Facially Selective Oxo-Diels-Alder Cycloadditions of α-dienyl-β-lactam: An entry to pyrano-tethered β-lactams bifunctional hybrids

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ABSTRACT

The functionalization of β-lactams at C-3 position are useful for the strategic improvement in both the dimensions, namely synthetic utility, as versatile intermediate in organic synthesis and biological potential of these heterocyclic systems. The present manuscript involved the π-facial selective synthesis β-lactam hybrids employing highly regioselective and diastereoselective Oxo-Diels–Alder reaction of diethyl ketomalonate with α-dienyl-β-lactam with stereocentres at its α- and β- positions. This protocol provided the cycloaddition of α- and β- stereocentric diene with symmetrical heterodienophiles forming biologically potent regioselective and diastereoselective α-lactams substituted pyrano bifunctional hybrids in good yields and β-facial selectivity.

Keywords: Regioselective synthesis, π-facial selective synthesis, Diastereoselective synthesis, β-lactams, Dienyl-β-lactams.

INTRODUCTION

The hetero-Diels–Alder (HDA) reactions1-5 are significant tools in establishing 6-membered heterocyclic scaffolds having immense biological relevance. A variety of hetero-Diels-Alder reactions ensured an opening for the development of diverse heterocyclic systems. HDA reactions drew a lot of attention because of their extensive industrial and other important applications.6-8 Different variants of HDA reactions have been explored for a highly efficient stereoselective9-13 synthesis of six-membered ring compounds. Of these, oxo-Diels-Alder (ODA)14-18 variant has considerable potential because of the tactical formation of a variety of six membered derivatives such as dihydropyrans, dihydropyrones etc.

On the other hand, the β-lactams C-3 functionalization19 has continual significant concern of chemists because of its use as important core in the fabrication of organic compounds and their therapeutic biological uses. These 3-substituted prototypes are an important building blocks for development of conformationally constrained and medicinally potent products or for library generation.
of highly functionalized β-lactams. These C-3 functionalized lactam can efficiently prepared by employing variety of synthetic transformations at its C-3 position.

On the other hand, Diels Alder cycloaddition of functionalized dienes having stereocenter at its α-position have earlier been explored for the preparation of number of functionalized carbocyclic/heterocyclic compounds using variety of functionalized dienophiles. However, the Diels-Alder cycloadditions of dienes involving stereocenters at its α and β-positions are still scare in literature. Earlier, diastereoselective Diels Alder cycloadditions of such functionalized dienes like 3-butadienyl-β-lactam are explored for the preparation of number of heterocycles. However, the concerned reports on the HDA reactions of 3-butadienyl-β-lactam with hetero-dienophiles are still need to be explored. The cycloadditions of 3-dienyl-2-azetidinones are an important in term of recent usefulness of 1, 3, 4-tri-substituted-β-lactams for various biological activities.

We report herein an earlier unexplored, useful uncatalyzed strategy for the synthesis of functionalized β-lactam pyrano bifunctional hybrids bearing different substituents at 1, 3 & 4-positions of lactam ring (Scheme 1). The methodology involved the synthesis of 3-butadienyl-β-lactams and their previously unexplored regio-, diastereo- and π-facially selective Oxo-Diels–Alder reactions with symmetrical Oxo-dienophile such as diethyl ketomalonate in absence of any catalyst to afford β-lactam pyrano bifunctional hybrids in excellent yields.

RESULTS AND DISCUSSION

The initial trans and cis-3-butadienyl-2-azetidinones 1a-c & 4a-b needed in this work were obtained through the reaction of in situ formed butadienylketene which is obtained in dry chloromethane from sorbyl chloride and triethylamine with N-aryl and N-aliphatic imines respectively.

