THE CHEMICAL REACTIVITY OF 2,2,3,3-TETRAMETHYL-1-AZIRIDINECARBOXIMIDATE

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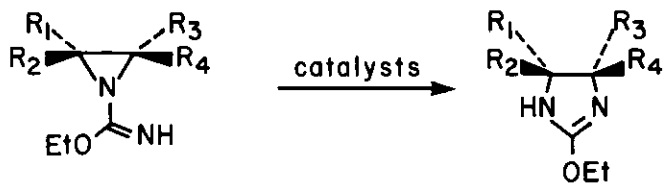
Abstract - The activated aziridine, 2,2,3,3-tetramethyl-1-aziridinecarboximidate, does not rearrange to the corresponding 4,5-dihydro-4,4,5,5-tetramethyl-2-ethoxyimidazole in the presence of either nucleophilic catalysts or acids, rather the major products obtained were ring-opened adducts. The mechanism of these atypical transformations are discussed.

Aziridinecarboximidates (1) are excellent synthetic precursors to 4,5-dihydro-2-ethoxyimidazoles (2). This rearrangement proceeds stereospecifically and in high yields with a variety of catalysts.[1,2]



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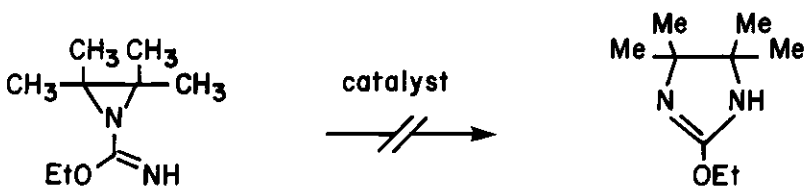
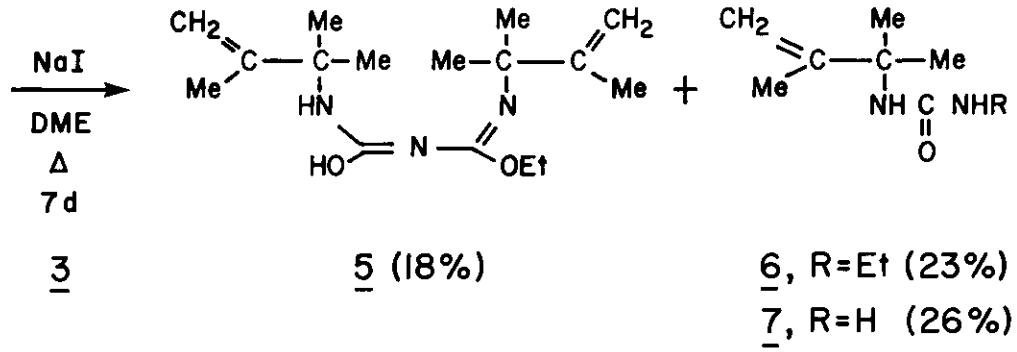
In this paper, we report the unusual reactivity profile observed during the attempted conversion of ethyl 2,2,3,3-tetramethyl-1-aziridinecarboximidate[1b] (3) to 4,5-dihydro-4,4,5,5-tetramethyl-2-ethoxyimidazole (4).



3 4

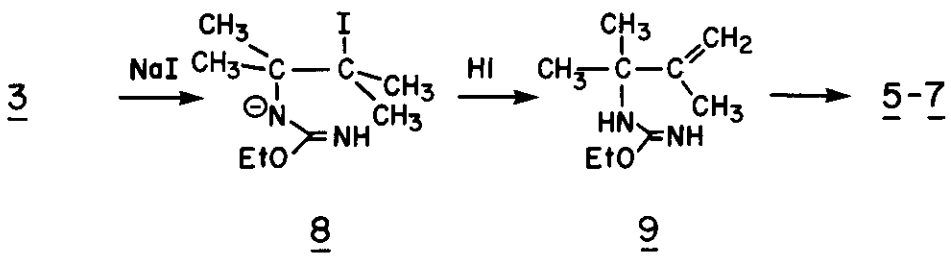
RESULTS AND DISCUSSION

Treatment of 3 with NaI (DME, reflux, 1 day[3]) gave no detectable product formation (i.e., 4). Extension of the reaction time from one to seven days yielded three major products (5-7) along with two unidentified minor compounds.



Several pathways are conceivable for the formation of adducts 5-7. One scenario involves initial ring opening of aziridine 3 by NaI to yield 8, followed by elimination of HI to generate 9 (Scheme 1). Compound 9 should serve as a viable precursor to the observed products. Displacement of the ethyl group in 9 by iodide ion leads to 7,[4] while O→N Chapman-type rearrangement[5] of 9 gives 6. Finally, condensation of 7 and 9 is expected to generate 5. The failure to form dihydroimidazole 4 in this reaction can be attributed to a variety of factors. First, cyclization of 8 to 4 would necessitate a bimolecular displacement reaction at a tertiary center. Second, ring closure of 8 to 4 should be accompanied by unfavorable eclipsing interactions of the methyl groups.

