2,3-Diaza-1,3-dienes (Azines) as Substrates for the Staüdinger Reaction. Synthesis and Reactivity of *N*-Imino-β-lactams

Benito Alcaide,* Miguel Miranda, Javier Pérez-Castells, Concepción Polanco, and Miguel A. Sierra

Departamento de Química Orgánica I, Facultad de Química, Universidad Complutense, 28040-Madrid, Spain

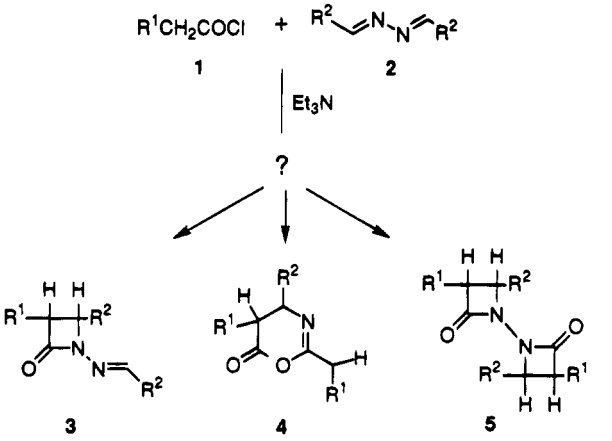
Received April 12, 1994®

The reaction of aromatic and aliphatic azines with different ketene precursors, such as the acid chloride/Et_3N system, alkoxychromium(0) carbenes, and free diphenyl ketene, gives *N*-imino-β-lactams in good to excellent yields, with good levels of *cis,trans*-selectivity. A wide variety of symmetrically-substituted azines derived from aldehydes and ketones are compatible with the Staüdinger reaction. Chiral *N*-imino-β-lactams derived from symmetrically or unsymmetrically (mixed) chiral azines are also obtained in good yields as essentially single enantiomers (de > 95%). Different reaction intermediates, including hemiaminals, oxadiazols, and hydrazides have been isolated. Free diphenyl ketene forms Diels–Alder adducts and *N*-acylazadienes in addition to the previously reported *N*-imino-β-lactams. The usual reactivity of the β-lactam ring is modified in *N*-imino-β-lactams by the presence of the imino group. Thus, β-hydrazonoesters, *N*-alkylamino-β-lactams, and *NH*-β-lactams can be efficiently obtained by base-catalyzed 2-azetidinone ring opening, catalytic hydrogenation, and ozonolysis, respectively.

Introduction

The use of 2,3-diaza-1,3-dienes (azines) as starting materials in organic synthesis is well documented.[1] These readily available compounds have been widely used as substrates in the synthesis of substituted hydrazones[2] and heterocyclic compounds.[3] However, their role as components in cycloaddition reactions has been limited. Examples of azines participating as 4π components of Diels–Alder reactions are restricted to cyclic azines confined to an *s-cisoid* diazadiene conformation.[4] The usual products in these reactions are 2:1 adducts, or [3+2] crisscross products.[5] The lack of reactivity of simple acyclic 2,3-diaza-1,3-butadienes may be attributed to their strong preference for an *s-transoid* conformation. Moreover, there have been few reports of [2+2] cycloadditions of heterocumulenes with azines. In this context, it is known that some isocyanates yield crisscross products with aromatic azines,[6] and recently crisscross processes have been reported in the reactions of vinylidene or carbyne metal complexes and azines.[7] Diphenyl ketene reacts with some aromatic azines to form a [2+2] adduct.[8] Thus, the thermal reaction of diphenyl ketene and azines, **2**, derived from *p*-substituted benzaldehydes yields *N*-imino-β-lactams of type **3**, while aliphatic azines form 4,5-dihydro-1,3-oxazin-6-one derivatives of type **4** (Scheme 1). Finally, when azines derived from propanal and benzaldehyde are treated with lithium isobutyrate, *N*-imino-β-lactams as well as variable amounts of *N,N,-bis*-β-lactams (type **5**) are formed.[9]

Scheme 1



This paper reports a general study of the reaction of ketenes and ketene precursors with azines to yield *N*-imino-β-lactams. Some reactions of *N*-imino-β-lactams will be also considered.

Results and Discussion

The reaction between an acid chloride and an azine may, according to the literature,[8,9] follow three possible reaction pathways, namely to form *N*-imino-β-lactams, **3**, 4,5-dihydro-1,3-oxazin-6-one derivatives, **4**, or *N,N-bis*-β-lactams, **5**, (Scheme 1).

® Abstract published in *Advance ACS Abstracts,* November 15, 1994.

(1) For a general review of the synthesis, chemistry and synthetic uses of azines see: Tennant, G. In *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Eds.; Pergamon Press: New York, 1979; Vol. 2, pp 455–465.

(2) Barluenga, J.; Muñiz, L.; Iglesias, M. J.; Gotor, V. *J. Chem. Soc., Perkin Trans. I* **1984**, 611.

(3) See, for example: Schweizer, E. E.; Cao, Z.; Hayes, J. E.; Rheingold, A. L. *J. Org. Chem.* **1990**, *55*, 1687 and pertinent references therein.

(4) 2,3-Diazabutadiene systems incorporated into larger rings systems also show Diels–Alder like reactivities: Cioslowski, J.; Sauer, J.; Hetznegger, J.; Karcher, T.; Hierstetter, T. *J. Am. Chem. Soc.* **1993**, *115*, 1353.

(5) For a review on the crisscross reaction, see: Grashey, R. *Azomethine imines* in Padwa, A. In *1,3-Dipolar Cycloaddition Chemistry*; Taylor, D. C., Weissberger, A., Eds.; General Heterocyclic Chemistry Series; John Wiley: New York, 1984; Vol. 1, pp 733. The crisscross reaction is remarkable in that other related aza derivatives always react as azadienes in a Diels–Alder fashion.

(6) (a) Bailey, J. R.; Moore, N. H. *J. Am. Chem. Soc.* **1917**, *39*, 279. (b) Bailey, J. R.; McPherson, A. T. *J. Am. Chem. Soc.* **1917**, *39*, 1322.

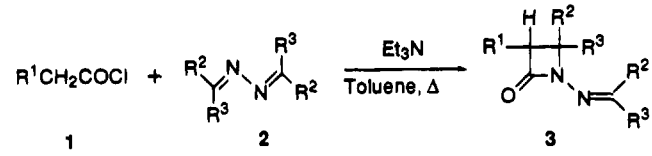
(7) Kelley, C.; Mercando, L. A.; Terry, M. R.; Lugan, N.; Geoffroy, G. L.; Xu, Z.; Rheingold, A. L. *Angew. Chem. Int. Ed. Eng.* **1992**, *31*, 1053.

(8) Satsumabayuski, S.; Motoki, S.; Nakano, H. *J. Org. Chem.* **1976**, *23*, 677.

(9) Komatsu, M.; Yamamoto, S.; Ohshiro, Y.; Agawa, T. *Heterocycles* **1985**, *23*, 677.

0022-3263/94/1959-8003$04.50/0 © 1994 American Chemical Society

Table 1



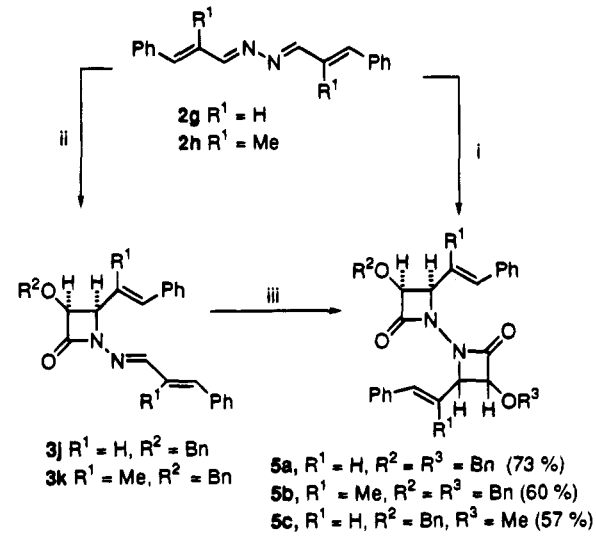
1 2 3

	R1		R2	R3		cis:trans[a]	yield[b] (%) cis	trans
1a	PhO	**2a**	*p*-MeOC$_6$H$_4$	H	**3a**	66:44	60	20
1b	MeO	**2a**			**3b**	89:11	48	17
1c	BnO	**2a**			**3c**	84:14	70	8
1d	*t*-BuO	**2a**			**3d**	100:0	74	
1c	BnO	**2b**	Ph	H	**3e**	100:0	98	
1c		**2c**	*p*-MeC$_6$H$_4$	H	**3f**	100:0	87	
1c		**2d**	*m*-ClC$_6$H$_4$	H	**3g**	100:0	90	
1c		**2e**	*p*-NO$_2$C$_6$H$_4$	H	**3h**	100:0	60	
1c		**2f**	2-Furyl	H	**3i**	100:0	94	
1c		**2g**	Zi[f]	H	**3j**	100:0	51[d]	
1c		**2h**	MeZi[g]	H	**3k**	100:0	48[d]	
1a	PhO	**2h**			**3l**	100:0	75	
1c	BnO	**2i**	*i*-Pr	H	**3m**	1:2[c]	15	37
1c		**2j**	*t*-Bu	H	**3n**	100:0	74	
1d	CH_3CO_2	**2a**	*p*-MeOC$_6$H$_4$	H	**3o**	0:100		60
1c	BnO	**2k**	Ph	Me	**3p**	100:0[e]	75	
1e	Pht[h]	**2h**	MeZi[g]	H	**3q**	65:35	38	34

[a] Determined by integration of the signals corresponding to H3–H4 in the ^{1}H NMR spectra of the crude mixtures. [b] Of pure, isolated compound with correct spectroscopic and analytical data. [c] The *cis:trans* ratio is variable. The reported ratios are for the reaction conditions detailed in the Experimental Section. See text for a detailed discussion. [d] Obtained together with the corresponding *bis*-β-lactam. [e] Traces of the *trans* isomer might be present but are undetectable because of the complexity of the ^{1}H NMR spectra of the crude mixtures. [f] Zi = CH=CH–Ph. [g] MeZi = (CH$_3$)C=CHPh. [h] Pht = phthalimidyl.

