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One pot, three component synthesis of spiroindenoquinoxaline pyrrolidine fused nitrochromene derivatives following 1,3-dipolar cycloaddition

Sabita Nayak[a], Priyabrata Pattanaik[a], Seetaram Mohapatra[a], Deepak Ranjan Mishra[a], Pravati Panda[a], Bishnuprasad Raiguru[a], Nilima Priyadarshini Mishra[a], Subhrakant Jena[b], and Himansu Sekhar Biswal[b]

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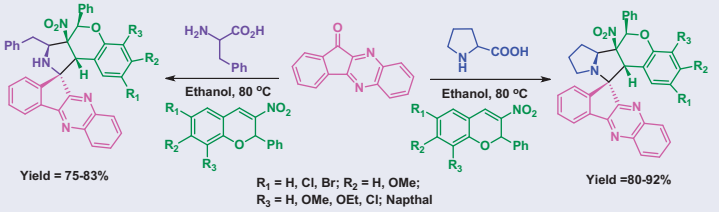
ABSTRACT

An expedient one-pot sequential three-component synthesis of a series of diverse spiroindenoquinoxaline pyrrolidine fused nitrochromene derivatives following 1,3-dipolar cycloaddition of azomethine ylides generated *in situ* by the condensation of indenoquinoxalone and α-amino acids (L-proline and L-phenyl alanine) with 3-nitrochromenes as dipolarophile under classical as well as microwave irradiation is described. The protocol provides a mild reaction condition, high yield of the products, high regioselectivity, and operational simplicity to assemble complex structural entity in a single operation with good to excellent yield. The regio and stereochemical outcome of the cycloaddition reaction is ascertained by spectroscopic and single crystal X-ray analysis.

GRAPHICAL ABSTRACT



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KEYWORDS
Azomethine ylides; 1,3-dipolar cycloaddition; indenoquinoxaline; multi-component reactions; spiro compounds; nitrogen heterocycles; 3-nitro-2*H*-chromene

Introduction

The search for the efficient transformation of simple starting materials to highly functionalized complex products that combine economic, environmental and green aspects has been an active objective in organic synthesis. In this regard, the development and use of multi-component reactions (MCRs) have emerged as a highly valuable synthetic tool to fulfill this goal. In recent years, the area of 1,3-dipolar cycloaddition reactions has been well developed for the synthesis of spiro-heterocycles in a multicomponent

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fashion. Spiro heterocycles are ubiquitously imperative structural units of many natural or synthetic molecules and constitute the largest diversity of organic molecules of chemical, biomedical, and industrial significance.[1,2] One of the most effective direct methods for the synthesis of spiroheterocycles with pyrrolidine and pyrrolizidine rings following intermolecular 1,3-dipolar cycloaddition of azomethine ylides to dipolarophiles has attracted the attention of synthetic organic chemists because of their highly pronounced pharmacological and biological activities such as anti-tumor, anti-cancer, anti-bacterial, antioxidant and acetylcholine esterase inhibitory activity etc and also serve as synthetic intermediates of drug precursors.[3,4] The 1,3-dipolar cycloaddition (1,3-DC) reactions of azomethine ylides with olefin is an elegant and efficient methodology for regio- and stereoselective synthesis of structurally complex pyrrolidine and spiropyrrolidine heterocycles from relatively simple precursors.[5–8] Nitrogen-containing heterocycles constructed through 1,3-dipolar cycloaddition of azomethine ylides generated *in situ* from the decarboxylative condensation of carbonyl compounds with α-amino acids have been well documented and are widely applied in organic synthesis for the construction of an important cluster of significant bioactive compounds.[9–12] In recent years, spiro indenoquinoxaline-pyrrolidines, prepared from 1,3-DC between azomethine ylides with olefinic dipolarophiles, have attracted the increasing interests due to their potentially pronounced biological activities such as acetylcholine esterase inhibitory activity, anticancer and antioxidant properties (Fig. 1).[13–16] The abundance of natural and unnatural bioactive spiroquinoxaline pyrrolizine derivatives have encouraged the design and synthesis of novel spirocyclic indenoquinoxaline with relevant and notable medicinal properties.

