

Article

A Novel One-Pot Green Synthesis of Dispirooxindolo-pyrrolidines via 1,3-Dipolar Cycloaddition Reactions of Azomethine Ylides

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Abstract: A facile synthesis of dispirooxindolopyrrolidines has been accomplished via a one-pot three component 1,3-dipolar cycloaddition reaction. The reaction of azomethine ylides generated *in situ* from L-phenylalanine and substituted isatins with a series of unusual (*E*)-2-oxoindolino-3-ylidene acetophenone dipolarophiles in the ionic liquid 1-butyl-3-methylimidazolium bromide [bmim]BF₄, furnished the cycloadducts in good yields, with the regioisomers **5a–f** being obtained with high selectivity. Furthermore, the recyclability of [bmim]BF₄, up to five times, was also investigated.

Keywords: 1,3-dipolar cycloaddition; azomethine ylide; dispiropyrrolidines; ionic liquids

1. Introduction

Ionic liquids are widely recognized as “green” solvents in organic synthesis because of their unique properties, such as low vapor pressure, high chemical and thermal stability, good solvating

ability, non-flammability, behavior as acidic or basic catalysts and recyclability [1–5]. In this context, ionic liquids have emerged as new green solvents to replace volatile organic compounds and they are suitable for executing many diverse organic reactions [6–8]. One-pot three component reactions, widely useful in both combinatorial and medicinal chemistry arenas, with their powerful bond forming and atom efficiencies, represent another eco-friendly synthetic approach for the expedient construction of molecules of structural diversity and complexity [9–12]. These reactions also assume importance from the viewpoint of minimized waste generation due to the avoidance of intermediate isolation and purification steps. For these reasons, the development of multi-component reactions in ionic liquids, although relatively unexplored [13], is of great interest.

The spirooxindole core is a privileged heterocyclic system that is featured in a large number of bioactive naturally occurring alkaloids (Figure 1) that display a wide spectrum of biological activities such as antimicrobial [14], inhibition of human NK-1 receptor [15] and potent non-peptide inhibition of the p53–MDM2 interaction [16]. Particularly, the spiropyrrolidinyloxindole nucleus is often found in the molecular framework of many natural products, *viz.*, horsfiline [17], coerulescine [18], and elacomine [19] (Figure 1) which possess a myriad of biological activities such as inhibition of the mammalian cell cycle at G2/Mphase [20,21], inhibition of microtubule assembly [22], modulation of the function of muscarinic serotonin receptors [23], antitumor activity against human brain cancer cell lines, neuroblastoma SKN-BE (2), and malignant glioma GAMG [24].

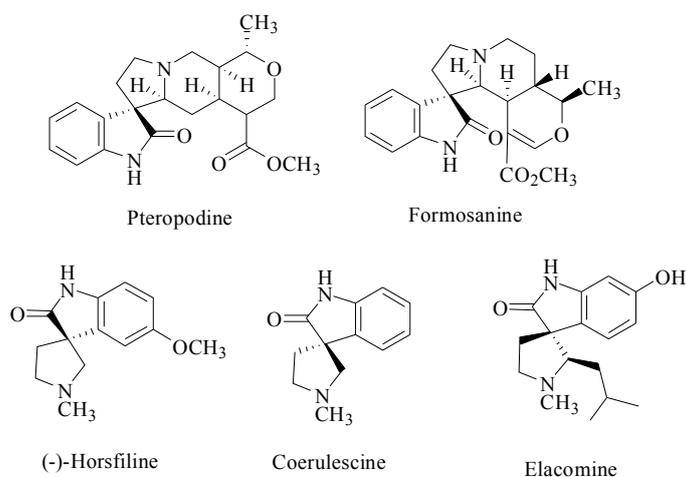


Figure 1. Biologically relevant spirooxindolopyrrolidine alkaloids and natural products.

The biological significance of the above heterocycles prompted us to explore the synthesis of novel hybrid spiroheterocycles comprising pyrrolidine and oxindole units via a one-pot three component 1,3-dipolar cycloaddition reaction. Recently, we embarked on a program for the synthesis and/or biological screening of structurally diverse novel spiroheterocycles, which has brought to light various antimicrobial leads [25–28]. In continuation of our research in the area of 1,3-dipolar cycloaddition reactions [29,30], herein we wish to report an expeditious and facile protocol for the synthesis of dispirooxindolopyrrolidines in ionic liquid medium; highly desirable from the viewpoint of green chemistry. Furthermore, to the best of our knowledge, this is the first report on the generation of azomethine ylide from L-phenylalanine and isatin in ionic liquid medium.

Table 1. Solvent condition and yield optimization of cycloaddition reaction.

