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An efficient, green synthesis of novel regioselective and stereoselective indan-1,3-diones grafted spirooxindolopyrrolizidines linked 1,2,3-triazoles *via* one-pot five-component using PEG-400

Rajeswari M, Jayant Sindhu, Harjinder Singh and Jitender M. Khurana *

Department of Chemistry, University of Delhi, New Delhi -110 007, India.

Fax: +91 11 27666605; Tel: +91 11 27667725; Email: jmkhurana@chemistry.du.ac.in.

Abstract:- An efficient synthesis of highly diversified novel functionalized indan-1,3-dione grafted spirooxindolopyrrolizidines linked 1,2,3-triazole conjugates *via* one-pot, five-component condensation of indan-1,3-diones, aldehydes, sarcosine, N-propargylated isatin and azides using Cu(I) as a catalyst in PEG-400 as a reaction medium. The reaction proceeds in a highly regio- and stereo selective manner involving catalyst free Knoevenagel condensation followed by two successive 1,3-dipolar cycloaddition reactions. This protocol is suitable for aromatic, heteroaromatic and aliphatic aldehydes. *In situ* generation of azomethine ylides and their selectivity towards exocyclic double bond results in highly functionalized molecular hybrids. All the compounds are obtained in high yield (6a – 6s) and were characterized by spectroscopic methods.

Keywords: Spirooxindolopyrrolizidines, 1,2,3-Triazoles, Azomethine Ylides, 1,3-Dipolar cycloaddition, Polyethylene Glycol- 400.

Introduction

Designing highly efficient protocols for accessing biologically active compounds possessing structural diversity from simple starting compounds is one of the major challenges in organic synthesis.[1] Multi-component reaction (MCR) protocol offers remarkable advantages such as high selectivity, operational simplicity, reduction in the number of work-ups, high yields and

structural diversity of drug-like compounds.[2] 1,3-Dipolar cycloaddition reaction of azomethine ylides with olefinic dipolarophiles and Cu(I) catalyzed [3+2] cycloadditions of azides with triple bond constitute facile approaches for the construction of five-membered nitrogen containing heterocycles.[3] Azomethine ylides can be generated *in situ* for the construction of highly functionalized spirooxindolopyrrolizidines in an efficient manner.[4] Spirooxindolopyrrolizidines exhibit wide range of biological activities such as anticonvulsant,[5] antileukaemic,[6] anesthetic,[7] antiviral[8] and antibacterial.[9] In addition spirooxindolopyrrolizidines ring system also occurs in alkaloids,[10] for example, (-)-horsfiline[10a] and spirotryprostatin A[10b] (Fig. 1).

<Figure 1>

1,2,3-Triazoles are privileged structures associated with biological activities such as anti-HIV, [11] antimicrobial,[12] antiviral,[13] antiproliferative,[14] insecticidal,[15] and fungicidal.[16] Fluconazole is a well-known antifungal drug consisting of 1,2,3-triazole moiety (Fig. 1). 1,2,3-Triazoles can be readily constructed from alkynes and azides by Cu(I) catalyzed 1,3-dipolar addition. Indanone-fused heterocycles (Fig. 1) have also attracted the attention of chemists and pharmacologists [17] due to their role as topoisomerase-I inhibitors.[18,19]

Therefore, in continuation of our work on the synthesis of potentially bioactive heterocyclic compounds with diverse applications through hybridization,[20,21] we decided to link spirooxindolopyrrolizidines, indanone and 1,2,3-triazoles in a single matrix through one-pot five-component reaction using PEG-400 as an efficient and green reaction media.

Results and Discussion

The present manuscript reports a new, diversity oriented and highly efficient green protocol for the synthesis of novel functionalized indan-1,3-dione grafted spirooxindolopyrrozolidines linked

1,2,3-triazole conjugates *via* one-pot, five-component reaction by using Cu(I) as catalyst in PEG-400 as an efficient and green reaction medium (Scheme 1).

