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Synthesis of some mono- and bis-spiro-β-lactams of benzylisatin

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Abstract—Some new mono- and bis-spiro-β-lactams of benzylisatin were prepared by Staudinger's ketene–imine [2+2] cycloaddition reaction. The cycloadducts were characterized by spectral data including ^{1}H NMR, ^{13}C NMR, IR and mass spectra. The configuration of benzylisatin and one of mono-spiro-β-lactams (**5a**) was established by X-ray crystal analysis.

The β-lactam skeleton is the key structural unit of β-lactam antibiotics. The importance of β-lactams for the treatment of bacterial infections have been amply established. Although β-lactam derivatives are well known for their antibiotic activities,[1] they have also been used as synthons for the synthesis of various natural and unnatural products.[2] 1,3,4-Trisubstituted β-lactams were found to be potent cholesterol absorption inhibitors,[3] human cytomegalovirus protease inhibitors,[4] and thrombin inhibitors.[5] Ojima et al. have shown the utility of bis-β-lactams for the synthesis of peptides.[6] Raghunathan et al. have synthesized a series of macrocyclic bis-β-lactams via a highly stereoselective [2+2] cycloaddition reaction.[7] The rapid emergence of bacterial strains resistant to members of this class of compounds require a continuous effort for the design and synthesis of novel derivatives. Spiro compounds represent an important class of naturally occurring compounds characterized by pronounced biological properties.[8] Spiro-β-lactams are interesting compounds due to their antiviral[9] and antibacterial properties.[10] Several syntheses of spiro-β-lactams have been described in the literature,[11] but to the best of our knowledge, there have been no reports of bis-spiro-β-lactams. Therefore in continuation of our work on the synthesis of novel β-lactams,[12] we present here the results obtained in the synthesis of isatin-derived mono- and bis-spiro-β-lactams using the efficient Staudinger reaction.

Isatin **1** was selected as the starting material because it has shown a wide variety of biological and pharmacological activities.[13,14] Since isatin is not soluble in the conventional solvents used for β-lactam synthesis, it was converted into its benzyl derivative **2** by reaction with benzyl bromide in the presence of calcium hydride in DMF.[15] The structure of **2** was confirmed by single-crystal X-ray diffraction. The molecular structure and labelling scheme are shown in Figure 1.[16]

Schiff bases **3** and **4a–c** were prepared by stirring 2,4-dimethoxyaniline and various aromatic di-amines with *N*-benzylisatin in the presence of a catalytic amount of acetic acid in refluxing ethanol. Crude imines **3** and **4a–c**were treated with different acyl chlorides in the presence of triethylamine in dichloromethane for

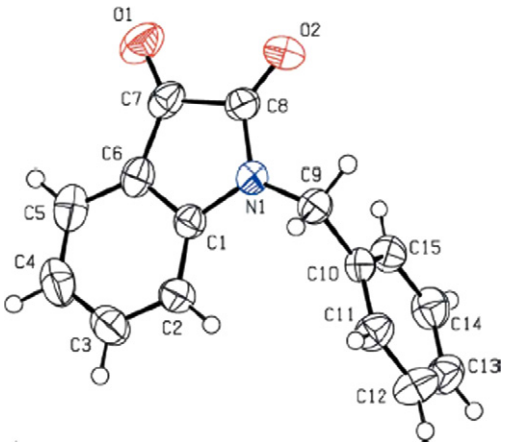

Figure 1. An ORTEP-3 drawing of **2**, with the atom-numbering scheme and 50% probability displacement ellipsoids.

Keywords: Isatin; Benzylisatin; Bis-spiro-β-lactam; Staudinger reaction.
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several hours to give mono- and bis-spiro-β-lactams **5a–d**[17] and **6a–f** in 50–70% yields (Scheme 1), as single diastereomers.

The reaction progress was monitored by TLC and the presence of a new compound was confirmed. In addition, the cycloadducts were characterized by spectral analysis. For **5a**, the IR spectrum shows the characteristic absorption of a β-lactam carbonyl at 1766 and isatin carbonyl at 1728 cm^{-1}. The ^1H NMR spectrum shows the methoxy protons as two singlets at 3.39 and 3.75, the benzylic protons as a doublet of doublets at 4.73 ppm ($J = 15$ Hz) and 5.10 ppm ($J = 15$ Hz), the β-lactam H-3 proton as a singlet at 5.64 and aromatic protons as a multiplet at 6.29–7.93. The ^{13}C NMR spectrum exhibited the following signals: CH_2 benzylic at 44.2, OMe at 55.2 and 55.5, C-3 of azetidinone ring at 69.9, C-4 (spiro carbon) at 86.0, and aromatic carbons at 99.5–159.3, the β-lactam carbonyl appeared at 163.4 and the isatin carbonyl at 173.8. The structure of mono-spiro-β-lactam **5a** was further confirmed by a single-crystal X-ray analysis (Fig. 2). In **5a**, the four- and five-membered rings are nearly planar, the dihedral angle between these two rings is 86.44°. The crystal structure is stabilized by intramolecular C—H···O hydrogen-bonding and van der Waals interactions.[18] The results for other mono-spiro-β-lactams are shown in Table 1.