Entry	Solvent System	Yield (%)		Time (h)
		5a	6a	
1	Methanol	28	12	6
2	Ethanol	30	15	6
3	Dry Dioxane	34	16	5
4	Dioxane/Methanol	38	18	4
5	[bmim]Br	69	8	2
6	[bmim][BF ₄]	77	7	2
7	[bmim][BF ₄]/CuI (10 mol %)	60	15	2
8	[bmim][BF ₄]/Zn(OTf) ₂ (10 mol %)	62	18	2

Notes: Optimized reaction condition is in bold (entry 6); Ionic liquids were subjected to high vacuum before use (entry 5–8).

Table 2. Yield and distereoselectivity of the cycloadducts **5a–f** and **6a–f**.

Entry	Derivatives (a–f)	Yield of the Cycloadducts (%) [#]		Diastereoselectivity (5/6)
		5	6	
1	a	77	7	91/9
2	b	70	5	85/15
3	c	75	6	89/11
4	d	73	5	90/10
5	e	72	5	88/12
6	f	71	5	87/13

Note: [#] All reactions were carried out with [bmim]BF₄ ionic liquid under 2 h refluxion.

Table 3. Reusability of the ionic liquid in the synthesis of **5a** and **6a**.

Experiment	First	Second	Third	Fourth	Fifth
[Bmim]Br(Yield %)	69:8	67:7	63:6	61:4	60:3
[Bmim]BF ₄ (Yield %)	77:7	75:6	72:5	68:4	65:3

The structure of regioisomers was elucidated using IR, ¹H-, ¹³C-NMR spectroscopic and mass spectrometry studies. For instance, the IR spectrum of the cycloadduct **5a** displayed characteristic bands at 1628, 1706, 1710 cm⁻¹ corresponding to the two oxindoles and benzoyl carbonyls, respectively. In the ¹H-NMR spectrum of **5a**, the benzylic and H_a protons appeared as multiplets in the region δ_H 3.08–3.12 and 5.57–5.61 ppm, respectively. The H_b proton attached to the benzoyl group appeared as doublet at δ_H 4.29 ppm and the *trans* stereochemistry was confirmed through coupling constant of H_b proton (*J* = 8.8 Hz). The aromatic protons appear as multiplets around 6.43–7.78 ppm. In the ¹³C-NMR spectrum, the signals at δ_C 177.2, 180.5 and 195.4 ppm were attributed to two oxindole and benzoyl ring carbonyls. The two spiro carbons resonated at δ_C 63.9 and 83.3 ppm. Furthermore, the presence of the molecular ion peak at *m/z* 533 (M⁺) in the mass spectrum of **5a** supported the formation of the cycloadduct. The stereochemistry of compound **5a** has been assigned based on the fact that the carbonyls of the two isatin rings are in *trans* relationship as to minimize the repulsion between the two isatin carbonyl as evidenced in the literature [31–33]. The structure of other regioisomer **6a** was also elucidated by similar straight forward considerations. The singlet at δ_H 4.90 ppm in the ¹H-NMR spectrum, confirms the formation of

regioisomer **6a**. A pictorial representation of the ^1H - and ^{13}C -NMR chemical shifts of **5a** and **6a** is shown in Figure 2.