The optimized reaction conditions for the above synthesis were identified by attempting the reaction of N-propargylated isatin (1.0 mmol) (1), indane-1,3-dione (1.0 mmol) (2), 4-cholorobenzaldehyde (1.0 mmol) (3), 4-fluorophenyl azide (1.0 mmol) (4) and sarcosine (1.0 mmol) (5) under different conditions. Initially the reaction was attempted in ethanol (10 mL) in presence of aq. $CuSO_4.5H_2O$ (10 mol%) and sodium ascorbate (20 mol%) (in a 50 mL round-bottomed flask) maintained at 80^{o}C in an oil-bath. The reaction was incomplete even after 2 h as indicated by TLC (ethyl acetate: petroleum ether, 30:70, v/v) (Table 1, entry 1). The reaction was quenched and worked up. After flash chromatography, a solid was obtained which was identified as 1-*N*-methyl-spiro[2.3']-1'-*N*-((1-(4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)oxindole-spiro [3.2"]-indan-1,3-dione-(4-chlorophenyl)-pyrrolidine (6a) (55%) yield by ^{1}H NMR, ^{13}C NMR, Mass, IR and X-ray crystallography. Spectroscopic studies revealed the formation of only one isomer though other isomeric products are possible.

The above reaction was then attempted in different reaction media under otherwise identical conditions (Table 1, entries 2-8). Reactions carried out in methanol, acetonitrile, THF, AcOH and water were not complete and gave inferior yields of **6a** after work-up (entries 2-6). The same reaction attempted in PEG-400 and PEG-600 at 80^{o}C was complete in 45 min and yielded 85% and 82% of the desired product (6a) respectively (Table 1, entries 7-8). The five-component reaction was then attempted at different temperatures, under ultrasonic irradiation and in presence of catalysts in PEG-400 (Table 1 entries 9-13).

<Scheme1>

<Table1>

It can be inferred from Table 1 that above one-pot five-component reaction in PEG-400 using aq. $CuSO_4$. $5H_2O$ (10 mol%) and aq. sodium ascorbate (20 mol%) as catalyst at 80°C gave the highest yield of **6a** (85%) (Table 1, entry 7).

The structure of **6a** was elucidated using one and two-dimensional NMR, IR and HRMS spectra. The HMBC and COSY correlations are useful in the signal assignments of **6a**, and various characteristic signals are shown in Fig. 2. The ^{1}H NMR spectrum of **6a** revealed one sharp singlet at δ 2.0 due to the N-methyl protons. The benzylic proton on C_4 carbon of pyrrolidine ring exhibits a multiplet at δ 5.05-5.01. Two protons of C_5 carbon of pyrrolidine exhibit a multiplet at δ 4.01-3.97 and 3.61-3.56. Two protons of N-CH_2 appear as multiplet at δ 4.97-4.91. One proton at C-5 carbon of triazole appears at δ 8.12 which confirms the formation of triazole ring. Aromatic protons appeared as a multiplet in the region of δ 7.92–6.71.

<Figure 2>

The regiochemistry of the **6a** formed in the reaction was confirmed by ^{1}H NMR. The regioisomer **6a** should exhibit a multiplet for the benzylic proton on C_4 carbon of pyrrolidine ring, whereas the other possible regioisomer **8** (see Fig. 4) would show a singlet. The ^{1}H NMR of the product showed a multiplet at δ 5.05-5.01 rather than a singlet thus suggesting the formation of regioisomer **6a**. Further, the off-resonance decoupled ^{13}C NMR of the product exhibited signals at δ 76.8 and 69.6 which correspond to the spiro carbon C_3 and C_2 of the pyrrolidine ring of **6a**. The signals at δ 197.3 and δ 196.3 of the product **6a** correspond to keto carbonyls of indan-1,3-dione. The resonance at δ 173.4 is due to the oxindole carbonyl carbon. Signal at δ 34.6 is due to N-CH_3 and peaks at δ 45.3 and 55.9 are due to C_4 and C_5 carbon of pyrrolidine ring. The mass spectrum of **6a** showed a molecular ion peak at m/z **618.1705 (M^++1)**. The

formation of only one regioisomer i.e. **6a** was also confirmed by the single crystal X-ray structural analysis **(Fig. 3)**

<Figure 3>

The generality of the above protocol was confirmed by carrying out the reactions of N-propargylated isatin (1), indane-1,3-dione (2) and sarcosine (5) with aromatic/ aliphatic azides and aromatic/aliphatic aldehydes. All the reactions proceeded smoothly to yield a diverse library of 1-*N*-methyl-spiro[2.3']-1'-*N*-((1-(aryl/alkyl)-1*H*-1,2,3-triazol-4-yl)methyl)oxindole-spiro[3.2"]-indan-1,3-dione-(aryl/alkyl)-pyrrolidines (6a-6s**)** in high yields under the optimized protocol (**Scheme 2**). The results are summarized in Table 2.

