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Addition Reactions of Iodomethyllithium to Imines. A Direct and Efficient Synthesis of Aziridines and Enantiopure Amino Aziridines

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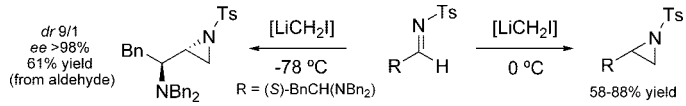
ABSTRACT



An efficient and general synthesis of aziridines by the reaction of imines derived from *p*-toluenesulfonamides with in situ generated iodomethyllithium, with a simple and rapid experimental protocol, is reported for the first time. The reaction with the chiral aldimine derived from phenylalaninal allowed access to (2*R*,1′*S*)-2-(1′-aminoalkyl)aziridine with very high diastereoselectivity, in enantiopure form. A mechanism to explain this novel reaction is proposed.

Organolithium reagents are probably the most popular organometallic compounds in contemporary organic synthesis.[1] Moreover, functionalized organolithium compounds are especially useful to transfer functionality in a single synthetic operation.[2] However, some functionalized organolithium compounds are unstable. For example, halomethyllithium compounds decompose through an α-elimination process at temperatures as low as −100 °C.[3] To carry out the reaction of halomethyllithium reagents with electrophiles, these anions must be generated in situ, generally by treatment of dihalomethane with methyllithium at −78 °C.[4] In this way, reactions of halomethyllithium with various electrophiles have been reported.[5] However, the in situ generated halomethyllithium reagents did not react with poorly electrophilic reagents. Thus,

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a general method for the addition of halomethyllithium to imines has not been published to date, despite the fact that this reaction would afford aziridines, which present important synthetic applications[6] and biological activity.[7] Due to their important applications, several methods to transform imines into aziridines through methylene transfer using sulfur ylides[8] or α-halogenated organometallic reagents derived from other metals[8g,9] have been reported. In addition, aziridines could be also obtained by the nucleophilic addition reaction of various nucleophiles (hydride, cyanide, Grignard reagents, etc.) to α-chloroimines.[10] In general, the reported methods required long reaction times, and in some cases, the yields were low.

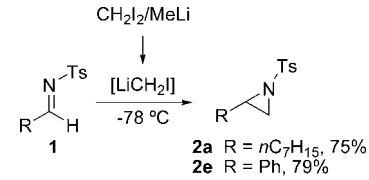
In this context, to the best of our knowledge, only one example of an aziridine ring has been reported through the reaction of in situ generated chloromethyllithium and a specific imine derived from 2-pyridinecarboxaldehyde. The authors stated in their report that the presence of the 2-pyridineimine moiety is a necessary requirement for the successful aziridination, and no reaction with other imines such as those derived from benzaldehyde took place.[11] In addition, the removal of the N-substituent or the ring opening of this aziridine with various nucleophiles could not be performed. Even more important is the preparation of enantiopure aziridines. However, the synthesis of aziridines in enantiopure form from chiral aldimines and halomethyllithium has not been reported to date. On these premises, the development of a general and novel method to obtain a range of structurally diverse and enantiopure aziridines, through the addition of halomethyllithium to imines, would be desirable.

In this communication, we describe our preliminary results concerning a novel and simple method to efficiently prepare aziridines **2** by reaction of imines, derived from *p*-toluenesulfonamide, with in situ generated iodomethyllithium, in which the experimental protocol is simple and rapid. The chiral version has also been developed on the enantiopure α-dibenzylaminoaldimine derived from phenylalaninal affording the corresponding (2*R*,1′*S*)-2-(1′-aminoalkyl)aziridine **7** in enantiopure form with high diastereoselectivity and in good yield.

Synthesis of Aziridines Derived from Sulfonamides 2. Initial attempts to prepare aziridines were performed on imines derived from *p*-methoxyphenylamine and octanal or benzaldehyde using conditions similar to those previously described by Reetz;[12] however, no addition of iodomethyllithium took place under various reaction conditions, and the starting imines were recovered unchanged.

This lack of reactivity could be overcome when using imines with a more electrophilic C═N bond. Thus, we prepared imines derived from *p*-toluenesulfonamide and octanal or benzaldehyde (**1a** and **1e**), following a method previously reported.[13] The reaction of **1a** and **1e** with iodomethyllithium at low temperature (−78 °C) for 30 min and additional stirring at room temperature for 30 min afforded the corresponding aziridines **2a** and **2e** in 75 and 79% yield, respectively (Scheme 1).

