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The conversion of an aziridine plus a phenyl-substituted amine oxide or aminoether to a benzodiazepine derivative☆

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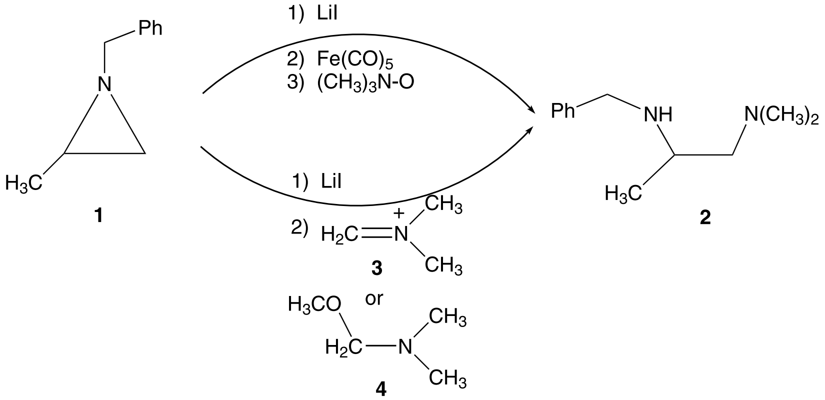
Abstract—The conversion of an aziridine to a tetrahydrobenzodiazepine derivative using LiI, an iron carbonyl complex, and an amine oxide, or using LiI and a *gem*-aminoether is studied. The reaction of an aziridine with LiI and a phenyl-substituted iminium salt generates mainly a 1,2-diamine. The addition of *t*-butoxide to the iminium reaction changes the product ratio leading to a diamine as the minor product and a benzodiazepine as the major product. The structure proof of the tetrahydrobenzodiazepine derivative and the mechanism of these transformations are discussed.

Because 1,2-diamines, also known as vicinal diamines, are biologically and medically important compounds, starting materials in organic synthesis, chiral auxiliaries, and chiral ligands to a variety of metal complexes,[1–5] as shown in Scheme 1, initially we studied the conversion of an aziridine (**1**) to a 1,2-diamine (**2**) using LiI, an iron carbonyl complex, and an amine oxide.[6] More recently, we have studied the conversion of an aziridine to a 1,2-diamine using LiI, and an iminium salt (**3**) or a *gem*-aminoether (**4**).[7] We have extended these reactions to a large variety of aziridines, and alkyl-substituted amine oxides, iminium salts, and aminoethers. Our conversions, unlike others in the literature,[1,8–16] do not require an electron-withdrawing group on the nitrogen, a strong nucleophile, or formation of an aziridinium ion.

However, as shown in Scheme 2, when using the iron carbonyl reaction and a phenyl substituted amine oxide, we obtained exclusively a new product (45% yield) and none of the expected diamine. When using aminoether **6**, again none of the diamine is generated and only the new product is formed (31% yield). In contrast, when using a phenyl-substituted iminium salt,



Scheme 1.

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an inseparable product mixture is obtained consisting of a compound which has tentatively been identified as the expected diamine and the new product. As we will discuss below, the unexpected new product is tetrahydrobenzodiazepine derivative **5**.

