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γ-Heteroatom directed stereocontrolled Staudinger cycloaddition reaction of vinylketenes and imines

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Abstract—Vinylketenes possessing a γ-heteroatom, on Staudinger cycloaddition reaction with imines gave *trans*-3-vinyl-β-lactams in very good yields. The vinyl side chain stereoselectively adopts the *Z*-configuration in the transition state to stabilize the vinylketene and produces, exclusively, *trans*-3-vinyl-β-lactams.

The β-lactam skeleton is recognized as a key structural unit of the most widely employed class of β-lactam antibiotics.[1] The constant need for new drugs displaying broader antibacterial activity and the necessity for new β-lactam antibiotics to combat microorganisms that have built up resistance against traditional drugs,[2] have maintained the interest of organic chemists for decades. As a consequence, a large number of methods are available for their syntheses and the topic has been extensively reviewed.[3] The most convenient procedure for the synthesis of the β-lactam ring skeleton is the [2+2] cyclocondensation of ketenes with imines, a procedure commonly known as the Staudinger reaction.[4] In particular, this method has provided useful and economic entries to β-lactams, mainly due to the ready availability of both Schiff's bases and ketenes. In this context, in spite of the high level of achievement reached in the Staudinger reaction, the subject still continues to be an active area of research,[5] both from synthetic and mechanistic points of view. We have been using the Staudinger cycloaddition reaction[6] for the diastereoselective synthesis of β-lactams and studied their synthetic utility[7] for the synthesis of various biologically active compounds for several years. In this letter, we report our work on the synthesis of *trans*-3-vinyl-β-lactams employing the cycloaddition reaction of vinylketenes with imines.

3-Vinyl-β-lactams are important intermediates in the synthesis of biomedicinally interesting compounds such as carbapenem,[8] asparenomycin[9] and thienamycin.[10] These β-lactams are prepared by cycloaddition of vinylketenes with imines. In most of the cases, the vinyl ketenes are generated from either crotonoyl chloride or β,β-dimethylacryloyl chloride.[11,12] Although normal ketenes are extensively used in ketene–imine cycloaddition reactions, vinylketenes, also referred to as Sheehan's ketenes,[11] have not been fully explored. This may be due to lower yields and variable diastereoselectivities of the β-lactam formation.[13] In general, the stereochemical outcome of the reaction depends upon the substituents present on the imine. Imines prepared from aromatic aldehydes and arylamines give *trans*-β-lactams, while imines with alkyl or electron-withdrawing substituents give either cis or a mixture of cis and trans products.[14]

Bose et al. have shown that ketenes generated from an acid chloride with a heteroatom, such as oxygen or nitrogen at the α-position, in general, give moderate to good yields of β-lactams with a preference for the cis product.[15] We envisaged that vinylketenes with a heteroatom at the γ-position would also have some influence on the diastereoselectivity in the [2+2] cycloaddition reactions with imines. With this idea in mind we prepared 4-phenoxybut-2-enoyl chloride (**4a**), a precursor for phenoxyvinyl ketene, from methyl-4-bromo-2-butenoate **1** (Scheme 1).

Initially imine **5a** was reacted with the ketene, generated from 4-phenoxybut-2-enoyl chloride (**4a**) and

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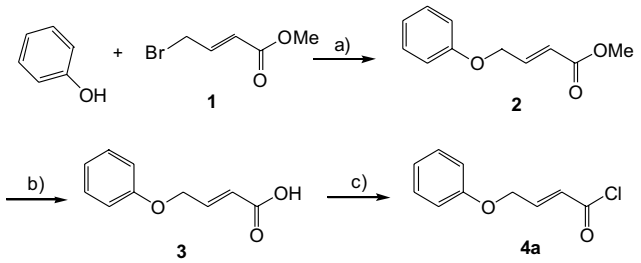


Scheme 1. Reagents and conditions: (a) K_2CO_3, PTCs, acetone, reflux, 2 h; (b) 1 M NaOH, THF, rt, 15 h; (c) $(COCl)_2$, DCM, reflux 4 h.

triethylamine, at −40 °C for 30 min and then further stirred at room temperature for 15 h. A small amount of *trans*-vinyl-β-lactam **6a** (10%) was isolated from the reaction mixture. The structure of **6a** was established by IR and ^{1}H NMR spectroscopy. The IR spectrum showed an absorption at 1756 cm^{-1} for the β-lactam carbonyl group. The ^{1}H NMR spectrum revealed the trans stereochemistry for the β-lactam ring ($J = 2.5$ Hz for the ring protons) and a *Z* geometry at the C3 vinyl side chain ($J = 6.0$ Hz for the *Z*-protons of the double bond). The structure was further confirmed by single crystal X-ray analysis (Fig. 1).[16]

