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Ring-Selective Functionalization of *N,N′*-Diarylureas by Regioselective N-Alkylation and Directed Ortho Metalation

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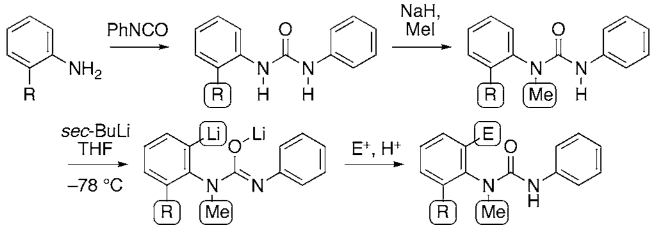
ABSTRACT



Unsymmetrical *N,N′*-diarylureas may be alkylated regioselectively at the more sterically congested nitrogen atom. The resulting mono-N-alkylated ureas undergo directed metalation (ortholithiation) with *sec*-BuLi to yield, on electrophilic quench, products functionalized regioselectively at the ring bearing the alkylated nitrogen atom.

The conformation of *N,N′*-diarylureas **1** has been of interest for some time because of the tendency, with certain substitution patterns, for the two urea N−CO bonds to adopt a conformation placing the aryl rings cis,[1] allowing them to engage in $\pi-\pi$ interactions. As part of a research program investigating the possibility of conformational control in amide-like systems,[2] we are interested in developing reliable routes to unsymmetrical *N,N′*-diarylureas.[3] Many N + O-containing functional groups, particularly secondary and tertiary amides **2**,[4] oxazolines **3**,[5] tertiary *O*-aryl carbamates **4**,[6] and anilides **5**,[7] are powerful directors of ortholithiation.[8] In contrast, the synthetic potential of ortholithiation in ureas has remained largely unexplored.[9]

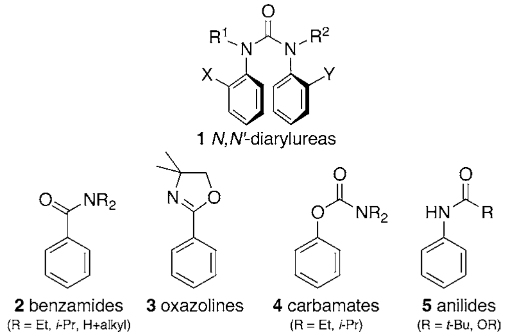


Figure 1. *N,N′*-Diarylureas and N + O-based metalation-directing groups.

N,N′-Diarylureas are readily available by addition of anilines to isocyanates, and our first attempts at ortholithia-

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[1] (a) Lepore, G.; Migdal, S.; Blagdon, D. E.; Goodman, M. *J. Org. Chem.* **1973**, *38*, 2590. (b) Lepore, U.; Castronuovo Lepore, G.; Ganis, P.; Germain, G.; Goodman, M. *J. Org. Chem.* **1976**, *41*, 2134. (c) Yamaguchi, K.; Matsumura, G.; Kagechika, H.; Azumaya, I.; Ito, Y.; Itai, A.; Shudo, K. *J. Am. Chem. Soc.* **1991**, *113*, 5474. (d) Tanatani, A.; Kagechika, H.; Azumaya, I.; Fukutomi, R.; Ito, Y.; Yamaguchi, K.; Shudo, K. *Tetrahedron Lett.* **1997**, *38*, 4425. (e) Kurth, T. L.; Lewis, F. D.; Hattan, C. M.; Reiter, R. C.; Stevenson, C. D. *J. Am. Chem. Soc.* **2003**, *125*, 1460. (f) Lewis, F. D.; Kurth, T. L.; Hattan, C. M.; Reiter, R. C.; Stevenson, C. D. *Org. Lett.* **2004**, *6*, 1605.

[2] For recent papers, see: Clayden, J.; Lund, A.; Vallverdú, L.; Helliwell, M. *Nature (London)* **2004**, *431*, 966 and references therein.

[3] Batey, R. A.; Santhakumar, V.; Yoshina-Ishii, C.; Taylor, S. D. *Tetrahedron Lett.* **1998**, *39*, 6267.

