Synthesis of Enamides

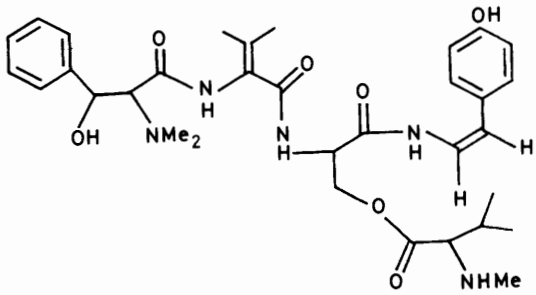
Roger Brettle * and Alan J. Mosedale
Department of Chemistry, The University, Sheffield S3 7HF

(*Z*)-3-Arylprop-2-enoic acids can be converted by the Curtius procedure, through the acyl azides, into (*Z*)-2-arylethenyl isocyanates, which with methanol give methyl (*Z*)-*N*-(2-arylethenyl)carbamates. Acylation of the (*Z*)-enecarbamates, through their anions, leads to methyl (*Z*)-*N*-acyl-*N*-(2-arylethenyl)carbamates, which on treatment with lithium iodide in boiling *N*,*N*-dimethylformamide or acetonitrile undergo demethoxycarbonylation to give (*Z*)-enamides. This stereospecific route to enamides can also be used in the *E*-series. Treatment of (*Z*)- or (*E*)-2-arylethenyl isocyanates with trifluoroacetic acid gives (*E*)-*N*-(2-arylethenyl)trifluoroacetamides, the anions of which, with acylating agents, give (*E*)-enamides directly.

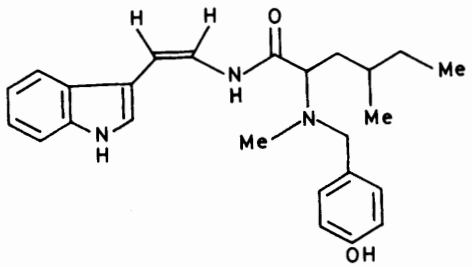
Naturally occurring secondary enamides with a 1,2-disubstituted olefinic bond in which the enamide function does not form part of a ring include tuberin,[1] erbstatin,[2] (*E*)-*N*-2-(3,4-dihydroxyphenyl)ethenylacetamide,[3] (*E*)-*N*-[2-(4-methoxyphenyl)ethenyl]-3-phenylprop-2-enamide,[4] lasiodine A,[5] clionamide,[6] celenamides A—D,[7] tunichrome B-1,[8] fragilamide,[9] myxopyronins A and B,[10] corallopyronins A—C,[11] scytophycins A—E,[12] tolytoxin,[13] kabiramide C,[14] and ulapualides A and B.[15] Periphylline[16] was also originally assigned a structure of this type, but this was later revised to a structure in which the enamide function forms part of a ring. Of these enamides only lasiodine A[5] (**1**) and fragilamide[9] (**2**) have the *Z*-configuration. No stereospecific synthesis of a (*Z*)-enamide of this type with a complicated *N*-acyl group has yet been reported.

We have been interested in developing a stereospecific route to enamides in which the olefinic geometry would be established at the start of the synthesis and retained throughout (Scheme). Since in most naturally occurring enamides the *N*-acyl groups are of some complexity we have also sought a method which would allow that acyl group to be introduced at a late stage in a synthesis in exchange for a much simpler acyl group [*e.g.* (**5**) ⟶ (**7**)].

One attractive route which we have investigated for the synthesis of (*Z*)-enamides (**7**) is based on the Curtius reaction for the conversion of (**3**; X = N_3) into (**4**) followed by reaction of the (*Z*)-isocyanate (**4**) with trifluoroacetic acid to obtain (**5**; $R^1 = CF_3$). Selective cleavage of the trifluoroacetyl group from an *N*,*N*-diacyl enamine (**6**; $R^1 = CF_3$) to give the (*Z*)-enamide (**7**) might then prove possible. Vinyl and styryl isocyanates can be prepared by the Curtius reaction with α,β-olefinic azides, and on mechanistic grounds one would expect the olefin configuration to be retained during the C ⟶ N migration.[17] Indeed, this has been shown to be the case, contrary to an early report,[18] for (*Z*)-but-2-enoyl azide.[19] Treatment of a 97% pure sample of (*Z*)-but-2-enoyl chloride[20] with sodium azide in cold aqueous acetone gave a product containing 84% of (*Z*)-but-2-enoyl azide. Thermal decomposition of the azide in deuteriochloroform at 33 °C, a temperature at which the contaminating (*E*)-azide hardly reacted, gave a mixture containing 78% of the (*E*)-isocyanate, the rate of loss of the (*Z*)-azide being exactly matched by the rate of appearance of the (*Z*)-isocyanate.[19] The earlier paper[19] also reported that the conversion of (*Z*)-3-phenylprop-2-enoic acid into its azide (**4a**; X = N^{13}) *via* the acyl chloride, followed by the Curtius reaction and conversion of the isocyanate into the styrylurea with ammonia, gave exclusively (*E*)-*N*-2-phenylethylurea (**10a**; $R^1 = NH_2$); the stereochemistry was not monitored at any of the intermediate stages. More recently the reaction of the (*Z*)-acid (**3a**; X = OH) with diphenylphosphoryl azide in the presence of triethylamine was reported[21] to give the azide, thermal decomposition of which and treatment with ammonia gave a low yield of a mixture of the (*Z*)- and (*E*)-ureas (**10a**) and (**5a**) ($R^1 = NH_2$) containing 28% of the (*E*)-isomer. Similar stereochemical results were reported for related acids, but again the failure to monitor the reactions in detail makes it impossible to pinpoint the stage at which partial inversion of the olefin configuration occurs.

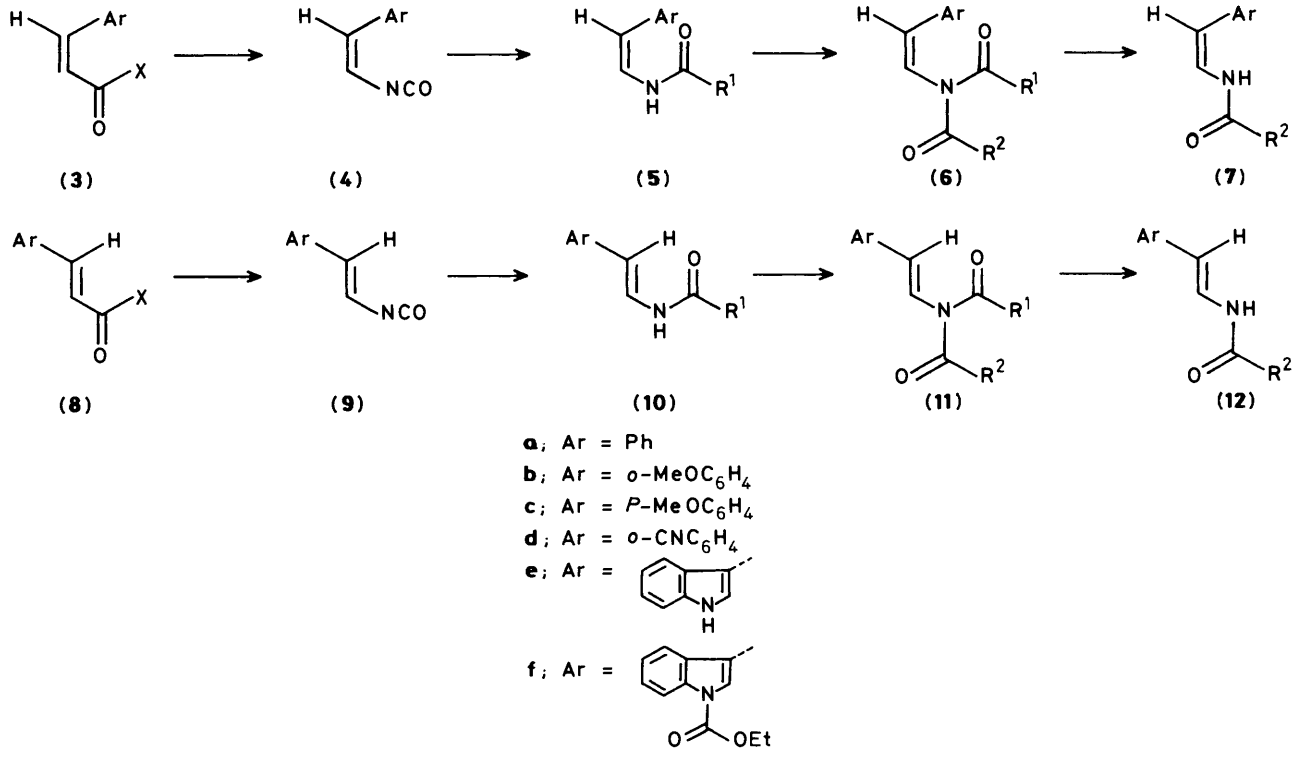


(**1**)



(**2**)

(*E*)-2-Phenylethenyl isocyanate (**9a**) has been reported[22] to react with an excess of trifluoroacetic acid in refluxing chloroform to give the (*E*)-enamide (**10a**; $R^1 = CF_3$) in 60% yield. The thermal decomposition of cinnamoyl azides in trifluoroacetic acid has been described elsewhere[23] as 'apparently unsuitable for the preparation of *N*-trifluoroacetyl enamines,' but in our hands compound (**10a**; $R^1 = CF_3$) could be obtained in 45% yield by this method. The direct production of the *N*-trifluoroacetyl amine with loss of carbon dioxide is characteristic of the reactions of isocyanates with strong acids.[24] The isocyanate (**9c**) is reported[25] to give tuberin (**10c**; R^1 = H) with formic acid, although the reaction of other substituted styryl isocyanates with formic acid is stated to give no significant yields of the

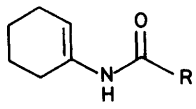


Scheme.

corresponding formamides.[26] The reaction of (*Z*)-styryl isocyanates (**4**) with strong acids has not previously been investigated.

