Reactions of α-Halo Acid Chlorides with Diisopropylcarbodiimide. 5-Oxazolidinones

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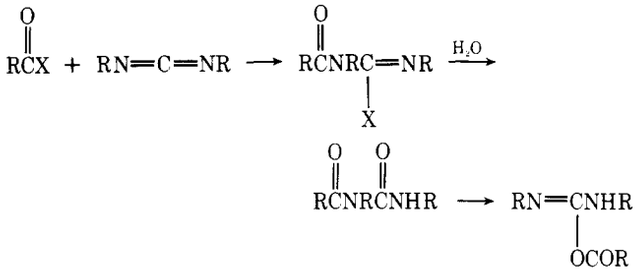
The reaction of diisopropylcarbodiimide with chloroacetyl, α-chloropropionyl, and α-bromoisobutyryl chlorides yields the corresponding acylchloroformamidines. Hydrolysis of the formamidines yields the acylureas, which under the acid conditions of the hydrolysis rearrange to the *O*-acylureas, which undergo ring closure to the 5-oxazolidinones upon heating. Chloroacetylchloroformamidine undergoes ring closure in the presence of triethylamine and water to yield the 4-oxazolidinone. The hydrolysis and rearrangement of the 5-oxazolidinones as well as the mechanism of ring formation are discussed.

Acid halides react with carbodiimides to form *N*-acylhaloformamidines, which readily hydrolyze to form *N*-acylureas.[1,2] These ureas may also be formed by the controlled reaction of acids and carbodiimides and by the reaction of an acid halide and an appropriately substituted urea.[3-9] *N*-

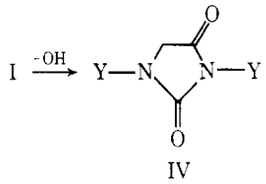


Acylureas rearrange to *O*-acylisoureas under appropriate conditions; i.e., the *N*-acylureas are favored under basic conditions and the *O*-acylisoureas are predominant under acid conditions[4,5,9]

We would like to describe a study of the reactions of some α-halo acid chlorides and diisopropylcarbodiimides to yield *N*-acylchloroformamidines, hydrolysis to the corresponding ureas, and subsequent formation of 5-oxazolidinones and 4-oxazolidinones. We have recently described the conversion of acylchloroformamidines derived from α-halo acid halides and diisopropylcarbodiimide to 2-azetidinones.[11]

The α-halo acid chlorides were reacted with diisopropylcarbodiimide to yield the acylchloroformamidines, which were hydrolyzed to the acylureas. The acylureas apparently rearranged to the *O*-acylisoureas under the acid conditions of the hydrolysis and either on standing or upon heating underwent ring closure to the 3-isopropyl-2-isopropylimino-5-oxazolidinones (I–III). The solid acylureas did not undergo oxazolidinone formation until molten. If the acylureas were heated rapidly, sublimation occurred instead of ring closure.

Upon washing I with a suspension of ether and dilute potassium hydroxide solution for 5 min, 1,3-diisopropyl-1,3-diazolidine-2,4-dione (IV) was recovered from the ether layer.

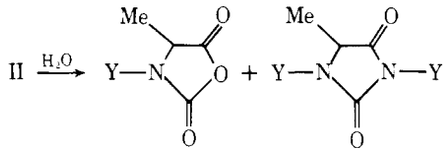


IV

Y = *i*-Pr

This rearrangement apparently involves a nucleophilic attack by base at the carbonyl carbon with subsequent ring opening forming a resonance stabilized oxyanion involving the imino group. A subsequent ring closure would yield the diazolidinedione. When the reaction was allowed to proceed for more than 5 min, the diazolidinedione was hydrolyzed further, in which case the products were not identified.

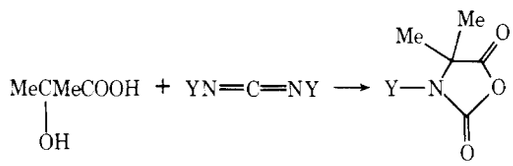
The 5-oxazolidinones are sensitive to moisture and undergo rearrangement and hydrolysis upon exposure to the atmosphere. A sample of II was allowed to stand in air for 2 weeks. The initially solid 5-oxazolidinone reacted with the moisture in the air and was converted to a viscous oil. This oil was dissolved in ether and analyzed by VPC and identified as 4-methyl-3-isopropyl-2,5-oxazolidinedione (V) and 4-methyl-1,3-diisopropyl-1,3-diazolidine-2,5-dione (VI). The diazolidinedione is the rearrangement product and the oxazolidinedione is the result of hydrolysis of the carbon–nitrogen double bond of the 5-oxazolidinone. A similar 3-cyclohexyl-4,4-dimethyl-2,5-oxazolidinedione was obtained by Robba and Maume from the reaction of α-hydroxyisobutyric acid with dicyclohexylcarbodiimide.[12]