10.1021/ol0508025 CCC: $30.25

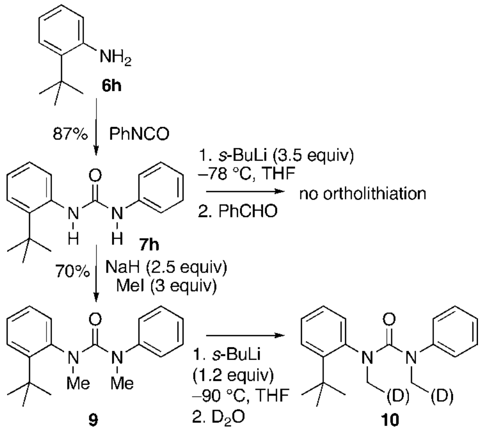
Table 1. Regioselective Alkylation of Unsymmetrical Ureas

entry	starting material	X	Y	Z	product **7**	yield of **7** (%)	R	product	yield of **11** (%)	yield of **12** (%)
1	**6a**	F	H	H	**7a**	83	Bn	**11a**	56	0
2	**6b**	Cl	H	H	**7b**	71	Bn	**11b**	42	0
3	**6c**	Br	H	H	**7c**	70	Bn	**11c**	39	0
4	**6d**	I	H	H	**7d**	81	Bn	**11d**	42	0
5	**6e**	Me	H	H	**7e**	86	Bn	**11e**	44	0
6	**6f**	Et	H	H	**7f**	94	Bn	**11f**	33	0
7	**6g**	*i*-Pr	H	H	**7g**	65	Bn	**11g**	60	0
8	**6h**	*t*-Bu	H	H	**7h**	90	Me	**11h**	86	0
9		*t*-Bu	H	H			Bn	**11i**	58	0
10	**6e**[a]	*t*-Bu	Me	H	**7j**	54	Me	**11j**, **12j**	65	12
11	**6h**	*t*-Bu	Me	Me	**7k**	55	Me	**12k**	0	75

[a] From *o*-toluidine and **14**.

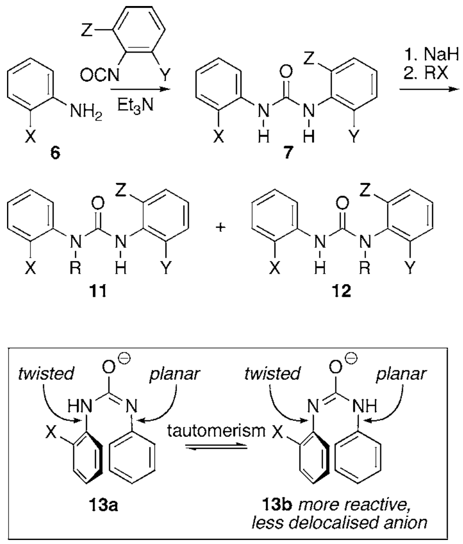
tion were made using the simple urea **7h** obtained by addition of phenyl isocyanate to 2-*tert*-butylaniline **6h**. However, treatment with up to 3.5 equiv of *s*-BuLi in THF at −78 °C gave no discernible ring lithiation products (by electrophilic quench with benzaldehyde). Double alkylation of **7h** with an excess of methyl iodide gave the fully substituted urea **9**. Treatment with *s*-BuLi gave an anion, which deuteration (to give **10**)[10] showed was not an ortholithiated but an α-lithiated compound, namely, the dipole-stabilized carbanion[11] formed by preferential lithiation at one of the methyl groups.

Scheme 1. Attempted Lithiation of Simple Ureas



Perhaps counterintuitively, but probably owing to greater stability to nucleophilic attack, along with the assistance to aggregate formation offered by the electron-rich heteroatom, anionic directing groups frequently perform better than their neutral analogues in metalation reactions.[12] We hoped therefore that ortholithiation of the monoanions of some *N*-alkyl *N*,*N′*-diarylureas **11** or **12** arising from monoalkylation of a series of unsymmetrical ureas **7** would be more successful.

Scheme 2. Regioselective N-Alkylation of Unsymmetrical Ureas



The ureas were made by addition of some 2-substituted anilines **6** to phenyl isocyanate, 2-methylphenyl isocyanate or 2,6-dimethylphenyl isocyanate. Alkylation of the products **7** with a single equivalent of methyl iodide or of benzyl bromide (Scheme 2 and Table 1) resulted in regioselective monoalkylation in all cases but one, with the nitrogen carrying the more heavily substituted ring being reliably alkylated preferentially (with the possible exception of **11a**, whose regiochemistry we were unable to establish unequivocally[13]). Thus, alkylation of **7b**−**h** gave **11** only, with no trace of **12**, while alkylation of **7k** gave only **12**. With the unsymmetrically 2,2′-dialkylated urea **7j**, a mixture of **11**

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(4) (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (b) Beak, P.; Brown, R. A. *J. Org. Chem.* **1977**, *42*, 1823. (c) Beak, P.; Brown, R. A. *J. Org. Chem.* **1982**, *47*, 34. (d) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306.

(5) Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *51*, 837.

(6) Sibi, M. P.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1935 and ref 4a.

(7) Führer, W.; Gschwend, H. W. *J. Org. Chem.* **1979**, *44*, 1133

(8) For reviews, see: (a) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: Oxford, 2002; Chapter 2, p 28. (b) Clayden, J. In *The Chemistry of Organolithium Compounds*; Rapoport Z., Marek, I., Ed.; Wiley: New York, 2004; 495.

