ORGANIC LETTERS

2005
Vol. 7, No. 17
3749−3752

Directed Ortho Lithiation of *N*-Alkylphenylaziridines

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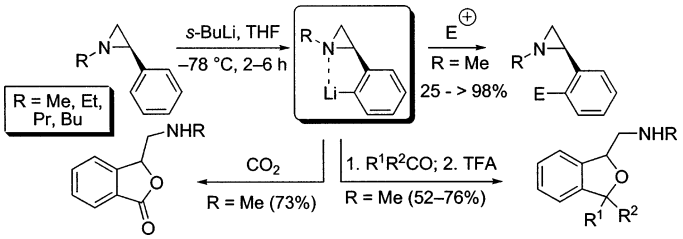
Received June 17, 2005

ABSTRACT



The ortho lithiation–trapping sequence of phenylaziridines is described. This methodology, which counts on the ability of the aziridino group to act as a directed metalation group (DMG), provides an easy access to functionalized arylaziridines as well as to phthalans and phthalides. The importance of the aziridine N-substituent in this DoM reaction is stressed as well.

In the directed ortho metalation (DoM) reaction, a useful strategy for regioselective functionalization of arenes, the directed metalation group (DMG) plays an extremely important role.[1] Substrate coordination capability alone for the metalating agent is in some cases sufficient to allow ortho deprotonation, and, indeed, benzylamines are rapidly ortho lithiated upon treatment with organolithiums.[2] However, good DMGs must have ideal basic properties for the organolithium precomplexation, a good electron-withdrawing effect for a rapid and efficient deprotonation, and a stabilizing ability for the resulting ortho-lithiated species.[3] Mechanisms have been proposed to account for the DoM reaction.[4]

Among the various nitrogen-containing DMGs (carboxamido, *O*- and *N*-carbamate, sulfonamido, oxazolino, imino and alkylamino), aziridino groups have never previously been considered in this capacity, as far as we are aware. This is a surprising omission considering that the aziridino moiety has an electron pair that can be used for the precomplexation of the metalating agent and/or for coordination to the corresponding ortho-lithiated species. The fact that aziridines are amenable to synthetic manipulation makes this even more surprising.

Data from the literature indicate that lithiation of aziridines occurs at the α-position.[5] Indeed, *N*-alkyloxazolinyl- and thiazolylaziridines undergo aziridine ring hydrogen abstraction upon treatment with organolithiums, and the resulting lithiated intermediates can be trapped with electrophiles.[6] Moreover, diastereomeric *N*-sulfonyloxazolinyl phenylaziri-

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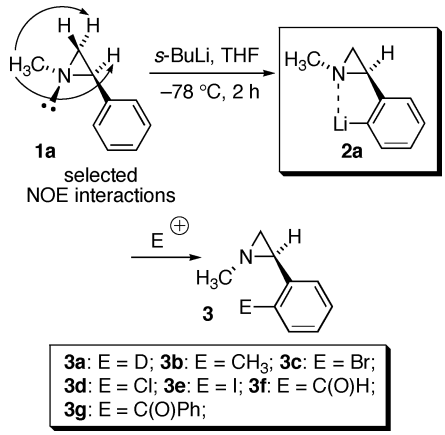
10.1021/ol051412l CCC: $30.25
Published on Web 07/23/2005

dines undergo benzylic deprotonation upon treatment with *s*-BuLi/TMEDA.[7] The N-substituent effect in the lithiation of oxazolinylphenylaziridines has also been investigated.[8] In no case was ortho lithiation observed. In addition, it had been reported that lithiation of *N*-tosylphenylaziridine occurs at the benzylic position and that the resulting lithio derivative adds to the aryl group of the *N*-tosyl substituent with subsequent dearomatization.[9]

Herein, we report for the first time that some *N*-alkyl phenylaziridines can be cleanly and very efficiently ortho lithiated upon treatment with organolithiums. Treatment of aziridine **1a**, which was easily prepared from styrene and $Br_2/Me_2S/MeNH_2$,[10] with *s*-BuLi (1.5 equiv) in THF at −78 °C produced a yellow solution that turned colorless upon quenching with D_2O to furnish *N*-methyl (*ortho*-deuteriophenyl)aziridine **3a** (>98%), with no trace of the α-deuteriophenylaziridine.[11] The ortho-lithiated phenylaziridine **2a** likely intervenes in the conversion of **1a** into **3a** (Scheme 1, Table 1).

