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Dearomatizing Anionic Cyclization of Substituted *N*-Cumyl-*N*-benzylbenzamides on Treatment with LDA: Synthesis of Partially Saturated Substituted Isoindolones

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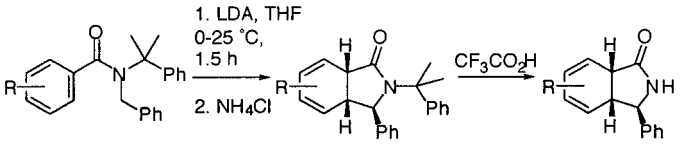
ABSTRACT



On treatment with LDA, substituted *N*-benzylbenzamides (including those bearing electron-withdrawing, electron-donating, or conjugating groups) become lithiated and cyclize to give, after aqueous quench, a range of partially saturated isoindolones as single regio- and stereoisomers. In general, the isoindolones resist rearomatization. Reaction of *N*-cumyl-*N*-benzylbenzamides leads to cyclized products which may be deprotected to give *N*-unsubstituted isoindolones.

LDA can deprotonate tertiary amides and is known to effect ortholithiation,[1] lateral lithiation,[2] or lithiation α to nitrogen[3] according to the amide's substitution pattern. For cases in which the Complex-Induced Proximity Effect[4] (which governs the regioselectivity in kinetic-controlled lithiation) and thermodynamic stability are opposed, LDA favors formation of the most thermodynamically stable organolithium.[5] α-Lithiation can be forced by blocking all alternative positions for deprotonation,[6] but the α position is also the preferred site of lithiation of simple *N*-benzyl amides.[7]

In this paper, we confirm that LDA successfully deprotonates simple *N*-benzylbenzamides, but we report that the product of the deprotonation is unstable at temperatures approaching 0 °C and undergoes a remarkable dearomatizing cyclization reaction. We have previously reported a similar cyclization of simple benzamides[8] and of 1-naphthamides,[9] and we used the *t*-BuLi/HMPA-initiated cyclization of *p*-methoxybenzamide **1b** in a synthesis of (±)-kainic acid.[10] However, the conditions we now report are much milder and more versatile, avoiding the highly basic, toxic, and nucleophilic reagents *t*-BuLi and HMPA. We also now establish that the reaction tolerates a variety of substitution patterns.

N-Benzylbenzamides are readily lithiated by *t*-BuLi α to nitrogen at −78 °C, and we had already noted that HMPA

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(1) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.
(2) Clark, R. D.; Jahangir, A. *Org. React.* **1995**, *47*, 1.
(3) Beak, P.; Reitz, D. B. *Chem. Rev.* **1978**, *78*, 275.
(4) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356.
(5) Court, J. J.; Hlasta, D. J. *Tetrahedron Lett.* **1996**, *37*, 1335.
(6) See, for example: Schlecker, R.; Seebach, D.; Lubosch, W. *Helv. Chim. Acta* **1978**, *61*, 512.
(7) Fraser, R. R.; Boussard, G.; Potescu, I. D.; Whiting, J. J.; Wigfield, Y. Y. *Can. J. Chem.* **1973**, *51*, 1109.
(8) Ahmed, A.; Clayden, J.; Yasin, S. A. *J. Chem. Soc., Chem. Commun.* **1999**, 231.
(9) Ahmed, A.; Clayden, J.; Rowley, M. *J. Chem. Soc., Chem. Commun.* **1998**, 297.
(10) Clayden, J.; Tchabanenko, K. *J. Chem. Soc., Chem. Commun.* **2000**, 317.

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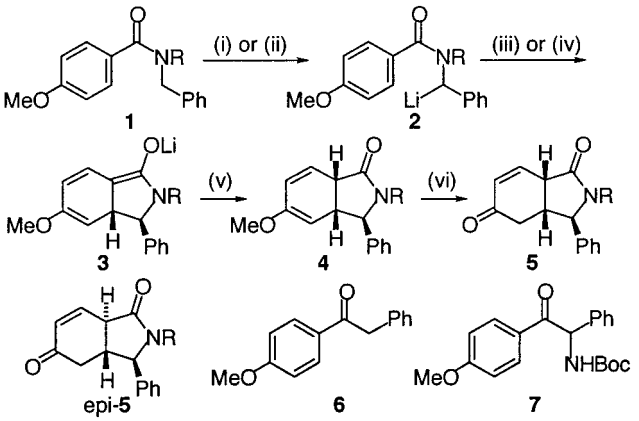
was essential for good yields in the cyclization reaction between −78 and −40 °C.[8] However, we found that by lithiating the benzamide **1a** at −78 °C and then raising the temperature to 0 °C, it was possible to obtain the acid-sensitive cyclized dienyl ether **4a** even without HMPA (Scheme 1, Method A). Mild acid hydrolysis returned the