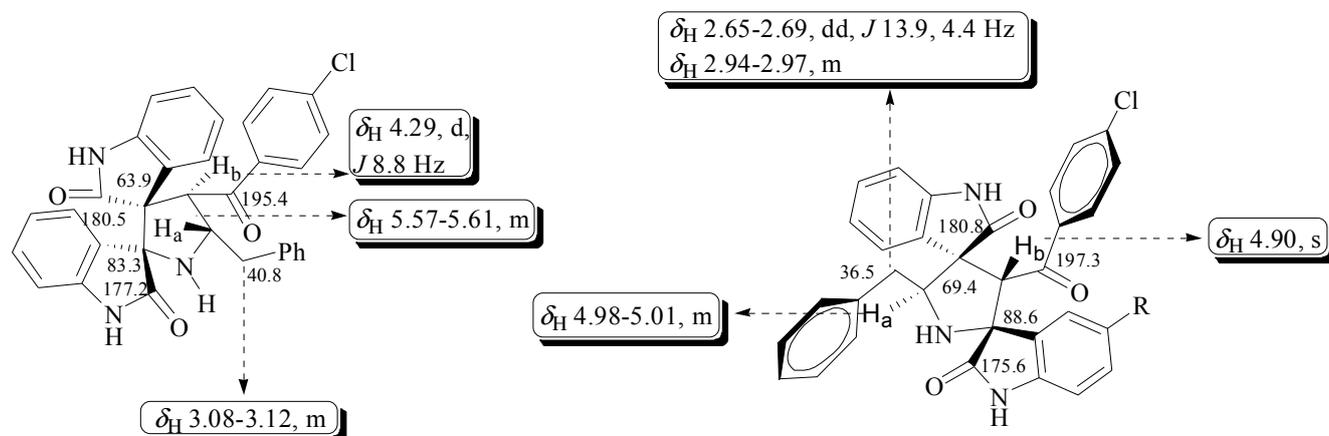
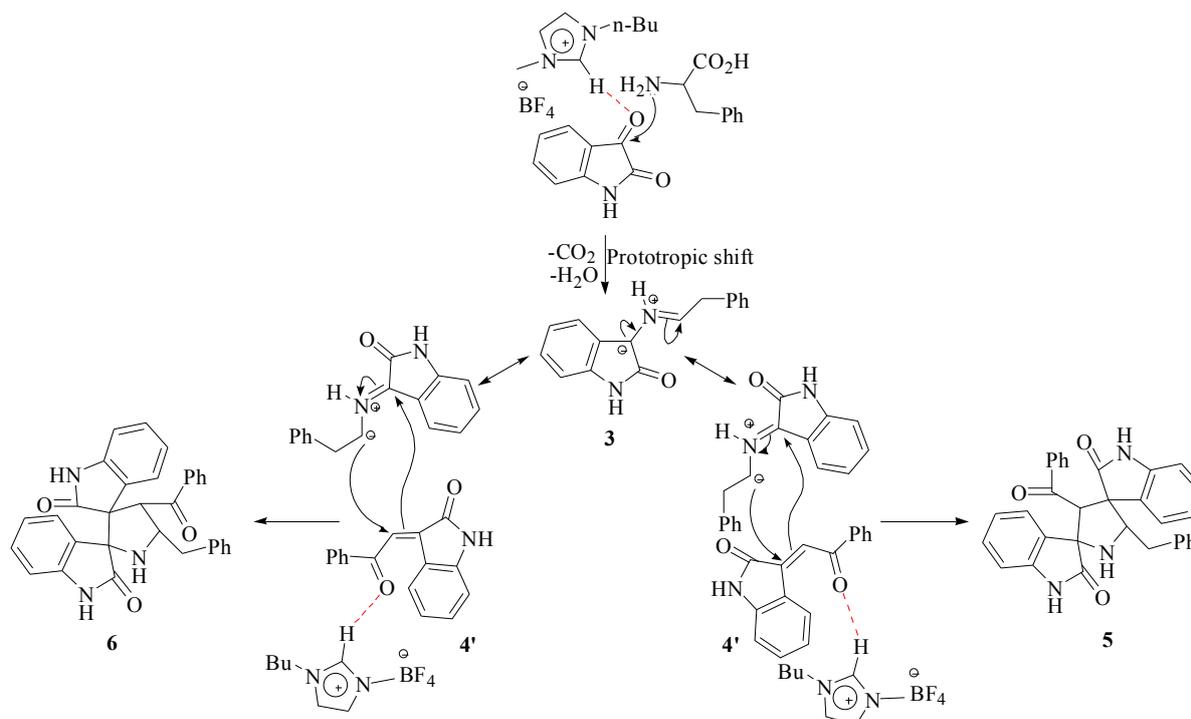


Figure 2. Selected ^1H - and ^{13}C -NMR signals of compounds **5a** and **6a**.

A rational mechanism for the formation of the cycloadducts **5** and **6** in the presence of $[\text{bmim}]\text{BF}_4$ is described in Scheme 2. It is known that ionic liquid play dual roles as solvent and catalyst. For instance, the hydrogen atom of $[\text{bmim}]^+$, being electron-deficient can form hydrogen bonds with heteroatoms thereby catalyzing reactions. Thus, in the present transformation, a hydrogen bond between the imidazole ring hydrogen atom of $[\text{bmim}]^+$ and the carbonyl group of **4** furnishes **4'**, which readily reacts with azomethine ylide to afford **5** and **6**. The azomethine ylide may also be catalyzed by $[\text{bmim}]\text{BF}_4$ via hydrogen bonding. This catalysis presumably expedites the reaction in ionic liquid relative to other solvents.



Scheme 2. Plausible mechanism for the synthesis of dispirooxindolopyrrolidine regioisomers.

