A Facile Synthesis of *N*-Substituted 2-Acylamino-2-alkenamides

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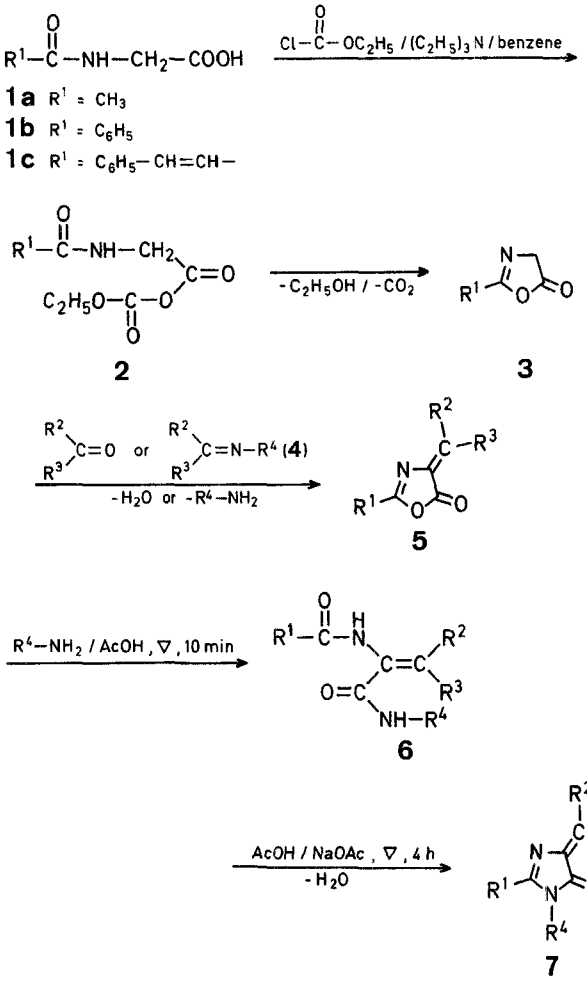
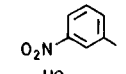
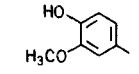
Some dehydropeptides and *N*-substituted amides, for example **6**, which may be obtained by aminolysis of azlactones have been reported to possess antitumor[1,2,3] and CNS-inhibiting[4] properties. They also are useful synthetic intermediates. For example, the asymmetric hydrogenation of dehydrodipeptides affords chiral dipeptides[5,6]. Similarly, some *N*-substituted amides are intermediates in the synthesis of 1,2-disubstituted 4-arylmethylene-5-oxo-4,5-dihydroimidazoles (**7**)[7,8,9]. It is worthy of note that aminolysis of azlactones is also important because of its application in polymer chemistry[10,11]. The compounds **6** are in general prepared by the reaction of suitable amines with 4-alkylidene-5-oxo-4,5-dihydro-1,3-oxazoles (**5**) which are in turn obtained by Erlenmeyer azlactone synthesis[12]. We describe here a new modification for the fast and convenient synthesis of *N*-substituted 2-acylamino-2-alkenamides (**6**).

An *N*-acylglycine (**1**) is converted into the 5-oxo-4,5-dihydro-1,3-oxazole (**3**) by reaction with ethyl carbonochloridate in dry benzene in the presence of triethylamine. Subsequent treatment with an aldehyde and heating of the mixture at reflux temperature for 10 min affords the corresponding 4-alkylidene-5-oxo-4,5-dihydro-1,3-oxazole (**5**) which is not isolated but directly subjected to aminolysis by boiling with a suitable amine in benzene in the presence of glacial acetic acid. Alternatively, the aminolysis can be carried out by boiling compound **5** in glacial acetic acid alone. The time required in both cases is ~ 10 min. The reaction was applied to the condensation of azlactone **3** with suitable *N*-substituted aldimines and also with one ketimine (cyclohexanone *N*-phenylimine). When an imine is used as reactant, formation of the azlactone is accompanied by extrusion of the amine moiety so that for rapid aminolysis of the compound **5** the presence of acetic acid is required. In the case of 2-methyl-5-oxo-4,5-dihydro-1,3-oxazole (**3h**), benzaldehyde as well as *N*-phenylbenzaldimine[13,14] also condense with the methyl group; the corresponding unsaturated oxazolone, for example **5h**, should therefore be employed only after separation to obtain better results. As we have demonstrated earlier[15], ketimines require short reaction times to afford azlactones, unlike the corresponding ketones; thus, their use in the present reaction seems to be advantageous.

