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A regio and diastereoselective transformation of 3-dienyl-2-azetidinones to novel pyrroloxazine

Amit Anand, Gaurav Bhargava, Vipan Kumar, Mohinder P. Mahajan *

Department of Applied Chemistry, Guru Nanak Dev University, Amritsar 143005, India

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ABSTRACT

The regioselective nitroso Diels–Alder (NDA) cycloadditions of 3-dienyl-2-azetidinones with nitrosobenzene to generate oxazine-substituted β-lactams in excellent yields are reported. The amidiolytic ring opening of the cycloadducts with sodium methoxide followed by iodocyclization using I_2/K_2CO_3 etiquette to capitulate previously unknown, multisubstituted pyrroloxazine in outstanding yields is also accounted.

1. Introduction

The β-lactam nucleus has fascinated synthetic and medicinal chemists worldwide because of its biological significance and synthetic potential.[1–3] The synthetic versatility of these systems, in general, is based on the impressive variety of transformations derived through the ring cleavage of any of the four single bonds of the β-lactam ring.[5] Following the well-documented β-lactam synthon methodology,[4,5] β-lactams are precursors to β-amino alcohols and β-amino acids, which are useful building blocks for peptides containing nonproteinogenic amino acids.[6] This skeleton has also been used to introduce the C-13 side chain of the anticancer compound paclitaxel (taxol)[7] and has been employed for the synthesis of δ-lactone moiety in the total synthesis of the macrolide antitumor antibiotic, lankacidin C.[8] The β-lactams have also been employed in the preparation of bis-γ-lactams, pyrrolizidines, indolizidines, pyrrolidines, piperidines, cyclic enaminones, pyridones, oxazinones, and complex natural products through N1–C2 bond cleavage coupled with rearrangement reactions.[5,9] Despite the well-established synthetic versatility, the literature rationale suggests only a few reports on their transformation to novel azacycles.[9a,10]

As part of our enduring interest in building heterocyclic systems of biological enormity, the dienyl functionality of the diastereoselectively synthesized 3-dienyl-β-lactams[11] has been employed as 4π and 2π components in simple[12] and Lewis acid-mediated carbo[13] and hetero Diels–Alder reactions, respectively.[14] In continuation of these studies and as an extension to explore the utility of 3-dienyl-2-azetidinones in the synthesis of azaheterocycles, we report herein, a simple protocol on their transformations to novel pyrolloxazines. The methodology involves the regioselective nitroso Diels–Alder (NDA) cycloaddition of 3-dienyl 2-azetidinones followed by the distereoselective transformation of the cycloadducts to yield pyrolloxazines.

Thus, the treatment of **1a–e** with 1.1 equiv of nitrosobenzene **2** in dry dichloromethane resulted in the formation of regio- and diastereoselective NDA adducts **3a–e** in excellent yields (85–90%) (Scheme 1).

The cycloadducts **3a–e**, so obtained, were characterized as 1,4-disubstituted-3-(2-phenyl-3,6-dihydro-2*H*-1,2-oxazin-6-yl)azetidin-2-ones on the basis of analytical data and spectral evidences. The ^{1}H NMR spectra of the crude adducts revealed the exclusive formation of the *meta* regiomer **3** through the approach of nitrosobenzene toward the *Re* face of the preferred conformation of the 3-dienyl-β-lactam **1.** The formation of the other regiomer **3'** was not observed even in traces.

The compound **3a**, for example, analyzed for $C_{25}H_{22}N_2O_2$ showed the molecular ion peak at 382. Its IR spectrum exhibited sharp absorptions at 1384 and 1484 cm^{-1} corresponding to cyclic nitroso compound and a sharp absorption at 1747 cm^{-1} due to the carbonyl of the lactam ring. The salient features of the ^{1}H spectrum include a doublet of a doublet at δ 3.44(J = 2.4 Hz, 7.5 Hz) corresponding to H^2, a doublet of an AB quartet at δ 3.85(J = 2.1 Hz, 2.4 Hz, 16.2 Hz) due to H^6 and H^7, a doublet at δ 5.08(J = 7.5 Hz) corresponding to H^3, and a doublet at δ 5.12(J = 2.4 Hz) due to H^1. Its ^{13}C spectrum also attests to the presence of the requisite number of carbons which include the characteristic carbon peaks

* Corresponding author. Tel.: +91 183 225880209x3320; fax: +91 183 2258819/2258820.
E-mail address: mahajanmohinderp@yahoo.co.in (M.P. Mahajan).

