FACILE SYNTHESIS OF 2-AZETIDINONES WITH AN OLEFINIC SUBSTITUENT AT THE C-4 POSITION

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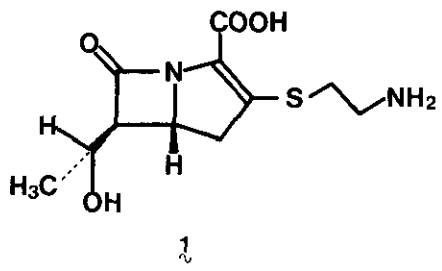
Abstract — A novel, facile synthesis of 2-azetidinones having an olefinic side chain at the C-4 position is described. Isoxazolones (7) derived from β-keto esters (6) were converted to β-amino esters (8) in excellent yield by reduction with sodium *in isopropyl alcohol* followed by esterification. Then reaction of the β-amino esters with o-tolylmagnesium bromide in dichloromethane gave the desired 2-azetidinones (2) ∿ (5).

The recent discoveries of the potent antibiotics thienamycin (1)[1] and its analogues[2] have stimulated investigations on synthesis of the carbapenem ring system. 2-Azetidinones having an olefinic substituent at the C-4 position have been found to be good intermediates for preparation of the carbapenem skeleton.[3] A general process reported for the syntheses of these 2-azetidinone derivatives is the formal [2 + 2] cycloaddition of chlorosulfonyl isocyanate to the corresponding dienes.[3a∿c,4] We now report the syntheses of novel 2-azetidinones (2) ∿ (5)[4] by the reaction of Grignard reagents with β-amino esters prepared by the pathway presented in scheme 1. The procedure is applicable to a wide range of complex 2-azetidinones.



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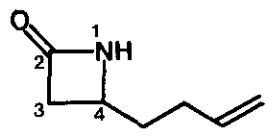

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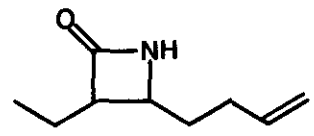

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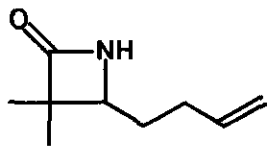

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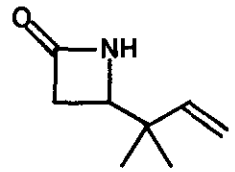

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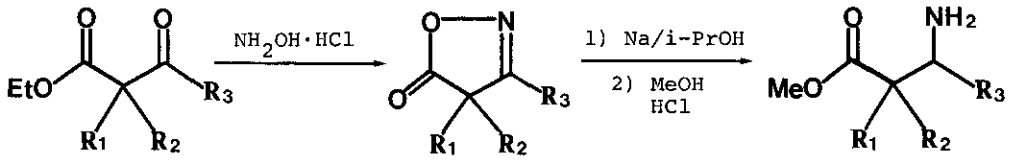

6 7 8

a : $R_1=R_2=H$, $R_3=CH_2CH_2CH=CH_2$
b : $R_1=H$, $R_2=CH_2CH_3$, $R_3=CH_2CH_2CH=CH_2$
c : $R_1=R_2=CH_3$, $R_3=CH_2CH_2CH=CH_2$
d : $R_1=R_2=H$, $R_3=C(CH_3)_2CH=CH_2$