On the other hand, pyrans and chromenes are important classes of heterocycles because of their core fragments are incorporated in a large variety of natural products and biologically active compounds. They are of considerable interest as they display a broad range of pharmaceutical properties such as anti-tumor, anti-cancer, anti-microbial, anti-fungal and anti-HIV character.[17,18]Among the different types of chromenes, we focused on 3-nitro-2*H*-chromene scaffolds due to their interesting biological activities, such as anticancer (S14161, BENC511) antimicrobial, antioxidant, and anti-inflammatory, etc (Fig. 1).[19,20]

Literature survey reveals a large number of reports on 1,3-dipolar cycloaddition reaction of indenoquinoxalone derivatives with vinyl nitro olefins, α,β-unsaturated carbonyl,

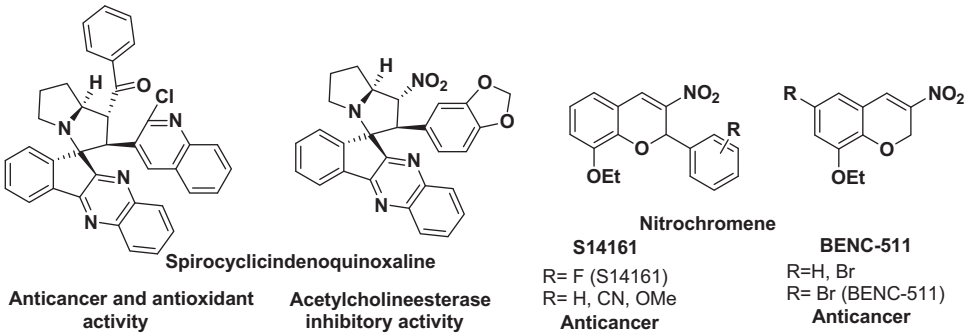


Figure 1. Some important bioactive spiroindenoquinoxaline/nitrochromene containing molecules.

α,β-unsaturated ester and α,β-unsaturated nitrile compounds, etc.[13–16] Despite these recent advances, to the best of our knowledge, stereoselective 1,3-dipolar cycloaddition reaction of indenoquinoxalone derivatives with cyclic α,β-unsaturated nitro has not been reported yet.

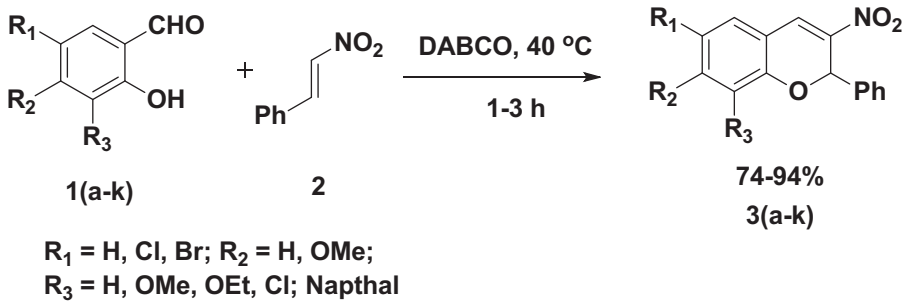
As a continuation of our interest in developing a new methodology for the synthesis of highly functionalized spiro compounds and 3-nitro-2*H*-chromene containing heterocycles, we have reported a three component 1,3-dipolar cycloaddition reaction to form spiropyrrolidinyl indenoquinoxaline derivatives.

Herein we report an atom economic, high yielding, regio- and diastereoselective multicomponent protocol for facile synthesis of highly substituted spiro-indenoquinoxaline pyrrolizine fused 3-nitro-2*H*-chromene scaffold by the reaction of indenoquinoxalone, L-proline/L-phenyl alanine, and 3-nitro-2*H*-chromene in ethanol under conventional heating/microwave irradiation. It is interesting that regio- and sterospecifically a single product was obtained.

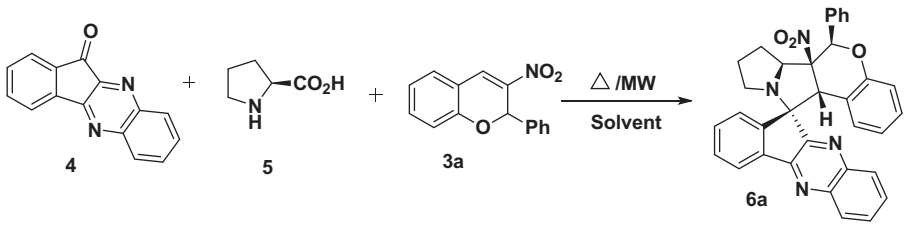
Results and discussion

Initially, the 3-nitro-2*H*-chromene derivatives **3**(**a–k**) utilized for 1,3-dipolar cycloaddition were prepared by the treatment of trans-β-nitro styrene **2** with salicylaldehydes **1**(**a–k**) in the presence of DABCO under solvent-free conditions in a single step following oxa-Michael-Aldol reaction. Synthesized 3-nitro-2*H*-chromene derivatives were characterized by ^{1}H, ^{13}C, and HRMS spectra (Scheme 1).[21]

