Journal of the Chinese Chemical Society, 1992, *39*, 87-90

Enantioselective Addition of Iodine Azide to α,β-Unsaturated Carboxylic Acid Derivatives

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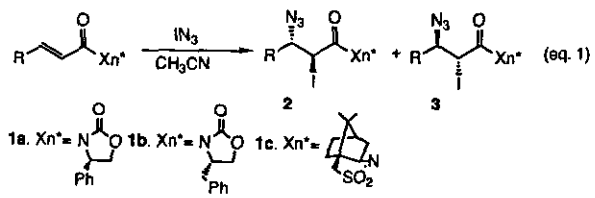
The addition of iodine azide to chiral conjugated *N*-enoyl-sultam or α,β-unsaturated *N*-acyloxazolidinones generated two asymmetric centers at C(α) and C(β) with high π-face differentiation and regioselectivity. The diastereomerically pure product was easily obtained by crystallization with purity up to 94% de. The structure of **2a** was determined by X-ray diffraction analysis which also indicated that **B** and **4** are reactive conformations.

INTRODUCTION

The stereospecific addition of iodine azide to olefins providing 2-iodoalkylazides has been widely used to introduce nitrogen functions into organic compounds.[2] For example, 2-iodoalkylazides undergo a facile reaction with aryl- and alkyldichloroboranes to produce β-iodo secondary amines. These amines without isolation undergo ring closure with base to provide the corresponding *N*-aryl and *N*-alkyl aziridines.[3] The reaction of β-azido-α-iodomethylpropionates with tributyltin hydride leads to β-aminoesters.[4] The application of these reactions to the preparation of optically active compounds has not yet been reported. We describe here the first instance of asymmetric addition of iodine azide to chiral α,β-unsaturated *N*-acyloxazolidinones and *N*-enoylsultames. (Scheme I)

Scheme I



RESULTS AND DISCUSSION

Table 1 presents our results in the enantioselective addition of iodine azide to α,β-unsaturated *N*-acyloxazolidinones **1a, 1b,** and *N*-enoyl-sultams **1c**. These starting *N*-enoyl-sultames or *N*-acyloxazolidinones were readily prepared by successive treatment of the corresponding acylchloride with the bornane sultam (after deprotonation with NaH)[5] or oxazolidinones (after deprotonation with BuLi).[6] Iodine azide was generated from iodine monochloride and sodium azide in acetonitrile solution[7] and was added in situ to olefins at -5 °C leading to α-iodo-β-azidopropionic acid derivatives **2** and **3** with commonly averaging 34% de as determined by ^{1}H NMR (200-MHz) spectroscopy. The diastereomerically pure products were obtained by crystallization from benzene-cyclohexane or methanol. The purity was up to 94% de (entry 1) with respectable chemical yield.

Table 1. Asymmetric Conjugated Addition of Iodine Azide to Chiral *N*-acylamide

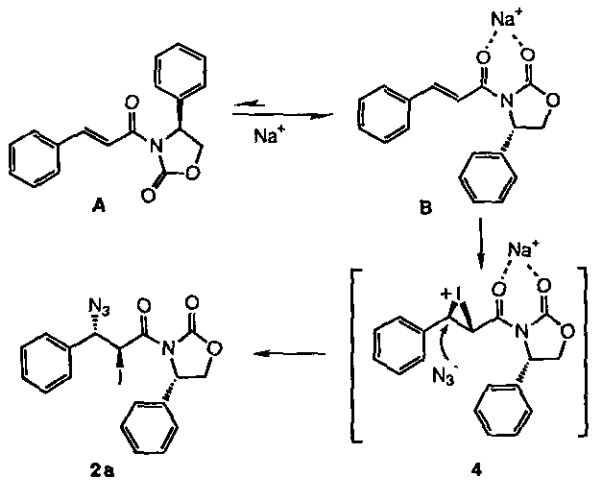
Entry	*N*-acylamide 1	Yield/%[a]	d.e./%[a]	Product	Configuration, 2[b]
1	**1a**, (R = Ph)	97(34)	42(94)	**2a**	(2*S*, 3*S*)
2	**1b**, (R = Ph)	76(35)	28(76)	**2b**	(2*S*, 3*S*)
		(16)	(66)	**3b**	(2*R*, 3*R*)
3	**1b**, (R = CH_3)	59(15)	14(80)	**2c**	(2*S*, 3*S*)
4	**1c**, (R = Ph)	84(30)	47(82)	**2d**	(2*S*, 3*S*)
5	**1c**, (R = CH_3)	91(58)	34(47)	**2e**	(2*S*, 3*S*)

[a] Values in parentheses refer to crystallized product.
[b] Based on the X-ray structure of **2a**.