These 3-butadienyl-2-azetidinones 1a-c & 4a-b were investigated for oxo-DA cycloaddition reactions with symmetrical oxo-dienophile viz. diethyl ketomalonate 2. Our studies were initiated with the treatment of 3-butadienyl-2-azetidinones 1a and symmetrical diethylketomalonate 2 using different set of reaction conditions to get these conditions optimized for cycloadducts Table 1.

| Entry | Solvent       | Yield(%) | Reaction conditions |
|-------|---------------|----------|---------------------|
| 1     | Dichloromethane | 0        | 48 rt               |
| 2     | Dichloromethane | 10       | 48 40               |
| 3     | Chloroform    | 25       | 48 62               |
| 4     | Toluene       | 62       | 48 rt               |
| 5     | Toluene       | 82       | 36 110              |
| 6     | Xylene        | 52       | 48 rt               |
| 7     | Xylene        | 73       | 36 110              |
| 8     | Dioxane       | 20       | 48 100              |
| 9     | DMF           | 15       | 48 110              |

The oxo-DA cycloaddition delivered the diastereo- and π-facially selective 2-azetidinone substituted pyrano-lactam bifunctional hybrid in good yields. Very low yields were detected in the reactions of 1 with 2 in solvent such as dichloromethane and chloroform even upon refluxing (Table 1, entries 1-3). Gratifyingly, toluene was found to be the appropriate solvent to give the optimized yield of diastereoselective and regioselective cycloadduct 3 at refluxing temperature (110°C, Table 1, entries 4-5) in comparison to the other solvents with the target product in 82% yield. Xylene also provided the same product in 73% yield (110°C; time 36 h; Table 1, entries 6-7). The oxo-DA cycloaddition of 1 and 2 in dioxane and DMF also proved ineffective and afforded poor yields (Table 1, entries 8-9).

Treatment of 3-butadienyl-2-azetidinones 1a & 1b and 4 with symmetrical oxo-dienophiles 2 without using any Lewis acid give rise to the selective construction of exo-adducts 3a & 3b and 5 respectively in good yields Table 2. Diastereomerically pure, functionalized 6-(2-oxo-1,4-diphenyl-azetidin-3-yl)-3,6-dihydro-pyran-2,2-dicarboxylic acid diethyl ester 3 thus achieved were characterized based on analytical data and spectroscopic studies.

Treatment of 1a & 1b with diethylketomalonate 2 produced very good yield of exo adducts 3a & 3b (77-84%, Table 2). The desirable output with respect to yields with good selectivities is obtained in refluxing toluene at 110°C. However, this synthesis
was also studied in xylene under similar conditions but poor yield was obtained Table 2.

Table 2: Oxo-DA reactions of 3-butadienyl-2-azetidinones

| Reaction | Toluene (%) | Xylene (%) |
|----------|-------------|------------|
| 3a        | 82%         | 73%        |
| 3c        | 84%         | 74%        |

The compound, 3a (C_{26}H_{27}O_{6}N) was characterized by mass spectrometry that showed a molecular ion peak m/z at 449. A sharp absorption peak at 1727 cm^{-1} is observed in its IR spectrum because of the presence of carbonyl group of \( \beta \)-lactam ring. \(^1\)H NMR (400 MHz) spectrum characterization represented a distinctive multiplet at δ 5.04 corresponding is shown due to the presence of H4 of the \( \beta \)-lactam ring. Further, two doublets at δ 2.90 (\( J = 17.44 \) Hz) and δ 2.72 (\( J = 17.32 \) Hz) corresponding to 8a & 8b respectively, a doublet at δ 4.96 due to H5 (\( J = 2.44 \) Hz), two multiplets at δ 3.55 and δ 6.07 are also shown due to H3 and H6 respectively in the \(^1\)H NMR spectrum of 3a. Three carbonyl carbons at δ 164.2, 167.8 and 168.4 ppm have been observed in the \(^13\)C NMR spectrum of 3a.

We further, explored the synthesis of trans 3-butadienyl-2-azetidinones 4 using heterodienophile 2. Diastereoselective, regioselective and \( \pi \)-facially selective pure functionalized exo 6-(1-cyclohexyl-2-oxo-4-phenyl-azetidin-3-yl)-3,6-dihydro-pyran-2,2-dicarboxylic acid diethyl ester 5 is yielded in the reaction. The reaction between 4 and diethylketomalonate 2 gave endo adduct in very good yields (81-83%). Reactions in refluxing toluene (110°C) by employing diethyl ketomalonate 2 as a heterodienophile provided the better yields of products as compared to the xylene (69-72%, Table 2.

