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Communication

Novel side reactions accompanying activation and aminolysis of *N*-benzoyl-2-alkylserines★✪

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2-Phenyl-4-alkyl-4-hydroxymethyl-1,3-oxazolones (2a–d**) have been identified as side products accompanying activation of *N*-benzoyl-2-alkylserines (**1a–d**). Oxazolones** 2a–d **in the presence of amine rearrange subsequently to corresponding 4-alkyl-2-phenyl-4,5-dihydro-1,3-oxazole-5 carboxylic acids (**4a–d**) at a 20–68% yield.**

2-Alkylserines, chimeric amino acids bearing at the α-carbon atom two side chains, have found numerous synthetic applications. They are building blocks often used in the synthesis of oxoproline analogues [1–5], preparation of polyazole antibiotics [6], etc. Due to the presence of an additional OH functional group in the side chain and severely increased steric hindrance caused by the presence of two side chains attached to the C-2 atom, their incorporation into the peptide chain in many cases proceeds ineffectively [7] and usually requires powerful coupling reagents [8] and vigorous reaction conditions.

Recently, our studies revealed that incorporation of oligopeptides bearing 2-alkylserine as the C-terminal residue into the peptide chain [9] is accompanied by the formation of an acidic side-product. Experiments involving activation and coupling of model substrates, *N*-benzoyl-2-alkylserines (**1a–d**) [10] with aniline confirmed our preliminary observation and documented that the amount of the side-product depends on reaction conditions and bulkiness of 2-alkyl side chain.

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MATERIALS AND METHODS

Synthesis of 4-isobutylo-2-phenyl-4,5-dihydro-1,3-oxazole-4-carboxylic acid (4d). Typical procedure

a) 4-Hydroxymethyl-4-isobutyl-2-phenyl-1,3-oxazolone-(5) (**2d**) (247 mg, 1 mmol) in THF (10 ml) was treated with aniline (0.1 ml, 1.1 mmol) at room temp. for 12 h. The solvent was evaporated and the residue dissolved in ethyl acetate and washed successively with water, 1 M aq. $KHSO_4$, water, 3 × saturated aq. $NaHCO_3$ and again with water, dried with anhydrous $MgSO_4$, filtered and concentrated to dryness yielding anilide of *N*-benzoyl-2-isobutylserine (**3d**) (51 mg, 15%). TLC: R_f ($CHCl_3$/isopropanol, 9:1) = 0.76. FAB MS: 341 (12.7%, M+H). ^{1}H-NMR ($CDCl_3$) δ = 0.92 (d, 3H, J = 6.5 Hz, $\underline{CH_3}$-CH), 0.95 (d, 3H, J = 6.5 Hz, $\underline{CH_3}$-CH), 1.77 (m, 1H, CH), 2.07 (dd, 1H, J^1 = 14.5 Hz, J^2= 6.5 Hz, $\underline{CH_2}$-CH), 2.72 (dd, 1H, J^1 = 14.5 Hz, J^2 = 6.5 Hz, $\underline{CH_2}$-CH), 3.80, 4.66 (AB system, 2H, J = 12.5 Hz, $\underline{CH_2}$-OH), 4.70 (bs, 1H, CH_2-O$\underline{H}$), 6.95 (bd, 1H, J = 6.5 Hz, N$\underline{H}$), 7.10–7.57 (m, 8H, C_6H_5), 7.82–7.88 (m, 2H, C_6H_5), 9.64 (s, 1H, CO-NH-C_6H_5).

IR (film) ν: 3360 (NH, OH), 3064 (CH aromat.), 2960, 2872 (CH alifat.), 1640 (C=O), 1600 (C=O), 1572 (NHCO) cm^{-1}.

b) Aqueous phases separated after washing the preparation described in a) were combined, cooled to 5°C and than acidified with 5 N HCl (Congo red). Acidic product was extracted with ethyl acetate. Combined organic extracts were dried with $MgSO_4$, filtered and evaporated to dryness in a vacuum desiccator yielding crystalline 4-isobutylo-2-phenyl-4,5-dihydro-1,3-oxazole-4-carboxylic acid (**4d**) (168 mg, 68%), mp 84–85°C. TLC: R_f ($CHCl_3$/isopropanol, 9:1) = 0.76. FAB MS: 248 (100%, M+H), 202 (20.9%, M-COOH). ^{1}H-NMR ($CDCl_3$) δ = 0.95 (d, 3H, J = 6.5 Hz, $\underline{CH_3}$-CH), 0.99 (d, 3H, J = 6.5 Hz, $\underline{CH_3}$-CH), 1.76–2.02 (m, 3H, $\underline{CH_2}$-CH), 4.36, 4.90 (AB system, 2H, J = 9.0 Hz, $\underline{CH_2}$-OH), 7.37–7.57 (m, 3H, C_6H_5), 7.97–8.00 (m, 2H, C_6H_5), 8.61 (bs, 1H, COOH).

