Formation of 1,2,3,4-Tetrahydro-2-pyridones by Aza-Annulation of Imines with Acrylate Derivatives

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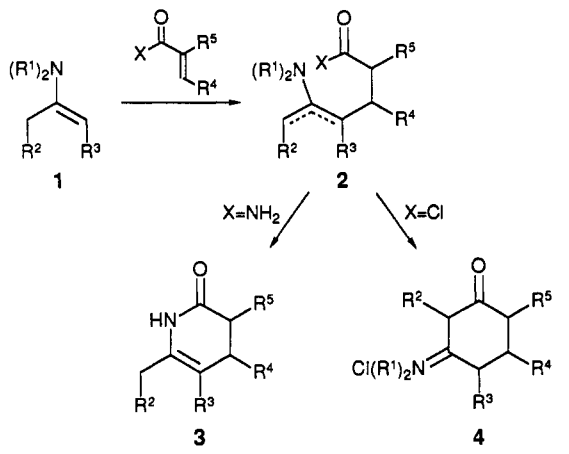
The aza-annulation of imines with activated acrylate derivatives was studied as a means of preparing the corresponding 1,2,3,4-tetrahydro-2-pyridones. Through the use of reagents known to facilitate the formation of amide bonds from carboxylic acids, several methods of activating the acrylate species were compared. The acrylate derivatives studied were acryloyl chloride and acrylic anhydride as well as acrylic acid activated by reaction with EtO_2CCl, $(PhO)_2P(O)N_3$, or MCPI. Optimum annulation was obtained with imines derived from cyclohexanone to produce octahydro-2-quinolone products. The *N*-isobutylimine prepared from cyclopentanone also produced selective ring annulation to efficiently produce the corresponding bicyclic product, but the reaction with the imine of *n*-butanal produced lower yields of cyclic product. Ring formation was relatively unaffected by substituents at the α-position of the acrylate derivative, demonstrated by the use of methacrylate, but β-substituents hindered the annulation process and, in turn, increased the amounts of byproduct resulting from only N-acylation of the imine. Increasing the steric bulk of the imine alkyl substituent produced the opposite effect; the relative amount of N-acylation compared to complete aza-annulation was diminished as the size of the substituent was increased. Mechanistic features of the reaction are discussed in terms of product distribution and competition experiments.

Introduction

Alkaloids containing saturated six-membered nitrogen heterocycles, such as the piperidines and decahydroquinolines, are prevalent in nature, and many of these compounds display potent biological activity.[1] The wide range of physiological effects, dependent upon the unique structure of each molecule, have put these compounds in a position of biological, pharmacological, and synthetic importance. A convergent approach to the preparation of δ-lactams, which can be reduced to the corresponding nitrogen-containing six-membered ring systems, has been through aza-annulation of the C(β)–C(γ) bond and C–N bond from two separate fragments.

There have been several related strategies for the sequential formation of these two bonds. One approach led to formation of the carbon-carbon bond first by conjugate addition of an *N,N*-dialkyl enamine **1** to the acrylate derivative to produce **2** (Scheme I). When acrylamide derivatives were used (X = NH_2), subsequent cyclization was promoted at temperatures above 80 °C to form **3**.[2] The use of a more active acylating agent (X = Cl) with **1** instead resulted in formation of a second carbon–carbon bond and the generation of **4**.[3] A similar approach made use of the ketimine substrates **5** as a source of the tautomeric *N*-alkyl enamine **6** (Scheme II). In examples where R^2, R^3 = $-(CH_2)_3-$ and X = NH_2, ring formation occurred with loss of R^1NH_2 to give **8** (R^1 = H).[2c,4] *N*-Alkylamides have not been used for the preparation of **8** in which $R^1 \neq H$. The same ring formation has been observed with the use of either methyl acrylate (X = OMe)[5] or the analogous acrylonitrile derivatives.[5e,6] For cyclic imine substrates (**5**; R^2, R^3 = $-(CH_2)_n-$), **8** has also been produced from the carboxylic acid (X = OH).[7]

Scheme I. Pathways for Reaction of Acrylate Derivatives with *N,N*-Dialkyl Enamines



An alternative two-step approach to the formation of six-membered rings has been through initial formation of the C–N bond by N-acylation of the tautomeric enamine **6** to give **9**. The second step of this sequence, the C–C bond formation, has been more problematic. Although the transformation of **9** to **8** has been attempted using a

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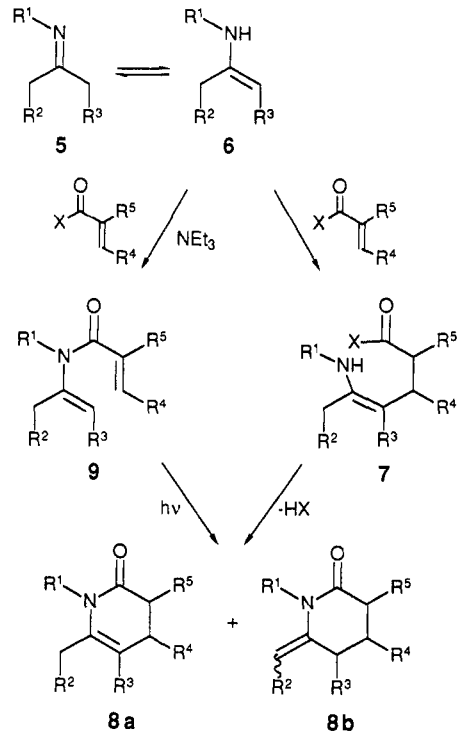
Scheme II. Pathways for Reaction of Acrylate Derivatives with *N*-Alkylimines[a]



[a] The pathways for only one of the two possible regioisomers of **6** are shown.

number of thermal, protic, and Lewis acidic conditions,[8] the only successful method reported for conversion of **9** to **8** has involved photochemical activation using a low-pressure mercury lamp.[9] This work has been investigated by Ninomiya throughout the past 20 years, but has been restricted in its synthetic utility.

The transformation of **9** to **8** has been demonstrated most often on enamide substrates in which either the enamine or acrylate double bond of **9** was in conjugation with or a part of an aromatic ring system.[10] However, for compounds which lack aromatic assistance, this photochemical method of lactam formation had a number of limitations. First and foremost were the low optimized yields, which were reported to be as high as 61%, but were more commonly in the range of 40–50%. A second important restriction was the low concentration (0.02 M) normally required for this photochemical transformation, which constrained the practical use of this procedure to a small reaction scale. In addition, this procedure has not been demonstrated to be useful for the cyclization of enamides of aldehyes. These limitations, in conjunction with the need for photolysis equipment, have provided incentive to search for alternatives to this two step methodology.

Although the reaction of **5** and acryloyl chloride produced entirely **9** in the presence of NEt_3, Hickmott and Sheppard found that performing the reaction without added NEt_3 resulted in competitive product formation of both **8** and **9**.[8a,11] The formation of **8** was favored under these conditions, and products were generated in an 80:20 ratio of **8**:**9**. Despite the modest selectivity, this reaction was still found preferable to the photochemical process for the synthesis of costaclavine.[12] More recently, variations on this method have been observed using acrylic acid derivatives activated by $(PhO)_2P(O)N_3$ and have produced very promising results with the more reactive imines having an aromatic substituent (**5**, R^2 = Ar).[13] Similarly, heterocycle formation has also been achieved by the reaction of α,β-unsaturated anhydrides with substrates conjugated with ester functionality.[14]

Further development of these methods for the selective and convergent formation of δ-lactams through the one-pot aza-annulation of imine substrates and acrylate derivatives has been explored. Of particular interest was the general and high yield aza-annulation with both substrates and acrylate derivatives which were not in conjugation with other functionality. A key feature of the success and efficiency of this reaction was the use of different acyl substituents X (Scheme II) as a means of activating the carboxylate functionality. In addition to the acyl group variation, the effects of imine substrate and acrylate substituent pattern on the outcome of the reaction were es-

Table I. The Reaction of Cyclohexanone Imines with Acrylic Acid Derivatives (eq 1)

R	method[a]	temp (°C)/ time (h)	isolated yield (%)[b]	product mixture[c]
iBu				**11:12 (a:b)**
	A	66/7	68	96:4
	B	25/31	16	23:77 (86:14)
	B	66/17	32	13:87 (83:17)
	C	−45/3	59	0:100 (26:74)
	C	25/1	67	0:100 (45:55)
	C	66/1.5	70	0:100 (81:19)
	D	25/3.5	77	4:96 (34:66)
	E	0/2	69	5:95 (76:24)
	F	66/2	58	21:79 (38:62)
	G	66/33	81	0:100 (74:26)
$PhCH_2$				**14:15 (a:b)**
	A	66/3	70	99:1
	B	66/12	60[d]	15:85
	C	66/2	70	0:100 (33:67)
	D	66/2	77	0:100 (76:24)
	E	0/2	71	3:97 (74:26)
iPr				**17:18 (a:b)**
	A	66/2	87	100:0
	B	66/10	32	5:95 (81:19)
	C	66/2	67	0:100 (81:19)
	D	66/2	77	0:100 (84:16)
	E	25/4	53	0:100 (91:9)
Me_2N				**20:21 (a:b)**
	A	66/21	77	96:4
	B	66/22		64:36
	C	66/18	77	1:99 (83:17)

[a] Method A: X = Cl; NEt_3 added. Method B: X = Cl. Method C: X = Cl; H_2CCHCO_2Na added. Method D: X = OH; EtO_2CCl added. Method E: X = OH; $(PhO)_2P(O)N_3$ added. Method F: X = OH; MCPI/NEt_3 added. Method G: X = Cl; imidazole added. [b] Isolated yield of major product. [c] Ratios of acrylamide:δ-lactam were obtained by capillary gas chromatography; olefin isomer ratios were determined by ^1H NMR. [d] Yield obtained as a mixture of **14** and **15**.

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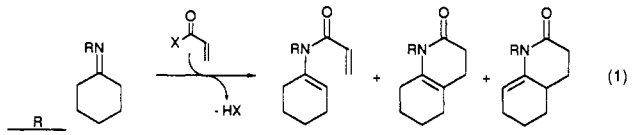
tablished. Determination of substrate variability provided insight into the role of N-acylation versus N-alkylation/conjugate addition mechanistic pathways and provided a means by which syntheses of more complex heterocycles can be rationally planned.

