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Experimental and theoretical investigation of benzyl-*N*-pyrrolylketene, one- step procedure for preparing of new β-lactams by [2+2] cycloaddition reaction

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Abstract. 3-Phenyl-2-(1-*H*-pyrrol-1-yl) propanoic acid has been used as a ketene source in synthesizing of monocyclic-2-azetidinones. Hindrance in ketene and imines successfully controlled the diastereoselectivity of the reaction. For example, in some cases only one isomer was achieved. By using Mukaiyama reagent, the leaving group in acid was activated and the by-products were separated by simple aqueous work-up. DFT calculation indicated that the benzyl-*N*-pyrrolylketene has nonconjugated structure and the pyrrolyl ring is perpendicular to the ketene plane in both the twisted and planar structures.

Keywords. β-Lactam; [2+2] Cycloaddition; Benzyl-*N*-pyrrolylketene; NMR; NOE; Diasteroselectivity.

1. Introduction

2-Azetidinones, commonly known as β-lactams, are found to be associated with various antibacterial drugs and medicinal activities. Ezetimibe (a cholesterol absorbing inhibitor),[1] Taxol and taxorate (antitumor drugs),[2] monobactams such as aztreonam and carumonam[3] (figure 1) and norcardicins[1] (displaying antibacterial activities) have β-lactam skeleton in their structures.

Besides the utility of β-lactams as biologically active agents, they are used as intermediates in the synthesis of organic compounds having functionalized group, for example, α- and β-amino acid synthesis[4] and in particular, natural products (alkaloids and medicines),[5] aminosugars,[6] different peptidomimetics[7] and chiral catalysts.[8] The general procedure for the synthesis of amino acids is known as the β-lactam synthon method.[9] Consequently, the biological activities of β-lactam elements depend on the stereo structure of them.[10] Thus, it is more important to synthesize such derivatives with special stereostructures.[11]

One of the most powerful methods for the preparation of these compounds is the [2+2] cycloaddition reaction of ketenes to imines (the Staudinger reaction). This reaction usually generates two new stereocenters (C_3 and C_4 in the β-lactam ring). So the product might be *cis*-, *trans*-, or a mixture of *cis*- and *trans*-β-lactam derivatives.

Both experimental and theoretical investigations explain the relative stereoisomers. The reaction conditions such as temperature,[12] solvent,[13] and base,[14] may affect the stereo chemical outcomes. In the Staudinger reaction, ketenes are generated *in situ* and the reaction is stepwise. The mechanism is involving the nucleophilic attack of an imine to a ketene that generates a zwitterionic intermediate and subsequently closure of the ring occurs and therefore β-lactam has been produced. If cyclization step is faster than zwitterion production, the final product is *cis*. Otherwise the *trans* isomer would be the outcome of the reaction when formation of intermediate is faster.[15] The relative (*cis/trans*) stereoselectivity is a result of the competition between the direct ring closure and the imine moiety in the zwitterionic intermediate.[12a] The polar solvent is suitable for trans−β-lactam formation because this condition affects the stability and half-time of the zwitterionic intermediate.[13]

The investigations on 2-azetidinones revealed that the electron-donating ketene substituents, electron-withdrawing and more bulky imines are convenient for *cis*-β-lactam formation. Imines with less steric hindrance give *trans* stereoisomer.[12a,16]

On the basis of the first previous report with pyrrolylketene in Tidwell laboratories by Islami *et al.*,[17] we now wish to report the synthesis of β-lactam by using benzyl-*N*-pyrrolylketene. On the

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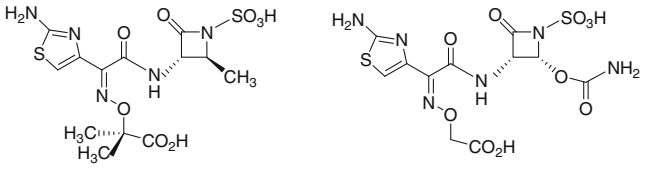


Figure 1. Clinically used monobactams.

other hand, computation by B3LYP/6-31G+D) showed that benzyl-*N*-pyrrolylketene has twisted structure such that pyrrolyl plane is perpendicular to the ketene and as a result, there is no interaction between the ketenyl group and the pyrrolyl π-system and this structure is more stable for benzyl-*N*-pyrrolylketene.

2. Experimental

2.1 *Chemical reagents*

All required chemicals were purchased from Merck and Fluka chemical companies. All the known compounds were identified by comparison of their spectral data and physical properties with those of the authentic samples. ^{1}H NMR and ^{13}C NMR spectra were recorded on a BRUKER DRX-300 AVANCE NMR spectrometer using $CDCl_3$ as a solvent and using tetramethylsilane (TMS) as an internal standard. Chemical shifts were reported in parts per million (δ) downfield from TMS. All of the coupling constants (J) are in hertz. IR spectra were recorded on Bruker Tensor-27 FTIR spectrometer using KBr pellets. Melting points were recorded on an Electrothermal-9100 melting point apparatus and were uncorrected. Mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were run on a Perkin-Elmer USA-2400 series. Column chromatography was performed on silica gel 40 (Merck, 70-230 mesh).Thin-layer chromatography plate was carried out on silica gel 60 Gf-254 analytical sheets. UV light (λ =254) was used.

