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Intramolecular PhI═O Mediated Copper-Catalyzed Aziridination of Unsaturated Sulfamates: A New Direct Access to Polysubstituted Amines from Simple Homoallylic Alcohols

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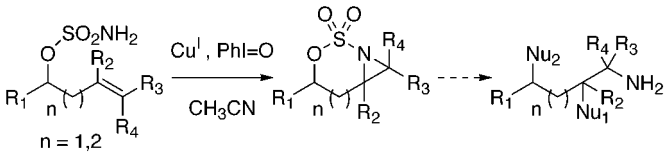
ABSTRACT



Olefinic sulfamates derived from primary and secondary alcohols undergo intramolecular copper-catalyzed aziridination in the presence of iodosylbenzene to afford novel bicyclic fused aziridines. The latter were opened by various nucleophiles to give the corresponding substituted cyclic sulfamates, which in turn reacted, after nitrogen activation, with a second nucleophile at the carbon atom bearing the oxygen atom. Concomitant removal of the sulfonyloxy moiety thus gave access to polysubstituted amines.

Since its discovery in the early 1990s,[1] the copper-catalyzed aziridination of olefins has been applied to the total synthesis of natural and/or biologically active compounds, albeit in a restricted number of cases.[2] Given the simplicity of this nitrene transfer onto olefins, such a limited interest could appear paradoxical. In this context and in order to increase the scope of this reaction, we have recently found new iminoiodinanes useful for this process,[3] and in particular, we have developed an intramolecular version of the copper-catalyzed aziridination.[3c] The efficiency of the latter was improved by the discovery of a one-pot procedure mediated by iodosylbenzene,[4] allowing access to substituted cyclic sulfonamides with potential biological activity. However, since the SO_2-N moiety is only rarely found in nature,[5] this intramolecular process appears to be of very limited usefulness for the total synthesis of natural products.

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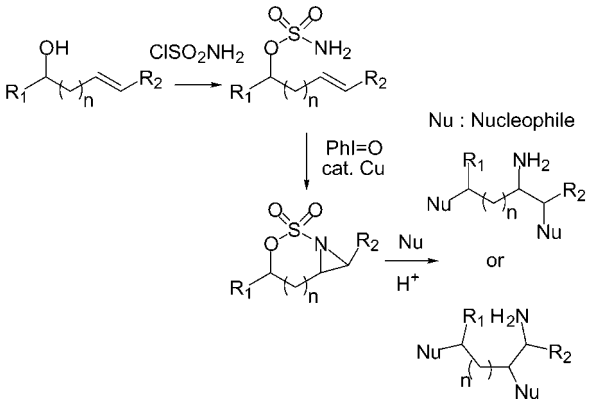
Accordingly, we felt it necessary to find a procedure which would permit removal of the undesired sulfonyl moiety. To this end, the application of the intramolecular copper-catalyzed aziridination to unsaturated sulfamates was considered (Scheme 1). Thus, in addition to both electrophilic

Scheme 1

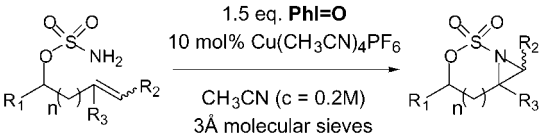


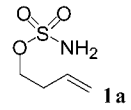
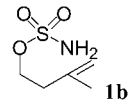
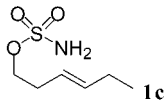
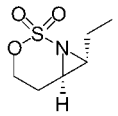
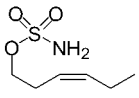
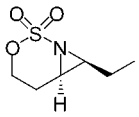
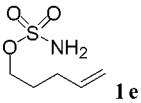
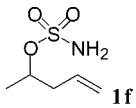
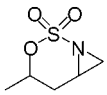
carbon atoms of the expected aziridines, a third center, i.e., the carbon atom bearing the oxygen functionality, could theoretically react with a nucleophile. The resulting displacement would then lead to formation of a sulfamate salt, which could be easily removed by acidic hydrolysis. Therefore, starting from unsaturated alcohols, the preparation of polysubstituted amines could be envisaged.

During the course of our investigations, several publications appeared in which the use of cyclic sulfamidates for the preparation of modified amino acids was described.[6] These studies all rely on a single regioselective nucleophilic ring opening of the cyclic sulfamidates. By comparison, our strategy should in principle pave the way to the development of a more versatile methodology. In this context, we describe our preliminary results in this field and, in particular, report *the selective introduction of nucleophiles onto these new ambident synthons*.

The starting unsaturated sulfamates **1a**−**f** were prepared from the corresponding primary or secondary alcohols by reaction with an in situ generated sulfamoyl chloride[7] using a recently described sulfamoylation reaction.[8] Yields were generally very good, typically in the 80−95% range. These unsaturated sulfamates are stable at room temperature and were stored for several weeks at 4 °C without notable decomposition. Compounds **1a**−**f** were then engaged in a direct intramolecular copper-catalyzed aziridination mediated by iodosylbenzene.[4] Results are summarized in Table 1.[9]

Table 1. Intramolecular Copper-Catalyzed Reactions



substrate	% yield[a]	product
 **1a**	**2a** : 69	
 **1b**	**2b** : 53	
 **1c**	**2c** : 94	
 **1d**	**2d** : 80	
 **1e**	**2e** : 50	
 **1f**	**2f** : 72	

[a] Isolated yield after flash chromatography.