Scheme 1



By way of comparison, it is worth noting that styrene oxide[12a,b,e] and derivatives[12c,e] undergo clean α-lithiation and that ortho lithiation competes only in the case of *trans*-stilbene oxides.[12d,e] The lower kinetic acidity of hydrogens α to nitrogen compared with hydrogens α to oxygen may be playing a role.[13] Therefore, we conclude that in the lithiation of **1a**, the *N*-methyl aziridino group acts as an ortho-directing group. This has no literature precedent, although it is known that benzylamines undergo ortho lithiation upon treatment with organolithiums.[2]

Ortho-lithiated phenylaziridine **2a** proved to be extraordinarily stable: once generated at low temperature it could be warmed to room temperature without undergoing any transformation, and addition of D_2O furnished **3a** almost quantitatively. Support of the hypothesis that the aziridine nitrogen coordinates to the ortho-lithiated species **2a** comes from the observation that the aziridine **1a** is configurationally stable[14] and puts the nitrogen lone-pair on the same side of the phenyl group with respect to the N−C bond, as clearly established by two-dimensional NOESY correlations (Scheme 1).

Table 1. Reaction of Ortho-Lithiated Phenylaziridine **2a** with Electrophiles

electrophile	aziridine **3** (% yield)	phthalan **5** (% yield)	dr
D_2O	**3a** (>98)[a,b]		
CH_3I	**3b** (85)[a]		
1,2-dibromoethane	**3c** (63)[a]		
hexachloroethane	**3d** (81)[a]		
I_2	**3e** (80)[c]		
DMF	**3f** (98)[a]		
PhCONMeOMe	**3g** (50)[a,d]		
$(CH_3)_2CO$	**3h**[e]	**5a** (>95)[a]	
CH_3CHO	**3i** (76)[f]	**5b**[g]	50/50[h]
PhCHO	**3j** (47)[f]	**5c** (>95)[f]	60/40[h,i]
Ph_2CO	**3k** (52)[a]	**5d** (>95)[a]	
$CH_3(CH_2)_2COPh$	**3l** (55)[f]	**5e** (>95)[f]	50/50[i,j]
CO_2		**5f** (73)[a]	
$ClCOOCH_2CH_3$	**3m** (25)[f]	**5g** (25)[f]	50/50[h]
$ClCOOCH_3$		**5h** (55)[f]	50/50[h]

[a] Isolated yields. [b] >98% D. [c] Yield calculated by weighing the crude reaction product, after washing it with Et_2O and ^1H NMR analysis; this product tends to decompose very quickly over time. [d] Yield decreases to 26% with DMB. [e] Not isolated. [f] Overall isolated yields in both diastereomers. [g] Aminomethylphthalan **5b** could not be isolated. [h] Inseparable mixture of diastereomers. [i] Relative configuration ascertained as described in ref 15. [j] Diastereomers separated by column chromatography on silica gel (see Supporting Information for details).

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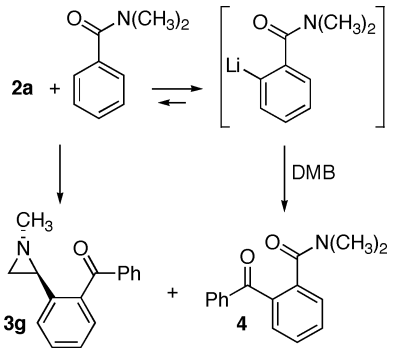
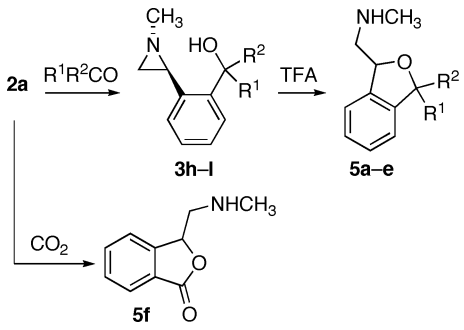
The ortho-directing ability of the aziridino group of **1a** was confirmed by its lithiation and trapping with electrophiles other than D_2O. Addition of MeI to the solution of **2a** provided *ortho*-tolylaziridine **3b** in very good yield, while the reaction with 1,2-dibromoethane, hexachloroethane, I_2, and DMF led to the formation of *ortho*-bromophenylaziridine **3c**, *ortho*-chlorophenylaziridine **3d**, *ortho*-iodophenylaziridine **3e**, and *ortho*-formylphenylaziridine **3f** in very good to excellent yields, respectively (Scheme 1, Table 1). The reaction of **2a** with *N*,*N*-dimethylbenzamide (DMB) gave a chromatographically separable mixture of *ortho*-benzoylphenylaziridine **3g** (26%) and *ortho*-benzoyl-*N*,*N*-dimethylbenzamide **4** (34%), very likely derived from ortho-deprotonated DMB and subsequent debenzoylation of its precursor (Scheme 2). A better yield of **3g** (50%) was obtained when the Weinreb amide (PhCONMeOMe) was used as the benzoylating agent.

