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Vinyl Carboxylate, An Acylating Reagent for Selective Acylation of Amines and Diols.

S. -T. Chen[1]*, S. -Y. Chen, S. -J. Chen, K. -T. Wang[1,2]*.

1. Institute of Biological Chemistry, Academia Sinica,
2. Department of Chemistry, National Taiwan University.

Abstract: Vinyl group of vinyl alkylate (C=2 or 16) and vinyl benzoate have been found to be a good leaving group in acylation of alcohols (40-50% yield) and amines (in 60-90% yield).

Selective acylation of the amino group and hydroxyl group is useful in organic synthesis[1]. We found that Ac-D-Pro-NH_2 could be obtained in reaction of vinyl acetate with D-Pro-NH_2.This result led us to further look into the selectivities and reactivities of the vinyl carboxylates toward the nucleophile-attack (amino or hydroxyl) reaction.

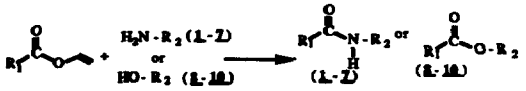
Acylation of amino acids was studied first.[2] In a typical reaction, Pro-NH_2 (1.14 g, 10 mmol) in 2-methyl-2-propanol (10 mL) and vinyl acetate (3mL, 31 mmol) was stirred at 25°C. After all the Pro-NH_2 disappeared (24 hrs), the mixture was diluted with ethyl acetate (100 mL). The resulting solution was washed with 5% citric acid (3x 15 mL), water (3x 15), dried over anhydrous sodium sulfate, and evaporated to offer Ac-Pro-NH_2 (1.04 g, 67% yield). In the same manner, Ac-Val-OBzl, Bz-Val-OBzl, Ac-Ser-OBzl, Ac-Phe-OBu^t, and Ac-Phe-OH were prepared in yields of 60-86%. Using Ser-OBzl in reaction, acetylation occurred exclusively at the amino group. Acylation of a salt of proline with one equivalent of tetrabutylammonium hydroxide dissolved in 2-methyl-2-propanol, Ac-Pro-OH was obtained with a 57% yield.[2] The results are shown on Table 1. When the temperature was increased to 37°C, the reaction was accelerated and completed within 8 hrs. All the amino groups had nearly the same nucleophilicity toward vinyl acetate. No racemization was observed.

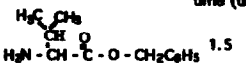
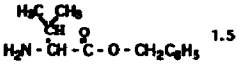
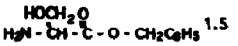
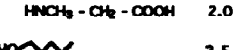
Under the same conditions, using 1,4-pentanediol and 1-phenylethanediol as the nucleophile, no reaction occurred. In the presence of N,N-dimethylaminopyridine or triethylamine, 1,4-pentanediol and 1-phenylethanediol were monoacetylated to give 1-acetoxy-4-pentanol and 2-acetoxy-1-phenylethanol with yields of 41% and 49% respectively. When vinyl palmitate reacted with sarcosine, and L-ascorbic acid[2], respectively, the correspondent product was obtained in yields of 55% and 79%.

2-Propenyl ester and 2-hexenyl ester have been used in acylation of amino group but cannot acylate secondary amine or bulky amino acids without KCN as catalyst.[3] In conclusion, comparing the reactivities

of various enol esters, the vinyl ester was more reactive than did the 2-propenyl and 2-hexenyl ester in reaction with the amino-nucleophiles. The chain length of carboxylate will not affect the reactivity of the vinyl ester. In the presence of amino and hydroxyl groups, vinyl carboxylate was selectivily acylated at the amino group in mild conditions. When a catalytic amount (5%) of N,N-dimethylaminopyridine or triethylamine was present in the reaction solution, the hydroxyl group could be acylated. In selective acylation of primary and secondary hydroxyl groups, the reaction occurred exclusively at the primary hydroxyl group.In the case of an amino acid with a hydroxyl group at side-chain, such as serine, acylation only occurred at the amino group.

Table 1. Selective acylation at amino and hydroxyl group by vinyl alkylate



	R_1	$H_2N\text{-}R_2$ or HO - R_2	reaction time (day)	yield (%)	mp: °C / $[\alpha]_D^{25}$: c 5 MeOH
1	CH_3		1.5	69	oil/ -40.35
2	C_6H_5		1.5	63	66-67/ -16.13
3	CH_3		1.5	68	oil/ -16.79
4	CH_3		1.5	86	91-91/ +4.05
5	CH_3		1.5	67	100-103/ -92.75
6	CH_3		2.0	57	109-111/ -79.75
7	$C_{15}H_{31}$		2.0	84	74-76/ –
8	CH_3		3.5	41	oil/ –
9	CH_3		3.5	49	oil/ –
10	$C_{15}H_{31}$		4.0	60	112-114/ +22.93

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2) Vinyl palmitate was prepared according to the procedure of Swern et al. (Organic Synthesis Coll. IV, 977.) mp 26-27°C, bp 175-180°C (7-10 mmHg); Salts of proline or sarcosine dissolved in 2-methyl-2-propanol were prepared as follows: i. the amino acid (10 mmol) was dissolved in water (50 mL) containing tetrabytylammoniumhydroxide (14 mL, 20% solution in water, E. Merck). ii. the aqueous solution was lyophilized, and the resulting white powder dissolved in 2-methyl-2-propanol. for detail see, Chen, S. T., Wang.K. T., J. Chem. Soc. Chem. Commu. **1990**, 1045. and Chen, S. T., Wang. K. T., J. Chin. Chem. Soc. **1991**, 38, 93.; L-ascorbic acid was nearly insoluble in 2-methyl-2-propanol. Phenylboronic acid was used as a solubilizing agent, and refluxed in a mixture of methanol/acetone (3:1) was used to decompose the complex according to the procedure of Schlotterbeck et al,. (Ref 6e). To a solution of L-ascorbic acid (10 mmol) dissolved in water (100 mL) was added a solution of phenylboronic acid (15 mmol) dissolved in 2-methyl-2-propanol (10 mL). The mixture was lyophilized, and the resulting white powder was dissolved in a mixture of 2-methyl-2-propanol (20 mL), N,N-dimethylaminopyridine (1 mL), and vinyl palmitate (4.65 g, 15 mmol). After L-ascorbic acid was completely acylated, the solvent was evaporated, and to the residue was added a mixture of acetone/methanol (3:1, 50 mL). The resulting mixture was heated at 55°C for 1 hour and then evaporated. The residue was dissolved in methanol and eluted through a gel filtration column packed with TSK HW40S gel, and the desired fractions were collected and evaporated to obtain pure product.

3) Hogberg, T., Strom, P., Ebner, M., Ramsby, S., *J. Org. Chem.* **1987**, 52, 2033.; Kabouche, Z., Bruneau, C., Dixneuf, P.H., *Tetrahedron Lett.* **1991**, 32, 5359.

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