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Theoretical and Synthetic Approach to Novel Spiroheterocycles Derived from Isatin Derivatives and L-Proline via 1,3-Dipolar Cycloaddition

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ABSTRACT: *A cyclic secondary α-amino acid, viz. L-proline, reacts with isatin derivatives via decarboxylative azomethine ylide formation and subsequent cycloaddition with various dipolarophiles to give cycloadducts in moderate to good yield. Theoretical studies have been performed to study the stereochemistry of the products formed.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:36–41, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10063

INTRODUCTION

Heterocyclic compounds fall into an important class of organic compounds. These compounds are found in various natural products as fundamental nuclei and are well recognized for their wide spectrum of pharmacological and biochemical behavior. The indole derivatives have received the attention of biochemists because of their therapeutic and biochemical activities [1–3]. These derivatives undergo various organic reactions including cycloaddition reaction [4]. Similarly pyrrolidine-2-carboxylic acid, commonly known as L-proline, possesses significant biological and medicinal properties [5–7]. Therefore any heterocyclic compound containing these two moieties might be expected to have considerably enhanced biological activities.

The 1,3-dipolar cycloaddition reaction of an azomethine ylide with an alkene leads to the formation of pyrrolidine derivatives [8] (Scheme 1). Theoretical studies of the simplest azomethine ylide with an alkene have been carried out by Annunziata and co-workers [9] in an attempt to understand the reaction mechanism. Recently, we have reported theoretical as well as experimental results as applied to the azomethine ylide derived from isatin and thiazolidine-4-carboxylic acid in reaction with different dipolarophiles [10,11]. In this work, we have extended our investigations to the azomethine ylide derived from the isatin and the L-proline in reactions with different dipolarophiles, viz. phenylacetylene and ethyl phenylpropiolate, and the results are presented herein.

THEORETICAL STUDIES

Theoretical studies have been carried out using PCWIN and MOPAC6 programs on a PCL Pentium I computer. The oxazolidinone compound **4**, derived from the condensation of isatin **1** with L-proline **2** (Scheme 2), contains two chiral centers and therefore a total of four stereoisomers **4a–d** are possible. We are able to optimize the geometry of all the four

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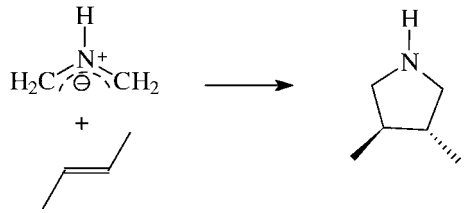
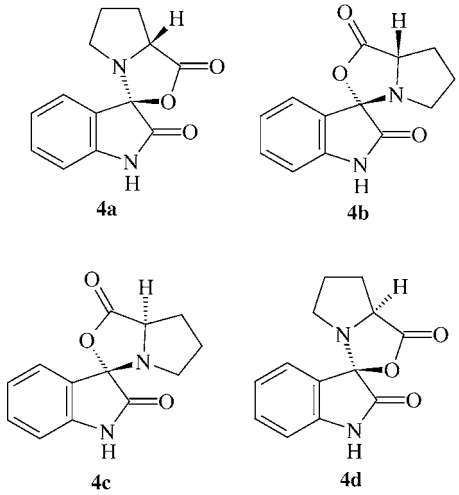
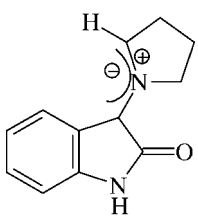


SCHEME 1 Schematic representation of 1,3-Dipolar-cycloaddition of azomethine ylide with alkene.

isomers. Since product **4** is formed upon dehydration of intermediate iminium species **3**, the stereochemistry at C-5 should remain unchanged with regard to the proline. On this basis, the possibility of stereoisomers **4a** and **4b** may be ruled out. Of the remaining isomers, **4c** has a high ΔH_f value and hence the expected product is **4d**.