An excellent yield of **6a** along with a small amount of the *E*-isomer **7a** ($J = 2.5$ Hz for the ring protons and $J = 12.0$ Hz for the *E*-protons of the double bond) was obtained ($Z/E = 9/1$) when a solution of acid chloride **4a** in dichloromethane was added to a solution of imine **5a** and triethylamine at 0 °C and then refluxed for 15 h. Both the isomers (**6a** and **7a**) were separated by flash column chromatography.[17] The ^{1}H NMR spectrum of the crude product revealed the formation of only the *trans*-β-lactam and no trace of the *cis*-β-lactam was detected (Scheme 2).

Several vinyl-β-lactams were prepared in very good yields from 4-phenoxybut-2-enoyl chloride (**4a**) and

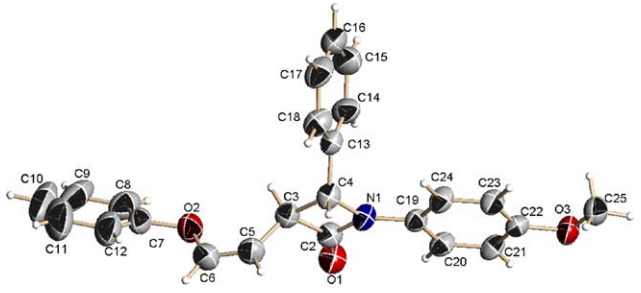
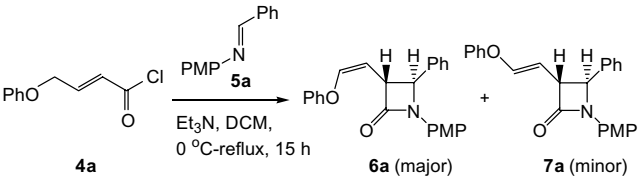


Figure 1. ORTEP diagram of **6a**.



Scheme 2.

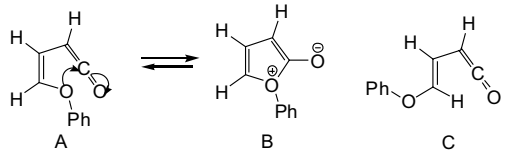


Figure 2. Confirmations of the phenoxyvinyl ketene.

imines **5a**–**g** with various substituents. In all the cases, irrespective of the substituents on the imine, only *trans*-β-lactam formation was observed.

We believe that the phenoxyvinyl side chain stereoselectively adopts the *Z*-configuration to stabilize the ketene via participation of the oxygen lone pair of electrons (Fig. 2). In the cycloaddition reaction, the stereochemical outcome can depend upon the configuration of the imine.[18] The *Z*-imine can react with the ketene in an *exo*-mode to give the zwitterionic transition state TS-1. Similarly, the *E*-imine can react only in an *endo*-mode to give TS-2 (Fig. 3).

TS-1 on conrotatory ring closure would provide a *trans*-β-lactam, while TS-2 should give a *cis*-β-lactam. Although, the *E*-imine is more stable compared to the corresponding *Z*-imine, it is less reactive due to severe steric interaction between the phenoxy group and the aryl group of the imine in the transition state TS-2. This steric interaction is absent in TS-1, which arises from the *exo* attack of the *Z*-imine to the vinylketene. Therefore, TS-1 is preferentially formed, which on conrotatory ring closure gives *trans*-β-lactams. The rate of the reaction depends upon the rate of equilibrium of the *E* and *Z*-imines.

The formation of the *trans*-β-lactams can also be explained by the isomerization of TS-2 to the more favorable TS-1 followed by conrotatory ring closure. However, this seems to be less likely as this would provide, in some cases, depending upon the nature of the substituents present on the imine,[19] a mixture of *cis* and *trans*-β-lactams. In fact, irrespective of the substituents on the imine, only *trans*-3-vinyl-β-lactam formation was observed in the cycloaddition reaction (Table 1).