Alkoxy-substituted acetyl chlorides reacted smoothly with a wide variety of azines derived from aliphatic, aromatic, α,β-unsaturated aldehydes as well as ketones, in the presence of Et_3N, to yield *N*-imino-β-lactams, **3**, in good to excellent yields (Table 1). Pure compounds, **3**, were obtained by recrystallization of solid compounds from hexane/EtOAc, or by flash chromatography of oils or isomeric mixtures. In the latter case chromatography separates both isomers as analytically pure compounds. Compounds **3** were formed as *cis-trans* mixtures in some cases. The isomeric composition of the mixtures remained essentially unchanged with the reaction time. However, we observed a striking variation of the selectivity with the rate of addition of the acid chloride. Variation of the ketene moiety was studied next. Alkyl-, aryl-, and chloro-substituted acetyl chlorides were unreactive towards aliphatic or aromatic azines, which were recovered unaltered even after prolonged reaction times. Although several factors such as the reagent used for acid activation,[10] the order of addition of reagents,[11] solvent, and temperature[12] were modified, *N*-imino-β-lactams were not obtained with the exception of **3q**, as a mixture of *cis,trans*-isomers, from phtalimidylacetyl chloride and azine **2h** (Table 1).

Scheme 2



[a] Key: (i) R^{2}OCH$_2$COCl/Et$_3$N/toluene, Δ, (acid chloride–azine 3:1); (ii) R^{2}OCH$_2$COCl/Et$_3$N/toluene, Δ, (acid chloride–azine 2:1); (iii) R^{3}OCH$_2$COCl/Et$_3$N/toluene, Δ, (acid chloride–azine 2:1).

Azines are considerably less reactive than 1,4-diaza-1,3-dienes[13] which react smoothly with activated and deactivated ketenes at room temperature to yield 4-imino-β-lactams, in good to excellent yields. The decreased reactivity found for azines may be due to a lone pair-lone pair interaction between the proximal azine nitrogens, which renders the azine nitrogen less basic, hence the necessary use of activated ketenes in order to form β-lactams.

The C=N group of *N*-imino-β-lactams, **3**, was unreactive towards a second cycloaddition.[14] Azines, **2g** and **2h**, derived from α,β-unsaturated aldehydes, were the exception; they reacted with benzyloxyacetyl chloride under standard conditions (acid chloride/azine 2:1) to produce considerable amounts of *bis*-β-lactams, **5**. Compounds **5** became the major products when larger excesses of acid chloride were used. *Bis*-β-lactams **5** were alternatively prepared from *N*-imino-β-lactams, **3j** and **3k** by reaction with benzyloxyacetyl chloride with yields and selectivities analogous to the one-step procedure. The fact that the acid chlorides could react in sequence, allowed the preparation of unsymmetrically substituted compounds **5** (Scheme 2). Both four-membered rings have *cis*-stereochemistry as deduced from the coupling constants of the protons at the C3-C4 carbons ($J_{3,4}$ = 4.8–5.3 Hz) in both rings. Compounds **5a** and **5c** were formed as both possible *cis,cis*-diastereomers, while compound **5b** was a single *cis,cis*-diastereomer. Unfortunately, the high degree of internal symmetry present in both diastereomers, as deduced from their NMR spectra, did not allow us to differentiate between them.[15]

Azines **6**, derived from chiral aldehydes, yielded the corresponding β-lactams in good yields and selectivities.

(10) Other condensation agents such as cyanuric chloride and phenyl dichlorophosphate were used instead of Et_3N with negative results. See: (a) Van der Veen, J. M.; Bari, S. S.; Krishnan, L.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1989**, *54*, 5758. (b) Cossio, F. P.; Palomo, C. *Tetrahedron Lett.* **1985**, *26*, 4239.

(11) Azine addition to a previously generated ketene solution, according to Ojima's procedure resulted in complete recovery of unreacted azine. Ojima, I.; Komata, T.; Qiu, X. *J. Am. Chem. Soc.* **1990**, *112*, 770.

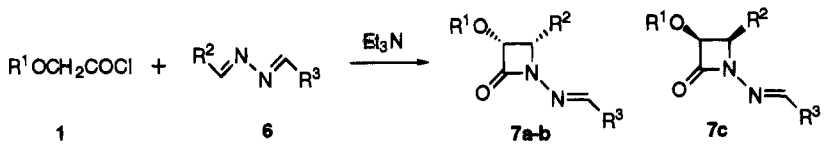
(12) It is known that the yields and stereochemical outcome of the Staüdinger reaction are very sensitive to factors such as temperature, the order of reagent addition, or the way the ketene is generated. For a detailed discussion on the mechanism of the Staüdinger reaction, see: Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH Publishers Inc., New York, 1993; pp 295–368.

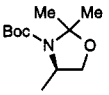
(13) (a) Alcaide, B.; Martín-Cantalejo, Y.; Plumet, J.; Rodríguez-López, J.; Sierra, M. A. *Tetrahedron Lett.* **1991**, *32*, 803. (b) Alcaide, B.; Martín-Cantalejo, Y.; Pérez-Castells, J.; Rodríguez-López, J.; Sierra, M. A, Monge, A.; Pérez-García, V. *J. Org. Chem.* **1992**, *57*, 5921.

(14) Attempts to promote a second cycloaddition to obtain *N,N*-bis-β-lactams by reaction of isolated *N*-imino-β-lactams with excess of acid chloride were fruitless as were attempted reactions of the corresponding azines with a large excess of acid chloride.

(15) Although compounds **5a** and **5b** are crystalline solids, all attempts to grow adequate crystals for X-ray diffraction analysis were unsuccessful.

Table 2



compd	R^1	R^2	R^3	de	yield[a] (%)
7a	Bn			>95 %	53
7b	Bn		*t*-Bu	>95 %	77
7c	Bn		*t*-Bu	>95 %	66

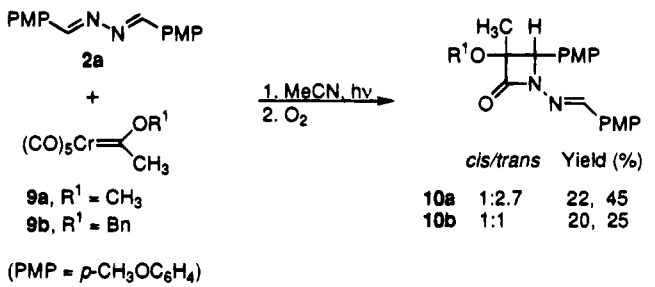
[a] Of pure, isolated compound.

Both symmetrical and mixed azines[16] derived from D-(*R*)-glyceraldehyde acetonide and *N,O*-diprotected L-serinal as chiral moieties, and pivalaldehyde as a bulky moiety, reacted with benzyloxyacetyl chloride to form the expected *N*-imino-β-lactams **7a**–**7c**, in good yields, as single *cis*-diastereomers. The mixed azines reacted with total regioselectivity. In fact, the bulky *tert*-butyl group directs the cycloaddition completely to the less hindered imino group (Table 2).

Compounds **7** were single *cis*-diastereomers. However, the absolute configuration at the 2-azetidinone ring could not be solved by single crystal X-ray diffraction because adequate crystals could not be obtained. Thus, the *N*-imino-β-lactams, **7**, were chemically correlated to *NH*-β-lactams **8c**–**d** (see below) with known stereochemistry (Table IV). Compounds **8** were identical ($[\alpha]_D$, and spectroscopic data) to authentic samples prepared by known routes (see supplementary material),[17,18] confirming the absolute stereochemistry of *N*-imino-β-lactams **7**.