For model studies we chose to start from the (*Z*)-acid (**3b**; X = OH),[27] which like the corresponding (*E*)-acid (**8b**; X = OH)[27] is easily obtained from coumarin. Reaction of the (*Z*)-acid (**3b**; X = OH) with thionyl chloride in ether at 0 °C gave material shown by ^{1}H n.m.r. spectroscopy (Table 1) to be a 1:4 mixture of the (*Z*)- and (*E*)-acyl chlorides (**3b**) and (**8b**) (X = Cl). We attribute this loss of stereochemical homogeneity to isomerisation caused by acidic by-products (*cf.* ref. 20). Reaction of the (*Z*)-acid (**3b**; X = OH) with ethyl chloroformate and triethylamine in acetone at 0 °C (*cf.* ref. 28) to give the mixed carbonic anhydride (**3b**; X = OCO_2Et), reaction with sodium azide in aqueous acetone at 15 °C,[28] and thermal decomposition of the resultant azide in refluxing benzene then gave exclusively the (*Z*)-isocyanate (**4b**). The *Z*-configuration of both the intermediate azide (**3b**; X = N_3) and the isocyanate (**4b**) was established by ^{1}H n.m.r. spectroscopy (Table 1); the corresponding (*E*)-azide (**8b**; X = N_3) and (*E*)-isocyanate (**9b**) were prepared for spectroscopic comparison (Table 1) by the same sequence, starting from the (*E*)-acid (**8b**; X = OH). These results confirm the expected retention of configuration during the C ⟶ N migration in the Curtius procedure. When the (*Z*)-isocyanate (**4b**) was treated with either 1 mol equiv. or an excess of trifluoroacetic acid in benzene at 65 °C the major product (42%*) was the (*E*)-enamide (**10b**; $R^1 = CF_3$), which was accompanied by a lesser amount (14%†) of the desired (*Z*)-enamide (**5b**; $R^1 = CF_3$) and a trace of an unidentified third product. The (*E*)-enamide was identical (m.p. t.l.c., and ^{1}H n.m.r. spectroscopy) with a sample prepared by the action of trifluoroacetic acid on the (*E*)-isocyanate (**9b**). It appears that the trifluoroacetic acid catalyses the isomerisation of either the starting isocyanate or the product enamide. This behaviour means that the reaction of styryl isocyanates with trifluoroacetic acid can effectively be used only for the preparation of (*E*)-enamides.

We have also briefly examined a second route to *N*-trifluoroacetyl enamines. Condensation of the acetal 1,1-diethoxycyclohexane with trifluoroacetamide in the presence of a trace of anilinium chloride gave variable but never high yields of *N*-(cyclohex-1-enyl)trifluoroacetamide (**13**; R = CF_3). The condensation of 1,1-diethoxycyclohexane with ethyl carbamate under the same conditions[29] proceeds reproducibly to give a considerably higher yield of the corresponding enecarbamate (**13**; R = OEt). The decreased nucleophilicity of the amide nitrogen in trifluoroacetamide in comparison with other amides has been noted[30] in another connection.



(13)

Our inability to obtain (*Z*)-*N*-(2-arylethenyl)trifluoroacetamides was unfortunate as in the *E*-series it proved possible to exchange the *N*-trifluoroacetyl group for a variety of other *N*-acyl groups. It has been reported[23] that recrystallisation of 9-(trifluoroacetamido)phenanthrene from methanol gives 9-(methoxycarbonylamino)phenanthrene, although other trifluoroacetyl amides are unaffected by boiling methanol.[31] The trifluoroacetamide (**10a**; $R^1 = CF_3$) was unchanged after prolonged heating in methanol. We therefore explored the preparation of *N*-acyl-*N*-trifluoroacetyl enamines [*e.g.* (**11**; $R^1 = CF_3$, R^2 = Me)] in the expectation that it would be possible to cleave the *N*-trifluoroacetyl group selectively by either the hydrolytic

* Based on (**3b**; X = N_3)

Table 1. ^{1}H N.m.r. chemical shifts (δ) and coupling constants (Hz) at 220 MHz in $CDCl_3$ for the vinylic protons in acids and acid derivatives (**3**) and (**8**) and isocyanates (**4**) and (**9**).

Compound	Chemical shifts		J_{AB}	Config.	M.p. (°C)	Lit. m.p. (°C)	Ref.
(**3a**; X = OH)	5.90	6.95	12.8	*Z*	65—67	67—68	45
(**8a**: X = OH)	6.50[a]	7.70[a]	16.0	*E*	132—133	130—132	45
(**3b**: X = OH)	5.96	7.24	12.2	*Z*	87—88	88—89	27
(**8b**; X = OH)	6.47	7.88	15.6	*E*	184—185	184—185	25
(**3c**; X = OH)	5.85	6.96	12.8	*Z*	62—64	65—66	45
(**8c**: X = OH)	6.38[b]	7.57[b]	15.6	*E*	174—175	170—171	45
(**3d**: X = OH)	6.22[a]	7.12[a]	12.2	*Z*	139	136.5	46
(**8d**; X = OH)	6.67[a]	7.84[a]	15.6	*E*	255—256	253—254	46
(**3e**: X = OH)	5.70	7.21	12.2	*Z*	*c*		50
(**8e**: X = OH)	6.39[a]	7.92[a]	15.6	*E*	189—191	191—193	80
(**3c**; X = OMe)	5.82	*d*	12.8	*Z*	*e*		
(**3e**; X = OEt)	5.76[b]	*d*	12.8	*Z*	154—156	*f*	
(**8e**; X = OEt)	6.40	7.92	15.6	*E*	117—119	119—120	47
(**3b**: X = Cl)	6.40	7.67	9.4	*Z*	*g*		
(**8b**: X = Cl)	6.74	8.11	14.4	*E*	*g*		
(**3b**: X = NH_2)	5.99	*d*	12.2	*Z*	61—62	62.5—63.5	27
(**8b**: X = NH_2)	6.68	7.83	15.5	*E*	193—194	194—195	27
(**3a**: X = N_3)	5.86	6.98	12.8	*Z*	*h*		
(**8a**: X = N_3)	6.40	7.74	15.6	*E*	85	86	79
(**3b**: X = N_3)	5.85	7.28	12.2	*Z*	38—42 (Decomp.)	*g*	
(**8b**: X = N_3)	6.51	8.07	16.7	*E*	55—57	*g*	
(**8c**: X = N_3)	6.25	7.67	15.6	*E*	98—100	98—100	25
(**3d**: X = N_3)	6.14	7.26	12.2	*Z*	*g*		
(**8d**: X = N_3)	6.11	8.05	16.1	*E*	77—78	*g*	
(**3f**: X = N_3)	5.86	7.14	12.2	*Z*	*g*		
(**8f**: X = N_3)	6.39	*d*	16.1	*E*	96—97 (Decomp).	*g*	
(**4a**)	5.92	7.13	12.8	*Z*	*i*		
(**9a**)	6.28	6.42	14.4	*E*	*j*		
					(B.p. 83—84 at 1.5 mmHg, 107 at 12 mmHg)		79
(**4b**)	6.07	6.34	9.4	*Z*	*g*		
(**9b**)	6.52	6.63	14.4	*E*	*g*		
(**9d**)	6.63	6.77	12.8	*E*	*g*		
(**9f**)	6.29	6.48	13.9	*E*	*g*		

[a] Sufficient [$^2H_6$]acetone was added to dissolve the sample. [b] In [$^2H_6$]acetone. [c] Obtained only in admixture with (**8e**; X = OH); spectrum recorded on the mixture. [d] Signal obscured by the signal for the aromatic protons. [e] Oil, not distilled. [f] New compound, recrystallised from light petroleum and benzene (Found: C, 72.7; H, 6.1; N, 6.7. $C_{13}H_{13}NO_2$ requires C, 72.6; H, 6.05; N, 6.5%); *m/z* (M^+) 215. [g] Only characterised spectroscopically. [h] Obtained in admixture with (**4a**); spectrum recorded on the mixture. [i] Obtained in admixture with (**3a**; X = N_3); spectrum recorded on the mixture. [j] B.p.

Table 2. ^{1}H N.m.r. chemical shifts (δ) and coupling constants (Hz) for the vinylic protons, in $CDCl_3$ at 220 MHz, yields of isolated material and analytical data for the enamides (**10a**) and (**10b**) and (**5b**) (R^1 = CF_3)

Enamide	Chemical shifts		J_{AB}	Yield (%)	M.p. (°C)	Found (%)			Calc. (%)			Formula†
						C	H	N	C	H	N	
(**5a**: R^1 = CF_3)	5.85	6.77	10.6	14[b]	Oil	(*m/z* 245.0671)			(*m/z* 245.0665)			$C_{11}H_{10}F_3NO_2$
(**10b**; R^1 = CF_3)	6.67	7.50	14.4	30[c]	112—113[d]	53.9	4.15	5.6	53.9	4.1	5.7	$C_{11}H_{10}F_3NO_2$
(**10b**: R^1 = CF_3)	6.40	*a*	14.4	45[c]	143—145[e]							

[a] Obscured by aromatic proton signal. [b] Plus 42% of (**10b**; R^1 = CF_3); based on azide. [c] Based on isocyanate. [d] From light petroleum and benzene. [e] Lit.,[22] 141—143 °C. † All new compounds showed a parent ion peak corresponding to M^+ in the low resolution mass spectrum.

or the reductive methods known to be successful with simple *N*-trifluoroacetamides.[32] Some enamides have been *N*-acetylated by acetic anhydride at 140 °C,[33] or acetic anhydride in pyridine at 100 °C,[34] although other enamides do not undergo *N*-acetylation at the enamide nitrogen under such conditions.[6–8] The *N*-acylation of one enamide through the reaction of its potassium salt with a pseudo-acid chloride has also been reported.[35] Treatment of (**10a**; R^1 = CF_3) with acetic anhydride and pyridine at 100 °C gave (*E*)-*N*-(2-phenylethenyl)acetamide (**12a**; R^2 = Me) directly in 42% yield; it was identified by direct comparison (m.p., ^{1}H n.m.r., and mass spectrometry) with an authentic sample prepared by the Beckmann rearrangement.[36]