In the presence of a dipolarophile, the intermediate iminium species **3** undergoes decarboxylation to give the azomethine ylide **5**, which subsequently undergoes 1,3-dipolar cycloaddition reactions to give spiro polycyclic compounds. Geometry optimization of azomethine ylide **5** indicates that it has a planar structure. The proline ring, instead of having an envelope shape, is planar and lies in the same plane as that of the isatin moiety (Fig. 1).



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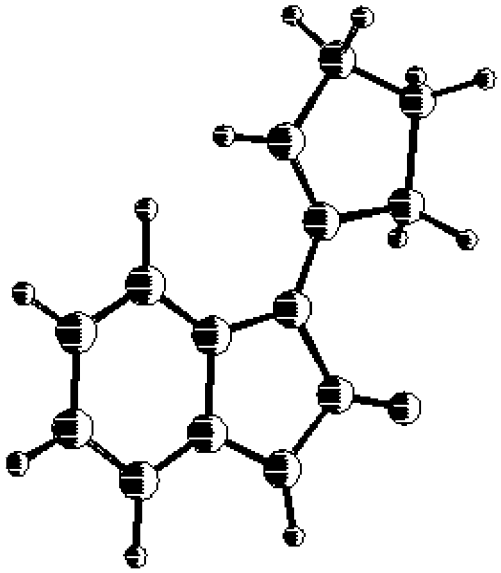


FIGURE 1 Optimized geometry of azomethine ylide **5**.

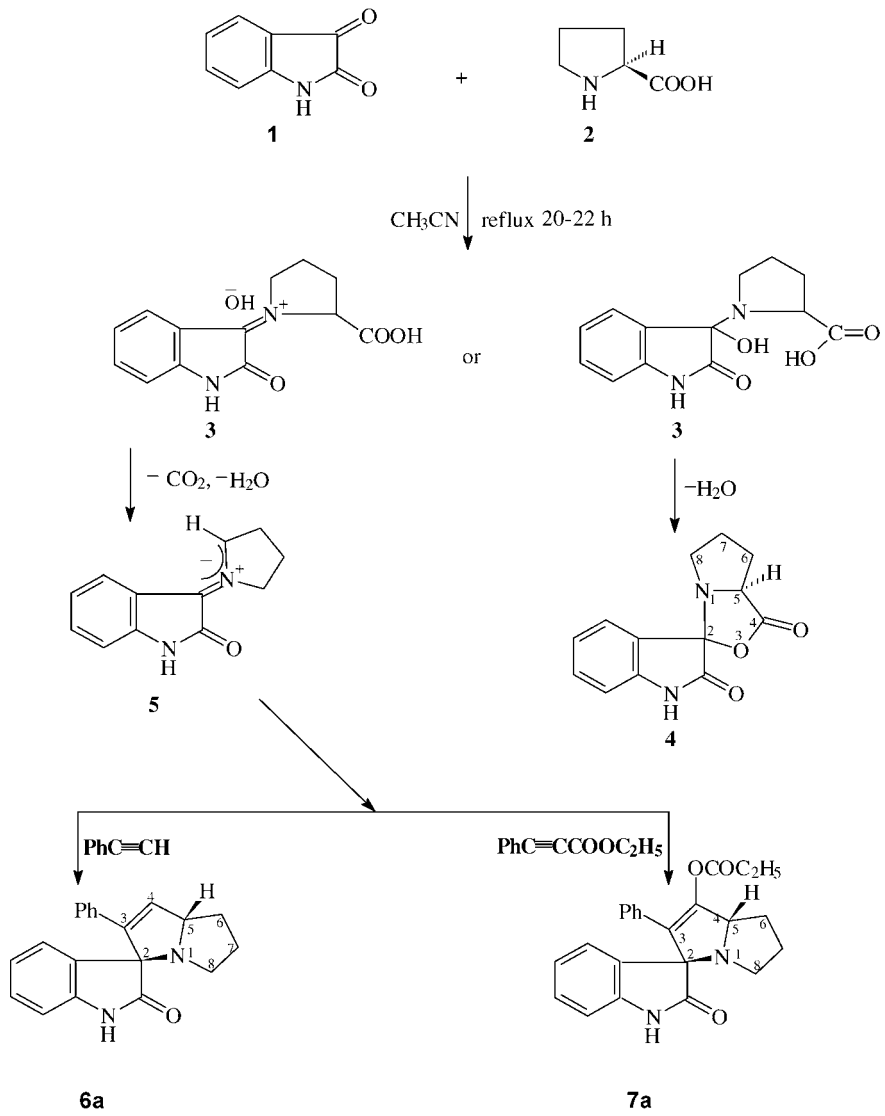
The ΔH_f, HOMO, and LUMO energies and HOMO–LUMO and LUMO–HOMO energy gaps of azomethine ylide **5** with dipolarophiles are given in Table 1. The transition state of the concerted 1,3-dipolar cycloaddition reaction is usually controlled by frontier molecular orbitals (FMO's) of dipolarophiles and dipoles. From Table 1 we may conclude that the $HOMO_{dipole}$–$LUMO_{dipolarophile}$ energy gap is lower than the $LUMO_{dipole}$–$HOMO_{dipolarophile}$ gap and therefore the dominant FMO approach is $HOMO_{dipole}$–$LUMO_{dipolarophile}$.

