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Ring opening of aziridines by aromatic thiols followed by amino-substitution

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Abstract—Ring opening of 2-aziridinecarboxylic acid methyl ester by a number of aromatic thiols under solvent-free and non-catalytic conditions resulted in bis-arylsulfanyl propanoic acid esters.

Aziridines have attracted considerable attention as starting materials in numerous applications and a number of papers dealing with synthesis of aziridines[1] as well as the use of aziridines in synthetic applications have been published.[2–4] In ring-opening reactions, it is common either to perform the reactions employing Lewis acid catalysis[5–7] or to activate the aziridines by substitution on the nitrogen,[2,8] thus increasing the ability of the nitrogen to function as a leaving group. It has been shown by Stamm and co-workers that in order to carry out the reaction on non-activated aziridines, and in the absence of a catalyst, it is imperative that the nucleophile supplies a proton in order to create a neutral leaving group.[9] In our studies, we have been focusing on the synthesis of mexiletine derivatives (Fig. 1)[10,11] by ring-opening reactions under non-catalytic conditions and without activating the aziridine.

The reaction is somewhat limited with regard to nucleophilic reactivity as there seems to exist a delicate balance between the basicity of the amine and the acidity of the nucleophile; if the nucleophile is too acidic, the aziridine polymerizes and if the nucleophile is not acidic enough no reaction takes place. However, aromatic thiols have proven excellent in this respect even though their acidity is much higher than that of other substrates that do not attack even at elevated temperatures (e.g., phenols and anilines). This is not surprising in view of sulfur being a good nucleophile, and reactions proceed smoothly at ambient temperature in the absence of solvent.

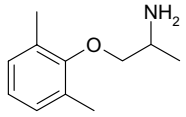
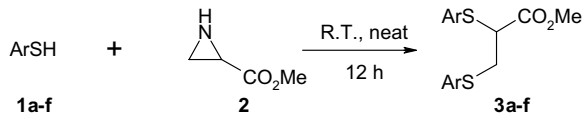


Figure 1. Mexiletine.

However, to our surprise, ring opening of **2** by benzenethiol revealed unreacted aziridine while all of the benzenethiol had been consumed. As in other similar reactions, disulfides were found in the reaction mixture but not in amounts that would explain the consumption of thiol. (Purging the reaction vessel with argon suppressed the amount of disulfide produced without complete removal.) Addition of more thiol resulted in a compound lacking the amine moiety and instead, two molecules of thiol had been inserted into the substrate (Scheme 1).[12] This was also confirmed by X-ray analysis of **3c** (Fig. 2).

A similar reaction was described earlier for *N*-tosyl-2-phenylaziridine which was alkylated by two molecules of benzene, in the presence of a Lewis acid, followed by amine expulsion.[13]

Since only traces of the monosubstituted compound were occasionally found in the crude reaction mixture,



1a-f **2** **3a-f**

Scheme 1.

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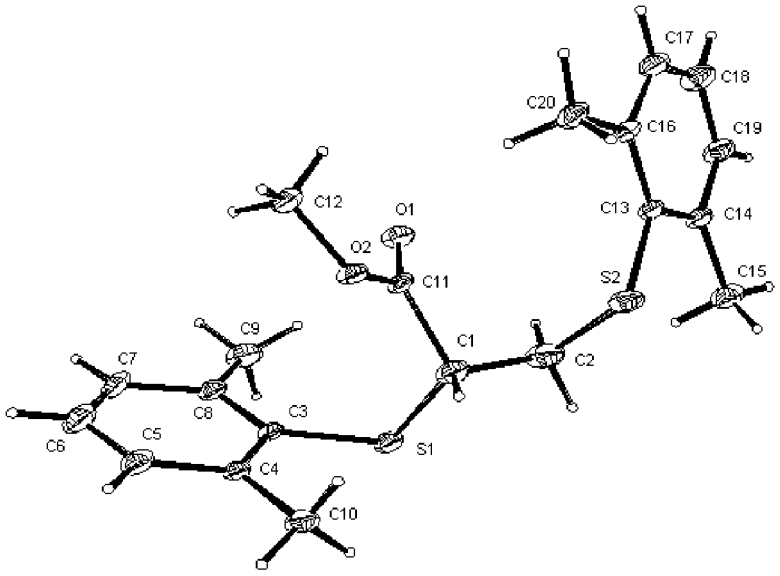
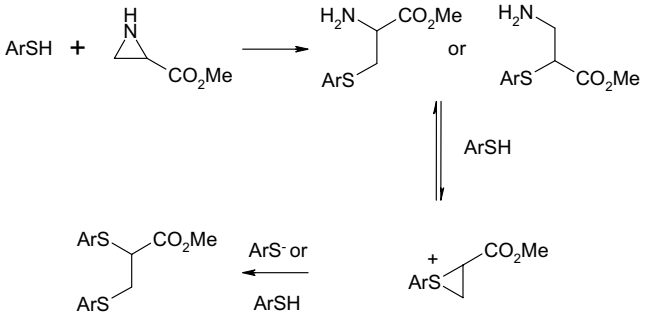


Figure 2. ORTEP drawing of 2,3-bis-(2,6-dimethylphenylsulfanyl)propanoic acid methyl ester **3c**.



Scheme 2.