Results and Discussion

Dependence on Acyl Reactivity. In order to calibrate our studies with those previously reported,[8a,11] imine **10** was treated with acryloyl chloride in THF with added NEt_3, and a 96:4 ratio of **11**:**12** was produced (method A, eq 1, Table I). When the same reaction was conducted



R				
iBu-	**10**	**11**	**12a**	**12b**
$PhCH_2$-	**13**	**14**	**15a**	**15b**
iPr-	**16**	**17**	**18a**	**18b**
Me_2N-	**19**	**20**	**21a**	**21b**

in the absence of NEt_3, an inverted 13:87 selectivity for the formation of **11**:**12** was obtained (method B). Purification of the mixture by removal of **11** gave only a 32% yield of a mixture of **12a** and **12b** (83:17). Having obtained these standard samples of **11**, **12a**, and **12b** for comparison, systematic studies were performed to determine the effect of the acyl species on this distribution of products.

The reactivity of the acyl group was found to have a significant effect on product selectivity. The first reagent studied, acrylic anhydride, was prepared in situ by the reaction of acryloyl chloride with sodium acrylate (method C). With the reduced acylating activity of acrylic anhydride as compared to the acryloyl chloride, the bicyclic products **12a** and **12b** were formed to the exclusion of **11**. In addition, a significant dependence of the ratio of **12a**:**12b** upon reaction temperature was found. At −45 °C, **12** was produced as a mixture of inseparable isomers **12a**:**12b** in a 26:74 ratio, while performing the reaction at reflux in THF produced the standard 81:19 mixture of **12a**:**12b**. By treating the 26:74 kinetic mixture of isomers with pTsOH in refluxing MeOH, the mixture was converted by equilibration to the 81:19 thermodynamic ratio of isomers. The annulation efficiency with acrylic anhydride was slightly better with increased reaction temperature, and the effectiveness of this reagent was greatly increased relative to that of the acryloyl chloride (32% isolated yield). However, an obvious deterrent to the use of the symmetrical anhydride approach with more complex acrylate derivatives was the need for 2 equiv of valuable acrylate species.

In order to circumvent this limitation, our attention turned to the study of unsymmetrical activated acrylic acid derivatives. Formation of the mixed anhydride of acrylic acid from ethyl chloroformate, commonly used in peptide bond formation,[15] was achieved by sequential reaction of acrylic acid with NEt_3 followed by treatment with EtO_2CCl (method D). Reaction of the resulting mixed anhydride with **10** gave nearly complete formation of the annulation products with a 4:96 ratio of **11**:**12**, and diphenylphosphorazidate, $(PhO)_2P(O)N_3$,[13,16] also activated acrylic acid in the reaction with **10** (method E) to generate a similar product distribution. The use of methyl-2-chloropyridinium iodide (MCPI)[17] resulted in poor product selectivity and lower product recovery (method F). The acylimidazole species[18] was found to produce specific formation of **12** (method G), but this method was less desirable due to difficulties encountered during reaction workup and product isolation. Two other methods known for promoting the coupling of carboxylic acids with amines, Mukaiyama's conditions ($Ph_3P/[PyrS]_2$)[19] and dicyclohexylcarbodiimide (DCC),[20] each produced lower yields or poor **11**:**12** product selectivity.

Table II. The Reaction of Cyclohexanone Imines with Methacrylic Acid Derivatives (eq 2)

R	method[a]	temp (°C)/ time (h)	isolated yield (%)[b]	product mixture[c]
iBu				**22:23 (a:b)**[e]
	A	66/8	67	96:4
	B	66/24	54[d]	39:61
	C	66/1	69	2:98 (>95:5)
	D	25/3	87	1:99 (93:7)
	E	25/0.7	64	0:100 (95:5)
	F	66/2.5	82[d]	24:76
$PhCH_2$				**24:25 (a:b)**
	A	66/4	80	98:2
	B	66/22	39[d]	52:48
	C	66/2.5	81	0:100 (>95:5)
	D	66/2	81	1:99 (>95:5)
	E	25/2	63	0:100 (>95:5)
iPr				**26:27 (a:b)**
	A	66/4	86	95:5
	B	66/10	50	3:97 (93:7)
	C	66/2	82	0:100 (93:7)
	D	66/3	62	0:100 (>95:5)
	E	25/4	47	0:100 (>95:5)

[a] Method A: X = Cl; NEt_3 added. Method B: X = Cl. Method C: X = Cl; $H_2CCMeCO_2Na$ added. Method D: X = OH; EtO_2CCl added. Method E: X = OH; $(PhO)_2P(O)N_3$ added. Method F: X = OH; MCPI/NEt_3 added. [b] Isolated yield of major product. [c] Ratios of methacrylamide:δ-lactam were obtained by capillary gas chromatography; olefin isomer ratios were determined by ^1H NMR. [d] Yield obtained as a mixture of the isomeric products. [e] See text. Most ratios were determined after treatment with *p*-TsOH/MeOH.

Variation of the Imine N-Substituent. This annulation method of forming δ-lactams was also compatable with other substituents on the nitrogen of the imine. In fact, substituents which are more easily removed after annulation would have much greater potential for subsequent modification of the product for use in organic synthesis. One such group, the *N*-benzyl substituent (**13**), produced δ-lactam formation which was equally as effective as that for the *N*-isobutyl group (**10**). The results of these reactions are summarized in Table I. Decreasing the accessibility of the nitrogen, by changing the substituent from an isobutyl to an isopropyl group (**16**), did not significantly reduce the product yield or slow the rate of the annulation process. In fact, increasing the effective size of this *N*-alkyl group resulted in enhancement of annulation product formation in comparison with the products resulting from annulation with **10**.

The use of the imine formed from cyclohexanone and *N*,*N*-dimethylhydrazine proved to be an interesting alternative to the alkyl substituents similar to the reaction

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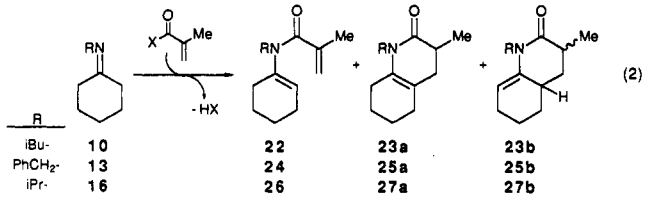
Table III. The Reaction of Cyclohexanone Imines with Crotonic Acid Derivatives (eq 3)

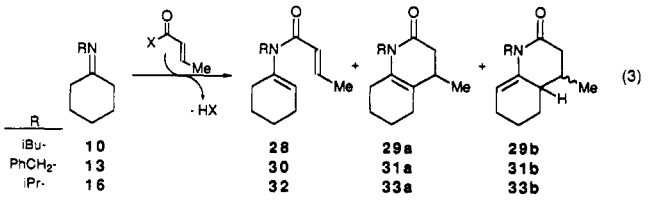
R	method[a]	temp (°C)/ time (h)	isolated yield (%)[b]	product mixture[c]
iBu-				**28:29 (a:b)**
	A	66/4	76	100:0
	B	66/20	34[d]	82:18
	C	66/5	33	36:64 (81:19)
	D	66/15	79[d]	45:55 (79:21)
	E	25/7	51[d]	48:52 *e*
	F	66/3	50[d]	62:38 *e*
$PhCH_2$-				**30:31 (a:b)**
	A	66/4	55	100:0
	B	66/20	73[d]	91:9 *f*
	C	66/12	62[d]	36:64 *f*
	D	66/24	65[d]	44:56 *f*
iPr-				**32:33 (a:b)**
	A[g]	66/4	25	100:0
	B	66/10		69:31
	C	66/10	77	0:100 (>95:5)
	D	66/12	66	4:96 (89:11)

[a] Method A: X = Cl; NEt_3 added. Method B: X = Cl. Method C: X = Cl; $MeHCCHCO_2Na$ added. Method D: X = OH; EtO_2CCl added. Method E: X = OH; $(PhO)_2P(O)N_3$ added. Method F: X = OH; MCPI/NEt_3 added. [b] Isolated yield of major product. [c] Ratios of crotonamide:δ-lactam were obtained by capillary gas chromatography; olefin isomer ratios were determined by ^1H NMR. [d] Yield obtained as a mixture of the isomeric products. [e] Ratio not determined. [f] Isomer ratio could not be accurately determined. [g] Pyridine was used instead of NEt_3.

of acryloyl chloride with **10**, N-acylation of **19** with acryloyl chloride in the presence of NEt_3 selectively produced the corresponding acrylamide **20**. However, the reaction with acryloyl chloride without the addition of NEt_3 produced much less of the desired δ-lactam (64:36, **20:21**) when compared with formation of **11** and **12** from **10**. In contrast, treatment of **19** with acrylic anhydride selectively and efficiently produced **21**. The other reagents, such as $(PhO)_2P(O)N_3$, were ineffective at formation of **20** or **21**.

Effects of Acrylate Substitution Pattern. Methacrylic acid (eq 2, Table II) and crotonic acid (eq 3, Table III) derivatives were used to determine the effects of acrylate olefin substitution on the annulation reaction.



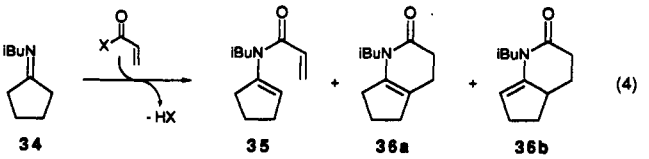


Substitution at the α-position produced little difference in the outcome of the reaction (eq 2, Table II). Product formation by annulation of methacrylic acid with **10**, **13**, or **16** was essentially the same as that for the reaction with the acrylic acid derivatives. Slight exception was noted in the reaction of methacryloyl with either **10** or **13**. In these cases, the balance between N-acylation (**22**, **24**) and annulation (**23**, **25**) was tipped away from the bicyclic products.