<Scheme2>

<Table2>

The proposed pathway for the formation of **6** is given in Fig. 4. The pathway consists of two sequential steps. The first step involves formation of intermediate **7** by Cu(I) catalyzed [3+2] azide-alkyne cycloaddition. The Cu(I) is generated *in situ* by reduction of Cu(II) to Cu(I) by sodium ascorbate [21]. In the second part, the azomethine ylide, generated *in situ via* decarboxylative condensation of sarcosine with intermediate **7**, undergoes [3+2] cycloaddition reaction with the Knoevenagel condensation product of indan-1,3-dione and aldehyde, resulting in the formation of product **6**. The [3+2] dipolar cycloaddition reaction of azomethine ylide and exocyclic double bond can proceed through two paths i.e. path a and path b. However, in case of path b, there are secondary orbital interactions in the transition state between the carbonyl group of indan-1,3-dione with carbonyl group of isatin which results in the formation of only **6**. The formation of intermediate preformed **7** was confirmed by CO-TLC with an authentic sample of **7**. The intermediacy of **7** was confirmed by an independent reaction of preformed **7** with

Knoevenagel product of indan-1,3-dione and sarcosine in PEG-400 which led to the formation of **6**.

<**Figure 4**>

The role of Cu(I) in catalyzing only the first part of the pathway was also confirmed by an independent reaction of **7** with Knoevenagel product and sarcosine. The reaction was attempted both in the presence and absence of $CuSO_4.5H_2O$ (10 mol%) and sodium ascorbate (20 mol%). The reactions resulted in the formation of **6a** in 85 and 82% yield, respectively, in 45 min, which suggests that Cu(I) has no effect on an dipolar cycloaddition reaction of azomethine ylide and double bond. The formation of regioisomer **8**, as shown in Fig. 4, has already been ruled out based on ^{1}H NMR, 2D NMR and X-ray structure.

Conclusion

In conclusion, we have reported an efficient multicomponent methodology for the synthesis of indan-1,3-dione grafted spirooxindolopyrrolizidines linked 1,2,3-triazole hybrids namely 1-*N*-methyl-spiro[2.3']-1'-*N*-((1-(aryl/alkyl)-1*H*-1,2,3-triazol-4-yl)methyl)oxindole-spiro[3.2"]-indan-1,3-dione-(aryl/alkyl)-pyrrolidines (**6a-6s**) by the reaction of N-propargylated isatin (**1**), indane-1,3-dione (**2**), aldehydes (**3**), azides (**4**) and Sarcosine (**5**) using Cu(I) as catalyst in PEG-400 at 80^{o}C. The products could be obtained in high yields by a simple work-up.

Experimental

Chemistry

Silica gel 60 F_{254} (Precoated aluminium plates) from Merck was used to monitor reaction progress. Melting points were determined on Buchi melting point 545 apparatus and are

uncorrected. IR (KBr) spectra were recorded on a Perkin Elmer FTIR spectrophotometer, and the values are expressed as ν_{max} cm^{-1}. The ^{1}H and ^{13}C spectra were recorded on Jeol JNM ECX-400P at 400 MHz and 100 MHz, respectively. Chemical shift values are recorded on δ scale, and the coupling constants (J) are in Hertz. Mass spectra were recorded at Bruker Micro TOF Q – II. The aryl azides and propargylated isatin were prepared from aromatic amines and isatin respectively by reported procedure.[22]

General procedure for the synthesis of 1-*N*-methyl-spiro[2.3']-1'-*N*-((1-(aryl/alkyl)-1*H*-1,2,3-triazol-4-yl)methyl)oxindole-spiro[3.2'']-indan-1,3-dione-(aryl/alkyl)-pyrrolidine (6a–6s)