The product was separated chromatographically from a second product, identified as the *N*,*N*-diacetyl enamine (**11a**; R^1 = R^2 = Me), which was formed in 18% yield. When the enamide (**10a**; R^1 = CF_3) was converted into its anion with sodium hydride, and treated with acetic anhydride in refluxing *N*,*N*-dimethylformamide (DMF) the enamide (**13a**; R^2 = Me) was formed in 33% yield as the only product; in tetrahydrofuran (THF) with acetyl chloride the isolated yield of (**12a**; R^2 = Me) was 25%, and with acetic anhydride the yield was 23%. Starting material was also recovered in each case. Other acyl groups could be introduced similarly by acylation of *N*-trifluoroacetyl enamines. Thus acylation of the anion from (**10a**; R^1 = CF_3)

Table 3. ^{1}H N.m.r. chemical shifts (δ) and coupling constants (Hz) at 220 MHz in $CDCl_3$ for the vinylic protons, yields of isolated material, and analytical data for the enecarbamates (**5**) and (**10**) (R^1 = OMe) prepared by the Curtius method

Compound	Chemical shifts		J_{AB}	Solvent for recryst.*	Yield (%)	M.p. (°C)	Lit. m.p. (°C)	Ref.	Found (%) C	H	N	Calc. (%) C	H	N	Formula†
(**5a**; R^1 = OMe)	5.55	6.63	10.0		62[a]	(Oil)			67.5	6.5	7.6(5)	67.8	6.2	7.9	$C_{10}H_{11}NO_2$
(**10a**; R^1 = OMe)	6.00	*b*	14.4	A	55[c,d]	121—122	122—123	37							
(**5b**; R^1 = OMe)	5.60	6.70	10.0	X	91[c]	39	39—40	27							
(**10b**; R^1 = OMe)	6.25	*b*	14.4	B	46[c,e]	113—114	114—115	27							
(**5c**; R^1 = OMe)	5.52	6.57	9.4	X	62[a,f]	43—44			63.5	6.2	6.6	63.8	6.3	6.8	$C_{11}H_{13}NO_3$
(**10c**; R^1 = OMe)	6.05	7.05	15.0	C	56	133—134	134—135	27							
(**10d**; R^1 = OMe)	6.43	*b*	14.4	D	97[g]	175.5—176.5			65.1	5.2	13.7	65.3(5)	4.9(5)	13.9	$C_{11}H_{10}N_2O_2$
(**5f**; R^1 = OMe)	5.62	6.80	9.4	E	68[g]	113—114			62.4	5.6	9.7	62.5	5.6	9.7	$C_{15}H_{16}N_2O_4$
(**10f**; R^1 = OMe)	6.17	*b*	14.4	C	73[a]	124—125			62.4(5)	5.8	9.8	62.5	5.6	9.7	$C_{15}H_{16}N_2O_4$

[a] Based on the acid. [b] Signal obscured by the aromatic proton signal. [c] Prepared by the Hofmann route; yield based on the amide. [d] Also prepared from (**10a**; R^1 = CF_3) as the anion and $ClCO_2Me$ in 60% yield (37% of starting material recovered). [e] Also prepared from (**10b**; R^1 = CF_3) as the anion and $ClCO_2Me$ in 23% yield (52% of starting material recovered). [f] Plus 0.2% of (**8c**; X = N_3) and 0.6% of (**10c**; R = OMe). [g] Based on the azide. * A, ethanol–water; B, light petroleum–benzene; C, methanol–water; D, light petroleum–THF; E, light petroleum–ethyl acetate; X, not recrystallised. † All new compounds showed a parent ion peak corresponding to M^+ in the low resolution mass spectrum.

with methyl chloroformate gave (**12a**; R^2 = OMe)[37] in 60% yield, with acetic formic anhydride gave (**12a**; R^2 = H)[38] in 23% yield, and with L-*N*-phthaloylalanyl chloride gave [**12a**: R^2 = $CHMeN(CO)_2C_6H_4$] in 21% yield. Similarly acylation of the anion from (**10b**; R^1 = CF_3) with methyl chloroformate gave (**12b**; R^2 = OMe)[27] in 23% yield and of the anion from (**13**; R = CF_3) with ethyl chloroformate gave (**13**; R = OEt)[29] in 54% yield. From all these reactions substantial amounts of the starting enamides were recovered.

The one-step replacement of an *N*-trifluoroacetyl group by an acetyl group has been reported previously.[39] Treatment of the anion from 4-benzyl-2-methyl-5-(trifluoroacetamido)-oxazole (prepared with sodium hydride in THF) with acetyl chloride gave the corresponding 5-acetamido-4-benzyl-2-methyloxazole. It seems likely that the loss of the trifluoroacetyl groups in these replacements occurs through an *N*,*N*-diacyl compound, since the anions from simple trifluoroacetamides behave normally on *N*-alkylation.[10] The susceptibility to hydrolysis and methanolysis of *N*-acyl-*N*-trifluoroacetylanilines has been noted,[41] as has the instability of *N*-trifluoroacetyl β-lactams, which lose the trifluoroacetyl group during chromatography on Florisil.[42] We failed to effect such a replacement with the (*Z*)-enamide (**5b**; R^1 = CF_3). When it was treated with sodium hydride in THF and then heated under reflux with methyl chloroformate the only compounds isolated after the usual work-up were starting material (**5b**; R^1 = CF_3) (51%) and the isomerised *N*-trifluoroacetyl enamine (**10b**; R^1 = CF_3) (23%).

We next turned our attention to enecarbamates (**5**) and (**10**) (R^1 = OMe) and were pleased to discover that treatment of the (*Z*)-isocyanate (**4b**) with anhydrous methanol at room temperature gave exclusively the (*Z*)-enecarbamate (**5b**; R^1 = OMe).[27] In the absence of a strong acid partial isomerisation was avoided. The product had been described previously by Weerman in the only report[27] of the use of the Hofman amide degradation to prepare a (*Z*)-enecarbamate. We have repeated Weerman's classical experiment. The requisite amide (**3b**; X = NH_2) was prepared, as before,[27] by converting the acid (**3b**; X = OH) into the acid chloride (**3b**; X = Cl) with phosphorus pentachloride, and then treating the acid chloride with liquid ammonia. Provided that great care was taken to avoid traces of acid, which caused partial double-bond isomerisation, treatment of the amide (**3b**; X = NH_2) with aqueous methanolic sodium hypochlorite at 0 °C then gave the (*Z*)-enecarbamate (**5b**; R^1 = OMe). We found it preferable to activate the acid (**3b**; X = OH) by formation of the mixed anhydride[43] (**3b**; X = O·CO_2Et), as already described, and in this way to avoid problems of partial isomerisation. The configuration of the (*Z*)-enecarbamate (**5b**; R^1 = OMe) was confirmed by its ^{1}H n.m.r. spectrum, which was in accord with the proposed geometry, and differed from that of the corresponding (*E*)-enecarbamate already discussed (Table 3). Encouraged by finding that the (*Z*)-isocyanate (**4b**) could be prepared by the Curtius reaction and that it could be converted into the (*Z*)-enecarbamate (**5b**; R^1 = OMe) by methanol, we studied further examples of this sequence to establish its generality. The stereochemistry at the olefinic double bond was monitored at the intermediate azide and isocyanate stages and in the final products by ^{1}H n.m.r. spectroscopy, and the sequence was also applied to the corresponding (*E*)-acids so that spectroscopic comparisons could be made (see Tables 1 and 3). (*Z*)-3-(4-Methoxyphenyl)prop-2-enoic acid (**3c**; X = OH) was obtained by methylation[44] of the commercially available hydroxy acid, followed by hydrolysis of the resultant methyl ester (**3c**; X = OMe), (*Z*)-3-phenylprop-2-enoic acid (**3a**; X = OH) was prepared from the ethyl ester of DL-phenylalanine *via* ethyl 2-diazo-3-phenylpropanoate using Yamada's method,[45,46] and (*Z*)-3-(2-cyanophenyl)prop-2-enoic acid (**3d**; X = OH) was made by the Beckmann fragmentation of 1-nitroso-2-naphthol.[47,48] (*E*)-3-(2-Cyanophenyl)-prop-2-enoic acid (**8d**; X = OH) was prepared by heating the pyridine salt of the (*Z*)-acid,[47] and the other (*E*)-acids were commercial samples. All six of the acids were activated by formation of their mixed carbonic anhydrides (**3**) or (**8**) (X = OCO_2Et) and converted into their azides (**3**) or (**8**) (X = N_3) with sodium azide in aqueous acetone. The (*E*)-azides slowly decomposed even at room temperature and were converted into the enecarbamates by heating in boiling methanol. The (*Z*)-acid (**3a**; X = OH) gave exclusively the expected (*Z*)-enecarbamate (**5a**; R^1 = OMe) in 62% yield of isolated product. Our results contradict two earlier reports[18,21] on the application of the Curtius reaction to the (*Z*)-acid (**3a**; X = OH). In the case of the (*Z*)-acid (**5c**; X = OH) the (*Z*)-enecarbamate (**5c**; R^1 = OMe) was obtained in 62% yield after chromatographic separation from 0.2% of the (*E*)-acyl azide (**8c**; X = N_3) and 0.6% of the (*E*)-enecarbamate (**10c**; R^1 = OMe). These minor products were identified by direct comparison with those obtained by application of the sequence to the (*E*)-acid (**8c**; X = OH). The (*E*)-azide (**8c**; X = N_3), in contrast to the (*Z*)-azide (**3c**; X = N_3), was a stable crystalline solid at room