Attack of phenylacetylene on the planar azomethine ylide from either side results in the formation of products having three chiral centers. Therefore, a total of $2^3 = 8$ isomers **6a–h** are possible (Scheme 3). We have optimized the geometry of all the eight isomers. Results show that all the eight isomers have almost the same ΔH_f, indicating that thermodynamically all are nearly equally stable. Front-side attack

TABLE 1 ΔH_f , HOMO, and LUMO Energies and H–L and L–H Energy Gaps

	ΔH_f (kcal/mol)	HOMO (kcal/mol)	LUMO (kcal/mol)	Energy Gaps (kcal/mol) H–L	Energy Gaps (kcal/mol) L–H
Dipoles					
Amy (**5**)	11.51	−7.80	−0.54	–	–
Dipolarophiles					
Phac	74.65	−9.39	−0.07	7.73	8.85
Et Ph	−10.80	−9.71	−0.66	7.14	9.17

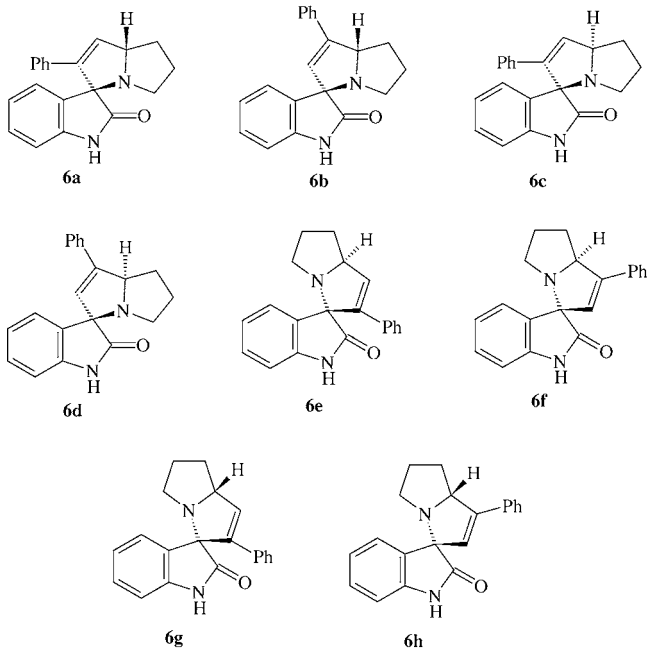
Amy: Azomethine ylide; Phac: Phenylacetylene; Et Ph: Ethyl phenylpropiolate.



