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REACTION OF 2-PHENYL-5-TRIMETHYLSILOXYOXAZOLE WITH CARBONYL COMPOUNDS OR ACETALS: SYNTHESIS OF α,β-DEHYDRO-α-AMINO ACID DERIVATIVES

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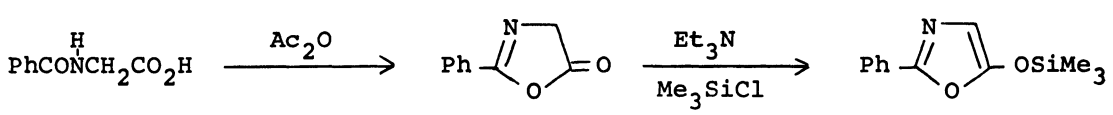
Various N-benzoyl-α,β-dehydro-α-amino acids were synthesized in high yields by the reaction of 2-phenyl-5-trimethylsiloxyoxazole with aldehydes or acetals in the presence of tin(IV) chloride.

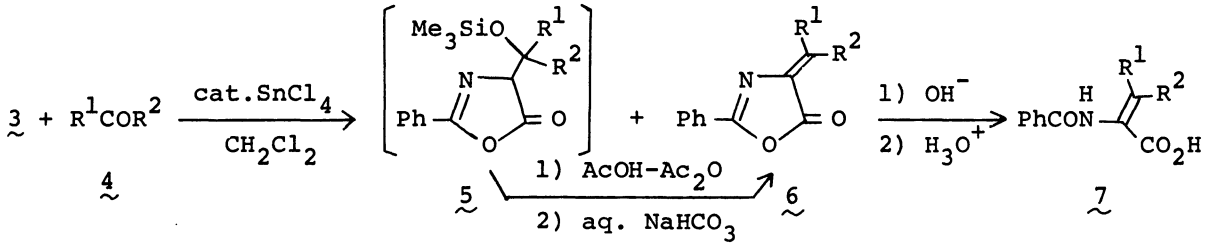
The Erlenmeyer synthesis is the most popular method for the synthesis of α,β-dehydro-α-amino acid derivatives[1,2] starting from acylated glycine derivatives and aldehydes or ketones[3], but the carbonyl compounds employed in this reaction are practically restricted to aromatic ones.[2-4] In this paper, we describe a synthetic method of α,β-dehydro-α-amino acid derivatives by the reaction of 2-phenyl-5-trimethylsiloxyoxazole (3)[5], prepared from N-benzoyl glycine (1) via 2-phenyl-2-oxazolin-5-one (2), with carbonyl compounds or acetals in the presence of tin(IV) chloride.

The oxazole (3)[5] was prepared as follows. Acetic anhydride (120 ml) was added to 1 (11.0 g, 61 mmol) and the mixture was heated at 80 °C for 30 min. Acetic acid and acetic anhydride were removed under reduced pressure and the resulted crude 2 was dissolved in 100 ml of 1,2-dimethoxyethane. Chlorotrimethylsilane (8.0 g, 73 mmol) and triethylamine (7.4 g, 73 mmol) were added to the solution, and the mixture was stirred at room temperature overnight under argon atmosphere. Triethylammonium chloride was filtered off and the filtrate was distilled to give 11.3 g (79%) of 3, bp 102 °C/2 mmHg.



1 2 3

First we examined the reaction of 3 with benzaldehyde (4a) as a model reaction. To a solution of 3 and 4a in dichloromethane was added a catalytic amount of tin(IV) chloride[6] at -78 °C and the reaction mixture was warmed to room temperature. At this stage, the formation of phenylserine derivative (5a) and 2-aminocinnamic acid derivative (6a) was recognized by TLC. In order to complete the conversion of 5a to 6a, acetic acid and acetic anhydride were added. After 3 h, the reaction mixture was treated with aqueous sodium hydrogen carbonate solution and extracted with dichloromethane. During these operations, the unreacted 3 and/or 2 were hydrolyzed to 1 which moved to the aqueous layer. Thus removal of the solvent and a small amount of unreacted 4a under reduced pressure gave almost pure 6a. Hydrolysis of 6a with potassium hydroxide and a usual work-up gave 2-benzamidocinnamic acid (7a) in high yield. Similarly, the reaction of 3 with various aldehydes and ketones gave the corresponding dehydroamino acids (7) and the results are summarized in Table 1. The structure of the products except their stereochemistry was confirmed by spectroscopic data (IR and NMR) and elemental analysis (7b, 7c) or comparison of melting point with that reported in the literature (7a, 7d-f). As to the stereochemistry, geometric isomerism is possible in 6 and 7 prepared from aldehydes, but all the dehydroamino acids obtained by this reaction have one isomeric structures. 2-Benzamidocinnamic acid (7a) was confirmed to have (Z) configration[7], though the stereochemistry of the other amino acids (7b-d) could not be decided.