Scheme 1. Aziridination of Aldimines **1**



The same reactions were performed utilizing chloromethyllithium (generated from chloroiodomethane) instead of iodomethyllithium, obtaining in this case the corresponding aziridines in yields about 10% lower. On the basis of these results and taking into account that diiodomethane is cheaper than chloroiodomethane, further reactions were performed employing iodomethyllithium. In addition, other reaction conditions for the optimization of the aziridination reaction were tested. The best results were obtained by treating a solution of 1.5 equiv of diiodomethane and 1 equiv of the imine in THF with 1.2 equiv of MeLi at 0 °C for 30 min and further stirring at room temperature for an additional 30 min. Under these reaction conditions, the aziridines shown in Table 1 were obtained.

As can be observed in Table 1, the reaction seems to be

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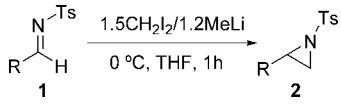
Table 1. Aziridination of Aldimines

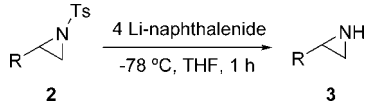


entry	2	R	yield (%)[a]
1	**2a**	nC_7H_{15}	80
2	**2b**	*sec*Bu	71[b]
3	**2c**	Cy	87
4	**2d**	$PhCH_2$	58
5	**2e**	Ph	88

[a] Isolated yield after flash chromatography based on compound **1**. [b] Obtained as an inseparable mixture of diastereoisomers.

general, and linear, branched, and cyclic aliphatic or aromatic aldimines could be used as the starting material, affording the corresponding aziridines in good to high yields (>71%), except when using the imine derived from the easily enolizable phenylacetaldehyde. However, it is noteworthy that, in general, organolithium compounds cannot be added to phenylacetaldehyde or to its derivatives since the lithium reagent is hydrolyzed under these conditions to give the corresponding lithium enolate.The N-substituent on aziridines **2** could be easily removed by using lithium naphthalenide, following a method previously reported, but with modifications of the isolation and purification technique for the deprotected aziridines[14] since the previously described purification by column chromatography afforded poor yields of deprotected aziridines **3**. These poor yields are in disagreement with the good purity observed on the crude reaction, [^{1}H (300 MHz) and ^{13}C (75 MHz) NMR]. Therefore, we tested other isolation and purification methods. The best yields of pure compounds **3** were obtained performing an acid−base treatment of the crude reaction products (Table 2).

Table 2. Deprotection of *N*-Tosyl Aziridines



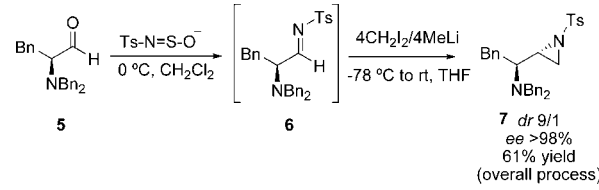
entry	3	R	yield (%)[a]
1	**3a**	nC_7H_{15}	62
2	**3c**	Cy	65
3	**3d**	$PhCH_2$	75

[a] Isolated yield after column chromatography based on compound **2**.

Synthesis of Enantiopure 2-(1-Dibenzylaminoalkyl)aziridines.[15] Given the synthetic utility of optically active *syn*-aminoaziridines,[5i,16] we performed the aziridination reaction described above, utilizing enantiopure aldimine **6** derived from *N*,*N*-dibenzyl phenylalaninal, with the goal of synthesizing the *anti*-aminoaziridine (diastereoisomer of that previously reported by us).[5i] The synthesis of similar *anti*-aminoaziridines with moderate diastereoselectivity has been reported by the reaction of sulfur ylides with chiral amino aldimines (from anisidine instead of *p*-toluenesulfonamide).[12]

The required aminoimine **6** was prepared by the Weinreb procedure,[17] but it could not be isolated due to its instability. Therefore, the reaction with iodomethyllithium was carried out on the crude aminoimine, rendering aminoaziridine **7** in 61% overall yield for the two transformations (from **5** to **7**) (Scheme 2). After testing several reaction conditions, the best

Scheme 2. Synthesis of (2*S*,1′*S*)-2-(1-Aminoalkyl)aziridine **7**



result was obtained by treating a solution of crude aminoimine **6** in THF with 4.0 equiv of diiodomethane and 4.0 equiv of MeLi at −78 °C for 2 h.[18] After hydrolysis and usual workup, crude aminoaziridine **7** was obtained in 79% yield. Purification by conventional column chromatography afforded the expected pure aminoaziridine **7** in lower yield (42% yield), which disagrees with the good purity observed in the crude reaction material (^{1}H and ^{13}C NMR). The yield of the pure aziridine **7** was increased by avoiding the hydrolysis step and directly purifying the crude material by column chromatography.