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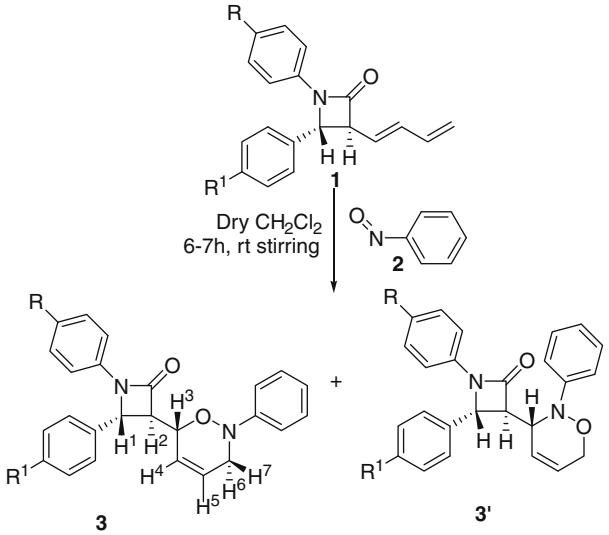


Entry	R	R^1	Reaction Time (min)	% yield
3a	H	H	6.1	90
3b	Cl	H	6.0	90
3c	H	Cl	6.3	88
3d	CH_3	H	6.7	85
3e	CH_3	Cl	7.0	86

(i)All the reactions were conducted using CH_2Cl_2 as solvent.
(ii) Yields of the adducts were recorded prior to crystallization

Scheme 1. Regioselective preparation of NDA cycloadducts **3**.

for methylene at δ 51.6 and carbonyl at δ 164.1, respectively.[15] The observed cycloadducts were configured as *meta*-regiomers on the basis of literature reports on the cycloaddition reactions of 1-substituted dienes with nitroso dienophiles.[16] The observed *meta*-regioselectivity in these nitroso Diels–Alder cycloadditions is probably due to the favorable electronic factors and unfavorable steric interaction between the phenyl groups of nitrosobenzene and lactam ring as the diene approaches the dienophile for the formation of *ortho*-isomer.

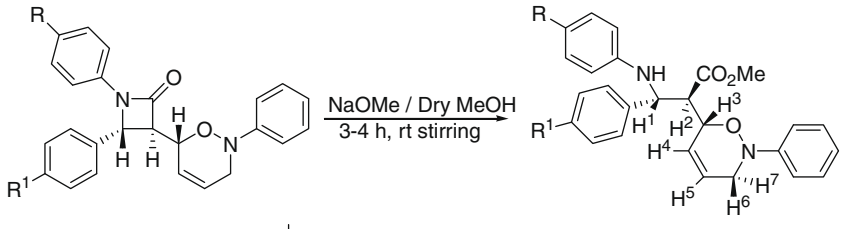
Our next synthetic target, the selective cleavage of N1–C2 bond 6a,b of the cycloadduct **3** leaving rest of the molecule impervious, was achieved by the treatment of **3** with two molar equivalents of sodium methoxide for 3–4 h in dry methanol at room temperature. It resulted in the isolation of 3,3-disubstituted-2-(2-phenyl-3,6-dihydro-2*H*-[1,2]oxazin-6-yl)-propionic acid methyl ester **4** in good yields (60–65%) (Scheme 2).

The compound 3-phenyl-3-phenylamino-2-(2-phenyl-3,6-dihydro-2*H*-[1,2]oxazin-6-yl)-propionic acid methyl ester **4a**, for example, analyzed for $C_{26}H_{26}N_2O_3$ showed a molecular ion peak at *m/z* 414. Its IR spectrum exhibited sharp absorptions at 1452, 1382, and 1250 cm^{-1} corresponding to cyclic nitroso compound and a sharp absorption at 1740 cm^{-1} due to the carbonyl of the ester. The salient features of its ^1H spectrum include a singlet at δ 3.43 corresponding to three methoxy protons, a doublet of a doublet at δ 3.56(J = 4.8 Hz, 9.6 Hz) corresponding to H^2 proton, a doublet of an AB quartet at δ 3.86(J = 2.1 Hz, 2.7 Hz, 16.2 Hz) due to the methylene H^6 and H^7 protons, a doublet at δ 4.77(J = 4.5 Hz) corresponding to H^1 proton, and another doublet at δ 5.07(J = 9.6 Hz) due to H^3 proton. Its ^{13}C spectrum showed the presence of the required carbons including the characteristic methylene carbon at δ 51.7 and carbonyl carbon at δ 173.1.[17]

Intramolecular cyclization of the product **4**, through the attack of free nitrogen atom onto the olefenic double bond of the oxazine ring was our subsequent synthetic endeavor and was conveniently realized using the usual iodocyclization protocol. Thus, the amino-esters **4a–e** on treatment with I_2 / K_2CO_3 in dry dichloromethane resulted in the isolation of octahydropyrroloxazines derivatives **5a–e** in excellent yields (85–90%). The iodocyclization resulted in an exclusive formation of a single diastereomer as evident through the single bond rotation of the amino ester **4** as depicted in Scheme 3.