The compound, 5 (Fig. 1) upon mass spectrometric characterization indicated a molecular ion peak at m/z 455. IR spectrophotometric analysis presented a peak at 1727 cm^{-1}, because of C=O group of \( \beta \)-lactam ring. Further, the \(^1\)H NMR presented a characteristic multiplet at δ 5.33 corresponding to CH of cyclohexyl ring, a doublet at δ 4.88 pertaining to \( \beta \)-lactam ring H₅ (\( J = 5.4 \) Hz), a dd at δ 2.57 (\( J = 2.2, 4.96 \) & 17.1 Hz) corresponding to 8a and a dd at δ 2.28 (\( J = 2.72 \) & 17.24 Hz) corresponding to 8b, dd at δ 3.45 is assigned to H3 proton (\( J = 5.4, 10.2 \) Hz). The presence of 10.2 Hz coupling between H3 and H5 confirm the cis stereochemistry. The \(^13\)C NMR of 5 also gave the presence of three carbons of C=O group at δ 166.8, 167.9 and 168.0 ppm pertaining to the carbonyl of \( \beta \)-lactam and esters respectively.

In accordance with expectations, the DA synthesis of cis-/trans-3-dienyl-azetidin-2-ones 1a & 1b and 4 with oxo-dienophiles 2 led to exo adducts exclusively. The presence of \( \alpha \)-and \( \beta \)-stereocentres at the vicinity of the diene of 3-dienyl-\( \beta \)-lactams creates both facial sides of dienyl component distinguishable. Two possible exo adducts are expected, varying in stereo-relationship among the stereo-centres on the lactam and on the cyclohexyl scaffolds.
Due to the endo addition of dienophiles to lower facial side of butadiene, 3a & 3b adducts are formed. Steric hindrance between the approaching dienophiles and substitution at C-4 of lactam ring, upper facial attack of dienophiles is excluded.

**Experimental information**

Anhydrous solvents were obtained from Sigma Aldrich. Thin layer chromatographic technique (TLC) is performed on procured silica plates from Merck (0.2mm F254 Kieselgel). Visualisation of compounds is carried out under UV light. Bruker 400MHz spectrometer and 75MHz were utilized to record 1H NMR spectra and 13C NMR spectra respectively. Chemical shifts (δ) are quoted in ppm (parts per million) in reference to the internal solvent (d-CHCl₃) δ=7.26 for 1H and δ=77.2 for 13C NMR. Coupling constants (J) are presented in Hz and chemical shifts values are shown in δ (ppm) values. Characterization data is described as followed: chemical shift, multiplicity (singlet-s, broad singlet-br s, doublet-d, triplet-t, double of doublet-dd, double of triplet-dt, multiplet-m), coupling constant (Hz) and integration. Brucker-microOTOF-Q II mass spectrometer was utilized to get the high resolution mass spectra. Melting points determined are uncorrected and recorded using open capillary method on Digital Melting Point Apparatus. Perkin Elmer-Spectrum II spectrophotometer was used for recording IR spectra.

**General synthetic Procedure for the formation of 3 and 5**

Diethyl ketomalonate (2) was added to a well-stirred solution of cis/trans-3-butadienylazetidin-2-one 1a & 1b and 4 (1eq.) in toluene (5 mL) at room temperature. The reaction was allowed to reflux for 24 hours. The monitoring of the progress was done using TLC considering 3-butadienylazetidin-2-one as a limiting reactant. After the reaction gets completed, removal of the solvent was achieved under reduced pressure. The purification of the initially obtained product was done through column chromatography employing a mixture of hexane-EtOAc (80:20) as an eluent. The recrystallization of the products was performed with a mixture of diethyl ether and hexane which yielded pure products 3a, 3b and 5 Table 1 & 2.

