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A Directed Amidohalogenation Reaction An Unusual Reaction of Azidoformates

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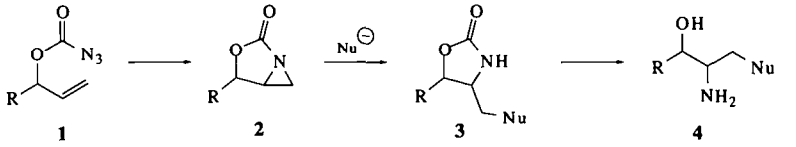
Abstract: The thermal intramolecular reaction of an azidoformate and an olefin does not provide the expected aziridine, but rather an amidohalide. This unusual product is formed via an intramolecular nitrene addition to the olefin to initially provide an aziridine. Under the reaction conditions HCl is generated from the solvent which protonates and opens the aziridine providing the observed product. This reaction proceeds with good stereoselectivity giving stereoisomeric ratios of 3:1 to 6.7:1.

The intermolecular reactions of azidoformates with olefins is a well known method for the synthesis of aziridines.[1] The formation of aziridines can proceed via a nitrene intermediate[2] or via the dipolar cycloaddition of the azide across the double bond followed by loss of N_2.[3]

Only one intramolecular reaction of an azidoformate and an olefin has been reported.[4] In this report the thermolysis of an aryl azidoformate gave a good yield of a bicyclic aziridine. An intramolecular dipolar cycloaddition of a carbamoyl azide has recently been reported.[5] This reaction does not yield an aziridine, but rather nucleophilic addition to a betaine intermediate provides an imidazolidinone.

Our plans were to utilize an intramolecular azidoformate cyclization (**1** → **2**) to provide a directed aziridination reaction as shown in Scheme 1. Oxazolidinones such as **3** should be very useful for the stereoselective preparation of a variety of 1,2-aminoalcohol derivatives (**3** → **4**).

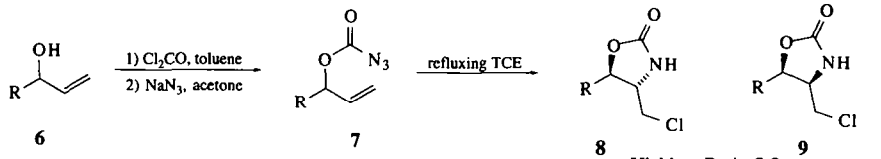


Scheme 1

Our studies started with the preparation of the azidoformates **7a-7f**.[6] The azidoformates are synthesized from the allylic alcohols **6a-6f** by initial preparation of the chloroformate which is not isolated, but treated with sodium azide to give azidoformates **7a-7f** in 51-67% overall yield.[7] The azidoformate is a stable, isolable molecule. When the azidoformates are heated to reflux in 1,1,2,2-tetrachloroethane (TCE) containing trace amounts of water the oxazolidinones **8** and **9** are isolated in excellent yield.[9] The stereochemistry of the oxazolidinones were determined by NOE difference experiments as well as an examination of the coupling constants of the ring methines.[10] It is worth noting that a number of groups that might be expected to react with an azidoformate are well tolerated by this reaction. This includes a phenyl ring (**6b**, **6e**) and an olefin (**6f**).

The observed relative stereochemistry in these reactions can be rationalized by the transition states **A**

and **B**-in Figure 1. In both transition states the R group occupies a quasi-equatorial position. When R is large (**7a**, **7d**) the unfavorable interaction between the large R group and the olefin in transition state **B** may



6 **7** **8** **9**

		Yield	Ratio 8:9
6a, R = -cyclohexyl	67%	83%	6.7:1
6b, R = -$(CH_2)_3$NPht	51%	78%	3:1
6c, R = -$(CH_2)_4CH_3$	54%	77%	5:1
6d, R = -tBu	40%	54%	45:1
6e, R = -$(CH_2)_2$Ph	51%	50%	3:1
6f, R = -$CH(CH_3)(CH_2)_2CHC(CH_3)_2$	60%	77%	1:1

