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Reaction of Ethyl Azidoformate with Morpholines

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Synopsis. Ethyl azidoformate (**1**) reacts rapidly with morpholine to give morpholinium azide and 4-(ethoxycarbonyl)morpholine in good yields. With 4-methylmorpholine (**3**), however, the azide **1** reacts at 115 °C with evolution of nitrogen to give formal nitrene-insertion products, 4-methyl-3-(ethoxycarbonylamino)morpholine and 4-(ethoxycarbonylaminomethyl)morpholine. There has not been found any product which might arise from the nitrene-insertion into C–H bond adjacent ot oxygen of **3**. These results can be accounted for on the basis of the n-donor abilities of heteroatoms, O and N.

Ethoxycarbonylnitrene generated photochemically or thermally from ethyl azidoformate inserts exclusively into C–H bonds adjacent to oxygen of cyclic and open-chain ethers.[1–3] The nitrene also exclusively reacts with CH_3 groups of *N*,*N*-dimethylaniline to give formal insertion product.[4]

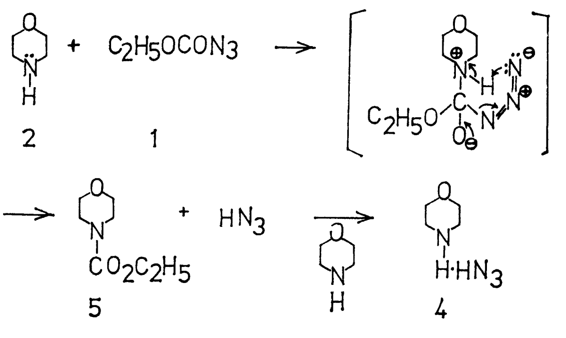
The exclusive reactions at these activated C–H bonds have been considered to proceed with the initial formation of O–N or N–N ylids by coordinative attack of the electron-deficient nitrene on the heteroatoms with nonbonded electron pair, followed by the rearrangement to give formal insertion products.

Morpholine and its *N*-substituted derivatives are, therefore, particularly interesting in connection with the possibility of intervention of such ylid intermediates, because of bearing two kinds of C–H bonds activated by the adjacent oxygen and nitrogen atoms, respectively.

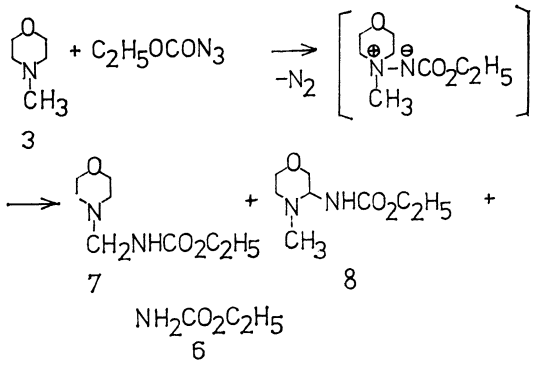
Results and Discussion

The reaction of ethyl azidoformate (**1**) with morpholine (**2**) was conducted by adding the azide **1** to **2** at room temperature and heating the solution to 120 °C for 2 h with stirring. A white solid formed immediately at the stage of the addition was separated by filtration, and proved to be morpholinium azide (**4**, 86% yield) on the basis of its spectral data. In addition, 4-(ethoxycarbonyl)morpholine (**5**) was obtained in 57% yield from the filtrate by the vacuum distillation. The structure of **5** was characterized by comparison with the authentic sample.

The result described above clearly indicates that the products **4** and **5** were formed by a simple displacement of azide ion[5] from **1** with **2**, which is a strong nucleophile[6] with mobile hydrogen atom on nitrogen, but via neither nitrene nor ylid intermediate, as shown in Scheme 1.



Scheme 1.



Scheme 2.

The thermolysis of the azide **1**, however, smoothly proceeded in 4-methylmorpholine (**3**) with evolution of nitrogen at 115 °C. After usual workup involving removal of unchanged **3**, three major products isolated by preparative VPC from a residual oil were identified as ethyl carbamate (**6**), 4-(ethoxycarbonylaminomethyl)morpholine (**7**) and 4-methyl-3-(ethoxycarbonylamino)morpholine (**8**), respectively. The structural assignment of these products, **6**, **7** and **8**, was based on their ^1H NMR and mass spectral data. The product distribution in the oily residue has tentatively been determined as 61.1% of **6**, 13.4% of **7**, 2.5% of **8** and 23% (total) of three unidentified products, instead of their exact yields, on the basis of their VPC peak areas. A further examination of the reaction mixture gave no evidence for the presence of any product which might arise from the reaction at C–H bond activated by the adjacent oxygen.

Of interest is the fact that the reaction occurs exclusively at C–H bonds adjacent to nitrogen. This can be rationalized in terms of the mechanism in which the N–N ylid is involved as an intermediate. Since nitrogen is a much stronger n-electron donor than oxygen and the N–N ylid is more stable than the O–N ylid, the electron-deficient nitrene attacks preferentially nitrogen over oxygen to give a more stable ylid followed by rearrangement leading to formal nitrene-insertion products, **7** and **8**, even though the detailed mechanism for the rearrangement has not been clear yet.