Two types of fascinating chiral auxiliaries, which have recently been used in asymmetric synthesis[5,6] were employed in this study. Although the chiral oxazolidinone **1b** derived from phenylalaninol has been shown by Evans to provide the best asymmetric induction in Diels-Alder reactions,[6] we found that this reagent produced the least selectivity in this reaction (entries 2 and 3). The diastereoselectivity was in the range 34-47 with the other two chiral auxiliaries. Iodine azide was also generated from iodine monochloride and sodium azide in dimethylformamide solution.[7] Attempt to optimize the selectivity using dimethylformamide as solvent instead of acetonitrile resulted in a complicated mixture of products.

The structure and stereochemistry of **2a** were unambiguously established by single-crystal X-ray analysis[9] (Fig. 1). Atomic parameters of all non-hydrogenic atoms are listed in Table 2. Selected bond lengths and angles are presentted in Table 3. Our interpretation of the formation and stereochemistry of **2a** is summarized in Scheme II. The metal-coordinated cinnamoyloxazolidinones exist exclusively in the S-cis arrangement of the C=O and NC=O groups and the same arrangement of the C=O and C(α)=C(β) bonds,[6] such as transition state **B**. Formation of iodonium ion occurs favoring top-side attack. Finally, azide ion undergoes S_N2 displacement at the more electron-positive C(β) leading to the trans-addition products. The stereochemistry of compounds **2b**, **2c**, **2d**, and **2e** were basically assigned according to the proposed reaction mechanism shown in Scheme II and presumed that these major components outcome from entries 2, 3, 4, and 5 would have the same absolute configurations at C(α) and C(β) as compound **2a**. Although the addition of iodine azide to unsymmetric olefins always come along with the regioisomer where the azide ion attack at C(α),[8] in our work we found that most cases are regiospecific; only in entries 2 and 3, less than 5% regioisomer was detected by ^{1}H NMR (200-MHz) spectroscopy of crude materials.

Scheme II



In conclusion, we have developed the enantioselective addition of iodine azide to olefins although in modest diastereomeric differentiation. The highly optically pure product was easily obtained by simple crystallization. The conversion of these addition products to the synthesis of optically pure aziridines and β-aminoacids will be reported in due course.

Table 2. Atomic Parameters x,y,z and Beq of **2a**

	X	Y	Z	Beq
I	-0.32389(4)	-0.02629	-0.020369(25)	6.70(3)
C	-0.2601(5)	-0.2777(8)	-0.0054(3)	3.7(3)
C1	-0.1605(5)	-0.2756(9)	-0.0206(3)	4.2(3)
N1	-0.1124(4)	-0.4371(8)	0.0101(3)	5.9(3)
N2	-0.1197(4)	-0.5590(10)	-0.0357(3)	5.3(3)
N3	-0.1172(6)	-0.6753(10)	-0.0716(4)	8.6(5)
C11	-0.1554(5)	-0.2406(9)	-0.1077(3)	3.9(3)
C12	-0.0882(5)	-0.1293(9)	-0.1243(3)	4.3(3)
C13	-0.0795(5)	-0.1067(9)	-0.2018(4)	5.3(4)
C14	-0.1362(5)	-0.1978(10)	-0.2621(3)	5.0(4)
C15	-0.2050(5)	-0.3059(12)	-0.2474(4)	5.5(4)
C16	-0.2140(5)	-0.3278(10)	-0.1701(4)	5.3(4)
C2	-0.2595(4)	-0.3276(9)	0.0816(3)	3.7(3)
O2	-0.2069(3)	-0.2606(6)	0.13732(21)	4.96(24)
N21	-0.3210(3)	-0.4567(6)	0.09428(24)	3.58(24)
C22	-0.3635(5)	-0.5828(9)	0.0433(4)	6.2(4)
O23	-0.4022(4)	-0.7011(7)	0.0802(3)	7.0(3)
C24	-0.3939(5)	-0.6522(10)	0.1602(4)	5.3(4)
C25	-0.3265(4)	-0.5010(13)	0.1771(3)	3.9(3)
O22	-0.3653(5)	-0.5919(7)	-0.0288(3)	10.6(4)
C51	-0.3694(4)	-0.3590(9)	0.2184(3)	3.7(3)
C52	-0.3449(5)	-0.3537(9)	0.3018(3)	4.1(3)
C53	-0.3867(6)	-0.2339(10)	0.3415(3)	5.5(4)
C54	-0.4505(5)	-0.1172(10)	0.3034(4)	5.2(4)
C55	-0.4741(5)	-0.1212(10)	0.2217(4)	5.9(4)
C56	-0.4351(5)	-0.2431(10)	0.1789(3)	5.6(4)