Scheme 2

be the reason for very little of the *cis* compound being formed. The primary product formed then will be through transition state **A** in which the steric interactions between R and the olefin are greatly reduced. When the R group is a single methylene (**7b**, **7c**, **7e**), the unfavorable steric interactions between R and the olefin will be diminished, leading to a greater amount of the *cis* isomer through transition state **B**. Based on this model, it is not clear why only a 1:1 mixture of isomers is obtained in the reaction of **7f**. While this compound is a single diastereomer (^{1}H NMR) we do not know the stereochemistry of the C4-methyl group relative to the oxygen.

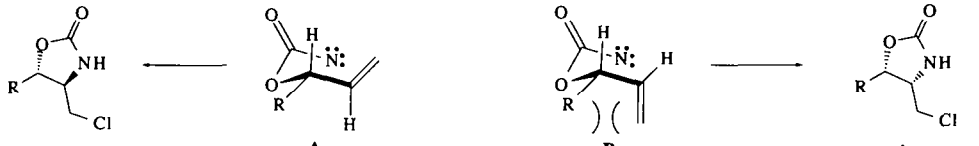
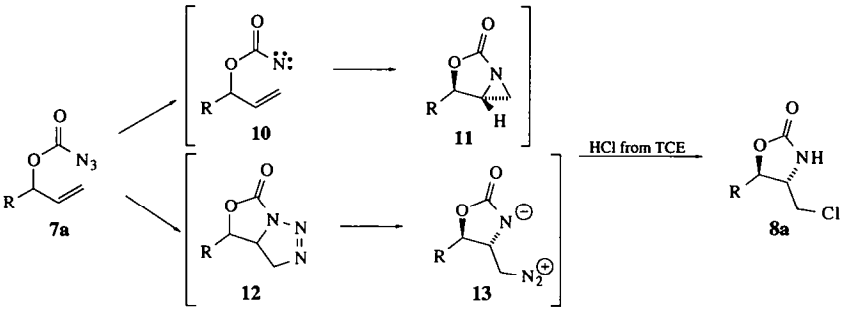


Figure 1

The isolation of the chloride came as something of a surprise. We had expected to isolate an aziridine. In an effort to discern how **8** and **9** were being formed the reaction was carried out in an NMR tube with TCE-d_2 as the solvent. Heating to 70 °C or 90 °C for up to 24 h at each temperature showed virtually no reaction. Warming to 110 °C gave a very slow rate of reaction, after 12 h only a 5% conversion was seen. Upon increasing the temperature to 125 °C a rapid formation of what appeared to be aziridine **11** was seen.[11] When the reaction reached approximately 25% conversion (2 h) the signals corresponding to chloride **8a** appeared and the signals corresponding to the aziridine decreased and maintained at a very low level until the reaction was complete (6 h). This seemed to indicate that something was formed in the reaction which was leading to the decomposition of the aziridine. Halogenated solvents are known to produce HCl upon heating.[12] We believe that the HCl being produced is opening the aziridine.[13]

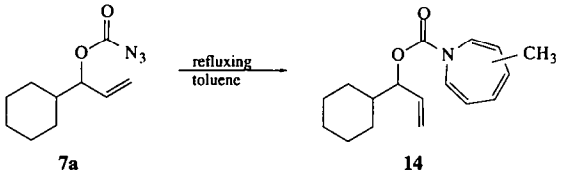
A second concern is the mechanism of the aziridine formation. Two possibilities present themselves. First the azidoformate upon heating may be forming a nitrene (**10**) which is adding to the olefin to produce the aziridine intermediate **11**. The aziridine then undergoes acid catalyzed nucleophilic attack to yield the chloride **8a**. A second possibility is that the azidoformate is undergoing a dipolar cycloaddition across the

double bond to yield an intermediate triazoline **12**. Thermal decomposition of the triazoline leads to the betaine intermediate **13**. Chloride attack on the $-CH_2N_2$ yields the observed product.[14] Alternatively the betaine intermediate **13** is converted to the aziridine **11** which is opened to yield **8a**.



