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Tetrahedron Letters 47 (2006) 6945–6946
Tetrahedron Letters

Lateral lithiation of N,N'-diaryl ureas

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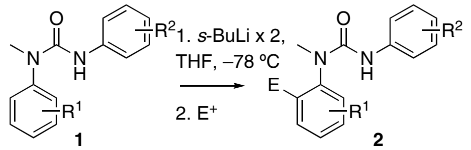
Received 28 June 2006; revised 24 July 2006; accepted 25 July 2006

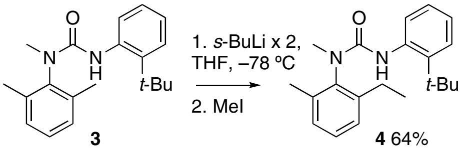
Abstract—Aromatic ureas bearing *N*-(2-alkylaryl) groups may be laterally lithiated by treatment with *sec*-butyllithium. Quenching with a range of electrophiles yields functionalised aryl ureas in excellent yield. Lateral lithiation is favoured when the urea nitrogen adjacent to the aromatic ring in question is alkylated, and when competitive lithiations of such a ring are possible, lateral lithiation is more favourable than the alternative ortholithiation.

Directed metallation has become the most powerful way of functionalising aromatic systems regioselectively.[1,2] Despite their importance in medicinal chemistry, the directed metallation of ureas has received little attention,[3,4] even though ureas share with some of the most powerful metallation directing groups, features such as an electron-rich carbonyl group and electron-deficient nitrogen atoms. We recently reported that *N*,*N*-diarylureas **1** may be ortholithiated regioselectively when one (and only one) of the two nitrogen atoms is alkylated (Scheme 1).[3]

Urea **3** has no available *ortho* protons on one ring, and yet it still undergoes lithiation, at a *lateral* (benzylic)[2] position (Scheme 2).[3] This promising result suggested that lateral lithiation might be a useful, and previously unknown, way of elaborating ureas, and we set out to investigate the generality of this reaction and to assess regioselectivity in substrates containing both *ortho* and lateral lithiation sites.[5]

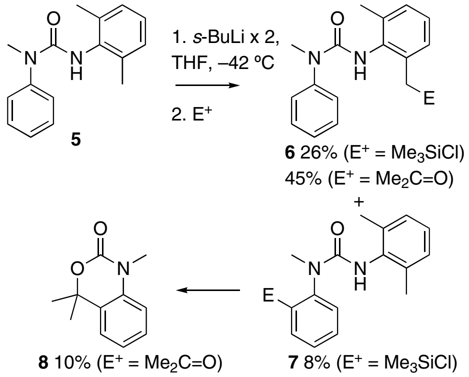


Scheme 1. Ortholithiation of ureas.



Scheme 2. Lateral lithiation of ureas.

Importantly, although **3** undergoes lateral lithiation in preference to ortholithiation, the competition between the two reactivities is also subject to the influence of the site of *N*-alkylation: it is clear for example that ortholithiation of mono-*N*-alkylated ureas **1** exhibits a strong preference for functionalisation of the ring carrying the *alkylated* nitrogen atom.[3] We investigated a potential reversal of this bias by lithiating a urea **5** carrying benzylic methyl group on the ring adjacent to the unsubstituted nitrogen atom (Scheme 3). In this case, a slower reaction (significant amounts of starting material remained at −78 °C) gave a mixture of regioisomeric



Scheme 3. *ortho* versus lateral lithiation.

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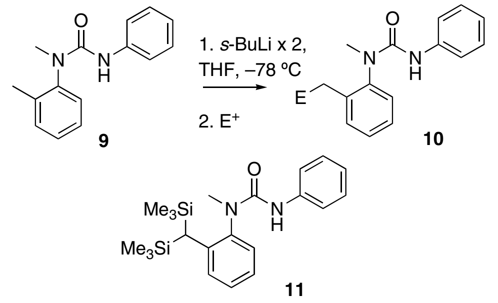
doi:10.1016/j.tetlet.2006.07.134



Scheme 4. Efficient lateral lithiation.

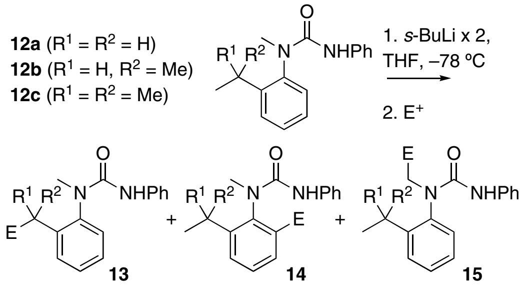
Table 1. Lateral lithiation of **9**

Entry	E^+	E	Yield **10**	Remaining **9**
1	$Me_2C{=}O$	Me_2COH	91	6
2	PhCHO	PhCHOH	89	10
3	MeCHO	MeCHOH	89	3
4	$(CH_2)_5C{=}O$	$(CH_2)_5COH$	88	9
5	Me(C=O)Ph	Me(COH)Ph	92	7
6	PhCH=NMe	PhNMeCH	89	—
7	PhCH=NPh	PhNPhCH	97	—
8	Me_3SiCl	Me_3Si	7 + 47 **11**	3

products (**6** arises from lateral lithiation, while **7** and **8** arise from ortholithiation, **8** forming spontaneously under the conditions of the reaction) with no useful synthetic outcome. Like ortholithiation,[3] lateral lithiation favours functionalisation of the less electron-rich ring adjacent to the alkylated nitrogen atom.

When the sites of possible *ortho* and lateral lithiation lie in the same, favoured ring, a broad preference for lateral lithiation is observed. Thus treatment of **9** with *sec*-butyllithium and a range of electrophiles (Scheme 4) gave the excellent yields of laterally lithiated products **10** indicated in Table 1. No sign of products arising from alternative lithiations was observed, although the product of silylation (entry 9) was susceptible to further lithiation to form doubly silylated **11**.[6]

Secondary benzylic sites are less acidic than primary benzylic sites,[5] but lateral lithiation of an ethyl group is still favoured over ortholithiation: lithiation and quench of **12a** give good yields of products **13** (Scheme 5 and Table 2). Interestingly, while we would not expect the 2-isopropyl substituted compound **12b** to undergo lateral lithiation, it is surprising that it undergoes ortholithiation much less efficiently than the 2-*t*-butyl substituted urea **12c**, and significant quantities of α-lithiated[7] products **15** are observed (Table 2). α-Lithiation is well known in amides, the products being dipole stabilised carbanions.[8]



Scheme 5. More substituted benzylic sites.

Table 2. Lithiation of **12**

Entry	SM	E^+	Yield **13**	Yield **14**	Yield **15**	Remaining **12**
1	**12a**	$Me_2C{=}O$	81	0	0	15
2		Me_3SiCl	62	0	0	14
3	**12b**	$Me_2C{=}O$	0	9	4	60
4		$Me_2C{=}O$[a]	0	21	5	40
5		Me_3SiCl	0	11	39	36
6	**12c**	PhCHO	—	83[b]	0	0
7		Me_3SiCl	—	81	0	0

[a] –42 °C.

[b] From Ref. 3.

In conclusion, lateral lithiation of benzylic sites adjacent to urea functions is a favourable reaction pathway and may be of use for the functionalisation of aromatic ureas.

Acknowledgments

We thank the EU Erasmus programme and the *Programme de Mobilité Internationale de la Région Languedoc-Roussillon* for support.

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