Scheme 1. Dearomatizing Anionic Cyclization[a]



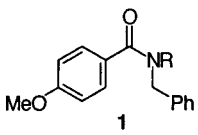
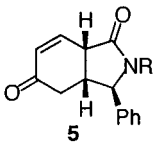
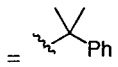
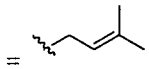
[a] Reagents: (i) *t*-BuLi, −78 °C, THF; (ii) LDA, 0 °C, THF; (iii) −78 to 0 °C, 120 min; (iv) 0 to 20 °C, 90 min; (v) NH_4Cl, H_2O; (vi) HCl, H_2O. Method A = (i), (iii), (v), (vi). Method B = (ii), (iv), (v), (vi).

more readily handled enone **5a** as a single diastereoisomer.[11] Simplifying this procedure, we carried out the lithiation of **1a** at 0 °C with LDA and simply allowed the mixture to warm to 20 °C over 1.5 h (Method B). The enone **5a** was obtained (after an acidic workup) in 73% yield. In both cases, α-lithiation to give **2a** appears to be followed by attack of the organolithium on the aromatic ring, forming an extended enolate **3a** which is protonated on workup.[12]

The reaction is tolerant of other *N*-substituents in place of the *tert*-butyl group (Table 1). Yields of the enones **5b**−**e** were acceptable from the *N*-cumyl-*N*-benzyl amide **1b**, the *N*,*N*-dibenzyl amide **1c** and its *p*-methoxy analogue **1d** (in which only the unsubstituted benzyl group cyclizes),[13] and the *N*-benzyl-*N*-prenyl amide **1e**. Bulky (*tert*-butyl or cumyl) nitrogen substituents appear to be necessary for fully diastereoselective formation of the cyclized products **5**,[14] and out of *tert*-butyl and cumyl, the latter is preferable because it can be removed by acid-catalyzed elimination (see below).[15] We found the *tert*-butyl group to be much harder to remove from the cyclized products.

The *N*-allyl and *N*-Boc amides underwent quite different rearrangement reactions to give ketones **6** and **7**, respectively,

Table 1. Dearomatizing Anionic Cyclizations of *N*,*N*-Dialkylbenzamides

starting material	R =	product, yield (%)[b]
 **1**		 **5**
1 a	*t*-Bu	**5a** 73, 65[a]
1 b	cumyl = 	**5b** 53
1 c	Bn	**5c** + *epi*-**5c** 63 (7:1)
1 d	PMB	**5d** + *epi*-**5d** 63 (7:1)
1 e	prenyl = 	**5e** + *epi*-**5e** 50 (3:1)
1 f	allyl	**6**[c]
1 g	Boc	**7** 86

[a]Using *t*-BuLi (Method A); [b]using LDA (Method B); [c]Sole product in crude reaction mixture (by NMR).

by mechanisms involving nucleophilic attack at their carbonyl groups.[16]

Next, we assessed the scope for modification of the benzamide ring. *N*-Benzylcumylamine **8** was acylated with a range of acid chlorides in parallel using a Carousel Reaction Station (Radleys), giving the amides **9** shown in Table 2. The amides were then treated with LDA in THF at 0 °C, allowed to warm to room temperature over a period of 1.5 h, and quenched with ammonium chloride or ammonium chloride and dilute hydrochloric acid (Scheme 2) The results are shown in Table 2.

The cyclization tolerates electron-withdrawing and electron-donating groups; importantly, the use of LDA allows the cyclization of compounds containing functionality with reactivity toward *t*-BuLi such as cyano and bromo groups (**9h**−**j**). Excellent yields are obtained with the 1- and 2-naphthamide derivatives **9b**,**c**: 2-naphthamides fail to

(11) Relative stereochemistry was assigned by analogy with previous work (refs 8−10), in which structures were determined using a combination of NMR, synthetic, and X-ray crystallographic studies.

