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Practical preparation and substitution of configurationally stable aziridinyl ester anions

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Abstract

Configurationally and chemically stable aziridine carboxylate anions have been generated. These intermediates are stable at −78°C for several hours and react with electrophiles with good to excellent retention of configuration.

Chiral non-racemic aziridines are known to be useful electrophilic synthetic intermediates, mainly because of their regio- and stereoselective ring-opening reactions.[1] However, very limited work on the use of aziridinyl anions as configurationally stable nucleophilic species has so far been published, despite their obvious potential for asymmetric synthesis.[2] For example, practical generation and handling of anionic aziridine-esters would be of particular interest for the elaboration of functionalized α- or β-quaternary amino acid derivatives.[3] This problem was studied by Seebach and co-workers, who reported that all attempts to deprotonate an aziridine ester led to degradation and/or self-condensation of these reactive species.[4] However, these authors were able to prepare several aziridine thiolesters which could be functionalized at a very low temperature (−100°C) with retention of configuration for compound **1** and moderate d.s. (33–60%) for its diastereomer **2** (Scheme 1). To our knowledge, no practical use of this strategy for the elaboration of quaternary aziridine-esters has been reported since these pioneering works, probably because of the low chemical and, in some cases, configurational stability of such reactive species.

The practical preparation of 'non-stabilized' metalated aziridines was recently studied by Vedejs and co-workers. They showed that these compounds could be obtained by direct lithiation after nitrogen complexation with borane,[2c] or by a tin–lithium exchange.[2b] In the latter case, a beneficial role of a neighboring methoxymethyl (MOM) group in this exchange was observed.

With respect to these results, and in continuation of our work on the use of (*R*)-phenylglycinol as the source of chirality and nitrogen,[5] we investigated the deprotonation and functionalization of

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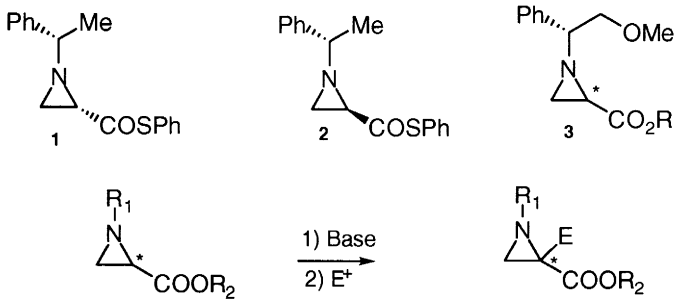
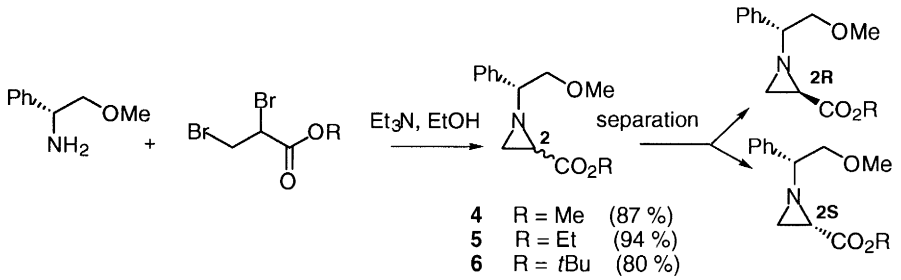


Scheme 1.

aziridine esters of type **3**, with the expectation that the methoxyl group could improve the chemical and configurational stability of the reactive species (Scheme 1).[6]

Several aziridine esters **4**–**6** were prepared, according to a reported procedure.[7] All the diastereomers could be separated by column chromatography (Scheme 2).



Scheme 2.

As expected, deprotonation of the compounds **4**–**6** proved to be troublesome. Among all the bases tested (NaH, LiHMDS, KHMDS, *t*-BuLi, LDA) only LDA (in THF) appeared to be the appropriate reagent for completion of deprotonation. Of the aziridine esters prepared, *t*-butyl ester **6** (2*S*) proved to be a suitable substrate for our study (Table 1),[8] whereas aziridines **4** and **5** bearing less hindered esters led only to self-condensation.

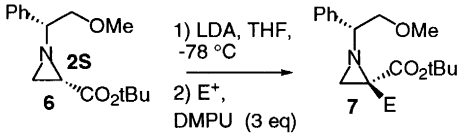


Table 1

E^+	yield (%) (b) (without DMPU)	Yield (%) (b) (with DMPU)	d.r. (%) (a)	Product
$(CH_3)_3SiCl$	37	41	> 98/2	**7a (2R)**
CH_3I	47	59	> 98/2	**7b (2S)**
$CH_2=CHCH_2Br$	44	64	> 98/2	**7c (2S)**
$BrCH_2CO_2tBu$	-	54	> 98/2	**7d (2S)**
$BrCH_2Ph$	-	28	> 98/2	**7e (2S)**

(a) Determined by ^1H NMR spectroscopy of the crude reaction mixture.
(b) yields of isolated product.