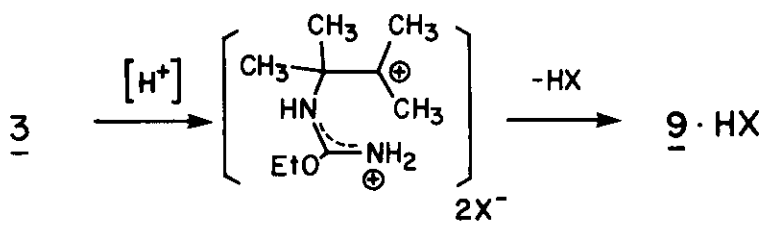
Scheme 1. Potential Pathway for the Formation of Compounds 5-7.



Conversion of aziridine 3 to dihydroimidazole 4 was also attempted under acid catalyzed conditions. Treatment of 3 with picric or methanesulfonic acid in toluene produced the corresponding salts of compound 9. Identification of the methanesulfonate salt of 9 was accomplished by conversion of this compound to the picrate salt. Addition of a catalytic amount of aluminum chloride to a heptane solution containing 3 yielded multiple products. Use of buffered reaction conditions[3] ($Et_3N \cdot HI$) for this transformation led to the recovery of the starting material.

Formation of 9 with acid can be rationalized by the E1 pathway depicted in Scheme 2. The corresponding intramolecular S_N1 process to give 4 was not observed. Although this hypothesis is mechanistically plausible, we note that in previously reported examples N-acyl activated aziridines smoothly underwent ring expansion with non-nucleophilic acid catalysts. For example, 2,2,3,3-tetramethyl-N-benzoylaziridines isomerized to the corresponding oxazolines with acid.[6,7] Presumably, an intramolecular S_N1 pathway was involved in these processes. This unusual product discrepancy (elimination versus ring expansion) may be attributed to the relative basicities of the departing isourea moiety versus the amide group in these two sets of ring cleavage reactions. Under the acid conditions employed, protonation of the isourea moiety[8] in 10 should readily occur, thereby decreasing the liklihood of subsequent recyclization of this adduct to the corresponding imidazoline derivative.

Scheme 2. Formation of 9·HX with Acid.



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trace amount of the unknown material and was not further identified. The second fraction contained 6. Recrystallization from hexane gave pure 6 (0.16 g, 23%): mp 105-107°C; IR (KBr) 3300, 2960, 2930, 1630, 1560 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07(t, 3H, J=7 Hz), 1.39(s, 6H), 1.78(s, 3H), 3.18(dq, 2H, J=5,7 Hz), 4.89-4.98(m, 2H), 5.10-5.38(m, 2H). Selective irradiation of the signals centered at δ 1.07 led to a collapse of the doublet of quartets at δ 3.18 to a doublet. Irradiation of the signals at δ 3.18 simplified the triplet at δ 1.07 to a singlet. Irradiation of the signal at δ 4.89-4.98 did not change the rest of the spectrum. ^{13}C NMR ($CDCl_3$) 15.6, 19.0, 28.0, 34.7, 55.2, 110.3, 151.1, 158.3 ppm; MS, m/e (relative intensity) 170(8), 155(18), 127(8), 126(1), 98(8), 84(100), 83(9); mol wt 170.1425 (calcd for $C_9H_{18}N_2O$ 170.1419).

The third fraction (R_f 0.30, 10% ethanol-chloroform) from the column contained compound 7 (0.15 g, 26%). Recrystallization from benzene-hexane (1:1) gave an analytical sample: mp 165-167°C; IR (KBr) 3440, 3340, 3200, 1640, 1610, 1540 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.29(s, 6H), 1.67(s, 3H), 4.67-4.76(m, 2H), 5.16-5.36(s, 2H, exchangeable with D_2O), 5.74-6.04(s, 1H, exchangeable with D_2O); ^{13}C NMR ($CDCl_3$) 19.1(q, J=127 Hz), 27.5(q, J=127 Hz), 54.3(s), 108.4(t, J=155 Hz), 151.1(s), 157.7(s) ppm; MS, m/e (relative intensity) 142(14), 127(95), 98(20), 84(100).

Anal. Calcd for $C_7H_{14}N_2O$: C, 59.12; H, 9.92; N, 19.70. Found: C, 59.10; H, 9.77; N, 19.68.