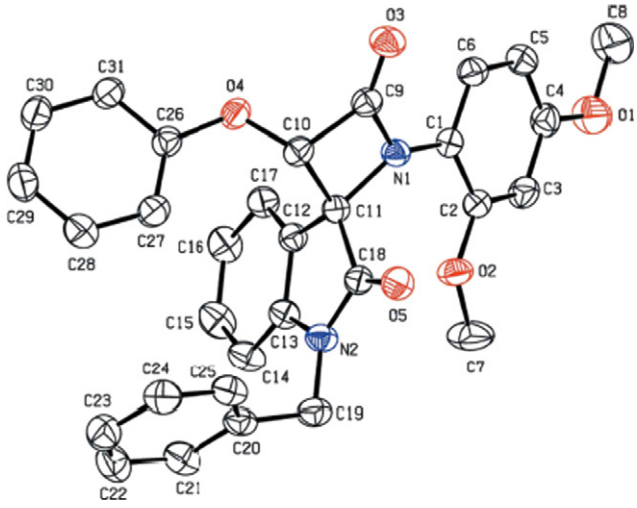
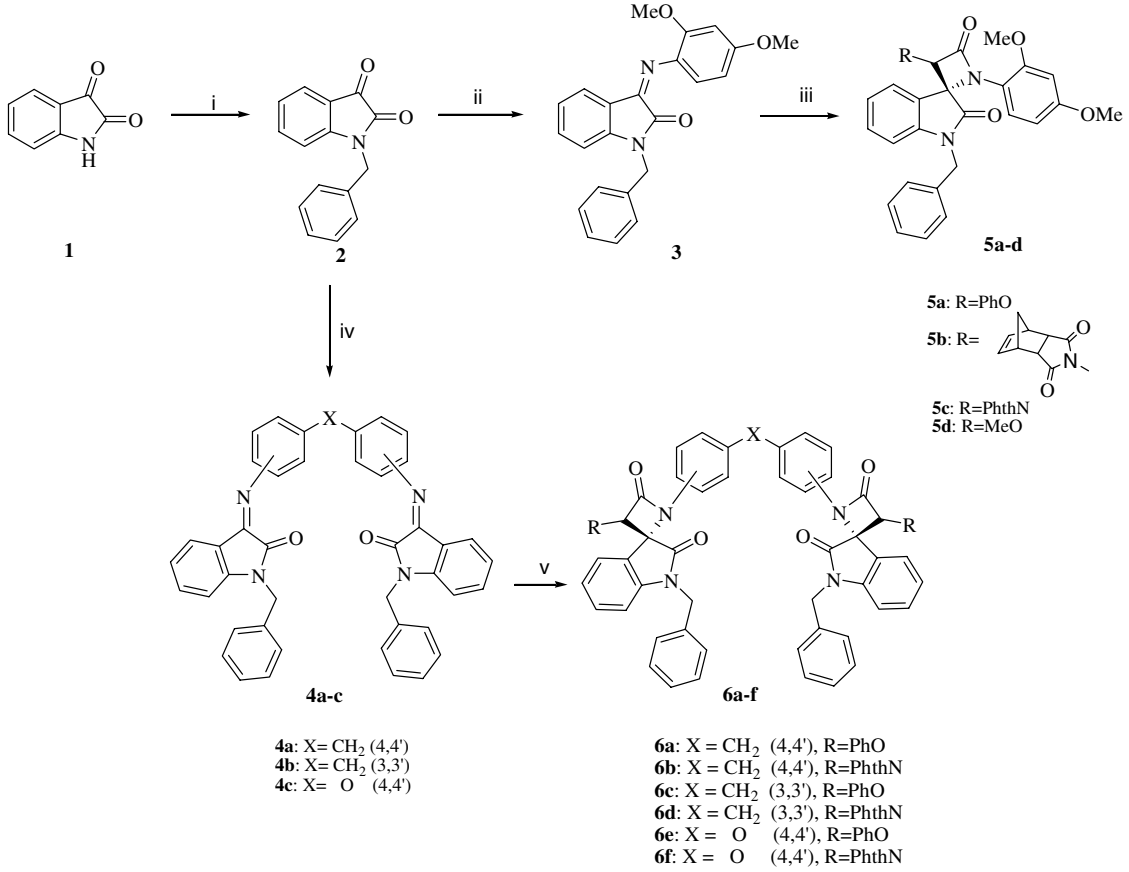


Figure 2. A view of **5a**, with the atom-numbering scheme and 30% probability displacement ellipsoids. All H atoms have been omitted for clarity.

In the synthesis of mono-spiro-β-lactams, it was found that the use of alkyloxy acetyl chlorides increase the yield of cycloaddition products. Furthermore, when this reaction was performed with phthaloylglycyl and 5-norbornene-2,3-dicarboxyloylglycyl chloride, similar products (**5b**,**c**) were obtained but with lower yields.