The diastrereomerically pure, novel, and highly functionalized pyrroloxazine **5a**, for example, analyzed for $C_{26}H_{25}IN_2O_3$ showed a molecular ion peak at *m/z* 540(M^+) in its mass spectrum. Its IR spectrum exhibited sharp absorptions at 1450, 1352, and 1250 cm^{-1} corresponding to cyclic nitroso compound and a sharp absorption at 1738 cm^{-1} due to the carbonyl of the ester.

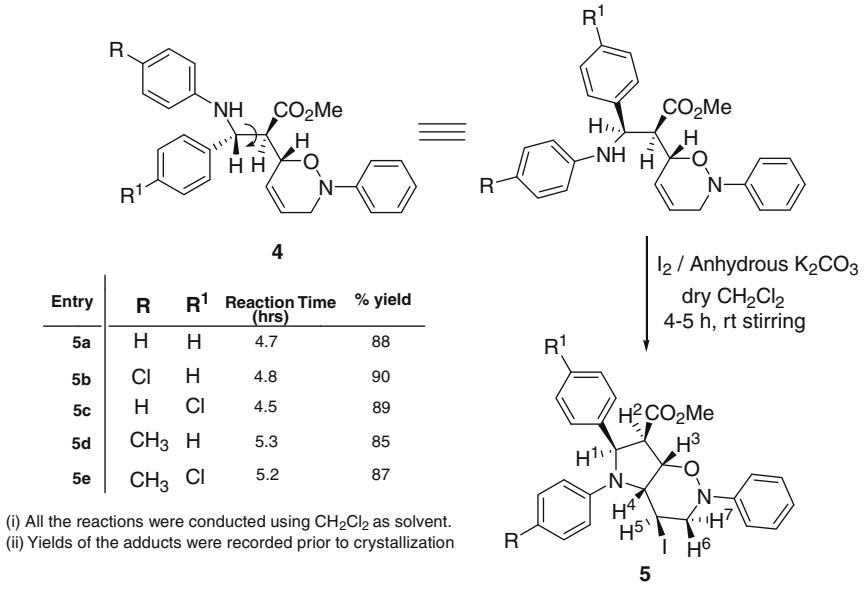
The salient features of its ^1H spectrum include a singlet at δ 3.13 corresponding to three methoxy protons, a doublet of an AB quartet at δ 3.47(J = 2.7 Hz, 3.3 Hz, 13.8 Hz) due to methylene H^6 and H^7 protons, a doublet of a doublet at δ 3.58(J = 1.8 Hz, 7.5 Hz) corresponding to H^2 proton, a doublet of a doublet at δ 5.07(J = 3.0 Hz, 5.4 Hz) corresponding to H^4 proton, a doublet of a doublet δ 5.17(J = 3.0 Hz, 5.4 Hz) due to H^5 proton, a doublet of a doublet at δ 5.31(J = 1.8 Hz, 3.0 Hz) corresponding to H^3 proton and a dou-



Entry	R	R^1	Reaction Time (hrs)	% yield
4a	H	H	3.3	65
4b	Cl	H	3.0	64
4c	H	Cl	3.2	62
4d	CH_3	H	3.9	60
4e	CH_3	Cl	4.0	61

(i)All the reactions were conducted using CH_2Cl_2 as solvent.
(ii) Yields of the adducts were recorded prior to crystallization

Scheme 2. Sodium methoxide interceded N1–C2 ring cleavage of cycloadducts **3**.



Entry	R	R^1	Reaction Time (hrs)	% yield
5a	H	H	4.7	88
5b	Cl	H	4.8	90
5c	H	Cl	4.5	89
5d	CH_3	H	5.3	85
5e	CH_3	Cl	5.2	87

(i) All the reactions were conducted using CH_2Cl_2 as solvent.
(ii) Yields of the adducts were recorded prior to crystallization

Scheme 3. Iodocyclization of amino esters **4**.

blet at δ 5.61(J = 7.5 Hz) assigned to H^1 proton. Its ^{13}C spectrum showed characteristic methylene carbon at δ 58.2 and carbonyl carbon at δ 170.0 to substantiate the assigned structure.[18] The assigned structure was unambiguously confirmed as pyrroloxazine, **5a** with the help of X-ray diffraction studies.[19] (Fig. 1).