Table 4. ^{1}H N.m.r. chemical shifts (δ) and coupling constants (Hz) at 220 MHz in $CDCl_3$ for the vinylic protons, yields of isolated material, and analytical data for *N*,*N*-diacyl enamines (**6**) and (**11**) prepared by the acylation of an anion of the enecarbamates (**5**) and (**10**) (R^1 = OMe)

Compound	Chemical shifts		J_{AB}	Recryst. solvent*	Yield (%)	Recovered starting material (%)	M.p. (°C)	Found (%) C	H	N	Calc. (%) C	H	N	Formula†
(**11a**; R^1 = R^2 = Me)	6.42	6.89	14.4		*a*		(Oil)	(*m*/*z* 203.0945			203.0940)			$C_{12}H_{13}NO_2$
(**11a**; R^1 = OMe, R^2 = Me)	6.54	6.87	14.4		64[b,c,d]	22[b,c,d]	(Oil)	65.8	6.1	6.5	65.7(5)	5.9	6.4	$C_{12}H_{13}NO_3$
(**11b**; R^1 = OMe, R^2 = Me)	6.77	6.91	14.4		43	32	(Oil)	62.6	6.1	5.7	62.6(5)	6.0	5.6	$C_{13}H_{15}NO_4$
(**11c**; R^1 = OMe, R^2 = Me)	6.46	6.72	14.4	F	33	48	56—58	62.6	6.3	5.3	62.6(5)	6.0	5.6	$C_{13}H_{15}NO_4$
(**11d**; R^1 = OMe, R^2 = Me)	6.92	7.18	14.4	B	50	26	89—91	63.7	5.0	11.8	63.9	4.9	11.5	$C_{13}H_2N_2O_3$
(**11f**; R^1 = OMe, R^2 = Me)	6.61	6.94	13.9	E	34	13	71—72	61.8(5)	5.5	8.7	61.8	5.4(5)	8.7	$C_{17}H_{18}N_2O_5$
(**6b**; R^1 = OMe, R^2 = Me)	6.33	6.55	9.4		66	25	(Oil)	62.4	6.1	5.6	62.6(5)	6.0	5.6	$C_{13}H_{15}NO_4$
(**6c**; R^1 = OMe, R^2 = Me)	6.16	6.35	8.9	F	46	36	44—45	62.0	6.0	5.6	62.6(5)	6.0	5.6	$C_{13}H_{15}NO_4$
(**11a**; R^1 = OMe, R^2 = H)	7.00	7.16	14.4		48	16	(Oil)	64.3	5.4	6.6	64.4	5.4	6.8	$C_{11}H_{11}NO_3$
(**6c**; R^1 = OMe. R^2 = H)	6.04	6.47	8.9		43	46	(Oil)	61.0	5.7	5.8	61.3	5.5	6.0	$C_{12}H_{13}NO_4$
[**11a**; R^1 = OMe, R^2 = $CHMeN(CO)_2C_6H_4$]	6.64	6.86	14.7		42	24	(Oil)	66.7	4.6	7.5	66.7	4.8	7.4	$C_{21}H_{13}N_2O_5$
[**6a**; R^1 = OMe, R^2 = $CHMeN(CO)_2C_6H_4$]	6.25	6.45	8.9	G	31	26	110—111	66.8(6)	5.0	7.6	66.7	4.8	7.4	$C_{21}H_{18}N_2O_5$
[**6b**: R^1 = OMe, R^2 = $CHMeN(CO)_2C_6H_4$]	6·28	6.53	9.4	G	43	41	96.5—98	64.5	4.9(5)	6.8	64.7	4.9	6.6	$C_{22}H_{20}N_2O_6$
[**6c**: R^1 = IMe. R^2 = $CHMeN(CO)_2C_6H_4$]	6.14	6.36	8.3	G	46	16	121—122	64.7	5.1	6.9	64.7	4.9	6.9	$C_{22}H_{20}N_2O_6$
(**11c**: R^1 = OMe, R^2 = CHBrMe)	6.46	6.69	14.4		*e*	33	(Oil)	48.9	4.7	4.0[f]	49.1	4.7	4.1	$C_{14}H_{16}{}^{79}BrNO$

[a] Formed in 18% yield by the reaction of (**10a**; R^1 = CF_3) with acetic anhydride and pyridine. [b] From (**10a**; R^1 = OMe) using acetic anhydride. [c] From (**10a**; R^1 = OMe) using acetyl chloride (yield 18%; recovered starting material 36%). [d] From (**10a**; R^1 = OMe) using acetic anhydride (yield 57%; recovered starting material 15%). [e] Analytical sample isolated by h.p.l.c. [f] (Found: Br, 23.3. Calc. for $C_{14}H_{16}BrNO_4$: Br, 23.4%).
† All new compounds showed a parent ion peak corresponding to M^+ in the low resolution mass spectrum.
* B, light petroleum–benzene; E, light petroleum–ethyl acetate; F, light petroleum; G, light petroleum–ether.

temperature and was decomposed in refluxing benzene to give the (*E*)-isocyanate (**9c**), which on treatment with methanol gave the enecarbamate (**10c**; R^1 = OMe). To our surprise, thermal decomposition of the (*Z*)-azide (**3d**; X = N_3) in refluxing benzene gave the (*E*)-isocyanate (**9d**), identical with the material from the (*E*)-azide (**8d**; X = N_3), which with methanol gave the (*E*)-intermediate (**10d**; R^1 = OMe). ^{1}H N.m.r. spectroscopy confirmed that the (*Z*)-azide (**3d**; X = N_3) had been formed from the (*Z*)-acid and could be differentiated from the (*E*)-azide (see Table 1). In view of this failure we thought that it might be possible to obtain the (*Z*)-enecarbamate (**5d**; R^1 = OMe) by the Hofmann route which had been successful in giving the analogous methoxy compound (**5b**; R^1 = OMe). However, as we have reported elsewhere,[49] reaction of the (*Z*)-amide (**3d**; X = NH_2) with aqueous methanolic sodium hypochlorite gives 1-aminoisoquinoline and not the desired enecarbamate.

These largely successful results led us to investigate the synthesis of the (*Z*)-enecarbamate from (*Z*)-3-(indol-3-yl)prop-2-enoic acid (**3e**; X = OH) which would be a key intermediate for a synthesis of fragilamide (**2**). Attempts to use Yamada's method [35] to prepare this (*Z*)-acid were unsuccessful: we could find no conditions which would convert methyl 2-diazo-3-(indol-3-yl)propanoate,[45] readily available from DL-tryptophan, into the desired α,β-olefinic ester of either the (*Z*)- or the (*E*)-configuration (**8e**) or (**3e**) (X = OMe). The (*E*)-acid (**8e**; X = OH) was conveniently prepared from indole-3-carbaldehyde by condensation with ethyl hydrogen malonate,[50] followed by saponification. In agreement with earlier work,[51] u.v. irradiation of the (*E*)-acid (**8e**; X = OH) in ethyl acetate led to an equilibrium mixture containing *ca.* 25% of the required (*Z*)-acid (**3e**; X = OH), but complete separation of the two diastereoisomers could not be achieved. Photoequilibration starting with the ethyl ester (**8e**; X = OEt) gave a mixture containing *ca.* 35% of the (*Z*)-ester (**3e**; X = OEt), which could be isolated in a pure state chromatographically. Unfortunately attempted hydrolysis of the (*Z*)-ester with ethanolic sodium hydroxide at room temperature led to a mixture of the (*E*)-acid (**8e**; X = OH) and the (*E*)-ester (**8e**; X = OEt): under similar conditions the (*Z*)-methyl ester (**3b**; X = OMe) was completely hydrolysed to the corresponding (*Z*)-acid (**3b**; X = OH). Consequently the Curtius reaction was applied to a 1:1 mixture (^{1}H n.m.r. spectroscopy) of the (*Z*)- and (*E*)-acids (**3e**) and (**8e**) (X = OH) obtained by fractional crystallisation of the 1:3 mixture produced by photoequilibration. Treatment with ethyl chloroformate and triethylamine, and then sodium azide, in the usual way gave a mixture of the *N*(1)-ethoxycarbonyl-substituted acyl azides (**3f**) and (**8f**) (X = N_3) which could be separated by column chromatography; the (*E*)-isomer (**8f**; X = N_3) was identical with material made from the pure (*E*)-acid. The *N*(1)-ethoxycarbonylation of indole during the activation of an indolecarboxylic acid as a mixed anhydride has been observed previously.[52] Decomposition of the (*Z*)-azide (**3f**; X = N_3) in boiling methanol then gave the (*Z*)-enecarbamate (**5f**; R^1 = OMe). Decomposition of the more stable (*E*)-azide (**8f**; X = N_2) in hot dry benzene gave the (*E*)-isocyanate (**9f**), which with methanol gave the diastereoisomeric (*E*)-enecarbamate (**10f**; R^1 = OMe). In practice it proved to be more convenient in later work to carry through the Curtius sequence on the mixture of the (*Z*)- and (*E*)-acids as far as the final enecarbamate stage and then to separate the enamides (**5f**) and (**10f**) (R^1 = OMe) by chromatography. In view of the greater accessibility of the (*E*)-enecarbamate (**10f**; R^1 = OMe), the feasibility of photoisomerisation as a source of the (*Z*)-isomer (**5f**; R^1 = OMe) was investigated. Several similar enamide photoisomerisations have been reported.[36] U.v. irradiation did produce a mixture of the (*Z*)- and (*E*)-enecarbamates from which the (*Z*)-enamide (**5f**; R^1 = OMe) was isolated in 29% yield, but the method was not attractive as an alternative to the route based on photoequilibration at the acid stage, followed by enrichment in the (*Z*)-acid (**3e**; X = OH).