Table 1. Ring openings of aziridine **2**

Entry	Nucleophile	Isolated yields (%)
3a	Benzenethiol	94
3b	4-Methylbenzenethiol	84
3c[a]	2,6-Dimethylbenzenethiol	46
3d	3-Methoxybenzenethiol	79
3e	2-Naphthalenethiol	54
3f	1,2-Benzenedithiol	57

[a] Structure confirmed by X-ray analysis (Fig. 2).

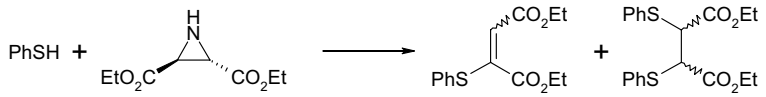
the conclusion must be that the product formed from the initial attack by thiol reacts much faster than the starting aziridine. This could be due to the higher basicity of the amine formed and/or to anchimeric assistance from an intermediate episulfonium ion (Scheme 2).

The latter agrees well with the results of Concellón and co-workers who described a similar reaction when ring-opening amino aziridines with thiols under Lewis acidic conditions.[14] In these reactions, attack only at the least hindered position was observed, and assuming that the bulk of the substituent is similar in our studies, it was not considered necessary to reinvestigate the regio- or stereochemical outcome of the reaction.

In order to further investigate the scope and limitations of the reaction, other thiols were examined. This revealed that a variety of aromatic thiols exhibited the same reactivity, for example, sterically hindered thiols with substituents in the 2- or 2,6-positions, including 2-naphthylthiol, or thiols substituted in the 3- or 4-positions (Table 1).

Similar products have been obtained from the reaction between organic disulfides and ethyl acrylate using ruthenium catalysis,[15] by reacting 1,3-dichloropropene oxide with benzenethiol,[16] or reaction between α-bromoacrylates and benzenethiol.[17] An investigation of a number of phenols and anilines only resulted in isolation of the starting materials even if reaction temperatures were raised to 160 °C. The results were also negative for any alkanols, alkylamines and alkylthiols. Since the second nucleophilic attack by thiol seemed favourable, it was decided to investigate whether two sulfur atoms as part of the same carbon skeleton in the nucleophile would result in 1,4-dithiine carboxylic acid esters. There are a few known compounds of this type, for example, the substituted benzo-1,4-dithiazines published by Parham et al.[18] The reaction between 1,2-benzenedithiol and **2** was very exothermic and GC analysis revealed that the reaction was completed in less than 5 min with the expected benzo-1,4-dithiine carboxylic acid methyl ester isolated in 57% yield. Encouraged by this, 2-aminobenzenethiol was also employed under the same reaction conditions, but the expected product was only detected by GC–MS. Conversely 1,2-ethylene dithiol reacted readily if the temperature was raised to 90 °C, but a complex mixture of compounds was detected after solvent removal and the reaction was not pursued further.

The only nucleophile that reacted with 2,3-aziridinedicarboxylic acid diethyl ester, having two strongly electron-withdrawing substituents, was benzenethiol. The



Scheme 3.

reaction temperature had to be raised to 160 °C for 24 h in order for any reaction to occur and as with the earlier substrate no amine-containing compounds were produced. Instead, a mixture of 2-phenylsulfanyl fumaric acid diethyl ester, 2-phenylsulfanyl maleic acid diethyl ester and meso and racemic 2,3-bis-(phenylsulfanyl)succinic acid diethyl esters was produced in low yield (~5 % of each), indicating the limitations of the reaction (Scheme 3).

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Supplementary data

Supplementary data (experimental details and analytical data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.03.150.

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12. General procedure: The starting materials, aziridine (1.1 mmol) and arylthiol (2.2 mmol), except for **1f** (1.1 mmol), were mixed in an ampoule which was flushed with argon, sealed, and then left at room temperature for 10–14 h. The products were purified by flash column chromatography on silica gel using heptane/diethyl ether (97:3) or heptane/ethyl acetate. Compound **3c** was isolated as white crystals (180 mg, 46%) Mp: 76.5–78 °C (from diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$): 7.18–7.05 (m, 6H), 3.56 (s, 3H), 3.44 (dd, 1H, $J =$ 3.6, 11.2 Hz), 3.29 (dd, 1H, $J = 11.4$, 13.4 Hz), 2.96 (dd, 1H, $J = 3.4$, 13.0 Hz), 2.46 (s, 6H), 2.39 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): 171.2, 143.6, 143.0, 131.8, 130.9, 129.2, 128.5, 128.28, 128.26, 52.2, 49.5, 35.8, 21.9, 21.8; MS (*m*/*z*): 360 (4), 225 (5), 224 (10), 223 (77), 163 (7), 151 (9), 149 (9), 139 (8), 138 (18), 137 (100), 136 (6), 135 (12), 134 (6), 121 (7), 105 (17), 103 (9), 93 (9), 91 (22), 78 (5), 77 (12), 65 (5), 59 (6), 55 (8), 45 (27); IR (film) ν_{max} 3052, 2955, 2363, 2338, 1733, 1458. Anal. Calcd for $C_{20}H_{24}O_2S_2$: C, 66.63; H, 6.71; S, 17.79%. Found: C, 66.4; H, 6.5; S, 18.2%. The X-ray structure of **3c** CCDC 279186 has been deposited at the Cambridge Crystallographic Data Centre.
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