Analyses of the reaction products were slightly more complicated due to the presence of the newly formed stereocenter, giving products **a**, **b**, and the diastereomer **b′**.[21] Use of methacrylic anhydride gave a 40:53:7 ratio of **23a:23b:23b′**, which was converted to a >95:5 mixture of **23a**:(**23b** + **23b′**) by treatment with MeOH/*p*-TsOH. When using the mixed anhydride method by activation with EtO_2CCl (method D), removal of the methacrylamide from **23** was facilitated by treating the mixture with *p*-TsOH in refluxing MeOH to degrade the anhydride reagent and **22**. Although the isomer ratio of the crude reaction mixture was not determined for the reaction with the mixed anhydride, a 93:5:2 ratio of **23a:23b:23b′** was obtained after treatment under the acid-catalyzed equilibrating conditions. Ring formation with methacrylic acid activated by $(PhO)_2P(O)N_3$ produced formation of **23** to the exclusion of **22**, and the ratio of bicyclic products without subsequent acid-catalyzed isomerization was 95:4:1 for **23a:23b:23b′**. Thus, when compared to formation of **12**, the presence of an α-methyl substituent on the lactam ring greatly enhanced the selectivity for formation of the isomeric olefin **a** in preference to the less substituted olefin isomer **b**.

In contrast to the similarities observed for annulation with acrylate and methacrylate species, substitution at the β-carbon produced results that differed significantly from those of the acrylic acid derivative (eq 3, Table III). In addition to requiring more vigorous conditions and slightly longer reaction times, the reaction with crotonic acid derivatives also reduced the preference for heterocycle formation. Although the N-acylation of **10** with crotonyl chloride and NEt_3 occurred selectively to form **28**, the reaction in the absence of NEt_3 produced smaller amounts of **29** than the analogous reaction with acryloyl chloride. In fact, the preference for crotonamide product formation (82:18) was opposite that observed for the analogous reaction with acryloyl chloride (13:87). Optimum annulation results were obtained by reaction of **10** with crotonic anhydride (method C) as well as with the mixed anhydride (method D) to give **28:29** in ratios of 36:64 and 45:55, respectively. Isolation of **29** was achieved in 33% and 34% yields for the two methods, providing the same 80:20 mixture of olefin isomers **29a**:(**29b** + **29b′**). The reaction of **13** with the crotonate derivatives produced similar results. Increasing the size of the imine substituent, by reaction of **16** with the crotonate anhydride derivatives, showed greater propensity for annulation by producing >95% conversion to **33** (methods C and D).

Variation of Imine Carbonyl Derivative. An indication of the dependence of reaction success on substrate variability was obtained through studies with imines of isobutylamine derived from cyclopentanone and butanal. Enamide **35** was readily prepared from the reaction of the cyclopentanone imine **34** with acryloyl chloride and NEt_3 (eq 4, Table IV). On the other hand, the complementary



routes to **36** were much less efficient. As observed for the formation of **11** and **12** and **10**, reaction of **34** with acryloyl chloride also produced a mixture of **35** and **36** with a very low product yield. The reaction of imine **34** with the other acrylate derivatives resulted in product recovery which was greater than that observed with the acid chloride, yet yields

(21) The relative stereochemistry of the two diastereomers **b** and **b′** was not determined.

Table IV. The Reaction of Cyclopentanone Imine 34 with Acrylic Acid Derivatives (eq 4)

method[a]	temp (°C)/ time (h)	isolated yield (%)[b]	product mixture[c] 35:36	(a:b)
A	25/8	87	100:0	
B	66/30	29[d]	15:85	(46:54)
C	66/1	53	2:98	(43:57)
D	66/4	63	5:95	(46:54)
E	25/2.5	51	0:100	(54:46)

[a] Method A: X = Cl; NEt_3 added. Method B: X = Cl; Method C: X = Cl; H_2CCHCO_2Na added. Method D: X = OH: EtO_2CCl added. Method E: X = OH; $(PhO)_2P(O)N_3$ added. [b] Isolated yield of major product. [c] Ratios of acrylamide:δ-lactam were determined by capillary gas chromatography; olefin isomer ratios were determined by ^1H NMR. [d] Yield represents a purified mixture of 35 and 36.

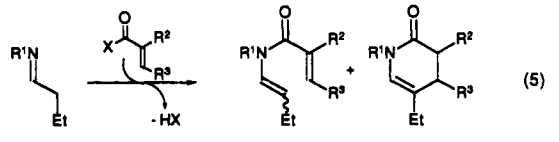
Table V. The Reaction of Isobutyraldehyde Imine 37 with Acrylic Acid Derivatives (eq 5)

method[a]	temp (°C)/ time (h)	yield (%)	product mixture[b] 38:39
A	66/5.5	84[c]	100:0
B	25/11	14[d]	96:4
C	66/12	47[c]	15:85
D	25/7	15[e]	78:22
E	0/2	39[e]	3:97

[a] Method A: X = Cl; NEt_3 added. Method B: X = Cl; Method C: X = Cl; H_2CCHCO_2Na added. Method D: X = OH; EtO_2CCl added. Method E: X = OH; $(PhO)_2P(O)N_3$ added. [b] Ratios of acrylamide:δ-lactam were determined by capillary gas chromatography. [c] Isolated yield of major product. [d] Yield represents a purified mixture of isomeric products. [e] Gas chromatography yield of 39 using internal standards and correcting for detector response.

were significantly decreased in comparison to the analogous reactions that produced 12. These results were most likely due to the greater sensitivity of 34 to the reaction conditions. Although the ratios of 35:36 were consistent with those observed for 11:12, the typical distribution of 36a:36b (45:55) showed a change from that of 12a:12b (usually about 80:20) and were not altered upon treatment with *p*-TsOH under equilibrating conditions.

The greater value of the activated derivatives of acrylic acid as compared to the reaction of the acryloyl chloride became very apparent when studying the reaction with imine 37 (eq 5, Table V). Again, the corresponding en-



(5)

R¹=iBu; 37
R¹=iPr; 44

R¹	R²	R³		
iBu	H	H	38	39
iBu	Me	H	40	41
iBu	H	Me	42	43
iPr	H	H	45	46
iPr	H	Me	47	48

amide 38 was efficiently formed as a 2:1 mixture of *E*:*Z* isomers by the reaction of acryloyl chloride in the presence of NEt_3. However, even without added NEt_3, the reaction of acryloyl chloride still produced a 96:4 ratio of 38:39. The poor generation of annulation products through the use of the acryloyl chloride were magnified by the poor purified yield (14%) obtained for the mixture of 38 and 39; the reduced efficiency of this reaction resulted primarily from the generation of oligomeric products from the more reactive imine. Formation of the δ-lactam from 37 was most effective with the use of acrylic anhydride. In this case, a 15:85 ratio of 38:39 was obtained with only minor amounts of condensation byproducts. In order to facilitate isolation of the lactam, the small amount of enamide 38 present in the mixture was selectively hydrolyzed by stirring in MeOH with *p*-TsOH prior to chromatography. With the use of this purification sequence, lactam 39 was isolated in 47% yield from the mixture.[22] The use of EtO_2CCl or $(PhO)_2P(O)N_3$ resulted in significantly lower product yields.

The reaction of imine 37 with methacrylic anhydride produced results similar to those of the reaction with acrylic anhydride. An 11:89 ratio of 40 to 41 was obtained, and the major product was isolated in 25% yield. Treatment of 37 with crotonic anhydride produced even less heterocycle formation. In this case, only a 63:37 ratio of 42:43 was produced. From this mixture, an 18% isolated yield of 43 was obtained. Although formation of the δ-lactam products through this method was poor when β substituents were present, alternate methods that were previously reported failed completely with crotonic acid derivatives.

The ability to control the N-acylation versus annulation pathways, by modifying the steric bulk of the imine substituent, allowed the enhancement of annulation product formation from aldimine substrates. This greater degree of annulation was demonstrated with the *N*-isopropyl-substituted 44 and the reaction with acrylate and crotonate derivatives (eq 5). Enamides 45 and 47 were prepared by the reaction of the corresponding acid chlorides and NEt_3 with 44 in 49% and 37% yields, respectively. Without the addition of NEt_3, the reaction with acryloyl chloride gave a 65:35 ratio of 45 to 46. The resulting product distribution demonstrated enhancement of the annulation process from that of the reaction of acryloyl chloride and 37 (38:39, 96:4). Similarly, treatment of 44 with crotonyl chloride produced a 30:70 ratio of 47 to 48. However, in both cases these compounds represented only a small portion of the product mixture and, thus, the relative comparison with the results obtained from 37 and acryloyl and crotonyl chloride could not be made accurately. Further accentuating the annulation process through the use of the anhydride acylating agents, produced promising results. The reaction of 44 with acrylic anhydride produced a 7:93 distribution of 45 to 46 in 27% yield, which represents an increase in annulation from the reaction of 37 with this reagent (38:39, 15:85). The formation of 47 and 48 in a 6:94 ratio was achieved in 47% yield upon treatment with crotonic anhydride and demonstrated significant improvement over the 63:37 formation of the analogous 42:43.

