SYNTHESIS OF DERIVATIVES OF OXAZOLIDIN-5-ONES

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A method has been developed for the synthesis of derivatives of oxazolidin-5-one by the reaction of the corresponding N-benzyloxycarbonylaminoacid with formaldehyde in the presence of formic acid. Yields of derivatives of 3-benzyloxycarbonyloxazolidin-5-one increase with increased molecular weight of the initial compound. For the synthesis of 3-benzyloxycarbonyl-4-benzyloxazolidin-5-one the proposed method gives a higher yield than previously known methods. The reaction mechanism is discussed.

Derivatives of oxazolidin-5-ones are widely used for the synthesis of modified aminoacids including Nmethylaminoacids and heterocyclic compounds [1, 2]. One of the methods for the synthesis of these compounds involves the cyclization of N-benzyloxycarbonylaminoacids in the presence of p-toluenesulfonic acid and paraformaldehyde in solution in benzene or dry toluene (Method A) [1, 3-5]. To prevent the formation of by-products the reaction is carried out at high dilutions.

We have established that cyclization of N-benzyloxycarbonylaminoacids can also be effected in an aqueous medium using formaldehyde (formalin) as reagent in formic acid (Method B). This reagent has been used previously for the N-methylation of N-benzylaminoacids to the corresponding N-benzyl-N-methylamino acid (hydrogenolysis of the latter gives N-methylaminoacids) and in other reactions [3, 4].



I, II a R=Me,b R=CHMe₂, c R=CHMeCH₂Me, d R=CH₂Ph

Methods A and B were compared for the synthesis of oxazolidin-5-ones and the results are collected in Table 1.

The yields of oxazolidin-5-one derivatives obtained by Method A decrease with increase in the number of carbon atoms in the aminoacid molecule. Method B, on the other hand, shows an increase in yields as the molecular weight of the aminoacid increases. Method B is convenient for the synthesis of 3-benzyloxycarbonyl-4-benzyloxazolidin-5-one and, it would seem, of other oxazolidine derivatives having more hydrophobic radicals at position 4.

In the reaction of N-benzyloxycarbonylaminoacids with CH_2O and HCO_2H a hydroxymethyl derivative is first formed and this then cyclizes to the oxazolidin-5-one.



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Aminoacid	Oxazolidin-5- one derivative	Yield, %		
		method A	method B	,
Ia	lla	97	51	88
Ib	ПЪ	90	58	55
Ic	Ис	87	64	68
Id	Пđ	87	96	82

TABLE 1. Synthesis of Derivatives of Oxazolidin-5-ones*

*Method A: reagents) paraformaldehyde, *p*-toluenesulfonic acid; solvent) toluene; temperature 110°C; reaction time 45 min. Method B: reagents) formalin, formic acid. Ratio of starting materials aminoacid-formaldehyde-formic acid = 1:1.5:5; temperature 100°C; reaction time 5-7 h.

TABLE 2. PMR Spectra of 3-Benzyloxycarbonyloxazolidin-5-ones

Com- pound	Chemical shifts, δ ppm (J Hz)
II a	1,60 (3H, d, ' = 7,2; CH ₃), 4,27 (1H, m, $J = 7,2 & 1,1$, NCH), 5,15 (2H, s, OCH ₂ -Ph), 5,24 & 5,43 (2H, m & d $J = 4,3 & 1,1$, NCH ₂ -O), 7,31 (5H, s, C ₆ H ₅)
II.b	0,98 $\[mu]$ 1,06 (6H, d & d J=6; CH ₃), 2,35 (1H, m, CH), 4,23 (1H, m, N-CH), 5,18 & 5,22 (2H, m & d J=4,4; N-CH ₂ -O), 5,20 (2H, s $\[mu]$ -CH ₂ -Ph), 7,37 (5H, m C ₆ H ₅)
Цс	0,97 & 0,93 (6H, t&d, CH ₃), 1,40 & 1,62 (2H, m&m, CH ₂ C), 2,11 (1H, m CCHC), 4,30 (1H, m, NCH), 5,19 μ 5,22 (2H, d&d, J=4.5; NCH ₂ O), 5,21 (2H, s OCH ₂ Ph), 7,38 (5H, m, C6H ₅)
Цđ	3,053,20 (2H, m,CH ₂ —Ph), 4,63 (1H, m,N—CH ₂ —C), 5,19 (2H, s,O—CH ₂ —Ph), 5,255,28 (2H, m,N—CH ₂ —O), 7,0 & 7,45 (10H, s&s, C ₆ H ₅)

The cyclodehydration of the hydroxymethyl derivative to oxazolidine can be accompanied by reduction of the hydroxymethyl group, the direction of the process being determined by the nature of the substituent on the nitrogen. Thus, whereas cyclodehydration predominates in the case of N-benzyloxycarbonyl derivatives **1a-d**, the presence of an N-benzyl group leads to the formation of N-methylaminoacids as the chief product (Quitt's method).