Scheme 1

The starting β-keto esters (6b) and (6c) were obtained by alkylation of known compound (6a).[5] Compound (6d) was prepared in 84 % yield by the reaction of lithio ethyl acetate with 2,2-dimethyl-3-butenoyl chloride[6] (THF/-78°C). Formation of 5-isoxazolones (7) from β-keto esters (6) was achieved with good yields by the established method.[7] Compound (7b) was found to be a 2 : 1 tautomeric mixture of the Δ^2-isoxazol-5-one form and Δ^3-isoxazol-5-one form[7] from its ir and nmr spectra. Although the reductive ring opening of isoxazoles can be accomplished by catalytic hydrogenation or Birch reduction,[8] these methods are not applicable to compounds (7), because the olefinic side chain is sensitive to such reductions.[9] We reasoned that by analogy with the reduction of aliphatic oximes to amines,[10] sodium in alcohol should bring about this reduction. Actually, reduction of 7 with sodium in boiling isopropyl alcohol produced the amino acids, which gave esters in excellent yield when treated with methyl alcohol saturated with hydrogen chlodide. This procedure represents a practical method for the conversion of 5-isoxazolones to β-amino esters.[11] The method of ring closure of β-amino esters to give 2-azetidinones using Grignard reagents is well established.[12] For obtaining compounds (2) ∿ (5), we chose o-tolylmagnesium bromide as a Grignard reagent and dichloromethane[13] as a solvent. Table 1 summarizes data on the spectroscopic properties of these compounds with their yields. The yields of compounds (2)[14] and (5), which have no alkyl substituent at the C-3 position were low as expected.[12] Compound (3) was found to be a 1 : 1 mixture of cis and trans isomers,[15] which were separable by silica gel chromatography.

Table 1 Spectral Properties of 2-Azetidinones

Compound	Yield (%)	IR($CHCl_3$) cm^{-1} NH	C=O	$CH=CH_2$	NMR($CDCl_3$) δ
2	33	3415	1754	1641	[a]
3cis	86	3405	1747	1640	1.05 (3H, t, J = 7 Hz), 1.40 ∿ 2.30 (6H, m), 3.05 (1H, ddt, J = 1.5, 5, 8 Hz), 3.62 (1H, dt, J = 5, 8 Hz),[b] 4.84 ∿ 6.00 (3H, m), 7.05 (1H, br)
3trans		3405	1752	1640	1.00 (3H, t, J = 7 Hz), 1.40 ∿ 2.28 (6H, m), 2.66 (1H, dddd, J = 1, 2, 6, 8 Hz), 3.25 (1H, dt, J = 2, 6.5 Hz),[c] 4.84 ∿ 5.96 (3H, m), 6.84 (1H, br)
4	95	3405	1753	1640	1.16 (3H, s), 1.29 (3H, s), 1.48 ∿ 2.24 (4H, m), 3.27 (1H, dd, J = 6, 8 Hz), 4.84 ∿ 5.97 (3H, m), 6.18 (1H, br)
5	44	3410	1753	1637	1.02 (6H, s), 2.60 (1H, ddd, J = 1, 3, 14 Hz), 2.80 (1H, ddd, J = 2, 4.5, 14 Hz), 3.44 (1H, dd, J = 3, 4.5 Hz), 4.88 ∿ 5.92 (3H, m), 6.60 (1H, br)

a) Nmr data for this compound are identical with reported values.[4]

b) D_2O treatment and decoupling showed that the coupling constant between the protons at C-3 and C-4 positions was 5 Hz.

c) The coupling constant between the protons at C-3 and C-4 positions was shown to be 2 Hz.

EXPERIMENTAL

All melting points were determined by the capillary method and are uncorrected. Ir spectra were measured with a JASCO DS-701G spectrometer, nmr spectra with a JEOL PS-100 spectrometer (tetramethylsilane as internal reference), and mass spectra with a JEOL JMS-D 300 mass spectrometer.

Ethyl 2-ethyl-3-oxo-6-heptenoate (6b)