SCHEME 2 Schematic representation of reaction of Isatin with Proline in the absence and presence of dipolarophiles.

of phenylacetylene results in the formation of products **6e–h**. However, in the case of the front-side attack of phenylacetylene, the transition state could not be located even in a single case. This may be attributed to the steric hindrance between the isatin ring and the proline ring because front-side attack would result in the inward movement of the proline ring towards the isatin ring, making the system unstable and hence failing to produce the transition-state geometry. This leaves only the possibility of a backside attack. Of these possibilities, in two cases **6c** and **6d** where N and H atom on the adjacent carbon do not lie on the same side, the transition state could not be located because a concerted mechanism is not possible in such a situation. This leaves only two structures **6a** and **6b** for consideration. Out of the remaining two possibilities, we could optimize the transition state in the case of **6a** only. This can be explained using the FMO approach along with the *endo approach* of the phenyl ring. The favored path involves the $HOMO_{dipole}$ and the $LUMO_{dipolarophile}$. Both the HOMO and the LUMO of the dipole show uneven distribution of electronic density along the C—N—C dipole. In the HOMO case, the orbital coefficient is larger at C1 than at C2.

Similarly, in the LUMO of phenylacetylene, the orbital coefficient on the C-atom bearing the phenyl group is larger than that of the C-atom away from it. Thus, there is a better orbital overlap between C1 of the azomethine ylide and the C-atom bearing the phenyl group. This results in the formation of product **6a**, thus ruling out the possibility of **6b**, in which case we could not optimize the transition state. Besides, a secondary interaction between



SCHEME 3 Possible stereoisomers of **6**.

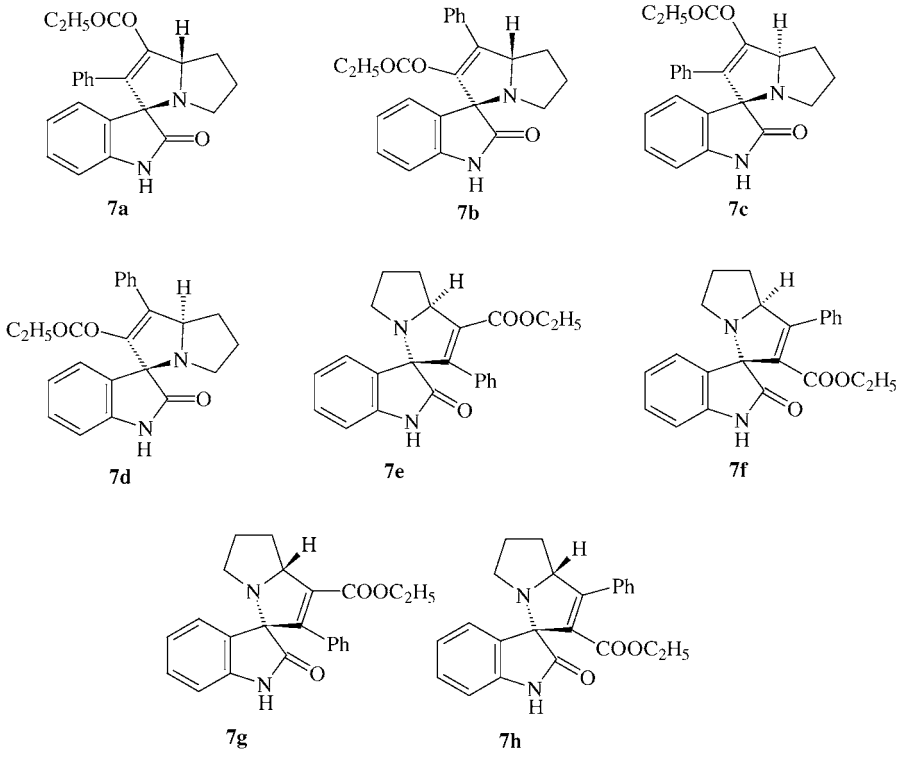
the two phenyl rings, the *endo approach* also favors the formation of product **6a**. Analogous to phenylacetylene, ethyl phenylpropiolate can also attack the azomethine ylide from either side, with the formation of a product having three chiral center and therefore a total of $2^3 = 8$ isomers, **7a–h** being possible (Scheme 4). Out of these eight isomers, the probable isomer formed is **7a**, as discussed in the case of the phenylacetylene reaction.