Treatment of Ethyl 2,2,3,3-Tetramethyl-1-aziridinecarboximidate (3) with Picric Acid. A solution of 3 (0.40 g, 2.35 mmol) and picric acid hydrate (0.64 g, 2.38 mmol) in toluene (10 mL) was heated at reflux (8h). The resulting solution was set aside (6h) at room temperature and then cooled (18h) in a refrigerator. The yellow precipitate was collected and dried in a vacuum desiccator (18h) to give 0.70 g (75%) of the picrate salt of 9. Recrystallization from toluene gave an analytical sample: mp 170-171°C; IR (KBr) 3390, 3320, 3250, 1640, 1600, 1565 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.30(t, 3H, J=7 Hz), 1.41(s, 6H), 1.71(s, 3H), 4.37(q, 2H, J=7 Hz), 4.90(s, 2H), 7.72-8.62(s, 3H, exchangeable with D_2O), 8.62(s, 2H); ^{13}C NMR (DMSO-d_6) 13.7(q, J=127 Hz), 18.5(q, J=126 Hz), 27.0(q, J=129 Hz), 57.8(s), 68.0(t, J=151 Hz), 110.6(t, J=168 Hz), 124.2(s), 125.2(d, J=168 Hz), 142.0(s), 147.6(s), 159.8(s) ppm.

Anal. Calcd for $C_{15}H_{21}N_5O_8$: C, 45.11; H, 5.30; N, 17.54. Found: C, 45.04; H, 5.24; N, 17.45.

EXPERIMENTAL SECTION

General. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were run on a Beckman IR 4250 spectrophotometer and calibrated against the 1601 cm^{-1} band of polystyrene. Nuclear magnetic resonance spectra were recorded on Varian Associates Model XL-100-15, FT-80A and T-60 instruments with tetramethylsilane as an internal standard. Mass spectral data were obtained at an ionizing voltage of 70 eV on a Hewlett-Packard 5930 gas chromatograph-mass spectrometer. High-resolution (E1 mode) mass spectra were performed by Drs. James Hudson and John Chinn at the Department of Chemistry, University of Texas at Austin, on a CEC21-110B double-focusing magnetic-sector spectrometer at 70 eV. Exact masses were determined by peak matching. Elemental analyses were obtained at Spang Microanalytical Laboratories, Eagle Harbor, MI.

Treatment of Ethyl 2,2,3,3-Tetramethyl-1-aziridinecarboximidate (3) with NaI. A solution containing aziridine 3 (0.70 g, 4.12 mmol) and NaI (1.23 g, 8.20 mmol) in 1,2-dimethoxyethane (20 mL) was heated at reflux (7d) under N_2. After 6 days, no significant change in the product composition was noted by TLC analysis (Rf 0.92, 0.50, 0.30 [major], 0.53, 0.16 [minor], 10% ethanol-chloroform). After evaporation of the volatile components in vacuo, the residue was triturated with ether (100 mL). Concentration of the ethereal solution under reduced pressure gave 0.60 g of residue. Column chromatography (SiO_2, 3% ethanol-chloroform) of the product mixture led to the isolation of the three major products. The first fraction (R_f 0.92, 10% ethanol-chloroform) was identified as compound 5 (0.11 g, 18%): mp 69-70°C; IR (KBr) 3325, 2980, 2940, 1615, 1515, 1425 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19(t, 3H, J=7 Hz), 1.40(s, 6H), 1.43(s, 6H), 1.69(s, 3H), 1.78(s, 3H), 4.16(q, 2H, J=7 Hz), 4.74-4.92(m, 4H), 5.08-5.38(s, 1H), 8.92-9.22(s, 1H); ^{13}C NMR ($CDCl_3$) 14.2, 19.1, 19.3, 27.8, 28.3, 55.4, 56.5, 62.1, 109.1, 150.3, 160.7, 164.0 ppm; MS, m/e (*relative intensity*) 198(13), 197(24), 181(8), 170(7), 169(9), 155(25), 141(28), 127(11), 126(6), 115(100), 98(20), 87(29), 84(35), 83(56); MS (CI) 296; mol wt 295.2267 (calcd for $C_{16}H_{29}N_3O_2$ 295.2260).

The second fraction was a binary mixture composed of 6 (R_f 0.50, 10% ethanol-chloroform) and a small amount of an unknown material (R_f 0.53, 10% ethanol-chloroform). These two compounds were further separated by flash column chromatography (SiO_2, ether). The first fraction contained a

Treatment of Ethyl 2,2,3,3-Tetramethyl-1-aziridinecarboximidate (3) with Methanesulfonic Acid. A solution containing aziridine 3 (0.20 g, 1.18 mmol) and methanesulfonic acid (0.12 g, 1.25 mmol) in toluene (15 mL) was stirred (18 h) at room temperature. The solution was concentrated in vacuo and then the residue dissolved in H_2O (30 mL), made basic with Na_2CO_3 and extracted with ether (3 x 30 mL). The organic layers were combined, dried (Na_2SO_4), and evaporated in vacuo to give 0.13 g of residue. ^1H NMR analysis indicated the presence of 3 and 9 in a ratio of 1:4. The O-ethylisourea adduct 9 was identified as its picrate salt. Accordingly, a solution of picric acid (0.21 g, 0.77 mmol) in toluene (15 mL) was added to a solution containing the above residue in toluene (20 mL) leading to the formation of a precipitate. The solid was recrystallized from toluene to yield 0.20 g (66%) of the picrate salt of 9: mp 170-172°C.

ACKNOWLEDGMENT

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