A mixture of ethyl 3-oxo-6-heptenoate 6a[5] (10 g, 59 mmol) and ethyl iodide (9.176 g, 59 mmol) was added to a solution of sodium (1.353 g, 59 mmol) in dry ethanol (30 ml) and refluxed under argon for 5 h. After evaporation of the solvent, the residue was mixed with water, and extracted with ether. The extract was washed with brine,

dried over $MgSO_4$ and evaporated. Repeated distillations of the oily residue under reduced pressure gave 6b (10.433 g, 90 %) as a colorless liquid, bp 98 ∿ 99°C/3 mm, ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 1738, 1710 (C=O), 1640 ($CH=CH_2$) ; nmr ($CDCl_3$) δ : 0.92 (3H, t, J = 7 Hz, $CHCH_2\underline{CH}_3$), 1.25 (3H, t, J = 7 Hz, $OCH_2\underline{CH}_3$), 1.86 (2H, dq, J = 7, 7 Hz, $CH\underline{CH}_2CH_3$), 2.16 ∿ 2.72 (4H, m, CH_2CH_2), 3.32 (1H, t, J = 7 Hz, CH), 4.14 (2H, q, J = 7 Hz, $O\underline{CH}_2CH_3$), 4.80 ∿ 6.00 (3H, m, $CH=CH_2$) ; ms m/e Calcd for $C_{11}H_{18}O_3$: 198.1256 (M^+). Found : 198.1241 (M^+).

Ethyl 2,2-dimethyl-3-oxo-6-heptenoate (6c)

By use of the same procedure as that for 6b, 6c was obtained from ethyl 3-oxo-6-heptenoate 6a (10 g, 59 mmol), methyl iodide (18.376 g, 129 mmol) and sodium (2.706 g, 118 mmol) in dry ethanol (40 ml) as a colorless liquid (9,990 g, 86 %), bp 83 ∿ 84°C/3 mm, ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 1738, 1710 (C=O), 1640 ($CH=CH_2$) ; nmr ($CDCl_3$) δ : 1.24 (3H, t, J = 7 Hz, $OCH_2\underline{CH}_3$), 1.35 (6H, s, $C<^{CH_3}_{CH_3}$), 2.15 ∿ 2.65 (4H, m, CH_2CH_2), 4.13 (2H, q, J = 7 Hz, $O\underline{CH}_2CH_3$), 4.80 ∿ 5.95 (3H, m, $CH=CH_2$) ; ms m/e Calcd for $C_{11}H_{18}O_3$: 198.1256 (M^+). Found : 198.1257 (M^+).

Ethyl 4,4-dimethyl-3-oxo-5-hexenoate (6d)

A solution of n-butyllithium (121.2 ml, 0.2 mol) in hexane (1.65 M) was added dropwise to a solution of hexamethyldisilazane (35.5 g, 0.22 mol) in anhydrous ether (20 ml) with stirring at 0°C under argon. After stirring at room temperature for 1 h, the mixture was cooled to -78°C and dry tetrahydrofuran (100 ml) was added to dissolve the lithium hexamethyldisilazanate formed. To the solution, dry ethyl acetate (18.06 g, 0.205 mol) was added within 20 min and stirring was continued for a further 40 min. To the resulting lithio ethyl acetate solution, a solution of 2,2-dimethyl-3-butenoyl chloride[6] (13.25 g, 0.1 mol) in tetrahydrofuran (30 ml) was added dropwise over 20 min. The mixture was stirred at -78°C for 2 h. After quenching with 10 % hydrochloric acid the solution was extracted with ethyl acetate. Repeated distillations of the extract under reduced pressure gave 6d (15.500 g, 84 %, based on 2,2-dimethyl-3-butenoyl chloride) as a colorless liquid, bp 88 ∿ 91°C/3 mm, ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 1740, 1710 (C=O), 1638 ($CH=CH_2$) ; nmr ($CDCl_3$) δ : 1.25 (6H, s, $C<^{CH_3}_{CH_3}$), 1.25 (3H, t, J = 7 Hz, $OCH_2\underline{CH}_3$), 3.48 (2H, s, $COCH_2$), 4.12 (2H, q, J = 7 Hz, $O\underline{CH}_2CH_3$), 4.92 ∿ 6.08 (3H, m, $CH=CH_2$) ; ms m/e Calcd for $C_{10}H_{16}O_3$: 184.1099 (M^+). Found : 184.1099 (M^+).