(*E*)-Azlactones are thermolabile and isomerise to the corresponding (*Z*)-isomers in the presence of a tertiary base[16]. However, cleavage of the 1,5-bond in these compounds does not affect the stereochemistry of the olefinic centre during hydrolysis[17,18] and aminolysis[19]. The stereospecific nature of the aminolysis was verified in the present investigation by converting **5d** and **5e** into **6d** and **6e**, respectively. In the U.V. spectrum, both **6d** and **6e** absorb in nearly the same regions, but the ε_{max} values are higher for the (*Z*)-isomer than for the corresponding (*E*)-compound, thereby confirming the assigned stereochemistry of the products.

It is noteworthy that the formation of imidazolones (**7**) was detected by T.L.C. in some of the cases, but these compounds could not be isolated except when heating was continued for a few hours. From the (*Z*)-azlactones only the (*Z*)-imidazolones are formed; the intermediates **6** must therefore have the (*Z*)-configuration.



5,6,7	R^1	R^2	R^3	R^4
a	C_6H_5	C_6H_5	H	C_6H_5
b	C_6H_5		H	C_6H_5
c	C_6H_5		H	C_6H_5
d	C_6H_5	H	C_6H_5–CH=CH–	C_6H_5
e	C_6H_5	C_6H_5–CH=CH–	H	C_6H_5
f	C_6H_5	$-(CH_2)_5-$		C_6H_5
g	C_6H_5–CH=CH–	C_6H_5	H	C_6H_5
h	CH_3	C_6H_5	H	C_6H_5
i	C_6H_5	C_6H_5	H	n-C_4H_9
j	C_6H_5	C_6H_5	H	C_6H_5–CH_2–
k	C_6H_5	C_6H_5	H	HOOC–CH_2–

The present procedure is superior to other methods. For example, the Erlenmeyer azlactone synthesis employs acetic anhydride for cyclisation, affording a mixture of the (*E*)- and (*Z*)-isomers of the unsaturated oxazolones which have to be separated by fractional crystallisation before using them for aminolysis. This is rather time consuming and it lowers the overall yields of the amides **6**. Also, aminolysis itself requires longer reaction times in most of the cases.

For the synthesis of dehydrodipeptides, for example **6k**, the reaction of azlactones with the ester or the potassium salt of an amino acid in acetone[20] may not be always suitable because it requires more steps and the alkaline medium may bring about isomerisation and/or hydrolysis of the azlactone itself. The present procedure for the generation of the unsaturated oxazolones **5** is quite convenient: the crude product is subjected to aminolysis without isolation so that the reactions can be carried out in one flask. The steric integrity of the products is maintained at the same time. Considering the easy availability of the starting materials, the speed of the reaction, the mild experimental conditions, and the simplicity of the work-up, the present method appears to be useful.

All melting points are uncorrected. The I.R. and U.V. spectra were recorded on Perkin-Elmer 720 and/or 257, and Cary-14 spectrophotometers, respectively.

N-Substituted 2-Acylamino-2-alkenamides (6); General Procedures:

Method A: To a suspension of the *N*-acylglycine (**1**; 1.0 mol) in dry benzene (25 ml/g of the acid) containing triethylamine (121.5 g, 1.2 mol), ethyl carbonochloridate (119.4 g, 1.1 mol) is added and the mixture is shaken at room temperature until the crystals of the acid disappear and triethylamine hydrochloride separates. The aldehyde (**4**, R^2 = H; 1.0 mol) is added to the mixture which is then heated under reflux for ~ 10 min. Triethylamine hydrochloride is filtered off

Table 1. Preparation of *N*-Substituted 2-Acylamino-2-alkenamides (**6**)