The regio- and stereo- chemistry of cycloadduct **6f** was further supported by single crystal X-ray diffraction studies [34] (Figure 3). The molecule **6f** is composed of a central pyrrolidine ring with benzoyl group at C9, benzyl group at C11, spiro-carbons fused with oxindoles at C7 and C10 (Figure 3). The dihedral angle between the pyrrolidine ring A (N2/C7/C9/C10/C11), indolin-2-one ring B (C1-C8/N1) and 2,3-dihydro-1*H*-inden-1-one ring C (C19-C26) are 77.96(2)°, 84.72(3)° and 24.07(2)° for A/B, A/C and B/C, respectively. The torsion angle in between C11-N2-C7-C9 is 40.0(2)°. There are three intramolecular interactions between C9–H9A···O3, C11–H11A···O1 and C20–H20A···O1. In the crystal structure, seven intermolecular N–H···O and C–H···O hydrogen bonds are observed. The selected geometric parameters and distances of the donor–H, acceptor/H, donor/acceptor and donor–H/acceptor angles are presented in Tables S1 and S2 (*vide* Supplementary Data).

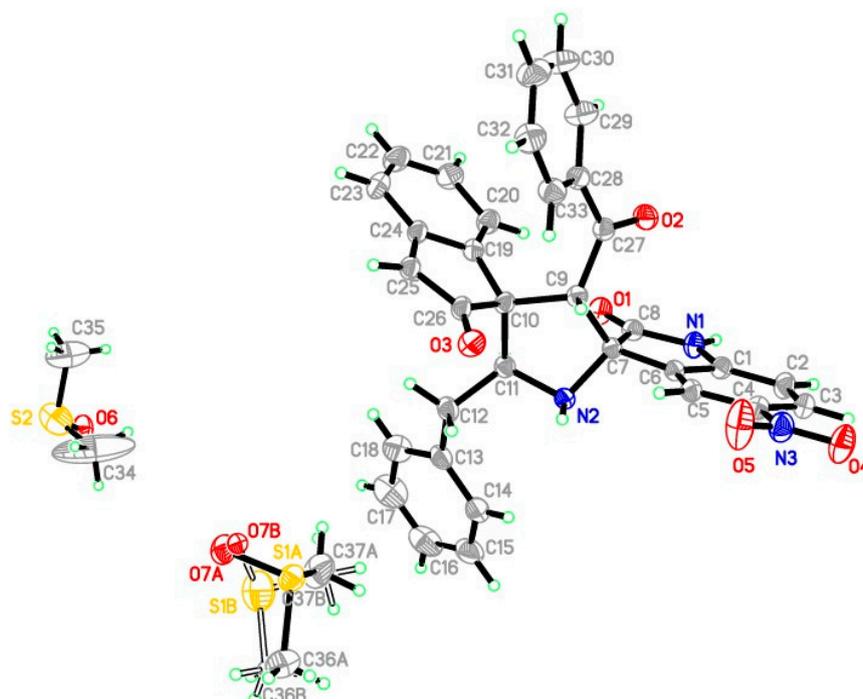


Figure 3. ORTEP diagram of **6f**, showing the atom-numbering. Displacement ellipsoids are drawn at the 40% probability level and all *H*-atoms are shown as small spheres of arbitrary radii.

3. Experimental Section

3.1. General Methods

Melting points were taken using open capillary tubes and are uncorrected. Unless stated otherwise, solvents and chemicals were obtained from commercial sources and used without further purification. IR Spectra were measured as KBr pellets on a Nicolet 6700 FT-IR spectrophotometer (Madison, WI, USA). ¹H- and ¹³C-NMR spectra were recorded on a Varian Mercury JEOL-400 NMR spectrometer (Tokyo, Japan) and Bruker 500 MHz NMR spectrometers (Faellanden, Switzerland) operating at 400, 500, 100 and 125 MHz, respectively, and chemical shifts are reported as δ values (ppm) relative to tetramethylsilane. Elemental analyses were performed on a Perkin-Elmer 2400 series II elemental CHNS analyser (Waltham, MA, USA). Flash column chromatography was performed on silica gel (230–400 mesh) using petroleum ether (60–80 °C)/EtOAc as eluent.

3.2. General Procedure for Synthesis of Dispirooxindoles 5a–f and 6a–f

A mixture of isatin (1 mmol), L-phenylalanine (1 mmol) and (*E*)-2-oxoindolino-3-ylidene acetophenone (1 mmol) was heated with stirring in [bmim]BF₄ medium (3 mL) for 2 h at 100 °C. After completion of the reaction as evidenced by TLC analysis, ethyl acetate (10 mL) was added and the reaction mixture was stirred for 10–15 min. The organic layer was separated and removed under reduced pressure. The crude cycloadducts were isolated through flash column chromatography. The ionic liquid [bmim]BF₄ after extraction of the product was dried under vacuum at 40 °C for 2 h overnight to eliminate any water trapped from moisture and reused for subsequent runs.