The long-term goal of our research is to expand the useful repertoire of 3-nitro-2*H*-chromene, which are important as complexity-generating tools in both combinatorial and diversity-oriented synthesis. Having 3-nitro-2*H*-chromene in hand, the one-pot sequential three-component reaction involving, indenoquinoxalone **4**, L-proline **5** and 3-nitro-2*H*-chromene **3a** were investigated to establish the feasibility of the strategy and optimize the reaction conditions (Scheme 2). The reaction was examined by taking an equimolar reaction mixture in different solvents such as methanol, ethanol, acetonitrile, benzene, toluene, and H_2O at a different temperature ranging from room temperature to refluxing. As shown in Table 1, ethanol as solvent provided a higher yield of 75% (Table 1, entry 5) in the case of conventional oil bath heating. Therefore, ethanol and refluxing condition were chosen as optimal conditions for all further reactions. The



Scheme 1. Synthesis of 3-nitro-2*H*-chromene.



Scheme 2. Model reaction.

Table 1. Solvent and temperature for the synthesis of spiroindenoquinoxaline pyrrolidine fused 3-nitro-2*H*-chromene.

Entry	Solvent	Temp (°C)	Time (h)	Yield (%)	MW	Temp (°C)	Time (min)	Yield (%)[a]
1	Methanol	r.t	12	n.r	50	40	10	30
2	Ethanol	r.t	12	n.r	50	40	10	40
3	CH_3CN	r.t	12	n.r	50	40	10	30
4	Methanol	80	3	50	50	80	10	68
5	**Ethanol**	**80**	**3**	**75**	**50**	**80**	**10**	**90**
6	CH_3CN	80	3	45	50	80	10	50
7	Benzene	100	3	30	50	80	10	50
8	Toluene	100	3	30	50	80	10	50
9	H_2O	100	3	n.r	50	100	10	n.r

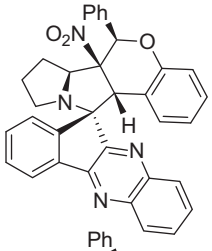
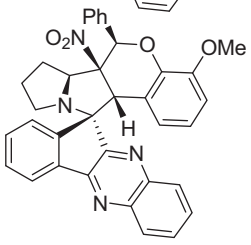
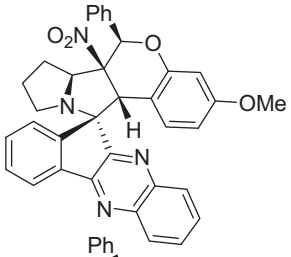
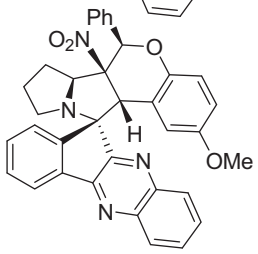
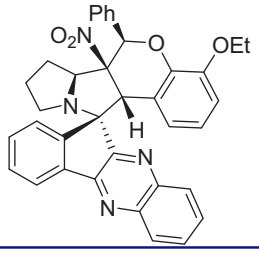
[a]Isolated yields. n.r means no result obtained and the entry in bold indicates optimal condition.

reaction afforded highly substituted spiroproduct **6a** as single diastereoisomer in 75% yield after recrystallization.

