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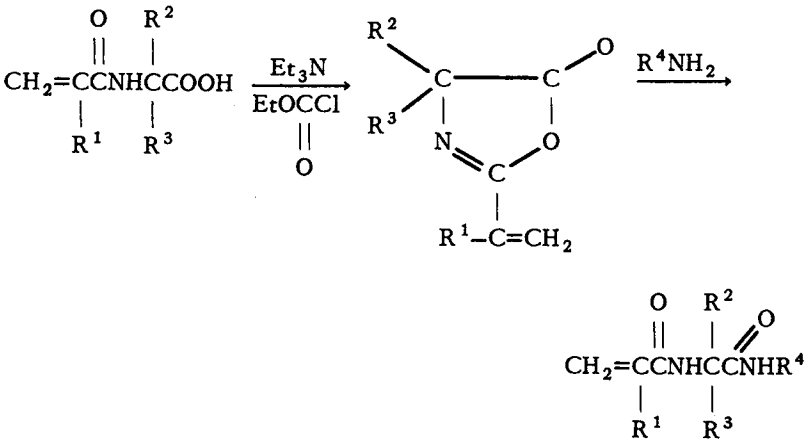
THE SYNTHESIS OF VINYL PEPTIDE MONOMERS

Our laboratory has reported that poly-N-acrylylglycinamide, a simple vinyl dipeptide polymer, forms thermoreversible gels in water in a manner similar to gelatin (1). 2-Vinyl-5-oxazolones are thus key intermediates for a large number of novel monomers and polymers (2). Examples of an outstanding synthetic procedure for preparing vinyl peptide monomers through the 2-vinyl-5-oxazolone are reported herein.

2-Vinyl-4-isopropyl-5-oxazolone has been prepared previously by the classical method involving cyclization of N-acrylyl-valine with acetic anhydride (3). Some recent interesting work describes the reactivity of this type of compound and the tendency toward rearrangement to pseudo-oxazolones (4) and also further reaction with acetic anhydride to give a Dakin-West reaction (5). These rearrangements as well as the side reaction of dimerization, currently under investigation, interfere with the desired formation of vinyl peptides. The synthetic procedure reported here obviates this difficulty and produces pure monomers suitable for vinyl polymerization. Our method has even been used successfully in cases of extreme reactivity such as with oxazolones with very reactive 4-positions derived from glycine or alanine.

Use of the mixed carbonic-carboxylic acid anhydride synthesis, used previously to prepare saturated oxazolones (6,7) is an outstanding method of preparing unsaturated oxazolones. Due to the reactivity of the product, the yield of pure material in most cases is drastically reduced by attempted purification. We therefore generate the vinyl oxazolone in an inert solvent and allow it to react in situ with ammonia or primary or secondary amines, producing the vinyl peptide.

In practice a slurry of an N-acrylyl-α-amino acid in a nonreactive solvent such as ether, dichloromethane, benzene, hexane, or acetone is prepared and equivalents of triethylamine and ethyl chloroformate are added keeping the temperature at 30°C or below. After the evolution of carbon dioxide ceases, the triethylamine hydrochloride is filtered, and the reactant amine is added to the filtrate. The desired vinyl peptide usually crystallizes from the solution in high yield and purity. The required general synthesis of N-acrylyl-α-amino acids already exists (4). These procedures allow great latitude for monomer-polymer construction, since depending on the structure of the original α-amino acid and the reacting amine, monomers can be made which possess a variety of functional groups and hydrophilic-hydrophobic balance.



The vinyl peptides are monomers of the acrylamide type and as such are readily polymerized or copolymerized in both water and organic solvents. This synthetic method is thus very suitable for the construction of polymers with specific solution properties as models of natural polymers such as gelatin. Different polymers which we have prepared have shown all types of solubility behavior including the ability to gel in water either with increasing or decreasing temperature. This synthetic method is also useful in meeting those special requirements in which a polymer containing specific functional groups is desired. Illustrative examples of monomers prepared are given in Table I.