6	Method	Yield[a] [%]	m.p. [°C]	Literture Data			
				Method	Yield[b] [%]	m.p. [°C]	Ref.
a	A	56	235–237°	As a side-product in the synthesis of azlactone using imine.	3.5	235–237°	15
	B	59					
	C	55		Heating azlactone and amine in benzene or ethanol for 4 h.	32	235–237°	15
	D	88		Rearrangement of 3-benzoylamino-1,4-diphenyl-2-azetidinone	19		21
b	A	50	223–224°	As a side-product in the synthesis of azlactone using imine.	8	223–224°	15
	B	56					
	C	38		Heating azlactone and amine in benzene or ethanol for 4 h.	16	223–224°	15
	D	75					
c	A	26	224–225°	As a side-product in the synthesis of azlactone using imine.	10	225°	15
	B	33					
	C	42		Heating azlactone and amine in benzene or ethanol for 4 h.	35	225°	15
	D	88					
d	A	59	253–254°	[c]			
	B	60					
	D	93					
e[d]	A	50	247–248°	[e]			
	D	77					
f	C	48	259–260°	Aminolysis of azlactone at 180°C for 0.5 h	75	245°	22
	D	78					
g	A	44	230–232°	Aminolysis of azlactone	85	230°	22
	B	63					
	D	72					
h	D	90	188–189°	Aminolysis of azlactone in benzene.	73	188–190°	23
				As a side product in the synthesis of azlactone using imine	4.2	187–190°	15
i	A	44	188–190°	As a side product in the synthesis of azlactone using imine.	6.2	190°	24
	B	62					
	D	93		Aminolysis of azlactone in benzene or ethanol	93	190°	24
j	A	44	170–171°	As a side product in the synthesis of azlactone using imine.	16.5	170°	24
	B	58					
	D	80		Aminolysis at elevated temperature	–	173–174°	25
k	A	72	205–206°	Aminolysis of azlactone with sodium glycinate in acetone	92	208–209°	20
	D	82					

[a] Yield of pure product is given. For the methods A, B, and C, yields are based on acetyl-, benzoyl-, and/or cinnamoylglycine, in the case of the method D, the yield is based on the azlactone **5**.

[b] Yield based on azlactones unless indicated in the method.

[c] $C_{24}H_{20}N_2O_2$ (368) calc. C 78.26 H 5.43 N 7.60; found 78.57 5.34 7.63

[d] The (*Z*)-isomer was obtained by isomerization of the (*E*) compound by heating in dry pyridine for 15 min.

[e] $C_{24}H_{20}N_2O_2$ (368) calc. C 78.26 H 5.43 N 7.60; found 78.60 5.42 7.55

Table 2. Spectral Data of Compounds **6**[a] and **7**[b]

Compound	I.R. (Nujol) ν [cm^{-1}]	U.V. (95% ethanol) λ [nm] ($\varepsilon \cdot 10^{-4}$)
6a	3300, 3260, 1640	
6b	3245, 1660, 1640	
6c	3400, 3300, 1680, 1640	
6d	3340, 3240, 1660, 1640	330 (3.25), 235 (2.01)
6e	3340, 3240, 1660, 1645	330 (4.10), 235 (2.45)
6f	3280, 1655, 1635	
6g	3340, 3260, 1650	
6h	3340, 3220, 1660, 1640, 1620	
6i	3280, 1660, 1645, 1630	
6k	3550, 3350, 3220, 1720, 1660, 1620	
7a	1710, 1650	340 (2.0), 290 (1.21), 235 (1.26)
7b	1710, 1630	380 (0.83), 250 (1.01)
7c	3300, 1690, 1650	412 (3.70), 265 (2.44), 230 (2.22)
7g	1710, 1630, 1620	405 (1.7), 295 (2.14), 235 (1.26)
7j	1710, 1630	370 (2.09), 296 (1.01), 248 (1.37)

[a] U.V. spectra of only the new compounds are given.
[b] For ^{1}H-N.M.R. spectral data see Ref.[9].

under reflux for ~ 10 min. Triethylamine hydrochloride is filtered off under suction and washed twice with dry benzene. The filtrate and washings are combined and to this the amine (1.2 mol) and glacial acetic acid (3–5 ml/g of the *N*-acylglycine) are added. The mixture is heated under reflux for 5–10 min. On cooling, a solid separates. The solid product is isolated by suction, washed with benzene, and recrystallised from aqueous ethanol.