(12) The detailed mechanism of the attack on the ring is under investigation but may be regarded as a six-electron electrocyclic ring closure.

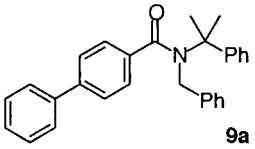
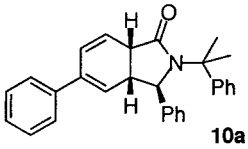
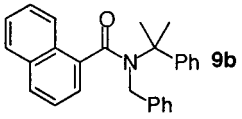
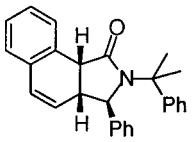
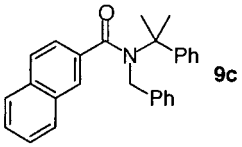
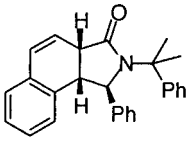
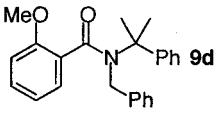
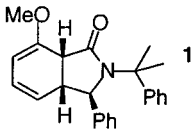
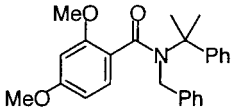
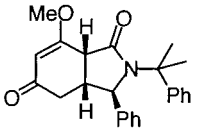
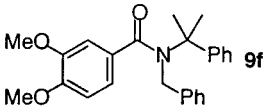
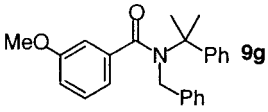
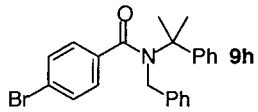
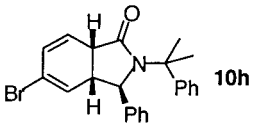
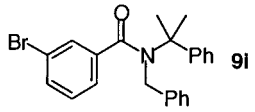
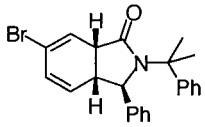
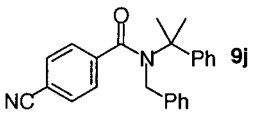
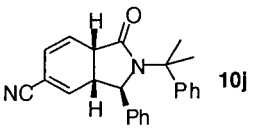
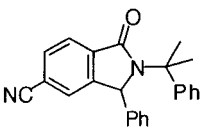
(13) The selectivity presumably arises from destabilisation by the *p*-OMe group of the alternative benzylic organolithium.

(14) The minor diastereoisomer is tentatively assigned the *trans* ring junction from the fact that each pair of **5** and *epi*-**5** have similar $^3J_{HH}$ coupling constants between H-3 and H-3a. Unfortunately, the H-3a to H-7a coupling is not resolved.

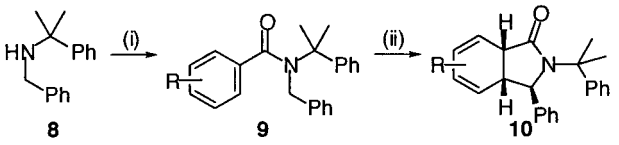
(15) We introduced the cumyl group as an alkyllithium-stable, acid-labile protecting group for our synthesis of (±)-kainic acid (ref 10). Snieckus has independently reported the use of the cumyl group in ortholithiation reactions: see Metallinos, C.; Nerdinger, S.; Snieckus, V. *Org. Lett.* **1999**, *1*, 1183.

(16) The formation of compounds related to **7** by acyl transfer from N to C is known (see Hara, O.; Ito, M.; Hamada, Y. *Tetrahedron Lett.* **1998**, *39*, 5537), but the origin of benzyl phenyl ketone **6** is less obvious. We assume **6** arises by elimination of benzyllithium after lithiation of the allyl group, followed by attack of BnLi inter- or intramolecularly on the amide carbonyl group. We have observed the occasional formation of **6** in lithiations of other *N*-benzylbenzamides bearing two N-substituents prone to metalation (ref 17).