TABLE I

Examples of Monomers

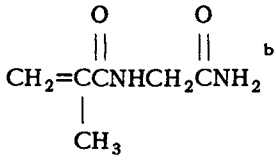
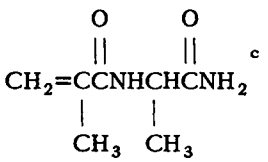
Monomer	Mp, °C	% Anal. calcd.	% Anal. found	Yield, %[a]
 [b]	139–140	—	—	90
 [c]	146–148	C-53.9 H- 7.7 N-17.9	C-53.8 H- 7.8 N-17.9	75

TABLE I continued

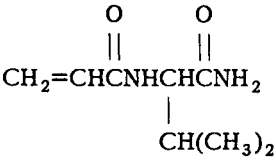
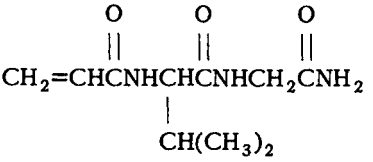
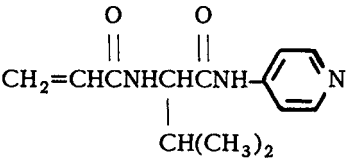
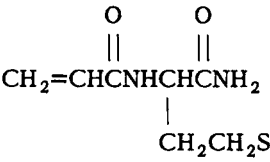
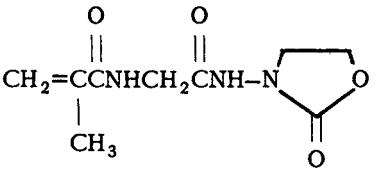
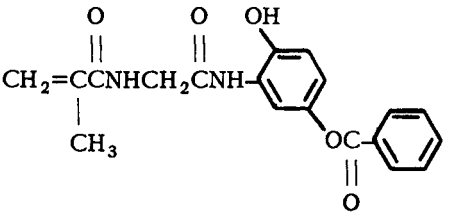
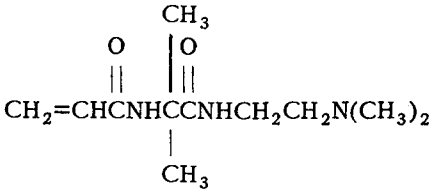
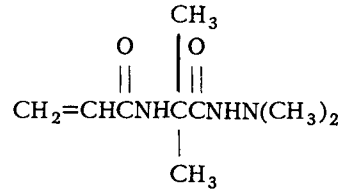
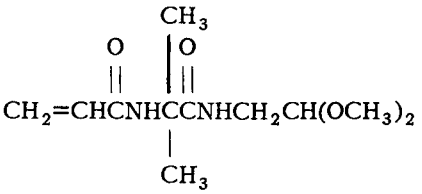
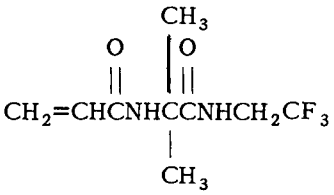
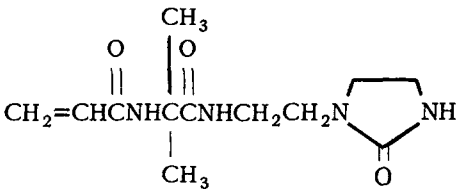
Monomer	Mp, °C	% Anal. calcd.	% Anal. found	Yield, %[a]
	205–206	C-56.5 H- 8.2 N-16.5	C-56.5 H- 8.5 N-16.4	68
	183–185	C-52.8 H- 7.5 N-18.5	C-52.9 H- 7.7 N-18.4	75
	172–173	C-64.4 H- 7.2 N-16.2	C-64.2 H- 7.3 N-16.1	65
	153–154	C-47.5 H- 6.9 N-13.9 S-15.8	C-47.3 H- 6.9 N-13.6 S-16.0	75
	170–171	C-47.6 H- 5.8 N-18.5	C-47.7 H- 6.0 N-18.8	82
	180	C-64.4 H- 5.1 N- 7.9	C-64.2 H- 5.2 N- 7.9	75

TABLE I continued

Monomer	Mp, °C	Anal. calcd. %	Anal. found %	Yield, %[a]
	72–73	C-58.2 H- 9.3 N-18.5	C-58.1 H- 9.4 N-18.4	85
	157–159	C-54.3 H- 8.5 N-21.1	C-54.4 H- 8.6 N-21.0	60
	79–80	C-54.1 H- 8.2 N-11.5	C-54.3 H- 8.2 N-11.4	76
	135–136	C-45.4 H- 5.5 N-11.7 F-23.9	C-45.3 H- 5.6 N-11.5 F-23.7	50
	178d	C-53.7 H- 7.5 N-20.9	C-53.8 H- 7.6 N-20.9	93

[a] Based upon N-acrylyl-α-amino acid.

[b] This product was identical to that prepared by the previously reported method (8) in terms of infrared spectrum and mixed melting point.

[c] This product has recently been synthesized by another method (9).

