A Simple and Efficient Two-step Synthesis of Hexahydro-diazecane-dione Derivatives

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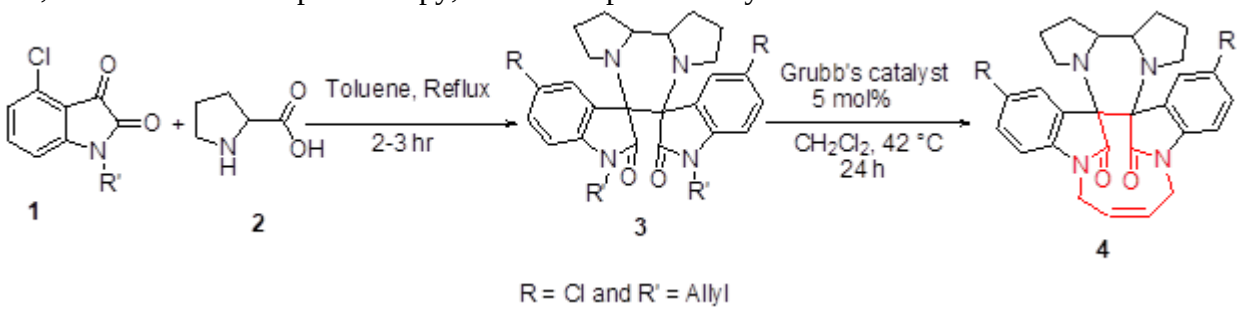
Abstract

Various substituted Dispiro [pyrrolo-piperazino-oxindole] have been synthesized by utilizing a simple and efficient two-step synthetic protocol by Grubbs metathesis in dichloromethane at 40°C. The structures and relative stereochemistry of the cycloadduct were confirmed by single-crystal X-ray diffraction, ^{1}H and ^{13}C NMR spectroscopy, and mass spectrometry.



Keywords: Hexahydro-diazecane-dione, Metathesis, Cycloaddition, Grubbs Catalyst.

1. Introduction

Recent challenges in organic synthesis encompass the development of methodologies that afford complex structural diversity in fewer steps from simple substrates with high yields (Molineux, R. J, 1987). Dispiro [pyrrolo-piperazino-oxindole] (Fujimori, S., 1990), the fused structural frameworks of three privileged motifs pyrrole, piperazine, and oxindole are present as basic scaffolds in natural products and pharmaceuticals consist of 10 membered rings (Hong et al., 2011, Howe et al., 1990, Amici et al., 1975). All the scaffolds have received much attention and there have been considerable efforts towards their synthesis (Kobayashi et al., 1991 and James et al., 1991) in recent years as they display significant biological (Cohen et al., 1995, Caroll et al., 1993, Early et al., 1988, Bban et al., 1976, ban et al 1975) commercial applications (Ban et el., 1974 and Van et al., 1969). But to our surprise, there appears no report of pyrrolo-piperazino-oxindole synthesis in the literature although this motif is present as a core structure in many natural products (Singh et al., 2012). Most of the spiro-oxindole alkaloids possess a common basic framework derived from tryptamine and are characterized by a unique spiro fusion to a pyrrolidine ring at the 3-position of the oxindole core. They can be further classified into two substructural classes: the tetracyclic secoyohimbane type [e.g. rhynchophylline (A)] and the pentacyclic heteroyohimbane type [e.g. formosanine (B)]. Other spiro[pyrrolidine-3,3'-oxindole] alkaloids that have been isolated are

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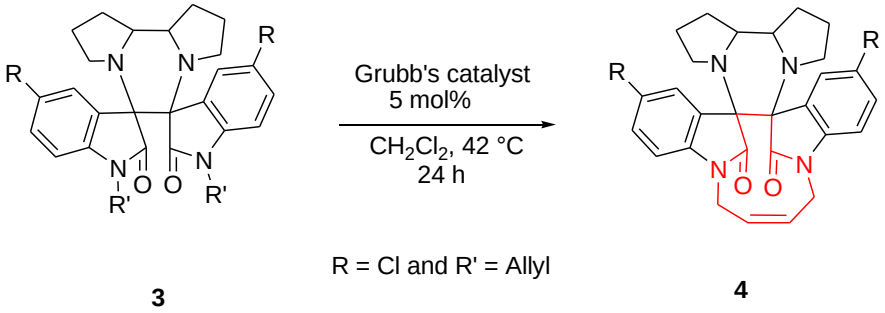
exemplified by (-)-horsfiline (C), (Jossang et al., 1991) spirotryprostatin A (D), spirotryprostatin B (E), (Cui et al., 1996) and (+)-elacomine (F) (Pellegrini et al. 1996).