V VI

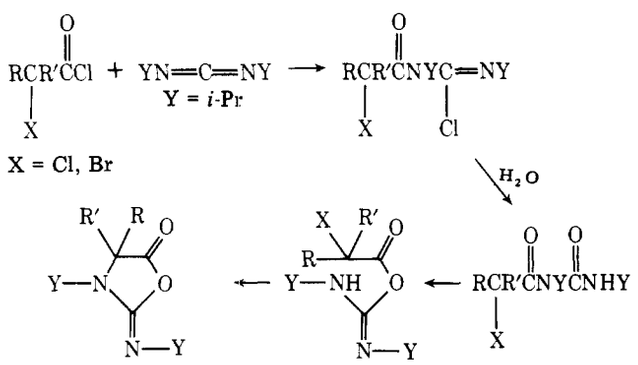
Y = *i*-Pr

In an effort to verify the intermediacy of the *O*-acylisourea



Y = C_6H_{11}

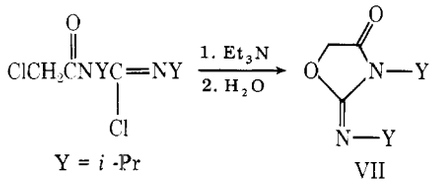
Scheme I



I, R = R′ = H
II, R = H; R′ = Me
III, R = R′ = Me

in the formation of the 5-oxazolidinones, chloroacetic acid and diisopropylcarbodiimide were allowed to react in carbon tetrachloride. The 5-oxazolidinone was isolated along with some disubstituted urea, which is the by-product of chloroacetic anhydride formation. The 5-oxoazolidinone formation from the *O*-acylisourea is the result of a nucleophilic displacement of the α-chloro substituent on the acyl group by the imino group of the isourea with the subsequent loss of hydrogen chloride as illustrated in Scheme I.

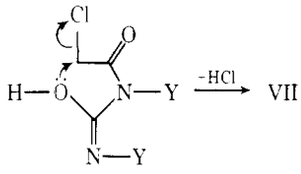
The treatment of the acylchloroformamidine derived from chloroacetyl chloride and diisopropylcarbodiimide in hexane with triethylamine at room temperature followed immediately by the addition of water resulted in the formation of 3-isopropyl-2-isopropylimino-4-oxazolidinone (VII). The acyl-



Y = *i*-Pr VII

chloroformamidine will react slowly with the triethylamine at room temperature to yield the 2-azetidinone, so the addition of water is critical. The presence of the amine scavenges the hydrogen chloride that is eliminated from both the hydrolysis of the acylchloroformamidine and the ring closure, thus inhibiting the formation of *O*-acylisourea, which is favored under acid conditions, and preventing the formation of the 5-oxazolidinone. Mironova and Dvorko have reported a similar reaction of chloroacetic anhydride or chloroacetyl chloride with dicyclohexylurea in benzene in the presence of pyridine.[10]

The 4-oxazolidinone ring formation arises from the nucleophilic displacement of the α-chloro substituent on the acyl group by the oxygen of the carbonyl of the urea with subse-



Y = *i*-Pr

quent loss of hydrogen chloride. There was no evidence for the formation of the diazolidinedione, which would arise from the nitrogen of the amino group of the urea displacing the chloride ion.

While there are several reports in the literature on the reaction of carboxylic acids, acid halides, and other acid derivatives with carbodiimides, there are very scattered reports whereby the acid derivative contains an α-halo substituent. This feature enables a facile ring closure of the α-haloacylurea or the corresponding *O*-acylisourea to 5-oxazolidinones and 4-oxazolidinones, respectively. Therefore, in summary, the reaction of α-halo acid halides with carbodiimides, hydrolysis to the ureas, spontaneous rearrangement to the *O*-acylisourea, and subsequent ring closure provides an excellent general synthesis for 5-oxazolidinones.