We used chromium alkoxy carbenes (Hegedus' methodology)[19] to prepare *N*-imino-β-lactams disubstituted at C3. Irradiation (visible light, 400 W medium pressure Hg lamp, Pyrex filtered) of either complex **9a** or **9b** with azine **2a**, gave the corresponding *N*-imino-β-lactams, **10a** and **10b**, as *cis-trans* mixtures in good yields (Scheme 3). Both isomers were readily separated by flash chromatography, and their stereochemistry was established by NOE measurements.[20] These results showed that azines are compatible with chromium complexes allowing the preparation of C3-disubstituted *N*-imino-β-lactams, in a process which is complementary to the classical acid chloride route discussed above.

Scheme 3



We found some anomalous results in the reaction of azines and diphenylketene. Although the reaction of this ketene with aromatic azines should yield *N*-imino-β-lactams, in our hands the reported conditions[8] yielded a new product (20%, pure material), together with ketene dimer, unreacted azine and *N*-imino-β-lactam **11**. This new compound was pyridazin-4-one, **12** as deduced from its analytical and spectroscopic data. Compound **12** may be formed by the Diels–Alder reaction of diphenyl ketene and the azine to form **13**, followed by a 1,3-hydrogen shift (Scheme 4). *N*-imino-β-lactam **11**, was obtained (60%, pure compound) together with traces of adduct **12** (<3%) when ketene and azine were treated under analogous conditions but in a 2:1 molar ratio.

These results prompted us to reinvestigate the reaction of diphenylketene and aliphatic azines, which, according to the published results, should form a 2:1 adduct of type **4** (see Scheme 1). The reaction of diphenyl ketene and isobutyraldehyde azine, **2i**, (molar ratio 2:1) carried out under the reported conditions (refluxing ether) gave extremely complex reaction mixtures. Unreacted azine was the only spectroscopically identifiable product. However, when diphenylketene and azine **2i** were allowed to react in boiling benzene, a non-β-lactamic product, **14**,

(16) The main synthetic application of *N*-imino-β-lactams is their transformation to enol–ethers by reaction with ozone. In this process the group attached to the exocyclic imino group is lost as the corresponding alcohol. Therefore, it is interesting to use mixed azines in order to save chiral material. See: Alcaide, B.; Miranda, M.; Pérez-Castells, J.; Sierra, M. A. *J. Org. Chem.* **1993**, *58*, 297.

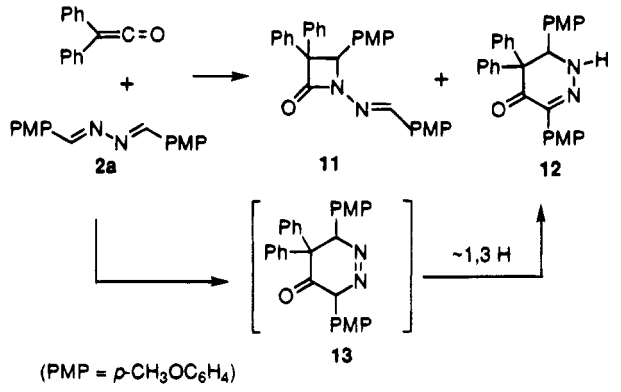
(17) β-Lactams **7a** and **7b** were correlated with the β-lactam derived from protected glyceraldehyde imine obtained according to Bose's procedure. See: Wagle, D. R.; Garai, C.; Chiang, J.; Monteleone, M. G.; Kurys, B. E.; Strohmeyer, T. W.; Hedge, V. R.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1988**, *53*, 4226. β-Lactam **7c** was correlated with the β-lactam derived from protected serinal prepared by Palomo's method. See: Palomo, C.; Cossio, F. P.; Cuevas, C.; Lecea, B.; Mielgo, A.; Román, P.; Luque, A.; Martínez-Ripoll, M. *J. Am. Chem. Soc.* **1992**, *114*, 9360.

(18) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.

(19) For some recent references on the photochemistry of chromium-(0) carbenes applied to β-lactam synthesis, see: (a) Narukawa, Y.; Juneau, K.; Snustad, D.; Miller, D. B.; Hegedus, L. S. *J. Org. Chem.* **1992**, *57*, 5453. (b) Betschart, C.; Hegedus, L. S. *J. Am. Chem. Soc.* **1992**, *114*, 5010. (c) Thompson, D. K.; Suzuki, N.; Hegedus, L. S.; Satoh, Y. *J. Org. Chem.* **1992**, *57*, 1461. (d) Alcaide, B.; Domínguez, G.; Plumet, J.; Sierra, M. A. *J. Org. Chem.* **1992**, *57*, 447.

(20) Irradiation of the CH_3 at δ = 1.67 in *cis*-**10a** resulted in an NOE increment of 5 % for H4 at δ = 4.87. Irradiation of H4 at δ = 4.99 in *cis*-**10b** resulted in an NOE increment of 8% for the CH_3 at δ = 1.77. Analogous experiments on the *trans*-isomers showed no NOE increments.

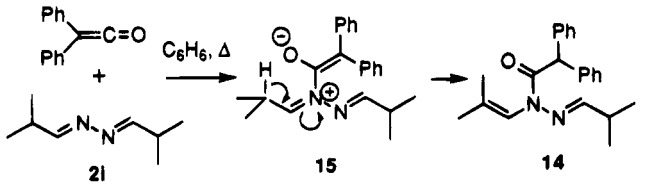
Scheme 4



Ref. 8: Xylene, Δ, (1:1) Yield: **11** (50 %), **12** (Not detected)
This work : Xylene, Δ, (1:1) Yield: **11** (50 %), **12** (20 %)
Xylene, Δ, (2:1) Yield: **11** (60 %),**12** (traces)

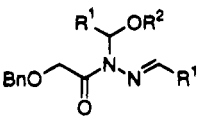
(51%, pure compound after chromatographic purification) was formed (Scheme 5). Compound **14** may be formed by intramolecular abstraction of the β-hydrogen on zwitterion **15** followed by 1,3-hydrogen shift. Alternatively, the ketene may acylate the enamine tautomer of azine **2i** to yield the observed product.[21] Formation of compounds of type **14**, through a ketene-imine reaction is, to the best of our knowledge, unknown. A detailed study of this process is underway in our laboratories.

Scheme 5

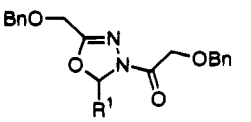


To ascertain the role of the second azine nitrogen in the reaction of ketenes or ketene precursors and azines, we studied the reaction between benzyloxyacetyl chloride and compounds **2a** and **2i**, as models for aromatic and aliphatic azines, under different reaction conditions. The effects of the order of reagent addition, reaction temperature, the absence or presence of Et_3N and the period of time between base addition and reaction quenching were studied. Besides *N*-imino-β-lactams, **3**, at least three different types of products were isolated and/or detected in these experiments. The structures of these intermediates are depicted in Figure 1.

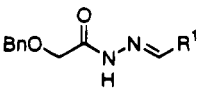
Hemiaminals **16** were formed together with oxadiazols **17** in the reaction of benzyloxyacetyl chloride with the corresponding azine, when the Et_3N was initially excluded. Thus, after a variable amount of time and immediately after addition of Et_3N, the reaction mixture was quenched with H_2O (for compounds **16c**, **17a,b**) or alcohols (for compounds **16a,b**). Hydrazide **18** became the major reaction product when the final treatment with base was omitted. Furthermore, *N*-imino-β-lactam **3m** was formed exclusively as the *trans*-isomer in all the reactions of azine **2i** except those in which base treatment was omitted. On the other hand, no β-lactam products



16a R^2 = Me, R^1 = *i*-Pr
16b R^2 = Et
16c R^2 = H
16d R^2 = H, R^1 = PMP



17a R^1 = *i*-Pr
17b R^1 = PMP



18 R^1 = ^{i}Pr

(PMP = p-MeOC6H4)

Figure 1. Products from the reactions of azines **2a** and **2i** with benzyloxyacetyl chloride under different experimental conditions.

were observed from azine **2a** at room temperature even after prolonged reaction times. Heating was essential for the formation of *N*-imino-β-lactam **3c**.[22] Compounds **16, 17** and **18** are stable and could be obtained as analytically pure compounds except for hemiaminals **16c** and **16d** which were transformed during chromatographic purification to *trans*-*N*-imino-β-lactam **3m** and a mixture of *cis,trans*-*N*-imino-β-lactams (60:40), **3c**, respectively. Moreover, upon treatment with *p*-toluenesulfonic acid (TsOH − $1H_2O$) in $CHCl_3$ at room temperature, hemiaminal **16b** reacted to give *trans*-*N*-imino-β-lactam **3m** together with hydrazide **18**.

The formation of the isolated compounds described above can be rationalized as taking place through the intermediate iminium salts **19** or zwitterions **20** (Scheme 6). Compounds **17** may arise from intermediates **20** through oxadiazol **21** after hydrolysis of the iminium group and acylation with excess acid chloride. Intermediates related to **21** are usual in crisscross reactions of azines and activated alkenes and have been used to prepare mixed crisscross products.[5] The isolation of compounds **17** suggests a mixed reaction course between the classical mechanism for the Staüdinger reaction and the crisscross reaction. Thus, the second azine nitrogen appears to influence the reactivity of azines towards ketenes or their precursors. Nevertheless, evidence will be needed before a general reaction pathway for these processes can be written.