It is contemplated to synthesize the pyrrolo-piperazino-oxindole motif through the development of novel methodologies, particularly [3+3] cycloaddition within a multi-component module employing an azomethine ylide as the 1,3-dipole which has been used widely to construct complex cyclic systems from relatively simple precursors (Stanley et al., 2008). This mode of cycloaddition simultaneously constructs two carbon-carbon bonds and forms complex ring systems with regio- and stereo control. In continuation of our search in the area of 1,3-dipolar cycloaddition, (Das et al., 2013) herein reported the simple and efficient approach for the synthesis of hexahydro-diazecane-dione from dispiro [pyrrolo-piperazino-oxindole] using Grubbs 2nd generation catalyst in presence of dichloromethane as solvent (**Scheme-1**).

The present study focuses on the synthesis not conducted of various polynuclear heterocyclic ring systems based on oxindoles as well as spiro-oxindoles.



Scheme 1. Synthesis of hexahydro-diazecane-dione derivatives 5(a-d).

2. Methods and Materials

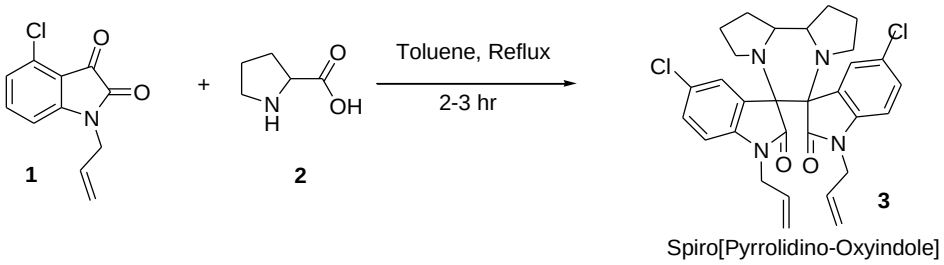
Chloro isatin, allyl bromide, Grubbs catalyst, L-proline, toluene, dichloromethane, silica for thin-layer chromatography, anhydrous sodium sulfate, silica for column chromatography, hexane, chloroform were purchased from Sigma Aldrich with analytical grade. All chemicals were used as received without any further purification.

Reactions were carried out in a temperature controlled magnetic stirrer from REMCO fitted with silicon oil-bath. The 1H NMR and 13C NMR of the synthesized compounds were recorded on a Bruker Avance DPX 300 NMR spectrometer using Tetramethylsilane (TMS) as an internal reference and chemical shifts were reported as δ ppm units. Spectral data were presented as s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad, app=apparent, coupling constant (*J*) in Hertz (Hz). IR spectra are recorded on a Shi-madzu FTIR-8300 spectrometer with samples prepared as KBR pallets.

The chloro substituted N-allyl isatin (0.147 g, 1 mmol) was reacted with L-proline (0.115 g, 1 mmol) and N-benzyl Glycine, respectively. The mixture was stirred in toluene (20 mL) and refluxed for 2-3 h (Scheme-2). After completion of the reaction (monitored by TLC), the content was transferred to a separatory funnel and the organic layer was separated, washed, freed from water, and evaporated to dryness under reduced pressure. The residue was purified using flash silica gel column chromatography using a mixture of hexane and ethyl acetate in 2:1 ratio. After separation of, the compounds were recrystallized using hexane-chloroform mixtures.