Scheme 1. Reagents and conditions: (i) benzyl bromide, CaH_2, DMF, 50 °C; (ii) 2,4-dimethoxyaniline, reflux in EtOH; (iii) RCH_2COCl, Et_3N, −10 °C to rt, CH_2Cl_2; (iv) Diamine, reflux in EtOH; (v) $R'CH_2COCl$, Et_3N, −10 °C to rt, CH_2Cl_2.

Table 1. Synthesis of mono-spiro-β-lactams **5a–d** from Schiff base **3** and different acyl chlorides in CH_2Cl_2

β-Lactam	R–CH_2COCl	Time (h)	Yield (%)
5a	PhO–	15	71
5b	5-Norbornene-2,3-dicarboxyloyN–	18	54
5c	PhthN–	18	60
5d	MeO–	15	70

Table 2. Synthesis of bis-spiro-β-lactams **6a–f** using different acyl chlorides in CH_2Cl_2

β-Lactam	Schiff base	R–CH_2COCl	Yield (%)
6a	**4a**	PhO–	67
6b	**4a**	PhthN–	63
6c	**4b**	PhO–	70
6d	**4b**	PhthN–	58
6e	**4c**	PhO–	66
6f	**4c**	PhthN–	66

Bisimines **4a–c** on reaction with various acid chlorides in the presence of triethylamine resulted in bis-spiro-β-lactams **6a–f** in moderate to good yields (Scheme 1, Table 2).

The cycloadducts were characterized by spectral analysis. The IR spectrum of 2-azetidinone **6a** shows a carbonyl peak at 1774 and the isatin carbonyl at 1720 cm^{-1}. The ^1H NMR spectrum exhibited the methylene protons at δ 3.77, the signals in the 4.69–5.02 correlated with benzylic protons, the signals in the 5.52 correlated with H(3) and the aromatic protons resonated in the 6.58–7.62 region. The ^{13}C NMR spectrum exhibited the following signals: Ph–C–Ph at 40.6, benzylic carbons at 44.5, C(3) at 66.9, the spiro carbon at 85.3, the aromatic carbons at 109.8–142.9, the β-lactam carbonyl at 156.6 and the isatin carbonyl at 161.4. The mass spectrum shows a peak at *m/e* 577 corresponding to $C_{37}H_{27}N_3O_4$. Changing the phenoxyacetyl chloride to the phthaloylglycyl chloride resulted in a lower yield of cycloaddition product.

This Letter describes the first examples of bis-spiro-β-lactams from reaction of di-imines and ketenes derived from phenoxy and phthaloylglycyl chlorides. These spiro β-lactams are now being studied as precursors of modified β-amino acids, β-peptides and monobactam analogues.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.07.199.

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17. *General procedure for the synthesis of mono- and bis-spiro-β-lactams*: A solution of the acid chloride (6.00 mmol) in dry CH_2Cl_2 (15 mL) was slowly added to a solution of Schiff base (1.0 mmol) and triethylamine (9 mmol) in CH_2Cl_2 (15 mL) at −10 °C. The reaction mixture was then allowed to warm to room temperature and stirred for 15 h. It was then washed with water (2 × 20 mL), saturated $NaHCO_3$ (15 mL), brine (15 mL), dried (Na_2SO_4) and evaporated to give the crude product, which was purified by column chromatography over silica gel. Spectral data of compound **5a**: Mp 176 °C. IR (KBr, cm^{-1}): 1728 (CO_{Is}), 1766 cm^{-1} (CO, β-lactam). ^1H NMR ($CDCl_3$, 250 MHz): δ 3.39, 3.75 (6H, s, OMe), 4.73 (1H, d, $H_{a\ Bn}$, $J = 15$ Hz), 5.10 (1H, d, $H_{b\ Bn}$, $J = 15$ Hz), 5.64 (1H, s, CH_{lactam}), 6.29–7.93 (17H, m, ArH). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 44.17 ($CH_{2\text{-benzylic}}$), 55.17 and 55.50 (OMe), 69.90 (C3), 85.98 ($C4_{spiro\ carbon}$), 99.50–159.25 (aromatic carbons), 163.44 ($CO_{\beta\text{-lactam}}$), 173.77 (CO_{isatin}). MS (*m*/*z* %): 506 (28.8), 372 (16.0), 328 (22.8), 327 (55.7). Spectral data for **6a**: Mp 144 °C, IR (KBr, cm^{-1}): 1720 (CO_{Is}), 1774 (CO, β-lactam). ^1H NMR ($CDCl_3$, 250 MHz): δ 3.77 (2H, s, CH_2), 4.69–5.02 (4H, m, H_{Bn}), 5.52 (2H, s, H_{lactam}), 6.58–7.62 (36H, m, ArH). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 40.63 (Ph–C–Ph), 44.46 ($CH_{2\text{-benzylic}}$), 66.87 (C3), 85.29 (C4), 109.80–142.91 (aromatic carbons), 156.57 ($CO_{\beta\text{-lactam}}$), 161.41 (CO_{isatin}), MS (*m*/*z* %): 577 (2.9), 443 (1.6), 327 (18.5).
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