Experimental Section

Proton NMR spectra were recorded on a Hitachi Perkin-Elmer R-24B spectrometer employing tetramethylsilane as an internal standard. VPC separations were achieved using a 10 ft × ½ in. outside diameter glass column packed with 10% SE-30 on Chromosorb WAW, 60/80 mesh, in a Varian 1525-B gas chromatograph with a thermal conductivity detector. Mass spectra were obtained using a Hitachi Perkin-Elmer RMU-6E double focusing mass spectrometer. The infrared spectra were recorded on a Perkin Elmer Model 237 and Beckman Model 33 grating infrared spectrometers.

Solvents were dried and purified by distillation from sodium–potassium alloy under a nitrogen atmosphere prior to use. Commercially available triethylamine was dried over sodium metal and distilled prior to use.

N-tert-Butylbenzylimine was prepared from benzaldehyde and *tert*-butylamine according to standard procedure.[13] *N,N'*-Diisopropylcarbodiimide was commercially available and used without further purification.

General Procedure for Acylformamidines. A 0.05-mol portion of the α-haloacid halide was added with stirring to 0.5 mol of diisopropylcarbodiimide in 100 mL of ether at room temperature. After about 30 min, the ether was evaporated to yield the *N*-(α-haloacyl)-*N,N'*-diisopropylformamidine.

Chloro-*N*-chloroacetyl-*N,N'*-diisopropylformamidine. This formamidine decomposed upon distillation: IR 1670 and 1695 cm^{-1}; NMR (CCl_4) δ 1.23 (d, 6 H), 1.35 (d, 6 H), 3.90 (h, 1 H), 4.15 (s, 2 H), and 4.46 (h, 1 H).

Chloro-*N*-(α-chloropropionyl)-*N,N'*-diisopropylformamidine. This adduct distilled at 34 °C (0.025 Torr): 1665 and 1700 cm^{-1}; NMR (CCl_4) δ 1.23 (d, 6 H), 1.35 (d, 6 H), 1.58 (d, 3 H), 3.90 (h, 1 H), 4.45 (h, 1 H), and 4.67 (q, 1 H).

Anal. Calcd for $C_{10}H_{18}Cl_2N_2O$: N, 11.06. Found: N, 11.39.

General Procedure for Acylureas. An ether solution containing 0.05 mol of acylformamidine was prepared as described above. A 10-mL portion of water was added with stirring and stirring was continued for 1 h. The ether layer was separated, dried over anhydrous $CaCl_2$, and evaporated to yield the urea.

***N*-Chloroacetyl-*N,N'*-diisopropylurea.** A viscous oil was obtained which was unstable at room temperature: IR 1670, 1720, and 3300 cm^{-1}; NMR (CCl_4) δ 1.15 (d, 6 H), 1.25 (d, 6 H), 4.0 (m, 2 H), 4.18 (s, 2 H), and 7.50 (br d, 1 H).

***N*-(α-Chloropropionyl)-*N,N'*-diisopropylurea.** This urea was recrystallized from petroleum ether (100%): mp 92 °C; IR 1660, 1695, 1740, and 3260 cm^{-1}; NMR (CCl_4) δ 1.25 (d, 6 H), 1.35 (d, 6 H), 1.62 (d, 3 H), 4.2 (m, 2 H), 4.54 (q, 1 H), and 6.95 (s, 1 H).

Anal. Calcd for $C_{10}H_{19}ClN_2O_2$: C, 51.17; H, 8.16; N, 11.93. Found: C, 51.37; H, 8.29; N, 12.07.

***N*-(α-Bromoisobutyryl)-*N,N'*-diisopropylurea.** This urea was recrystallized from petroleum ether (75%): mp 87–89 °C, slowly decomposed at room temperature; IR 1640, 1675, 1700, and 3300 cm^{-1}; NMR (CCl_4) δ 1.30 (d, 6 H), 1.45 (d, 6 H), 2.05 (s, 6 H), 4.02 (h, 1 H), 4.62 (h, 1 H), and 6.98 (br d, 1 H).

General Procedure for 5-Oxazolidinones. A 0.01-mol portion of the acylurea prepared as described above was heated slightly above the melting temperature until the solid 5-oxazolidinone had formed.

3-Isopropyl-2-isopropylimino-5-oxazolidine (I). This oxazolidinone was obtained at room temperature upon standing overnight. Purification was accomplished by sublimation (77%): mp 192 °C; IR 1670 and 1795 cm^{-1}; NMR (Me_2SO-d_6) δ 1.35 (d, 6 H), 1.44 (d, 6 H), 4.10 (h, 1 H), 4.58 (h, 1 H), and 5.05 (s, 2 H); mass spectrum parent peak at *m/e* 184 (theory 184).