Having established a fairly general route to (*Z*)-enecarba-

mates (**5**; R^1 = OMe) we next turned to the exchange of the methoxycarbonyl group for other acyl groups. To this end the *N*-acylation of enecarbamates was investigated, with the expectation that the methoxycarbonyl group could be cleaved selectively from the resultant *N,N*-diacyl enamines. Our preliminary studies were carried out on the most readily available enecarbamate (**10a**; R^1 = OMe). When this was acetylated with acetic anhydride some of the required *N,N*-diacyl enamine (**11a**; R^1 = OMe, R^2 = Me) was formed, but the reactions were not clean and the yields were low. With acetic anhydride and pyridine at 100 °C,[34] the yield of (**11a**; R^1 = OMe, R^2 = Me) was 20% and in addition to starting material (**10a**; R^1 = OMe) a 6% yield of the exchanged enamide (**10a**; R^1 = Me) was also isolated. A 30% yield of the *N,N*-diacyl enamine (**11a**; R^1 = OMe, R^2 = Me) was obtained after 65 h reflux in acetic anhydride,[33] together with two unidentified minor products. Evidence that the acetyl group is attached to the nitrogen atom, although possibly as a result of O ⟶ N migration,[53] is provided by two experiments described later; the spectroscopic data (*cf.* Table 4) are consistent with the structure (**11a**; R^1 = OMe, R^2 = Me). Reaction of (**10a**; R^1 = OMe) with acetic anhydride in acetonitrile at room temperature in the presence of 4-dimethylaminopyridine[54] gave only a 7% yield of the *N,N*-diacyl enamine (**11a**; R^1 = OMe, R^2 = Me). No acetylation was observed when the enamide (**10a**; R^1 = OMe) was treated with acetyl chloride in boiling dichloromethane in the presence of pulverised Linde 4 Å molecular sieves,[55] or with acetic anhydride in refluxing THF containing tetrabutylammonium fluoride,[56] and the enamide (**10a**; R^1 = OMe) was recovered. The *N*-alkylation of enamides through their anions has been studied in some detail.[36] Treatment of (**10a**; R^1 = OMe) with sodium hydride gave the anion, which with acetyl chloride in boiling THF gave the *N,N*-diacyl enamine (**11a**; R^1 = OMe, R^2 = Me) in 18% yield, but substitution of acetic anhydride improved the yield to 64%; no other products were detected. The formulation of the product as the *N*-acetylated material (**11a**; R^1 = OMe, R^2 = Me) was supported by its identity with material made by treating the anion of the *N*-acetyl enamine (**10a**; R = Me) in boiling THF with methyl chloroformate, since *O*-acylation in these two cases would not have given the same product. By proceeding *via* the anion it was also possible to prepare [**11a**; R^1 = OMe, R^2 = H or CHMeN$(CO)_2C_6H_4$] in 48 and 42% yield, respectively, using acetic formic anhydride and *N*-phthaloylalanyl chloride as the acylating agents. The acetylated compounds (**11b, c, d, f**; R^1 = OMe, R^2 = Me) were prepared in 43, 48, 50, and 34% yield, respectively, by the same method. Treatment of the anion from (**10c**; R^1 = OMe) with 2-bromopropanoyl bromide in boiling THF gave a mixture which appeared from analytical t.l.c. to contain a single product, together with starting material. The oily product was separated by column chromatography and analysed by high performance liquid chromatography (h.p.l.c.), which showed the presence of two components in the ratio 6:1. These could be separated by preparative h.p.l.c. The major component was identified as the desired *N,N*-diacyl enamine (**11c**; R^1 = OMe, R^2 = CHBrMe). The minor product was shown by mass spectrometry to contain two bromine atoms, and on the basis of a parent ion peak at *m/z* 477 and mechanistic considerations is assigned the structure (**11c**; R^1 = OMe, R^2 = CBrMeCOCHBrMe), although other structures are clearly compatible with the limited data available.

This acylation methodology was then applied to several (*Z*)-enecarbamates (**5**; R^1 = OMe) with the expectation that *N*-acylation would occur with retention of the olefin geometry. Benzylation of the anion from the (*Z*)-enamide (**5a**; R^1 = Me) has earlier been shown[36] to occur on nitrogen with retention of the olefin configuration, and the alkylation of the anions from two (*Z*)-alk-3-enoate esters has been shown to occur at C-2 with retention of the *Z*-configuration.[57] When the anion from the (*Z*)-enamide (**5a**; R^1 = OMe) was treated with *N*-phthaloylalanyl chloride in boiling THF the (*Z*)-*N,N*-diacyl enamine [**6**; R^1 = OMe, R^2 = CHMeN$(CO)_2C_6H_4$] was indeed formed, and could be isolated in 31% yield, together with a 26% yield of starting material (**5a**; R^1 = OMe). The material was different from the *E*-diastereoisomer already described, and the *Z*-configuration of the double bond was confirmed by the magnitude of the vinylic proton–proton coupling constant in the ^{1}H n.m.r. spectrum (see Table 4). In five further examples the acylation of (*Z*)-enecarbamates (**5b** and **c**; R^1 = OMe) also gave the corresponding (*Z*)-*N,N*-diacyl enamines [R^2 = Me, H, or CHMeN$(CO)_2C_6H_4$].

To achieve our synthetic objective it was finally necessary to effect the selective cleavage of the *N*-methoxycarbonyl group from the *N,N*-diacyl enamines (**6**) and (**11**) (R^1 = OMe). Several attempts, under a variety of conditions, to bring about the selective hydrolysis or methanolysis of the *N,N*-diacyl enamine (**11a**; R^1 = OMe, R^2 = Me) all led to cleavage of the *N*-acetyl group and gave the enecarbamate (**10a**; R^1 = OMe). Similar results have been noted in the aminolysis and base-catalysed methanolysis of *N*-acyl carbamates,[58] although one set of conditions we investigated has been reported to debenzyloxycarbonylate cleanly the *N*-benzyloxycarbonyl derivative of a lactam.[59] Adsorption of the *N,N*-diacyl enamine (**11a**; R^1 = OMe, R^2 = Me) on alumina, a procedure reported[34,60] to convert an *N,N*-diacetyl enamine into the corresponding mono-*N*-acetyl enamine, gave both the desired enamide (**12a**; R^2 = Me) and the unwanted enecarbamate (**10a**; R^1 = OMe), in 2:1 ratio. However this procedure was found to be of limited value, since when it was applied to the *N*-formyl-*N*-methoxycarbonyl enamine (**11a**; R^1 = OMe, R^2 = H) the sole product was the unwanted enecarbamate (**10a**; R^1 = OMe). These results led us to consider an alternative strategy, based on nucleophilic demethylation.[51] Trimethylsilyl iodide, either used directly, or prepared *in situ*, has been recommended[62] for the dealkoxycarbonylation of simple alkyl carbamates, but the recorded yields for methyl carbamates are variable, low recoveries having sometimes been reported,[62,63] and two cases where the reagent fails totally to effect demethoxycarbonylation of methyl carbamates having been reported.[64] Trimethylsilyl iodide might also produce trace amounts of hydrogen iodide and we therefore rejected this reagent and also the system dimethyl sulphide–methanesulphonic acid which has been used[65] for the cleavage of carbamates, in view of the tendency of (*Z*)-enamides to be transformed into the corresponding (*E*)-enamides by traces of strong acids. The necessity to avoid traces of acid was demonstrated by the reaction of the (*Z*)-*N,N*-diacyl enamine (**6c**; R^1 = OMe, R^2 = Me) with boron trichloride in dichloromethane at −25 °C, conditions used to demethylate a sterically hindered methyl ester,[66] where careful work-up led to the product of demethoxycarbonylation, but with the *E*-configuration (**12c**; R^2 = Me). Several simple inorganic ions have been used for nucleophilic demethylation.[61,67] Iodide ion has often been used,[61,68,69] in the form of lithium iodide, and in a reported study[70] of one particular methyl ester it was shown that DMF was the solvent of choice. We therefore adopted this system, which proved to be highly successful when applied to (*E*)-*N,N*-diacyl enamines (**11**; R^1 = OMe). When the compound (**11a**; R^1 = OMe, R^2 = Me) was heated for 24 h in DMF containing 1.5 mol equiv. of lithium iodide trihydrate and 2.0 mol equiv. of added water,[69] the desired enamide (**12a**; R^2 = Me) was obtained as the only product in 85% yield. Similarly [**11a**; R^1 = OMe, R^2 = CHMeN$(CO)_2C_6H_4$] gave [**12a**; R^2 = CHMeN$(CO)_2C_6H_4$) in 90% yield, but when this procedure was applied to compound (**11a**; R^1 = OMe; R^2 = H), although the desired enamide (**12a**; R^2 = H) was isolated, in 53% yield, it was accompanied by 20% of the alternative

Table 5. ^{1}H N.m.r. chemical shifts (δ) and coupling constants (Hz) in $CDCl_3$ at 220 MHz for the vinylic protons, yields of isolated material, and analytical data for enamides (**7**) and (**12**) prepared from *N*,*N*-diacyl enamines (**6**) and (**11**)

