Studies of 2-Oxazolidinones. I. A Convenient Synthesis of 3-Substituted 2-Oxazolidinones

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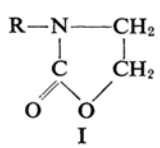
Although several methods for the formation of 3-substituted 2-oxazolidinones (I) are known, these preparative routes may be classified into three general groups: (i) the condensation of β-hydroxyethylamines with carbonic acid derivatives such as dialkyl carbonates[1], urea[2], or phosgene[3]; (ii) the addition of isocyanates to



I

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3) P. Otto, *J. prakt. Chem.*, [2], **44**, 17 (1891).

TABLE I. β-CHLOROETHYL CARBAMATES

N-Sub. β-chloroethyl carbamates	Method	Total yield[a]	M. p.	Solvent of crystn.[b]	C, %		H, %		N, %	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
n-Butyl	B	66	113(4.3)[c,d]							
t-Butyl	A	58	90(7)[c]		46.80	46.69	7.86	7.80	7.96	7.96
Phenyl	B	80	160(5)[c]; 49[e]							
p-Tolyl	B	75	61[f]	B						
o-Tolyl	A	91	45[g]	L						
p-Nitrophenyl	B	88	116	B	44.19	44.47	3.71	3.97	11.45	11.57
o-Nitrophenyl	A	91	70.5	B-L	44.19	44.80	3.71	4.09	11.45	11.65
p-Carbethoxyphenyl	A	86	145	B-E	53.05	53.09	5.19	5.05	5.16	5.38
p-Chlorophenyl	A	69	69[h]	B						
1-Anthraquinonyl	A	84	184[i]	E-Dm						
Ethylene-bis	A	39	136[j]	E						
Tetramethylene-bis	B	50[k]	118[l]	B						
m-Phenylene-bis	B	79	115.5	Dm-W	44.88	45.13	4.39	4.63	8.37	8.36
p-Phenylene-bis	B	78	202	Dm-W	44.88	45.15	4.39	4.48	8.37	8.25

a. In method A the yield was calculated as 93% for β-chloroethyl chloroformate synthesis (see Experimental). b. B=Benzene, Dm=Dimethylformamide, E=Ethanol, L=Ligroin, W=Water. c. B. p. (mmHg). d. Reported b. p. 98°C (1 mmHg), Ref. 11. e. Reported b. p. 134°C (2 mmHg), Ref. 11; m. p. 51°C, Ref. 6. f. Reported m. p. 63°C, Ref. 8. g. Reported m. p. 46°C, Ref. 8. h. Reported m. p. 63°C, Ref. 7; 69°C, Ref.8. i. Reported m. p. 186°C, A. Noguchi, *J. Soc. Org. Synth. Chem. Japan (Yūki Gōsei Kagaku Kyokai Shi)*, **13**, 78 (1955). j. Reported m. p. 136.5°C, R. Delaky et al., *Bull. soc. chim. France*, 396 (1951). k. This low value is due to a poor yield of the diisocyanate prepared from the corresponding acid. l. Reported m. p. 118.5°C, Ref. 10.

epoxides[4,5]; (iii) the dehydrochlorination of β-chloroethyl carbamates[6-9]. Among instances of route iii, β-chloroethyl carbamates have recently been obtained by the condensation of amines with ethylene carbonate, followed by the chlorination of the resulting β-hydroxyethyl carbamates[9,10]. However, the authors have considered that Nemirowsky's well-known method A[6-8,11] may have an abvantage over the above method from the synthetic standpoint.

Method A:

$$COCl_2 + HOCH_2CH_2Cl \rightarrow ClCOOCH_2CH_2Cl$$

$$RNH_2 + ClCOOCH_2CH_2Cl \rightarrow RNHCOOCH_2CH_2Cl$$

Making another combination of the three reactants, the following method B may be considered, although it has not previously been reported.

Method B:

$$RNH_2 + COCl_2 \rightarrow RNCO$$

$$RNCO + HOCH_2CH_2Cl \rightarrow RNHCOOCH_2CH_2Cl$$

Method B is a modification of the method ii mentioned above.

This paper deals with the preparation of β-chloroethyl carbamates by method A or B and with the ring-closure of these compounds to form 3-substituted 2-oxazolidinones. The results of the carbamate syntheses are summarized in Table I. These results seem to prove that our method B is comparable to method A in yields and is applicable as a convenient method of 2-oxazolidinone synthesis.