An equimolar mixture of N-propargylated isatin (**1**) (1.0 mmol)**,** indane-1,3-dione (**2**) (1.0 mmol), aldehydes (**3**) (1.0 mmol), azides (**4**) (1.0 mmol) and sarcosine (**5**) (1.0 mmol) was dissolved in PEG-400 (10 mL) in a 50 mL round-bottomed flask. Aqueous solution of $CuSO_4.5H_2O$ (10 mol%) followed by an aqueous solution of sodium ascorbate (20 mol%) were then added to the reaction mixture. The reaction contents were stirred magnetically in a pre-heated oil-bath maintained at 80^{o}C for 45-70 min (Table 2). The progress of the reaction was monitored by TLC (eluent: ethyl acetate: petroleum ether, 30:70 v/v). After completion of the reaction, the reaction mixture was allowed to cool at room temperature and was quenched with water (~5 mL). The precipitate formed was collected by filtration at the pump and washed with water. The crude material was purified by flash chromatography over silica gel (230–400 mesh) to afford pure products. The products were characterized by IR, ^{1}H NMR, ^{13}C NMR and Mass spectra.

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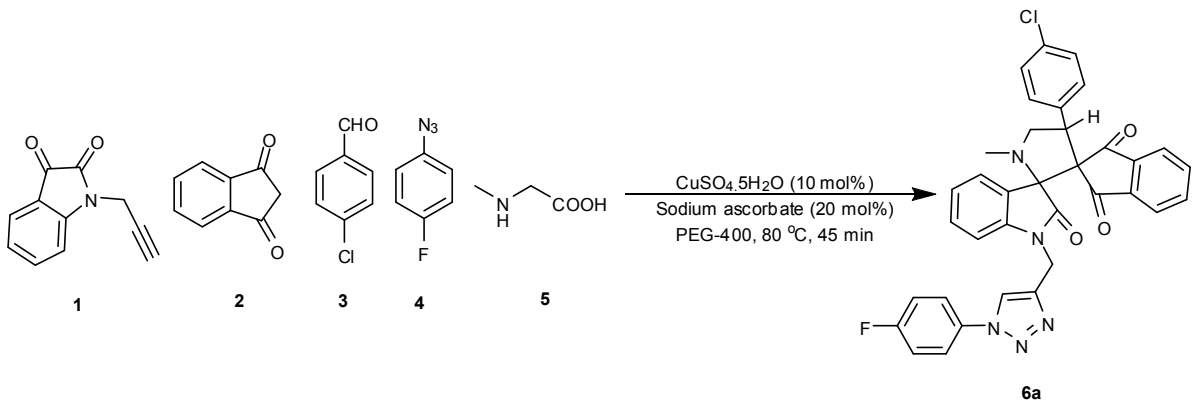
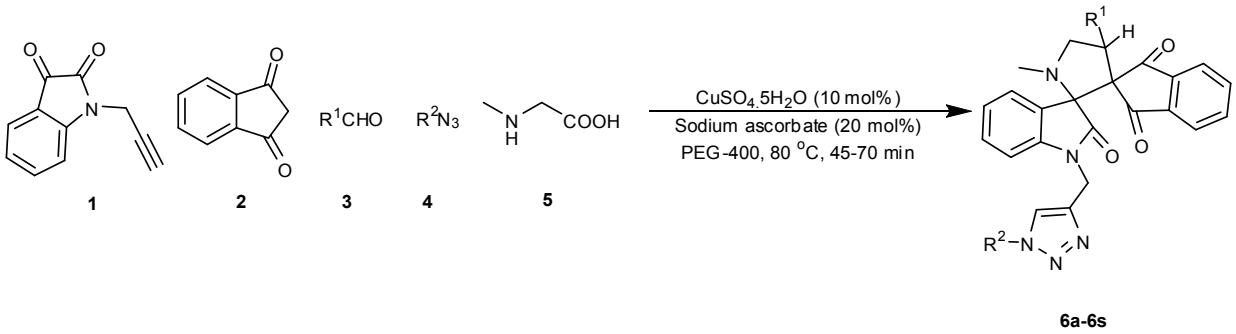


1 2 3 4 5 6a

Scheme 1: Synthesis of 1-*N*-methyl-spiro[2.3']-1'-*N*-((1-(4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)oxindole-spiro[3.2"]-indan-1,3-dione-(4-chlorophenyl)-pyrrolidine.