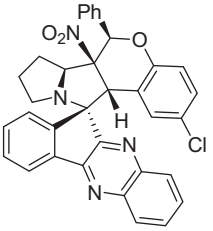
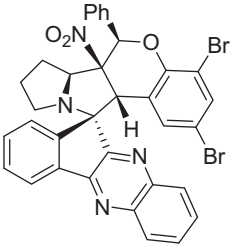
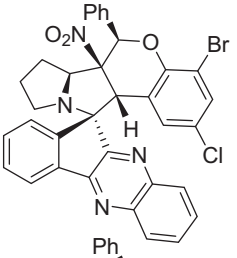
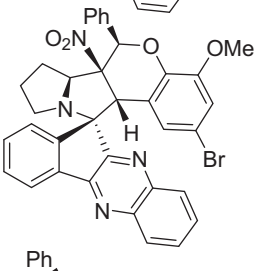
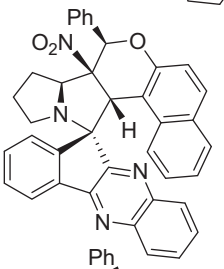
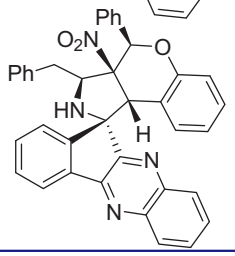
In order to reduce the reaction time interval as well as to enhance the yield of spiro cycloadducts, the reactions were subsequently investigated under microwave irradiation. This technique is a valuable alternative to conventional heating, introduces energetic radiations into the reaction and thereby enhances the rate and yields of the reaction and simultaneously decreases the reaction time. Similar to the conventional heating reactions, an equimolar reaction mixture in different solvents such as methanol, ethanol, acetonitrile, benzene, toluene, and H_2O was subjected to the microwave irradiation. It has been observed that among all the solvents, in ethanol at 50W/80 °C for 10 min, an excellent yield of the product was formed. Increasing the time interval for more than 10 min leads to a decrease in the yield of the product. To our delight, in microwave irradiation, an excellent yield of the product formation was observed as well as the reaction time period reduced from hours to minutes which encouraged us to move further.

To check the generality as well as the effectiveness of the developed protocol, a number of 3-nitro-2*H*-chromene derivatives having substituents such as methoxy, ethoxy, naphthyl, halogens were reacted with indenoquinoxalone and L-proline/L-phenyl alanine using ethanol under reflux conditions. All of them underwent the reaction smoothly affording the corresponding spiro cycloadducts. The yields were not improved further even on raising the temperature over reflux temperature in a sealed tube. The results obtained for both conventional as well as microwave irradiation methods are summarized in Table 2, which clearly shows that microwave irradiation led to an enhancement in the rate as well as the yield of the products (75–92%) over the conventional thermal method (55–80%).

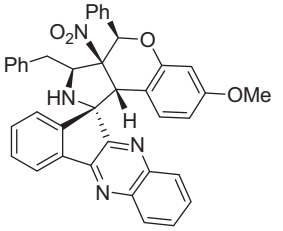
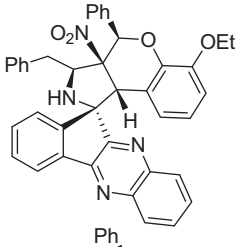
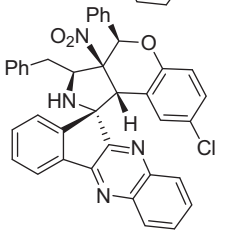
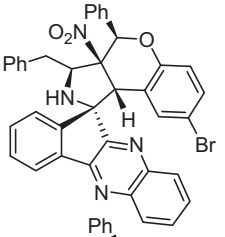
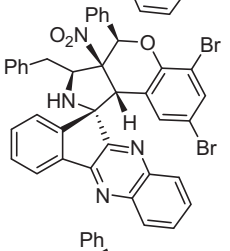
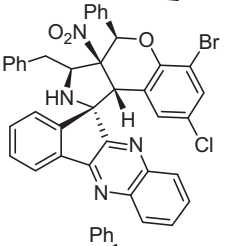
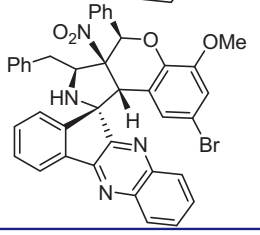
Table 2. Synthesis of spiro indenoquinoxaline pyrrolidine fused 3-nitro-2*H*-chromene.