[a] Estimated standard errors refer to the last digit printed

$$Beq = \frac{8}{3}\pi^2\Sigma_{i,j}U_{ij}a_ia_ja_i^*a_j^*$$

EXPERIMENTAL SECTION

Melting points were determined on a Fargo MP-1 D apparatus and are uncorrected. Infrared spectra were recorded on a Hitachi 260-30 spectrameter, ^{1}H NMR spectra were recorded on a Varian XL-200E (200-MHz) spectrometer. All chemical shifts are reported in ppm using tetramethylsilane as internal standard. Elemental

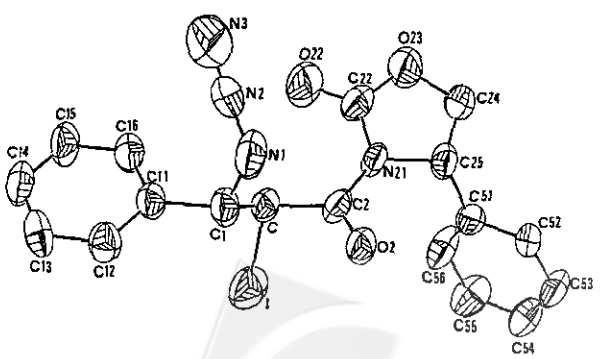


Fig. 1. ORTEP drawing of **2a**.

Table 3. Selected Bond Lengths and Bond Angles of 2a

Bond Length/Å			
I-C	2.159(7)	C(2)-N(21)	1.383(8)
C-C(1)	1.489(9)	N(21)-C(22)	1.366(8)
C-C(2)	1.537(8)	N(21)-C(25)	1.478(7)
C(1)-N(1)	1.477(9)	C(22)-O(23)	1.309(8)
C(1)-C(11)	1.533(8)	C(22)-O(22)	1.231(7)
N(1)-N(2)	1.226(9)	O(23)-C(24)	1.400(8)
N(2)-N(3)	1.104(10)	C(24)-C(25)	1.508(12)
C(11)-C(12)	1.367(9)	C(25)-C(51)	1.516(11)
C(11)-C(16)	1.376(9)	C(51)-C(52)	1.391(8)
C(12)-C(13)	1.370(9)	C(51)-C(56)	1.366(10)
C(13)-C(14)	1.359(10)	C(52)-C(53)	1.369(9)
C(14)-C(15)	1.357(11)	C(53)-C(54)	1.347(11)
C(15)-C(16)	1.368(9)	C(54)-C(55)	1.363(9)
C(2)-O(2)	1.193(7)	C(55)-C(56)	1.392(10)
Bond Angle/deg			
I-C-C(1)	110.9(4)	C(2)-N(21)-C(22)	129.2(5)
I-C-C(2)	105.0(4)	C(2)-N(21)-C(25)	119.5(5)
C(1)-C-C(2)	111.9(5)	C(22)-N(21)-C(25)	109.4(6)
C-C(1)-N(1)	107.9(5)	N(21)-C(22)-O(23)	112.1(5)
C-C(1)-C(11)	115.1(5)	N(21)-C(22)-O(22)	126.1(6)
N(1)-C(1)-C(11)	112.4(5)	O(23)-C(22)-O(22)	121.7(6)
C(1)-N(1)-N(2)	118.3(5)	C(22)-O(23)-C(24)	108.9(5)
N(1)-N(2)-N(3)	172.2(7)	O(23)-C(24)-C(25)	108.3(5)
C(1)-C(11)-C(12)	120.1(5)	N(21)-C(25)-C(24)	99.6(5)
C(1)-C(11)-C(16)	120.9(6)	N(21)-C(25)-C(51)	112.8(7)
C(12)-C(11)-C(16)	118.9(5)	C(24)-C(25)-C(51)	111.4(5)
C(11)-C(12)-C(13)	120.0(6)	C(25)-C(51)-C(52)	117.8(6)
C(12)-C(13)-C(14)	120.1(6)	C(25)-C(51)-C(56)	123.8(5)
C(13)-C(14)-C(15)	121.0(6)	C(52)-C(51)-C(56)	118.3(6)
C(14)-C(15)-C(16)	118.9(7)	C(51)-C(52)-C(53)	119.6(6)
C(11)-C(16)-C(15)	121.2(7)	C(52)-C(53)-C(54)	122.9(6)
C-C(2)-O(2)	121.9(6)	C(53)-C(54)-C(55)	117.6(6)
C-C(2)-N(21)	118.1(5)	C(54)-C(55)-C(56)	121.4(7)
O(2)-C(2)-N(21)	120.0(5)	C(51)-C(56)-C(55)	120.1(6)