In conclusion, a novel route to previously unknown multi functionalized pyrroloxazine utilizing the well-established β-lactam synthon methodology has been developed. This approach further assumes significance as this happens to be the first report on the synthesis of novel pyrroloxazine derivatives.

2. Experimental section

2.1. General procedure for the preparation of 3-oxazinyl-substituted 2-azetidinones 3a–e

To a well stirred green colored solution of nitrosobenzene **2** (1.1 mmol) in dry dichloromethane (20 ml) was added a solution of 3-dienyl-2-azetidinone **1** (1.0 mmol) in dry dichloromethane (25 ml). The reaction mixture was stirred for a period of 6–8 h and the progress of the reaction was monitored through TLC. The crude product was extracted with dichloromethane (50 ml) and washed with water (25 ml). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuo. The product so obtained was purified by flash chromatography on silica gel using mixture of (4:1) hexane and ethyl acetate as the eluent.

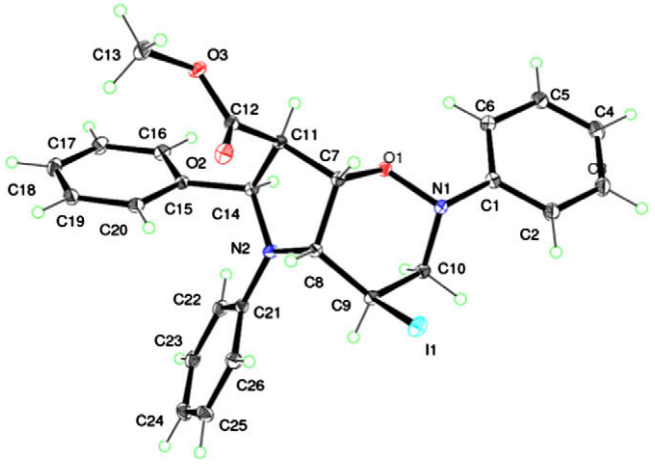


Figure 1. ORTEP diagram of pyrroloxazine **5a**.

2.2. General procedure for the N1–C2 bond cleavage of 3-oxazinyl-substituted 2-azetidinones 3

2.2.1. Synthesis of 2-oxazinyl substituted propionic acid methyl esters 4

A solution of sodium methoxide (2 mmol) in dry methanol was added dropwise to a stirred solution of **3** (2 mmol) in dry methanol. The progress of the reaction was monitored through TLC and on completion was quenched with water (50 ml) and extracted with dichloromethane (50 ml). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuo. The crude product thus obtained was purified by flash chromatography on silica gel using mixture of (5:1) hexane and ethyl acetate as the eluent.

2.3. General procedure for Iodocyclization of esters 4 to pyrroloxazines 5

To a well stirred suspension of K_2CO_3 (5 mmol) in dry dichloromethane (50 ml) was added molecular iodine (1 mmol) till the solution acquires violet coloration. To this was added a solution of ester **4** (1 mmol) in dry dichloromethane (20 ml) and the progress of the reaction was monitored through TLC. The reaction mixture was then filtered, washed with water (50 ml), and extracted with dichloromethane (50 ml). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuo. The crude product so obtained was purified by flash chromatography on silica gel using a mixture of (5:1) hexane: ethyl acetate as the eluent and recrystallized using hexane: ethyl acetate mixture (10:1).