Reactivity of *N*-imino-β-lactams, 3. The hydrolysis of the 2-azetidinone ring by bases was explored first. *N*-Imino-β-lactams, **3**, react almost instantaneously with alcohols containing catalytic amounts of NaOH at room temperature to yield β-hydrazonoesters **22**, quantitatively. Compounds **22** were obtained as essentially pure compounds and were characterized by their spectroscopic data (Table 3). However, they were unstable and correct analytical data could not be obtained. Primary, and secondary alcohols react smoothly to give the corresponding esters, while tertiary alcohols gave complex reaction mixtures. The reaction does not depend on the nature of the groups attached to N1 and C4 of the 2-azetidinone ring. The stereochemistry at C3−C4 in the 2-azetidinone

(21) Acylation of the enamine tautomer occurs, for example, in the reaction of the imine derived from crotonaldehyde and propargyl amine with benzyloxyacetyl chloride to form *N*-(2,4-pentadienyl)-*N*-propargylbenzyloxyacetamide together with the corresponding β-lactam. However, no products related to **14** were formed in the reactions of acid chlorides with azines reported in here. This casts doubt on the likelihood of enamine acylation.

(22) All the experiments directed toward the isolation of reaction intermediates were repeated at least twice to ensure that the results obtained were reproducible. See Supplementary Material for a full experimental procedure, as well as spectroscopic and analytical data for compounds **16**−**18**.

Scheme 6

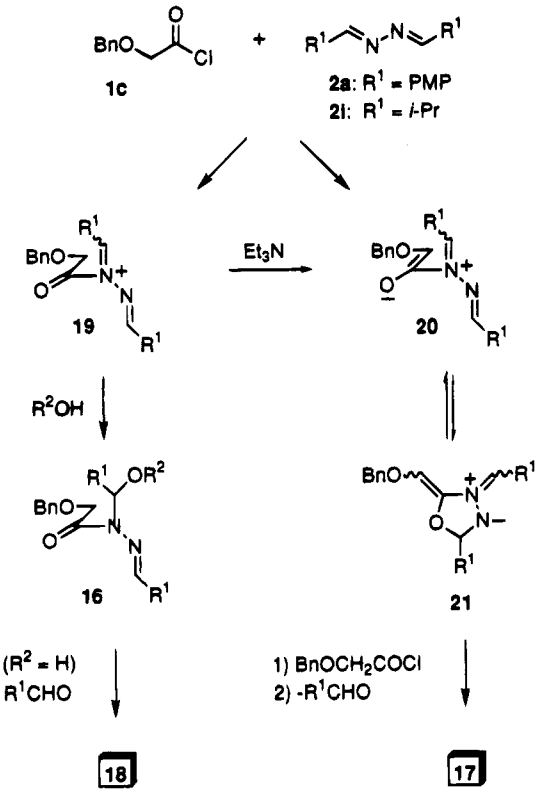
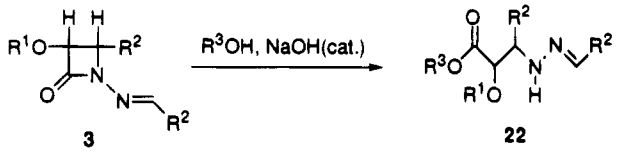


Table 3



entry	substrate	R^1	R^2	R^3	product[a]	yield[b] (%)
1	*cis*-**3a**	Me	*p*-$MeOC_6H_4$	Me	*anti*-**22a**	95
2				Et	*anti*-**22b**	97
3				*i*-Pr	*anti*-**22c**	90
4	*cis*-**3c**	Bn	*p*-$MeOC_6H_4$	Me	*anti*-**22d**	99
5	*cis*-**3i**	Bn	2-Furyl	Me	*anti*-**22e**	97
6	*cis*-**3m**	Bn	*i*-Pr	Me	*anti*-**22f**	95
7	*trans*-**3m**	Bn	*i*-Pr	Me	*syn*-**22g**	90

[a] Compounds **22** are unstable and decompose within hours at room temperature. [b] Of crude material with correct spectroscopic data (^1H, ^{13}C NMR).

ring is transferred unaltered to the hydrazono esters, independent of the starting isomer of the β-lactam used (see entries 6 and 7, Table 3). It is noteworthy that this transformation proceeds under extremely mild conditions.[23] The presence of the imino group attached to N1 labilizes the 2-azetidinone ring towards nucleophiles, probably reducing the amide resonance and, therefore, the strength of the N1-C2 bond.[24] Compounds **22** are the 3-analogs of biologically active 2-hydrazino acid derivatives,[25] which are important as enzyme inhibitors,[26] and as components of peptide analogs which are metabolically more stable than the natural peptides in mammalian systems.[27]

The imino group in β-lactams, **3**, was remarkably resistant to hydrolysis under heterogeneous conditions. Thus, no reaction was observed after acid hydrolysis (HCl 10%, water/Cl_3CH) or complex mixtures were formed under homogeneous conditions (HCl 15%, THF/water). Standard methods used for hydrazone hydrolysis such as bakers yeast,[28] $Pd(C)/NH_4CO_2H$,[29] $Ce(NH_4)_2(NO_3)_6$,[30] and silica[31] resulted in quantitative recovery of unreacted **3**. Other reagents including SnF_2,[30] $NOBF_4$,[32] and $BF_3{\cdot}Et_2O$[33] yielded the corresponding aldehyde together with extremely complex reaction mixtures. These disappointing results precluded an easy entry to *N*-amino-β-lactams from *N*-imino-β-lactams, **3**. Nevertheless, the corresponding *N*-alkylamino-β-lactams, **23**, were obtained in fair yields by catalytic hydrogenation of the imino group. Results are summarized in Scheme 7. The hydrogenation conditions had to be carefully controlled in order to avoid the C4-N1 bond cleavage when an aromatic group was attached to C4.[34]

Cleavage of the N-N bond to give *N*-unsubstituted β-lactams **8** (Table 4), occurs through ozonolysis of *N*-imino-β-lactams, **3**, in CH_2Cl_2 at −78 °C, followed by quenching with Zn[35] in AcOH. Other quenching agents, including Me_2S, KOH/H_2O_2, and DMSO produced complex reaction mixtures.[16] This approach is suitable for making homochiral β-lactams from their *N*-imino-β-lactam precursors without racemization. As stated above, the stereochemistry of compounds **7** has been determined by taking advantage of this fact.

All these reactions show that the reactivity of *N*-imino-β-lactams is considerably influenced by the presence of an additional imine double bond attached to the amide nitrogen. Further aspects of this rich reactivity are currently under investigation in our laboratories and will be reported in due time.

In conclusion, the Staüdinger reaction of aromatic and aliphatic azines with different ketene precursors, including isolated diphenyl ketene, has been studied. Racemic and homochiral *N*-imino-β-lactams are efficiently formed in these reactions, provided that activated ketenes are used. Chromiumalkoxy carbenes are also suitable reagents for the synthesis of *N*-imino-β-lactams. Some reaction intermediates have been isolated under different

(23) 2-Azetidinone ring opening usually requires heating with either 6N HCl, or solutions of concentrated base. Ojima, I.; Pei, Y. *Tetrahedron Lett.* **1990**, *31*, 977.

(24) The effect of an electron-withdrawing group attached to the amide nitrogen on the reactivity of the 2-azetidinone ring is well known. See: (a) Baldwin, J. E.; Adlington, R. M.; Godfrey, C. R. A.; Gollins, D. W.; Smith, M. L.; Russell, A. T. *Synlett.* **1993**, 51. (b) Baldwin, J. E.; Edwards, A. J.; Farthing, C. N.; Russell, A. T. *Synlett.* **1993**, 49. (c) Baldwin, J. E.; Adlington, R. M.; Gollins, D. W.; Schofield, C. J. *Tetrahedron* **1990**, *46*, 4733.

(25) For different syntheses of α-hydrazino acid derivatives, see: (a) Niederer, D. A.; Kapron, J. T.; Vederas, J. C. *Tetrahedron Lett.* **1993**, *34*, 6859. (b) Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron* **1988**, *44*, 5553. (c) Oppolzer, W.; Moretti, R. *Tetrahedron* **1988**, *44*, 5541. (c) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *Tetrahedron* **1988**, *44*, 5525. (d) Trimble, L. A.; Vederas, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 6397.

(26) Scamen, C. H.; Palcic, M. M.; McPhalen, C.; Gore, M. P.; Lam, L. K. P.; Vederas, J. C. *J. Biol. Chem.* **1988**, *263*, 11814, and references therein.

(27) Chen, S.; Chrusciel, R. A.; Nakanishi, H.; Raktabutr, A.; Johnson, M. E.; Sato, A.; Weiner, D.; Hoxie, J.; Saragovi, H. U.; Greene, M. I.; Kahn, M. *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 5872.

(28) Kamal, A.; Rao, M.; Mesrham, H. *Tetrahedron Lett.* **1991**, *32*, 2657.

(29) **29.** Adger, B. M.; O'Farrell, C.; Lewis, N. J.; Mitchell, M. B. *Synthesis* **1987**, 53.