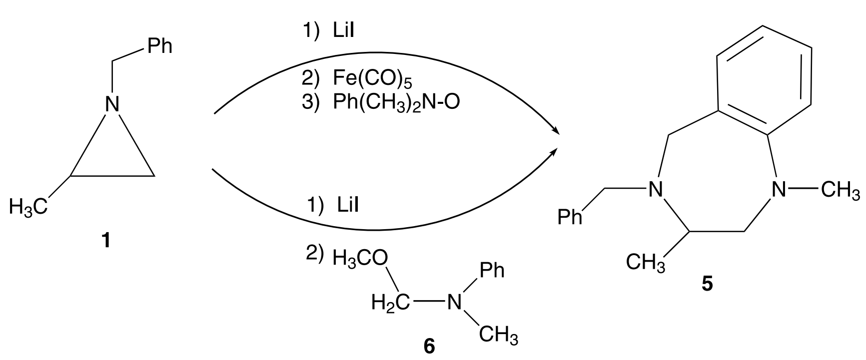
The product of the iron carbonyl or of the aminoether reaction was isolated as a yellowish oil that was inert to 1° and 2° amine derivatization methods. Its molecular formula was established as $C_{18}H_{22}N_2$ based upon electrospray HRMS and NMR spectroscopic data. IR data are consistent with the presence of a tertiary amine functionality, and mono- and disubstituted aromatic rings. Exposure of **5** to HCl vapor led to the appearance of two broad, medium intensity absorbances at 3417 and 2540 cm^{-1}, the latter band being diagnostic for a tertiary amine hydrochloride.

The ^{13}C NMR spectrum in acetone-d_6 contained 16 signals including 10 aromatic carbons bearing 7 hydrogens. These signals were assigned to a mono- and a disubstituted aromatic ring. Thus, they accounted for 8 of the 9 units of unsaturation deduced from the molecular formula and indicate the presence of a heterocyclic core. The ^{1}H NMR spectrum is complex, containing a series of overlapping aromatic resonances, several AB patterns between 3.5 and 4.5 ppm, a methyl singlet overlapping several multiplets, and a methyl doublet at 1.26 ppm.

Analysis of COSY and HETCOR data defined five spin systems that included an asymmetric 1,2-diaminopropane fragment, two methylene AB patterns, and the mono- and disubstituted benzene ring systems. Multibond correlations were initially accessed by a COLOC experiment that verified the existence of the intact benzyl group (C-12 to C-16), the C$_3$ fragment derived from the aziridine, and the 1,2-disubstituted benzene ring.

To organize definitively the fragments around the seven-membered ring, 2D-INADEQUATE and NOESY experiments were employed. In addition to verifying the COSY and COLOC results, the INADEQUATE experiment solidified the connectivity via a correlation between methylene C-5 and the disubstituted benzene at C-5a (Fig. 1). Three NOE enhancements were observed between H-10/H-9, H-5 and H-5′/H-6, H-3/H-12 that unambiguously identify the 2,3,4,5-tetrahydro-1*H*-benzo[e][1,4]diazepine structure.

Our proposed mechanism for the reaction with aminoether **6** leading to benzodiazepine **5** is shown in Scheme 3. The first few steps mirror our previously proposed mechanism,[7] i.e. LiI opens the aziridine ring to give **7**, reaction with aminoether **6** yields **8**, which undergoes rapid ring closure to produce **9**. The direct hydrolysis of compound **9** would generate diamine **11**, and is the most likely path when starting with *N*,*N*-



Scheme 2.

