ORGANIC LETTERS

2007
Vol. 9, No. 17
3295−3298

Regio- and Stereoselective Lithiation of Terminal Oxazolinylaziridines: The Aziridine *N*-Substituent and the Oxazolinyl Group Effect†

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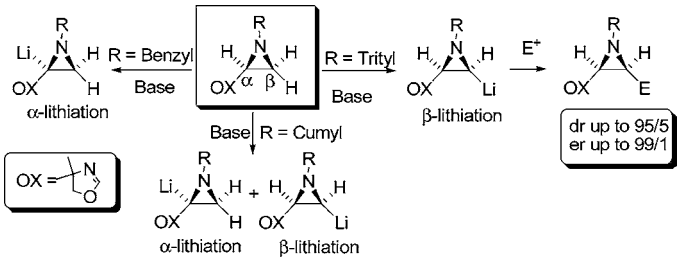
Received May 29, 2007

ABSTRACT



The regioselective lithiation of terminal oxazolinylaziridines has been investigated. The steric hindrance of the nitrogen substituent in 1-trityl-2-oxazolinylaziridine 3a, combined with the coordinating ability of the oxazolinyl group, causes *β*-lithiation, whereas a completely regioselective α-lithiation is observed with the much less sterically demanding 1-benzyl-2-oxazolinylaziridine 3c and a competition between α- and *β*-lithiation occurs with 1-cumyl-2-oxazolinylaziridine 3b in which the *N*-substituent has a steric hindrance in between the trityl and the benzyl groups. The application of the lithiation-trapping sequence for the preparation of enantioenriched 2,3-*cis*-disubstituted oxazolinylaziridines and aziridino-*γ*-lactones is also reported.

Lithiation-induced functionalization of simple and easily available aziridines has become a very useful synthetic strategy for the preparation of more functionalized aziridines and products that can be derived from them.[1]

Regioselectivity of the lithiation reaction of aziridines is dramatically dependent upon the aziridine ring substitution: e.g., 1-alkyl-2-phenyl aziridines are smoothly *ortho*-lithiated, *trans*-1-alkyl-2,3-diphenylaziridines are cleanly α-lithiated, and the corresponding cis isomers are not lithiated at all (Figure 1).[2] Moreover, it occurs that with an electron-withdrawing group (EWG) on one of the aziridine ring atoms, lithiation takes place normally α to that group,[3] whereas with alkyl-substituted terminal aziridines (bearing

† Dedicated to the memory of Professor Yoshihiko Ito of the University of Kyoto for his outstanding contribution in the fields of synthetic and organometallic chemistry.

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10.1021/ol071264u CCC: $37.00
Published on Web 07/26/2007

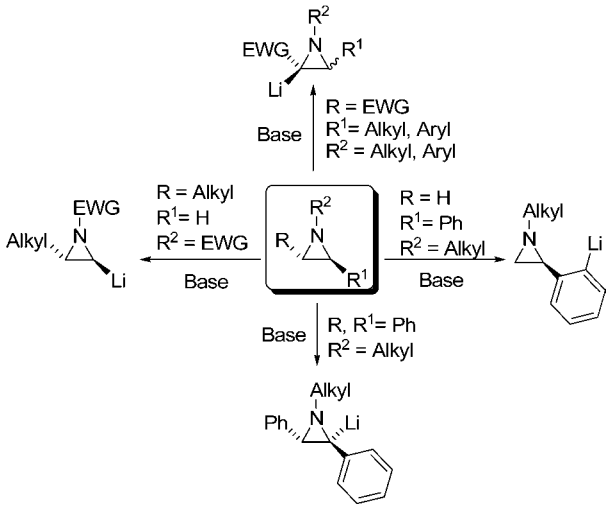
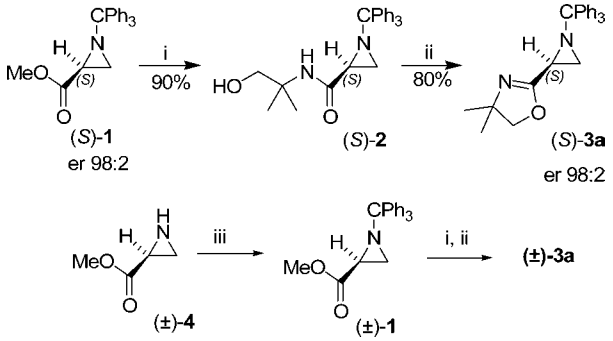