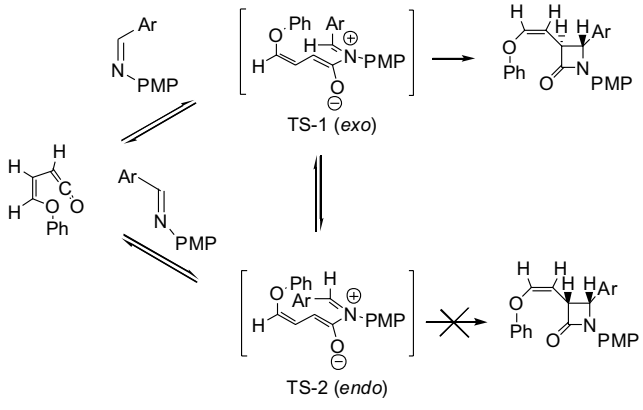
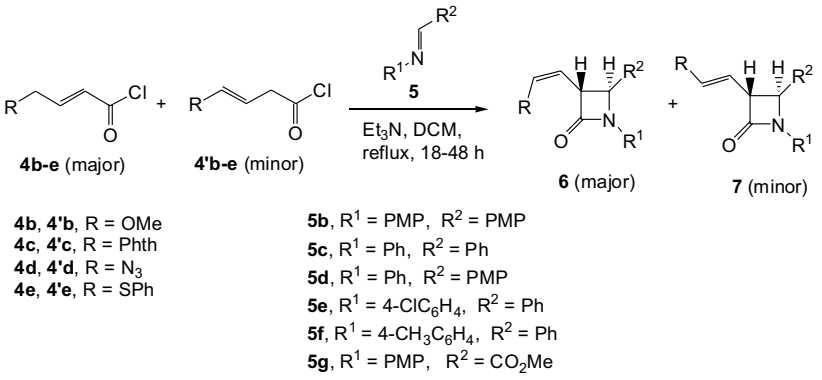


Figure 3. Plausible mechanism for the formation of a *trans*-β-lactam.

Table 1. Synthesis of *trans*-3-vinyl-β-lactams **6a–k** and **7a–k**

β-Lactams **6** and **7**	R	R^1	R^2	Ratio of **6**:**7**[b]	Yield[c] (%)	Mp of **6** (°C)	Mp of **7** (°C)
a	OPh	PMP[a]	Ph	90:10	80	128–129	Thick oil
b	OPh	PMP	PMP	92:8	77	125–126	Thick oil
c	OPh	Ph	Ph	91:9	75	131–132	Thick oil
d	OPh	Ph	PMP	93:7	73	139–140	Thick oil
e	OPh	4-ClC_6H_4	Ph	89:11	78	112–113	Oil
f	OPh	4-$CH_3C_6H_4$	Ph	90:10	83	122–123	Oil
g	OPh	PMP	CO_2Me	100:0	70	Oil	—
h	OMe	Ph	Ph	92:8	75	88–89	Oil
i	OMe	PMP	Ph	90:10	85	95–96	Oil
j	Phth[a]	Ph	Ph	85:15	61	109–110	Oil
k	N_3	Ph	Ph	80:20	66	Oil	Oil

[a] Phth = phthalimido, PMP = 4-$MeOC_6H_4$.
[b] The ratio of the diastereomers **6** and **7**, from ^1H NMR.
[c] Isolated yields of the diastereomeric mixture of **6** and **7**.



Scheme 3.

Similar results were obtained with ketenes having γ-methoxy, azido and phthalimido groups (Scheme 3, Table 1). In all the cases, irrespective of the substituents on the imine, only *trans* 3-vinyl-β-lactams with *Z*-stereochemistry at the vinyl side chain were formed. A small amount of the *E*-isomer possibly arose from thermal isomerization of the *Z*-vinyl side chain.

Also, the ketenes generated from **4c** and **4d** (R = Phth, N_3) gave *trans*-β-lactams **6j–k** and **7j–k**. However, the reaction was slow and gave lower yields of the vinylazetidin-2-one. The thiophenoxyketene generated from **4e** did not undergo the cycloaddition reaction with imine **5a**.

In conclusion, we have shown that the γ-heteroatom on a vinylketene directs imine approach in the Staudinger cycloaddition reaction. Irrespective of the substituents on the imine, only *trans*-3-vinyl-β-lactam formation was observed. Further work on the applications of *trans*-3-vinyl-β-lactams as building blocks in organic synthesis is in progress.