Experimental

IR spectra were recorded on a Hitachi Model EPI-G3 and ^1H NMR spectra on a JEOL JNM 4H 100 spectrometer.

Mass spectra were obtained by JEOL JMC O1SG-2 spectrometer.

Commercially available morpholine and 4-methylmorpholine were used after distillation. Ethyl azidoformate was prepared according to the method of Lwowski and Mattingly.[7)]

Authentic 4-(ethoxycarbonyl)morpholine was prepared from morpholine and ethyl chloroformate by usual procedures.[7)]

*Reaction of Ethyl Azidoformate (**1**) with Morpholine (**2**).* The azide **1** (2.0 g; 0.017 mol) was added at room temperature to **2** (7.5 g; 0.087 mol) with stirring. During the addition, a white solid rapidly separated without any evolution of gases. The mixture was then heated to 120 °C and kept at that temperature for 2 h. After cooling to room temperature the resulting solid was separated on a filter, washed with ether, dried *in vacuo* and recrystallized from hot methanol to give **4** as white needles, mp 129.2—130.2 °C (yield; 1.89 g; 86.1%). Soluble in water but insoluble in ether and benzene. IR (KBr) 2450 ($\overset{+}{N}H_2$), 2030 (N_3^-) and 1590 cm^{-1} ($\overset{+}{N}H_2$); ^1H NMR ($(CD_3)_2SO$) $\delta=3.15$ (4H, m, N-CH_2), 3.8 (4H, m, O-CH_2) and 7.35 (2H, br, NH_2, disappered by treatment with D_2O); MS *m/e*: 87 ($M-HN_3$) and 43 (HN_3); Found: C, 36.82; H, 7.58; N, 43.20%. Calcd for $C_4H_{10}ON_4$: C, 36.91; H, 7.74; N, 43.50%.

The filtrate was fractionally distilled *in vacuo* to give **5** (yield; 1.53 g; 57%): bp 111.2 °C/25 mmHg: IR (neat) 2950 (-CH_3), 1700 (C=O) and 1240 cm^{-1} (=C-O-C); ^1H NMR (CCl_4) $\delta=1.29$ (3H, t, CH_3-), 3.36—3.8 (8H, m, ring proton) and 4.1 (2H, q, -CH_2-); MS *m/e*: 159 (M); Found: C, 52.60; H, 8.49; N, 8.61%. Calcd for $C_7H_{13}O_3N$: C, 52,82; H, 8.23; N, 8.80%. IR spectrum of **5** was identical in all respects with that of an authentic sample.

*Thermolysis of **1** in 4-Methylmorpholine (**3**).* A stirred solution of **1** (2.3 g; 0.02 mol) in **3** (10.1 g; 0.1 mol) was heated to 115 °C and kept at this temperature for 3 h during which time nitrogen was smoothyl evolved. After the nitrogen evolution has ceased, removal of the excess **3** from the reaction mixture *in vacuo* left a residual oil (4.2 g). The residual oil was subjected to preparative VPC on a column (8 mm × 2 m) packed with 5% Silicone OV-22 on 60/80 Uniport KS (oven temperature, initial: 110 °C, final: 230 °C, rate: 10 °C/min) to separate four components. Among them, three major components were identified as ethyl carbamate (**6**), 4-(ethoxycarbonylaminomethyl)morpholine (**7**) and 4-methyl-3-(ethoxycarbonylamino)morpholine (**8**), respectively. The product **6** was characterized by comparison of its VPC retention time and IR spectra with those of the authentic sample. The structural assignment of the components **7** and **8** was performed on the basis of their IR, ^1H NMR and mass spectral data. Analytical data for **7**: IR (neat) 3400 (NH), 1720 (C=O) and 1250 cm^{-1} (=C-O-C); ^1H NMR ($CDCl_3$) $\delta=1.28$ (3H, t, CH_3-), 2.05—3.08 (2H, m, N-CH_2), 3.5 (4H, m, H_2C-N-CH_2), 3.71 (4H, m, H_2C-O-CH_2) and 4.2 (2H, q, -CH_2-); MS *m/e* (rel intensity): 159 ($M-C_2H_5$ 24.1), 115 ($M-CO_2C_2H_5$ 7.4), 100 ($M-NHCO_2C_2H_5$ 29.2) and 86 ($M-CH_2NHCO_2C_2H_5$ 30.7). Analytical data for **8**: IR (neat) 3325 (NH), 2800 (N-CH_3) and 1710 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) $\delta=1.25$ (3H, t, CH_3-), 2.3 (3H, s, N-CH_3), 2.4—2.9 (3H, m, HC-N-CH_2), 3.3—3.85 (4H, m, H_2C-O-CH_2), 4.12 (2H, q, -CH_2) and 5.6 (1H, br, -NH-); MS *m/e* (rel intensity): 188 (M 45.5), 173 ($M-CH_3$ 5.4), 159 ($M-C_2H_5$ 69.7), 115 ($M-CO_2C_2H_5$ 17.2) and 100 ($M-NHCO_2C_2H_5$ 72.9).

The fourth component collected by preparative VPC was failed in its structural determination, although ^1H NMR spectra showed no peaks assignable to CH_3-, CH_2- or CH- adjacent to N.

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