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15. *1,4-Diphenyl-3-(2-phenyl-3,6-dihydro-2H-1,2-oxazin-6-yl)azetidin-2-one* (**3a**): white solid, mp: 118–119 °C δ_H ($CDCl_3$, 300 MHz), 3.44(dd, 1H, J = 2.4 Hz, 7.5 Hz, H_2), 3.85(dABq, 2H, J = 2.1 Hz, 2.4 Hz, 16.2 Hz, $-CH_2$), 5.08(d, 1H, J = 7.5 Hz, H_3), 5.12(d, 1H, J = 2.4 Hz, H_1), 6.1(s, 2H, $H_{4,5}$), 6.95–7.36(m, 15H, ArH, aromatic). δ_C ($CDCl_3$, 75 MHz), 51.6, 58.3, 62.6, 75.7, 115.8, 117.0, 122.4, 123.9, 124.8, 125.9, 126.8, 128.3, 128.4, 129.0, 129.1, 137.4, 137.5, 149.8, 164.1, m/z 382 (M^+). ν_{max} (KBr)/cm^{-1} 1747, 1484, 1384. Anal. Calcd for $C_{25}H_{22}N_2O_2$: C, 78.51; H, 5.80; N, 7.32. Found: C, 78.67; H, 5.95; N, 7.15.
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17. *Methyl 3-phenyl-2-(2-phenyl-3,6-dihydro-2H-1,2-oxazin-6-yl)-3-(phenylamino)-propanoate* (**4a**): white solid, mp: 132–133 °C δ_H ($CDCl_3$, 300 MHz) 3.43(s, 3H, $-OCH_3$), 3.56(dd, 1H, J = 4.8 Hz, 9.6 Hz, H_2), 3.86(dABq, 2H, J = 2.1 Hz, 2.7 Hz, 16.2 Hz, $-CH_2$), 4.77(d, 1H, J = 4.5 Hz, H_1), 5.07(d, 1H, J = 9.6 Hz, H_3), 6.08(s, 2H, $H_{4,5}$), 6.54–7.28(m, 15H, ArH, aromatic). δ_C($CDCl_3$, 75 MHz), 50.2, 51.5, 51.8, 55.6, 77.3, 113.2, 115.3, 117.4, 122.1, 125.6, 126.1, 126.2, 127.3, 128.5, 128.6, 129.2, 140.4, 146.3, 173.1, m/z 414 (M^+). ν_{max} (KBr)/cm^{-1} 1740, 1452, 1382, 1250. Anal. Calcd for $C_{26}H_{26}N_2O_3$: C, 75.34; H, 6.32; N, 6.75. Found: C, 75.57; H, 6.86; N, 6.39.
18. *Methyl 4-iodo-2,5,6-triphenyloctahydropyrrolo[2,3-e][1,2]oxazine-7-carboxylate* (**5a**): pale yellow solid, mp: 110–111 °C δ_H ($CDCl_3$, 300 MHz) 3.13 (s,3H, $-OCH_3$), 3.47 (dABq, 2H, J = 2.7 Hz, 3.3 Hz, 13.8 Hz, $-CH_2$), 3.58 (dd, 1H, J = 1.8 Hz, 7.5 Hz, H_2), 5.07 (dd, 1H, J = 3.0 Hz, 5.4 Hz, H_4), 5.17 (dd, 1H, J = 3.0 Hz, 5.4 Hz, H_5), 5.31 (dd, 1H, J = 1.8 Hz, 3.0 Hz, H_3), 5.61 (d, 1H, J = 7.5 Hz, H_1) 6.56–7.30 (m, 15H, ArH, aromatic). δ_C ($CDCl_3$, 75 MHz), 25.5, 51.5, 53.7, 58.2, 63.5, 66.3. 79.1, 116.3, 118.4, 118.7, 123.1, 127.4, 127.8, 128.6, 128.8, 137.5, 143.3, 149.6, 170.0, m/z 540 (M^+). ν_{max} (KBr)/cm^{-1} 1738, 1450, 1352, 1250. Anal. Calcd for $C_{26}H_{25}IN_2O_3$: C, 57.79; H, 4.66; N, 5.18. Found. C, 57.96; H, 4.95; N, 5.04.
19. *X-Ray crystal data and structure refinement for* **5a**. CCDC 728091 (for **5a**) contains the supplementary crystallographic data for this Letter. $C_{26}H_{25}IN_2O_3$, V = 2326.05(13) $Å^3$ Mr = 540.38 Z = 4 Monoclinic, $P21/c$ Mo $K\alpha$ a = 13.2246(4) Å, μ = 1.41 mm^{-1}, b = 15.7738(5) Å, T = 100(2) K, c = 11.5290(4) Å 0.27 × 0.22 × 0.02 mm, β = 104.719(2)° *Data collection* BrukerAXS ApexII-CCD area detector diffractometer 6811 independent reflections Absorption correction: multi-scan BRUKER SADABS 5820 reflections with $I > 2\sigma(I)$, T_{min} = 0.843, T_{max} = 0.97, R_{int} = 0.038 73968 measured reflections. *Refinement* $R[F2 > 2\sigma(F2)]$ = 0.026 290 parameters, $wR(F2)$ = 0.063 H-atom parameters constrained Acta C preprint 2 S = 1.06, $\Delta\rho_{max}$ = 1.07 $eÅ^{-3}$, 6811 reflections, $\Delta\rho_{min}$ = −0.37 $eÅ^{-3}$.