Figure 1. Regioselective lithiation of aziridines: the ring substituents effect.

an EWG on the nitrogen), lithiation takes place at the β-position trans to the alkyl group (Figure 1).[4]

The oxazolinyl group has proven to be an extraordinary good stabilizing group either for oxiranyl or aziridinyl anions.[3a,5] In its presence, lithiation occurs always α to it if there is an α hydrogen; it occurs β only when there is no α hydrogen. We report here the first example of a stereoselective lithiation taking place β to the electron-withdrawing aziridine ring substituent as in the case of 1-trityl-2-oxazolinylaziridine **3a** (Scheme 1).

Scheme 1[a]



[a] Key: i: (a) 2-methyl-2-amino-1-propanol (2.5 equiv); (b) *n*-BuLi (2.2 equiv), toluene, $LaCl_3$, 100 °C. ii: DAST (1 equiv), CH_2Cl_2, −78 °C. iii: Ph_3CBr, NaH, THF, 25 °C.

Optically active 1-trityl-2-oxazolinylaziridine (*S*)-**3a** [enantiomeric ratio (er): 98/2] was prepared from the commercially available (*S*)-1-trityl-2-methoxycarbonyl aziridine **1** (er: 98/2) (Scheme 1) upon treatment with 2-methyl-2-amino-1-propanol and *n*-BuLi in toluene[6] and subsequent reaction of the resulting amide (*S*)-**2** with diethylamino sulfurtrifluoride (DAST),[7] whereas the corresponding racemic aziridine (±)-**3a** was prepared starting from racemic aziridine (±)-**1**, which in turn was obtained from the commercially available methylaziridine-2-carboxylate (±)-**4** upon alkylation with tritylbromide (Scheme 1).[8]

Aziridine (*S*)-**3a** was spectroscopically characterized: dynamic NMR proved that, under the used reaction conditions (THF, −70 °C), (*S*)-**3a** is present as one main invertomer, the one that sets the oxazolinyl and trityl groups trans to each other (Figure 2), as ascertained by NOESY experiments.[9]

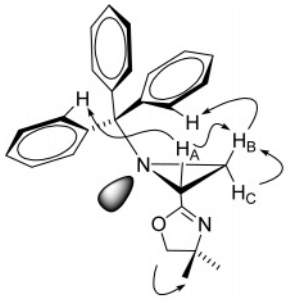


Figure 2. Selective NOEs interactions.

With the aziridine (*S*)-**3a** in hand, we subjected it to deprotonation, making use of strong bases. It was found that the best conditions of deprotonation are: *s*-BuLi (2 equiv), TMEDA (2 equiv), THF, 2h, −70 °C. Under these conditions, the aziridine (*S*)-**3a** gave a deep-red solution likely containing the lithiated species (*S*,*S*)-**3a**-Li, which decolorized upon quenching with excess D_2O; usual workup furnished almost quantitatively 3-deuterio aziridine **5a** (Table 1), as ascertained by ESI-MS and NMR analysis.

It is remarkable that lithiation occurs at the β position cis with respect to the oxazolinyl group although in the presence of the more acidic α hydrogen. This result can be explained with the strong stabilizing effect of the oxazolinyl group[10] which chelates the β-lithiated species (*S*,*S*)-**3a**-Li and the presence of the sterically demanding *N*-trityl group which protects the other two aziridine-ring hydrogens from lithiation by creating a sort of "umbrella" on them. This hypothesis is

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(9) Dynamic ^{1}H NMR experiments performed in THF-d_8 on aziridine **3a** revealed only one set of signals for the aziridine protons in the range 293−195 K.