Scheme 2. Synthesis of 1-*N*-methyl-spiro[2.3']-1'-*N*-((1-(aryl/alkyl)-1*H*-1,2,3-triazol-4-yl) methyl)oxindole-spiro[3.2"]-indan-1,3-dione-(aryl/alkyl)-pyrrolidine

Table 1: Optimization of reaction conditions for the synthesis of1-*N*-methyl-spiro[2.3']-1'-*N*-((1-(4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)oxindole-spiro[3.2"]-indan-1,3-dione-(4-chlorophenyl)-pyrrolidine

Entry	Solvent	Catalyst (mol %)	Temp (^{o}C)	Time (min)	Yield (%)
1	EtOH	-	80	120	55[a]
2	MeOH	-	80	120	60[a]
3	CH_3CN	-	80	100	65[a]
4	THF	-	80	100	60[a]
5	CH_3COOH	-	80	90	70[a]
6	H_2O	-	80	120	35[a]
7	PEG-400	-	80	45	85
8	PEG-600	-	80	45	82
9	PEG-400	-	100	45	80
10	PEG-400	-	60	70	75
11	PEG-400	-	40[b]	120	70
12	PEG-400	p-*T*SA (20)	80	45	82
13	PEG-400	*L*-Proline (20)	80	45	80

[a]Incomplete reaction, [b]Reaction performed under ultrasonic irradiation.

Table 2. Synthesis of 1-*N*-methyl-spiro[2.3']-1'-*N*-((1-(aryl/alkyl)-1*H*-1,2,3-triazol-4-yl)methyl) oxindole-spiro[3.2"]-indan-1,3-dione-(aryl/alkyl)-pyrrolidine

Product code	R^1	R^2	Time (min)	Yield (%)
6a	4-ClC_6H_4	4-FC_6H_4	45	85

6b	4-ClC_6H_4	4-$(CH_3)C_6H_4$	50	80
6c	4-BrC_6H_4	4-FC_6H_4	50	83
6d	4-FC_6H_4	4-$(CH_3)C_6H_4$	40	82
6e	4-BrC_6H_4	4-$(CH_3)C_6H_4$	50	81
6f	4-FC_6H_4	4-FC_6H_4	45	84
6g	4-ClC_6H_4	4-$(NO_2)C_6H_4$	50	82
6h	4-BrC_6H_4	4-$(NO_2)C_6H_4$	45	86
6i	4-$(CH_3)C_6H_4$	4-$(NO_2)C_6H_4$	40	79
6j	4-$(NO_2)C_6H_4$	4-$(OCH_3)C_6H_4$	45	84
6k	4-FC_6H_4	4-$(NO_2)C_6H_4$	40	82
6l	4-$(CF_3)C_6H_4$	4-$(NO_2)C_6H_4$	40	87
6m	4-$(CF_3)C_6H_4$	7-Chloroquinoline	50	80
6n	4-$(CF_3)C_6H_4$	4-FC_6H_4	45	85
6o	4-$(CH_3)C_6H_4$	7-Chloroquinoline	50	74
6p	Furfuraldehyde	n-butyl	50	80
6q	Piperonal	4-FC_6H_4	50	86
6r	Isobutyl	7-Chloroquinoline	60	78
6s	Isobutyl	4-$(OCH_3)C_6H_4$	65	74

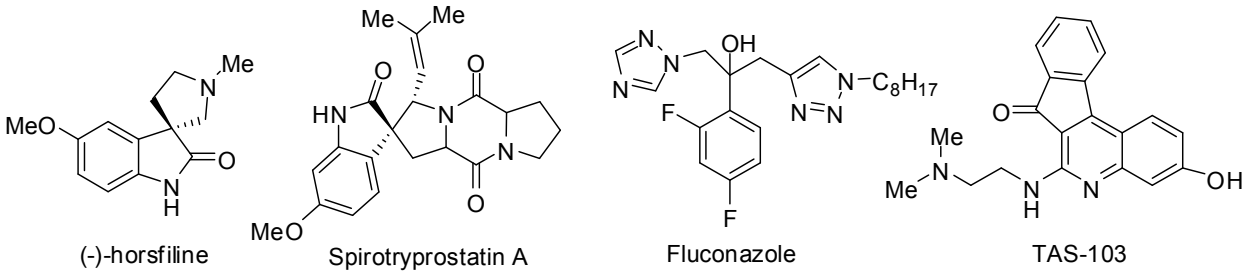


Figure 1: Some representative compounds containing spirocyclic oxindole, indanone and 1,2,3-triazole moiety.