(2'*R*,3'*R*,4'*S*,5'*S*)-4'-(4-Chlorobenzoyl)-5'-benzyl-spiro[3,2']oxindolo-spiro[3,3'']oxindolopyrrolidine (**5a**). Colorless solid (290 mg, 77%), mp 195–197 °C (EtOAc); *R*_F 0.4 (pet. ether/EtOAc, 1:1); IR (KBr): 1628, 1706 and 1710 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃): δ_H 7.78–6.43 (m, 17H, aromatic), 5.61–5.57 (m, 1H), 4.29 (d, *J* = 8.8 Hz, 1H), 3.12–3.08 (m, 2H); ¹³C-NMR (100 MHz, CDCl₃): δ_C 195.4, 180.5, 177.2, 141.3, 140.3, 138.8, 138.2, 135.9, 130.0, 129.8, 129.4, 128.9, 128.8, 128.5, 127.7, 126.6, 125.6, 125.3, 124.3, 122.6, 109.5, 109.3, 83.3, 63.9, 61.4, 59.5, 40.8. LC/MS (ESI): *m/z* 533 [M]⁺. Anal. Calcd for: C₃₂H₂₄ClN₃O₃: C, 71.97; H, 4.53; N, 7.87. Found: C, 71.81; H, 4.68; N, 7.93%.

(2'*S*,3'*S*,4'*S*,5'*S*)-3'-(4-Chlorobenzoyl)-5'-benzyl-spiro[3,2']oxindolo-spiro[3'',4']oxindolopyrrolidine (**6a**). Colorless solid (26 mg, 7%), mp 162–164 °C (EtOAc); *R*_F 0.5 (pet. ether/EtOAc, 1:1); IR (KBr): 1626, 1708 and 1710 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃): δ_H 7.69–6.37 (m, 17H, aromatic), 5.01–4.98 (m, 1H), 4.90 (s, 1H), 2.97–2.94 (m, 1H), 2.69–2.65 (dd, *J* = 13.9, 4.4 Hz, 1H); ¹³C-NMR (100 MHz, CDCl₃): δ_C 197.3, 180.8, 175.6, 141.3, 140.2, 139.6, 135.5, 131.3, 129.5, 128.8, 128.6, 128.4, 128.4, 128.4, 128.2, 127.8, 126.3, 125.3, 124.8, 122.6, 110.0, 109.8, 88.6, 69.4, 68.6, 61.6, 36.5. LC/MS (ESI): *m/z* 533 [M]⁺. Anal. Calcd for: C₃₂H₂₄ClN₃O₃: C, 71.97; H, 4.53; N, 7.87. Found: C, 71.88; H, 4.65; N, 7.96%.

(2'*R*,3'*R*,4'*S*,5'*S*)-4'-Benzoyl-5'-benzyl-spiro[3,2']oxindolo-spiro[3,3'']oxindolopyrrolidine (**5b**). Colorless solid (281 mg, 70%), mp 145–147 °C (EtOAc); *R*_F 0.4 (pet. ether/EtOAc, 1:1); IR (KBr): 1628, 1706 and 1710 cm⁻¹; ¹H-NMR (500 MHz, CDCl₃): δ_H 6.31–7.42 (m, 16H, aromatic), 5.56–5.54 (m, 1H), 4.30 (d, *J* = 8.8 Hz, 1H), 3.04–3.02 (m, 2H); ¹³C-NMR (125 MHz, CDCl₃): δ_C 196.7, 181.0, 177.7, 177.7, 141.5, 140.5, 138.3, 137.6, 132.5, 129.9, 129.4, 128.7, 128.6, 128.6, 128.4, 128.2, 127.5, 126.4, 125.5, 125.4, 124.4, 122.4, 109.6, 109.2, 83.9, 63.9, 61.2, 59.5, 40.7. LC/MS (ESI) *m/z* 499 [M]⁺; Anal. Calcd for: C₃₂H₂₅N₃O₃: C, 76.94; H, 5.04; N, 8.41. Found: C, 76.88; H, 5.16; N, 8.52%.

(2'*S*,3'*S*,4'*S*,5'*S*)-3'-Benzoyl-5'-benzyl-spiro[3,2']oxindolo-spiro[3'',4']oxindolopyrrolidine (**6b**). Colorless solid (20 mg, 5%), mp 117–119 °C (EtOAc); *R*_F 0.5 (pet. ether/EtOAc, 1:1); IR (KBr): 1628, 1706 and 1710 cm⁻¹; ¹H-NMR (500 MHz, CDCl₃): δ_H 7.48–6.26 (m, 18H, aromatic), 5.39–5.37 (m, 1H), 4.88 (s, 1H), 3.48–3.47 (m, 1H), 3.17–3.16 (m, 1H); ¹³C-NMR (125 MHz, CDCl₃): δ_C 197.9, 179.8, 174.6, 142.2, 141.1, 139.8, 137.3, 132.5, 129.5, 129.1, 128.9, 128.2, 128.4, 128.3, 128.1, 127.5, 126.3, 125.8, 125.5, 121.1, 109.6, 109.5, 75.2, 67.1, 64.8, 61.3, 39.7. LC/MS (ESI) *m/z* 499 [M]⁺; Anal. Calcd for: C₃₂H₂₄N₃O₃: C, 76.94; H, 5.04; N, 8.41. Found: C, 76.85; H, 5.21; N, 8.54%.