Scheme 3

In order to discern which mechanism might be prevailing the reaction was carried out in toluene. Benzene is known for its facile reaction with nitrenes to produce azepines.[15] Upon carrying out the reaction in refluxing toluene the azepine **14** was isolated as a mixture of isomers in 71% yield. This product clearly indicates that the reaction is proceeding through a nitrene intermediate and not via a dipolar cycloaddition.



Scheme 4

We have observed a novel reaction of azidoformates. This intramolecular cyclization of a nitrene proceeds through an aziridine intermediate. A ring opening of the aziridine by solvent generated HCl yields a chloromethyl oxazolidinone. These compounds will be very useful for the synthesis of a variety of natural products. The cyclization of the nitrene additionally proceeds with excellent stereoselectivity, giving primarily the *trans*-oxazolidinones. Further studies on the use of this reaction as well as modifications of this reaction are currently underway in our laboratories.

References and Notes

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2. For a general discussion of nitrene chemistry see (a) Lwowski, W.: Carbonylnitrenes In *Nitrenes*; Lwowski, W., Ed.; Interscience: New York, 1970; pp 185-224. (b) Edwards, O.E.: Acylnitrene Cyclizations In *Nitrenes*; Lwowski, W., Ed.; Interscience: New York, 1970; pp 225-304. (c) Lwowski, W.: Acyl Azides and Nitrene In *Azides and Nitrenes*; Scriven, E., Ed.; Academic: Orlando, 1984; pp 205-246. (d) Lwowski, W.: Nitrenes. *React. Intermed.* **1985**, *3*, 305-332.
3. Padwa, A. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 2, Chapter 12, pp 277-406. See also references 14 and 15 in reference 12 below.
4. Rhouati, S.; Bernou, A. *J. Chem. Soc., Chem. Commun.* **1989**, 730-732.
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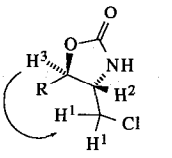
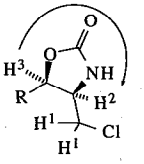
6. All compounds showed spectra (^1H, ^{13}C, IR, HRMS) consistent with the reported structure.

7. Allylic alcohols **6a**, **6b**,[8] **6d**, **6e** and **6f** were prepared by the addition of vinylmagnesium bromide to the corresponding aldehyde in yields of 93%, 73%, 54%, 28% and 63% respectively. Allylic alcohol **6c** is commercially available.
8. This aldehyde was prepared in 79% yield via the Et_3N catalyzed condensation of *N*-carbethoxyphthalimide with 4-aminobutyraldehyde diethyl acetal in THF. Hydrolysis of the acetal in THF with 0.6 M HCl yielded the aldehyde in 89% yield. For an alternate preparation see: Hamilton, R.; Walker, B.J.; Walker, B. *Tetrahedron Lett.* **1993**, *34*, 2847-2850.
9. A typical procedure for the cyclization of **7a** to **8a/9a**: A solution of the azidoformate (2.1 g, 10 mmol) in TCE (200 mL, distilled but not stored under N_2) was heated to reflux for 4 h. The solvent was then removed under vacuum. The crude oil was chromatographed (25% ethyl acetate in hexane) to give 1.9 g (87%) of **8a/9a** as an off-white solid in a 6.7:1 mixture. Recrystallization from Et_2O/hexane gave 1.51 g (70%) of **8a** as a white solid; mp 93-96 °C. ^1H NMR ($CDCl_3$, 250 MHz) δ 4.10 (dd, J = 4.4, 6.3 Hz, 1 H), 3.83 (m, 1 H), 3.51 (d, J = 5.52, 2 H), 1.89-1.57 (m, 6 H), 1.29-1.04 (m, 5 H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 158.9, 83.9, 62.1, 46.2, 43.7, 41.9, 27.7, 27.2, 26.1, 25.5, 25.4; HRMS calcd for $C_{10}H_{16}ClNO_2$, 217.0871; found, 217.0848.
10. For compound **8a**, irradiation of H3 produced a 3.3% enhancement of the signal for H1. Similarly for **8b**, irradiation of H3 showed a 1.7% enhancement of the signal for H1. For compound **9b**, an irradiation of H3 showed a 5.4% enhancement of the signal for H2. Additionally the coupling constant $J_{2,3}$ for **8a** (*trans*) was 3.23 Hz. The coupling constant $J_{2,3}$ for **8b** (*trans*) was 4.32 Hz and the coupling constant $J_{2,3}$ for **9b** (*cis*) was 7.55 Hz. The stereochemistry of the remaining compounds **8c-8f** and **9c-9f** were determined by comparison of the coupling constant between the major and minor isomers. This is consistent with the observations that *trans*-oxazolidinones have smaller coupling constants than the corresponding *cis*-oxazolidinones. See: Seebach, D.; Beck, A.K.; Mukhopadhyay, T.; Thomas, E. *Helv. Chim. Acta* **1982**, *65*, 1101-1133.