The results of the above discussion are summarized in Table 2 and Fig. 2, and the following points may be concluded from the above discussion.

1. Geometry optimization of the azomethine ylide **5** indicated that it has an almost planar structure. The proline ring, instead of having an envelope shape, is planar and lies in the same plane as that of the isatin.
2. In the normal case, the dominant FMO approach is $HOMO_{dipole}$–$LUMO_{dipolarophile}$ as this energy gap is lower than the $LUMO_{dipole}$–the $HOMO_{dipolarophile}$ gap.
3. The *endo approach* is favored and the phenyl group lies towards the isatin ring.

SYNTHETIC STUDIES

The reaction of isatin **1** with L-proline **2** was carried out in a molar ratio of 1:1 in refluxing acetonitrile for 20 h to give an oxazolidinone derivative (2-*S*, 5-*S*)-spiro{1-aza-3-oxa-bicyclo[3,3,0]octane-2, 3′-indol}4,2′-dione (**4**). Such an oxazolidinone derivative has been prepared by the reaction of the



SCHEME 4 Possible stereoisomers of **7**.

TABLE 2 ΔH_f-R, ΔH_f-TS, ΔH_f-P, E_a, and Stablization Energy of Amy with Different Dipolarophiles

Product	ΔH_f (kcal/mol) R	TS	P	E_a (kcal/mol)	Stablization Energy (kcal/mol)
Amy + Phac	86.16	116.08	35.06	29.92	51.10
Amy + Et Ph	0.71	29.09	−49.54	28.38	50.25

R: Reactant; TS: Transition state; P: Product; E_a: Energy of activation; Amy: Azomethine ylide: Phac: Phenylacetylene; Et Ph: Ethyl phenylpropiolate.

L-proline and pivalaldehyde as reported by Seebach et al. [12]. However, when the same reaction was carried out with phenylacetylene and ethyl phenylpropiolate as dipolarophiles, spiro polycyclic compounds (2-*R*, 5-*S*)-spiro{3-phenyl-1-aza-bicyclo-[3,3,0]3-octene-2,3′-indol}2′-one (**6a**) and (2-*R*, 5-*S*)-spiro{3-ethoxycarbonyl-4-phenyl-1-aza-bicyclo-[3,3,0]3-octene-2,3′-indol}2′-one (**7a**), respectively, were obtained in moderate to good yield. The reaction proceeds by the formation of an intermediate azomethine ylide **5**, which subsequently undergoes 1,3-dipolar cycloaddition with the cited dipolarophiles to give spiro compounds. These results are in good agreement with theoretical calculations as well as those reported by Grigg et al. [13,14] for the reaction of carbonyl compounds with amines.

The structures of all the products (**4a, 6a**, and **7a**) have been ascertained by their spectral data. In the IR spectrum of typical compound **4a**, characteristic absorption bands were observed at 3500–3100 cm^{-1} for NH, at 1720 cm^{-1} for >C=O, and at 1400 cm^{-1} for C—N. The band at 1190 cm^{-1} was associated with the ether linkage. The ^{1}H NMR spectrum of compound **4a** consisted of a multiplet for 7-H at δ 1.64–1.90, a quartet for 6-H at δ 2.53, a triplet for 5-H at δ 4.24, a triplet for 8-H at δ 4.62, a multiplet for 4 × ArH at δ 6.47–8.26, and a singlet for NH at δ 8.47. In the ^{13}C NMR of compound **4a**, C=O appeared at δ 178.5, lactone C=O at δ 173.7, aromatic carbons in the region δ 143.1–108.7, spiro carbon at δ 79.1, tertiary carbon at δ 58.2, and CH_2 at δ 46.8–23.7. Similarly, the IR spectrum of compound **6a**, showed bands 3500–3100, 3010, 2950, 1700, 1620, and 1400 cm^{-1} assignable to NH str, C—H str (aromatic), >C=O str, NH def, and C—N str respectively.