Scheme 2



The addition of acetone to **2a** gave the aminomethylphthalan **5a**: the probable intermediate **3h** could not be intercepted. In contrast, the reaction of **2a** with acetaldehyde, benzaldehyde, benzophenone, and butyrophenone furnished aziridinylphenyl carbinols **3i**−**l** as almost 1:1 diastereomeric mixtures (yields ranging from 47 to 76%, see Table 1). However, treatment of carbinols **3j**−**l** in THF with few drops

Scheme 3

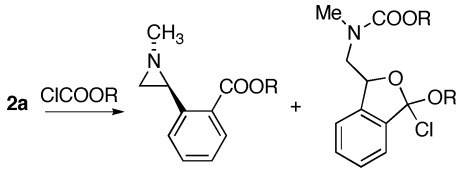


3h,5a: $R_1 = R_2 = CH_3$; **3i,5b**: $R_1 = H$, $R_2 = CH_3$
3j,5c: $R_1 = H$, $R_2 = Ph$; **3k,5d**: $R_1 = R_2 = Ph$;
3l,5e: $R_1 = Ph$, $R_2 = (CH_2)_2CH_3$

of TFA caused cyclization to aminomethylphthalans **5c**−**e** quantitatively,[15] while bubbling CO_2 into the solution of **2a** generated aminomethylphthalide **5f** (Table 1, Scheme 3).

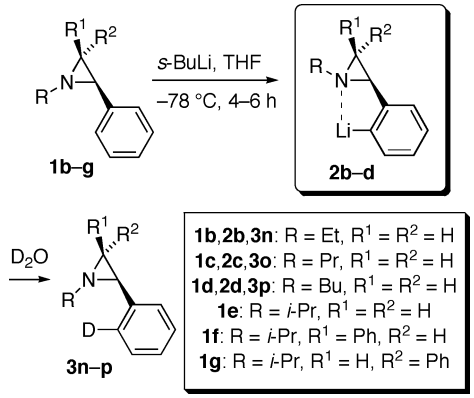
Interestingly, the capture of **2a** with ethyl chloroformate afforded the ethoxycarbonylaziridine **3m** (25%) together with the chloroethoxyphthalan **5g** (25%). The latter was probably formed as a result of a cascade reaction initiated with the nucleophilic addition of **2a** to $ClCO_2C_2H_5$, followed by aziridine ring-opening-promoted phthalan formation, and N-ethoxycarbonylation. It is worth noting that the aziridine ring-opening proceeds much faster than chlorine elimination. Phthalan **5h** (55%) was formed when **2a** was reacted with $ClCO_2CH_3$ (Table 1, Scheme 4).

Scheme 4



To check the importance of the aziridine N-substituent in the aforementioned ortho lithiation, we prepared some other N-alkylaziridines and compared them with the *N*-methyl derivative **1a**. *N*-Ethyl-, *N*-propyl-, and *N*-butylaziridines **1b**−**d** behaved like aziridine **1a** undergoing ortho lithiation with *s*-BuLi to give **2b**−**d** but required a longer reaction time, thus confirming that probably the N-substituent plays an important role in the lithiation process. Quenching with D_2O after 4 h for **1b** and **1c** and after 6 h for **1d**, at −78 °C, furnished ortho-deuterated aziridines **3n**−**p** (98%, >98% D) (Scheme 5).