		Conventional Method (EtOH, 80 °C)		Microwave Method (EtOH, 80 °C, 50W)	
Entry	Product[a]	Time (h)	Yield(%)[b]	Time (mins)	Yield(%)[b]
1		3	75	10	90
2		3	78	10	92
3		3	80	10	92
4		3	78	10	90
5		3	78	10	88

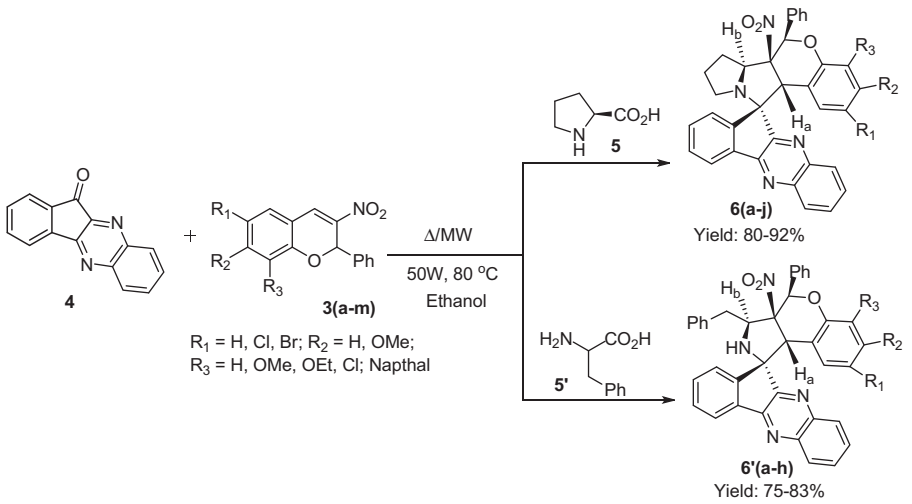
(*continued*)

6		3	80	10	90
7		3	70	10	85
8		3	70	10	80
9		3	72	10	82
10		3	75	10	90
11		3	62	10	78

(*continued*)

12		3	65	10	78
13		3	62	10	83
14		3	63	10	78
15		3	63	10	78
16		3	55	10	75
17		3	60	10	78
18		3	65	10	80

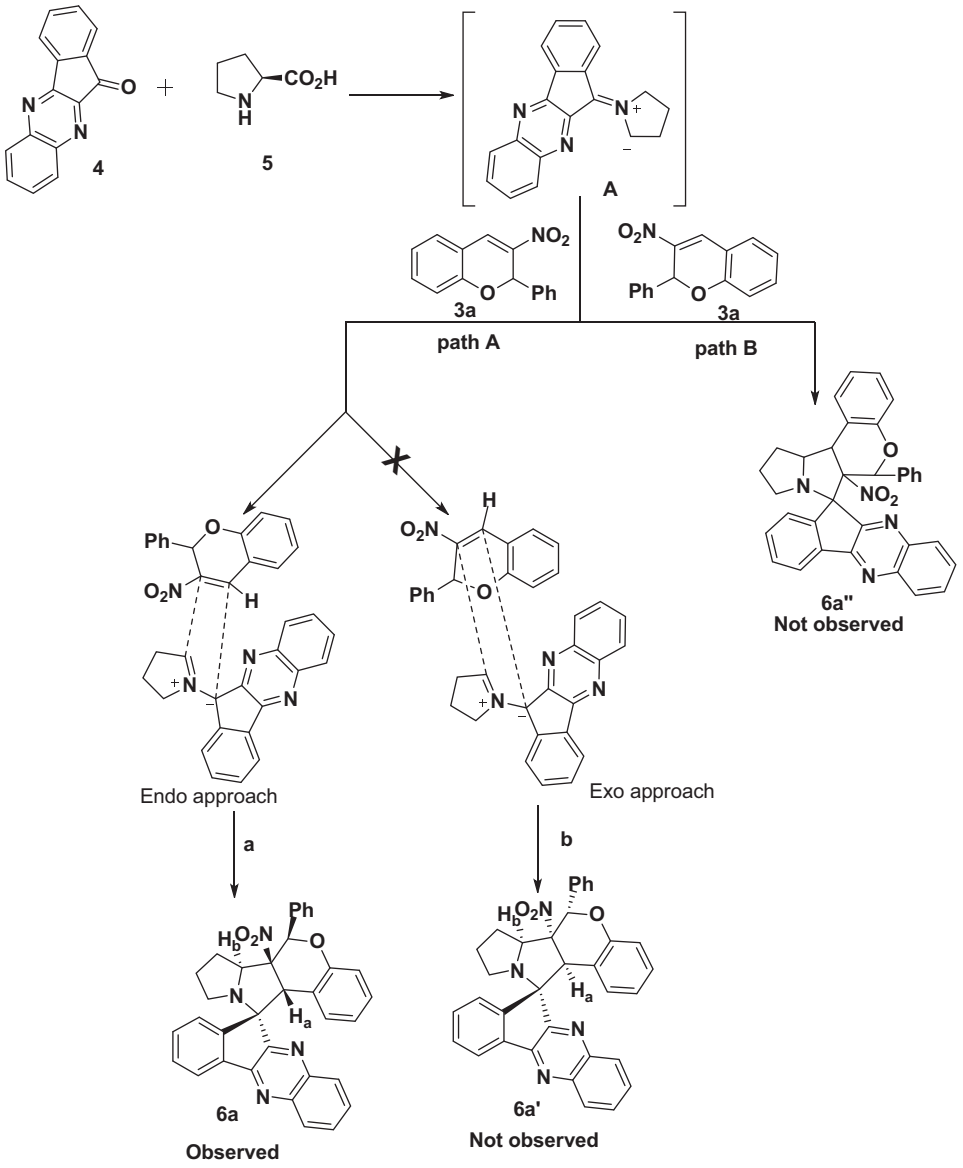
[a]The products were characterized by NMR, IR and Mass spectroscopy.
[b]Isolated yield after purification.