The ^{1}H NMR spectrum of compound **6a**, showed a quintet at δ 1.80 for 7-H, a quintet at δ 2.07 for 5-H, a quartet at 2.88 for 6-H, a triplet for 8-H at δ 4.67, a multiplet in the region of 6.36–7.64 for the aromatic protons, and a singlet at δ 9.30 for NH. Its ^{13}C NMR showed peaks for C—O at δ 175.3, aromatic carbons at δ 142.8–120.9 olefinic carbons at δ 117.1–108.6, spiro carbon at δ 78.9, and CH_2 at δ 48.2–26.2. All these spectral data are in harmony with the assigned structures. Additional evidence has been obtained by their elemental analyses.

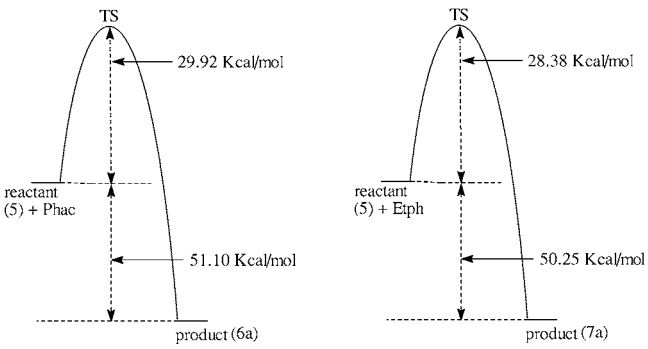


FIGURE 2 Stablization energy and activation energy of amy **5** with phenylacetylene and ethyl phenylpropiolate.

EXPERIMENTAL

All the reactions were carried out under a nitrogen atmosphere. Acetonitrile was dried by refluxing with anhydrous calcium chloride for 5–6 h and was then distilled. Melting points of newly synthesized compounds were determined in open glass capillaries and are uncorrected. The IR spectra were recorded on a Nicolet Magna IR™ spectrometer Model 550 in KBr pellets. The ^{1}H NMR spectra were recorded on a Brucker 300 MHz model using tetramethylsilane as an internal standard. The ^{13}C NMR spectra were recorded on a Bruker 300 MHz model. Chemical shifts are given in δ values. Elemental analyses were performed on a Perkin-Elmer Series C, H, N, S Analyzer 2400. In order to purify the synthesized compounds column chromatography was performed on silica gel 60 (Merck).

Representative method for the synthesis of compounds **4, 6**, and **7** is described below.

*Synthesis of (2-S, 5-S)-spiro{1-aza-3-oxa-bicyclo-[3,3,0]octane-2,3′-indol}4,2′-dione (**4a**)*

A mixture of isatin **1** (0.37 g, 2.5 mmol) and L-proline **2** (0.29 g, 2.5 mmol) in a molar ratio of 1:1 was refluxed under a nitrogen atmosphere for 20 h in dry acetonitrile (60 ml). Unreacted acid was filtered from the cooled reaction mixture. The filtrate was evaporated in vacuo to half of its volume. It was then allowed to stand overnight, but no crystallization occurred. Hence, it was further concentrated to half of its volume and allowed to crystallize to afford oxazolidinone derivative **4a**. Compound **4a** was obtained as a brown solid (0.39 g, 59%) mp 150°C. Calculated (found): C, 63.93 (63.25); H, 4.92 (4.73); N,