In the dehydrochlorinative ring-closure of β-chloroethyl carbamates, many workers have used more than one molar equivalent of alkali. However, it is known that the oxazolidinones are less stable in alkaline media and are easily hydrolyzed by aqueous alkali to yield β-hydroxyethylamines[3,7]. In this research, optimum yields were obtained by the use of approximately one molar equivalent of sodium ethoxide in dioxane or ethanol. For example, although Naiki[12] failed in the synthesis of 3-(1-anthraquinonyl)-2-oxazolidinone using aqueous alkali as a ring-closure agent, we have succeeded in this synthesis using an equivalent amount of

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TABLE II. 3-SUBSTITUTED 2-OXAZOLIDINONES

3-Sub. 2-Oxazolidinone	Solvent of reaction[a]	Yield %	M. p.	Solvent of crystn.[a]	C, %		H, %		N, %	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
n-Butyl	D	80	122(4)[b,c]							
t-Butyl	E	62	94(2)[b]		58.72	58.88	9.51	9.44	9.78	9.90
Phenyl	E	94	118[d]	B						
p-Tolyl	D	70	91[e]	B-L						
o-Tolyl	E	81	170(4)[b,f]							
p-Nitrophenyl	E	95	154.5	B-E	51.92	52.14	3.87	4.06	13.46	13.31
o-Nitrophenyl	E	94	165	B	51.92	52.21	3.87	4.10	13.46	13.61
p-Carbethoxyphenyl	E	97	110[g]	B						
p-Chlorophenyl	E	85	121[h]	B						
1-Anthraquinonyl	D	85	226.5	Dm	69.62	69.36	3.78	4.00	4.78	4.76
Ethylene-bis	E	80	107[i]	E						
Tetramethylene-bis	D	85	118	E	52.62	52.68	7.07	7.32	12.27	12.00
m-Phenylene-bis	D	62	175	B	58.06	57.78	4.87	5.05	11.29	11.40
p-Phenylene-bis	D-Dm	68	253	Dm	58.06	58.31	4.87	5.02	11.29	11.49

a. D=Dioxane, E=Ethanol, B=Benzene, L=Ligroin, Dm=Dimethylformamide. b. B. p. (mmHg). c. Reported b. p. 94°C (1 mmHg), Ref. 1. d. Reported m. p. 118°C, J. R. Caldwell, U. S. Pat. 2656328 [*Chem. Abstr.*, **48**, 2415 (1954)]; 122°C, Ref. 3; 124°C, Ref. 6. e. Reported m. p. 91°C, Ref. 7. f. Reported b. p. 180~185°C (3 mmHg), Ref. 7. g. Reported m. p. 110°C, Ref. 4. h. Reported m. p. 121°C, Ref. 8. i. Reported m. p. 108°C, Ref. 10.

alcoholate. In preparing 3-*p*-nitrophenyl-2-oxazolidinone, the use of alcoholate gave a satisfactory result, but the use of aqueous alkali resulted in the formation of *N*-*p*-nitrophenylethanolamine. Data on the dehydrochlorination of β-chloroethyl carbamates are given in Table II.

Experimental

All melting and boiling points are uncorrected.

β-Chloroethyl Chloroformate.—The preparation of the ester was carried out by a modification of the procedure of Nekrassow et al.[13] Phosgene was passed rapidly into 161 g. of ethylene chlorohydrin for 3 hr. at 0°C. The reaction mixture was then allowed to stand at room temperature (approximately 15°C) until the evolution of hydrogen chloride had subsided; it was then weighed. If the weight increase did not approach the theoretical expectation, this procedure was repeated. The resulting liquid was then refluxed for 2 hr. Upon distillation, 263 g. (93%) of the ester, b. p. 149~153°C (lit.[13] b. p. 152~153°C), was obtained.

Isocyanates.—Except for tetramethylenediisocyanate, all isocyanates were prepared from the corresponding amine hydrochlorides according to the well-known phosgene method[14]. The boiling points (or melting points) and yields of the isocyanates obtained were as follows: *n*-butyl-, b. p. 114°C (lit.[14] 115°C), 80%; phenyl-, b. p. 50~51°C/10 mmHg lit.[14] 56°C/16 mmHg, 82%; *p*-tolyl-, b. p. 110°C/72 mmHg lit.[14] 67.7°C/10 mmHg, 75%; *p*-nitrophenyl-, m. p. 57°C (lit.[14] 56~57°C), 88%; *m*-phenylenedi-, m. p. 51°C (lit.[14] 51°C), 79%; *p*-phenylenedi-, m. p. 94°C (lit.[14] 95°C), 85%. Tetramethylenediisocyanate was synthesized by a Curtius rearrangement of adipodiazide prepared from adipic acid[15]. The over-all yield was 50%. The product boiled at 80.5°C/5 mmHg, lit.[15] 93°C/7 mmHg.

***N*-Substituted β-Chloroethyl Carbamates.**—Typical examples are given below.

By Method A.—(*a*) *N-tert-Butyl-β-chloroethyl Carbamate.*—β-Chloroethyl chloroformate (59 g., 0.41 mol.) was stirred, drop by drop, into a mixture of 25 g. (0.34 mol.) of *tert*-butyl amine and 41 g. (0.41 mol.) of triethylamine. The reaction mixture was heated to 70°C for 30 min. and then poured into 200 ml. of water. The mixture was extracted with two 100 ml. portions of ether. The extract was dried over anhydrous sodium sulfate, and the ether was distilled off. When the residue was fractionated under reduced pressure, 38 g. (63%) of the carbamate, b. p. 90°C/7 mmHg, was obtained.