Mechanistic Discussion. There are a number of potential mechanistic routes available for this aza-annulation process, and several of these pathways are shown in Scheme III. In general, the options can be divided into two divergent routes, those that acylate first at nitrogen and those that undergo initial conjugate addition to form the carbon–carbon bond prior to lactam formation. Initial formation of the amide bond produces acrylamide 11, which cannot be converted to 12 under protic, Lewis acidic, or thermal (200 °C) conditions.[8] An alternative route is the formation of the carbon–carbon bond as the first step of the reaction through conjugate addition to the acrylate derivative. Once this bond is formed, two sequential steps must occur involving overall loss of HX. These steps include intramolecular acylation to form the amide and deprotonation to produce either the kinetic or thermody-

(22) A very efficient method of preparing an analogous product through aza-annulation of an *N,N*-dialkyl enamine was recently reported using methyl acrylate.[5d]

Scheme III. Mechanistic Pathways for Aza-Annulation of Imines with Acrylate Derivatives

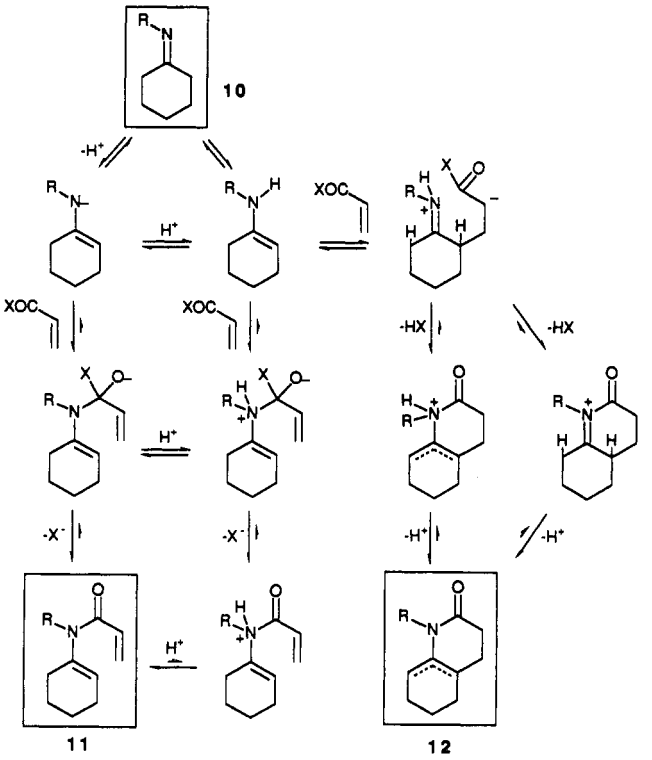


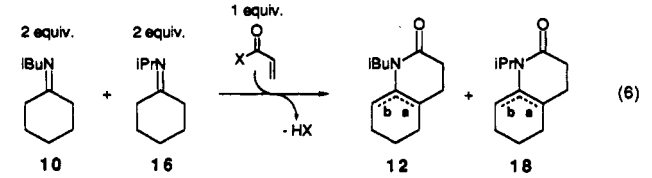
Table VI. Competitive Reaction of Imines 10 and 16 for Acrylic Acid Derivatives (eq 6)

	reaction products[c]			
method[a]	11	12	17	18
A	71	3	24	2
B	13	48	1	38
C		64		36
D		56		44
E		63		37

[a] Reactions were conducted with 2.0 equiv of 10 and 2.0 equiv of 16 with 1.0 equiv of acrylic acid derivatives in THF at 66 °C. [b] Method A: X = Cl; NEt_3 added. Method B: X = Cl. Method C: X = Cl; H_2CCHCO_2Na added. Method D: X = OH; EtO_2CCl added. Method E: X = OH; $(PhO)_2P(O)N_3$ added. [c] Relative amounts of products (scaled to 100) in the crude reaction mixture as determined by ^1H NMR.

namic enamine isomer of the corresponding δ-lactam. Two of several possible pathways for the process involving initial C-alkylation are shown in Scheme III. The relative product distribution resulting from the reaction of imines with acrylate derivatives appeared to correlate with the relative N-acylation versus initial C-alkylation/addition properties of the reactants.

Experiments in which 2 equiv each of 10 and 16 compete for reaction between 1 equiv of different acrylic acid derivatives substantiated this balance between divergent pathways and provided interesting insight into the mechanism of the reaction (eq 6, Table VI). Several



(6)

important trends were apparent upon variation of the acyl substituent. The first noticeable feature was that N-acylation of the imine was dependent on the nature of the *N*-alkyl substituent. In the case where the imines were treated with acryloyl chloride in the presence of NEt_3, product formation was biased toward acylation of the least sterically hindered amine as evident by the 71:24 ratio of 11 to 17. When formed as minor products during the reaction with acryloyl chloride in the absence of NEt_3, 11 and 17 were formed in a ratio of 13:1 (93:7). The reagents showed much less discrimination between 10 and 16 during formation of annulation products than during the N-acylation process. For example, the reaction with acryloyl chloride produced a 56:44 ratio of 12 and 18 as 48% and 38% of the reaction mixture, respectively, which was far less selective than the 93:7 ratio of 11:17 resulting from N-acylation. Other activated acryloyl derivatives showed little variation from this mild selectivity and only ranged from 56:44 to 64:36 for the ratio of 12 to 18. Because the annulation product ratios did not parallel the N-acylation selectivities, the slight preference for the formation of 12 probably reflected the relative rates of the initial conjugate addition of the two different imines to each acrylate derivative. Subsequent intramolecular acylation did not appear to significantly affect the relative ratio of products and, as a result, was relatively independent of the differing acyl substituents.

Competition between these two divergent competing pathways can be used to rationalize the results obtained for the variety of imines, acrylate derivatives, and reaction conditions that were studied. The balance between these two pathways was most apparent by comparison to the cases where only moderate product selectivity was observed for the reaction of acrylate derivatives with imines. Because of the incomplete selectivity in product formation, these reactions served as sensitive probes in determining the effect of substituents as reflected by changes in the product distribution. In the presence of NEt_3, the N-acylation by acryloyl chloride was accelerated relative to other pathways by deprotonation of the imine, or possibly one of the N-acylated intermediates, to give predominantly 11. However, when NEt_3 was not added, conjugate addition became competitive with the N-acylation pathway for acryloyl chloride to generate a 13:87 ratio of 11:12. The product distribution was readily modified by changing the reactivity of the acylating agent. The use of a less reactive acyl derivative such as an anhydride slowed the initial N-acylation pathway relative to that of conjugate addition and produced 12 as the sole product. Following C–C bond formation, the different acyl derivatives had little effect on the subsequent intramolecular lactam formation.

Increasing the bulk of the *N*-alkyl substituent from an isobutyl to isopropyl group made the N-acylation process less favorable than that of initial conjugate addition. While the reaction of acryloyl chloride with 10 resulted in a 13:87 ratio of 11:12, treatment of 16 with acryloyl chloride produced a slightly increased annulation with a 17:18 product selectivity of 5:95. Similarly, the reaction of methacryloyl chloride with 16 produced a greater amount of heterocycle formation demonstrated by a 3:97 ratio of 26:27 as compared to the analogous 39:61 ratio of 22 to 23. As expected, the balance between the two product pathways, N-acylation versus C-alkylation, was relatively unaffected by a substituent at the α position of the acrylate derivative.

Substituents at the β-position showed a significant effect on the outcome of the reaction. For example, while the reaction of 10 with acryloyl chloride produced predominant annulation to give 12, the reaction with crotonyl chloride favored the formation of the enamide 28 because the methyl group hindered conjugate addition of the enamine substrate. Even though reducing the reactivity of the

acylating agent by the use of the anhydride could enhance formation of **29**, the best ratio obtained for **28** to **29** was 36:64. Offsetting the effects that a β substituent had on hindering the conjugate addition pathway, the delicate balance could be tipped back in the favor of annulation by slowing the intermolecular N-acylation process through increasing the steric bulk at nitrogen. The reaction of **16** with crotonic anhydride resulted in complete selectivity in the formation of **33**. Similarly, the reaction of **10** with the mixed crotonic anhydride (method D) gave a 45:55 ratio of **28:29** while the reaction with **16** produced a 4:96 ratio of **32:33**. From these studies of the effects that substituents had on the resulting product ratios, this annulation process appeared to proceed by initial conjugate addition followed by subsequent amide bond formation. Product selectivities cannot be rationalized by invoking initial N-acylation followed by electrocyclic rearrangement[7b] of [3,3]-rearrangement[8a,11] to form the C–C bond.

Summary

The reaction of activated acrylate derivatives with ketimines has led to efficient heterocyclic annulation in the formation of δ-lactam products. In comparison to the use of the analogous acid chlorides, these alternatives not only produced greater overall product recovery but also produced higher selectivity in lactam formation. Both of these features contribute to the significantly higher isolated yields obtained using acrylate derivatives when compared to those obtained from the acid chloride reaction. Imines derived from aldehydes proved to be less effective in this ring-forming process. A study of substituent effects has provided information as to the scope and utility of the reaction as well as provided insight into the mechanistic features of this annulation process. Initial conjugate addition of the imine tautomer to the acrylate derivative, by decreasing the reactivity of the acylating agent and/or increasing the steric hinderance of the imine substituent, was the key to selectively obtaining annulation products.

Experimental Section

General Methods. All reactions were carried out by performing standard inert atmosphere techniques to exclude moisture and oxygen.[23] Acrylic acid, methacrylic acid, methacrylic anhydride, crotonic anhydride, methacryloyl chloride, and crotonoyl chloride were purchased from Aldrich Chemical Co. and distilled before use. Acryloyl chloride was purchased from Fluka and used without purification. Aldrithiol-2 (2,2′-dipyridyl disulfide), and 2-chloro-1-methylpyridinium iodide were purchased from Aldrich Chemical Co. and used without purification. Diphenyl phosphorazidate (DPPA) was prepared according to a literature procedure.[24] Unless specified, concentration of mixtures was performed using a rotary evaporator.

General Procedure for the Preparation of Ketimines. A mixture of the primary amine (313 mmol) and ketone (250 mmol) in 750 mL of benzene was heated at reflux until >90% of the H_2O had been azeotropically removed from the reaction mixture with a Dean–Stark trap. After draining the H_2O from the Dean–Stark apparatus, the trap was filled with 4-Å molecular sieves, and the reaction was heated for up to an additional 24 h to produce complete imine formation. The solution was then cooled to ambient temperature, concentrated, and distilled under vacuum to give the corresponding imine.

10 (bp 75 °C, 6 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, 6 H, J = 6.7 Hz), 1.59 (m, 4 H), 1.68 (m, 2 H), 1.85 (m, 1 H), 2.24 (m, 4 H), 3.06 (d, 2 H, J = 6.7 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.9, 25.2, 26.1, 27.0, 27.9, 28.9, 39.2, 57.5, 171.9; IR (neat) 2930, 2862, 1660, 1469, 1449 cm^{-1}.

13 (bp 92 °C, <1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59–1.83 (m, 6 H), 2.34 (t, 4 H, J = 5.8 Hz), 4.50 (s, 2 H), 7.15–7.30 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.6, 26.5, 27.3, 28.7, 39.6, 53.6, 126.1; IR (neat) 3085, 3062, 3028, 1660, 1495, 1452, 1346 cm^{-1}.