IR (film) ν: 3420 (OH), 3064 (CH aromat.), 2960 (CH alifat.), 1720 (C=O), 1628 (C=N) cm^{-1}.

RESULTS AND DISCUSSION

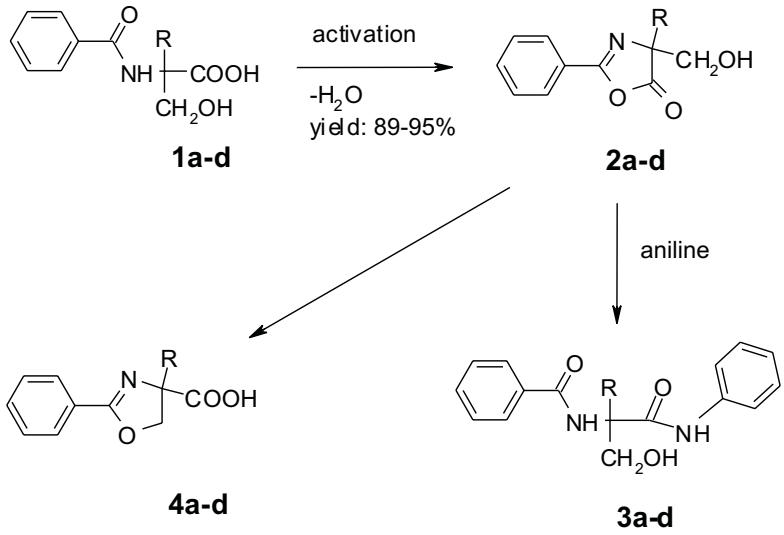
Determination of the contents of the mixture formed during synthesis of anilides **3a–d** documented that the amount of the side-product depended on reaction conditions and bulkiness of the 2-alkyl group. It was gradually increased from 0–20% for 2-methylserine (**1a**) to 24–68% for serines (**1b–d**) bearing more bulky side chains in the following order Me < Bn < *i*-Pr < *i*-Bu.

For the most hindered *iso*-propyl and *iso*-butyl substituent the formation of oxazole **4c–d** became the dominant reaction, substantially suppressing the formation of the expected anilides **3c–d**.

We found that isomerization of oxazolones proceeds also in the absence of aniline. A broad range of other compounds were found active as promoters of the formation of **3a–d,** including typical additives used in the synthesis of the peptide bond such as DMAP, HONSu, and HOBt (see Table 1).

The mechanism of the isomerization of *N*-benzoyl-2-alkylserines **1a–d** to oxazole-4-carboylic acids **4a–d** is not known. It seems likely that oxazolones **2a–d** are intermediates and the strain caused by the presence of two bulky substituents at C-2 promotes both the formation of **2** as well as their subsequent isomerization to **4**. Bearing in mind that **4a–d** form peptide bond more readily than the parent *N*-acyl-2-alkylserines **1a–d***, any strategy of synthesis of 2-alkyserine peptide

*Cierpucha, M., Woszczyna, A., Kolesińska B. & Kamiński, Z.J. (2000) The XVIII Annual Meeting of Polish Chemical Society, Łódź, Poland, p. 307 (in Polish?).



Scheme 1

Table 1. Anilides 3a–d and and/or 4-alkyl-2-phenyl-4,5-dihydro-1,3-oxazole-4-carboxylic acids 4a–d obtained from oxazolones 2a–d

	R	Reagent	Yield of anilides **3a–d**	Yield of oxazoles **4a–d**
		Aniline	73%	0
a	Me	DABCO	–	12%
		$MgBr_2$	–	16%
		DMAP	–	12%
		NEt_3	–	20%
		Aniline	40%	44%
b	Bn	NEt_3	–	26%
		DMAP	–	32%
		Aniline	16%	59%
c	*iso*-Pr	NEt_3	–	24%
		DMAP	–	32%
		Aniline	15%	69%
		N-methylaniline	–	54%
d	*soi*-Bu	N,N-dimethylaniline	–	42%
		HOBt	–	60%
		HONSu	–	55%

should avoid the conditions which facilitate formation of 4-alkyl-2-phenyl-4,5-dihydro-1,3-oxazole-5 carboxylic acids. On the other hand, the easily obtainable and highly reactive **4a–d** are interesting starting materials in the synthesis of polyazole antibiotics [6].

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