(9) See, however: (a) Cram, D. J.; Dicker, I. B.; Lauer, M.; Knobler, C. B.; Trueblood, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7150. (b) Smith, K.; El-Hiti, G. A.; Shukla, A. P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2305. (c) Smith, K.; El-Hiti, G. A.; Hawes, A. C. *Synlett* **1999**, 945. (d) Meigh, J.-P.; Alvarez, M.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2012.

and **12** was observed, the major product being alkylated at the nitrogen closer to the *tert*-butyl group. The regiochemistry of the products **11b**−**g** was assigned on the basis that their CH_AH_BPh groups display diastereotopic signals (due to slow rotation about an Ar−N axis[14]) and confirmed for **11g** by X-ray crystal structure (Figure 2), for **11h** by comparison with an authentic sample of the alternative regioisomer (see Scheme 3), and for **12j** and **12k** by NOE studies. Presumably, the twist in the Ar−N bond imposed by the steric requirements of a substituent in the ortho position prevents delocalization of the anion **13** into the more hindered ring, increasing electron density and reactivity at the nearer nitrogen atom, despite its more crowded environment.

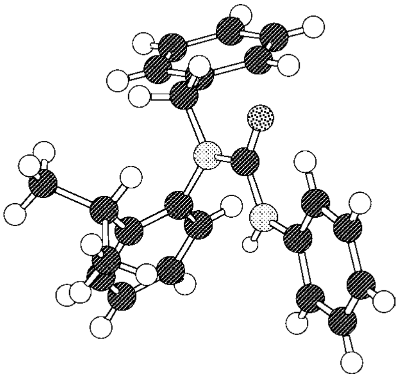
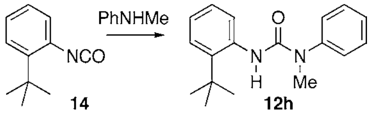


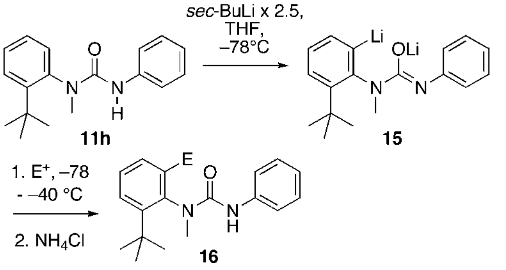
Figure 2. X-ray crystal structure of **11g**.

The alternative N-alkylated regioisomer **12h** was available simply by addition of *N*-methylaniline to isocyanate **14** (Scheme 3). Regioisomers **11h** and **12h** were clearly different by NMR.

Scheme 3. Alternative Regioisomer



Scheme 4. Lithiation of Unsymmetrically Methylated Ureas



With the regioselectively alkylated ureas **11** in hand, we proceeded to study their ortholithiation. Optimum conditions were established by treating **11h** with at least 2 equiv of organolithium base and quenching with an electrophile (Scheme 4 and Table 2) to yield the functionalized ureas **16**. We found that the best yields resulted from lithiating **11h** with 2.5 equiv of *sec*-BuLi in THF at −78 °C and allowing the mixture of dilithiourea **15** and electrophile to warm to −40 °C before aqueous quench of excess base. Other bases (*n*-BuLi, *t*-BuLi, *sec*-BuLi in the presence of TMEDA) generally gave lower yields. A range of electrophiles reacted with **15**, as shown in Table 2, providing ureas **16a**−**g**. In every case, regioselectivity was complete, with the newly introduced electrophile occupying the 6-position on the 2-alkylated ring, the left-hand ring of **16**.[15] No lithiation was observed on the right-hand phenyl ring.

Table 2. Regioselective Ortholithiation

entry	E⁺	E	product **16**	yield of **16** (%)
1	MeI	Me	**16a**	65
2	$BrCH_2CH_2Br$	Br	**16b**	80
3	I_2	I	**16c**	93
4	Me_2S_2	SMe	**16d**	95
5	Me_3SiCl	$SiMe_3$	**16e**	81
6	Me_2NCHO	CHO	**16f**	66
7	PhCHO	CH(OH)Ph	**16g**	83[a]

[a] Product formed as a separable mixture of two diastereoisomeric atropisomers.

Two structural features differentiate the two rings: the ring *tert*-butyl substituent and the *N*-methyl group, and we wanted to know which was governing this remarkable regioselectivity. We therefore made the two isomeric ureas **17a** and **17b** and lithiated them under our optimized conditions, quenching with trimethylsilyl chloride to determine regio-

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(10) Monodeuteration was indicated by a 1/6 decrease in the intergral of the NMe peaks of the ^1H NMR spectrum, but the regioselectivity remains unassigned.

(11) Beak, P.; Reitz, D. B. *Chem. Rev.* **1978**, *78*, 275.