2.2 *Preparation benzyl-N-pyrrolylacetic acid* ***(2)***

A mixture of S(-)-phenyl alanine **1** (4.48 g, 27.2 mmol,), sodium acetate anhydrous (2 g, 27.2 mmol) and 300 mL glacial acetic acid was stirred under reflux for 1 h. Then, 2,5-dimethoxy tetrahydrofuran 10 mL was added dropwise for 30 min. The mixture was stirred for 1 h. Then the additional acetic acid was distillated (250 mL). The resultant solution was extracted with 5x50 mL ethyl acetate. Afterwards, the solution was washed with water (5x50 mL) and the organic layer was dried over MgSO4. The organic layer phase was concentrated and the oil was collected that crystalized with n-heptane and a white solid was obtained. M.p.: 94-98°C. IR (KBr) cm^{-1}: 1715.70 (CO).^{1}H NMR δ 3.20-3.50 (CH_2, qq, 2H), 4.73-4.83 (CH, dd, 1H), 6.13 (H-pyrrolyl, t, 2H, J=2.26), 6.73 (H-pyrrol, t, 2H, J=2.29), 7.03-7.28 (Ar-H, m, 5H).

2.3 *Synthesis of Schiff basses* ***(5)***

Imines from aldehydes, corresponding amines and $CaCl_2$ as a Lewis acid were prepared in dry toluene for 7 h.[22]

2.4 *General procedure for the synthesis of 2-azetidinones* ***6(a-j)***

3-phenyl-2-(1-*H*-pyrrol-1-yl) propanoic acid **2** (0.22 g, 1.0 mmol) was mixed with 2-chloro-N-methylpyridinium iodide **4** (0.30 g, 1.2 mmol) and dry Et_3N (5.0 mL, 3.6 mmol) in anhydrous CH_2Cl_2 (15 mL) under an argon atmosphere at room temperature. The suspension was stirred for 5 min and then a solution of imines (1.1 mmol) in dry CH_2Cl_2 (5 mL) was added, and the reaction mixture was stirred overnight. The red solution was washed with 8% aq. HCl and then with water. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure to give the crude products. β-Lactams were purified first, by column chromatography for separation of *cis/trans* mixture from other by-products and then plate chromatography gave *cis*- and *trans*-isomer which were identified with experimental analysis. Column chromatography **6a-b** (hexane/EtOAc 30:1 v/v), **6c** (hexan/EtOAc 19:1 v/v), **6d-e** (hexane/EtOAc 35:1 v/v),**6f-g** (hexane/EtOAc 38:1 v/v) and **6h-i** (hexane/EtOAc 42:1v/v), **6h** (hexane/EtOAc 15:1 v/v).

2.4a *(3R,4R)-3-benzyl-1,4-diphenyl-3-(1H-pyrrol-1-yl) azetidin-2-one (**6a**-trans)*: White yellow solid; Yield: (15.87%); M.p.: 54-57°C; IR (KBr, cm^{-1}): 1731 (C=O, β-lactam). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.81-3.13 (dd, 2H, CH_2), 5.42 (s, 1H, H-4), 6.19 (t, 2H, J = 2.12 Hz, H-pyrrolyl), 6.53 (d, 2H, Ar-H), 6.90 (t, 2H, J = 2.12 Hz, H-pyrrol), 7.05-7.57 (m, 13H, Ar-H,). ^{13}C-NMR (400 MHz, $CDCl_3$): δ 39.8 (CH_2), 67.8 (C-4 β-lactam), 76.1 (C-3 β-lactam), 108.9, 117.7, 119.1, 124.6, 126.8, 127.4, 127.7, 128.8, 129.1, 129.3, 129.7, 133.2, 133.6, 136.8 (aromatic carbons), 163.2 (C=O, β-lactam); MS: m/z 378 (100) (M^+), 311 (7.69) (M^+-[Ph]), 258 (35.89), 197 (92.30), 181 (79.48) ([PhCH=NPh]$^+$), 167 (79.48), 91 (46.15) ([PhCH$_2$]$^+$), 77 (41.02) ([Ph]$^+$). Anal.Calcd. for $C_{26}H_{22}N_2O$: C,

82.51; H, 5.86; N 7.40%; Found: C, 82.36; H, 5.77; N, 6.98%.