analyses were performed on a Heraeus CHNO rapid analyser. The starting α,β-unsaturated *N*-acyloxazolidinones and *N*-enoylsultams were prepared by the literature methods.[5,6]

General Procedure of Addition of Iodine Azide to the Olefins

To a stirred slurry of sodium azide (0.16 g, 2.5 mmol) in acetonitrile (5 mL) cooled in a methanol-ice cold bath was added slowly iodine monochloride (0.24 g,1.5 mmol). The reaction mixture was stirred for an additional 10 min and, after 1 mmol of olefin was added, allowed to warm to room temperature and stirred for 20 h. The red-brown slurry was poured into 20 mL of water, and the mixture was extracted with ether (3 x 20 mL). The combined ether extracts were washed with 30 mL of 5% aqueous sodium thiosulfate leaving a colorless, ethereal solution. This solution was washed with water (30 mL) and dried over anhydrous magnesium sulfate. Removal of solvent produced the iodo azide adduct. The chemical yield and diastereomeric excess are listed in Table 1. The pure isomer was separated by crystalization from benzene-cyclohexane or methanol. Details of spectral and analytical data are listed below.

(5*S*)-*N*-[(2*S*,3*S*)-3-zido-3-phenyl-2-iodopropanoyll-5-phenyloxazolidinone (2a)

mp 121-122 °C (from benzene-cyclohexane); IR (KBr) 2120 (N_3), 1780 (NC=O), 1705 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30-7.44 (*m*, 10H), 6.09 (*d*, 1H, J=11.2 Hz), 5.57 (*dd*, 1H, J=8.9, 4.3 Hz), 5.05 (*d*, 1H, J=11.2 Hz), 4.80 (*t*, 1H, J=8.9 Hz), 4.34 (*dd*, 1H, J=8.9, 4.3 Hz); Anal. Cacld for $C_{18}H_{15}N_4O_3I$: C, 46.77; H, 3.17; N, 11.76. Found: C, 47.12; H, 3.30; N, 12.10.

(5*S*)-*N*-[(2*S*,3*S*)-3-azido-3-phenyl-2-iodopropanoyl]-5-benzyloxazolidinone (2b)

mp 126-131 °C (from benzene-cyclohexane); IR (KBr) 2125 (N_3), 1775 (NC=O), 1700 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25-7.48 (*m*, 10 H), 6.06 (*d*, 1H, J=11.1 Hz), 5.19 (*d*, 1H, J=11.1 Hz), 4.84 (*m*, 1H), 4.27 (*m*, 2H), 3.35 (*dd*, 1H, J=13.5, 3.4 Hz), 2.82 (*dd*, 1H, J=13.5, 3.4 Hz), 2.82 (*dd*, 1H, J=13.5, 9.7 Hz). Anal. Calcd for $C_{19}H_{17}N_4O_3I$: C, 47.92; H, 3.60; N, 11.76; Found: C, 48.84; H, 3.70; N 11.91.