The *t*-butyl ester **6** (2*S*) could be deprotonated by LDA in THF and reacted with various halides at −78°C. The use of DMPU as a cosolvent led to an improvement in chemical yields, but was not essential, in contrast with previous observations on aziridine carbothioates anions.[4] In all the cases only one diastereomer could be detected by ^{1}H and ^{13}C NMR. Retention of configuration was demonstrated by chemical correlation of aziridine **7e** with (*S*)-α-benzylserine after ester hydrolysis, ring opening with $HClO_4$ and hydrogenolysis.[9]

We then turned our attention toward the functionalization of compound **6** (2*R*). Under the same conditions (LDA, THF, −78°C), only self-condensation was observed. Since intramolecular stabilization appeared to be ineffective with this compound, we tried to stabilize the highly reactive lithiated intermediate by intermolecular chelation. The use of TMEDA (3 equiv.) as a cosolvent led to the allyl compound **7c** when using allyl bromide as electrophile, but in a moderate yield (39%) and only 88/12 d.r. In contrast, in a 5:1 mixture of DME:Et_2O, aziridine **6** (2*R*) could be deprotonated and reacted with halides in a moderate yield but with good to excellent retention of configuration (Table 2).[10]

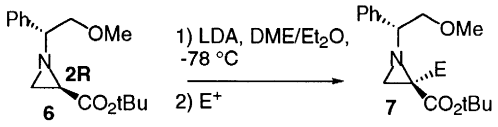


Table 2

E^+	yield (%) (a)	d.r. (%) (b)	Product
$(CH_3)_3SiCl$	38 (c)	89/11	**7a (2S)**
CH_3I	48	98/2	**7b (2R)**
CH_2=$CHCH_2Br$	49	94/6	**7c (2R)**
$BrCH_2CO_2tBu$	30	95/5	**7d (2R)**

(a) Isolated yields of diastereomerically pure compounds. 15-20 % of self-condensation product is observed in the crude reaction mixture.
(b) Determined by ^{1}H NMR spectroscopy of the crude reaction mixture.
(c) Diastereomers could not be separated

These results constitute a large improvement of the configurational stability observed in the analogous thiolester series.[11]

In conclusion, we were able to generate configurationally and chemically stable aziridine carboxylate anions. These intermediates are stable at −78°C for several hours and react with halides with good to excellent retention of configuration. The origin of chemical and configurational stability of such species is under investigation and will be reported in due course.

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8. Absolute configuration of **6** (2*S*) was assigned by chemical correlation of **6** (2*R*) with D-serine by ester hydrolysis, ring opening with $HClO_4$ and hydrogenolysis. $[\alpha]_D$=+7.7 (c=2.45, H_2O) lit.: +7 (c=1, H_2O) Watanabe, K. A.; Falco, E. A.; Fox, J. J. *J. Org. Chem.* **1972**, *37*, 1198–1201.
9. $[\alpha]_D$=+16 (c=1.1, H_2O) lit.: +16.4 (c=0.81, H_2O) Horikawa, M.; Nakajima, T.; Ohfune, Y. *Synlett* **1997**, 253–254.
10. Invertomers were noticed in ^1H NMR spectra of the quaternary aziridines derived from compound **6** (2*R*). This phenomenon helped us to evaluate inversion free energy for these compounds to be about 16–17 kcal/mol (T=333 K, DMSO) by classical NMR experiments.
11. Typical procedures for alkylation of compound **6** (2*S*): **With DMPU**: To a solution of aziridine **6** (2*S*) (150 mg, 0.54 mmol) in dry THF (10 mL) at −78°C under argon atmosphere was added LDA (1.5 M in cyclohexane, 722 μL, 1.08 mmol). After 1 h, the electrophile (1.62 mmol) and the DMPU (196 μL, 1.62 mmol) were consecutively added. The reaction mixture was maintained at −78°C for 7 h and then quenched with saturated aqueous NH_4Cl solution (5 mL). The cooling bath was removed, the solution was allowed to warm to room temperature and diluted with ether (5 mL). The aqueous layer was separated and extracted with two 10 mL portions of CH_2Cl_2, and the combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude reaction product was purified by flash chromatography on silica gel to give the pure alkylated aziridines as colorless oils. **Without DMPU**: To a solution of aziridine **6** (2*S*) (140 mg, 0.50 mmol) in dry THF (10 mL) at −78°C under argon atmosphere was added LDA (1.5 M in cyclohexane, 674 μL, 1.01 mmol) via cannula. After 1 h, the electrophile (1.52 mmol) was added. The reaction mixture was maintained at −78°C for 7 h and then quenched with saturated aqueous Na_2CO_3 solution (5 mL). The cooling bath was removed, the solution was allowed to warm to room temperature and diluted with EtOAc (5 mL). The aqueous layer was separated and extracted with two 10 mL portions of CH_2Cl_2, and the combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude reaction product was purified by flash chromatography on silica gel to give the pure alkylated aziridines as colorless oils.
    Typical procedures for alkylation of compound **6** (2*R*): To a solution of aziridine **6** (2*R*) (140 mg, 0.50 mmol) in a mixture of dry DME (5 mL) and Et_2O (1 mL) at −78°C under argon atmosphere was added LDA (1.5 M in cyclohexane, 674 μL, 1.01 mmol). After stirring for 15 min, the electrophile (1.52 mmol) was added. The reaction mixture was maintained at −78°C for 2 h and then quenched with saturated aqueous Na_2CO_3 solution (5 mL). The cooling bath was removed, the solution was allowed to warm to room temperature and diluted with EtOAc (5 mL). The aqueous layer was separated and extracted with two 10 mL portions of CH_2Cl_2, and the combined organic phases were dried over Na_2SO_4, filtered and concentrated. The crude reaction product was purified by flash chromatography on silica gel to give the pure alkylated aziridines as colorless oils and about 15–20% of self-condensation product.