16 (bp 68 °C, 20 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (d, 6 H, J = 6.3 Hz), 1.58–1.66 (m, 4 H), 1.66–1.75 (m, 2 H), 2.20–2.30 (m, 4 H), 3.68 (sept, 1 H, J = 6.3 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.9, 26.1, 27.4, 27.8, 28.8, 40.1, 48.8, 170.4; IR (neat) 1660, 1450, 1377 cm^{-1}.

19 (bp 66 °C, 14 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55–1.72 (m, 6 H), 2.21 (t, 2 H, J = 6.2 Hz), 2.40 (s, 6 H), 2.47 (t, 2 H, J = 6.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.9, 26.5, 27.4, 28.6, 35.9, 47.5, 170.1; IR (neat) 2858, 2815, 2771, 1635, 1468, 1449 cm^{-1}.

34 (bp 77 °C, 15 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, 6 H, J = 6.7 Hz), 1.71 (m, 2 H), 1.77 (m, 2 H), 1.92 (m, 1 H), 2.12 (m, 2 H), 2.31 (m, 2 H), 2.97 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.5, 23.9, 24.6, 28.7, 29.4, 36.0, 61.7, 179.9; IR (neat) 2958, 2858, 1678, 1466 cm^{-1}.

General Procedure for the Preparation of Aldimines. A mixture of amine (137 mmol), butyraldehyde (9.86 g, 137 mmol), and potassium carbonate (37.90 g, 274 mmol) in 200 mL of Et_2O was stirred for 12 h at ambient temperature. The solution was then removed from the insoluble material via cannula and distilled to give the corresponding imine.

37 (78% yield, bp 53 °C, 25 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (d, 6 H, J = 6.4 Hz), 0.87 (t, 3 H, J = 7.4 Hz), 1.48 (sext, 2 H, J = 7.4 Hz), 1.82 (non, 1 H, J = 7.4 Hz), 2.14 (td, 2 H, J = 7.4, 5.0 Hz), 3.10 (d, 2 H, J = 6.7 Hz), 7.5 (t, 1 H, J = 5.0 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.8, 18.6, 19.6, 28.3, 36.9, 68.9, 164.4; IR (neat) 2958, 2875, 2828, 1674, 1469 cm^{-1}.

44 (68% yield, bp 108 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, 3 H, J = 7.4 Hz), 1.11 (d, 6 H, J = 6.4 Hz), 1.51 (sext, 2 H, J = 7.4 Hz), 2.6 (dt, 2 H, J = 5.2, 7.4 Hz), 3.23 (sept, 1 H, J = 6.4 Hz), 7.61 (t, 1 H, J = 5.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.1, 19.1, 23.7, 37.1, 60.7, 161.6; IR (neat) 2969, 2935, 2874, 2830, 1669, 1466 cm^{-1}.

General Procedure for the Preparation of Enamides. To 40 mL of dry THF were added the imine (8.0 mmol) and NEt_3 (1.21 g, 12.0 mmol) at 0 °C. The appropriate α,β-unsaturated acid chloride (9.60 mmol) was added slowly to this solution at 0 °C. After the addition was complete, the reaction was carried out under the conditions listed in the tables. Solids were removed from the mixture by filtration and were then washed thoroughly with Et_2O. The combined filtrate was concentrated, and the corresponding enamide was isolated by Kugelrohr distillation.

11 (bp 70–80 °C, <1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, 6 H, J = 6.9 Hz), 1.60 (m, 2 H), 1.72 (m, 2 H), 1.87 (m, 1 H), 2.06 (m, 2 H), 2.13 (m, 2 H), 3.32 (bd, 2 H, J = 7.2 Hz), 5.51–5.59 (m, 2 H), 6.30 (dd, 1 H, J = 16.9, 2.4 Hz), 6.46 (dd, 1 H, J = 16.9, 10.0 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.2, 21.7, 22.9, 24.9, 27.3, 28.3, 52.4, 127.3, 128.3, 129.4, 138.7, 166.1; IR (neat) 2961, 2934, 1651, 1618 cm^{-1}; HRMS calcd for $C_{13}H_{21}NO$ m/z 207.1623, found m/z 207.1629.

14 (mp 67–68 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52 (m, 2 H), 1.64 (m, 2 H), 1.94–2.06 (m, 4 H), 4.67 (s, 2 H), 5.39 (m, 1 H), 5.61 (dd, 1 H, J = 9.7, 2.7 Hz), 6.38 (dd, 1 H, J = 16.9, 2.7 Hz), 6.49 (dd, 1 H, J = 16.9, 9.7 Hz), 7.20–7.28 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.5, 22.7, 24.7, 28.7, 49.7, 127.1, 127.3, 128.2, 128.5, 128.6, 128.7, 137.9, 165.2; IR (KBr) 3068, 3030, 2940, 2855, 1645, 1611, 1414 cm^{-1}; HRMS calcd for $C_{16}H_{19}NO$ m/z 241.1466, found m/z 241.1475.

17 (bp 70–80 °C, <1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15, (d, 6 H, J = 6.8 Hz), 1.62 (m, 2 H), 1.71 (m, 2 H), 2.06 (m, 2 H), 2.16 (m, 2 H), 4.66 (sept, 1 H, J = 6.8 Hz), 5.55 (dd, 1 H, J = 3.3, 9.2 Hz), 5.59 (m, 1 H), 6.31 (dd, 1 H, J = 16.8, 3.3 Hz), 6.40 (dd, 1 H, J = 16.8, 9.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.8, 21.4, 22.8, 25.0, 31.8, 46.4, 126.6, 129.5, 129.7, 136.0, 164.7; IR (neat) 2975, 2936, 2881, 2860, 1652, 1614, 1448, 1438 cm^{-1}; HRMS calcd for $C_{12}H_{19}NO$ m/z 193.1466, found m/z 193.1467.

20 (bp 50–60 °C, <1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotational isomers, −30 °C) δ 1.50–1.64 (m, 2 H), 1.64–1.75 (m, 2 H), 2.04–2.23 (m, 4 H), 2.47 (s, 3 H), 2.84 (bs, 3 H), 5.46–5.64 (m, 2 H), 6.25–6.36 (m), 7.14 (dd, J = 17.3, 10.3 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.2, 21.3, 22.2, 22.3, 24.52, 24.53,

(23) For more detailed general experimental procedures, see: Cook, G. R.; Barta, N. S.; Stille, J. R. *J. Org. Chem.* **1992**, *57*, 461.
(24) Shiori, T.; Yamada, S. *Org. Synth.* **1984**, *62*, 187.

27.5, 29.1, 43.2, 45.0, 126.4, 127.2, 127.4, 127.7, 128.9, 129.5, 132.3, 136.9, 164.6, 166.6; IR (neat) 2979, 2939, 2885, 2860, 1661, 1618, 1448, 1437 cm^{-1}; HRMS calcd for $C_{11}H_{18}N_2O$ m/z 194.1419, found m/z 194.1425.

22 (bp 65–75 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, 6 H, J = 6.7 Hz), 1.55 (m, 2 H), 1.66 (m, 2 H), 1.85 (m, 1 H), 1.90 (t, 3 H, J = 1.4 Hz), 2.06 (m, 4 H), 3.28 (d, 2 H, J = 7.5 Hz), 5.00–5.08 (m, 2 H), 5.50 (m, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.1, 20.6, 21.5, 22.7, 24.8, 26.9, 27.9, 52.1, 115.1, 125.6, 138.6, 142.3, 171.9; IR (neat) 3009, 2872, 2842, 1645, 1615 cm^{-1}; HRMS calcd for $C_{14}H_{23}NO$ m/z 221.1779, found m/z 221.1785.

24 (bp 110–120 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (m, 2 H), 1.56 (m, 2 H), 1.92–1.99 (m, 7 H), 4.65 (s, 2 H), 5.08 (m, 1 H), 5.17 (m, 1 H), 5.33 (m, 1 H), 7.22–7.28 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.5, 21.4, 22.6, 24.7, 28.4, 49.8, 116.0, 126.3, 127.1, 128.2, 128.4, 137.9, 138.7, 141.7, 171.6; IR (neat) 3088, 3066, 3008, 2935, 1648, 1619, 1496, 1453 cm^{-1}; HRMS calcd for $C_{17}H_{21}NO$ m/z 255.1612, found m/z 255.1615.

26 (bp 60–70 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (d, 6 H, J = 6.8 Hz), 1.53 (m, 2 H), 1.61 (m, 2 H), 1.89 (t, 3 H, J = 1.3 Hz), 1.99–2.12 (m, 4 H), 4.52 (m, 1 H), 4.87–5.00 (m, 2 H), 5.49 (m, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.8, 21.3, 22.7, 24.8, 31.3, 46.3, 114.1, 128.3, 136.5, 142.6, 171.3; IR (neat) 2974, 2934, 2882, 2860, 1649, 1628, 1450, 1408 cm^{-1}; HRMS calcd for $C_{13}H_{21}NO$ m/z 207.1623, found m/z 207.1625.

28 (bp 65–75 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, 6 H, J = 6.7 Hz), 1.60 (m, 2 H), 1.71 (m, 2 H), 1.82 (dd, 3 H, J = 1.7, 6.9 Hz), 1.85 (m, 1 H), 2.05 (m, 2 H), 2.13 (m, 2 H), 3.28 (m, 2 H), 5.58 (m, 1 H), 6.14 (dq, 1 H, J = 15.1, 1.7 Hz), 6.87 (dq, 1 H, J = 15.1, 6.9 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.1, 20.1, 21.6, 22.8, 24.8, 27.2, 28.2, 52.2, 123.0, 127.4, 138.4, 140.4, 165.8; IR (neat) 2874, 1670, 1649, 1446 cm^{-1}. Anal. Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 76.62; H, 10.26; N, 6.34.