2.4b *(3R,4S)-3-benzyl-1,4-diphenyl-3-(1H-pyrrol-1-yl) azetidin-2-one (**6b-**cis)*: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.41-3.62 (dd, 2H, CH_2), 5.07 (s, 1H, H-4), 5.73 (t, 2H, $J = 1.50$ Hz, H-pyrrolyl), 6.43 (t, 2H, $J = 1.50$ Hz, H-pyrrol), 6.99-7.17 (m, 15H, Ar-H). ^{13}C-NMR (400 MHz, $CDCl_3$): δ 42.9 (CH_2), 65.5 (C-4 β-lactam), 76.7 (C-3 β-lactam), 103.3, 117.3, 119.2, 124.6, 126.8, 127.4, 128.4, 128.5, 128.8, 129.0, 130.2, 133.2, 134.0, 135.5 (aromatic carbons), 163.2 (C=O, β-lactam); MS: m/z 378 (100) (M^+), 311 (7.69) (M^+-[Ph]), 258 (35.89), 197 (92.30), 181 (79.48) ([PhCH=NPh]$^+$), 167 (79.48), 91 (46.15) ([$PhCH_2$]$^+$), 77 (41.02) ([Ph]$^+$). Anal.Calcd. for $C_{26}H_{22}N_2O$: C, 82.51; H, 5.86; N 7.40%; Found: C, 82.36; H, 5.77; N, 6.98%.

2.4c *(3R,4S)-3-benzyl-1-(4-methoxyphenyl)-4-phenyl-3-(1H-pyrrol-1-yl)azetidin-2-one (**6c-**cis)*: White solid; Yield: (41.66%); M.p.: 132-133°C; IR (KBr, cm^{-1}): 1739 (C=O, β-lactam); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.49-3.73 (dd, 2H, CH_2), 3.73 (s, 3H, OMe), 5.11 (s, 1H, H-4), 5.88 (t, 2H, $J = 2.17$ Hz, H-pyrrolyl), 6.53 (t, 2H, $J = 2.16$ Hz, H-pyrrol), 6.72-7.28 (m, 14H, Ar-H); ^{13}C-NMR (400 MHz, $CDCl_3$): δ 42.9 (CH_2), 55.0 (OMe), 65.5 (C-4 β-lactam), 76.5 (C-3 β-lactam), 108.2, 114.2, 119.0, 119.2, 126.8, 127.4, 128.3, 128.4, 128.7, 129.9, 130.2, 133.4, 134.1, 156.2 (aromatic carbons), 164.0 (C=O, β-lactam); MS: m/z 408 (78.05) (M^+), 317 (9.76) (M^+-[$PhCH_2$]), 258 (17.07), 211 (100) ([PhCH=NPhOMe]$^+$), 196 (56.09) (M^+-[PhCH=NPhOMe]), 167 (34.15), 91 (36.58) ([$PhCH_2$]$^+$). Anal.Calcd. for $C_{27}H_{24}N_2O_2$: C, 79.39; H, 5.92; N 6.86%; Found: C, 78.96; H, 5.85; N, 6.71%.

2.4d *(3R,4R)-3-benzyl-1-(4-chlorophenyl)-4-phenyl-3-(1H-pyrrol-1-yl)azetidin-2-one (**6d-**trans)*: White solid; Yield (14.56%); M.p.: 164-165°C; IR (KBr, cm^{-1}): 1756 (C=O, β-lactam); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.79-3.10 (dd, 2H, CH_2), 5.40 (s, 1H, H-4), 6.20 (t, 2H, $J = 2.16$ Hz, H-pyrrolyl), 6.50 (d, 2H, Ar-H), 6.88 (t, 2H, $J = 2.17$ Hz, H-pyrrol), 7.04-7.58 (m, 14H, Ar-H); ^{13}C-NMR (400 MHz, $CDCl_3$): δ 39.8 (CH_2), 67.9 (C-4 β-lactam), 76.4 (C-3 β-lactam), 109.0, 119.0, 119.1, 126.8, 127.4, 127.7, 128.8, 129.2, 129.4, 130.9, 132.4, 132.8, 133.4, 135.3 (aromatic carbons), 167.7 (C=O, β-lactam); MS: m/z 414 (7.93) (M+2^{37}Cl), 412 (23.80) (M^{+35}Cl), 215 (35.71) ([PhCH=NPhCl]$^+$), 197 (50.00) (M^+-[PhCH=NPhCl]), 167 (92.85), 149 (100), 91 (26.19) ([$PhCH_2$]$^+$). Anal.Calcd. for $C_{26}H_{21}N_2OCl$: C, 75.63; H, 5.13; N, 6.78%; Found: C, 75.97; H, 5.33; N, 6.60%.