Compound	Chemical shifts		J_{AB}	Yield (%)	Yield of alternative cleavage product (%)	Reaction solvent	Recryst. solvent*	M.p. (°C)	Found (%) C	H	N	Calc. (%) C	H	N	Formula†
(**12a**; R^2 = Me)	6.14	7.53	14.4	85[a]	0	DMF	B	113—114		(Lit.,[36] m.p. 113—114 °C)					
(**12b**; R^2 = Me)	6.42	7.60	14.4	39	0	DMF	B	135—137	68.8(5)	7.0	7.3	69.1	6.8	7.3	$C_{11}H_{13}NO_2$
(**12c**; R^2 = Me)	6.08	7.38	15.0	54[b]	0	DMF	B	118		(Lit.,[81] m.p. 119—120 °C)					
(**12d**; R^2 = Me)	6.46	*c*	14.4	68	0	DMF	B	187—189	71.2	5.7	15.2	71.0	5.4	15.0(5)	$C_{11}H_{10}N_2O$
(**12f**; R^2 = Me)	6.24	*c*	14.4	44	16	MeCN	E	164—166	66.0	6.2	10.2	66.2	5.9	10.3	$C_{15}H_{16}N_2O_3$
(**7b**; R^2 = Me)	5.64	*c*	10.6	35	14	MeCN C_5H_5N	B	67	69.3	7.1	7.3	69.1	6.8	7.3	$C_{11}H_{13}NO_2$
(**7c**; R^2 = Me)	5.66	*c*	9.4	82	0	MeCN C_5H_5N	B	79—81	68.9	6.8	7.6	69.1	6.8	7.9	$C_{11}H_{13}NO_2$
(**12a**; R^2 = H)	6.27	7.52	14.4	53[d]	20[d]	DMF	B	102—103		(Lit.,[38] m.p. 100—101 °C)					
(**7c**; R^2 = H)	5.66[e] 5.74[d]	6.35	8.9	38	31	MeCN	G	76—77	67.5	6.4	7.7	67.8	6.2	7.9	$C_{10}H_{11}NO_2$
[**12a**; R^2 = $CHMeN(CO)_2C_6H_4$]	6.23	7.46	14.7	90[f]	0[f]	DMF	B	204—206[g]	71.2	5.2	8.6	72.1(5)	5.0	8.75	$C_{19}H_{16}N_2O_3$
[**7a**; R^2 = $CHMeN(CO)_2C_6H_4$]	5.72	6.74	9.4	36	15	MeCN	H	165—167[h]	71.4	5.3	8.6(5)	71.2(5)	5.0	8.75	$C_{19}H_{16}N_2O_3$
[**7b**; R^2 = $CHMeN(CO)_2C_6H_4$]	5.71	*c*	10.0	51	18	MeCN	G	96—98	68.6	5.4	8.3	68.6	5.1		$C_{20}H_{18}N_2O_4$
[**7c**; R^2 = $CHMeN(CO)_2C_6H_4$]	5.68	6.78	9.4	49	6	MeCN	B	110—111.5	68.3	5.0(5)	8.2	68.6	5.1	8.2	$C_{20}H_{18}N_2O_4$

[a] Also prepared from (**10a**; R^1 = CF_3): (i) with acetic anhydride and pyridine, yield 42% plus 20% of (**11a**; R^1 = R^2 = Me); (ii) *via* the anion, with acetic anhydride in DMF, yield 33%; (iii) *via* the anion with acetic anhydride in THF, yield 23%, plus 28% of (**10a**; R^1 = CF_3) recovered; (iv) *via* the anion with acetyl chloride in THF, yield 26%, plus 46% of (**10a**; R^1 = CF_3) recovered. [b] Also prepared from (**6b**; R^1 = OMe; R^2 = Me) in DMF in 56% yield. [c] Signal obscured by signal for aromatic protons. [d] Also prepared *via* the anion of (**10a**; R^1 = CF_3) and acetic formic anhydride in 23% yield with 56% of (**10a**; R^1 = CF_3) recovered. [e] Two rotamers present. [f] Also prepared *via* the anion from (**10a**; R^1 = CF_3) and L-phthaloylalanyl chloride in 21% yield with 52% of (**10a**; R^1 = CF_3) recovered. [g] $[\alpha]_D^{20}$ −2.1° (*c* 1.0 in $CHCl_3$). [h] $[\alpha]_D^{20}$ −1.5° (*c* 1.0 in $CHCl_3$).

† All new compounds showed a parent ion peak corresponding to M^+ in the low resolution mass spectrum.

* B, light petroleum–benzene; E, light petroleum–ethyl acetate; G light petroleum–ether; H, light petroleum–chloroform.

cleavage product (**10a**; R^1 = OMe). The ring-substituted (*E*)-enamides (**12b—d**; R^2 = Me) were also smoothly prepared in this way.

When the (*Z*)-*N*,*N*-diacyl enamine (**6b**; R^1 = OMe, R^2 = Me) was treated with lithium iodide in DMF, as already described, the only product isolated was an intractable dark resin. When the same procedure was applied to the (*Z*)-*N*,*N*-diacyl enamine (**6c**; R^1 = OMe; R^2 = Me) the (*E*)-enamide (**12c**; R^2 = Me) already described was unexpectedly obtained. Trost has briefly referred [71] to some loss of stereochemical homogeneity during the monodemethoxycarbonylation of dimethyl (2*E*, 6*E*)-3,7-dimethyl-9-(methoxycarbonyl)deca-2,6-dienoate by lithium iodide and sodium cyanide in hot DMF.[68] We circumvented this problem by changing to a different and lower-boiling solvent, acetonitrile, which has been used [72] as a solvent for sodium bromide and sodium iodide in the monodealkylation of phosphate and phosphonate esters. When the (*Z*)-*N*,*N*-diacyl enamine (**6c**; R^1 = OMe, R^2 = Me) was refluxed with lithium iodide trihydrate in acetonitrile containing 3 mol equiv. of pyridine for 16 h the only product was the desired (*Z*)-enamide (**7c**; R^2 = Me), isolated in 82% yield. Under the same conditions the isomer (**6b**; R^1 = OMe, R^2 = Me) gave a 5:2 mixture of the (*Z*)-enamide (**7b**; R^2 = Me) and the (*Z*)-enecarbamate (**5c**; R^1 = OMe), which could readily be separated chromatographically. When the reaction was repeated under similar conditions, but without the pyridine, the same two products were obtained in the ratio 9:2, with the desired (*Z*)-enamide (**7b**; R^2 = Me) as the major product. Similarly, reaction of the three amino-acid-related (*Z*)-*N*,*N*-diacyl enamines [**6a—c**; R^1 = OMe, R^2 = $CHMeN(CO)_2C_6H_4$] with lithium iodide in refluxing acetonitrile in the absence of pyridine gave the corresponding (*Z*)-enamides [**7a—c**; R^1 = OMe, R^2 = $CHMeN(CO)_2C_6H_4$] contaminated with up to 30% of the (*Z*)-enecarbamates (**5a—c**; R^1 = OMe), which could be removed by fractional crystallisation or chromatography. In the same way the (*Z*)-*N*-formyl derivative (**6c**; R^1 = OMe, R^2 = H) gave the diastereoisomer (**7c**; R^2 = H) of the natural product tuberin,[1] accompanied by 40% of the (*Z*)-enecarbamate (**5c**; R^1 = OMe). The *Z*-configuration of the double bonds in these (*Z*)-enamides (**7**) was established by a comparison of their ^{1}H n.m.r. spectral data (Table 5) with these of the corresponding (*E*)-enamides (**12**). Although the alternative cleavage leading to the enecarbamates occurs during these *N*-demethoxycarbonylations this is not a serious problem as both products (**7**) and (**5**) retain their *Z*-configurations and the enecarbamates (**5**) can be recycled by acylation to give the (*Z*)-*N*,*N*-diacyl enamines (**6**) again. In all the cases where the (*Z*)-*N*,*N*-diacyl enamine (**6**) is converted into a (*Z*)-enamide or a (*Z*)-enecarbamate the reaction presumably proceeds *via* an anion at nitrogen, but, as with the acylation of the (*Z*)-enecarbamates through their anions, already discussed, the stereochemistry at the double bond is retained. A successful and convenient route to a series of (*Z*)-enamides (**7**) has thus been established.

We also applied the lithium iodide–acetonitrile demethoxycarbonylation procedure to the *N*(1)-protected indole diacyl enamine (**11f**; R^1 = OMe, R^2 = Me). The major product was the enamide (**12f**; R^2 = Me), which could be separated chromatographically from *ca.* 20% of the enecarbamate (**10f**; R^1 = OMe) which was also formed. It is noteworthy that the *N*(1)-methoxycarbonyl group is unaffected by lithium iodide in refluxing acetonitrile.

Experimental

^{1}H N.m.r. spectra were recorded with a Perkin-Elmer R34 (220 MHz) instrument for solutions in $CDCl_3$ (unless otherwise stated) with Me_4Si as internal standard. Mass spectra were obtained with a Kratos MS25 or MS80 instrument, with a D55 data system. I.r. spectra were measured with a Perkin-Elmer 157G spectrophotometer and optical rotations with a Perkin-Elmer 141 polarimeter. Solutions in organic solvents were dried with anhydrous magnesium sulphate unless otherwise stated. Analytical t.l.c. was performed on glass plates (20 × 5 cm) coated with *ca.* 1 mm of Merck Kieselgel G, and preparative t.l.c. on larger plates (20 × 30 cm) similarly coated. Column chromatography was performed by the short-path technique with a column slurry-packed with Merck Kieselgel 60 silica. Unless otherwise specified the solvent systems used for preparative t.l.c. or column chromatography were the same as those described for analytical t.l.c. High pressure liquid chromatography (h.p.l.c.) was performed with a Gilson gradient system consisting of a Rheodyne 7125 injector, two Gilson 303 pumps, a Gilson holochrome u.v.-detector and a Gilson 131 refractive index detector. The columns used were 25 × 0.4 cm (analytical) or 25 × 1.2 cm (preparative) in dimensions, packed with 5 μ Hypersil and 14 μ Spherisorb, respectively. Liquid samples were all purified by preparative h.p.l.c. before combustion analysis. Medium pressure liquid chromatography (m.p.l.c.) was accomplished with Jobling columns: a 2.5 × 2.5 cm pre-column and a 2.5 × 100 cm main column packed with 60 μ silica gel (Kieselgel), with a Metering Pumps Ltd. pump, a Cecil 202 u.v. spectrophotometer and a Chemlab 270 fraction collector. M.p.s were determined with a Kofler hot-stage apparatus. The identity of samples of the same compound from different sources was established by comparing ^{1}H n.m.r. and i.r. spectral data and behaviour on t.l.c.

Solvents.—'Ether' refers to diethyl ether and 'light petroleum' to the fraction having b.p. 60—80 °C. DMF and acetonitrile were stirred overnight with calcium hydride, refluxed for 1 h, and then distilled at atmospheric pressure nitrogen. THF was refluxed wtih sodium metal and benzophenone under nitrogen until a permanent blue colour persisted, and then distilled at atmospheric pressure.

