Formation of 2-Oxazolidinones from N-Benzoxycarbonyl-2,2'-dichloro-diethylamine; Demonstration of Chloride Catalysis

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As part of our studies of nitrogen analogs of crown esters, we have tried to prepare the derivative I of 1,4,7,10-tetraazacyclododecane which after hydrogenolytic removal of the benzyloxycarbonyl group would permit selective alkylation reactions of one amine function. For this synthesis urethane-protected 2'-dichlorodiethylamine 2a was allowed to react with the disodium salt of \(N,N,N',N''\)-tris-p-toluenesulfonyl diethylenetriamine 3 in DMF. However, besides unreacted starting material 3 (7%), the only isolated products were the 2-oxazolidinone derivative 4 (9%), which is actually an isomer of the desired product 1, and the monobenzylated trisulfonamide 5 (12%).

Similarly, in an attempt to prepare the urethane derivative 6 of 1,4,7-trioxo-10-aza-cyclododecane from protected 2,2'-dichlorodiethylamine 2a and diethylene glycol with potassium tert-butoxide as a base, the benzyloxycarbonyl group proved to be unstable. The isolated products were 3-ethenyl-2-oxazolidinone 7 (25%), benzyl chloride (29%) and the monobenzyl ether of diethylene glycol (17%).

The formation of 2-oxazolidinones and the various benzylated products can be rationalized by either of the two reaction paths shown in Scheme 1. According to Path I, an \(S_N2\) substitution in the benzylic position of 2a gives a new benzylic compound PhCHX and a carbamate anion. This anion does not decompose until under the reaction conditions, but cyclizes to yield 3-(2-chloroethyl)-2-oxazolidinone 8, which is further transformed to 4 and 7. A pyrolytic mechanism, as proposed by Katchalsky et al. for the related formation of 2-oxazolidinone from N-carbalkoxy-2-haloalkylamines, seems unlikely here because of the low reaction temperatures (80–100°C).

In an experiment designed to exclude the less plausible alternative Path II, both urethanes 2 were allowed to react in DMSO at 170°C with one equivalent of NaCl and thereafter with NaCO₃. The benzyl derivative 2a furnished 40% of the cyclized product 7 besides benzyl chloride and other unidentified products, whereas the ethyl derivative 2b failed to yield any 2-oxazolidinones under the same conditions. These results render Path II very improbable, since both compounds 2 should show the same tendency to undergo the initial substitution of chloride by the carbonyl oxygen.

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The same two urethanes were then treated in refluxing benzene with catalytic amounts of chloride ion in the form of the 18-crown-6 complex of KCl. While the ethyl derivative 2b did not react at all, the benzyl derivative 2a gave the 2-oxazolidinone 8 in 66% yield. Since only Path I (X = Cl) of Scheme I constitutes a complete catalytic cycle, we conclude that all these reactions proceed by this same mechanism and at a temperature about 90°C lower than the pyrolytic process.*

*Experimental. The melting and boiling points are uncorrected. Gas liquid chromatography (GLC) analyses were performed on a Hewlett Packard 5700 A Gas Chromatograph. IR spectra were recorded on a Jasco IRA-1 spectrophotometer and NMR spectra on a Varian A 60A or a Joel JNM-FX60 Fourier Transform NMR spectrometer. MS data were collected with an A.E.I. MS 902 spectrometer. For the molecular weight determination a Knauer vapour pressure osmometer (Knauer Dampfdruck-­osmometer) was used. The elemental analysis was carried out at Mikroanalytisches Laboratorium Ilse Beetz, 8640 Kronach, West Germany.

Starting materials. N-Ethylxycarbonyl-2,2'-dichlorodiethylamine 2b, N,N',N''-tris-p-toluenesulfonyl diethylenetriamine 3, 3-ethenyl-2-oxazolidinone 7*, and 3-(2-chloroethyl)-2-oxazolidinone 8*, were prepared according to standard methods and had physical and spectroscopic properties in agreement with the literature.

N-Benzoxycarbonyl-2,2'-dichlorodiethylamine 2a, 2,2'-Dichlorodiethylamine hydrochloride 10
(26.6 g, 0.15 mol) in dry CHCl₃ (200 ml), freshly distilled benzyl chloroformate (25.4 g, 0.15 mol) in CHCl₃ (100 ml) and triethylamine (30.2 g, 0.30 mol) in CHCl₃ (120 ml) were mixed at 0 °C. The solution was stirred at room temperature overnight, warmed to 50 °C during 1 h and poured into a mixture of ice (200 g) and concentrated HCl (70 ml). Work-up with ether and distillation furnished the urethane 2a in 75 % yield, b.p. 122–136 °C/0.01–0.06 mmHg. MS, m/e (% rel. int.) 279 (0.1, M + 4), 277 (0.9, M + 2), 275 (1.4, M), 91 (100.0, C₆H₄). IR (film): 1690(s) cm⁻¹. ¹H NMR (CDCl₃): 273.06 (8 H, a), 5.16 (2H, s), 7.34 (5H, s), 1.3 C NMR (15 MHz, CDCl₃), δ 155.6 (C = O), 137.4, 136.2, 128.6 and 127.7 (aromatic carbons), 67.4 (CH₂O), 50.9, 50.4 (CH₃N), 41.9 (CH₂Cl).