2.4e *(3R,4S)-3-benzyl-1-(4-chlorophenyl)-4-phenyl-3-(1H-pyrrol-1-yl)azetidin-2-one (**6e-**cis)*: White solid; Yield (4.85%); IR (KBr, cm^{-1}): 1749 (C=O, β-lactam); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.49-3.79 (dd, 2H, CH_2), 5.12 (s, 1H, H-4), 5.88 (t, 2H, $J = 2.16$ Hz, H-pyrrolyl), 6.52 (t, 2H, $J = 2.16$ Hz, H-pyrrol), 7.03-7.80 (m, 14H, Ar-H); ^{13}C-NMR (400 MHz, $CDCl_3$): δ 42.9 (CH_2), 68.1 (C-4 β-lactam), 76.5 (C-3 β-lactam), 108.4, 119.1, 126.7, 127.6, 128.5, 128.8, 129.1, 129.7, 130.1, 130.8, 132.4, 132.8, 133.8, 135.0 (aromatic carbons), 163.1 (C=O, β-lactam); MS: m/z 414 (7.93) (M+2^{37}Cl), 412 (23.80) (M^{+35}Cl), 215 (35.71) ([PhCH=NPhCl]$^+$), 197 (50.00) (M^+-[PhCH=NPhCl]), 167 (92.85), 149 (100), 91 (26.19) ([$PhCH_2$]$^+$). Anal.Calcd. for $C_{26}H_{21}N_2OCl$: C, 75.63; H, 5.13; N, 6.78%; Found: C, 75.97; H, 5.33; N, 6.60%.

2.4f *(3R,4R)-3-benzyl-4-(4-chlorophenyl)-1-phenyl-3-(1H-pyrrol-1-yl)azetidin-2-one (**6f-**trans)*: White solid; Yield (48.54%); M.p.: 164-168°C; IR (KBr, cm^{-1}): 1760 (C=O, β-lactam); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.80-3.10 (dd, 2H, CH_2), 5.38 (s, 1H, H-4), 6.20 (t, 2H, $J = 2.09$ Hz, H-pyrrolyl), 6.58 (d, 2H, Ar-H), 6.88 (t, 2H, $J = 2.10$ Hz, H-pyrrol), 7.07-7.50 (m, 14H, Ar-H). ^{13}C-NMR (400 MHz, $CDCl_3$): δ 39.9 (CH_2), 67.2 (C-4 β-lactam), 76.1 (C-3 β-lactam), 109.1, 117.7, 119.0, 124.8, 126.9, 127.8, 128.7, 129.2, 129.6, 129.7, 131.8, 133.4, 135.1, 136.5 (aromatic carbons), 162.9 (C=O, β-lactam); MS: m/z 414 (7.93) (M+2^{37}Cl), 412 (23.80) (M^{+35}Cl), 215 (35.71) ([PhCH=NPhCl]$^+$), 197 (50.00) (M^+-[PhCH=NPhCl]), 167 (92.85), 149 (100), 91 (26.19) ([$PhCH_2$]$^+$). Anal.Calcd. for $C_{26}H_{21}N_2OCl$: C, 75.63; H, 5.13; N, 6.78%; Found: C, 75.97; H, 5.33; N, 6.60%.

2.4g *(3R,4S)-3-benzyl-4-(4-chlorophenyl)-1-phenyl-3-(1H-pyrrol-1-yl)azetidin-2-one (**6g-**cis)*: White solid; Yield (12.13%); M.p.: 139-145°C; IR (KBr, cm^{-1}): 1749 (C=O, β-lactam); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.48-3.72 (dd, 2H, CH_2), 5.12 (s, 1H, H-4), 5.91 (t, 2H, $J = 2.21$ Hz, H-pyrrolyl), 6.52 (t, 2H, $J = 2.19$ Hz, H-pyrrol), 7.02-7.30 (m, 14H, Ar-H); ^{13}C-NMR (400 MHz, $CDCl_3$): δ 42.8(CH_2), 64.8 (C-4 β-lactam), 76.5 (C-3 β-lactam), 108.7, 117.5, 119.1, 124.8, 127.5, 128.1, 128.5, 128.7, 129.0, 130.1, 131.9, 133.8, 135.0, 136.0 (aromatic carbons), 162.0 (C=O β–lactam); MS: m/z 414 (7.93) (M+2^{37}Cl), 412 (23.80) (M^{+35}Cl),

215 (35.71) ([PhCH=NPhCl]$^+$), 197 (50.00) (M$^+$-[PhCH=NPhCl]), 167 (92.85), 149 (100), 91 (26.19) ([PhCH$_2$]$^+$). Anal.Calcd. for $C_{26}H_{21}N_2OCl$: C, 75.63; H, 5.13; N, 6.78% Found: C, 75.97; H, 5.33; N, 6.60%.