As shown in Table 1, the reaction of 3 with ketones did not work well. But this disadvantage was overcome by the use of the corresponding acetals. The results of the reaction of 3 with acetals are also listed in Table 1.

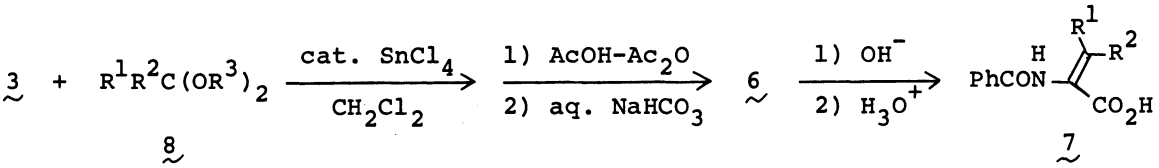


Table 1. Synthesis of N-benzoyl-α,β-dehydro-α-amino acids

Starting Material ($R^1R^2C=X$)				Amino Acid (7)				
	R^1	R^2	X		Yield (%)[a]	Mp (°C)[b]	Lit. Mp (°C)	PMR (DMSO) CH=C (ppm)
4a	Ph	H	=O	7a	93	223-224 (dec)[c]	225 (dec)[8]	7.1-7.8[d]
4b	$PhCH_2CH_2$	H	=O	7b	89	155-156		6.56 (t)
4c	C_4H_9	H	=O	7c	86	155-156		6.62 (t)
4d	Me_2CH	H	=O	7d	87	185-186	187[9]	6.43 (d)
4e	$-(CH_2)_5-$		=O	7e	23	241-243	244-246[10]	
4f	Me	Me	=O	7f	37	215-217	216-218[11]	
8a	Ph	H	$(OEt)_2$	7a	95	223-224 (dec)		
8e	$-(CH_2)_5-$		$(OEt)_2$	7e	89	241-243		
8f	Me	Me	$(OMe)_2$	7f	84	215-217		

a) Isolated yield by recrystallization from water and a small amount of ethanol. b) All the melting points are uncorrected. c) When the compound (white powder) was recrystallized from ethanol, different crystals (needles) were formed, mp 233-235 °C (dec); lit.[12], mp 235-236 °C (dec). d) Concealed in the aromatic region.

A typical example of the reaction of 3 with aldehydes is as follows. A catalytic amount of tin(IV) chloride was added to a dichloromethane (2 ml) solution of 3 (286 mg, 1.2 mmol) and 3-phenylpropionaldehyde (201 mg, 1.5 mmol) at -78 °C and the reaction mixture was allowed to warm to room temperature for 15 h. Then acetic acid (2 ml) and acetic anhydride (2 ml) were added to the reaction mixture. After stirring for 3 h, the mixture was treated with aqueous sodium hydrogen carbonate solution and extracted with dichloromethane. The organic layer was evaporated under reduced pressure and the crude product was hydrolyzed with 3M potassium hydroxide (5 ml) and methanol (2 ml). The solution was acidified with 3M hydrochloric acid to pH 1 and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and evaporated in vacuo. The residue was recrystallized from water and a small amount of ethanol to give pure 2-benzamido-5-phenyl-2-pentenoic acid (7b), 323 mg (89%), mp 155-156 °C.

It should be noted that the present method provided a useful synthetic route to α,β-dehydroamino acid derivatives starting from aliphatic aldehydes or acetals

as well as aromatic aldehydes. Moreover, the unsaturated oxazolones (6), which are known to be useful intermediates in peptide synthesis[2,3], are obtained in almost pure forms by the present procedure.

References and Notes

1) α,β-Dehydro-α-amino acid derivatives are known to be useful intermediates in the synthesis of α-oxocarboxylic acids[3] and racemic[3,4] and optically active[12] α-amino acids.

2) A number of biologically active peptides containing dehydro-α-amino acids have recently been found in nature. See review; Y. Shimohigashi and N. Izumiya, Yuki Gosei Kyokai Shi, 36, 1023 (1978).

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6) When titanium(IV) chloride or boron trifluoride etherate was used instead of tin(IV) chloride in this reaction, the yield of 7a was decreased.

7) Property of the (E)- and (Z)-isomers of 7a was reported in ref. 12.

	Mp(°C)(EtOH)	PMR(CH=C)(ppm)
(E)-isomer	189-191 (dec)	6.6
(Z)-isomer	235-236 (dec)	7.0-7.5[a)]

a) Concealed in the aromatic region.

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