Starting Materials and Reference Compounds.—Thionyl chloride was purified by the triphenyl phosphite method.[73] Acetic formic anhydride,[74] L-*N*-phthaloylalanyl chloride,[75] 2-bromopropanoyl chloride,[76] 1,1-diethoxycyclohexane,[77] (*Z*)-3-phenylprop-2-enoic acid,[45,46] ethyl (*E*)-3-(indol-3-yl)prop-2-enoate,[78] (*E*)- and (*Z*)-3-(2-methoxyphenyl)prop-2-enoic acids,[27] (*Z*)-3-(4-methoxyphenyl)prop-2-enoic acid,[44] (*E*)-2-phenylethenyl isocyanate,[79] (*E*)-*N*-(2-phenylethenyl)-2,2,2-trifluoroacetamide,[22] ethyl *N*-cyclohex-1-enylcarbamate,[29] methyl (*E*)-*N*-2-phenylethenylcarbamate,[27] and methyl (*E*)- and (*Z*)-*N*-2-(2-methoxyphenyl)ethenylcarbamates[28] were prepared by literature methods and had physical properties (m.p. or b.p.) in agreement with published data. Pertinent ^{1}H n.m.r. spectra data are given in Tables 1—3.

Ethyl (Z)-3-(*Indol-3-yl*)*prop-2-enoate.*—Ethyl (*E*)-3-(indol-3-yl)prop-2-enoate (0.5 g) (**8e**; X = OEt) in ethyl acetate (60 ml) was irradiated under nitrogen for 4 h with a medium-pressure Hanovia 100 W mercury compact arc lamp. Evaporation left an oil, shown by analytical t.l.c. (7:3 light petroleum–ethyl acetate) to consist of two components having R_F 0.60 and 0.37. ^{1}H N.m.r. spectroscopy showed two components to be present in the ratio 1:2. The mixture from four irradiations (1.95 g) was separated by column chromatography. The first component to be eluted was a solid, which crystallised from light petroleum–benzene to give *ethyl* (Z)-3-(*indol-3-yl*)*prop-2-enoate* (**3e**; X = OEt) (0.61 g, 31%), m.p. 154—156 °C. Spectroscopic and analytical data are in Table 1.

(E)-3-(*Indol-3-yl*)*prop-2-enoic Acid.*—Ethyl (*E*)-3-(indol-3-yl)prop-2-enoate (12.0 g) was heated under reflux for 3 h with sodium hydroxide (6.0 g) in water (140 ml) and ethanol (560 ml). The mixture was concentrated, diluted with water (100 ml), and acidified with 2M hydrochloric acid. The resultant solid was collected by filtration, washed well with water, and dried. Crystallisation from ethyl acetate gave (*E*)-3-(indol-3-yl)prop-2-enoic acid (**8e**; X = OH) (9.2 g, 80%), m.p. 189—191 °C (lit.,[80] 191—193 °C); ^{1}H n.m.r. spectroscopic data are given in Table 1. Similar treatment of ethyl (*Z*)-3-(indol-3-yl)prop-2-enoate (**3e**; X = OEt) but for 4 h at room temperature gave material shown by ^{1}H n.m.r. spectroscopy to be essentially ethyl (*E*)-3-(indol-3-yl)prop-2-enoate (**8e**; X = OEt).

Reaction of (Z)-3-(2-*Methoxyphenyl*)*prop-2-enoic Acid with Thionyl Chloride.*—Purified thionyl chloride (2.66 ml, 36.5 mmol) was added to a stirred solution of (*Z*)-3-(2-methoxyphenyl)prop-2-enoic acid (**3b**; X = OH) (5.0 g, 28.1 mmol) in anhydrous ether (10 ml) at 0 °C. After 1 h at 0 °C the solvent and the excess of thionyl chloride were evaporated off to leave an oil, which was shown by ^{1}H n.m.r. spectroscopy (Table 1) to be a 1:4 mixture of (*Z*)- and (*E*)-3-(2-methoxyphenyl)prop-2-enoyl chlorides (**3b**) and (**8b**) (X = Cl).

General Procedure for the Preparation of Methyl N-(2-*Arylethenyl*)*carbamates.*—Ethyl chloroformate (1 equiv.), in acetone, was added over 30 min to a stirred mixture of the 3-arylprop-2-enoic acid (1 equiv.) and triethylamine (1.24 equiv.), in acetone, at 0 °C under nitrogen. After a further 30 min at 0 °C the mixture was filtered* and most of the acetone was evaporated from the filtrate at room temperature. Sodium azide (1.26 g) in water was then added below 15 °C, with stirring. After being stirred for a total of 1 h the mixture was poured into water† and extracted (3 ×) with ether. The combined extracts were washed with water and dried over potassium carbonate and Linde 4 Å molecular sieves, and the solvent was removed to give the azide ($\nu_{max.}$ 2 130—2 150 cm^{-1}). The azide was then decomposed in one of two ways. If the azide was stable at room temperature it was heated in boiling anhydrous benzene (50 ml) under nitrogen until decomposition was complete (i.r. spectroscopy). Evaporation left the isocyanate‡ ($\nu_{max.}$ 2 250—2 260 cm^{-1}) which was left for 1 h in an excess of magnesium-dried methanol. The excess of methanol was then removed to give the crude enecarbamate, which was purified by recrystallisation or column chromatography. Other azides were heated in an excess of refluxing magnesium-dried methanol under nitrogen. When the reaction was complete (i.r. spectroscopy) the mixture was cooled and kept at room temperature for 1 h. The product was then isolated. Once isolated the intermediate azides and isocyanates were analysed spectroscopically and then used immediately without further characterisation for the next step. The ^{1}H n.m.r. data are given in Table 1. The methyl *N*-2-arylethenylcarbamates (**5**) and (**10**) (R^1 = OMe) prepared in this way are listed in Table 3, with their m.p.s and yields of isolated product, and the associated spectroscopic and analytical data.

Preparation of N-[2-(2-*Methoxyphenyl*)*ethenyl*-2,2,2-*trifluoroacetamides.*—The isocyanates (**4b**) and (**9b**) (1 equiv.) and

* Except in the case of (**8d**; X = O·CO_2Et) where the mixed anhydride co-precipitated with the triethylammonium chloride.

† The azides (**8c**) and (**8f**) (X = N_3) separated as solids at this stage and were collected by filtration.

‡ Under these conditions the (*Z*)-azide (**3d**; X = N_3) gave the (*E*)-isocyanate (**9d**).

trifluoroacetic acid (1.05 equiv.) were separately heated in benzene at 65 °C under nitrogen for 16 h. Evaporation left the crude products. The material from the (*E*)-isocyanate (**9b**) solidified on trituration with light petroleum and ether and was purified by crystallisation. The product from the (*Z*)-isocyanate (**4b**) was shown by analytical t.l.c. (7:3 light petroleum–ether) to be a mixture of three components. Column chromatography on silica gave the (*Z*)-enamide (**5b**; $R^1 = CF_3$), as an oil, and the (*E*)-enamide (**10b**; $R^1 = CF_3$), identical with the material from (**9b**). The products are listed in Table 2 together with the percentage yields of isolated product and the associated spectroscopic and analytical data.

Photoequilibration of Methyl (E)-N-{2-[N(1)-*Ethoxycarbonylindol-3-yl*]*ethyl*}*carbamate*.—The (*E*)-enecarbamate (**10f**; R^1 = OMe) (3.0 g, 10.4 mmol) in ethyl acetate (60 ml) was irradiated with a medium-pressure Hanovia 100 W mercury compact arc lamp for 4 h under nitrogen. Evaporation left a solid (2.8 g), which was shown by analytical t.l.c. (7:3 light petroleum–ethyl acetate) and by ^{1}H n.m.r. spectroscopy to be a *ca.* 1:3 mixture of the (*Z*)-enecarbamate (**5f**; R^1 = OMe), R_F 0.54 and the (*E*)-enecarbamate (**10f**; R^1 = OMe), R_F 0.46, which were separated in 29 and 58% yield, respectively, by column chromatography and shown to be identical with the materials prepared directly by applying the general procedure to a mixture of the (*Z*)- and (*E*)-acids (**3e**) and (**8e**) (X = OH).

N-(*Cyclohex-1-enyl*)-2,2,2-*trifluoroacetamide*. 1,1-Diethoxycyclohexane (3.0 g, 0.017 mol), 2,2,2-trifluoroacetamide (1.97 g, 0.017 mol), and anilinium chloride (*ca.* 20 mg) were slowly heated in 190 °C. At *ca.* 130 °C reaction commenced and the ethanol was distilled through a long fractionating column. The mixture was maintained at 190 °C for 4 h. Analytical t.l.c. (3:1 light petroleum–ethyl acetate) of the residue, after cooling, showed the presence of two components R_F 0.62 and 0.95. Column chromatography gave the material with R_F 0.62, which on crystallisation from light petroleum gave *N-(cyclohex-1-enyl)-2,2,2-trifluoroacetamide* (**13**; R = CF_3) (typically 0.9 g, 27%), m.p. 51—53 °C, $\nu_{max.}$ 3 300 (NH), 1 710 (CO), and 1 570 cm^{-1} (C=C); δ_H 7.53 (1 H, br s, NH), 6.18 (1 H, br s, =CH), 2.15 (4 H, m, 2 × CH_2C=C), and 1.65 (4 H, m, CH_2CH_2); *m/z* 193 (M^+) and 96 ($M^+ - CF_3CO$) (Found: C, 49.5; H, 5.2; N, 7.0. $C_8H_{10}F_3NO$ requires C, 49.7; H, 5.2; N, 7.2%).