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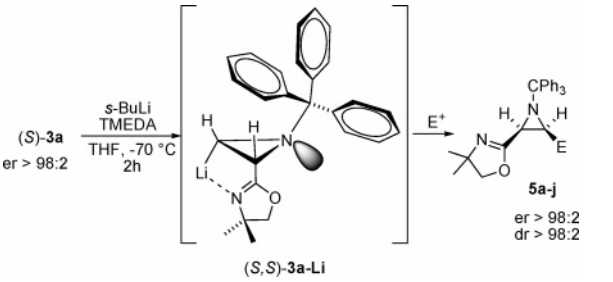
Table 1. Lithiation-Trapping Sequence of Aziridine (*S*)-**3a** with Electrophiles



electrophiles	aziridine **5**	yield (%)[a]	er
D_2O	**5a**	90	–[b]
Me_3SiCl	**5b**	70	–[b]
MeI	**5c**	75	>99:1[c]
BnBr	**5d**	55	>99:1[c]
Bu_3SnCl	**5e**	75	>99:1[c]
Allyl Me_2SiCl	**5f**	70	>99:1[c]
EtI	**5g**	60	–[b]
AllylBr	**5h**	66	–[b]
PhCON(Me)OMe	**5i**	70	–[b]
PhSSPh	**5j**	50	>99:1[c]

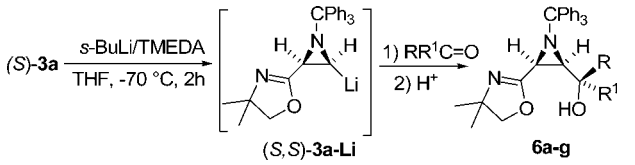
[a] Isolated yields. [b] Enantiomeric ratio not determined. [c] Enantiomeric ratio established by HPLC analysis on Chiracel OD−H or by ^{1}H NMR (see Supporting Information).

supported by the evidence that *cis*-2-(oxazolin-2-yl)-3-trimethylsilyl-1-tritylaziridine **5b**, prepared by capturing (*S*,*S*)-**3a**-Li with Me_3SiCl, could be neither β- nor α-lithiated under varied conditions (*s*-BuLi, *t*-BuLi, MeLi). Therefore, the lithiation-deuteration sequence carried out on (*S*)-**3a** proceeds regio and stereospecifically affording the aziridine **5a**. The role of the oxazolinyl group for the above-described regio- and stereoselectivity seems to be crucial as its precursor, the 1-trityl-2-methoxycarbonyl aziridine **1**, undergoes addition to the ester functionality upon treatment with *s*-BuLi or LDA.

The synthetic utility of lithiated aziridine (*S*,*S*)-**3a**-Li was then checked by its trapping with several electrophiles. Reactions with halides (MeI, Bu_3SnCl, Me_3SiCl, AllylMe_2-SiCl, AllylBr, EtI, BnBr) and other electrophiles led to the formation of highly enantiomerically enriched *cis*-2,3-disubstituted aziridines **5b**−**j** in good yields (Table 1): in all cases a $S_E$ret mechanism is likely to occur.[11] It might be useful to point out that while lithiation/trapping of a terminal aziridine such as (*S*)-**3a** leads to *cis*-configured oxazolinyl-aziridines, the reported lithiation/trapping of terminal *N*-*tert*-butylsulfonyl-2-alkylaziridines leads to *trans*-configured aziridines.[4]

The reaction of (*S*,*S*)-**3a**-Li, with carbonyl compounds (aldehydes and ketones) was successively studied. In all cases, the reactions with aldehydes proceeded with very high diastereoselectivity at the newly created stereocentre, as determined by an ^{1}H NMR analysis, to give hydroxyalkyl-aziridines **6b**−**f**, whereas very poor or no diastereoselectivity was observed with acetophenone to give **6g** (Table 2).[12]

Table 2. Lithiation-Trapping Sequence of Aziridine (*S*)-**3a** with Carbonyl Compounds