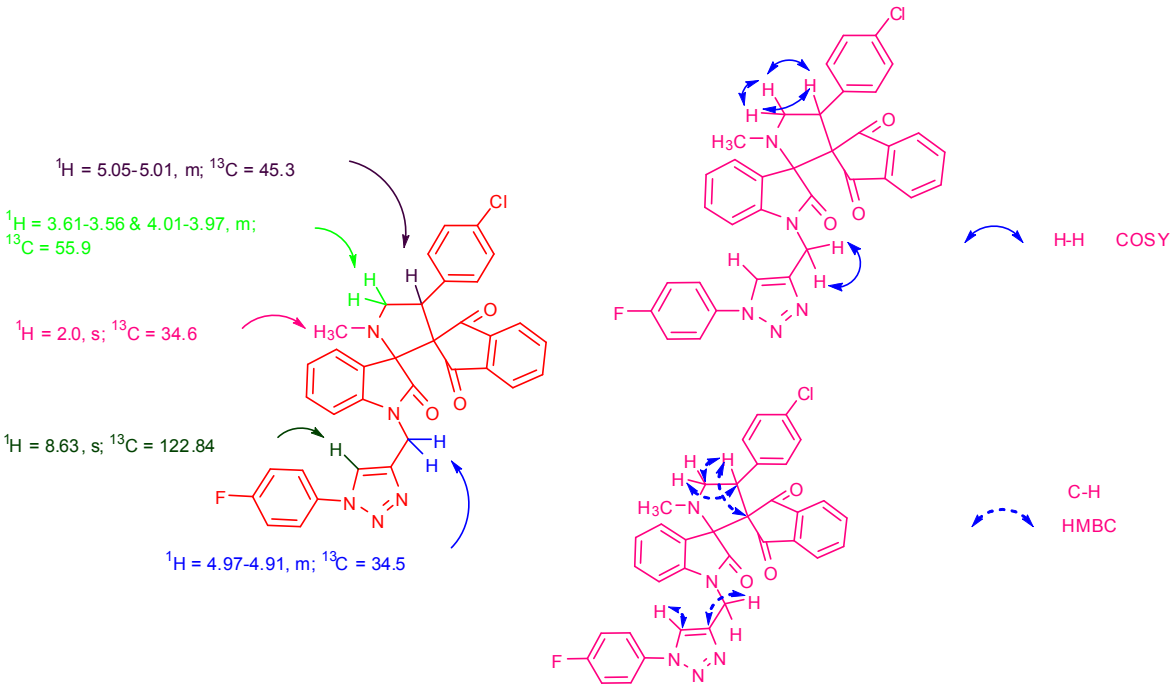


Figure 2. HMBC and COSY correlations useful in the signal assignments of **6a** and various characteristic ^{1}H and ^{13}C NMR peaks

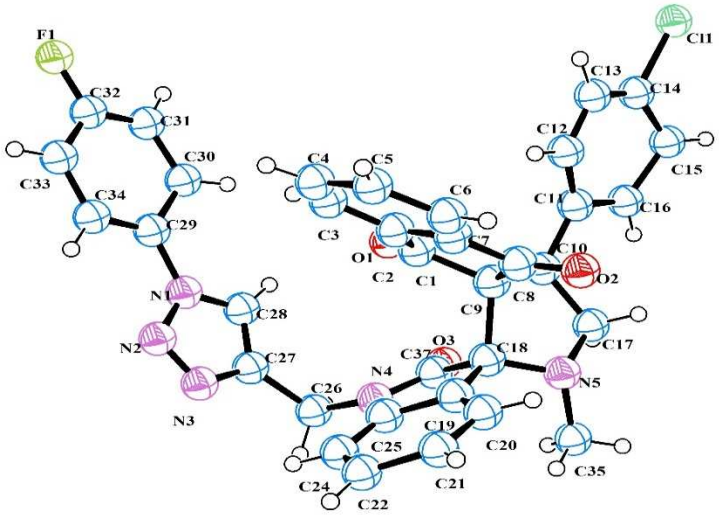


Figure 3. Single crystal X-ray structure of **6a**.