**6-(2-Oxo-1,4-diphenyl-azetidin-3-yl)-3,6-dihydropyran-2,2-dicarboxylic acid diethyl ester (3a):**

Solid; Pale Yellow; mp 103-105°C. 1H-NMR (d-CHCl₃, 400MHz): δH=7.29 (m, 10 Aromatic H), 6.07 (m, 1 H, H₆), 5.76 (d(t), J=10.48, 1 H, H₇), 5.04 (m, 1 H, H₈a), 4.96 (d, J=2.44 Hz, 1 H, H₈b), 4.22 (d, 4 H, OCH₂CH₃), 3.55 (m, 1 H, H₃), 2.90 (d, J=17.44Hz, 1 H, H₈b), 2.72 (d, J = 17.32Hz, 1 H, H₈a), 1.27 (t, 3 H, OCH₂CH₃), 1.19 (t, 3 H, OCH₂CH₃) ppm. 13C NMR (d-CHCl₃, 75MHz): δₐ=13.9 (OCH₂CH₃), 14.2 (OCH₂CH₃), 29.3 (C₃a), 56.3 (C₃b), 62.3 (OCH₂CH₃), 62.4 (OCH₂CH₃), 62.9 (C₅), 70.1 (C₇), 80.2 (C₆), 117.2, 124.0, 124.7, 126.0, 128.2, 129.0, 129.1, 137.5, 137.7, 164.2 (N-CO-CH₃), 167.8 (COOCH₂CH₃), 168.4 (COOCH₂CH₃) ppm. MS: m/z = 449 [M⁺]

**6-(2-Oxo-4-phenyl-1-tolyl-azetidin-3-yl)-3,6-dihydropyran-2,2-dicarboxylic acid diethyl ester (3b):**

Solid; Pale Yellow; mp 104-106°C. 1H-NMR (d-CHCl₃, 400MHz): δH=7.19 (m, 9 ArH), 6.06 (m, 1 H, H₆), 5.76 (d(t), J=10.48 Hz, 1 H, H₇), 5.03 (m, 1 H, H₈a), 4.92 (m, 4 H, OCH₂CH₃), 3.53 (m, 1 H, H₈b), 2.89 (d, J=17.28 Hz, 1 H, H₈b), 2.71 (d, J=16.16 Hz, 1 H, H₈a), 2.25 (s, 3 H, Ph-CH₃), 1.27 (t, 3 H, OCH₂CH₃), 1.20 (t, 3 H, OCH₂CH₃) ppm. 13C NMR (d-CHCl₃, 75MHz): δₐ=13.9
6-{1-Cyclohexyl-2-oxo-4-phenyl-azetidin-3-yl)-3,6-dihydro-pyran-2,2-dicarboxylic acid diethyl ester (5):

Solid; Pale yellow; mp 101-103°C. 1H-NMR (d-CHCl3, 400MHz): δH=7.32 (m, 5 ArH), 5.95 (d, J=10.5 Hz, 1 H, H), 5.76 (unresolved dddd, 3.5, 5.7, 10.4 Hz, 1 H, H), 4.88 (d, J=6.4 Hz, 1 H, H), 4.23 (m, 1 H, H), 4.13 (q, 2 H, OCH2CH3), 3.97 (dd, J=7.1, 10.6 Hz, 1 H of OCH2CH3), 3.77 (dd, J=7.1, 10.6 Hz, 1 H of OCH2CH3), 3.45 (dd, J=5.4, 10.2 Hz, 1 H, H), 3.33 (m, 1 H, Cyclohexyl-CH), 2.57 (dddd, J=2.2, 4.96, 17.1 Hz, 1 H, H), 2.28 (dd, J=2.72, 17.24 Hz, 1 H, H), 2.05-1.25 (m, 8 H, Cyclohexyl-CHH), 1.20 (t, 3H, OCH2CH3) 1.16-1.04 (m, 2 H, cyclohexyl-CH2), 1.00 (t, 3 H, OCH2CH3), 25.0, 25.3, 29.0 (Cδ), 30.6, 31.4, 53.4, 57.1 (Cβ), 59.0, 61.5 (OCH2CH3), 61.8 (OCH2CH3), 63.2 (Cβ), 68.2 (Cδ), 79.1 (Cβ), 122.9, 126.6, 127.8, 128.0, 136.3, 166.8 (N-CO-CH), 167.9 (COOCH2CH3), 168.0 (COOCH2CH3) ppm. MS: m/z=463 [M+]

CONCLUSION

In conclusion, oxo-DA cycloadditions of α- and β-stereocentric diene with symmetrical heterodieneophiles have been explored for the fabrication of biologically potent 2-azetidinones functionalized pyrano hybrids with diastereoselectivity and π-facial selectivity. The reported protocol is a significant direct approach for the regio-controlled synthesis of diastereo- and facially selective functionalized lactams.

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