinetic Isotope Effects and the lithiation of benzamides

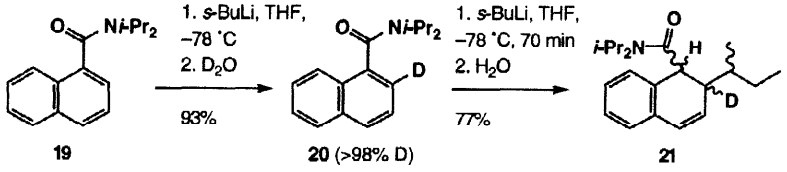
We have found that 2-alkyl-*N,N*-diisopropylbenzamides lithiate consistently at the lateral site rather than the *ortho* site[16,17] – this preference means that sequential ortholithiation reactions can not generally be used to make 2,6-disubstituted benzamides. To see whether the KIE of a lateral deuterium substituent could reverse the regioselectivity of the lithiation, we made 2-trideuteromethyl benzamide **10** by ortholithiation of **4**. However, when we lithiated **10**, quenching with methyl iodide, we got only the laterally methylated compound **11** and no ortholithiation (<2% by HPLC): the KIE in this case is insufficiently large to overturn the powerful preference for lithiation on a lateral methyl group. Lateral lithiation on *n*-alkyl groups is less favourable than on methyl groups,[5] so we lithiated **11** again to see whether the KIE could favour ortholithiation over the lateral lithiation of an ethyl group. We had some success, with an ethyl iodide quench giving 23% ortho-substituted product **13** – but lateral lithiation to give **12** was still the major reaction course (**12** and **13** were produced in a 1.6:1 ratio). Lithiation of undeuterated **11** gives >95% lateral lithiation products.[5,17-19]

In this case, the KIE was not exploitable for synthetic use. However, in another system we had more success. We needed the amide **18** (R = Me) for another project, and decided to make it by an anionic *ortho*-Fries rearrangement of a carbamate **15** (Scheme 3). Despite a literature precedent that lithiation of a similar carbamate promoted rearrangement onto the *ortho* position,[20] we found that lithiation and rearrangement of **15** gave only 18% of the *ortho* rearranged product **18** (R = Me) and 26% of **16**, the product of rearrangement onto the lateral position.[21] Ortholithiation and lateral lithiation appear to be more finely balanced in this case, so we decided to try using the KIE to control the regioselectivity. Having made the trideuteromethyl compound **17**, we lithiated under the standard conditions for anionic *ortho*-Fries rearrangement[20] and managed to obtain the desired product **18** (R = CD_3) in 86% yield.



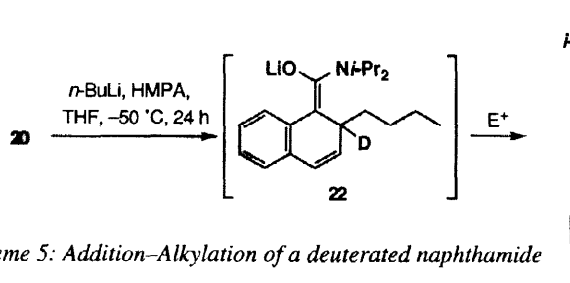
Scheme 3: Kinetic Isotope Effect and lateral vs. ortho lithiation–rearrangement

It is occasionally possible to add nucleophiles to electron-deficient naphthalene rings:[22] naphthyloxazolines in particular react with organolithium reagents at the 2-position.[23] However, it is in general not possible to carry out the corrresponding reaction with amides. A few isolated examples[24,25] of organolithium additions to naphthamides have been reported, and we have shown that an intramolecular version of the reaction is very effective.[10] The predominant reaction of 1-naphthamides with organolithiums is ortholithiation,[1,25] and treatment of *N,N*-diisopropyl-1-naphthamide **19** with *s*-BuLi followed by D_2O gives **20**, >98% deuterated, in 93% yield. When we tried to lithiate **20**, we found that the major product, obtained in 77% yield, was a mixture of diastereoisomers of the dihydronaphthalene **21**. The kinetic isotope effect has protected the 2-position from lithiation and forced the organolithium instead to undergo nucleophilic attack on the ring.



Scheme 4: Kinetic Isotope Effect and alkyllithium addition to a naphthamide

We tried this reaction with some other organolithiums: MeLi did not react with **20**, and *t*-BuLi gave <5% of the dihydronaphthalene ring addition products. *n*-BuLi did not react with **20** under the conditions of Scheme 4, but by adding HMPA and raising the temperature to –50 °C, we got it to add to the ring to give a moderate yield of a 4.8:1 mixture of diastereoisomers of **23** (R = H). The initial product of the addition reaction is enolate **22**, which reacted fully stereoselectively with methyl iodide or propyl iodide to give better yields of **23a** (R = Me or *n*-Pr), each as a single diastereoisomer (Scheme 5). The stereochemistry of **23a** (R = Me) was proved by X-ray crystallography (Figure), and the stereochemistry of **23a** (R = H) by NOE experiments on its undeuterated analogue.[26]



E^+	R =	yield	ratio 23a:23b
H_2O	H	24%	1:4.8
MeI	Me	61%	23a only
n-PrI	*n*-Pr	52%	23a only

Scheme 5: Addition–Alkylation of a deuterated naphthamide

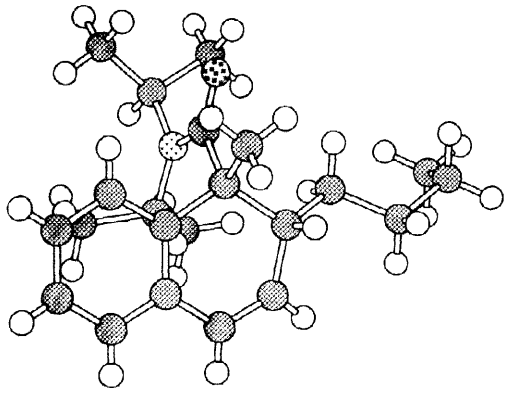


Figure: X-ray crystal structure of 23a (R = Me)

Protecting groups are of course widely used to avoid removal of acidic OH, NH or SH protons, much less so to prevent CH deprotonation.[27] The strategy of using of deuterium as a carbon-protecting group, diverting organolithiums towards alternative reactivity, could be of value where the presence of isotopomeric products is inconsequential or where subsequent exchange processes could be employed to replace D with H.

Acknowledgements

We are grateful to the EPSRC for a CASE award (to NW), to Dr C. Frampton (Roche) for the X-ray crystal structure of **23a** (R = Me), and to the Leverhulme Trust and the Royal Society for research grants.

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