To establish the generality, we employed different derivatives of isatin to carry out reactions under the optimized condition. But due to lack of funding, we didn't do the spectroscopic analysis of the other compounds. So we omitted those derivatives for better clarity. The result is summarized in Table 1. ^{1}H

and ^{13}C-NMR spectroscopy, and mass spectrometry of the synthesized compounds were done for further structure elucidation and characterization.



Scheme 2. Synthesis of Spiro [Pyrrolidino-Oxyindole].

3. Results and Discussion

HRMS (ESI) analysis of compound 3 gave a molecular ion (MH+) at m/z 548.1730 (calcd 548.1746), and is assigned to the molecular ion C30H30Cl2N4O2, indicating that two molecules of 1-allyl-5-chloroisatin 1 and two L-proline moieties were involved in the reaction. The FTIR strong absorption band (1608 cm-1) indicated the existence of a carbonyl of the amide group.

These results can be explained by the following mechanism (Scheme 3).15The condensation of L-proline with 1-alkyl-5-haloisatin derivatives gives an iminium carboxylate intermediate [I] which cyclizes into oxazolidin-5-one intermediate [II]. This undergoes thermal decarboxylation leading to the azomethine ylide. This dipole is present in two mesomeric forms, X and Y, which undergo dimerization ([3+3] cycloaddition, leading to the formation of compounds 3.

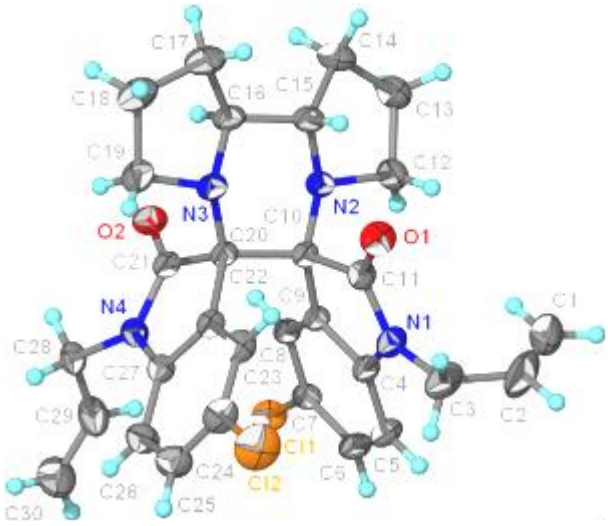


Figure 1. Use X-ray Crystallographic Structure of compound 3.

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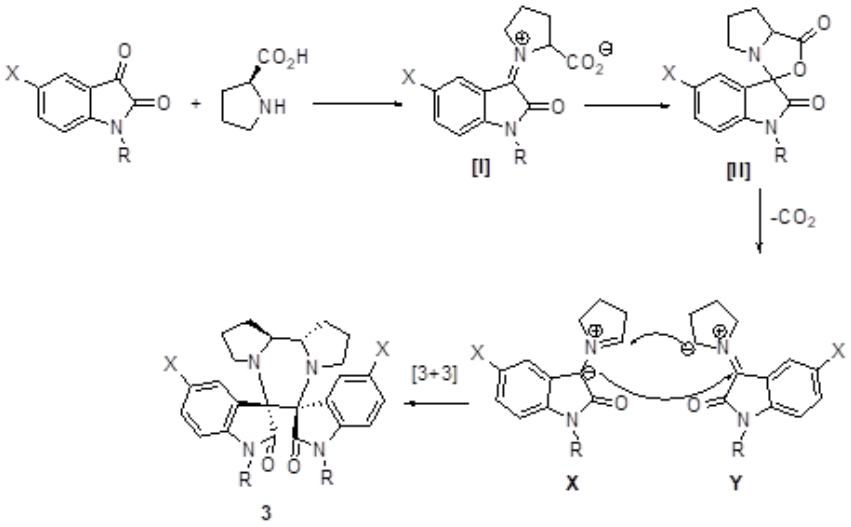

Scheme 3. A plausible mechanism for the synthesis of Spiro [Pyrrolidino-Oxindole].