(30) Enders, D.; Bhushan, V. *Z. Naturforsch., Teil B* **1987**, *42*, 1595.

(31) Armstead, D. A.; Mann, J. Armstead, D. A.; Mann, J. *Synth. Commun.* **1985**, *15*, 1147.

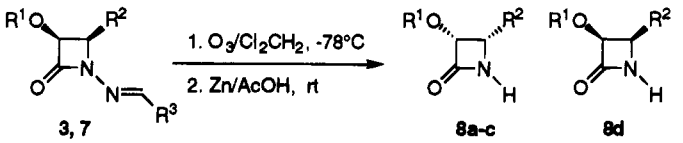
(32) Olah, G. A.; Ho, T.-L. *Synthesis* **1976**, 610.

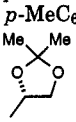
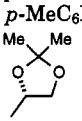
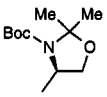
(33) Enders, D.; Bhushan, V. *Tetrahedron Lett.* **1986**, *29*, 2437.

(34) C4-N1 bond cleavage by hydrogenolysis of 2-azetidinones having an aromatic group attached at C4 is the basis of Ojima's β-lactam synthon method. See Ojima, I. in ref 12, pp 197−255.

(35) Optimum yields were obtained in some cases by using preactivated TMSCl/Zn-dust. Picotin, G.; Miginiac, P. *J. Org. Chem.* **1987**, *52*, 4796.

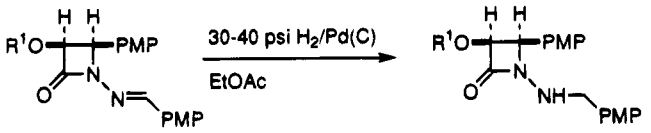
Table 4



substrate	R^1	R^2	R^3	product	yield[a] (%)
3c	Bn	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	**8a**	92
3f	Bn	*p*-MeC_6H_4	*p*-MeC_6H_4	**8b**	80
7a	Bn			**8c**	35
7b	Bn		*t*-Bu	**8c**	30
7c	Bn		*t*-Bu	**8d**	45

[a] Of pure, isolated compound.

Scheme 7



reaction conditions. When the second azine bond reacts, a variety of products are formed depending upon the reaction conditions. The second azine nitrogen influences both the nature and the stability of the reaction intermediates. An unusual result was that the reaction of aromatic azines with diphenyl ketene produces Diels–Alder adducts. Reactivity towards different reagents is enhanced or decreased in *N*-imino-β-lactams by the presence of the additional *N*-imino group. We have been able to take advantage of this fact to obtain β-hydrazono esters, *N*-protected *N*-amino-β-lactams, and *N*-unsubstituted β-lactams.

Experimental Section

General Procedure. General experimental data and procedures have been previously reported.[13b] Specific rotation, $[\alpha]_D$, was reported in deg per dm at the specified temperature and the concentration (*c*) given in g per 100 mL in $CHCl_3$.

All commercially available compounds were used without further purification. The following chemicals were prepared according to literature procedures: 2,3-*O*-(isopropylidene)-D-glyceraldehyde,[36] 1,1-dimethyl (*S*)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate,[37] (3*R*,4*R*)-1-(*p*-anisyl)-3-benzyloxy-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-azetidinone,[17] (3*S*,4*R*)-1-(*p*-Anisyl)-3-Benzyloxy-4-[(*R*)-3-(*tert*-butyloxycarbonyl)-2,2-dimethyl oxazolidin-4-yl]-2-azetidinone,[17] pentacarbonyl-(methoxymethylcarbene)chromium(0),[38] pentacarbonyl(benzyloxymethylcarbene)chromium(0).[39] Azines **2a–f** were prepared by refluxing a solution of aldehyde and hydrazine hydrate (80% in water) in ethanol.[40] Toluene, benzene, CH_2Cl_2, MeCN, and Et_3N were dried over CaH_2 and freshly distilled from CaH_2 prior to use.

General Procedure for the Synthesis of *N*-Imino-2-azetidinones 3 and 7. A solution of acid chloride (2 mmol for **3a–i**, **3m–q**, **7a-c** or 1 mmol for **3j–3l**) in anhydrous toluene (5 mL) was added dropwise via syringe to a refluxing solution of azine **2** (1 mmol) in toluene (10 mL) containing triethylamine (3 mmol for **3a–i**, **3m–q**, **7a–c** or 2 mmol for **3j–3l**) under argon. The mixture was stirred until complete disappearance of starting azine (tlc). Then, the reaction mixture was cooled, diluted with $CHCl_3$, and successively washed with aqueous $NaHCO_3$ (saturated solution, 20 mL), water (2 × 10 mL), and dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure, the crude products were separated by flash chromatography (silica gel, hexane/EtOAc mixtures), or crystallized from the solvent indicated in each case, to yield analytically pure compounds **3** and **7**. Flash chromatography allowed separation of *cis*- and *trans*-isomers as analytically pure compounds in those cases in which mixtures of isomers were obtained. Spectroscopic and analytical data for some representative forms of **3** and **7** follow.[41]

4-*p*-Anisyl-1-[(4′-methoxybenzylidene)amino]-3-benzyloxy-2-azetidinone (3c). Reaction time: 2h. ***cis*-Isomer:** White crystalline solid. Yield: 70%. Mp 163–165 °C, (EtOAc). ^1H NMR ($CDCl_3$) δ 3.73 (s, 3H), 3.75 (s, 3H), 4.25 (dd_{AB}, 2H, J_{AB} = 11.1 Hz), 4.81 (d, 1H, *J* = 4.5 Hz), 4.86 (d, 1H, *J* = 4.5 Hz), 6.76 (d, 2H), 6.86 (d, 2H), 6.92 (m, 2H), 7.16 (dd, 2H), 7.26 (d,2H), 7.46 (d, 2H), 7.66 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 162.7, 161.7, 160.0, 146.7, 136.3, 129.3, 128.3, 125.9, 124.1, 114.2, 114.1, 80.6, 72.5 , 64.5, 55.4, 55.3. IR ($CHCl_3$) 1765, 1710, 1605, 1510, 1400. Anal. Calcd for $C_{25}H_{24}N_2O_4$: C, 72.1; H, 5.81; N, 6.73. Found: C, 71.70; H, 5.79; N, 6.65. ***trans*-Isomer:** White crystalline solid. Yield: 8%. Mp 141–143 °C (EtOAc). ^1H NMR ($CDCl_3$) δ 3.79 (s, 6H), 4.42 (d, 1H, *J* = 1.8 Hz), 4.76 (dd_{AB}, 2H, J_{AB} = 11.7 Hz), 4.88 (d, 1H, *J* = 2.1Hz), 6.85 (dd, 4H), 7.08 (d, 2H), 7.33 (s, 5H), 7.52 (d, 2H), 7.68 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 162.6, 161.7, 159.9, 147.0, 136.8, 129.2, 128.5, 128.2, 127.3, 126.8, 126.0, 114.6, 114.0, 87.6, 73.1, 66.6, 55.3, 55.2. IR ($CHCl_3$) 1760, 1610, 1510, 1400, 1330, 1300. Anal. Calcd for $C_{25}H_{24}N_2O_4$: C, 72.1; H, 5.81; N, 6.73. Found: C, 71.84; H, 5.64; N, 6.96.

***cis*-4-*p*-Anisyl-1-[(4′-methoxybenzylidene)amino]-3-*tert*-butyloxy-2-azetidinone (3d).** Reaction time: 2h. White crystalline solid. Yield: 74%. Mp 212–213 °C (EtOAc). ^1H

(36) Schmid, C.; Bryant, J. D.; Dowlatzedah, M.; Phillips, J.; Prather, D. E.; Schantz, R. D.; Sear, N. L.; Vianco, C. S. *J. Org. Chem.* **1991**, *56*, 4056.
(37) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361.
(38) Fisher, E. O.; Aumann, R. *Chem. Ber.* **1968**, *101*, 960.
(39) Hafner, A.; Hegedus, L. S.; de Weck, G.; Hawckins, B.; Dötz, K. H. *J. Am. Chem. Soc.* **1988**, *110*, 8413.
(40) Henoch, E. E.; Hampton, K. G.; Hauser, C. R. *J. Am. Chem. Soc.* **1969**, *91*, 676.
(41) Full spectroscopic and analytical data for compounds not included in this Experimental Section are described in the supplementary material.

NMR ($CDCl_3$) δ 0.99 (s, 9 H), 3.80 (s, 3 H), 3.82 (s, 3 H), 4.98 (d, 1 H, J = 4.7 Hz), 5.16 (d, 1 H, J = 4.7 Hz), 6.84 (d, 2 H), 6.91 (d, 2 H), 7.29 (d, 2 H), 7.54 (d, 2 H), 7.72 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 164.9 , 161.7, 159.9, 146.2, 130.1, 129.4, 126.3, 125.1, 114.1, 113.8, 75.7, 66.1 , 55.5 , 55.4, 27.9. IR (KBr) 1750, 1610, 1520, 1400. Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.31; H, 6.79; N 7.31.