30 (mp 70–71 °C): ^1H NMR (300 MHz, $CDCl_3$) δ 1.53 (m, 2 H), 1.64 (m, 2 H), 1.83 (dd, 3 H, J = 6.9, 1.7 Hz), 1.96 (m, 2 H), 2.02 (m, 2 H), 4.65 (s, 2 H), 5.38 (m, 1 H), 6.15 (dq, 1 H, J = 15.1, 1.7 Hz), 6.94 (dq, 1 H, J = 15.1, 6.9 Hz), 7.17–7.28 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 17.7, 21.1, 22.3, 24.3, 28.3, 49.5, 122.3, 126.6, 127.8, 127.9, 128.2, 137.8, 140.6, 165.1; IR (KBr) 3046, 3032, 2858, 1661, 1615, 1494 cm^{-1}; HRMS calcd for $C_{17}H_{21}NO$ m/z 255.1612, found m/z 255.1623.

32 (bp 65–75 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (d, 6 H, J = 6.9 Hz), 1.61 (m, 2 H), 1.71 (m, 2 H), 1.82 (dd, 3 H, J = 6.9, 1.8 Hz), 2.04 (m, 2 H), 2.16 (m, 2 H), 4.66 (sept, 1 H, J = 6.9 Hz), 5.57 (m, 1 H), 6.05 (dd, 1 H, J = 15.1, 1.6 Hz), 6.87 (dq, 1 H, J = 15.1, 6.9 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.0, 21.0, 21.5, 22.9, 25.0, 31.8, 46.1, 123.6, 129.4, 136.1, 140.1, 165.0; IR (neat) 2973, 2935, 2841, 1662, 1626, 1477 cm^{-1}; HRMS calcd for $C_{13}H_{21}NO$ m/z 207.1623, found m/z 207.1625.

35 (bp 60–70 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, 6 H, J = 6.7 Hz), 1.86 (m, 1 H), 1.90–2.05 (m, 2 H), 2.39 (m, 4 H), 3.35 (d, 2 H, J = 7.5 Hz), 5.49 (m, 1 H), 5.57 (dd, 1 H, J = 10.2, 2.2 Hz), 6.33 (dd, 1 H, J = 16.9, 2.2 Hz), 6.52 (dd, 1 H, J = 10.2, 16.9 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.0, 22.3, 27.4, 30.3, 32.6, 52.2, 126.9, 129.1, 142.4, 165.6; IR (neat) 3020, 2965, 2931, 1644, 1611 cm^{-1}; HRMS calcd for $C_{12}H_{19}NO$ m/z 193.1466, found m/z 193.1469.

38 (bp 55–65 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$, 2:1 E:Z mixture of isomers) δ 0.86 (d, 6 H, J = 6.4 Hz, both isomers), 0.99 (t, 3 H, J = 7.4 Hz, both), 2.05 (m, 2 H, both), 3.36 (bd, 2 H, J = 7.3 Hz, minor), 3.44 (bd, 2 H, J = 7.3 Hz, major), 5.00–5.22 (m, 1 H, both), 5.63–5.70 (m, 1 H, both), 6.25 (d, 1 H, J = 17.0 Hz, major), 6.37 (m, 1 H, minor), 6.39 (d, 1 H, J = 12.9 Hz, major), 6.62 (dd, 1 H, J = 16.8, 10.3 Hz, both), 7.24 (bd, 1 H, J = 14.8 Hz, minor); ^{13}C NMR (75.5 MHz, $CDCl_3$) (major) δ 13.8, 19.7, 23.1, 26.0, 50.9, 119.4, 126.7, 127.1, 128.3, 165.2; (minor) 14.1, 19.7, 23.3, 26.8, 51.4, 114.5, 125.0, 127.5, 128.3, 164.4; IR (neat) 2964, 2930, 2875, 1646, 1612 cm^{-1}; HRMS calcd for $C_{11}H_{19}NO$ m/z 181.1467, found m/z 181.1473.

40 (bp 50–60 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, 6 H, J = 6.8 Hz), 0.98 (t, 3 H, J = 7.4 Hz), 1.96 (dd, 3 H, J = 1.1, 1.6 Hz), 1.97–2.14 (m, 3 H), 3.48 (d, 2 H, J = 7.5 Hz), 5.01 (m, 1 H), 5.08 (t, 1 H, J = 1.1 Hz), 5.25 (t, 1 H, J = 1.4 Hz), 6.60 (bd, 1 H, J = 12.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.6, 20.1, 20.4, 23.6, 26.0, 49.2, 113.2, 116.9, 128.1, 140.8, 171.5; IR (neat) 2963, 2932, 2874, 1670, 1649, 1454 cm^{-1}; HRMS calcd for $C_{12}H_{21}NO$ m/z 195.1623, found m/z 195.1629.

42 (bp 50–60 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$, 2:1 E:Z mixture of isomers) δ 0.86 (d, 6 H, J = 6.3 Hz, major), 0.88 (d, 6 H, J = 6.3 Hz, minor), 1.00 (t, 3 H, J = 7.3 Hz, both), 1.86 (dd, 3 H, J = 1.6, 6.8 Hz, both), 1.93–2.12 (m, 3 H, both), 3.35 (bd, 2 H, J = 5.3 Hz, minor, 3.44 (d, 2 H, J = 7.8 Hz, major), 4.98–5.20 (m, 1 H, both), 6.24–6.56 (m, 1 H, both), 6.74–7.00 (m, 1 H, both), 7.24 (bd, 1 H, J = 14.2 Hz, minor); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.5, 18.2, 20.1, 23.7, 26.4, 51.0, 118.5, 122.6, 127.3, 141.6, 165.8; IR (neat) 3031, 2963, 2874, 1653, 1628, 1448 cm^{-1}; HRMS calcd for $C_{12}H_{21}NO$ m/z 195.1623, found m/z 195.1627.

45 (bp 75–85 °C, 10 mmHg): ^1H NMR (300 MHz, $CDCl_3$, 93:7 ratio of E:Z isomers) δ 1.05 (t, 3 H, J = 7.5 Hz), 1.11 (d, 6 H, J = 6.8 Hz), 2.14 (m, 2 H), 4.77 (sept, 1 H, J = 6.8 Hz), 5.47 (dt, 1 H, J = 13.7, 6.9 Hz), 5.55 (dd, 1 H, J = 10.3, 2.2 Hz), 5.93 (bd, 1 H, J = 13.7 Hz), 6.28 (dd, 1 H, J = 16.9, 2.2 Hz), 6.55 (dd, 1 H, J = 16.9, 10.3 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.6, 19.9, 23.3, 45.4, 123.1, 126.2, 129.9, 135.9, 165.1; IR (neat) 2972, 2934, 2876, 1651, 1614, 1462, 1414 cm^{-1}; HRMS calcd for $C_{10}H_{17}NO$ m/z 167.1310, found m/z 167.1309.

47 (bp 90–100 °C, 7 mmHg): ^1H NMR (300 MHz, $CDCl_3$, 93:7 ratio of E:Z isomers) δ 1.02 (t, 3 H, J = 7.5 Hz), 1.07 (d, 6 H, J = 7.4 Hz), 1.79 (dd, 3 H, J = 6.9, 1.5 Hz), 2.12 (m, 2 H), 4.74 (sept, 1 H, J = 6.9 Hz), 5.46 (dt, 1 H, J = 1.37, 6.9 Hz), 5.90 (bd, 1 H, J = 13.7 Hz), 6.22 (dq, 1 H, J = 15.1, 1.5 Hz), 6.81 (dq, 1 H, J = 15.1, 6.9 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.3, 17.5, 19.6, 22.9, 44.9, 123.0, 123.7, 135.0, 139.5, 165.2; IR (neat) 2971, 2935, 2875, 2855, 1667, 1626, 1448 cm^{-1}; HRMS calcd for $C_{11}H_{19}NO$ m/z 181.1466, found m/z 181.1460.

General Procedure for the Reaction of Imines with Acid Chloride. The α,β-unsaturated acid chloride (8.84 mmol) in 15 mL of dry THF was slowly added to the imine (6.8 mmol) in THF (30 mL) at reflux, and the mixture was maintained at reflux for the required reaction time (see tables). After the reaction was complete, the solution was washed with 25 mL of saturated aqueous $NaHCO_3$ solution. The aqueous layer was then extracted with 4 × 40 mL of Et_2O, and the organic fractions were combined and dried over Na_2SO_4. Following removal of solvents, the residue was purified by flash column chromatography (eluent: 20:80 Et_2O–petroleum ether, 40:60 Et_2O–petroleum ether, or 50:50 Et_2O–petroleum ether). The solvents were removed, and the residue was distilled under vacuum to give lactam or a mixture of enamide and lactam.

General Procedure for the Reaction of Imines with Acrylic Anhydride. To a suspension of NaH (0.43 g, 17.9 mmol) in 35 mL of THF at −78°C was slowly added acrylic acid (0.87 g, 12.1 mmol). The mixture was warmed to ambient temperature and then stirred for 1 h. Acryloyl chloride (0.84 g, 9.28 mmol) was then added to the solution of sodium acrylate, and the reaction mixture was stirred for an additional 1 h at ambient temperature. The resulting solution of acrylic anhydride was transferred to a 100-mL flask containing the imine (7.15 mmol), and the original flask was rinsed with an additional 25 mL of THF.[25] After the reaction was carried out under the conditions listed in the tables, the solution was washed with 30 mL of saturated $NaHCO_3$ solution. The aqueous layer was then extracted with 4 × 50 mL of Et_2O, and the organic fractions were combined and dried over Na_2SO_4. After removal of solvents, the residue was purified by flash column chromatography (eluent: 50:50 Et_2O–petroleum ether), and the resulting lactam was distilled under vacuum.

General Procedure for the Reaction of Imines with Methacrylic Anhydride or Crotonic Anhydride. To a solution of imine (6.53 mmol) in 44 mL of THF was added methacrylic anhydride or crotonic anhydride (8.49 mmol), and the mixture was heated at reflux for the required reaction time (see tables). After the reaction was complete, the solution was washed with 25 mL of saturated aqueous $NaHCO_3$ solution. The aqueous layer was then extracted with 4 × 40 mL of Et_2O, and the organic fractions were combined and dried over Na_2SO_4. Following removal of solvents, the residue was purified by flash column chromatography (eluent: 20:80 Et_2O–petroleum ether or 40:60

(25) In order to avoid aldol type condensation products in the reaction with aldimine 37, acrylic anhydride was first transferred to a Schlenk flask followed by addition of the imine to the acrylic anhydride solution.