(12) See ref 8 for a discussion.

(13) No diastereotopic signals were seen for **11a** (see ref 14), but we cannot be sure whether this is due to fast Ar−N rotation resulting from the small size of the fluoro substituent or because electronegative F induces a reversal of reactivity in the two monoanion tautomers **13**.

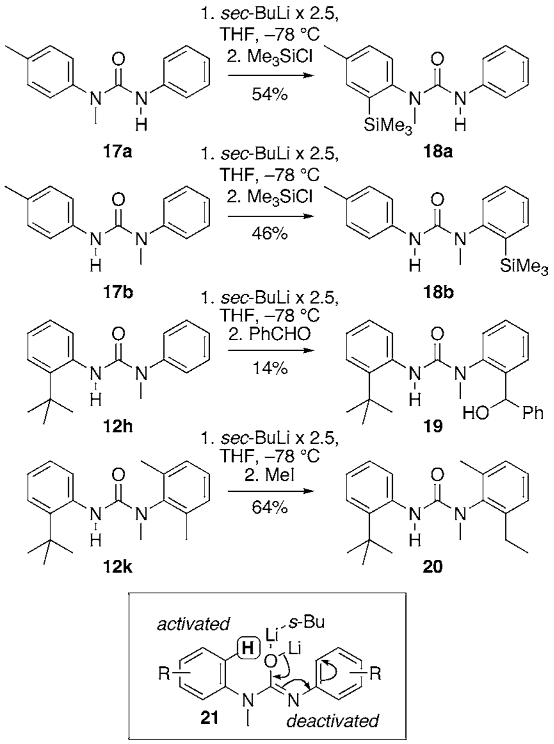
(14) An Ar−N axis rotating slow enough to indicate chirality on the NMR time scale is possible only if the nitrogen is fully substituted and the Ar group is unsymmetrically functionalized (Adler, T.; Bonjoch, J.; Clayden, J.; Font-Bardia, M.; Pickworth, M.; Solans, X.; Solé, D.; Vallverdú, L. *Org. Biomol. Chem.*, in press. These conditions are not met in compounds **12**, which cannot show chirality on the NMR time scale.

(15) Regioselectivity was assigned by analysis of coupling patterns in the aromatic region of the ^1H NMR spectra of **16**, and for **16g** by NOE indicating proximity of N*Me* and PhC*H*. Alcohol **16g** was isolated as two separable diastereoisomers: a future publication will report our observations on atropisomerism in related *N*,*N*′-diarylureas.

(16) Remainder is starting material. Urea **19** exists as an *inseparable* mixture of diastereoisomeric *conformers*. Compare ref 15.

(17) (a) Clark, R. D.; Jahangir, A. *Org. React.* **1995**, *47*, 1. (b) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: Oxford, 2002; Chapter 2.4, p 73. Lateral lithiation of ureas was, to our knowledge, previously unknown.

Scheme 5. Origin of the Regioselectivity



selectivity (Scheme 5). Lithiation took place exclusively on the ring bearing the methylated nitrogen to give **18a** and **18b**, respectively. Moreover, lithiation of **12h** gave, regioselectively, though in very low yield, the alcohol **19** on quenching with benzaldehyde, again indicating lithiation of the ring bearing the methylated nitrogen.[16] Finally, ortholithiation of **12k**, in which the ring bearing the methylated nitrogen has no ortho protons, was attempted: instead of ortholithiation of the other ring, lateral (benzylic) lithiation[17] gave **20** after quenching with methyl iodide. The results presented in Scheme 5 confirm that the presence of an *N*-alkyl group alone is sufficient to direct the regioselectivity of ortholithiation.

Ortholithiation results from a combination of two factors, the "complex-induced proximity effect"[18] offered by electron-rich centers, which delivers the organolithium to nearby C−H bonds, and the acidification of ortho hydrogen atoms (and consequent stabilization of the anion) resulting from inductive electron withdrawal by electronegative atoms.[19] In the generalized intermediate **21**, the lithiourea directing group contains an anionic oxygen atom placed equidistant from both rings, which might equally well direct lithiation of either. However, we propose that delocalization of charge through only the *unsubstituted* nitrogen atom deactivates the adjacent, leading to preferential lithiation adjacent ring to the *N*-alkyl group.

Acknowledgment. We are grateful to the EPSRC, Pfizer, Organon and the EU (Erasmus Program) for support, to Dr. Lyn Jones (Pfizer) and Dr, Elizabeth Moir (Organon) for helpful discussions, and to Dr. Madeleine Helliwell for determining the X-ray crystal structure of **11g**.

Supporting Information Available: Experimental procedures and data for all new compounds; X-ray crystallographic data for **11g** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL0508025

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[18] (a) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. (b) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206.

[19] Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1.