***cis*-3-Benzyloxy-1-(2-furfurylidene)amino-4-(2-furyl)-2-azetidinone (3i).** Reaction time: 1h. White crystalline solid. Yield: 94%. Mp 153–155 °C (EtOAc). ^1H NMR ($CDCl_3$) δ 4.48 (dd_{AB}, 2H, J_{AB} = 11.4 Hz), 4.93 (d, 1H, J = 4.8 Hz), 5.28 (d, 1H, J = 4.8 Hz), 6.47 (dq, 2H), 6.50 (d, 1H), 6.77 (d, 1H), 7.17 (m, 2H), 7.28 (m, 3H), 7.48 (s, 2H), 8.12 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 162.6, 148.9, 146.6, 145.1, 143.3, 138.2, 136.6, 128.1, 128.0, 114.4, 112.1, 111.1, 110.9, 80.8, 72.9, 58.9. IR ($CHCl_3$) 1770, 1610, 1590, 1570, 1390, 1360, 1305. Anal. Calcd for $C_{19}H_{16}N_2O_4$: C, 67.85, H, 4.79, N, 8.33. Found: C, 67.59; H, 4.84; N, 8.13.

***cis*-3-Benzyloxy-1-(α-methylcinnamylidene)amino-4-(2-methylstyryl)-2-azetidinone (3k).** Reaction time: 1 h. White crystalline solid. Yield: 48%. Mp 128–130 °C. ^1H NMR ($CDCl_3$) δ 1.99 (s, 3H), 2.17 (s, 3H), 4.76 (dd_{AB}, 2H, J_{AB} =11.7 Hz), 4.82 (d, 1H, J = 5.1 Hz), 4.88 (d, 1H, J = 5.1 Hz), 6.66 (s, 1H), 6.71 (s, 1H), 7.31–7.38 (m, 15H), 7.81 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 163.2, 151.4, 139.0, 136.7, 136.6, 136.1, 134.5, 132.2, 130.5, 129.4, 129.0, 128.4, 128.3, 128.2, 128.0, 127.9, 127.1, 80.6, 73.1, 68.5, 15.2, 12.8. IR ($CHCl_3$) 1760, 1485, 1440, 1395, 1310. Anal. Calcd for $C_{29}H_{28}N_2O_2$: C, 79.79, H, 6.46; N, 6.42. Found: C, 79.56; H, 6.34; N, 6.28.

3-Benzyloxy-1-isobutylideneamino-4-isopropyl-2-azetidinone (3m). Reaction time: 1 h. ***cis*-Isomer:** Yellow oil. Yield: 15%. ^1H NMR ($CDCl_3$) δ 1.00 (d, 3H, J = 6.6 Hz), 1.05 (d, 6H, J = 6.6 Hz), 1.08 (d, 3H, J = 6.6 Hz), 2.15 (m, 1H, J = 6.6 Hz), 2.49 (m, 1H,J = 6.6 Hz), 3.76 (dd, 1H, J_1 = 5.4 Hz, J_2 = 7.8 Hz), 4.60 (d, 1H, J = 5.4 Hz), 4.82 (dd_{AB}, 2H, J_{AB} = 11.7 Hz), 7.35–7.36 (m, 5H), 8.08 (d, 1H, J = 5.4 Hz). ^{13}C NMR ($CDCl_3$) δ 164.4, 161.3, 137.2, 128.3, 127.6, 79.1, 72.7, 66.9, 32.1, 28.3, 19.6, 19.5, 19.4, 19.1. IR ($CHCl_3$) 1740, 1470, 1380, 1330, 1305, 1150. Anal. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.79, H, 8.39; N, 9.72. Found: C, 70.87; H, 8.40; N, 9.76. ***trans*-Isomer:** Yellow oil. Yield 37%. ^1H NMR ($CDCl_3$) δ 0.86 (d, 3H, J = 6.9 Hz), 1.01 (d, 3H, J = 0.9 Hz), 1.06 (d, 3H, J = 0.9 Hz), 1.08 (d, 3H, J = 0.9 Hz), 2.06 (m, 1H, J = 6.9 Hz), 2.49 (m, 1H, J = 6.9 Hz), 3.75 (d, 1H, J_1 = 5.4 Hz), 4.31 (s, 1H), 4.74 (dd_{AB}, 2H, J_{AB} = 11.4 Hz), 7.25–7.35 (m, 5H), 7.98 (dd, 1H, J_1 = 0.9 Hz, J_2 = 0.6 Hz). ^{13}C NMR ($CDCl_3$) δ 162.9, 160.2, 136.7, 128.3, 127.9, 127.8, 79.8, 72.1, 66.5, 32.0, 28.0, 19.4, 18.4, 16.8. IR ($CHCl_3$) 1745, 1500, 1470, 1395, 1310, 1220. Anal. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.79, H, 8.39; N, 9.72. Found: C, 70.92 H, 8.29; N, 9.61.

***cis*-3-Benzyloxy-4-*tert*-butyl-1-*neo*-pentylideneamino-2-azetidinone (3n).** Reaction time 5 h. White crystalline solid. Yield: 74%. Mp 57–9 °C (EtOAc/hexane). ^1H NMR ($CDCl_3$) δ 1.06–1.08 (m, 18 H), 4.80 (dd_{AB}, 2 H, J_{AB} = 12.0 Hz), 3.73 (d, 1 H, J = 5.1 Hz), 4.62 (d, 1 H, J = 5.1 Hz), 7.21–7.35 (m, 5 H), 8.40 (s, 1 H). ^{13}C NMR ($CDCl_3$) δ 165.6, 164.5, 137.3, 128.3, 127.7, 127.5, 80.3, 73.0, 69,5, 33.54, 27.1, 26.6. IR (KBr) 1740, 1630, 1370, 1340. Anal. Calcd for $C_{19}H_{28}N_2O_2$: C, 72.12; H, 8.92; N, 8.85. Found: C, 72.19; H, 8.90; N, 8.91.

(3*R*,4*S*)-3-Benzyloxy-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-[((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methylideneamino]-2-azetidinone (7a). Reaction time: 0.5 h. White crystalline solid. Yield: 53%. Mp 99–101 °C (EtOAc) $[\alpha]_D^{22}$ = −31.2 (c = 0.20). ^1H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.38 (s, 3H), 1.41 (s, 3H), 1.43 (s, 3H), 3.67 (dd, 1H, J_1 = 6.3, J_2 = 8.7 Hz), 3.91 (dd, 1H, J_1 = 6.0, J_2 = 8.7 Hz), 4.12–4.21 (m, 3H), 4.32 (dt, 1H, J_1 = 15.3 Hz, J_2 = 6.3 Hz), 4.63 (d, 1H, J = 5.7 Hz), 4.64–4.68 (m, 2H, CH), 4.84 (d, 1H, J = 11.7 Hz), 7.24–7.34 (m, 5H), 7.71 (d, 1H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$) δ 163.9, 150.0, 136.4, 128.6, 128.3, 127.9, 110.4, 109.9, 76.0, 75.2, 73.2, 67.7, 66.9, 64.9, 26.6, 26.4, 25.5, 24.9. IR ($CHCl_3$) 1770, 1710, 1420, 1360. Anal. Calcd for $C_{21}H_{28}O_6N_2$: C, 62.35; H, 6.98; N, 6.93. Found: C, 62.49; H, 7.10; N, 6.81.

(3*R*,4*S*)-3-Benzyloxy-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-(*neo*-pentylideneamino)-2-azetidinone (7b). Reaction time: 30 min (refluxing benzene). White crystalline solid. Yield: 77%. Mp 129–130 °C (EtOAc). $[\alpha]_D^{22}$ = +92.9° (c = 0.27). ^1H NMR ($CDCl_3$) δ 1.11 (s, 9H), 1.32 (s, 3H), 1.45 (s, 3H), 3.69 (dd, 1H, J_1 = 6.3, J_2 = 9.0 Hz), 4.12 (dd, 1H, J_1 = 5.7 Hz, J_2 = 8.7 Hz), 4.21 (dd, 1H, J_1 = 6.3 Hz, J_2 = 9.0 Hz), 4.34 (dt, 1H, J_1 = 8.7 Hz, J_2 = 6.3 Hz), 4.60 (d, 1H, J = 5.7 Hz), 4.84 (dd_{AB}, 2H, J_{AB} = 11.4 Hz), 7.34 (m, 5H), 7.71 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 163.4, 160.2, 136.6, 128.5, 128.1, 127.9, 109.6, 77.5, 76.1, 73.0, 67.0, 64.1, 34.8, 27.1, 26.6, 24.9. IR ($CHCl_3$) 1770, 1710, 1420, 1360, 1260. Anal. Calcd for $C_{20}H_{28}O_4N_2$: C, 66.63; H, 7.83; N, 7.78. Found: C, 66.69; H, 7.88; N, 7.83.