The mixed carbonic-carboxylic acid anhydride as well as the oxazolone would lead to the final vinyl peptide product (10). We feel that most of our products are derived from oxazolones because of the copious carbon dioxide evolution prior to reactant amine addition and also because in some cases solid 2-vinyl-5-oxazolones have been isolated in high yield and purity. Such a case is illustrated by the synthesis of the very reactive 2-isopropenyl-5-oxazolone 1.

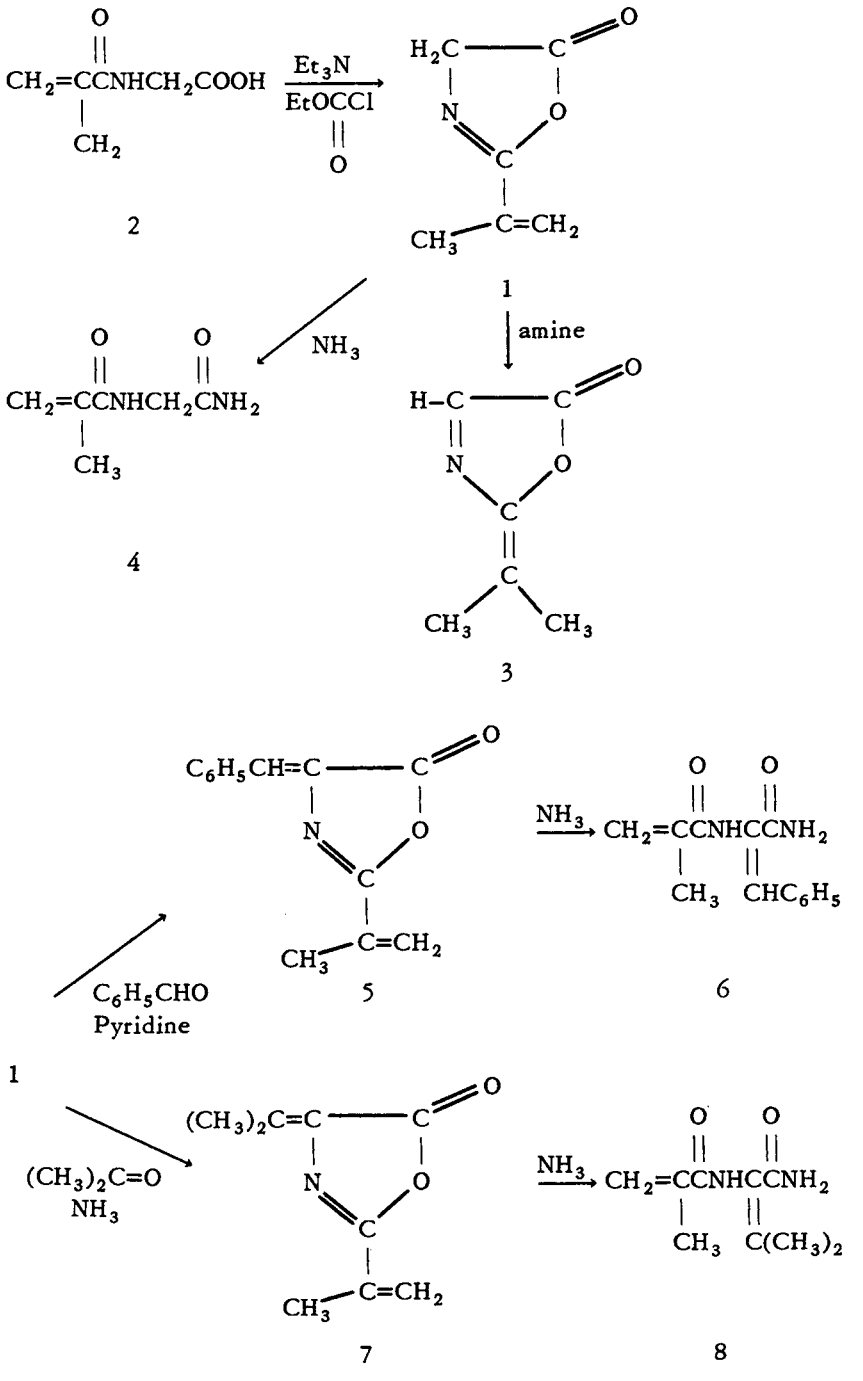
A solution of N-methacrylylglycine 2 (11) in dry acetone is allowed to react with equivalent amounts of ethyl chloroformate and triethylamine at room temperature. After one hour carbon dioxide evolution ceases and the triethylamine hydrochloride is removed. The filtrate is cooled to −30°C and the product, 2-isopropenyl-5-oxazolone, crystallizes usually in analytical purity, 80% yield: mp 77–78°C; ir (KBr) 1810 (C=O), 1650 (C=N), and 1610 cm^{-1} (C=C); nmr (DMSO-d_6) δ 1.99 (d,3,J=1H_z), 4.43 (s,2), 5.73 (m,1). The results calculated for $C_6H_7NO_2$ are (%): C, 57.6; H, 5.6; N, 11.2. Those actually found are (%): C, 57.5; H, 5.6; N, 11.1.