Et_2O–petroleum ether). The solvents were evaporated, and the residue was distilled under vacuum to give the lactam.

General Procedure for the Reaction of Imines with Acrylate Derivatives Activated by EtO_2CCl (the Mixed Anhydride Method). To a cooled solution (−30 to −25 °C) of α,β-unsaturated acid (8.49 mmol) in 43 mL of THF were added NEt_3 (0.86 g, 8.49 mmol) and ethyl chloroformate (0.92 g, 8.49 mmol). After the mixture was stirred for 1 h at this temperature, the imine (6.53 mmol) was added, and the resulting mixture was stirred for an additional 1 h. The reaction mixture was then stirred at the appropriate temperature for the required time. After the reaction was complete, the solution was washed with 25 mL of saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with 4 × 40 mL of Et_2O, and the organic fractions were combined and dried over Na_2SO_4. Following concentration of the solution, the residue was purified by flash column chromatography (eluent: 20:80 Et_2O–petroleum ether, 40:60 Et_2O–petroleum ether, or 50:50 Et_2O–petroleum ether). The solvents were evaporated and the residue was distilled under vacuum to give the lactam.

General Procedure for the Reaction of Imines with Acrylate Derivatives Activated by DPPA. To a solution of imine (6.53 mmol) in 30 mL THF at 0 °C were added NEt_3 (0.86 g, 8.49 mmol) and DPPA (2.34 g, 8.49 mmol), and the mixture was stirred for 30 min. The α,β-unsaturated acid (8.49 mmol) was added slowly, and the reaction mixture was stirred for 30 min at 0 °C, followed by stirring under the conditions listed in the tables.[26] After the reaction was complete, the solution was concentrated, the residue was extracted with 50 mL of $CHCl_3$, and the organic layer was washed with 30 mL of 10% HCl. The resulting aqueous layer was further extracted with 3 × 25 mL of $CHCl_3$, and the combined organic layers were subsequently washed with 35 mL of saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with 4 × 25 mL of $CHCl_3$. The combined organic layers were washed with 50 mL of H_2O, and this aqueous layer was then extracted with 4 × 25 mL of $CHCl_3$. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to give a crude residue. The crude residue was purified by flash column chromatography (eluent: 20:80 Et_2O–petroleum ether, 40:60 Et_2O–petroleum ether, or 50:50 Et_2O–petroleum ether). The solvents were evaporated, and the residue was distilled under vacuum to give the corresponding lactam.

General Procedure for the Reaction of Imines with Acrylate Derivatives Activated by MCPI. To 75 mL of dry THF were added MCPI (3.00 g, 11.74 mmol), imine (9.78 mmol), α,β-unsaturated acid (11.74 mmol), and NEt_3 (2.38 g, 23.48 mmol). The solution was heated to reflux for the corresponding reaction time (see tables). After the reaction was complete, the solution was concentrated and the crude product was purified by flash column chromatography (eluent: 20:80 Et_2O–petroleum ether, 40:60 Et_2O–petroleum ether, or 50:50 Et_2O–petroleum ether). The solvents were evaporated, and the residue was distilled under vacuum to give the lactam or a mixture of enamide and lactam.

General Procedure for the Reaction of Imines with Acylimidazole. To a solution of acryloyl chloride (0.77 g, 8.48 mmol) in 20 mL of dry THF was slowly added imidazole (1.16 g, 16.96 mmol) in 30 mL THF, and the resulting solution was stirred for 1 h at ambient temperature. Imine (6.53 mmol) was added into the reaction mixture, and the mixture was heated at reflux for the corresponding reaction time (see Table I). After the reaction was complete, the solution was washed with 30 mL of saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with 4 × 30 mL of Et_2O, and the organic fractions were dried over Na_2SO_4. Following concentration of the solution, the residue was purified by flash column chromatography (eluent 50:50 Et_2O–petroleum ether). The solvents were evaporated, and the residue was distilled under vacuum to give lactam.

12 (bp 75–85 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$, mixture of isomers) δ 0.83 (d, 3 H, J = 6.7 Hz, **12b**), 0.84 (d, 6 H, J = 6.7 Hz, **12a**), 0.85 (d, 3 H, J = 6.7 Hz, **12b**), 1.20–2.20 (m, both), 2.42 (dd, 2 H, J = 6.5, 8.4 Hz, **12a**), 2.48 (dd, 1 H, J = 6.0, 12.8 Hz, **12b**), 2.58 (ddd, 1 H, J = 17.7, 5.6, 2.0 Hz, **12b**), 3.40 (d, 2 H, J = 7.4 Hz, **12a**), 3.55 (d, 2 H, J = 7.4 Hz, **12b**), 5.03 (m, 1 H, **12b**); ^{13}C NMR (75.5 MHz, $CDCl_3$, major) δ 19.8, 22.0, 22.8, 25.2, 25.4, 28.3, 29.0, 32.0, 46.7, 116.3, 131.8, 170.9, (minor) δ 20.0, 20.2, 21.4, 24.5, 26.1, 27.4, 30.6, 32.9, 35.1, 48.5, 104.4, 138.6, 169.3; IR (neat) 3014, 2875, 1634, 1405 cm^{-1}. Anal. Calcd for $C_{13}H_{21}NO$: C, 75.31; H, 10.21; N, 6.76. Found: C, 75.18; H, 10.04; N, 6.74.

15 (bp 120–130 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$) δ 1.40–1.50 (m, 2 H, **15a**), 1.50–1.60 (m, 2 H, **15a**), 1.60–1.75 (m, **15b**), 1.80–2.00 (m, **15b**), 2.03 (m, 4 H, both), 2.14 (t, 2 H, J = 7.8 Hz, **15a**), 2.55–2.80 (m, 2 H, both), 4.61 (d, 1 H, J = 16.0 Hz, **15b**), 4.84 (s, 2 H, **15a**), 4.96 (m, 1 H, **15b**), 5.21 (d, 1 H, J = 16.0 Hz, **15b**), 7.05–7.30 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$, both isomers) δ 21.3, 21.9, 22.8, 24.4, 25.3, 25.4, 27.5, 29.0, 30.4, 31.7, 32.9, 35.0, 43.7, 46.4, 105.4, 115.3, 126.2, 126.3, 126.6, 126.7, 128.4, 128.5, 131.4, 137.7, 138.6, 138.7, 169.3, 170.4; IR (neat) 3087, 3064, 3030, 2932, 2858, 2839, 1669, 1641, 1496, 1454 cm^{-1}; HRMS calcd for $C_{13}H_{21}NO$ m/z 241.1466, found m/z 241.1473.

18 (bp 70–80 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$, major isomer) δ 1.40 (d, 6 H, J = 6.9 Hz), 1.50–1.70 (m, 4 H), 1.93–2.09 (m, 4 H), 2.09–2.18 (m, 2 H), 2.33 (m, 2 H), 3.97 (sept, 1 H, J = 6.9 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$ mixture of isomers) δ 20.5, 22.2, 23.2, 25.2, 26.3, 29.1, 33.2, 46.8, 116.4, 132.3, 171.1; IR (neat) 3019, 2972, 2937, 1639, 1428, 1419 cm^{-1}; HRMS calcd for $C_{12}H_{19}NO$ m/z 193.1466, found m/z 193.1464.

21 (bp 55–65 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$, major isomer) δ 1.50–1.69 (m, 4 H), 1.95–2.08 (m, 4 H), 2.13–2.23 (m, 2 H), 2.41 (m, 2 H), 2.81 (s, 6 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.3, 23.0, 24.7, 25.3, 28.8, 33.0, 43.3, 112.4, 134.1, 169.4; IR (neat) 2935, 2888, 1685, 1651, 1441 cm^{-1}; HRMS calcd for $C_{11}H_{18}N_2O$ m/z 194.1419, found m/z 194.1415.

23a (bp 75–85 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (d, 3 H, J = 6.7 Hz), 0.85 (d, 3 H, J = 6.7 Hz), 1.15 (d, 3 H, J = 6.9 Hz), 1.45–2.22 (m, 11 H), 2.43 (m, 1 H), 3.19 (dd, 1 H, J = 13.8, 6.9 Hz), 3.60 (dd, 1 H, J = 13.8, 7.9 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.5, 19.9, 20.0, 22.2, 23.0, 25.5, 28.4, 29.3, 33.5, 35.6, 47.1, 115.0, 131.0, 173.3; IR (neat) 2959, 2934, 2870, 2831, 1668, 1458 cm^{-1}; HRMS calcd for $C_{14}H_{23}NO$ m/z 221.1779, found m/z 221.1777.

25 (bp 120–130 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$, major isomer) δ 1.23 (d, 3 H, J = 6.9 Hz), 1.42–1.66 (m, 4 H), 1.94–2.10 (m, 4 H), 2.15 (dd, 1 H, J = 16.0, 6.5 Hz), 2.59 (m, 1 H), 4.73 (d, 1 H, J = 16.2 Hz), 4.97 (d, 1 H, J = 16.2 Hz), 7.10–7.32 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$, mixture of isomers) δ 15.2, 21.6, 22.4, 25.0, 28.7, 33.2, 35.0, 43.6, 114.0, 125.8, 126.2, 128.1, 130.5, 138.3, 173.1; IR (neat) 3087, 3062, 3032, 2931, 2867, 2832, 1665, 1495, 1453 cm^{-1}; HRMS calcd for $C_{17}H_{21}NO$ m/z 255.1612, found m/z 255.1619.

27 (mp 56–57 °C): ^1H NMR (300 MHz, $CDCl_3$, major isomer) δ 1.08 (d, 3 H, J = 6.9 Hz), 1.37 (d, 3 H, J = 6.9 Hz), 1.39 (d, 3 H, J = 6.9 Hz), 1.44–2.22 (m, 10 H), 2.32 (m, 1 H), 3.95 (sept, 1 H, J = 6.9 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.1, 20.5, 20.6, 22.3, 23.3, 26.4, 29.5, 33.4, 36.3, 46.9, 115.6, 131.8, 173.7; IR (KBr) 2966, 2931, 1664, 1451, 1418 cm^{-1}; HRMS calcd for $C_{13}H_{21}NO$ m/z 207.1623, found m/z 207.1630.