Table 2. Dearomatizing Anionic Cyclizations of Substituted *N*-Cumyl-*N*-benzylbenzamides

starting material	product	Yield %
 **9a**	 **10a**	88
 **9b**	 **10b**	88
 **9c**	 **10c**	98
 **9d**	 **10d**	60
 **9e**	 **10e**	62
 **9f**	–	0
 **9g**	–	0
 **9h**	 **10h**	59
 **9i**	 **10i**	44
 **9j**	 **10j**	20
	 **11**	40

Scheme 2. Dearomatizing Anionic Cyclization of Substituted Benzamides[a]



[a]Reagents: (i) ArCOCl, Et_3N, CH_2Cl_2, 20 °C, 16 h; (ii) LDA, THF, 0-25 °C, 90 min; NH_4Cl, H_2O; (HCl, H_2O).

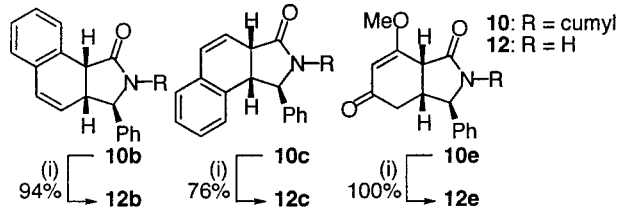
[a] Reagents: (i) ArCOCl, Et_3N, CH_2Cl_2, 20 °C, 16 h; (ii) LDA, THF, 0−25 °C, 90 min; NH_4Cl, H_2O; (HCl, H_2O).

cyclize in good yield with *t*-BuLi because of a competing addition of *t*-BuLi to the 1-position.[17] Substrates which failed to cyclize included those bearing methoxy substituents at the 3-position, **9f**−**g**. Compounds bearing other 3-substituents (**9c** and **9i**) cyclized to give single regioisomers, with the formation of **10c** presumably being under electronic control and the formation of **10i** being under steric control.

Most cyclization products were surprisingly resistant to aromatization in air, although we were unable to prevent significant rearomatization of the product **10j** from cyano-substituted **9j** to give **11**. The aromatization appears to be an oxidation of the enolate intermediate analogous to **3**; oxidation byproducts were occasionally observed in other cyclizations if the enolate was not quenched within 2 h.

Removal of the cumyl group from the partially saturated isoindolones **10** was achieved with strong acid (Scheme 3).[10,15] The amides **10b**, **10c**, and **10e** were heated with

Scheme 3. Removal of the Cumyl Group[a]



[a]Reagent: (i) CF_3CO_2H, CH_2Cl_2, Δ, 3 h.

[a] Reagent: (i) CF_3CO_2H, CH_2Cl_2, Δ, 3 h.

trifluoroacetic acid for 3 h to give the secondary amides **12b**, **12c**, and **12e**[18] in good to excellent yield. The simple route **9** → **10** → **12** constitutes a new and efficient route to a range of functionalized, substituted, and partially saturated isoindolones.

(17) Ahmed, A.; Clayden, J. Unpublished results

(18) The regiochemistry of **10e** and **12e** has not been firmly established. We have tentatively assigned the 5-oxo-7-methoxy (rather than the 5-methoxy-7-oxo) structure to **10e** and **12e** on the basis that the ^1H NMR signals for H-4 and H-3a are almost identical in chemical shift and coupling pattern with those of **5b**.

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Dearomatizing nucleophilic addition to *naphthalene* rings is well-known, both for naphthalene itself[19] and for naphthalenes substituted by electron-withdrawing groups.[20] Compounds in the naphthyloxazoline series have been extensively employed as starting materials for the synthesis of a range of carbocyclic synthetic targets,[21] and our discovery of the dearomatizing cyclization of lithiated amides was based upon an observation in the naphthamide series.[9,22] Dearomatizing nucleophilic addition to *benzene* rings has also been known for some time[23] but usually requires activation by metals or by substituents which are themselves susceptible to nucleophilic attack, limiting the versatility of the method. Nonetheless, the synthesis of carbocyclic and heterocyclic rings by the dearomatization of aromatic precursors allows the regiocontrol available with aromatic compounds to be exploited in the synthesis of saturated and partially saturated targets.[24] Stereocontrolled dearomatization is all the more powerful, and the reaction we report here adds to the number of methods are available for the stereoselective conversion of benzenoid[25] and heterocyclic[26] aromatic compounds to versatile, partially saturated, synthetic intermediates.

Acknowledgment. We are grateful to the EPSRC for a grant.

Supporting Information Available: Experimental details and characterization data for **5a**−**e**, **10a**−**e**, **10h**−**j**, **11**, **12b**, **12c**, and **12e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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