Scheme 3. Synthesis of compounds **6**(**a–j**) and **6′**(**a–h**).

The ^{1}H NMR spectrum of compound **6a** (Table 2, entry 1) exhibited a characteristic singlet at δ 5.11 ppm corresponding to benzylic Ha proton attached to the chromane core and also the Hb proton of the proline ring appeared as multiplet at δ 4.53 ppm, the 2*H*-protons of the 3-nitro-2*H*-chromene appeared as singlet at 6.34 ppm in the cycloadduct **6a** and all other protons appeared in respective positions clearly indicates the formation of spiropyrrolidinyl indenoquinoxalines. Furthermore, the characteristic singlet at δ 5.11 ppm corresponding to Ha proton proved the formation of regioisomer **6a**. If the other regioisomer has formed, the Ha proton would have appeared as a multiplet in the ^{1}H NMR spectrum. The carbon attached to Ha and Hb protons resonates at 46.6 and 69.0 ppm, the 2-C and 3-C of 3-nitro-2*H*-chromene, and spiro carbon of the cycloadduct appeared at 78.5, 117.0, and 95.3 ppm respectively in the ^{13}C NMR spectrum. The three pyrrolidine methylene carbon resonates at 25.0, 28.7, and 53.1 ppm and was confirmed by DEPT-135 NMR spectroscopy. These observed chemical shift values are in good agreement with the structure of the compound **6a**. Furthermore, the presence of the molecular ion peak at m/z 539.2542 (M + 1) in the mass spectrum confirmed the formation of the cycloadduct **6a**. Further extension of this protocol was carried out to delineate the scope of different nitrochromene **6**(**a–j**) with azomethine ylides generated *in situ* from indenoquinoxalone and L-proline and L-Phenyl alanine under optimized reaction conditions and the [3 + 2]cycloaddition reactions proceeded well to give **6**(**a–j**) and **6′**(**a–h**) in good yield (Scheme 3).

As shown in Table 2, this protocol could be applied to a large range of different substituted aromatic rings of 3-nitro-2*H*-chromene including electron-withdrawing groups (such as chloro and bromo groups) and electron donating groups (such as methoxy and ethoxy groups) as well as naphthalene ring. In all cases, the reaction proceeded smoothly and only a single diastereoisomer of spiro-pyrrolidines was afforded in good to excellent yields (75–92%). From Table 2, it is clear that product yields were dependent on the substituents and their positions at the aromatic ring of the 3-nitro-2*H*-chromene. Presence of electron donating groups gave 88–92% yield (Table 2, entries 2–5). However, in the case of 7-methoxy-3-nitro-chromene **6b** and **6c** (entries 2 and 3),



Scheme 4. Proposed mechanism for the formation of **6a**.