(3*S*,4*R*)-3-Benzyloxy-4-[(*R*)-3-(*tert*-butyloxycarbonyl)-2,2-dimethyl oxazolidin-4-yl]-1-(*neo*pentylideneamino)-2-azetidinone (7c). Reaction time: 2 h (benzene). Colorless oil. Yield: 66%. $[\alpha]_D^{22}$ = −189.2° (c = 0.47). ^1H NMR (DMSO-d_6, 70 °C) δ 1.00 (s, 9H), 1.33 (s, 9H), 1.42 (s, 3H), 1.54 (s, 3H), 3.62 (d, 1H, J = 9.3 Hz), 3.91 (dd, 1H, J_1 = 5.7 Hz, J_2 = 9.3 Hz), 4.14 (dd, 1H, J_1 = 5.4 Hz, J_1 = 9.0 Hz), 4.30 (dd, 1H, J_1 = 5.7 Hz, J_1 = 9.0 Hz), 4.66 (dd_{AB}, 2H, J_{AB} = 11.7 Hz), 4.82 (d, 1H, J = 5.4 Hz), 7.33 (m, 5H), 8.24 (s, 1H). ^{13}C NMR (DMSO-d_6, 70 °C) δ 164.1, 158.1, 151.5, 137.7, 128.6, 128.5, 127.9, 94.0, 79.4, 79.2, 79.0, 72.9, 65.8, 62.1, 55.9, 34.9, 28.3, 27.2, 26.9, 22.7. IR ($CHCl_3$) 1770, 1740, 1680, 1380, 1360. Anal. Calcd for $C_{25}H_{37}O_5N_3$: C, 66.32; H, 8.12; N, 9.15. Found: C, 66.45; H, 8.19; N, 9.21.

General Procedure for the Synthesis of *N*-Imino-2-azetidinones 10. The carbene (1.2 mmol) was placed in a Pyrex test tube which was sealed with a rubber septum, evacuated, and purged with argon three times. Degassed acetonitrile was added to obtain a solution 0.02–0.03 M in the complex. Azine **1a** (1.0 mmol) in 5 mL of degassed acetonitrile was added via syringe. The resulting solution was irradiated (450 W medium-pressure mercury lamp, pyrex well and pyrex filter) until complete reaction. The solvent was removed in vacuo. The brown residue was dissolved in ethyl acetate, filtered through a short path of Celite, diluted with a volume of hexane, and air oxidized under direct sun light (10–12 h were usually required for complete oxidation) or in a light box (9 × 20 W fluorescent tubes). Filtration through Celite of the dark brown precipitate and solvent removal gave a mixture of *cis*- and *trans*- β-lactams, **10**. Analytically pure isomers **10** were isolated by using flash chromatography (hexane-ethyl acetate mixtures).

4-*p*-Anisyl-1-[(4′-methoxybenzylidene)amino]-3-methyl-3-methoxy-2-azetidinone (10a). Reaction time: 24 h. ***cis*-Isomer:** Pale yellow oil. Yield: 22%. ^1H NMR ($CDCl_3$) δ 1.09 (s, 3H), 3.56 (s, 3H), 3.81 (s, 6H), 5.13 (s, 1H), 6.86 (d, 2H), 6.91 (d, 2H), 7.13 (d, 2H), 7.57 (d, 2H), 7.73 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 164.9, 161.5, 159.4, 147.1, 129.2, 127.7, 125.8, 124.9, 114.2, 113.9, 88.9, 68.1, 55.2, 55.1, 53.0, 15.0. IR ($CHCl_3$) 1750, 1610, 1520, 1400. Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.92; H, 6.20; N 7.93. ***trans*-Isomer:** White crystalline solid. Yield: 45%. Mp 134–5 °C (EtOAc/hexane). ^1H NMR ($CDCl_3$) δ 1.67 (s, 3H), 3.14 (s, 3H), 3.79 (s, 6H), 4.90 (s, 1H), 6.83 (d, 2H), 6.89 (d, 2H), 7.25 (d, 2H), 7.53 (d, 2H), 7.70 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 164.1, 161.6, 159.7, 146.8, 129.2, 128.8, 126.0, 124.7, 114.0, 111.3, 85.7, 71.0, 55.3, 55.2, 53.5, 17.9. IR ($CHCl_3$) 1760, 1610, 1520, 1400. Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.52; H, 6.45; N 8.17.

4-*p*-Anisyl-1-[(4′-methoxybenzylidene)amino]-3-benzyloxy-3-methyl-2-azetidinone (10b). Reaction time: 24 h. ***cis*- Isomer:** White crystalline solid. Yield: 20%. Mp 99–101 °C (EtOAc/hexane). ^1H NMR ($CDCl_3$) δ 1.18 (s, 3H), 3.79 (s, 3H), 3.80 (s, 3H), 4.82 (d, J = 11.1 Hz, 2H), 5.17 (s, 1H), 6.85 (d, 2H), 6.90 (d, 2H), 7.10 (d, 2H), 7.20–741 (m, 4H), 7.57 (d, 2H), 7.69 (s, 1H), 7.72–7.80 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 165.3, 161.9, 159.8, 147.5, 137.7, 130.3, 129.5, 128.6, 128.1, 128.0, 126.1, 125.1, 114.5, 114.2, 89.1, 69.3, 68.0, 55.5, 55.4, 15.8. IR (KBr) 1760, 1610, 1520. Anal. Calcd for $C_{26}H_{26}N_2O_4$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.43; H, 6.11; N, 6.58. ***trans*- Isomer:** White crystalline solid. Yield: 25%. Mp 113–4 °C (EtOAc/hexane). ^1H NMR ($CDCl_3$) δ 1.77 (s, 3H), 3.78 (s, 3H), 3.79 (s, 3H), 4.39 (d, J = 10.8 Hz, 2H), 4.99 (s, 1H), 6.83–6.91 (m, 6H), 7.15–7.17 (m, 3H), 7.29 (d, 2H), 7.56 (d, 2H), 7.76 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 165.0, 161.7, 160.4, 159.8, 146.9, 137.3, 129.3, 128.8, 127.9, 127.4, 126.0, 124.9,

114.1, 114.0, 86.0, 71.0, 67.9, 55.3, 19.3. IR (KBr) 1760, 1610, 1520. Anal. Calcd for $C_{26}H_{26}N_2O_4$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.28; H, 6.39; N, 6.16.

Synthesis of 4-*p*-Anisyl-1-[(4'-methoxybenzylidene)-amino]-3,3-diphenyl-2-azetidinone (11). A solution of recently distilled diphenyl ketene (4 mmol) in xylene (10 mL) was added dropwise via syringe to a refluxing solution of *p*-anisaldehyde azine (2 mmol) in xylene (10 mL) under argon. After 6 h the mixture was cooled and the solvent evaporated in vacuo. The crude mixture was dispersed in ether to obtain analytically pure *N*-imino-β-lactam **11**. White crystalline solid. Yield: 60%. Mp 144–6 °C (EtOAc). ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 3 H), 3.81 (s, 3 H), 5.83 (s, 1 H), 6.70 (d, 2 H), 6.84 (d, 2 H), 7.02–7.14 (m, 6 H), 7.26–7.53 (m, 3 H), 7.55 (d, 2 H), 7.66 (d, 2 H), 7.76 (s, 1 H). ^{13}C NMR ($CDCl_3$) δ 165.8, 165.7, 159.6, 147.5, 140.6, 137.0, 129.4, 128.9, 128.7, 128.1, 127.6, 127.0, 126.2, 125.7, 114.2, 114.0, 70.3, 69.8, 55.5, 55.3. IR (KBr) 1760, 1610, 1520, 1400. Anal. Calcd for $C_{30}H_{26}N_2O_3$: C, 77.90; H, 5.67; N, 6.06. Found: C, 77.99; H, 5.70; N, 5.97.

Synthesis of 1,6-Dihydro-3,6-di-*p*-anisyl-5,5-diphenyl-4-pyridazinone (12). The same procedure that for compound **11** but using a 1:1 molar relationship between the azine and diphenyl ketene. The crude mixture was dispersed in CCl_4 to obtain analytically pure compound **12.** White crystalline solid. Yield: 20%. Mp 231–2 °C. ^{1}H NMR ($CDCl_3$) δ 3.70 (s, 3 H), 3.87 (s, 3 H), 6.37 (s, 1 H), 6.68 (d, 2 H), 6.82 (d, 2 H), 6.94–7.05 (m, 6 H), 7.26 (s, 1 H), 7.27–7.34 (m, 4 H), 7.59 (d, 2 H), 8.34 (d, 2 H). ^{13}C NMR ($CDCl_3$) δ 183.4, 162.8, 159.7, 142.2, 139.6, 134.5, 134.1, 130.9, 129.8, 128.5, 127.8, 127.7, 127.5, 127.4, 122.2, 114.4, 113.9, 82.5, 66.6, 55.7, 55.3. IR (KBr) 1750, 1670, 1520, 1610, 1480, 1520. Anal. Calcd for $C_{30}H_{26}N_2O_3$: C, 77.90; H, 5.67; N, 6.06. Found: C, 77.76; H, 5.81; N, 5.87.