(2'R,3'R,4'S,5'S)-4'-(4-Chlorobenzoyl)-5'-benzyl-5-chlorospiro[3,2']oxindolo-spiro[3,3']oxindolopyrrolidine (**5c**). Pale yellow solid (301 mg, 75%), mp 205–207 °C (EtOAc); R_F 0.4 (Pet. Ether/EtOAc, 1:1); IR (KBr): 1625, 1708 and 1710 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ_{H} 8.31 (s, 1H, NH), 8.29 (s, 1H, NH), 7.48–6.45 (m, 16H, aromatic), 5.57–5.51 (m, 1H), 4.26 (d, $J = 8.1$, 1H), 3.08–3.03 (m, 2H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ_{C} 195.3, 177.2, 140.5, 140.2, 138.2, 139.0, 135.8, 130.0, 129.3, 129.0, 128.9, 128.5, 127.9, 127.6, 127.1, 126.6, 126.1, 124.0, 122.7, 110.8, 109.6, 83.0, 63.7, 61.5, 59.4, 41.0. LC/MS (ESI) m/z 567 $[\text{M}]^+$; Anal. Calcd. for: $\text{C}_{32}\text{H}_{23}\text{Cl}_2\text{N}_3\text{O}_3$: C, 67.61; H, 4.08; N, 7.39. Found: C, 67.76; H, 4.19; N, 7.47%.

(2'S,3'S,4'S,5'S)-3'-(4-Chlorobenzoyl)-5'-benzyl)-5-chlorospiro[3,2']oxindolo-spiro[3'',4']oxindolopyrrolidine (**6c**). Pale yellow solid (24 mg, 6%), mp 187–189 °C (EtOAc); R_F 0.5 (Pet. Ether/EtOAc, 1:1); IR (KBr): 1625, 1708 and 1710 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ_{H} 8.71 (s, 1H, NH), 8.53 (s, 1H, NH), 5.16 (s, 1H), 7.66–6.29 (m, 16H, aromatic), 5.00–4.96 (m, 1H), 3.52–3.46 (m, 1H), 3.26–3.23 (m, 1H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ_{C} 195.3, 177.2, 180.4, 139.0, 138.2, 135.8, 129.7, 129.5, 129.2, 128.8, 128.4, 128.5, 128.3, 128.0, 127.1, 126.6, 125.2, 122.6, 110.1, 83.0, 63.7, 61.5, 41.0. LC/MS (ESI) m/z 567 $[\text{M}]^+$; Anal. Calcd for: $\text{C}_{32}\text{H}_{23}\text{Cl}_2\text{N}_3\text{O}_3$: C, 67.61; H, 4.08; N, 7.39. Found: C, 67.74; H, 4.21; N, 7.43%.

(2'R,3'R,4'S,5'S)-4'-Benzoyl-5'-benzyl-5-chlorospiro[3,2']oxindolo-spiro[3,3']oxindolopyrrolidine (**5d**). Colorless solid (312 mg, 73%), mp 155–157 °C (EtOAc); R_F 0.4 (pet. ether/EtOAc, 1:1); IR (KBr): 1628, 1706 and 1710 cm^{-1} ; $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ_{H} 9.79 (s, 1H, NH), 9.77 (s, 1H, NH), 7.47–6.30 (m, 17H, aromatic), 5.54–5.49 (m, 1H), 4.24 (d, $J = 8.0$, 1H), 3.18–3.02 (m, 2H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3): δ_{C} 196.8, 180.0, 177.0, 141.6, 141.2, 137.4, 138.6, 132.3, 129.5, 129.1, 129.0, 128.7, 128.4, 128.3, 128.0, 127.9, 127.1, 126.7, 126.1, 124.3, 123.7, 122.6, 121.7, 110.7, 110.0, 85.5, 64.9, 61.3, 59.8, 41.0. LC/MS (ESI) m/z 533 $[\text{M}]^+$; Anal. Calcd for: $\text{C}_{32}\text{H}_{24}\text{ClN}_3\text{O}_3$: C, 71.97; H, 4.53; N, 7.87. Found: C, 71.89; H, 4.45; N, 7.95%.