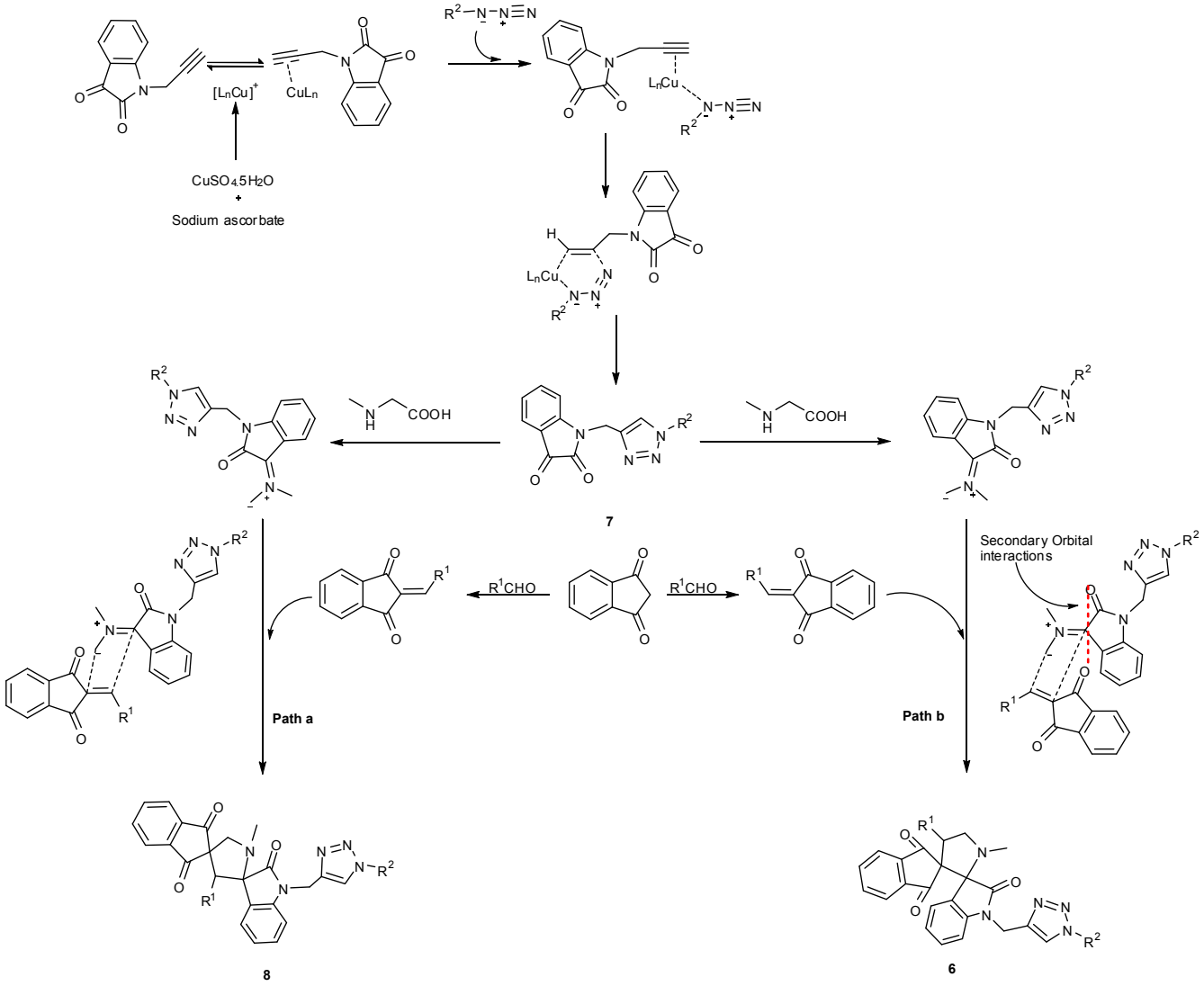


Figure 4. Plausible mechanism for the regio- and stereo-selective formation of 1-*N*-methyl-spiro[2.3']-1'-*N*-((1-(aryl/alkyl)-1*H*-1,2,3-triazol-4-yl)methyl)oxindole-spiro[3.2"]-indan-1,3-dione-(aryl/alkyl)-pyrrolidines.