The one-pot procedure appeared to be more efficient than the classical two-step procedure involving isolation of the intermediate iminoiodinane. In this case, the sulfamates **1a**,**b** gave the corresponding aziridines **2a**,**b** in yields that never exceeded 40% compared to 69 and 53% yields, respectively, for the one-pot procedure. The reaction was best run under moderately dilute conditions (concn = 0.2 M), and the aziridines were isolated in acceptable to very good yields in all cases.[10] Interestingly, the product isolated from substrate **1e** stands in sharp contrast to the C−H insertion product obtained from the analogous sulfonamide.[3c] The reaction is also stereospecific with respect to the alkene geometry; trans- and cis-aziridines **2c**,**d** were prepared respectively from trans- and cis-sulfamates **1c**,**d**. However, no diastereoselectivity was observed in the case of compound **1f** since the reaction afforded the corresponding aziridine **2f** in a 1:1 cis/trans ratio (C-4/C-6 relative stereochemistry).

We next turned our attention to the study of the electrophilic reactivity of these new types of heterocyclic structures particularly with respect to any possible regioselectivity of

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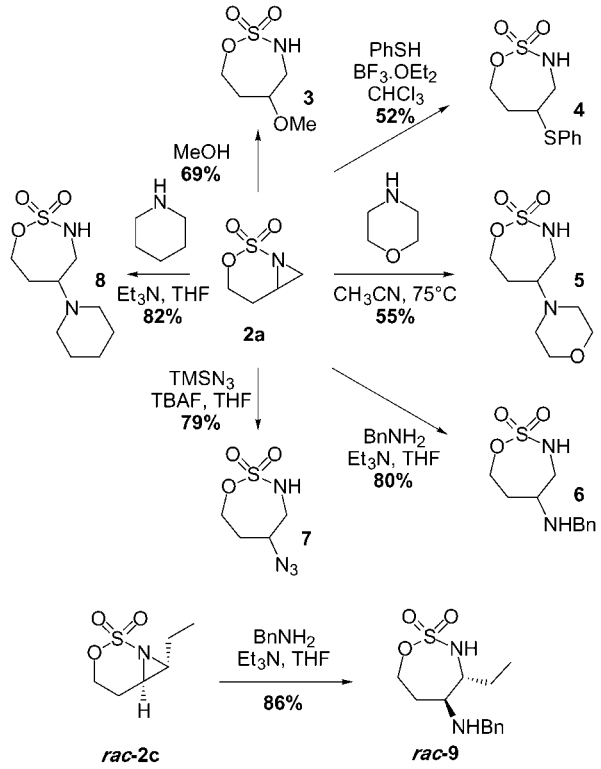
(9) See Supporting Information for typical aziridination procedures.

(10) Application of the intramolecular aziridination to the stable sulfamate derived from an allyl alcohol surprisingly did not give any traces of product. This could be related to the high strain of the expected bicyclic compound.

ring-opening. As previously observed with the aziridines derived from sulfonamides, we were pleased to find that reaction of **2a** with different types of nucleophiles (methanol, thiophenol, morpholine, benzylamine, trimethylsilyl azide, and piperidine) afforded in good yields the seven-membered ring products **3**−**8** resulting from opening of the aziridine at the more substituted site (Scheme 2). The structure of the

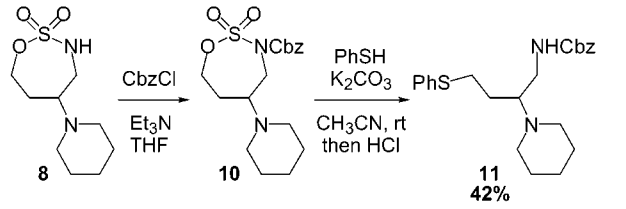
Scheme 2



seven-membered ring sulfamates was unambiguously determined by 2D NMR experiments. No other products could be detected by TLC or ^{1}H NMR analyses of the crude reaction mixture. More interestingly, only monosubstituted compounds were isolated even in the presence of excess nucleophile as was the case with methanol, thiophenol, and morpholine. The same result and, particularly, regioselectivity were observed when aziridine **2c** reacted with benzylamine. Nucleophilic attack occurred at the same position as before as indicated by the HMBC spectrum of product **9**.

This regioselective aziridine ring-opening reaction then afforded the opportunity to introduce a second nucleophile by reaction at the carbon atom bearing the sulfamate function. While nucleophilic ring openings of five-membered[6a,11] and, more rarely, six-membered[6b,c,12] cyclic sulfamidates have been reported, there are apparently no examples of such reactions of seven-membered cyclic sulfamidates. We presumed that the reactivity of the latter should be weaker than that of their lower homologues. On this basis, we decided to increase the electrophilic character of the sulfamidate by introducing an electron-withdrawing group on the nitrogen atom. Inspired by the report from Du Bois,[6c] compound **8** was transformed into its N−Cbz analogue **10**, which in turn was reacted with thiophenol under basic conditions. Acidic workup of the reaction mixture gave the expected diamino product **11** in an unoptimized 42% yield over two steps (Scheme 3).

Scheme 3



In conclusion, intramolecular copper-catalyzed aziridination applied to unsaturated sulfamates derived from primary and secondary alcohols allows access to new types of heterocycles. Their electrophilic reactivity can be controlled such that two different nucleophiles can be introduced selectively and consecutively, while the sulfonyloxy moiety is easily removed at the end of the reaction sequence. Application of this strategy to the total synthesis of natural products is currently under investigation.

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Supporting Information Available: Experimental details and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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