29a (bp 75–85 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, 3 H, J = 6.8 Hz), 0.88 (d, 3 H, J = 6.8 Hz), 0.98 (d, 3 H, J = 7.1 Hz), 1.35–1.90 (m, 5 H) 1.95–2.20 (m, 5 H), 2.26 (dd, 1 H, J = 15.6, 4.2 Hz), 2.56 (dd, 1 H, J = 15.6, 6.4 Hz), 3.09 (dd, 1 H, J = 13.9, 7.0 Hz), 3.71 (dd, 1 H, J = 13.9, 7.5); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.8, 20.1, 20.4, 22.2, 23.0, 25.6, 27.3, 28.6, 30.6, 39.2, 46.9, 120.0, 130.3, 169.7; IR (neat) 2957, 2870, 2837, 1670, 1639, 1466, 1435 cm^{-1}. Anal. Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 75.97; H, 10.30; N, 6.40.

31 (bp 120–130 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$, major isomer) δ 1.00 (d, 3 H, J = 7.1 Hz), 1.30–2.30 (m, 9 H), 2.39 (dd, 1 H, J = 15.6, 4.3 Hz), 2.70 (dd, 1 H, J = 15.6, 6.5 Hz), 4.70 (d, 1 H, J = 16.0 Hz), 5.03 (d, 1 H, J = 16.0 Hz), 7.10–7.32 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.7, 21.7, 22.4, 25.0, 26.7, 30.4, 38.6, 43.4, 119.2, 126.2, 126.3, 128.0, 129.7, 138.4, 169.5; IR (neat) 3087, 3062, 3031, 2932, 2862, 2836, 1665, 1641, 1496 cm^{-1}; HRMS calcd for $C_{17}H_{21}NO$ m/z 255.1612, found m/z 255.1622.

33 (bp 70–80 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$, major isomer) δ 0.92 (d, 3 H, J = 7.1 Hz), 1.38 (d, 3 H, J = 6.9 Hz), 1.40 (d, 3 H, J = 6.9 Hz), 1.30–2.20 (m, 9 H), 2.15 (dd, 1 H, J = 3.5, 15.4 Hz), 2.51 (dd, 1 H, J = 15.4, 6.2 Hz), 3.95 (sept, 1 H, J = 6.9 Hz): ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.5, 20.0, 20.5, 22.3, 23.2, 26.4, 27.4, 30.5, 40.2, 46.7, 121.1, 130.9, 170.2; IR (neat) 2960, 2933,

(26) In the reaction of imine **37** and crotonic acid, crotonic acid was taken up in the flask along with imine, and NEt_3 and DPPA were added slowly.

2866, 1666, 1418 cm^{-1}; HRMS calcd for $C_{13}H_{21}NO$ m/z 207.1623, found m/z 207.1627.

36 (bp 65–75 °C, <1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$, mixture of isomers) δ 0.83–0.89 (m, 6 H), 1.37–1.53 (m, 1 H), 1.73–2.24 (m), 2.30–2.82 (m), 3.29 (d, 2 H, J = 7.6 Hz, **36a**), 3.38 (dd, 1 H, J = 7.0, 13.4 Hz, **36b**), 3.56 (dd, 1 H, J = 8.2, 13.4 Hz, **36b**), 4.78 (m, 1 H, **36b**); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.0, 20.1, 20.2, 21.0, 21.7, 26.2, 27.1, 28.4, 29.9, 30.4, 31.2, 32.0, 32.8, 33.2, 41.9, 50.1, 102.9, 115.6, 137.0, 144.1, 169.4, 170.1; IR (neat) 3010, 2963, 2934, 2903, 2872, 2849, 1688, 1660, 1633, 1466, 1406 cm^{-1}. Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.13; H, 9.95; N, 7.19.

39 (bp 55–65 °C, <1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (d, 6 H, J = 6.7 Hz), 0.98 (t, 3 H, J = 7.4 Hz), 1.88 (m, 1 H), 2.00 (m, 2 H), 2.14 (t, 2 H, J = 7.9 Hz), 2.44 (t, 2 H, J = 7.9 Hz), 3.20 (d, 2 H, J = 7.5 Hz), 5.68 (m, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.5, 20.0, 24.2, 26.9, 27.9, 31.6, 53.4, 121.5, 124.4, 169.5; IR (neat) 2964, 2842, 1639 cm^{-1}. Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.72. Found: C, 72.85; H, 9.87; N, 7.72.

41 (bp 55–65 °C, <1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, 6 H, J = 6.7 Hz), 1.01 (t, 3 H, J = 7.4 Hz), 1.18 (d, 3 H, J = 7.0 Hz), 1.83–2.08 (m, 4 H), 2.26 (ddd, 1 H, J = 6.7, 16.4, 1.0 Hz), 2.48 (d quint, 1 H, J = 10.4, 7.0 Hz), 3.15 (dd, 1 H, J = 13.4, 7.4 Hz), 3.30 (dd, 1 H, J = 13.4, 7.6 Hz), 5.70 (s, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.4, 15.9, 19.9, 20.0, 26.9, 27.8, 32.1, 35.3, 53.4, 120.1, 123.6, 172.6; IR (neat) 2964, 2932, 2872, 1662, 1458 cm^{-1}; HRMS calcd for $C_{12}H_{21}NO$ m/z 195.1623, found m/z 195.1623.

43 (bp 55–65 °C, <1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, 6 H, J = 6.7 Hz), 1.02 (m, 6 H), 1.92 (m, 1 H), 2.04 (m, 2 H), 2.23–2.36 (m, 2 H), 2.58 (m, 1 H), 3.01 (dd, 1 H, J = 13.4, 7.1 Hz), 3.46 (dd, 1 H, J = 13.4, 7.7 Hz), 5.63 (t, 1 H, J = 0.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.7, 17.7, 19.9, 20.0, 24.8, 27.9, 29.8, 39.1, 53.2, 122.9, 125.9, 168.4; IR (neat) 2964, 2930, 2873, 1679, 1467, 1456, 1414 cm^{-1}; HRMS calcd for $C_{12}H_{21}NO$ m/z 195.1623, found m/z 195.1630.

46 (bp 85–95 °C, 3 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (t, 3 H, J = 7.4 Hz), 1.13 (d, 6 H, J = 6.8 Hz), 2.07 (bq, 2 H, J = 7.4 Hz), 2.18 (bt, 2 H, J = 8.1 Hz), 2.48 (dd, 2 H, J = 7.3, 8.7 Hz), 4.87 (sept, 1 H, J = 6.8 Hz), 5.85 (quint, 1 H, J = 1.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.4, 20.4, 23.5, 27.1, 31.6, 42.9, 117.7, 122.0, 168.1; IR (neat) 2968, 2934, 2898, 2877, 2842, 1657, 1463, 1437, 1410 cm^{-1}; HRMS calcd for $C_{10}H_{17}NO$ m/z 167.1310, found m/z 167.1309.

48 (bp 95–105 °C, 3 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (d, 3 H, J = 6.9 Hz), 1.04 (t, 3 H, J = 7.4 Hz), 1.10 (d, 3 H, J = 6.9 Hz), 1.13 (d, 3 H, J = 6.9 Hz), 2.02–2.11 (m, 2 H), 2.26 (m, 1 H), 2.26 (dd, 1 H, J = 3.8, 16.6 Hz), 2.57 (dd, 1 H, J = 16.6, 7.4 Hz), 4.87 (sept, 1 H, J = 6.9 Hz), 5.76 (t, 1 H, J = 1.4 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.7, 17.5, 20.0, 20.6, 25.2, 29.1, 39.3, 42.8, 116.5, 127.3, 167.6; IR (neat) 2965, 2932, 2876, 1671, 1463, 1410 cm^{-1}; HRMS calcd for $C_{10}H_{19}NO$ m/z 181.1466, found m/z 181.1462.

General Procedure for the Isomerization of Double Bonds and Hydrolysis of Enamides. To a solution containing a mixture of enamide and lactam or mixture of double bond isomers (1 mmol in 10 mL of methanol) was added p-toluenesulfonic acid (0.2 mmol), and the reaction mixture was heated at reflux or stirred at ambient temperature until either the enamide was hydrolyzed or isomerization demonstrated no further change.

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra for all reported compounds (66 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Aromatic Heteroannulation via Metalation–Cyclization of *N*-Acyl-2-chlorobenzenesulfonamides and *N*-Acylbenzenesulfonamides

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N-Acyl-2-chlorobenzenesulfonamides **7a–d** undergo competitive metal–halogen exchange and ortho-deprotonation or α-deprotonation reactions when treated sequentially with sodium hydride and *n*-butyllithium. The *o*-lithio intermediates derived from metal–halogen exchange and ortho-deprotonation undergo cyclization to afford 3-substituted 1,2-benzisothiazole 1,1-dioxides **10a–d** and 3-substituted 7-chloro-1,2-benzisothiazole 1,1-dioxides **14a–d**, respectively. Reaction time–temperature data show evidence for the slow conversion of the lateral dianion of *N*-acetyl-2-chlorobenzenesulfonamide (**7a**) to the corresponding N,ortho-dialkali salt. 1,2-Benzisothiazole 1,1-dioxides **14a–d** were obtained in good yield and free from products resulting from metal–halogen exchange by treatment of sulfonamides **7a–d** with 2 equiv of LDA in THF. In the presence of 2 equiv of LDA, *N*-acylbenzenesulfonamides devoid of or containing only weakly acidic α-hydrogens undergo α-deprotonation–cyclization to afford the respective 1,2-benzoisothiazole 1,1-dioxides.

Introduction

3-Substituted 1,2-benzisothiazole 1,1-dioxides **3** represent an important class of heterocycles with a broad range of biological activity. Compounds of this structural type have found application as diuretics,[1-3] hypotensive drugs,[4] antimicrobial agents,[5] and agricultural fungicides.[6,7] A variety of synthetic strategies have been developed for

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