4-Methyl-3-isopropyl-2-isopropylimino-5-oxazolidinone (II). The acylurea was heated at 100 °C for 1 h (98%): mp 110 °C; IR 1665 and 1790 cm^{-1}; NMR (Me_2SO-d_6) δ 1.35 (d, 6 H), 1.40 (d, 6 H), 1.55 (d, 3 H), 4.05 (h, 1 H), 4.93 (h, 1 H), and 5.17 (q, 1 H); mass spectrum parent peak at *m/e* 198 (theory 198).

4,4-Dimethyl-3-isopropyl-2-isopropylimino-5-oxazolidinone (III). The acylurea was heated at 95 °C for 1 h and sublimed in vacuo (90%): mp 185 °C; IR 1695 and 1785 cm^{-1}; NMR (Me_2SO-d_6) δ 1.35 (d, 6 H), 1.44 (d, 6 H), 1.62 (s, 6 H), 4.03 (h, 1 H), and 4.68 (h, 1 H); mass spectrum parent peak *m/e* 212 (theory 212).

1,3-Diisopropyl-1,3-diazolidine-2,4-dione (IV). A 1.0-g portion of I was added to a mixture of 20 mL of 1 M KOH solution and 20 mL of ether with stirring. After 5 min, the ether layer was separated, dried over $CaCl_2$, and evaporated to give 0.75 g of dione (75%). This dione is a viscous liquid and was collected by VPC for analysis; IR 1700 cm^{-1}; NMR (CCl_4) δ 1.05 (d, 6 H), 1.50 (d, 6 H), 3.8 (m, 2 H), and 4.35 (s, 2 H); mass spectrum parent peak *m/e* 184 (theory 184).

Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.20. Found: C, 58.55; H, 8.92; N, 15.21.

Hydrolysis and Rearrangement of II. An 0.8-g (0.004-mol) portion of II was allowed to stand in air and after 2 weeks, VPC revealed the presence of two components, which were collected and analyzed.

4-Methyl-3-isopropyl-2,5-oxazolidinedione (V). A liquid: IR 1745 and 1820 cm^{-1}; NMR (CCl_4) δ 1.35 (d, 6 H), 1.46 (d, 3 H), 4.01 (h, 1 H), and 4.43 (q, 1 H).

Anal. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.89; H, 7.47; N, 9.37.

5-Methyl-1,3-diisopropyl-1,3-diazolidine-2,4-dione (VI). A liquid: IR 1700 cm^{-1}; NMR (CCl_4) δ 1.05 (d, 6 H), 1.40 (d, 6 H), 1.45 (d, 3 H), 2.8 (m, 2 H), and 4.36 (q, 1 H).

Anal. Calcd for $C_{10}H_{18}N_2O_2$: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.28; H, 9.06; N, 13.95.

3-Isopropyl-2-isopropylimino-4-oxazolidinone (VII). To 0.01 mol of chloro-*N*-chloroacetyl-*N,N'*-diisopropylformamidine in 50 mL of hexane was added 1.4 mL (0.01 mol) of triethylamine at room temperature, followed immediately by the addition of excess water. After a few minutes the amine salt precipitated; the solution was filtered and the solvent evaporated to give 1.6 g (88%) of the 4-oxazolidinone; mp 46–48 °C; IR 1690 and 1750 cm^{-1}; NMR (CCl_4) δ 1.15 (d, 6 H), 1.35 (d, 6 H), 3.59 (s, 2 H), and 4.2 (m, 2 H); mass spectrum parent peak *m/e* 184 (theory 184).

Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.20. Found: C, 58.27; H, 8.48; N, 15.21.

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Registry No.—I, 63059-02-9; II, 63059-03-0; III, 63059-04-1; IV, 63059-05-2; V, 63059-06-3; VI, 63509-07-4; VII, 57095-80-4; diisopropylcarbodiimide, 693-13-0; chloro-*N*-chloroacetyl-*N,N'*-diisopropylformamidine, 63059-08-5; chloro-*N*-(α-chloropropionyl)-*N,N'*-diisopropylformamidine, 63059-09-6; chloroacetyl chloride, 79-04-9; α-chloropropionyl chloride, 7623-09-8; *N*-chloroacetyl-*N,N'*-diisopropylurea, 63059-10-9; *N*-(α-chloropropionyl)-*N,N'*-diisopropylurea, 63059-11-0; *N*-(α-bromoisobutyryl)-*N,N'*-diisopropylurea, 63059-12-1; α-bromoisobutyryl chloride, 20469-89-0; chloro-*N*-(α-bromosiobutyryl)-*N,N'*-diisopropylformamidine, 63059-13-2.