2.4h *(3R,4R)-3-benzyl-4-(2,4-dichlorophenyl)-1-phenyl-3-(1H-pyrrol-1-yl)azetidin-2-one (**6h-**trans)*: White solid; Yield (11.12%); IR (KBr, cm^{-1}): 1762 (C=O, β-lactam); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.92-3.16 (dd, 2H, CH_2), 5.73 (s, 1H, H-4), 6.19 (t, 2H, $J = 2.21$ Hz, H-pyrrolyl), 6.51 (t, 2H, $J = 2.20$ Hz, H-pyrrol), 7.08-7.58 (m, 13H, Ar-H); ^{13}C-NMR (400 MHz, $CDCl_3$): δ 39.0 (CH_2), 63.9 (C-4 β-lactam), 76.6 (C-3 β-lactam), 108.9, 117.6, 119.9, 125.0, 126.9, 127.8, 129.3, 129.5, 129.8, 129.9, 130.4, 133.1, 134.6, 135.7, 136.0 (aromatic carbons), 163.0 (C=O, β-lactam); MS: m/z 450 (2.92) (M+4 ^{37}Cl^{37}Cl), 448 (9.75) (M+2^{37}Cl), 446 (29.26) (M$^+$), 411 (9.75) (M$^+$-[Cl]), 249 (21.95) ([Cl$_2$PhCH=NPh]$^+$), 214 (12.19), 197 (100) ([PhCH$_2$C$_4$H$_4$NC=C=O]$^+$), 168 (97.56) ([PhC=CC$_4$H$_4$]$^+$), 149 (97.56), 91 (53.65) ([PhCH$_2$]$^+$. Anal.Calcd. for $C_{26}H_{20}N_2OCl_2$: C, 69.81; H, 4.51%; Found: C, 69.53; H, 4.70%.

2.4i *(3R,4S)-3-benzyl-4-(2,4-dichlorophenyl)-1-phenyl-3-(1H-pyrrol-1-yl)azetidin-2-one (**6i-**cis)*: White solid; Yield (2.24%); M.p.: 63-67°C; IR (KBr, cm^{-1}): 1763 (C=O, β-lactam); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.68-3.80 (dd, 2H, CH_2), 5.55 (s, 1H, H-4), 5.92 (t, 2H, $J = 2.15$ Hz, H-pyrrolyl), 6.73 (t, 2H, $J = 2.13$ Hz, H-pyrrol), 6.80-7.34 (m, 13H, Ar-H); ^{13}C-NMR (400 MHz, $CDCl_3$): δ 41.8 (CH_2), 61.1 (C-4 β-lactam), 76.6 (C-3 β-lactam), 109.1, 117.3, 118.8, 124.9, 127.1, 127.6, 128.5, 129.1, 129.6, 130.2, 133.5, 133.6, 134.8, 135.8, 136.0 (aromatic carbons), 163.0 (C=O, β -lactam). MS: m/z 450 (2.92) (M+4 ^{37}Cl^{37}Cl), 448 (9.75) (M+2^{37}Cl), 446 (29.26) (M$^+$), 411 (9.75) (M$^+$-[Cl]), 249 (21.95) ([Cl$_2$PhCH=NPh]$^+$), 214 (12.19), 197 (100) ([PhCH$_2$C$_4$H$_4$NC=C=O]$^+$), 168 (97.56) ([PhC=CC$_4$H$_4$]$^+$), 149 (97.56), 91 (53.65) ([PhCH$_2$]$^+$. Anal.Calcd. for $C_{26}H_{20}N_2OCl_2$: C, 69.81; H, 4.51%; Found: C, 69.53; H, 4.70%.

2.4j *(3R,4S)-3-benzyl-4-ethoxy-1-phenyl-3-(1H-pyrrol-1-yl)azetidin-2-one (**6j-**cis)*: White solid; Yield (17.34%); M.p.: 177°C (decomposed); IR (KBr, cm^{-1}): 1766 (C=O, β-lactam); ^{1}H-NMR (400 MHz, $CDCl_3$)δ 1.11 (t, 3H, CH_3), 3.20-3.45 (dd, 2H, CH_2), 5.55 (s, 1H, H-4), 5.93 (t, 2H, $J = 1.19$ Hz, H-pyrrolyl), 6.46 (t, 2H, $J = 0.99$ Hz, H-pyrrol), 7.08-7.31 (m, 10H, Ar-H). ^{13}C-NMR (400 MHz, $CDCl_3$): δ 15.2 (Me), 36.1(CH_2), 62.8 (OMe), 67.1 (C-4 β-lactam), 76.6 (C-3 β-lactam), 108.7, 121.6, 122.7, 124.4, 126.1, 128.2, 128.9, 129.0, 138.1 (aromatic carbons), 168.0 (C=O, β-lactam); MS: m/z 316 (15.38) (M$^+$-[Et,H], 197 (25.64) ([PhCH$_2$C$_4$H$_4$NC=C=O]$^+$, 168 (28.20) ([PhC=CC$_4$H$_4$]$^+$, 150 (48.71), 91 (84.61) ([PhCH$_2$]$^+$, 58 (100), 57 (100). Anal.Calcd. for $C_{26}H_{20}N_2OCl_2$: C, 76.28; H, 6.40; N, 8.09%; Found: C, 76.65; H, 6.44; N, 7.82%.