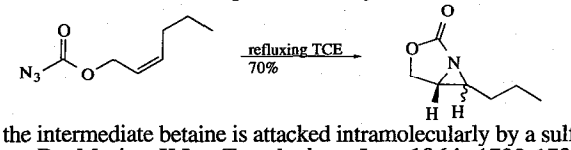


8a, R = cyclohexyl
8b, R = $(CH_2)_3$NPht



9b, R = $(CH_2)_3$NPht

11. The intermediate aziridine seen in the ^1H NMR shows characteristic signals at δ 2.98 (m, 1 H), 2.54 (d, J = 6.25 Hz, 1 H), 2.26 (d, J = 5.0 Hz, 1 H). The general pattern and chemical shift of these signals are consistent with other aziridines that we have prepared. See also: Bergmeier, S.C.; Lee, W.K.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 5019-5022.
12. Pearson, W.H.; Bergmeier, S.C.; Degan, S.; Lin, K.-C.; Poon, Y.-F.; Schkeryantz, J.M.; Williams J.P.; *J. Org. Chem.* **1990**, *55*, 5719-5738.
13. HCl readily opens an aziridine to give a β-chloroamine, see: Legters, J.; Willems, J.G.H.; Thijs, L.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 59-68. In an effort to generate only the aziridine **11** several attempts were made to preclude the formation of HCl. One possibility is that a trace amount of water in the reaction was reacting with the solvent to produce HCl. Thus both the solvent and reactant **5a** were thoroughly dried and then the reaction was carried out in the presence of either powdered 4Å molecular sieves or a drying agent such as $CaSO_4$ or $MgSO_4$. In all of these cases, the expected chloride was still obtained but as an approximately 1:1 mixture with a compound we have tentatively identified as coming from elimination of the azidoformate. We have also attempted to isolate the aziridine by the inclusion of an acid scavenger to remove the HCl as it is being formed. We thus carried out the reaction in the presence of poly(4-vinylpyridine) and 1,8-bis(dimethylamino)naphthalene. In the reaction with the polyvinyl pyridine only the normal reaction product was seen, albeit in a lower yield. When the reaction was carried out in the presence of 1,8-bis(dimethylamino)naphthalene only polymeric material was obtained. Thermolysis of the azidoformate of 3-hexen-1-ol produces the bicyclic aziridine in 70% yield. None of the usual β-chloroamide is formed. Apparently the more hindered aziridine is somewhat more resistant to nucleophilic attack by chloride.



14. In reference 5 above, the intermediate betaine is attacked intramolecularly by a sulfide side chain.
15. (a) Hafner, K.; Zinser, D.; Moritz, K.L. *Tetrahedron Lett.* **1964**, 1733-1737. (b) Baldwin, J.E.; Smith, R.A. *J. Org. Chem.* **1967**, *32*, 3511-3516.

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