References and Notes

(1) P. Fischer, German Patent 1 131 661 (1962); *Chem. Abstr.*, **58**, 1401d (1963).
(2) K. Hartke and E. Palou, *Chem. Ber.*, **99**, 3155 (1966).
(3) D. F. Mironova, G. F. Dvorko, and T. N. Skuratovskaya, *Ukr. Khim. Zh.*, **36**, 190 (1970).
(4) D. F. Mironova, G. F. Dvorko, and T. N. Skuratovskaya, *Urk. Khim. Zh.*, **35**, 726 (1969).
(5) D. F. Mironova and G. F. Dvorko, *Ukr. Khim. Zh.*, **37**, 458 (1971).
(6) I. Muramatsu and A. Hagitan, *Nippon Kagaka Zasshi*, **80**, 1497 (1959); *Chem. Abstr.*, **55**, 6394f (1961).
(7) W. S. Johnson, V. J. Bauer, J. L. Morgrave, M. A. Frisch, L. H. Dreger, and W. N. Hubbard, *J. Am. Chem. Soc.*, **83**, 606 (1961).
(8) D. Geffken and G. Zinner, *Chem. Ber.*, **108**, 3730 (1975).
(9) F. Kurzer and K. Douraghi-Zadeh, *Chem. Rev.*, **67**, 107 (1967).
(10) D. F. Mironova, and G. F. Dvorko, *Ukr. Khim. Zh.*, **38**, 60 (1972).
(11) W. T. Brady and R. A. Owens, *J. Heterocycl. Chem.*, **14**, 179 (1977).
(12) M. Robba and D. Maume, *C. R. Acad. Sci., Ser. C*, **272**, 475 (1971).
(13) L. A. Bigelow and H. Eatough, "Organic Synthesis", Collect. Vol. I, Wiley, New York, N.Y., 1946, p 80.

Substituent and Geometry Dependence of the Degenerate Ligand Exchange of Dialkoxysulfuranes with Hexafluoro-2-phenyl-2-propanol. Sulfuranes and Sulfilimines Derived from Thianthrene, Phenothiazine, and Phenoxathiin[1]

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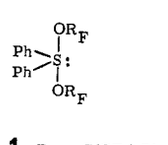
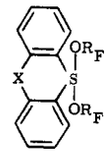
The oxidations of thianthrene, *N*-phenylphenothiazine, and phenoxathiin with bromine in the presence of the potassium salt of 1,1,1,3,3,3-hexafluoro-2-phenyl-2-propanol (R_FOH) lead to the formation of dialkoxysulfuranes. The characterization of sulfuranes is described. All three are very reactive in dehydrating *tert*-butyl alcohol at room temperature. The degenerate alkoxy ligand exchange with R_FOH is determined by NMR to be very fast, with the rates for sulfuranes derived from phenoxathiin, thianthrene, and *N*-phenylphenothiazine increasing in the order listed. The first two of these sulfuranes were shown to react with benzylamine to give the corresponding *N*-benzylsulfilimines.

Over the past few years several types of oxysulfuranes have been isolated and studied.[2] The chemistry of these species, notably that of dialkoxysulfurane **1**,[3] has been shown to derive from rapid ligand exchange reactions involving the weakly bound[2] apical alkoxy ligands. The mechanism for ligand exchange for **1** in solution has been found[4] to very probably be dissociative via the alkoxysulfonium ion. This paper reports the synthesis and some reactions, including a study of the rates of the degenerate ligand exchange with R_FOH, where R_F is $PhC(CF_3)_2$, of cyclic sulfuranes **2**, **3**, and **4**, in which an atom bridge is expected to allow a close approach to coplanarity of the two equatorial aryl ligands.



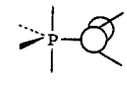
1, $R_F = C(CF_3)_2Ph$



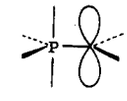
2, X = N-Ph
3, X = O
4, X = S

Results and Discussion

Experimental and theoretical bases exist[5] for the assertion that equatorial π-donor ligands in phosphoranes have a preferred orientation with the donor p orbital in the equatorial plane as in **5** rather than perpendicular to this plane as in **6**.[5k]



5



6

The situation is less clear cut in the case of sulfuranes, where calculations[6] suggest that the repulsive interaction of the π donor with the sulfur lone pair may predominate in a con-