Acknowledgments

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15. Bose, A. K.; Chiang, Y. H.; Manhas, M. S. *Tetrahedron Lett.* **1972**, *13*, 4091–4094.
16. *X-ray data for* **6a**: X-ray structure determination of $C_{24}H_{21}NO_3$: Colorless needles $0.39 \times 0.05 \times 0.02$ mm grown from methanol. $M = 371.42$, Monoclinic, $P2_1/n$, $a = 11.3472(2)$ Å, $b = 5.9741(8)$ Å, $c = 29.163(4)$ Å, $\beta = 91.397\ (2)°$, $V = 1976.3(5)$ Å^3, $Z = 4$, $D = 1.248$ mg/cm^{-3}, $\mu = 0.082$ mm^{-1}, $F(000) = 784$, $T = 293$ K. Data were collected on a SMART APEX CCD Single Crystal X-ray diffractometer using Mo-Kα radiation ($\lambda = 0.7107$ Å) to a maximum θ range of 25.00°. The structure was solved by direct methods using SHELXTL. Least squares refinement of scale, positional and anisotropic thermal parameters for non hydrogen atoms converged to $R = 0.0654$. $R_w = 0.1112$ for 3476 unique observed reflections. Hydrogen atoms were geometrically fixed. The refinements were carried out using SHELXTL-97. Largest diff. peak and hole 0.148 and -0.113e·Å^{-3}. Crystallographic data (excluding structure factors) for the structure **6a** in this letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 606327.
17. *A typical procedure for the synthesis of trans-3-vinyl-β-lactams* **6a** and **7a**: A solution of 4-phenoxybut-2-enoyl chloride (**4a**) (0.280 g, 1.42 mmol) in dry dichloromethane (20 mL) was added slowly to a mixture of imine **5a** (0.200 g, 0.94 mmol) and triethylamine (0.430 g, 4.26 mmol) in dry dichloromethane (20 mL) at 0 °C. After addition was complete, the reaction mixture was refluxed with stirring for 15 h. The reaction mixture was washed with water (2×10 mL), saturated sodium bicarbonate solution (10 mL) and saturated brine solution (10 mL). The organic layer was then dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to give a thick brown oil (0.280 g, 80%). ^{1}H NMR of the crude product showed it to be a mixture of *trans*-β-lactams **6a** and **7a** (*Z* and *E* isomers 90:10), which were separated by flash column chromatography (petroleum ether-ethyl acetate 8:2).

trans-1-(4-Methoxyphenyl)-3-(Z-2-phenoxyvinyl)-4-phenylazetidin-2-one (**6a**): White needles (MeOH), 0.238 g, 68%; mp 128–129 °C; IR ($CHCl_3$): 3018, 1741, 1664, 1595, 1512, 1245, 1217 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.75 (3H, s, Ph-OC*H*$_3$), 4.13–4.19 (1H, m, C3*H*), 4.87 (1H, d, $J = 2.5$ Hz, C4*H*), 5.10 (1H, dd, $J = 6.0$ Hz, $J = 8.0$ Hz, C*H*=CHOPh), 6.67 (1H, dd, $J = 6.0$ Hz, $J = 1.3$ Hz, CH=C*H*OPh), 6.77–7.38 (14H, m, Ar–*H*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 55.4, 55.6, 62.3, 103.9, 114.3, 116.5, 118.3, 123.2, 126.0, 128.4, 128.9, 129.6, 131.4, 137.8, 144.3, 155.9, 156.8, 165.6; MS (*m*/*z*): 372 (M+1); Anal. Calcd for $C_{24}H_{21}NO_3$: C, 77.60; H, 5.69; N, 3.77. Found: C, 77.54; H, 5.62; N, 3.70%.

trans-1-(4-Methoxyphenyl)-3-(E-2-phenoxyvinyl)-4-phenylazetidin-2-one (**7a**): Thick oil, 0.042 g, 12%; IR ($CHCl_3$): 3016, 2360, 1743, 1658, 1512, 1240 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.75 (3H, s, Ph-OC*H*$_3$), 3.68–3.80 (1H, m, C3*H*), 4.72 (1H, d, $J = 2.5$ Hz, C4*H*), 5.53 (1H, dd, $J = 9.3$ Hz, $J = 12.0$ Hz, C*H*=CHOPh), 6.71–7.38 (15H, m, Ar–*H* and CH=C*H*OPh); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.5, 59.4, 62.7, 104.8, 114.4, 117.1, 118.5, 123.4, 125.9, 128.6, 129.2, 129.7, 137.5, 146.4, 156.2, 156.7, 163.1; MS (*m*/*z*): 372 (M+1); Anal. Calcd for $C_{24}H_{21}NO_3$: C, 77.60; H, 5.69; N, 3.77. Found: C, 77.51; H, 5.60; N, 3.69%.
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