(2'S,3'S,4'S,5'S)-3'-Benzoyl-5'-benzyl-5-chlorospiro[3,2']oxindolo-spiro[3'',4']oxindolopyrrolidine (**6d**). Colorless solid (21 mg, 5%), mp 144–145 °C (EtOAc); R_F 0.5 (pet. ether/EtOAc, 1:1); IR (KBr): 1628, 1706 and 1710 cm^{-1} ; $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ_{H} 9.73 (s, 1H, NH), 9.16 (s, 1H, NH), 7.15–6.09 (m, 17H, aromatic), 5.22 (s, 1H), 4.76–4.72 (m, 1H), 3.32–3.30 (m, 1H), 3.03–2.99 (m, 1H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3): δ_{C} 197.7, 179.7, 174.5, 141.3, 141.1, 139.5, 137.2, 132.5, 131.9, 129.4, 129.2, 128.4, 128.2, 128.0, 127.5, 126.2, 126.0, 121.2, 110.3, 75.1, 64.8, 61.3, 39.6. LC/MS (ESI) m/z 533 $[\text{M}]^+$; Anal. Calcd for: $\text{C}_{32}\text{H}_{24}\text{ClN}_3\text{O}_3$: C, 71.97; H, 4.53; N, 7.87. Found: C, 71.86; H, 4.49; N, 7.25%.

(2'R,3'R,4'S,5'S)-4'-(4-Chlorobenzoyl)-5'-benzyl-5-nitrospiro[3,2']oxindolo-spiro[3,3']oxindolopyrrolidine (**5e**). Reddish brown solid (294 mg, 72%), mp 232–234 °C (EtOAc); R_F 0.3 (pet. ether/EtOAc, 1:1); IR (KBr): 1625, 1708 and 1710 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ_{H} 8.85 (s, 1H, NH), 8.62 (s, 1H, NH), 8.41–6.54 (m, 16H, aromatic), 5.54 (m, 1H), 4.34 (d, $J = 8.8$ Hz, 1H), 3.16–3.05 (m, 2H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ_{C} 195.2, 180.3, 177.5, 147.7, 143.3, 140.6, 139.3, 138.1, 135.6, 129.4, 129.3, 129.0, 128.7, 128.6, 126.7, 126.4, 123.6, 122.8, 122.0, 110.1, 110.0, 83.1, 63.7, 61.9, 59.4, 40.9. LC/MS (ESI) m/z 578 $[\text{M}]^+$; Anal. Calcd for: $\text{C}_{32}\text{H}_{23}\text{ClN}_4\text{O}_5$: C, 66.38; H, 4.00; N, 9.68. Found: C, 66.47; H, 4.16; N, 9.75%.

(2'S,3'S,4'S,5'S)-3'-(4-Chlorobenzoyl)-5'-benzyl-5-nitrospiro[3,2]oxindolo-spiro[3'',4']oxindolopyrrolidine (**6e**). Reddish brown solid (20 mg, 5%), mp 210–212 °C (EtOAc); R_F 0.4 (pet. ether/EtOAc, 1:1); IR (KBr): 1625, 1708 and 1710 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ_{H} 9.13 (s, 1H, NH), 7.99 (s, 1H, NH), 7.75–6.47 (m, 16H, aromatic), 5.31 (s, 1H), 5.03–5.01 (m, 1H), 3.51–3.45 (m, 1H), 3.28–3.25 (dd, 12.4, 4.4 Hz, 1H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ_{C} 195.7, 180.8, 174.5, 147.5, 142.6, 139.5, 138.9, 135.3, 129.8, 129.4, 128.9, 128.9, 128.7, 128.5, 127.7, 128.0, 126.9, 125.4, 124.5, 123.2, 110.2, 75.1, 65.0, 61.0, 42.1. LC/MS (ESI) m/z 578 $[\text{M}]^+$; Anal. Calcd for: $\text{C}_{32}\text{H}_{23}\text{ClN}_4\text{O}_5$: C, 66.38; H, 4.00; N, 9.68. Found: C, 66.49; H, 4.14; N, 9.79%.

(2'R,3'R,4'S,5'S)-4'-Benzoyl-5'-benzyl-5-nitrospiro[3,2]oxindolo-spiro[3,3'']oxindolopyrrolidine (**5f**). Brown solid (310 mg, 71%), mp 197–199 °C (EtOAc); R_F 0.3 (pet. ether/EtOAc, 1:1); IR (KBr): 1625, 1708 and 1710 cm^{-1} ; $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ_{H} 8.33 (s, 1H, NH) 7.96 (s, 1H, NH), 7.65–6.31 (m, 17H, aromatic), 5.30–5.25 (m, 1H), 4.32 (d, $J = 8.7$ Hz, 1H), 3.06–3.02 (m, 2H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3): δ_{C} 195.5, 180.5, 176.2, 149.3, 140.8, 141.7, 137.7, 136.4, 132.8, 129.6, 129.4, 128.8, 128.5, 128.4, 128.0, 126.4, 125.6, 125.2, 123.1, 120.8, 109.4, 83.1, 68.1, 61.2, 55.9, 40.1. LC/MS (ESI): m/z 544 $[\text{M}]^+$; Anal. Calcd for: $\text{C}_{32}\text{H}_{24}\text{N}_4\text{O}_5$: C, 70.58; H, 4.44; N, 10.29. Found: C, 70.66; H, 4.37; N, 10.18%.