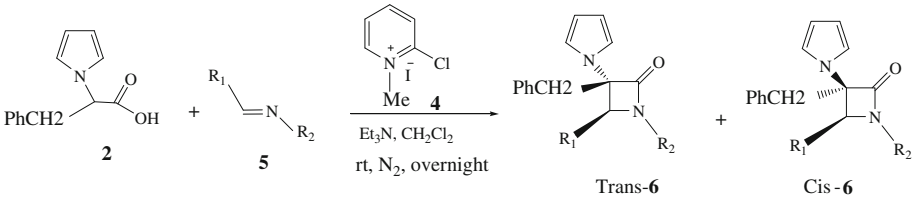
3. Results and Discussion

According to the model published by Tidwell and co-workers,[17] we decided to use synthesis of 3-phenyl-2-(1-*H*-pyrrol-1-yl) propanoic acid **2** from S(-)-phenyl alanine **1**, as the source of benzyl-n-pyrrolylketene **3**. Reaction of 3-phenyl-2-(1-*H*-pyrrol-1-yl) propionic acid 2 with Mukaiyama's reagent (4)[18] and Et_3N in CH_2Cl_2 in the presence of imines **5** gave azetidinones **6** as *cis/trans* mixtures (scheme 1). In some cases,*cis*-β-lactam was obtained. The results summarized in table 1.

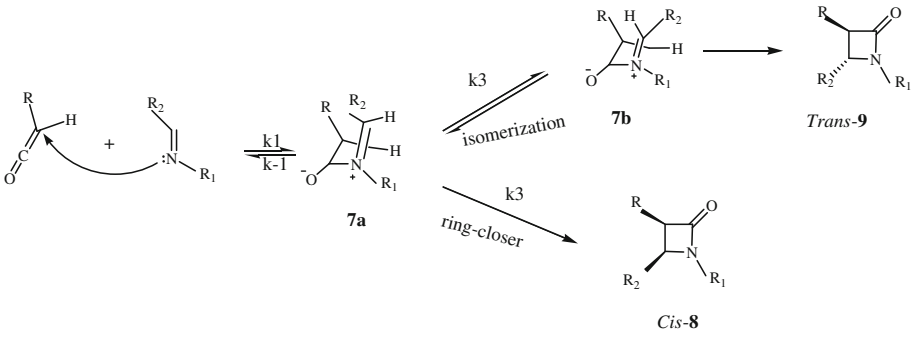
Both experimental and theoretical investigations at the B3LYP/6-31G* indicate that for various combinations

Table 1. β-lactams **6** from Benzyl-*N*-pyrrolylketene and imines **5**.

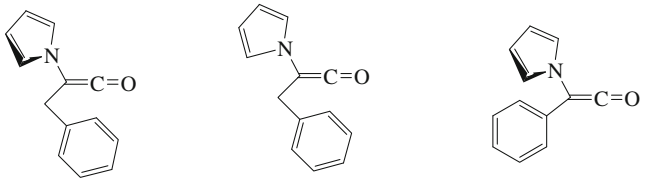
Entry	R^1	R^2	Product No.	*Cis/Trans*	Yield *Trans* (%)	Yield *Cis* (%)
1	Ph	Ph	**6a,b**	40:60	16.00	11.00
2	Ph	4-MeOPh	**6c**	100:0	–	42.00
3	Ph	4-ClPh	**6d,e**	24:76	15.00	5.00
4	4-ClPh	Ph	**6f,g**	20:80	49.00	12.00
5	2,4-ClPh	Ph	**6h,i**	83:17	11.00	3.00
6	OEt	Ph	**6j**	100:0	–	18.00



Scheme 1. Synthesis of cis/trans-β-lactams 6 and derivatives.



Scheme 2. Model for the relative stereoselectivity in the Staudinger reaction.



10a (twisted) 10b (planar) 11 (twisted)

Figure 2. The stable structures for the substituted N-pyrrolylketene.

of substituents, ketene gives stepwise reaction with imines with formation of zwitterions **7a** followed by conrotatory ring closure giving *cis*-product **8** and isomerization to less crowded intermediates **7b** and ring closure to trans-β-lactam **9** (scheme 2).