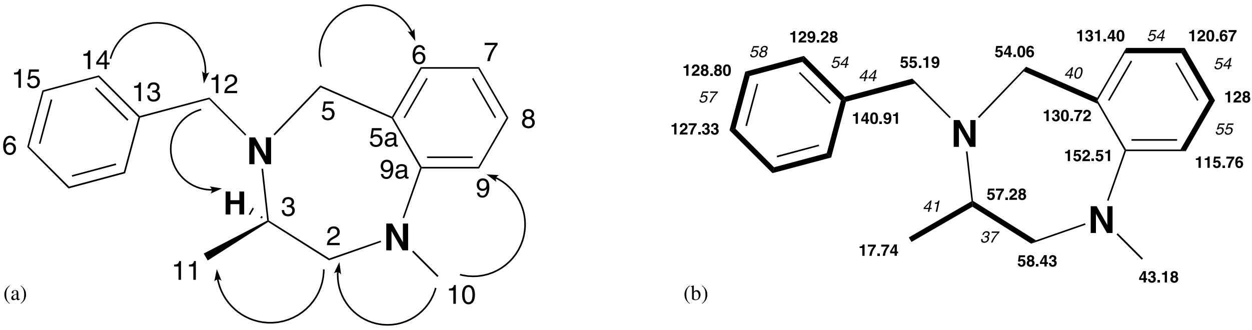
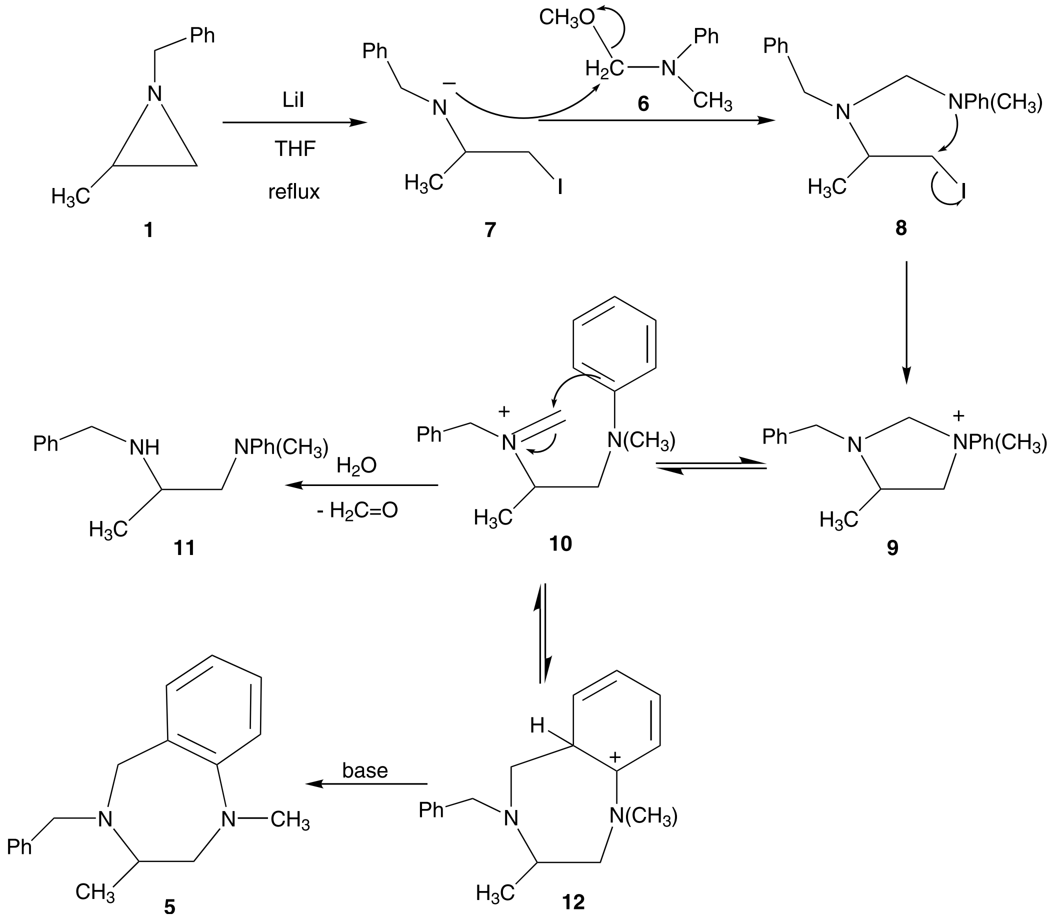


Figure 1. Tetrahydrobenzodiazepine skeleton derived from (a) NOE and (b) INADEQUATE correlations. With the initial structure, atom numbers are included and important observed NOE cross peaks are indicated by arrows. For the second structure, ^{13}C NMR assignments and italicized coupling constants ($^1J_{CC}$) are provided that verified the connectivity (shown in bold).



Scheme 3.

dialkylamino substituted iminium salts or amino ethers. However, compound **9** appears to be in equilbrium with compound **10**, which is activated to undergo an electrophilic aromatic substitution reaction to generate **12**. Upon deprotonation, benzodiazepine **5** is formed.