(2'S,3'S,4'S,5'S)-3'-Benzoyl-5'-benzyl-5-nitrospiro[3,2]oxindolo-spiro[3'',4']oxindolopyrrolidine (**6f**). Brown needles (21 mg, 5%), mp 175–177 °C (EtOAc/DMSO, 9:1); R_F 0.4 (pet. ether/EtOAc, 1:1); IR (KBr): 1625, 1708 and 1710 cm^{-1} ; $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ_{H} 10.28 (s, 1H, NH), 9.24 (s, 1H, NH), 7.70–6.22 (m, 17H, aromatic), 4.76–4.74 (m, 1H), 5.15 (s, 1H), 3.28–3.25 (m, 1H), 2.93–2.88 (m, 1H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3): δ_{C} 197.3, 180.3, 174.1, 148.9, 141.1, 137.3, 132.7, 130.8, 129.4, 128.4, 128.2, 127.9, 127.5, 126.2, 126.0, 124.9, 121.5, 110.0, 109.3, 74.7, 64.9, 61.2, 55.8, 39.9. LC/MS (ESI) m/z 544 $[\text{M}]^+$; Anal. Calcd for: $\text{C}_{32}\text{H}_{24}\text{N}_4\text{O}_5$: C, 70.58; H, 4.44; N, 10.29. Found: C, 70.68; H, 4.35; N, 10.21%.

3.3. X-ray Crystallography

A clear intense yellow block-like specimen of $\text{C}_{37}\text{H}_{36}\text{N}_3\text{O}_7\text{S}_2$, approximate dimensions $0.39 \times 0.457 \times 0.674$ mm, was used for the X-ray crystallographic analysis. A total of 684 frames were collected. The total exposure time was 2.85 h. The frames were integrated with the Bruker SAINT software package [35] using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell, space group $\text{P}2_1/\text{n}$, yielded a total of 35419 reflections to a maximum θ angle of 28.33° (0.75 Å resolution), of which 8504 were independent (average redundancy 5.743, completeness = 99.6%, $R_{\text{int}} = 3.18\%$, $R_{\text{sig}} = 2.93\%$) and 6264 (76.53%) were greater than $2\sigma(F^2)$. The final cell constants of $a = 13.5273(5)$ Å, $b = 14.8582(6)$ Å, $c = 17.1768(7)$ Å, $\beta = 95.0630(10)^\circ$, volume = $3437.3(2)$ Å³, are based upon the refinement of the XYZ-centroids of 9790 reflections above $20 \sigma(I)$ with $4.588^\circ < 2\theta < 56.36^\circ$. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.907. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.9490 and 0.9690.

The final anisotropic full-matrix least-squares refinement on F^2 with 388 variables converged at $R_1 = 6.41\%$, for the observed data and $wR_2 = 20.09\%$ for all data. The goodness-of-fit was 1.06. The largest peak in the final difference electron density synthesis was $8.210 \text{ e}/\text{\AA}^3$ and the largest hole

was $-1.079 \text{ e}/\text{\AA}^3$ with an RMS deviation of $0.325 \text{ e}/\text{\AA}^3$. On the basis of the final model, the calculated density was $1.067 \text{ g}/\text{cm}^3$ and $F(000)$ 1468.

4. Conclusions

A one-pot three component 1,3-dipolar cycloaddition reaction of azomethine ylide generated *in situ* from substituted isatins and L-phenylalanine to (*E*)-2-oxoindolino-3-ylidene acetophenones in [bmim]BF₄ afforded the dispirooxindolopyrrolidines **5a–f** and **6a–f** in good yields with high selectivity, the former isomer being obtained predominantly. This methodology gains importance as the reaction was completed in shorter reaction times with better yields/selectivity besides the recyclability of the green solvent [bmim]BF₄.

Supplementary Materials

Supplementary materials can be accessed at: <http://www.mdpi.com/1420-3049/20/01/0780/s1>.

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Author Contributions

A.I.A., N.A., R.S.K. and G.P. are design, synthesis and characterization of the molecules. X-ray crystallographic analysis by H.A.G. and H.-K.F. The manuscript was written by N.A.

Conflicts of Interest

The authors declare no conflicts of interest.

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Sample Availability: Samples of the compounds are available from the authors.