Scheme 5



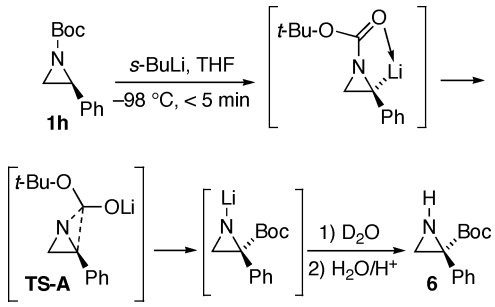
1b,**2b**,**3n**: R = Et, $R^1 = R^2 = H$
1c,**2c**,**3o**: R = Pr, $R^1 = R^2 = H$
1d,**2d**,**3p**: R = Bu, $R^1 = R^2 = H$
1e: R = *i*-Pr, $R^1 = R^2 = H$
1f: R = *i*-Pr, R^1 = Ph, $R^2 = H$
1g: R = *i*-Pr, $R^1 = H$, R^2 = Ph

In contrast, *N*-isopropylaziridine **1e** could not be ortho-lithiated under the conditions that caused lithiation of **1a**−**d**

(15) Relative configuration to aminomethylphthalans **5c** and **5e** could be assigned on the basis of two-dimensional NOESY correlations. In the case of the cis isomers, NOE interactions between the two benzylic-type protons on C1 and C3 were diagnostic of a proximity relationship.

even after a longer reaction time (10 h). No lithiation occurred also when *t*-BuLi was used. One possible explanation for the different behavior between **1e** and **1a**−**d** is that the above ortho lithiation requires a preliminary complexation of *s*-BuLi (or *t*-BuLi) on the nitrogen of the starting aziridine. This probably is not allowed in the case of the sterically hindered aziridine **1e**. For the same reason, *cis*- and *trans*-*N*-isopropyl-2,3-diphenylaziridines **1f** and **1g** were recovered substantially unchanged upon treatment with *s*-BuLi followed by D_2O quenching. We also investigated the lithiation reaction of *N*-Boc-phenylaziridine **1h**.[16] Its treatment with *s*-BuLi, even at short reaction time (less than 5 min), followed by addition of D_2O and aqueous workup gave 2-phenyl-2-Boc-aziridine **6**. This is likely the result of a [1,2] aza-Wittig rearrangement in which α-lithiation followed by Boc group migration from the nitrogen to the α-carbon atom presumably takes place through transition state TS-A (Scheme 6).

Scheme 6



In conclusion, we have discovered that N-substituted phenylaziridines, never studied before as DMGs, undergo smooth ortho lithiation depending upon the steric hindrance of the N-substituent: *N*-methyl- **1a**, *N*-ethyl- **1b**, *N*-propyl- **1c**, and *N*-butylaziridine **1d** undergo ortho lithiation quantitatively, whereas *N*-isopropylphenylaziridine **1e** and *N*-isopropyldiphenylaziridines **1f** and **1g** do not. This seems to suggest that a precomplexation between the aziridine and *s*-BuLi en route to ortho lithiation is necessary for the reaction to occur. This precomplexation could take place with *N*-alkylaziridines **1a**−**d** but not with **1e**−**g**. The involvement of the nitrogen lone pair in the ortho-lithiated intermediate coordination also has to be considered. The ortho lithiation of **1a**−**d** appears to be particularly appealing, as the trapping of **2a**−**d** allows for the regioselective ortho functionalization of phenylaziridines.[17] Moreover, the reactivity of the aziridine ring adds synthetic utility to the ortho-lithiated species **2**. Accordingly, systems such as phthalans and phthalides, interesting classes of compounds owing to their promising pharmacological potential,[18] can be prepared by the above methodology. More work is in progress to this end in our laboratory.

Acknowledgment. This work was carried out under the framework of the National Project "Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni" and the FIRB Project "Progettazione, preparazione e valutazione biologica e farmacologica di nuove molecole organiche quali potenziali farmaci innovativi" supported by the MIUR (Rome), by the University of Bari, and by the Interuniversities Consortium CINMPIS.

Supporting Information Available: Full experimental details and copies of ^1H and ^{13}C NMR spectra for compounds **3a** (S16, S17), **3b**−**g** (S24−S34), **3i**−**m** (S35−S46), **3n**−**p** (S18−S23), **5a** (S47, S48), **5c**−**h** (S49−S62), and **6** (S63, S64). This material is available free of charge via the Internet at http://pubs.acs.org.

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