3-(3-Butenyl)-Δ^2-isoxazol-5-one (7a)

A mixture of β-keto ester 6a[5] (17 g, 0.1 mol), hydroxylamine hydrochloride (13.9 g, 0.2 mol), sodium acetate (2.6 g), water (40 ml) and ethanol (180 ml) was heated at 80°C for 3h. Then conc hydrochloric acid (12 ml) was added and the solution was gently refluxed for 30 min more. Volatile matter was evaporated, water (50 ml) was added, and the mixture was extracted with ethyl acetate. Evaporation of the dried ($MgSO_4$) extract followed by distillation under reduced pressure gave 7a (10.01 g, 72 %) as a colorless oil, bp 126 ∿ 128°C/3 mm, ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 1802 (C=O), 1642 (CH=CH_2) ; nmr ($CDCl_3$) δ : 2.20 ∿ 2.75 (4H, m, CH_2CH_2), 3.37 (2H, s, CH_2CO), 4.92 ∿ 6.02 (3H, m, CH=CH_2) ; ms m/e Calcd for $C_7H_9NO_2$: 139.0633 (M^+). Found : 139.0625 (M^+).

3-(3-Butenyl)-4-ethyl-Δ^2-isoxazol-5-one (7b)

By use of the same procedure as that for 7a, β-keto ester 6b (10.5 g, 53 mmol), hydroxylamine hydrochloride (7.4 g, 106 mmol), sodium acetate (1.4 g) and conc hydrochloric acid (6 ml) afforded a 2 : 1 tautomeric mixture of 7b and 3-(3-butenyl)-4-ethyl-Δ^3-isoxazol-5-one (7.26 g, 82 %) as a colorless oil, bp 130 ∿ 131°C/3 mm, ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 1796, 1733 (C=O), 1642 (CH=CH_2) ; nmr ($CDCl_3$) δ : 0.94 (2H, t, J = 7.5 Hz, $CH_2\underline{CH}_3$), 1.09 (1H, t, J = 7 Hz, $CH_2\underline{CH}_3$), 1.60 ∿ 2.75 (6H, m, CH_2CH_2 and $\underline{CH}_2CH_3$), 3.34 (2/3 H, t, J = 5.5 Hz, COCH), 4.80 ∿ 6.05 (3H, m, CH=CH_2) ; ms m/e Calcd for $C_9H_{13}NO_2$: 167.0946 (M^+). Found : 167.0897 (M^+).

3-(3-Butenyl)-4,4-dimethyl-Δ^2-isoxazol-5-one (7c)

A mixture of β-keto ester 6c (9.9 g, 50 mmol), hydroxylamine hydrochloride (10.4 g, 150 mmol), sodium acetate (2 g), water (15 ml) and ethanol (70 ml) was refluxed for 6h. Then conc hydrochloric acid (6 ml) was added and the solution was refluxed further for 3h. The usual workup afforded crude 7c. Column chromatography of crude 7c on silica gel afforded the pure isoxazolone (7.458 g, 89 %), which is a crystalline solid at <0°C, ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 1793 (C=O), 1643 (CH=CH_2) ; nmr ($CDCl_3$) δ : 1.35 (6H, s, $C<^{CH_3}_{CH_3}$), 2.44 (4H, d, J = 3 Hz, CH_2CH_2), 4.92 ∿ 6.00 (3H, m, CH=CH_2) ; ms m/e Calcd for $C_9H_{13}NO_2$: 167.0946 (M^+). Found : 167.0923 (M^+).

3-(1,1-Dimethyl-2-propenyl)-Δ^2-isoxazol-5-one (7d)

A solution of β-keto ester 6d (18.4 g, 0.1 mole) and hydroxylamine hydrochloride (8.34 g, 0.12 mole) in dry pyridine (50 ml) was heated at 50°C for 3h. The reaction

mixture was cooled, diluted with ethyl acetate, thoroughly washed successively with 10 % hydrochloric acid and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Column chromatography of the residue on silica gel afforded the pure isoxazolone 7d (14.230 g, 93 %), which is a crystalline solid at <0°C, ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 1803 (C=O), 1638 ($CH=CH_2$) ; nmr ($CDCl_3$) δ : 1.36 (6H, s, $C<^{CH_3}_{CH_3}$), 3.37 (2H, s, CH_2), 5.00 ∿ 6.00 (3H, m, $CH=CH_2$) ; ms m/e Calcd for $C_8H_{11}NO_2$: 153.0790 (M^+). Found : 153.0806 (M^+).