excellent yields were obtained over **6d** and **6e**. Halogenated 3-nitro-chromene derivatives were also well tolerated and gave a better yield of the product **6**(**f–h**) (80–90%). Presence of halogens such as –Cl at 6-position of the chromene ring **6f** gave a slightly better yield (entries 6, 90%) in comparison to their halogenated derivative (**6g** and **6h**). However, when both the − I and + I-effect groups such as –Br and –OMe were present in the aromatic ring of 3-nitro-2*H*-chromene **6i,** a slight decrease in the yield of the product formation was observed (Table 2, entry 9, 82%). Excitingly, naphthalene derivatives **6j** also undergo the reaction to afford good yield of product (Table 2, entry 10, 90%). In order to extend the substrate scope of this protocol proline was replaced by pipecolic acid. Unfortunately, in the case of pipecolic acid, the desired product was not

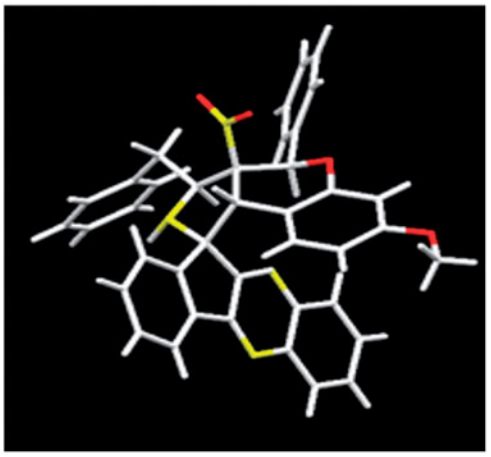


Figure 2. ORTEP diagram of compound **6′b**.

formed, starting materials remain unreacted even after a long period of heating. Only in the case of L-phenyl alanine, we were able to get the desired product with excellent diastereoselectivity which encouraged us to move further. Our experimental results showed that a slight decrease in the yield of the product formation was observed in the case of L-phenyl alanine in comparison to L-proline **6′**(**a–h**) (Table 2, entries 11–18, 75–83%). The identification of the spiro indenoquinoxaline pyrrolidines **6**(**a–j**) and **6′**(**a–h**) was unequivocally ascertained by their ^{1}H, ^{13}C NMR, IR, and HRMS spectra.

A reasonable mechanism of the reaction is given in Scheme 4. From mechanistic considerations, it is believed that the dipolar cycloaddition reaction of azomethine ylide generated in situ by the decarboxylative condensation reaction of indenoquinoxalone with proline to dipolarophile (3-nitro-2*H*-chromene), could proceed by two possible paths, A or B, leading to two corresponding regioisomers, as shown in Scheme 4. In fact, the reaction proceeded exclusively by path A, in which the electron-rich carbon of the azomethine ylide added to the β-carbon of the 3-nitro-2*H*-chromene, resulting in a single regioisomer **6a**, while no trace of another regioisomer **6a″** was detected. Furthermore, this reaction was also found to be diastereoselective. The 1,3-dipolar cycloaddition of the azomethine ylide with 3-nitro-2*H*-chromene could proceed by two methods a or b, as shown in Scheme 4, but only a single endo product was obtained (method a), whereas, exo isomers such as **6a′** resulting from method **b** was not observed. The formation of the regio- and diastereoisomer **6a** by method **a** is more favorable due to the presence of a secondary orbital interaction (SOI) occurring between the nitro group of dipolarophile **3a** with those of the azomethine ylide as shown in Scheme 4. This kind of SOI is not possible in method **b**. Hence, the reaction proceeded through method **a** only, leading to regio- and diastereoselective spiropyrrolidinyl indenoquinoxalines products. The stereochemistry of this cycloaddition was ascertained by single crystal X-ray, in which both the protons Ha and Hb are present in *trans*- orientation (Fig. 2).

Conclusions

In summary, we have developed an operationally simple, autocatalytic, one-pot, three-component reaction to synthesize new spiro indenoqunoxaline pyrrolidine by employing

indenoquinoxalone, L-proline/L-phenyl alanine and 3-nitro-2*H*-chromene. This multi-component reaction offers a high yield, short reaction time with simple experimental procedure, and formation of a single regio- and stereospecific product, without column chromatographic purification. Further, the biological activities of the synthesized compounds are currently under investigation.