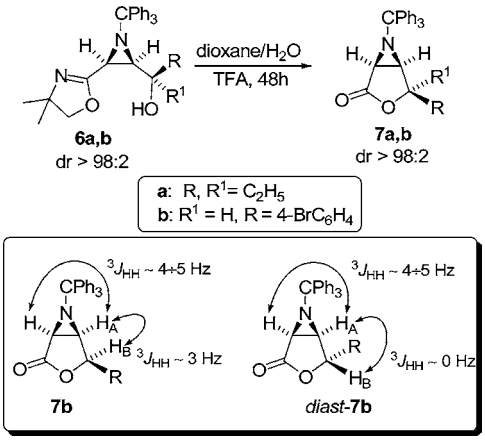


R	R^1	aziridine **6**	yield (%)[a]	dr[b]	er
Et	Et	**6a**	60	–	–[d]
4-BrC_6H_4	H	**6b**	80	90/10	> 99:1[c]
Ph	H	**6c**	80	90/10	> 99:1[c]
4-$MeOC_6H_4$	H	**6d**	70	95/5	–[d]
2-Furyl	H	**6e**	70	90/10	–[d]
t-Bu	H	**6f**	75	75/25	> 99 :1[c]
Ph	Me	**6g**	50	50/50	–[d,e]

[a] Isolated yields. [b] Diastereomeric ratio (dr) calculated on the basis of ^{1}H NMR spectrum of the crude reaction mixture. [c] Enantiomeric ratio established by HPLC analysis on a Chiracel OD−H column or by ^{1}H NMR (see Supporting Information). [d] Enantiomeric ratio not determined. [e] Stereochemistry not established for the two diastereomers.

Interestingly, treatment of racemic aziridines **6a**,**b** with trifluoroacetic acid (TFA) in dioxane/water at r.t. for 48 h resulted in the formation of 2,3-aziridino-γ-lactones **7a**,**b**, which are useful buiding blocks in the synthesis of analogues of L-glutamic acid, an important neurotransmitter of the central nervous system (Scheme 2).

Scheme 2

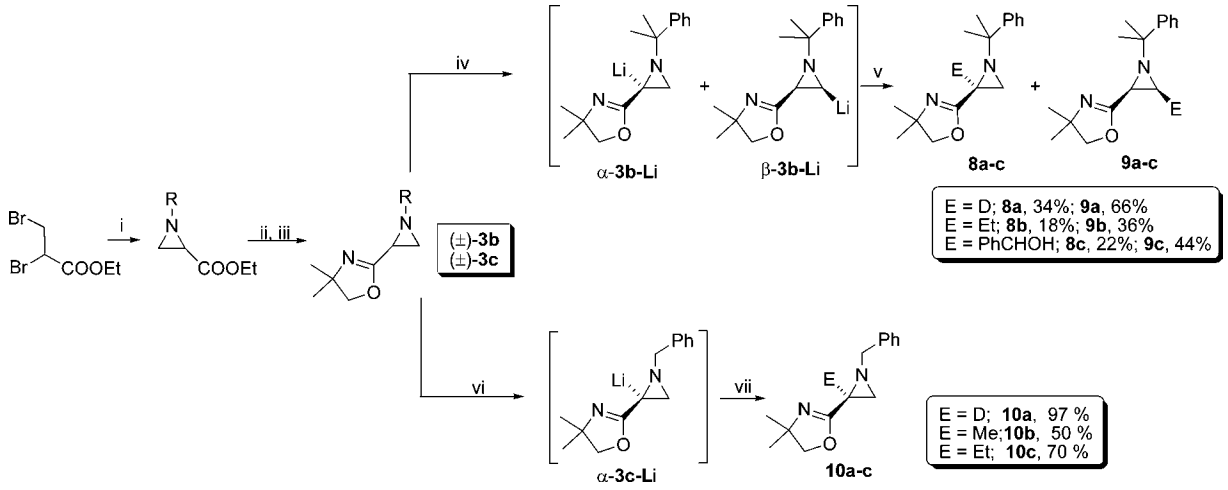


Stereochemistry of **7b** was determined by comparing the two vicinal coupling constant values found between H_A and H_B (see Scheme 2) for the two diastereomers **7b** and *diast*-

(11) The cis stereochemistry to aziridines **5** and **6** was assigned on the basis of the $^3J_{HH}$ coupling constants between the two aziridinyl protons ranging from 5.5 to 7.0 Hz, (see Supporting Information); see also: Yonezawa, T.; Morishima, I. *J. Mol. Spectrom*. **1968**, *27*, 210−217.