(Z)-3-(2-*Methoxyphenyl*)*prop*-2-*enamide*.—The (*Z*)-acid (**3b**; X = OH) (5.0 g) was converted into the mixed anhydride (**3b**; X = OCO_2Et) by the general procedure already described. The product was dissolved in anhydrous ether (50 ml) and added dropwise to liquid ammonia (*ca.* 75 ml) at −78 °C. Crystallisation of the product from light petroleum–ether gave the (*Z*)-amide (**3b**; X = NH_2) (3.4 g, 68%). The ^{1}H n.m.r. spectroscopic data, m.p. and literature m.p. are given in Table 1.

Reaction of (E)-N-(2-*Phenylethenyl*)-2,2,2-*trifluoroacetamide and Methyl* (E)-N-(2-*Phenylethenyl*)*carbamate with Acetic Anhydride*.—(i) The enamide (**10a**; $R^1 = CF_3$) (0.5 g, 2.3 mmol), acetic anhydride (5 ml, 53 mmol), and pyridine (20 ml) were heated at 100 °C for 40 h under nitrogen. The excess of solvents was evaporated off, and the residue was taken up in dichloromethane. The solution was washed with water, dried, and evaporated to give material which by chromatography on silica (with 4:1 light petroleum–ethyl acetate as eluant) gave (E)-N-*acetyl*-N-(2-*phenylethenyl*)*acetamide* (**11a**; $R^1 = R^2$ = Me) (85 mg, 18%), as an oil, and a solid which on crystallisation from light petroleum and benzene gave (*E*)-*N*-(2-phenylethenyl)acetamide (**12a**; R^2 = Me) (0.158 g, 42%), identical with an authentic sample.[36]

(ii) Under the conditions in (i) the enecarbamate (**10a**; R^1 = OMe) gave material from which *methyl* (E)-N-*acetyl*-N-(2-*phenylethenyl*)*carbamate* (**11a**; R^1 = OMe, R^2 = Me) (0.124 g, 20%), starting material (**10a**; R^1 = OMe) (85 mg, 17%), and (*E*)-*N*-(2-phenylethenyl)acetamide (**12a**; R^2 = Me)[36] (25 mg, 6%) were isolated by preparative t.l.c.

(iii) The enecarbamate (**10a**; R^1 = OMe) (0.5 g, 2.8 mmol) was heated in boiling acetic anhydride (9.55 g, 0.095 mol) for 65 h under nitrogen. The mixture, at room temperature, was stirred with aqueous sodium hydrogen carbonate until the excess of acetic anhydride had decomposed, and then extracted with dichloromethane (3 × 25 ml). The combined extracts were washed with water, dried, and evaporated to give an oil from which methyl (*E*)-*N*-acetyl-*N*-(2-phenylethenyl)carbamate (0.184 g, 30%) and starting material (**10a**; R^1 = OMe) (0.21 g, 42%) were isolated by preparative t.l.c. ^{1}H N.m.r. spectroscopic and analytical data for these compounds are given in Table 4 or 5.

General Procedure for the Acylation of Enamides and Enecarbamates via their Anions.—Sodium hydride (50% dispersion in oil; 1 equiv.) was added to a stirred solution of the enamide or enecarbamate (1 equiv.) in a dry solvent. The mixture was then cooled to 0 °C and the acylating agent (2 equiv.) was added in one portion. The resultant mixture was stirred at 0 °C for 5 min and then heated under reflux for 36 h. This procedure was conducted under nitrogen. Later the cold mixture was poured into water and extracted with dichloromethane (3×). The combined extracts were washed with water and dried and the solvent was evaporated off. The crude products were analysed by t.l.c. and ^{1}H n.m.r. spectroscopy and the components were separated and purified by preparative t.l.c. or column chromatography (light petroleum–ethyl acetate mixtures as solvent systems) or by crystallisation. The enamides and enecarbamates obtained from the *N*-trifluoroacetyl derivatives and the *N,N*-diacyl enamines (**6**) or (**11**) obtained from the methyl *N*-(2-arylethenyl)carbamates by this procedure are listed in Tables 4 and 5 together with the yields of isolated material (product and recovered starting material) and the associated spectroscopic and analytical data.

Methanolysis and Hydrolysis of Methyl (E)-N-*Acetyl*-N-(2-*phenylethenyl*)*carbamate*.—(i) The *N,N*-diacyl enamine (**11a**; R^1 = OMe, R^2 = Me) (0.2 g) in methanol (25 ml) was added to methanolic sodium methoxide [from sodium (30 mg) and methanol (50 ml)] and the mixture was stirred at room temperature for 1.5 h. The solvent was then removed under reduced pressure and water (50 ml) was added to the residue. The solid was collected by filtration, washed with water, and dried. Recrystallisation from light petroleum and benzene gave methyl (*E*)-*N*-(2-phenylethenyl)carbamate (**10a**; R^1 = OMe) (85 mg, 53%), identified by direct comparison with an authentic sample.

(ii) The *N,N*-diacyl enamine (**11a**; R^1 = OMe, R^2 = Me) (0.2 g) was heated for 3 h in methanol (35 ml) and water (5 ml) containing potassium hydrogen carbonate (0.35 g) under reflux. Work-up as in (i) gave the enecarbamate (**10a**; R^1 = OMe) (68 mg, 42%).

(iii) The *N,N*-diacyl enamine (**11a**; R^1 = OMe, R^2 = Me) (0.2 g) in 2M sodium hydroxide (0.1 ml) and methanol (50 ml) was kept at room temperature for 18 h. Work-up as in (i) gave the enecarbamate (**10a**; R^1 = OMe) (95 mg, 59%).

Deacylation of N,N-*Diacyl Enamines by Adsorption on Alumina*.—(i) The *N,N*-diacyl enamine (**11a**; R^1 = OMe, R^2 = Me) (0.2 g) in the minimum amount of 7:3 light petroleum–ethyl acetate was adsorbed onto a chromatographic column slurry-packed with Laporte (U.G.I.) alumina (6.0 g). After 1 h the material was eluted, with the same solvent mixture. Two

products were obtained with R_F values (analytical t.l.c.; same solvent system) 0.76 and 0.23. The faster running material was identified as methyl (*E*)-*N*-(2-phenylethenyl)carbamate (**10a**; R^1 = OMe) (27 mg, 17%), and the other as (*E*)-*N*-(2-phenylethenyl)acetamide (**12**; R^2 = Me) (52 mg, 36%).

(ii) Application of the same procedure to methyl (*E*)-*N*-formyl-*N*-(2-phenylethenyl)carbamate (**11a**; R^1 = OMe; R^2 = H) (0.2 g) gave a single product, identified as methyl (*E*)-*N*-(2-phenylethenyl)carbamate (**10a**; R^1 = OMe) (126 mg, 73%).

General Procedure for the Demethoxycarbonylation of Methyl N-Acyl-N-(2-arylethenyl)carbamates with Lithium Iodide Trihydrate and Wet Dimethylformamide.—A mixture of the methyl *N*-acyl-*N*-(2-arylethenyl)carbamate (1 equiv.), lithium iodide trihydrate (1.5 equiv.), and water (2.0 equiv.) in DMF (10 ml per mmol of diacyl enamine) was heated under reflux until the reaction was complete (analytical t.l.c.). The mixture, at room temperature, was poured into water and extracted with dichloromethane (3 ×). The combined extracts were then washed with water and dried, and the solvents evaporated off. The crude products were analysed by t.l.c. and ^{1}H n.m.r. spectroscopy and the components were separated and purified by preparative t.l.c. or column chromatography (light petroleum–ethyl acetate mixtures as solvent systems) or crystallisation. The yields of the products and the associated spectroscopic and analytical data are given in Table 5.

Reaction of Methyl (Z)-N-*Acetyl*-N-[2-(*4-methoxyphenyl*)-*ethenyl*]*carbamate with Boron Trichloride.*—Boron trichloride (0.375 g, 3.2 mmol) in dichloromethane (1 ml) was added to a stirred solution of methyl (*Z*)-*N*-acetyl-*N*-[2-(4-methoxyphenyl)ethenyl]carbamate (**6c**; R^1 = OMe, R^2 = Me) (0.2 g, 0.8 mmol) in dichloromethane (2 ml) cooled to −25 °C under nitrogen. After 4 h at 0 °C the mixture was cautiously poured into water (25 mol), and shaken to decompose unchanged boron trichloride. The product was extracted into dichloromethane (3 × 25 ml), the combined extracts were washed thoroughly with water and dried, and the solvent was evaporated off. Recrystallisation of the residue from light petroleum and benzene gave (*E*)-*N*-[2-(4-methoxyphenyl)ethenyl]acetamide (**12c**; R^2 = Me) (0.14 g, 92%), identical with an authentic sample.

General Procedure for the Demethoxycarbonylation of Methyl N-Acyl-N-(2-arylethenyl)carbamates with Lithium Iodide Trihydrate in Acetonitrile.—A mixture of the methyl *N*-acyl-*N*-(2-arylethenyl)carbamate (1 equiv.) and lithium iodide trihydrate (1.5 equiv.) in anhydrous acetonitrile (10 ml per mmol of diacyl enamine), and in some experiments (see Table 5) pyridine (3 equiv.), was heated under reflux until the reaction was complete. The cooled mixture was then poured into water and extracted with dichloromethane (3 ×). The combined extracts were washed with water and dried. Evaporation then left the crude product mixture, which was analysed by t.l.c. and from which the products were isolated by preparative t.l.c. or column chromatography (light petroleum–ethyl acetate mixtures as solvent systems) or by crystallisation. The products isolated are listed in Table 5 together with the experimental conditions, the yields of isolated material, and the associated spectroscopic and analytical data.

Note added in proof: Amathamides A, B, E, and F (A. J. Blackman and D. J. Matthews, *Heterocycles*, 1985, **23**, 2829; A. J. Blackman and R. D. Green, *Aust. J. Chem.*, 1987, **40**, 1655) are the diastereoisomeric *N*-[(2,4-dibromo-5-methoxyphenyl)-ethenyl]-1-methyl-4,5-dihydropyrrolecarboxamides and the corresponding 2,3,4-tribromo substituted enamides; amathamides B and F have the *Z*-configuration.

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