As discussed previously,[7] we do not believe that the iminium salt or the aminoether reacts with the aziridine to generate an aziridinium prior to the ring opening reaction because when a solution of aziridine **1** is concentrated, it is stable. However, when a solution of aziridine **1** and LiI is concentrated, a six-membered ring dimer (a piperidine) is formed. This suggests that the ring is opened prior to the addition of the iminium salt or the amino ether. It is possible that aminoether **6** dissociates into an iminium salt and CH_3O^- prior to reaction with intermediate **7**. We have no data consistent with or inconsistent with this possibility.

In agreement with the mechanism shown in Scheme 3, when deuterated formaldehyde is used to generate $Ph(CH_3)N\text{-}CD_2\text{-}OCH_3$, the deuterium atoms are found exclusively at carbon-5 (see Fig. 1 for carbon numbering). This result rules out an alternative mechanism in which the carbon–carbon bond of aziridine **1** is broken because that pathway would lead to a benzodiazepine with the deuterium labels located at carbon-2.

The important question that needs to be resolved is why aminoether **6** generates exclusively benzodiazepine **5**, but the analogous iminium salt generates a mixture of **5** and **11**. When the reaction is performed with the iminium salt, the anions present are the added I^- and the original counterion for the iminium cation, which is Cl^-. In contrast, when the reaction is performed with aminoether **6**, the anions are I^- and OCH_3^-, the leaving group from the aminoether. Thus, the latter reaction solution is much more basic than the former reaction solution. In addition, we believe that the solution containing the iron complex and the amine oxide (shown in Scheme 2) is quite basic.[17]

Contrary to most electrophilic aromatic substitution reactions,[18] if the cyclization of **10** to **12** is reversible and the deprotonation of **12** to **5** is the slow step, then it follows that with a strong base in solution, deprotonation occurs rapidly to give exclusively **5**, but with a much weaker base in solution, deprotonation is slow and a mixture occurs. This situation is anticipated in the presence of the amine-stabilized cation **12**. Consistent with this idea, when the reaction with the iminium is performed, but, prior to the aqueous work-up, 1 equiv. of *t*-butoxide is added, the product is now diazepine **5** with a minor amount of diamine **11**.

Thus, in conclusion, we have shown that the product from the reaction of a LiI ring-opened aziridine, either with iron carbonyl followed by a phenyl-substituted amine oxide or with a phenyl-substituted *gem*-aminoether, is a benzodiazepine derivative. This same product is formed using an iminium salt when a strong base is added. We have proposed a mechanism for the formation of this new compound. This methodology should prove a convenient way to generate many variations of these biologically important[19] benzodiazepine derivatives.[20,21]

Supplementary material

Tabular spectroscopic data for tetrahydrobenzodiazepine derivative **5**. The ^{1}H and ^{13}C NMR spectra of compound **5**.

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20. Iron carbonyl reaction procedure: The amine oxide was synthesized and the reaction was run using the same procedure as given in Ref. 6a, with aziridine **1** (0.15 g, 1.0 mmol), LiI (0.20 g, 1.5 mmol), $Fe(CO)_5$ (0.15 mL, 1.2 mmol), and the amine oxide (0.69 g, 5.0 mmol).
21. Aminoether/iminium reaction procedure: The iminium salt and the *gem*-aminoether were synthesized as described in Ref. 22. The reaction was run using the same procedure as given in Ref. 7, with aziridine **1** (0.15 g, 1.0 mmol), lithium iodide (0.20 g, 1.5 mmol), and the iminium salt (0.16 g, 1.0 mmol) or *gem*-aminoether 6 (0.15 g, 1.0 mmol). For the experiment with added base, after the 20 h of stirring and before the work-up, potassium *t*-butoxide (0.11 g, 1.0 mmol) was added and the reaction mixture was allowed to stir for at least 2 h.
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