Compound 1 is quite stable when refrigerated in a dry state. In solution it undergoes rearrangement to the pseudoxazolone 3 as well as forming a polymeric product of unknown structure which is under investigation. Compound 1 does not polymerize cleanly to high molecular weight material via standard vinyl polymerization techniques due to the above-mentioned rearrangement reactions.

Compound 1 is a valuable monomer intermediate. Solutions of 1 in inert solvents readily react with amines to yield novel methacrylamides. Treatment of 1 in dichloromethane with ammonia gas gives methacrylylglycinamide 4 in 90% yield. Polymers prepared from this compound possess the property of thermoreversible gelation in water (8).

The unsubstituted 4-position of compound 1 is reactive in Erlenmeyer condensations with aldehydes and ketones. The resulting doubly-unsaturated oxazolone can be ring-opened with amines to yield an unsaturated methacrylamide. Reaction of 1 with benzaldehyde in ethanol with a trace of pyridine gave 2-isopropenyl-4-benzylidene-5-oxazolone 5: mp 94–95°C; uv max (dichloromethane) 239 mμ (ϵ 12,600), 246 (12,000), 327 (27,200), 350 (35,200), 367 (26,800); ir (KBr) 1780, 1760, 1650, 1620 cm^{-1}; nmr ($CDCl_3$) δ 2.34 (d,3,J=1H_z), 5.73 (m,1), 6.6 (m,1), 7.15 (s,1), 7.40 (m,3), 8.10 (m,2). The amounts calculated for $C_{13}H_{11}NO_2$ are (%): C, 73.2; H, 5.2; N, 6.6. Those actually found are (%): C, 73.1; H, 5.2; N, 6.6.

Compound 5 was ring-opened with ammonia to give 6: mp 150°C; uv max(dichloromethane) 284 mμ (ϵ 14,700); ir (KBr) 1700, 1670, 1650, 1620 cm^{-1}; nmr (DMSO-d_6) δ 1.92 (d,3,J=1Hz), 5.47 (m,1), 5.85 (m,1), 7.17 (s,1), 7.40 (m,7), 12.6 (s,1). The amounts calculated for $C_{13}H_{14}N_2O_2$ are (%): C, 67.8; H, 6.1; N, 12.1. Those actually found are (%):


CH2=CCNHCH2COOH
CH2
Et3N
EtOCCl
O
H2C
C
N
O
CH3
C=CH2
2
1
NH3
amine
CH2=CCNHCH2CNH2
CH3
4
H–C
CH3
CH3
3
C6H5CH=C
5
NH3
CH2=CCNHCCNH2
CH3
CHC6H5
6
C6H5CHO
Pyridine
1
(CH3)2C=O
NH3
(CH3)2C=C
7
CH2=CCNHCCNH2
C(CH3)2
8

C, 67.9; H, 6.3; N, 11.9.

In a similar way condensations can be effected with ketones. In an attempt to react ammonia with our preparative solution of 1 in acetone, the major product isolated was 7: mp 60–61°C; uv max (dichloromethane) 289 mμ (ε 20,000), 297 (19,200); ir (KBr) 1770, 1740, 1660, 1620 cm^{-1}; nmr (DMSO-d_6) δ 2.02 (d,3,J=1Hz), 2.24 (s,3), 2.32 (s,3), 5.75 (m,1), 5.94 (m,1). The amounts calculated for $C_9H_{11}NO_2$ are (%): C, 65.4; H, 6.7; N, 3.5. Those actually found are (%): C, 65.2; H, 6.8; N, 8.3.

Compound 7 readily undergoes further reaction with ammonia to yield 8: mp 160–161°C; ir (KBr) 1675, 1650, 1620, 1500 cm^{-1}; nmr (DMSO-d_6) δ 1.65 (s,3), 1.88 (s,3), 1.97 (s,3), 5.40 (m,1), 5.79 (m,1), 6.91 (s,2), 8.84 (s,1). The amounts calculated for $C_9H_{14}N_2O_2$ are (%): C, 59.3; H, 7.7; N, 15.4. Those actually found are (%): C, 59.2; H, 7.7; N, 15.2.

Full accounts of the novel polymeric materials and also the intermediate oxazolones will be submitted for publication as this work progresses.

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