(*c*) *N-o-Nitrophenyl-β-chloroethyl Carbamate.*—A mixture of 43 g. (0.30 mol.) of β-chloroethyl chloroformate and 34.5 g. (0.25 mol.) of *o*-nitroaniline was heated to 120°C. Heating and stirring were continued for ca. 1 hr., until the evolution of hydrogen chloride ceased. Owing to the intermediate formation of the amine hydrochloride, the reaction mixture became heterogeneous, but subsequently it became clear again. This clear mixture was then cooled, and the precipitate of the carbamate was filtered, washed with ethanol, and dried. It weighed 61 g. (98%). Recrystallization from a benzene-ligroin mixture gave the pure product, m. p. 70.5°C.

By Method B. (*a*) *N-n-Butyl-β-chloroethyl Carbamate.*—A mixture of 25 g. (0.25 mol.) of *n*-butyl-isocyanate and 21 g. (0.26 mol.) of ethylene

13) W. Nekrassow and J. F. Komissarow, *J. prakt. Chem.*, [2], **123**, 163 (1929).

14) W. Siefken, *Ann.*, **562**, 75 (1949); R. L. Shriner et al., "Organic Syntheses", Coll. Vol. II., (1943), p. 453.

15) Y. Iwakura et al., "Experiments in Polymer Chemistry (Kōbunshi Zikken Kagaku Kōza)", Vol. II, Kyōritsu, Tokyo (1958), p. 141.

chlorohydrin in 50 ml. of dry benzene was refluxed for 5 hr. After evaporation of the benzene, distillation of the residue yielded 39 g. (83%) of the carbamate, b. p. 113°C/4.3 mmHg.

(*b*) *N-p-Tolyl-β-chloroethyl Carbamate.*—A mixture of 33.3 g. (0.25 mol.) of *p*-tolylisocyanate and 21 g. (0.26 mol.) of ethylene chlorohydrin in 50 ml. of dry toluene was refluxed for 2 hr. Removal of the solvent gave 54 g. of the crude product, and the yield was nearly quantitative. Recrystallization from benzene afforded the pure compound, m. p. 61°C.

3-Substituted 2-Oxazolidinones.—In all experiments, sodium ethoxide was used as a ring-closure agent and the reaction was carried out in dioxane or ethanol. A few examples follow.

(a) 3, 3'-Tetramethylene-bis-(2-oxazolidinone).—A solution of sodium ethoxide, prepared from 7.5 g. (0.33 g. atom) of sodium and 50 ml. of absolute ethanol, was stirred, drop by drop, into a solution of 48.5 g. (0.16 mol.) of *N, N'*-tetramethylene-bis-(β-chloroethyl carbamate) in 50 ml. of dioxane at 70~80°C. After completion of the addition, stirring and heating were continued for another hour. The precipitate of sodium chloride was filtered from the warm mixture. After evaporation of the solvent form the filtrate, 31 g. (95%) of the bis-(2-oxazolidinone) was obtained. The pure compound had a m.p. of 118°C after recrystallization from ethanol.

(b) 3-Phenyl-2-oxazolidinone.—A solution of 5.0 g. (0.22 g. atom) of sodium in 50 ml. of ethanol was gradually stirred into 39.5 g. (0.20 mol.) of *N*-phenyl-β-chloroethyl carbamate in 50 ml. of ethanol at 65~70°C. After the addition was complete, this temperature was maintained for 1 hr.; 100 ml. of water was then stirred into the reaction mixture to dissolve the sodium chloride. The crude 3-phenyl-2-oxazolidinone which separated on cooling was collected by filtration, washed with ethanol, and dried. The yield was 30 g. (94%). The pure product melted at 118°C after recrystallization from benzene.

(c) 3-p-Nitrophenyl-2-oxazolidinone.—A ca. 10% sodium ethoxide solution was stirred, drop by drop, into 46.5 g. (0.19 mol.) of *N-p*-nitrophenyl-β-chloroethyl carbamate in 150 ml. of ethanol at 75°C, until the reaction mixture became slightly brown. The consumption of the sodium ethoxide was nearly the theoretical expectation. Upon the stirring in of 300 ml. of water to the above mixture, 37.5 g. (95%) of 3-*p*-nitrophenyl-2-oxazolidinone crystallized out as yellow needles. Recrystallization from a benzene-ethanol mixture gave the pure compound, m. p. 154°C.

When an alcoholic solution of *N-p*-nitrophenyl-β-chloroethyl carbamate was treated with two molar equivalents of 30% aqueous potassium hydroxide at 60°C, crude *N-p*-nitrophenylethanolamine separated out in a nearly quantitative yield. This was recrystallized from benzene, and the pure product melted at 109°C. Its structure was confirmed by elemental analysis and by infrared measurement.

Found: C, 52.72; H, 5.79; N, 15.77. Calcd. for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38%.

Summary

A convenient synthesis of 3-substituted 2-oxazolidinones starting from three components —aliphatic or aromatic amines, phosgene and ethylene chlorohydrin—has been developed.

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