Methyl 3-amino-6-heptenoate (8a)

To a boiling solution of isoxazolone 7a (3.61 g, 26 mmol) in isopropyl alcohol (60 ml), sodium (4.78 g, 208 mmol) was added in small portions, with thorough stirring under argon, at a rate sufficient to maintain gentle boiling. After all the sodium had dissolved, the reaction mixture was cooled in ice, neutralized with conc hydrochloric acid, and extracted with ether to remove unreacted isoxazolone. Evaporation of the aqueous solution gave a solid mixture of the β-amino acid and sodium chloride. The mixture was treated with methanol saturated with hydrogen chloride for 2 days at room temperature and then filtered. The filtrate was evaporated and the residue was mixed with ice (50 g) and then with sufficient 10 % sodium carbonate to obtain a basic solution. The solution was extracted with chloroform, washed with brine, dried over $MgSO_4$, and evaporated. Column chromatography on silica gel afforded 8a (3.880 g, 95 %) as a colorless oil, ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 1730 (C=O), 1640 ($CH=CH_2$) ; nmr ($CDCl_3$) δ : 1.20 ∿ 1.76 (2H, m, CH_2), 1.62 (2H, s, NH_2), 1.98 ∿ 2.18 (2H, m, $C\underline{H}_2CH=CH_2$), 2.24 (1H, dd, J = 8, 15.5 Hz, COCH), 2.48 (1H, dd, J = 4.5, 15.5 Hz, COCH), 3.16 (1H, m, $C\underline{H}NH_2$), 3.64 (3H, s, OCH_3), 4.80 ∿ 6.00 (3H, m, $CH=CH_2$) ; ms m/e Calcd for $C_8H_{16}NO_2$: 158.1181 (M^++1). Found : 158.1177 (M^++1).

Methyl 3-amino-2-ethyl-6-heptenoate (8b)

The same procedure as that for 8a yielded 8b from isoxazolone 7b (6.20 g, 37 mmol) and sodium (6.83 g, 297 mmol) as a colorless oil (5.632 g, 82 %), ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 1724 (C=O), 1638 ($CH=CH_2$) ; nmr ($CDCl_3$) δ : 0.90 (3H, t, J = 7 Hz, $CH_2C\underline{H}_3$), 1.25 (2H, s, NH_2), 1.32 ∿ 2.40 (7H, m, CH_2CH_2 and $C\underline{H}C\underline{H}_2CH_3$), 2.86 (1H, m, $C\underline{H}NH_2$), 3.64 (3H, s, OCH_3), 4.80 ∿ 5.98 (3H, m, $CH=CH_2$) ; ms m/e Calcd for $C_{10}H_{20}NO_2$: 186.1494 (M^++1). Found : 186.1487 (M^++1).

Methyl 3-amino-2,2-dimethyl-6-heptenoate (8c)

By use of the same procedure as that for 8a, 8c was obtained from isoxazolone 7c (6.20 g, 37 mmol) and sodium (6.83 g, 297 mmol) as a colorless oil (4.905 g, 71 %), ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 1720 (C=O), 1640 ($CH=CH_2$) ; nmr ($CDCl_3$) δ : 1.00 ∿ 2.40 (4H, m, CH_2CH_2), 1.15 (6H, s, $C<^{CH_3}_{CH_3}$), 2.80 (1H, dd, J = 2.5, 11 Hz, $\underline{CH}NH_2$), 3.62 (3H, s, OCH_3), 4.80 ∿ 5.96 (3H, m, $CH=CH_2$) ; ms m/e Calcd for $C_{10}H_{20}NO_2$: 186.1494 (M^++1). Found : 186.1482 (M^++1).

