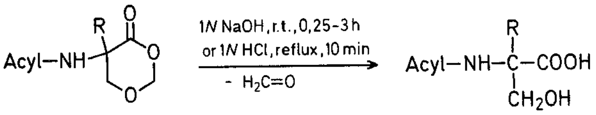
Preparation of *N*-Acyl-α-alkylserines by Selective Cleavage of 5-Acylamino-5-alkyl-4-oxo-1,3-dioxanes

Z. J. Kamiński, M. T. Leplawy*

Institute of Organic Chemistry, Technical University (Politechnika), 90-924 Łódź 40, Poland

The direct *N*-acylation of α-alkylserines is subject of limitations arising from steric hindrance and from concomitant *O*-acylation reactions[1]. Our interest in the incorporation of α-methylseryl units in a peptide chain led us to develop an efficient indirect route to *N*-acyl-α-alkylserines (**2**) which leads exclusively to the monoacylation product, and what is more important, is not affected by steric hindrance of the substrate. The method is based on our finding that 5-acylamino-5-alkyl-4-oxo-1,3-dioxanes (**1**) can be cleaved selectively to give the corresponding *N*-acyl-α-alkylserines (**2**).

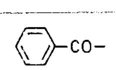
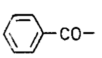
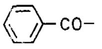
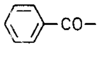
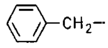
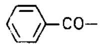
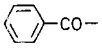
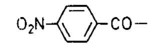
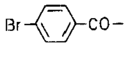


1 **2** (82–100%)

Dioxanes **1** are readily accessible from amino-acids containing an α-hydrogen atom[2,3]; they are key intermediates in our recently reported[3] method for the conversion of amino-acids into α-hydroxymethyl-α-amino-acids. Further investigation of this procedure revealed that under controlled conditions both alkaline and acidic cleavage of dioxanes **1** proceed selectively resulting in the formation of *N*-acyl-α-alkylserines in high yield.

The results of a series of cleavages of dioxanes **1** are summarized in the Table. The standard procedures for alkaline and acidic degradations are given below. The alkaline cleavage is preferred by us because in this procedure completion of the reaction can be seen from complete dissolution of the starting material.

Table[a]. *N*-Acyl-α-alkylserines (**2**) from 5-Acylamino-5-alkyl-4-oxo-1,3-dioxanes (**1**)

	R	Acyl	Reaction time (h)	Yield[b] (%)	m.p.[c]	^{1}H-N.M.R. (DMSO-d_6) δ ppm
2a	CH_3		0,25 0,20[d]	100 98	154–155°	1.48 (s, 3H), 3.69, 3.88 (AB system, 2H, J=9.8 Hz), 5.15 (broad s), 7.53 (m, 3H), 7.88 (m, 2H), 8.12 (s, 1H)
2b	C_2H_5		1	100	163–164°	0.81 (t, 3H, J=7.8 Hz), 2.03 (q, 2H, J=7.8 Hz), 3.91 (s, 2H), 5.66 (broad s), 7.56 (m, 3H), 7.90 (m, 3H)
2c	i-C_3H_7		2.5	82	149°	0.98 (d, 6H, J=7.2 Hz), 2.48 (m, 1H), 4.04 (s, 2H), 5.73 (broad s), 7.54 (m, 3H), 7.88 (m, 3H)
2d	i-C_4H_9		2	100	153°	0.84 (d, 6H, J=7.2 Hz), 1.19–2.38 (m, 3H), 3.76, 4.13 (AB system, 2H, J=11.1 Hz), 5.72 (broad s), 7.57 (m, 3H), 7.79 (m, 3H)
2e			2.5	87.5	160–162°	3.33 (s, 2H), 3.73, 3.87 (AB system, 2H, J=9.75 Hz), 4.95 (broad s), 7.20 (m, 5H), 7.49 (m, 3H), 7.74 (m, 3H).
2f	H_3C–S–CH_2–CH_2–		2.5	88	136°	2.06 (s, 3H), 2,36 (m, 4H), 3.89 (s, 2H), 4.87 (broad s), 7.55 (m, 3H), 7.94 (m, 3H)
2g	CH_3		0.25	92	165–166°	1.51 (s, 3H), 3.72, 3.94 (AB system, 2H, J=10.8 Hz), 4.12 (broad s), 8.29 (AA'BB' system, 4H), 8.56 (s, 1H)
2h	CH_3		1	94	151–152.5°	1.46 (s, 3H), 3.64, 3.85 (AB system, 2H, J=10.8 Hz), 7.72 (AA'BB' system, 4H), 8.15 (s, 1H)
2i	CH_3	t-C_4H_9–CO–	0.25	82	131–133°	1.25 (s, 9H), 1.53 (s, 3H), 3.91 (d, 2H, J=1.3 Hz)[e]

[a] All compounds **2** gave satisfactory C, H, N (±0.3%) analyses.

[b] Cited yields are of analytically pure products.

[c] Uncorrected.

[d] Cleavage in acidic medium, method B.

[e] In CD_3OD.

N-Acyl-α-alkylserines (2a–i) from Dioxanes 1:

The 5-acylamino-5-alkyl-4-oxo-1,3-dioxanes (**1**) were prepared according to our reported procedure[3].

Method A. Alkaline Cleavage of **1**: General Procedure: The appropriate dioxane **1** (100 mmol) was powdered and suspended in 1 *N* sodium hydroxide (110 ml). The mixture was shaken at room temperature until all solid material had dissolved (see Table). The solution was filtered, acidified with 5 *N* hydrochloric acid, and washed with ethyl acetate (3 × 50 ml). Evaporation of the dried ethyl acetate solution yielded the *N*-acyl-α-alkylserines **2** as readily crystallizing products; these were recrystallized from ethanol/light petroleum.

Method B. Acidic Cleavage: To a solution of 5-benzoylamino-5-methyl-4-oxo-1,3-dioxane[3] (11.76 g, 50 mmoles) in methanol (50 ml) was added 1 *N* hydrochloric acid (100 ml). The mixture was refluxed for 12 min, methanol evaporated under reduced pressure, and the aqueous layer washed with ethyl acetate (3 × 50 ml). Evaporation of the incompletely dried ethyl acetate solution gave *N*-benzoyl-α-methylserine; yield: 10.95 g (98%); m.p. 154°. Avoid complete drying of the ethyl acetate solution because *N*-benzoyl-α-methylserine is insoluble in the dry solvent.

Received: January 2, 1974

---

* To whom inquiries should be addressed.

[1] see references in: E. Schröder, K. Lübke, *The Peptides*, Academic Press, New York, 1965, p. 208.

[2] W. Steglich, G. Höfle, *Chem. Ber.* **102**, 1145 (1969).

[3] Z. J. Kamiński, M. T. Leplawy, J. Zabrocki, *Synthesis* **1973**, 792.