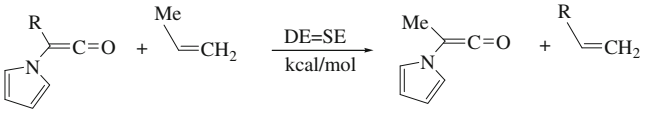
To assist in understanding the chemistry of benzyl-*N*-pyrrolylketene, the structure was calculated with the B3LYP/6-31G+d method, which predicts that the twisted structure **10a**, with the pyrrolyl plane perpendicular to the ketene plane, is more stable by 5.27 kcal/mol than the planar structure **10b**. For more comparision, we calculated various R groups based on stable structure for *N*-pyrrolylketene having 4.89 (MP2/6-31G*) and 3.91 (B3LYB/6-31G*)[17] with stable twisted structure. Methyl-*N*-pyrrolylketene twisted structure with 4.73 kcal/mol is more stable than the planar structure. Phenyl-*N*-pyrrolylketene **11** has only twisted structure such that Ph group is coplanar with ketene face and the hindrance phenyl branch induces the pyrrole ring to be nonconjugated (figure 2). Compared with phenyl-*N*-pyrrolylketene and methyl-*N*-pyrrolylketene, our ketene was more stable in the twisted form. ΔG are given in table 2.

For rotation around the ketenyl-pyrrolyl bond, calculated substituent effects on ketene stability evaluated as stabilization free energies (SE) from isodesmic energy comparisons by scheme 3 [19] are summarized in table 3.

For R= benzyl, value of 0.032 kcal/mol (B3LYP) was found as compared to 0.340 (B3LYP) for Ph. Thus, **10** is remarkably destabilized, in comparison with

Table 2. Calculated ΔG for ketene **10** compound with groups R in $RC_4H_4C{=}C{=}O$ (B3LYP/6-31G*).

Entry	R	Planar (a.u)	Twisted (a.u)	ΔG(kcal/mol)
1	H			–3.91
2	Me	–400.891	–400.898	–4.73
3	Ph	–	–592.636	–
4	$PhCH_2$	–631.922	–631.93	–5.27



Scheme 3. Calculated substituent effects on ketene stability.

phenyl-*N*-pyrrolylketene **11**. There is no evidence in **10a** for any bonding interaction between the ketenyl group and the pyrrolyl π system, as shown by the electronic contour depicted in figure 2. Higher reaction temperature results in the predominant formation of *trans*-β-lactams.

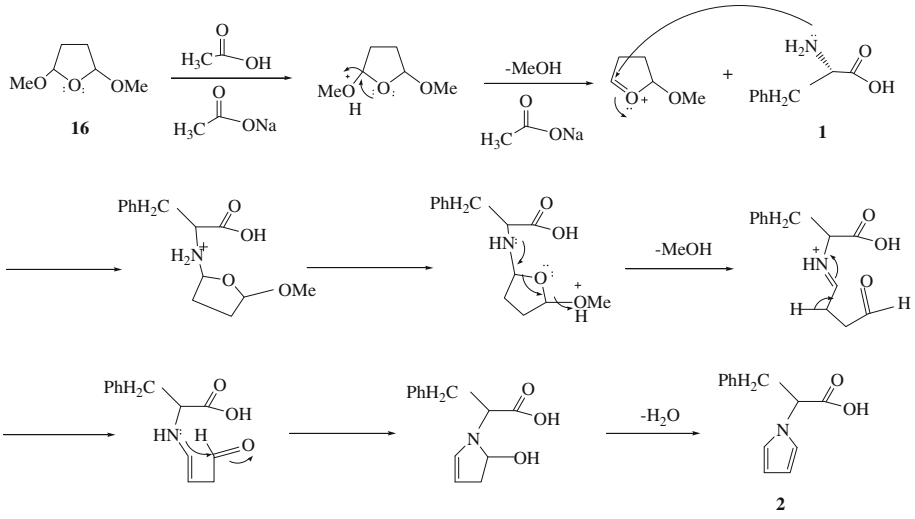
Diastereoselectivity and the ratio of *cis/trans*-products for cycloaddition reaction involving monosubstituted ketenes determined by ^{1}H NMR analysis of the reaction mixture from the signals of the 3- and 4-ring protons by their characteristic of coupling constants. Thus, *cis* stereoisomer has $J_{3,4} \geq 4.0$ Hz and for *trans*-β-lactams $J_{3,4} \leq 3.0$ Hz.[17]

Since the ketene 3 which has been used contains two substituents on the ketene functionality, there is no proton in C-4 of 2-azetidinones **6** which is present in mono substituted ketene.

Therefore, we had no $J_{3,4}$ for indication of stereochemistry and the ratio of *cis/trans* products. We resorted to NOE experiments. Irradiation of the methylene signal at $\delta = 3.606$ ppm in the ^{1}H NMR of *cis*-**6e** caused the intensity of the H signal at $\delta = 5.13$ ppm to increase by 4.62%, whereas, when the methylene signal $\delta = 2.945$ ppm in the ^{1}H NMR of *trans*-**6d** was

Table 3. Ketene stabilization energy (SE, kcal/mol), Eq 1, for R groups in $RC_4H_4C{=}C{=}O$ (B3LYP/6-31G*).