(12) In two cases (**6a** and **6b**), the configuration of the major diastereomer was unambiguously determined by further conversion into **7a**,**b** whose stereochemistry was deduced by NMR analysis (vide infra).

Scheme 3[a]



[a] Key: i: RNH_2, EtOH, Et_3N; ii: (a) 2-methyl-2-amino-1-propanol (2.5 equiv); (b) *n*-BuLi (2.2 equiv), toluene, $LaCl_3$. iii: Et_2NSF_3 (1 equiv), CH_2Cl_2, −98 °C (**3b**: R = $PhC(CH_3)_2$, 35%; **3c**: R = $PhCH_2$, 40%). iv: *s*-BuLi/TMEDA, 2h, THF −98 °C. v: Electrophile (D_2O, EtI, PhCHO). vi: *n*-BuLi, THF, 2h, −98 °C. vii: Electrophile (D_2O, MeI, EtI).

7b, as similarly reported for 2,3-aziridino-γ-lactones of the same configuration.[13]

For the sake of comparison and to get more insight about the role of the nitrogen substituent with reference to the steric demand, *N*-cumyl- and *N*-benzyl oxazolinylaziridines (±)-**3b** and (±)-**3c**[14] were prepared, as reported in Scheme 3, and investigated.

A competition between α and β lithiation (with respect to the oxazolinyl ring) occurred with the *N*-cumylaziridine (±)-**3b** as proved by the trapping of the lithiated intermediates α-**3b**-Li and β-**3b**-Li with D_2O, PhCHO, and EtI (Scheme 3). A careful examination of the ^{1}H NMR spectrum of the crude obtained in the deuteration reaction revealed that the α/β ratio (**8a**/**9a**, 94% D both) was 1:2 being the β product the most favored one. The same preference for the β product was observed in the reaction with EtI (**8b**/**9b** = 1/2) and with PhCHO (**8c**/**9c** = 1/2).[15]

Interestingly, the *n*-BuLi mediated lithiation of *N*-benzyl-oxazolinylaziridine (±)-**3c** occurred exclusively at the α position and the corresponding intermediate α-**3c**-Li could be trapped with electrophiles to furnish 2,2-disubstituted aziridines **10a**−**c**.[16]

In summary, 1-alkyl-2-oxazolinylaziridines undergo smooth α- and/or β-lithiation depending upon the steric demand of the nitrogen substituent, thus giving access to *cis*-configured 2,3-disubstituted and 2,2-disubstituted aziridines. It is quite remarkable that, for steric reasons, 1-trityl-2-oxazolinylaziridine **3a** undergoes exclusive β-lithiation despite the presence of a much more acidic hydrogen at the α-position, whereas 1-benzyl-2-oxazolinyaziridine **3c** gives only α-lithiation. The utility of the reported methodology resides in the stereoselectivity of the reaction of configurationally stable β-lithiated intermediates and also in the fact that the oxazolinyl group is amenable to synthetic eleboration as shown in the preparation of 2,3-aziridino-γ-lactones **7**. Further investigation will focus on the synthetic application of the above lithiated aziridines.

Acknowledgment. This work was carried out under the framework of the National Project "Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni" and supported by the University of Bari.

Supporting Information Available: Experimental procedures and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org

OL071264U

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(15) Compounds **8b** and **9b** were isolated in 18 and 36% yield, respectively. The reaction with PhCHO gave **8c** in 22% yield as 1:1 mixture of diastereomers and **9c** in 44% yield as a single diastereomer whose stereochemistry, at the newly created stereogenic centre, has not been determined yet.

(16) Compound **10a** was obtained with 97% of deuterium incorporation; compounds **10b** (50% yield) and **10c** (70% yield) show two slowly equilibrating invertomers in the ^{1}H NMR spectra.