Experimental section

General

Melting points were recorded on SMP10 digital melting point apparatus using open capillary tubes and uncorrected. IR spectra were recorded on a Nicolet FT-IR500 spectrophotometer using KBr. ^{1}H NMR spectra were recorded on 400 MHz (100 MHz for ^{13}C NMR) JEOL NMR spectrometer (JEOL, Japan) with $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard. Chemical shifts were reported in parts per million (ppm, δ scale) downfield from TMS at 0.00 ppm and referenced to the $CDCl_3$ at 7.26 ppm (for ^{1}H NMR) or 77.00 ppm (for ^{13}C NMR). HRMS analyses were conducted on a Bruker micro-TOF-Q-MS analyzer (Bruker, MA, USA). All reagents and solvents used in this study were commercially available (from Sigma-Aldrich) and were used without further purification.

Experimental

All reactions were carried out under a positive pressure of argon and with oven-dried glassware. Melting points are uncorrected and were determined with SMP10 digital melting point apparatus using open capillary tubes. Proton magnetic resonance (^{1}H NMR) spectra were recorded using JEOL 400 MHz spectrometers. Chemical shifts are reported in parts per million (ppm) relative to internal standards (tetramethylsilane, $\delta_H = 0.00$; $CDCl_3$, $\delta_H = 7.26$). Data are presented as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, dd = doublet of doublet, br = broad), coupling constant (*J*) values are presented in Hz, integration. Carbon magnetic resonance (^{13}C NMR) spectra were recorded using JEOL 400 MHz spectrometers. Chemical shifts are reported in parts per million (ppm) relative to internal standard (tetramethylsilane, $\delta_C = 0.00$; $CDCl_3$, $\delta_C = 77.00$). Reactions were monitored with analytical Thin Layer Chromatography (TLC) which was carried out using Merck commercial aluminum sheets coated (0.2mm layer thickness) with Kieselgel 60 F254 (Merck, NJ, USA), with visualization by ultraviolet light. Mass spectra were determined on an Agilent Technology (HP) mass spectrometer (CA, USA) operating at an ionization potential of 70 eV. The final products **6(a–j)** and **6′(a–h)** were synthesized using CEM microwave synthesizer (Model no.-908010). All reagents and solvents used in this study were commercially available (from Sigma-Aldrich) and were used without further purification. The intermediate compounds were prepared according to the literature methods.

General procedure for preparation of 3-nitro-2-phenyl-2H-chromenes 3(a–k)

Substituted salicylaldehydes **1**, (1.0 mmol), DABCO (0.2 mmol) and trans-β-nitrostyrenes **2** (1.0 mmol) were taken in one pot and stirred under reflux condition at 40 °C for 1–3 h. The reaction was monitored by TLC and after completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude reaction mixture was crystallized by isopropanol. Also in some cases, the crude product was purified by silica gel (100–200 mesh) column chromatography using ethyl acetate/hexane to furnish the pure compound **3** in 74–94% yield. All compounds were characterized by NMR and Mass spectral data.

General procedure for the synthesis of spiropyrrolidinyl indenoquinoxaline derivatives 6(a–j) and 6′(a–h)

Procedure A

L-Proline/L-phenyl alanine (1 mmol) and 2-phenyl-3-nitro-2H-chromene (1 mmol) were added to a solution of indenoquinoxalone (1 mmol) in EtOH (2 mL) and the mixture was refluxed for 3 h in a sealed tube. The progress of the reaction was monitored by TLC. On completion of the reaction, the reaction mixture was cooled to room temperature and the solid mass, precipitated out, was filtered off followed by washing with cold ethanol to obtain a crude product, which was further purified by recrystallization from EtOH:$CHCl_3$ (9:1) without carrying out column chromatography to obtain pure compound **6**(**a–j**) as a single diastereoisomer (80–92%).

Procedure B

L-Proline/L-phenyl alanine (1 mmol) and 2-phenyl-3-nitro-2H-chromene (1 mmol) were added into a sealed 10 mL glass tube containing a solution of indenoquinoxalone (1 mmol) in EtOH (2 mL) and the mixture was irradiated under microwave irradiation (50 W power) at 80 °C for 10 min. The progress of the reaction was monitored by TLC. On completion of the reaction, the reaction mixture was cooled to room temperature, whereupon a solid mass precipitated out. The precipitate was filtered off followed by washing with cold ethanol to obtain a crude product which was purified just by recrystallization from EtOH:$CHCl_3$ (9:1) without carrying out column chromatography to obtain pure compound **6′**(**a–h**) as a single diastereoisomer (75–83%).

Full experimental detail, ^{1}H and ^{13}C NMR spectra, HRMS spectra. This material can be found via the "Supplementary Content" section of this article's webpage.

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