In the reaction of benzyloxycarbonylaminoacids with paraformaldehyde in the presence of p-toluenesulfonic acid, a methylene derivative [3] of composition



is obtained as a secondary product.

Evidently the corresponding N-hydroxymethyl derivative is involved in the formation of this compounds also. In the method which we have proposed, the formation of the compound referred to is not observed.

Derivatives of N-benzyloxycarbonyl-N-hydroxymethylaminoacids enter into cyclodehydration reactions even in the presence of considerable amounts of water in the reaction mixture, particularly in the case of the corresponding aminoacid derivatives with more hydrophobic substituents.

EXPERIMENTAL

The N-benzyloxycarbonylaminoacids used in the work were "Analytically Pure" grade from Reanal. PMR spectra were run on a Bruker WM-90 instrument; the spectroscopic characteristics are given in Table 2. Derivatives of oxazolidin-5-one were synthesized in nonaqueous media by the method of [2]. The quality of the oxazolidin-5-one derivatives was determined by liquid chromatography on a Dupont 830 chromatograph with a column packed with Silasorb C_{18} adsorbent; the

eluent was 25% acetonitrile, 75% 0.2 mole/liter ammonium acetate, pH 5.0. An ultraviolet detector was used operating at 220 or 230 nm.

3-Benzyloxycarbonyl-4-methyloxazolidin-5-one (IIa). To a solution of 2.23 g (10 mmole) N-benzyloxycarbonylalanine (Ia) in 1.39 ml formic acid was added 1.87 ml formalin (molar ratio of starting materials Ia-CH₂O-HCOOH = 1:1.5:5). The reaction mixture was heated at bp for 5 h and then evaporated in vacuum. The residual oil was poured into 40 ml of 1.5N NaHCO₃. The white precipitate was filtered off and washed with 0.5N NaHCO₃ (2 × 5 ml) and with water until neutral. Yield 1.2 g (51%) N-benzyloxycarbonyl-4-methyloxazolidin-5-one (IIa), mp 87°C (from [2], mp 88°C), R_f 0.92 (85:3:5:8:0.25 chloroform-ethyl acetate-ethanol-acetic acid-water).

3-Benzyloxycarbonyl-4-isopropyloxazolidin-5-one (IIb). A mixture of 2.51 g (10 mmole) N-benzyloxycarbonylvaline (Ib), 1.39 ml formic acid, and 1.87 ml formalin was heated on a water bath for 7 h at bp and then evaporated in vacuum. The oily residue was dissolved in 50 ml ether and washed with 40 ml 0.5N NaHCO₃. The aqueous layer was extracted with ether. The ether extracts were combined and dried over anhydrous Na₂SO₄. Removal of the ether yielded 1.56 g (58%) 3-benzyloxycarbonyl-4-isopropyloxazolidin-5-one (IIb), mp 53°C (from [2], mp 55°C), R_f 0.3 (4:1 heptane-ethyl acetate).

3-Benzyloxycarbonyl-4(2-methylpropyl)oxazolidin-5-one (IIc). A similar synthesis to that for IIb from 2.65 g (10 mmole) N-benzyl-oxycarbonylisoleucine (Ic), 1.39 ml formic acid, and 1.87 ml formalin, yielding 1.77 g (64%) 3-benzyloxycarbonyl-4-(2-methyl)propyloxazolidin-5-one (IIc), mp 68°C (from [2], mp 68°C), R_f 0.47 (4:1 heptane-ethyl acetate).

3-Benzyloxycarbonyl-4-benzyloxazolidin-5-one (IId). A similar synthesis to that for IIa from 3.0 g (10 mmole) N-benzyloxycarbonylphenylalanine (Id), 1.39 ml formic acid, and 1.87 ml formalin, yielding 3.0 g (96%) 3-benzyloxycarbonyl-4-benzyloxazolidin-5-one (IId), mp 82°C (from [2], mp 82°C).

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