Synthesis of 4-(Diphenylacetyl)-2,7-dimethyl-4,5-diaza-2,5-octadiene (14). The same procedure that for compound **11** but using a 1:1 molar relationship between the azine and diphenyl ketene, and benzene as solvent. The crude product was purified by flash chromatography (silica gel, hexane/EtOAc mixtures). Reaction time: 3.5 h. Orange oil. Yield: 51%. ^{1}H NMR ($CDCl_3$) δ 1.05 (d, J = 6.8 Hz, 6H), 1.38 (d, J = 0.9 Hz, 3H), 1.83 (d, J = 1.2 Hz, 3H), 2.48 (m, 1H), 5.57 (s(b) 1H), 6.26 (s, 1H) 6.98 (d, J = 4.5 Hz, 1H) 7.18–7.29 (m, 6H), 7.34–7.38 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 173.0, 149.9, 140.2, 140.1, 129.4, 128.4, 126.7, 117.1, 53.6, 31.7, 22.1, 20.0, 18.3. IR ($CHCl_3$) 1660, 1630, 1600, 1500, 1450, 1400. Anal. Calcd for $C_{22}H_{26}N_2O$: C, 79.01; H, 7.84; N, 8.38. Found: C, 78.90; H, 7.77; N, 8.11.

General Procedure for the Synthesis of β-Hydrazono Esters 22. A catalytic amount of NaOH was added to a solution of azetidinone **3** (1 mmol), in the corresponding alcohol (5 mL). The resulting solution was stirred until total disappearance of starting material (tlc). The mixture was concentrated *in vacuo* and 5mL of water were added. Extraction with $CHCl_3$ (2 × 10 mL), drying of the organic layers ($MgSO_4$), and evaporation of the solvent gave the product **22**. These products decompose after a few hours at room temperature, and also when distilled or chromatographied. Spectroscopic and analytical data for some representative forms of **22** follow:[41]

Methyl 2,3-*anti*-3,6-Di-(*p*-anisyl)-4,5-diaza-2-methoxy-5-hexenoate (22a). Colorless oil. Yield 95%. ^{1}H NMR ($CDCl_3$) δ 3.41 (s, 3H), 3.67 (s, 3H), 3.78 (s, 6H), 4.06 (d, 1H, J = 4.2 Hz), 4.82 (d, 1H, J = 4.2 Hz), 6.81 (d, 2H), 6.86 (d, 2H), 7.31 (d, 2H), 7.40 (d, 2H), 7.60 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 171.2, 159.7, 158.9, 140.2, 131.0, 128.6, 128.2, 127.4, 113.8, 113.7, 83.1, 63.9 , 59.1, 55.1, 55.0, 52.0. IR ($CHCl_3$) 3480, 3360, 1740, 1610, 1510, 1460, 1440, 1305, 1250.

Methyl 2,3-*anti*-4,5-Diaza-2-benzyloxy-3,6-diisopropyl-5-hexenoate (22f). Colorless oil. Yield 95%. ^{1}H NMR ($CDCl_3$) δ 0.95 (d, 3H, J = 7.0 Hz), 0.97 (d, 3H, J = 7.0 Hz, 0.98 (d, 6H, J = 7.0 Hz), 1.90 (m, 1H, J = 7.0 Hz), 2.35 (m, 1H), 3.49 (t, 1H, J = 4.3 Hz), 3.75 (s, 3H), 4.14 (d, 1H, J = 4.3 Hz), 4.54 (dd_{AB}, 2H, J_{AB} = 11.7 Hz), 6.72 (d, 1H, J = 5.5 Hz), 7.33 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 172.7, 149.1, 137.7, 128.3, 127.7, 127.8, 78.9, 72.9, 65.3, 51.7, 31.1, 28.4, 20.8, 20.3, 20.1, 18.3. IR ($CHCl_3$) 3350, 1750, 1460, 1390, 1260.

Methyl 2,3-*syn*-4,5-Diaza-2-benzyloxy-3,6-diisopropyl-5-hexenoate (22g). Colorless oil. Yield 90%. ^{1}H NMR ($CDCl_3$) δ 0.83 (d, 3H, J = 6.5 Hz), 1.00 (d, 3H, J = 6.5 Hz), 1.01 (d, 6H, J = 6.5 Hz), 1.82 (m, 1H, J = 6.5 Hz), 2.35 (m, 1H), 3.45 (t, J = 8.7 Hz), 3.74 (s, 3H), 4.07 (s, 1H), 4.61 (dd_{AB}, 2H, J_{AB} = 11.3 Hz), 5.29 (d, 1H, J = 8.7 Hz), 6.82 (d, 1H, J = 6.6 Hz), 7.34 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 172.4, 147.8, 137.4, 128.3, 128.2, 127.8, 76.8, 72.4, 65.6, 51.6, 31.1, 29.8, 20.1, 20.1, 20.0, 19.8. IR ($CHCl_3$) 3460, 3290, 1755, 1480, 1430, 1390, 1370, 1350.

General Procedure for the Ozonolysis of *N*-Imino-azetidinones, 3 and 7: Synthesis of *NH*-β-Lactams 8. A stream of ozone was bubbled through a solution of compounds **3** or **7** in CH_2Cl_2 or methanol (10 mL) at −78 °C. After completion of the reaction (tlc), the excess of ozone was removed by bubbling argon through the mixture for 10 min. The resulting solution was then poured over a suspension of activated Zn (1g),[35] (Compounds **8a–b**) in ether, or Zn (1g) (Compounds **8c–d**) in CH_2Cl_2 or methanol, at 0 °C. After stirring for 12 h, the mixture was filtered, neutralized with saturated $NaHCO_3$ solution, and dried ($MgSO_4$). Evaporation of the solvents gave crude products **8** which were purified by flash chromatography (silica gel, hexane/EtOAc mixtures). Spectroscopic and analytical data for some representative forms of **8** follow.[41]

(3*R*,4*S*)-3-Benzyloxy-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-azetidinone (8c). From 7a: Reaction time: 1 h. Colorless oil. Yield: 35%. $[\alpha]_D^{22}$ = +55.2° (c = 0.52). ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.40 (s, 3H), 3.61 (dd, 1H, J_1 = 5.7 Hz, J_2 = 8.7 Hz), 3.67 (dd, 1H, J_1 = 5.7 Hz, J_2 = 8.7 Hz), 4.09 (t, 1H, J = 6.3 Hz), 4.14–4.32 (m, 1H), 4.62 (d, 1H, J = 12.0 Hz), 4.64 (m, 1H), 4.89 (d, 1H, J = 12.0 Hz), 6.24 (s(b), 1H), 7.30–7.34 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 158.4, 136.7, 128.8, 128.4, 128.1, 127.3, 109.4, 81.5, 81.3, 72.8, 66.5, 56.8, 26.7, 25.0. IR ($CHCl_3$) 3260, 1770, 1455, 1380, 1360. Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.95; H, 6.91; N, 5.05. Found: C, 64.89; H, 6.88; N, 5.10. **From 7b:** Reaction time: 1h. Colorless oil. Yield: 30%. $[\alpha]_D^{22}$ = +54.6° (c = 0.45).

(3*S*,4*R*)-3-Benzyloxy-4-[(*R*)-3-(*tert*-butyloxycarbonyl)-2,2-dimethyloxazolidin-4-yl]-2-azetidinone (8d). From 7c: Reaction time: 1h. Colorless oil. Yield: 45%. $[\alpha]_D^{22}$ = −50.38° (c = 0.26).^{1}H NMR (DMSO-d_6, 60 °C) δ 1.41 (s, 9H), 1.44 (s, 3H), 1.49 (s, 3H), 3.60–3.68 (m, 2H), 3.91 (dd, 1H, J_1 = 5.5 Hz, J_2 = 9.3 Hz), 4.13 (dd, 1H, J_1 = 5.5 Hz, J_2 = 9.3 Hz), 4.62 (d, 1H, J = 11.7 Hz), 4.74 (d, 1H, J = 6.0 Hz), 4.75 (d, 1H, J = 11.7 Hz), 7.32–7.37 (m, 5H), 7.93 (s(b), 1H). ^{13}C NMR (DMSO-d_6) δ 167.4, 151.5, 137.6, 129.3, 127.6, 127.4, 93.2, 82.5, 79.2, 72.3, 68.7, 56.0, 38.6, 38.3, 38.0, 28.0. IR ($CHCl_3$) 3400, 1760, 1680, 1520, 1390. Anal. Calcd for $C_{20}H_{28}N_2O_5$: C, 63.80; H, 7.50; N, 7.44. Found: C, 63.69; H, 7.58; N, 7.40.

Acknowledgment. The authors are grateful to the DGICYT (MEC-Spain, Grant PB90-0047) and the CAM (Madrid-Spain, Grant 290/92) for financial support. Predoctoral and undergraduate research grants from the UCM (J.P.-C.) and the MEC (C.P.) are gratefully acknowledged. We warmly thank Prof. A. Miller (University of Connecticut) for a careful editing of the manuscript.

Supplementary Material Available: Full experimental procedure for the synthesis of compounds **3, 5, 6, 8, 16, 17, 18, 22,** and **23** including IR, ^{1}H NMR, ^{13}C NMR, and analytical data (12 pages). This material is contained in 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.