11.48 (11.32); ν_{max} (KBr): 3500–3100sbr, 1720s,1400s, 1210m cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.64–1.90 (m, 7-H, 2 × H), 2.53 (q, 6-H, 2 × H), 4.24 (t, 5-H,1 × H), 4.62 (t, 8-H, 2 × H), 6.47–8.26 (m, 4 × ArH), 8.47 (s, NH); ^{13}C NMR (300 MHz, DMSO) δ 178.6 (C=O), 173.3 (lactone ring), 143.1–108.7 (6 aromatic carbons), 79.1 (spiro C2), 58.2 (C5), 46.8 (C8), 27.0 (C6), 23.7 (C7).

*Synthesis of (2-R,5-S)-spiro{3-phenyl-1-aza-bicyclo[3,3,0]octane- 2,3′-indol}2′-one (**6a**)*

A mixture of isatin **1** (0.37 g, 2.5 mmol), L-proline **2** (0.29 g, 2.5 mmol), and phenylacetylene (0.25 g, 2.5 mmol) in equimolar ratio was refluxed under a nitrogen atmosphere for 20 h, in dry acetonitrile. After completion of the reaction as monitored by TLC, unreacted proline was removed by filtration. The filtrate was evaporated in vacuo to half of its volume. The crude product so obtained was then subjected to column chromatography over silica gel by elution with solvents of rising polarity. Compound **6a** was obtained in the form of yellow-brown crystals from chloroform/ethyl acetate (4:1) fraction, mp 180°C. Calculated (found): C, 79.47 (78.78); H, 5.96 (5.38); N, 9.27 (9.54); ν_{max} (KBr): 3500–3150sbr, 3010s, 1700s, 1620s, 1400s cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.93 (q, 7-H, 2 × H), 4.67 (t, 8-H, 2 × H), 6.57–7.37 (m, 8 × ArH), 9.0 (s, NH); ^{13}C NMR (300 MHz, DMSO) δ 175.6 (C=O), 142.8–120.8 (12 aromatic carbons), 117.1 (C3), 110.0 (C4), 78.9 (spiro C2), 58.0 (C5), 48.2 (C8), 30.8 (C6), 26.2 (C7).

*Synthesis of (2-R, 5-S)-spiro{3-ethoxycarbonyl-1-aza-bicyclo[3,3,0]octane-2,3′-indol}2′-one (**7a**)*

A mixture of isatin **1** (0.37 g, 2.5 mmol), L-proline **2** (0.29 g, 2.5 mmol), and ethyl phenylpropiolate (0.44 g, 2.5 mmol) in an equimolar ratio was refluxed under a nitrogen atmosphere for 20 h, in dry acetonitrile. After completion of the reaction, as monitored by TLC, unreacted acid was removed by filtration. The filtrate was evaporated in vacuo to half of its volume. The crude product so obtained was then subjected to column chromatography over silica gel, whereby compound **7a** was obtained as a yellow-brown powder from chloroform/ethyl acetate (5:1) fraction, mp 165°C. Calculated (found): C, 73.80 (72.95); H, 5.88 (5.60); N, 7.49 (7.32); ν_{max} (KBr): 3300–3100sbr, 2980m, 1720s, 1480 m cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.99 (t, CH_3), 1.66–1.95 (m, 7-H, 2 × H), 2.05 (q, 5-H, 1 × H), 2.83 (q, 6-H, 2 × H), 4.03 (q, OCH_2), 4.7 (t, 8-H, 2 × H), 6.51–7.98 (m, 9 × ArH), 10.38 (s, NH); ^{13}C NMR (300 MHz, DMSO) δ 178.1, 174.7 (2 × C=O), 142.4–120.4 (12 aromatic carbons), 114.7 (C3), 108.9 (C4), 71.2 (spiro C2), 59.4 (C5), 57.9 (OCH2), 46.5 (C8), 31.1 (C6), 26.7 (C7), 13.1 (CH3).

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