Entry	R	12 (a.u)	13(a.u)	14 (a.u)	15 (a.u)	ΔE (kcal/mol)
1	Me	–400.856	–117.862	–117.86227	–400.856	0
2	Ph	–592.585	–117.862	–309.59134	–400.856	0.34
3	$PhCH_2$	–631.875	–117.862	–348.88203	–400.856	0.03



Scheme 4. A proposed mechanism for preparation of ketene precursor 2.

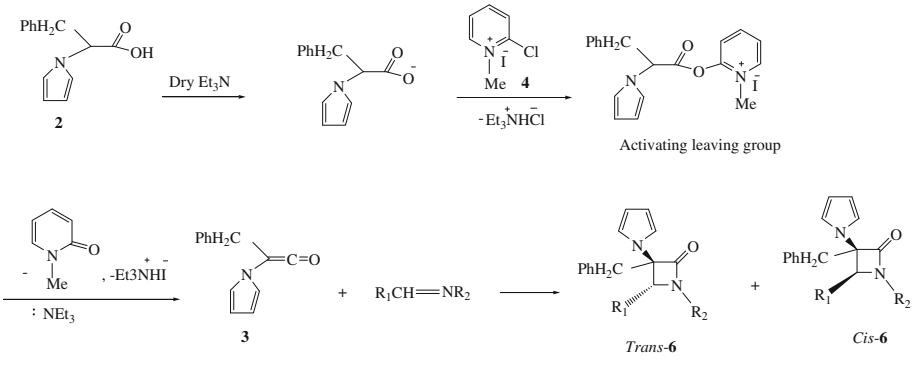
Table 4. Effect of reaction temperature on the product distribution of **6h-i**.

Entry	T(°C)	Time (h)	Yield **6h** (%)	Yield **6i** (%)
1	0	17	<5	0
25	17	11.12	2.24	

saturated, decrease by 3.75% was observed (all of the data analysis are shown in Supplementary Information).

For the preparation of β-lactams **6**, 2-chloro-*N*-methyl pyridinium iodide (Mukaiyama reagent) was used as the condensating agent, compounds **6c, 6j** were obtained as single *cis*-diastereomers. In contrast, 2-azetidinones **6a-b, 6c-d, 6e-f** and **6g-h** were obtained as a *cis–trans* mixture with low *cis*-selectivity. Because the RFs for *cis-trans* products were very low, all these products were easily separated by column and plate chromatography. Also the yields were higher at room temperature than 0°C.

At higher temperatures, ketene **3** was polymerized and the yields for 2-azetidinones **6** decreased. Benzyl-n-pyrrolylketene **3** had two electron-donating substituents and therefore steric hindrance was more. So, with imines which had methoxy substituent **6j** resulted in *cis*-β-lactam as the sole product. Also, the steric effect at the nitrogen substituent in imines PhCH=NR gave *cis*-isomer **6c**.



Scheme 5. A possible mechanism for the Staudinger reaction.

For preparation of 3-phenyl-2-(1-*H*-pyrrol-1-yl) propanoic acid S(-)-phenyl alanine **1** reacts with sodium acetate and 2,5-dimethoxy dihydrofuran **16** to generate this compound **2**, and the plausible mechanism is depicted in scheme 4.

To improve this particular procedure, the effect of the reaction temperature in the product distribution was analyzed at 25°C and 0°C. Experiments conducted at 0°C afforded much lower yields of product **6d** (table 4).

Based on the previous experiments on solvent effects, dry CH_2Cl_2 was chosen as a solvent in this report and our reaction was also done in dry solvent and under our argon atmosphere for 17-20 h.

A plausible mechanism has been suggested in scheme 5, which is in accordance with the proposed mechanism for Staudinger reaction.[21]

4. Conclusions

Summarizing, benzyl-*N*-pyrrolylketene proved to be adequate material for the synthesis of new and bulky 2-azetidinone ring from Staudinger reaction. The driving force for this reaction is the novelty of providing steric ketene with two substituents. Moreover, Mukaiyama reagent is as a versatile and available acid activator and its work-up procedure is simple. The methodology worked well with electron-donating substituent on N atom in imines. With electron-withdrawing substituent, for example, PhCH=N-4-O_2NPh, the yield was very low. We could distinguish between *cis*- and *trans*-products by two different methods: First, chemical shift of pyrrol ring hydrogens and CH_2 diastereotopic on C-3 *β*-lactam. Second, NOE-experiment that identified *trans*- product for **6d** and *cis*-isomer for **6e**.

Supplementary Information

Copies of IR, ^{1}H NMR, ^{13}C NMR and Mass spectra for a representative set of compounds **6a-j** and NOE-difference experiments for **6d-e**, are available at www.ias.ac.in/chemsci.

Acknowledgements

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