Methyl 3-amino-4,4-dimethyl-5-hexenoate (8d)

The same procedure as for 8a gave 8d from isoxazolone 7d (7.65 g, 50 mmol) and sodium (9.20 g, 400 mmol) as a colorless oil (8.015 g, 94 %), ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 1730 (C=O), 1638 ($CH=CH_2$) ; nmr ($CDCl_3$) δ : 1.00 (6H, s, $C<^{CH_3}_{CH_3}$), 1.27 (2H, s, NH_2), 2.08 (1H, dd, J = 10.5, 15.5 Hz, COCH), 2.52 (1H, dd, J = 2.5, 15.5 Hz, COCH), 2.97 (1H, dd, J = 2.5, 10.5 Hz, $\underline{CH}NH_2$), 3.64 (3H, s, OCH_3), 4.84 ∿ 5.90 (3H, m, $CH=CH_2$) ; ms m/e Calcd for $C_9H_{18}NO_2$: 172.1337 (M^++1). Found : 172.1382 (M^++1).

4-(3-Butenyl)azetidin-2-one (2)

To a solution of β-amino ester 8a (1.57 g, 10 mmol) in dry dichloromethane (10 ml) was added o-tolylmagnesium bromide (8.97 ml, 20 mmol) in ether (2.23 M) at -10°C. The resulting clear solution was stirred at room temperature under argon for 2 days. The solution was quenched with 20 % ammonium chloride, and neutralized with 10 % hydrochloric acid with cooling on ice. The solution was extracted with ethyl acetate, washed with brine, dried over $MgSO_4$, and evaporated. Column chromatography of the residue on silica gel afforded azetidinone 2 (415 mg, 33 %) as a colorless oil, ms m/e Calcd for $C_7H_{12}NO$: 126.0919 (M^++1). Found : 126.0917 (M^++1).

4-(3-Butenyl)-3-ethylazetidin-2-one (3)

β-Amino ester 8b (1.85 g, 10 mmol) was treated by the same procedure as that for 8a, but with stirring for 12 h to give a cis and trans mixture of 3 as a colorless oil (1.313 g, 86 %). Repeated chromatography on silica gel with chloroform-acetone mixture (9 : 1 v/v) as eluent gave 3_{cis} (582 mg) and 3_{trans} (545 mg). 3_{cis} ; ms m/e Calcd for $C_9H_{16}NO$: 154.1232 (M^++1). Found : 154.1230 (M^++1). 3_{trans} ; ms m/e Calcd for $C_9H_{16}NO$: 154.1232 (M^++1). Found : 154.1225 (M^++1).

4-(3-Butenyl)-3,3-dimethylazetidin-2-one (4)

Treatment of β-amino ester 8c (1.85 g, 10 mmol) by the same procedure as for 8a

gave 4 (1.455 g, 95 %) as a colorless solid, which was spectroscopically pure. Recrystallization from hexane afforded 1.205 g of colorless needles, mp 65 ∿ 66°C. Anal. Calcd for $C_9H_{15}NO$: C, 70.55 ; H, 9.87 ; N, 9.14. Found : C, 70.22 ; H, 9.60 ; N, 8.89.

4-(1,1-Dimethyl-2-propenyl)azetidin-2-one (5)

β-Amino ester 8d (1.71 g, 10 mmol) was treated by the same procedure as that for 8a to give 5 (615 mg, 44 %), which was spectroscopically pure. Recrystallization from hexane gave colorless needles, mp 45 ∿ 46°C. Anal. Calcd for $C_8H_{13}NO$: C, 69.03 ; H, 9.41 ; N, 10.06. Found : C, 69.25, H, 9.44 ; N, 9.97.

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15. Identification of cis and trans isomers is based on the coupling constant between the protons at the C-3 and C-4 positions in their nmr spectra.[3a,11]

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