Table 1: Synthesis of Spiro [Pyrrolidino-Oxindole]

Entry[a]	N-allyl Isatin	L-proline/N-Benzyl Glycine	Spiro [Pyrrolidino-Oxyindole]	
2	**1 R = Cl**	**2**	**3** (R = Cl)	92

[a]Reaction condition: N-Allyl Isatin (1 mmol), L-Proline (2 mmol), N-Benzyl Glycine (2 mmol), and Toluene (20 ml), in air for 1h at refluxing condition.
[b]Yield of isolated pure product.

At the outset, the chloro substituted Spiro [Pyrrolidino-Oxyindole], and Spiro [Piperazino-Oxyindole] derivatives were employed a ring metathesis reaction. The reaction was carried out using Grubbs catalyst in dichloromethane at 40 ^{0}C for 24 hours. Although the reaction rate was slow enough, the reaction yield was moderately good. After completion of the reaction, the product was separated from the reaction mixture using column chromatography. The product was amorphous in nature. Therefore, X-ray crystallography experiment was not performed. ^{1}H and ^{13}C-NMR spectroscopy and mass spectrometry of the synthesized compound were done for further structure elucidation and characterization.

Table 2: Synthesis of Spiro [Pyrrolidino-Oxyindole].

Entry[a]	Spiro [Pyrrolidino-Oxyindole]	**4**	Yield[b](%)
1.	**3 R = Cl**	**4** (R = Cl)	66

[a]Reaction condition: Spiro [Pyrrolidino-Oxyindole]/Spiro [Piperazino-Oxyindole], Grubb's 2nd generation catalyst and DCM (20 ml), at 40 ^{0}C for 24 h.
[b]Yield of isolated pure product.

Spectral data : Compound 3: Physical state: White powder; Yield: 81%; M.P: 179-181°C; IR (KBr, Vmax cm^{-1}): 814 (b), 1178 (b), 1608 (s), 1714 (w) ; ^{1}H NMR (300 MHz,$CDCl_3$): 1.65 (m, 2H), 1.84 (m, 2H), 2.06 (m, 1H) 2.61 (1H, m), 3.62 (m, 1H), 4.16 (m, 2H), 5.07 (m, 2H), 5.64 (m, 1H), 6.41 (d, 2H, *J* = 8.1 H_Z), 7.05 (dd, 1H, J_1 = 2.1 H_Z, J_2 = 5.1 H_Z), 7.31 (1H, d, J = 2.1 HZ); ^{13}C NMR (75 MHz, CDCl3): 20.8 CH_2, 27.3 (CH2), 41.8 CH_2, 47.5 CH_2, 59.0 CH, 68.3 C,109.4 CH, 118.1 CH_2, 126.1 CH, 127.0 C, 127.6 C, 129.1CH, 130.9 CH, 141.5 C, 173.3 C = O; ESI-MS, positive mode: M/z calcd. for $C_{30}H_{30}Cl_2N_4O_2$ found 548.97.

Compound 4: Physical state: Amorphous; Yield: 66%; M.P: 185-187°C; IR (KBr, $_V$maxcm^{-1}): 890 (b), 1213(b), 1608(s), 1714(w); ^{1}HNMR (300 MHz, $CDCl_3$): 1.64 (m, 2H), 1.81 (m, 2H), 2.20 (m, 1H), 2.31 (m, 1H), 3.60 (m, 1H), 4.05 (m, 2H), 5.07 (m, 1H), 6.40 (d, 1H, J = 8.1 H_Z), 7.08 (m, 1H),7.33 (d, 1H, *J* = 1.5 H_Z); 13C NMR (75 MHz, $CDCl_3$): 20.8 CH_2, 27.5 CH_2, 41.7 CH_2, 47.7 CH_2, 59.2 CH, 68.4 C, 120.3 CH, 127.3 C, 127.7 C, 129.4 CH, 131.4 CH, 141.6 C, 173.5 C = O; ESI-MS, positive mode: M/z calcd. For $C_{28}H_{26}Cl_2N_4O_2$ found 520.90.

4. Conclusion

A number of novel hexahydro-diazecane-dione derivatives containing oxyindole, pyrrolidine, and piperazine rings have been synthesized from commercially accessible Isatin and L-Proline. Here in, two of the compounds are reported for the preliminary initiation of the work and better clarity.

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