Attempted synthesis of 1-benzoxylcyclenol

\[ \text{yl-4,7,10-tris-p-toluenesulfonyl-1,4,7,10-tetraaza-cyclododecane} \]

1. N-Benzoxylcyclenyl-2,2′-dichlorodithiylethylamine 2a (13.7 g, 0.05 mol) and the disodium salt of 3 (30.5 g, 0.05 mol) were dissolved in dry DMF (500 ml) and stirred at 100 °C during 3 h. After cooling and filtering, the solution was concentrated until the volume was 250 ml, then diluted with water (1500 ml). The precipitate was extracted with ether-methanol (1:1) and benzene-hexane (9:2), the combined extracts washed with 5 % NaOH (6 × 50 ml), dried (MgSO₄) and the solvents evaporated. Recrystallization from methanol-ether (1:1) yielded 3.6 g (98 %) of the 2-oxazolidinone 4, m.p. 179–181 °C. Anal. C₁₀H₇N₂O₂S₂: C, H, N, and S, m/e (% rel. int.) 613(7.2, M+1), 155 (9.4, M0), 91 (100.0, C₆H₄). IR (KBr): 1740(s) cm⁻¹. ¹H NMR (CDCl₃-TFA): 2.44 (9H, CH₃), 3.4 (16H, complex, CH₂O and CH₂N), 4.27 (2H, s, benzyl protons), 7.31 and 7.5 (17H, s and AA'BB'-system, aromatic protons). The NaOH washing solution contained 1.9 g (7 %) of the unreacted diethylenetriamine derivative 3, m.p. 174–176 °C. To achieve selective fission of any benzoxycarbonyl groups present,¹ the remaining solid after extraction was dissolved in acetic acid containing 45 % HBr and left at room temp. for several days. On cooling 3.9 g (12 %) of the benzyl compound 5 crystallized, m.p. (ethanol) 144–151 °C. Mol. wt., calc. 655, found 655 ± 10. MS, m/e (% rel. int.) 500 (11.1 M − Tos), 155 (3.8, Tos) 91 (100.0, C₆H₄). IR (KBr): 3250(s) cm⁻¹. ¹H NMR (CDCl₃): 2.24 (2H, s, CH₂N), 3.0 (8H, complex, CH₃N), 4.29 (2H, s, benzyl protons), 7.36 and 7.6 (17H, s and AA'BB'-system, aromatic protons). No basic products were isolated.

Attempted synthesis of 10-benzyloxybenzyl-1,4,7,10-tetraaza-cyclododecane 6. A solution of potassium tert-butoxide (20 ml, 1.05 M) was diluted with benzene (20 ml) and heated to boiling. The benzyl urethane 2a (2.7 g, 0.01 mol) and distilled benzene (206 g, 0.01 mol) were added under vigorous stirring during 45 min. After 10 h the mixture was cooled, filtered and the solvents evaporated. Chromatography of the remaining oil on silica gel using light petroleum-ethyl acetate (2:1) furnished the known products, 3-ethenyl-2-oxazolidine 7* (25 %), benzyl chloride (29 %) and the monobenzyl ether of diethylene glycol 8* (17 %), which were identified by IR = H NMR = GLC analysis.

2-Oxazolidinone formation in DMSO in the presence of sodium chloride. The benzyl urethane 2a (2.76 g, 10 mol) and NaCl (0.59 g, 10 mmol) were dissolved in dry DMSO (50 ml) and stirred at 170 °C during 5 h. Na₂CO₃ (0.8 g, 7.5 mmol) was added and after additional 2 h the solution was cooled and diluted with water (100 ml). Work-up with ether gave 3-ethenyl-2-oxazolidinone 7* in 90 % purity (GLC), yield 0.5 g (40 %).

2-Oxazolidinone formation in benzene in the presence of potassium chloride. The benzyl urethane 2a (0.5 g, 1.8 mmol), KCl (28 mg, 0.38 mmol) and 18-crown-6 (0.11 g, 0.42 mmol) were stirred in boiling benzene during 20 h. After evaporation of the solvent in vacuo it was shown by ¹H NMR-GLC analysis that the remaining mixture consisted of the 2-oxazolidinone 8* (47 %) and benzyl chloride (29 %), besides unreacted starting material 2a (24 %). This corresponds to a formation of the 2-oxazolidinone 8 in 66 % yield.


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