The high stereoselectivity of the addition reaction of iodomethyllithium (dr 9/1, Scheme 2) was determined, on the crude reaction products, by 300 MHz ^{1}H NMR. It is noteworthy that the previously reported synthesis of (2*R*,1′*S*)-2-(1′-dibenzylamino-2′-phenylethyl)-1-(4-methoxyphenyl)aziridine by reaction of the corresponding α-aminoaldimine with dimethylsulfonium methylide took place with lower stereoselectivity (dr 4/1).[12]

In general terms, it is noteworthy that this reported method for the synthesis of aziridines **2** and **7** is experimentally simple, the reaction time is short, and it takes place with

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(15) (a) Previously, we reported the synthesis of nonactivated enantiopure *syn*-aminoalkyl aziridines by reduction of α-amino ketimines derived from 1-aminoalkyl chloromethyl ketones. See ref 5i. (b) Reetz et al reported the synthesis of nonactivated enantiopure *anti*-aminoalkyl aziridines. See ref 12.

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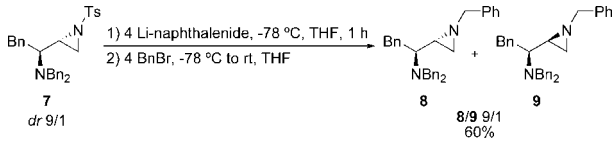
(17) Sisko, J.; Weinreb, S. M. *J. Org. Chem.* **1990**, *55*, 393–395.

(18) An excess of iodomethyllithium was necessary due to the presence of *N*-tosylamine in the mixture reaction, as a consequence of the *N*-sulfinyl-*p*-toluenesulfonamide required for the synthesis of aldimines **6**, which is purchased from TCI with a purity ∼70%.

high stereoselectivity. The structure and absolute configuration of the aziridine ring was unambiguously established through a deprotection/benzylation protocol of compound **7** (Scheme 3).

Scheme 3. Deprotection/Benzylation of Compound **7**



7 *dr* 9/1 — **8** — **9**; **8**/**9** 9/1, 60%

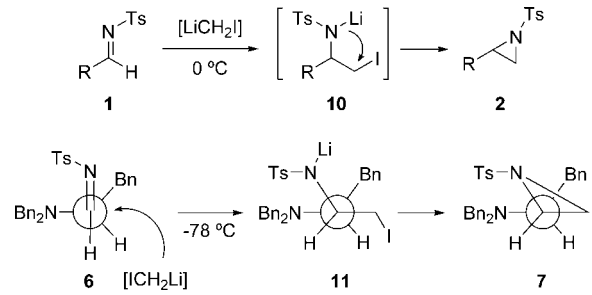
^{1}H and ^{13}C NMR of the minor product **9** was consistent with the aminoaziridine previously reported by us and synthesized via the reduction and further heterocyclization of the corresponding chloromethyl ketimine derived from phenylalanine.[5i] Consequently, we deduced that the absolute configuration of the major stereoisomer **8** was 2*R*. The assigned structure for compound **8** was corroborated by its spectroscopic data.

Finally, the enantiomeric purity of **7** was evaluated by chiral HPLC. To carry out this analysis, a racemic mixture of **7** was previously prepared from racemic phenylalaninal. The chiral HPLC analysis of this racemic mixture allowed the discovery of the best conditions to separate both enantiomers. These conditions were used to analyze the obtained aziridine **7** and showed an enantiomeric purity >98%. This fact excluded a partial racemization of the starting phenylalaninal **5** during its transformation into **7**.

The synthesis of aziridines can be explained by assuming the addition reaction of iodomethyllithium to the imine group generating an iodated lithium amide **10** or **11**, which spontaneously undergoes a heterocyclization to afford the corresponding aziridines **2** or **7**, respectively (Scheme 4).

In this process, the addition of iodomethyllithium to aminoimine **6** takes place under nonchelation control which can be explained assuming that the energetically more favored transition state has the larger substituent (*N*,*N*-dibenzylamino group) *anti* to the attack of the iodomethyllithium (Scheme 4). The same stereochemical course was

Scheme 4. Mechanism of the Aziridination Process



established to explain the reduction of chloromethyl ketones[5h] or chloromethyl ketimines.[15a] In addition, the stereochemistry of aziridine **7** was also in agreement with the *anti* epoxides obtained by treatment of α-aminoaldehydes **5** with iodomethyllithium, previously described.[5h]

In conclusion, an efficient aziridination process by reaction of imines derived from *p*-toluenesulfonamides with in situ generated iodomethyllithium is reported. The reaction with the aldimine derived from phenylalaninal afforded the corresponding enantiopure (2*R*,1′*S*)-2-(1′-aminoalkyl)aziridine with very high diastereoselectivity. Generalization of this reaction and studies to fully delineate all the factors involved in these transformations are currently under investigation in our laboratory.

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Supporting Information Available: General, general procedures, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds **1**−**3** and **7**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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