Method C: To a suspension of the *N*-acylglycine (**1**; 1.0 mol) in dry benzene (25 ml/g of the acid) containing triethylamine (121.5 g, 1.2 mol), ethyl crbonochloridate (119.4 g, 1.1 mol) is added and the mixture is shaken at room temperature until the crystals of the acid disappear and triethylamine hydrochloride separates. The solid is filtered off and washed twice with dry benzene. The filtrate and the washing are combined and the imine (**4**; 1.0 mol) is added to the combined solution. The mixture is heated under reflux for ~ 10 min, cooled, and glacial acetic acid (3–5 ml/g of the *N*-acylglycine) is added. This mixture is heated for 5–10 min. Work-up is same as in Method B.

Method D: The 4-alkylidene-5-oxo-4,5-dihydro-1,3-oxazoles[15] (**5**; 1.0 mol) and the amine (1.2 mol) are mixed in glacial acetic acid (5–10 ml/g of the oxazolone) and the mixture is heated under reflux for 5–10 min. Work-up is the same as in Method A. Except for the case of **6k**, the reaction can be carried out in dry benzene (25 ml/g of the oxazolone) containing glacial acetic acid (3–5 ml/g of the oxazolone) by heating the mixture under reflux for 5–10 min. Work-up is the same as in Method B.

Table 3. Preparation of 1,2-Disubstituted 4-Arylmethylene-5-oxo-4,5-dihydroimidazoles (**7**)

7[a]	Yield [%]	m.p. [°C]	Literture Data			
			Method	Yield [%]	m.p. [%]	Ref.
a	60[b,c]	180°	Cyclisation of 2-benzoylaminocinnamanlilide in boiling xylene for 13 h.	–	180°	25
			Rearrangement of 3-benzoylamino-1,4-diphenyl-2-azetidinone.	6	180°	21
b	66[b,c]	198–199°	[d]		198–199°	9
c	24[b,c]	190°	[d]		190°	9
g	68[b,e]	240–241°	Cyclisation of 2-cinnamoylamino-cinnamanilide in boiling xylene for 13 h.	52	245°	22
j	28[b,c]	140–142°	Cyclisation of *N*-benzyl-2-benzoylamino-cinnamide		143–144°	25

[a] These products have been published earlier and their stereochemistry has been assigned on the basis of their ^{1}H-N.M.R. spectra[9].
[b] Obtained only in trace amounts in the preparation of **6** (detected by T.L.C.; silica gel, benzene).
[c] Yield based on hippuric acid (**1b**) used.
[d] The procedure and the yields are the same as given in the experimental section.
[e] Yield is based on cinnamoylglycine (**1c**) used.

under suction and washed twice with dry benzene. The filtrate and washings are combined and the solvent is completely removed under reduced pressure. To the residue, the amine (1.2 mol) and glacial acetic acid (10 ml/g of the acid) are added and the mixture is heated under reflux for 5–10 min. On cooling, a solid separates which is isolated by suction and washed with glacial acetic acid.

In the preparation of product **6k**, the acetic acid solution is concentrated to dryness and the residue dissolved in saturated sodium hydrogen carbonate solution (15 ml/g of **1**). This solution is acidified with conc. hydrochloric acid at low temperature. The resultant precipitate is isolated by suction, washed with water, and recrystallized from aqueous ethanol.

Method B: To a suspension of the *N*-acylglycine (**1**; 1.0 mol) in dry benzene (25 ml/g of the acid) containing triethylamine (121.5 g, 1.2 mol), ethyl carbonochloridate (119.4 g, 1.1 mol) is added and the mixture is shaken at room temperature until the crystals of the acid disappear and triethylamine hydrochloride separates. The aldehyde (**4**, R^2 = H; 1.0 mol) is added to the mixture which is then heated

1,2-Disubstituted 4-Arylmethylene-5-oxo-4,5-dihydroimidazoles (7); General Procedure:

The 4-arylmethylene-5-oxo-4,5-dihydro-1,3-oxazole (**5**) is generated by Method C, and benzene is completely removed under reduced pressure. To the residue, glacial acetic acid (20 ml/g of the *N*-acylglycine) and freshly fused sodium acetate (0.2 g/g of the *N*-acylglycine) are added and the mixture is heated under reflux for 4 h. The solvent is then removed under reduced pressure or by heating the solution on a steam bath. The residue is triturated with ethanol, and the product isolated by suction, washed with ethanol, and recrystallized from ethanol.

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