(5*S*)-*N*-[(2*R*,3*R*)-3-azido-3-phenyl-2-iodopropanoyl]-5-benzyloxazolidinone (3b)

mp 115-117 °C (from methanol of the residue of mother liquid of **2b**); IR (KBr) 2120 (N_3), 1780 (NC=O), 1695 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25-7.48 (*m*, 10H), 6.10 (*d*, 1H, J=11.1 Hz), 5.20(*d*, 1H, J=11.1 Hz), 4.78(*m*, 1H), 4.29(*m*, 2H), 3.36(*dd*, 1H, J=13.5, 3.3 Hz), 2.93 (*dd*, 1H, J=13.5, 9.1 Hz). Anal. Calcd for $C_{19}H_{17}N_4O_3I$: C, 47.92; H, 3.60; N, 11.76; Found: C, 48.16; H, 3.64; N, 11.78.

(5*S*)-*N*-[(2*S*,3*S*)-3-azido-2-iodobutanoyl]-5-benzyloxazolidinone (2c)

mp 97-100 °C (from benzene-cyclohexane); IR (KBr) 2130 (N_3), 1785 (NC=O), 1700 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25-7.40 (*m*, 10H), 5.65 (*d*, 1H, J=10.2 Hz), 4.78 (*m*, 1H), 4.27 (*m*, 2H), 3.33 (*dd*, 1H, J=13.4, 3.4 Hz), 2.78 (*dd*, 1H, J=13.4, 9.8 Hz); Anal. Cacld for $C_{14}H_{15}N_4O_3I$: C, 40.60; N, 13.53; H, 3.65; Found: C, 41.40, N, 13.17; H, 3.78.

N-[(2S,3S)-3-azido-3-phenyl-2-iodopropanoyl]bornane-10,2-sultam (2d)

mp 163-165 °C (from methanol); IR (KBr) 2120 (N_3), 1680 (C=O), 1330, 1220 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.26-7.48 (*m*, 5H), 5.21 (*d*, 1H, J = 10.7 Hz), 5.08 (*d*, 1H, J = 10.7 Hz), 4.09 (*t*, 1H, J = 7.0 Hz), 3.54 (*s*, 2H), 0.95-2.25 (*m*, including two singlets at 1.20, 1.00, 3H each, 13H overall); Anal. Calcd for $C_{19}H_{23}N_4O_3SI$: C, 44.37; N, 10.89; H, 4.51; Found: C, 44.43; N, 10.96; H, 4.47.

N-[(2S,3S)-3-azido-2-iodobutanoyl]bornane-10,2-sultam (2e)

mp 152-154 °C (from benzene-cyclohexane); IR (KBr) 2120 (N_3), 1690 (C=O), 1330, 1220 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.86 (*d*, 1H, J = 9.6Hz), 3.96-4.09 (*t* and *m*, 1H each, J = 6.6Hz), 3.50 (*d*, 2H, J = 2 Hz), 0.9-2.15 (*m*, including two singlets at 1.19, 0.98, 3H each, 13H overall); Anal. Calcd for $C_{14}H_{21}N_4O_3SI$: C, 37.18; N, 12.38; H, 4.68; Found: C, 37.38; N, 11.46; H, 4.65.

ACKNOWLEDGMENT

We thank the National Science Council of the Republic of China for financial support of this work. We are grateful to Dr. Lendon Pridgen, SmithKline Beecham Pharmaceuticals for the gift of chiral oxazolidinones

Received October 14, 1991.

Key Words

Enantioselective; *N*-Enoyl-sultam; *N*-Acyloxazolidinones.

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9. Crytal Data of **2a**: space group 12 with cell dimentions a = 14.153(5), b = 7.839(3), c = 17.11(1) A; β = 102.94(5)°. Intensity data were collected with monochromated Mo Kα radiation (λ = 0.7107 A). Least squares refinements were based on 1565 observed reflections ($I \geq 2\sigma(I)$). The final agreement indices are R = 0.035, R_w = 0.026.